The epidemiology of acute lower respiratory infections in young children in a rural area of The Gambia.

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"The most widespread and fatal of all acute diseases, pneumonia, is now Captain of the Men of Death"

Sir William Osler, 1901

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ABSTRACT

For children growing up today in the developing world, acute respiratory infection (ARI) is the "Captain of the men of death". The World Health Organisation estimate that 4.3 million young children die every year from ARI making it the largest single cause of death. Given the magnitude of this problem, relatively little research has been carried out in developing countries. In keeping with this observation, ARI was known to be a major cause of childhood mortality and morbidity in The Gambia but little was known about their epidemiology or aetiology. Suitable methods for their treatment or prevention had not been investigated.

A one year community based longitudinal study was undertaken in a rural area of The Gambia in which approximately 500 young children were monitored for signs of acute lower respiratory infection (ALRI). An attempt was made to determine the incidence of ALRI in this community; all identified episodes of ALRI were investigated in order to try to establish the cause of the infection; the association between a number of possible risk factors with ALRI incidence was explored; and two different regimens of antibiotic treatment were compared. A survey was made of the knowledge, attitudes and practices of mothers with respect to acute respiratory infections in their children.

The study documented very high incidence rates of ALRI among children in the study villages. The use of simple clinical criteria for the diagnosis of ALRI, which could be taught to health workers, was investigated and the most valid criteria for this community identified. Preliminary evidence suggests that bacterial infections are important causes of community acquired ALRI. These infections responded well to a 5 day course of an inexpensive, oral antibiotic (cotrimoxazole) which was well tolerated. An important clinical overlap between ALRI and malaria was suggested by the study data. Widespread recognition of fast breathing was found among rural mothers and valid traditional concepts of difficulty breathing discovered.

ABBREVIATIONS

ALRI	Acute lower respiratory infection
ARI	Acute respiratory infection
BOSTID	Bureau of Science and Technology for International Development (National Academy of Sciences)
CDD	Control of diarrhoeal diseases
CFT	Complement fixation test
CHN	Community health nurse
CMV	Cytomegalovirus
CRP	C- reactive protein
EPI	Expanded programme of immunisation
ESU	Epidemiology and Statistics Unit
ICD	International classification of diseases
IFA	Immunofluorescent antibody
KAP	Knowledge, attitudes and practices
MCH/FP	Maternal and child health and family planning
MRC	Medical Research Council
NCHS	National Child Health Standards
NGO	Non governmental organisation
PHC	Primary health care
RSV	Respiratory syncytial virus
TBA	Traditional birth attendant
URD	Upper river division
UV	Ultraviolet
VHW	Village health worker
WHO	World Health Organisation

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PREFACE

Two issues require a preliminary introduction and discussion before the main body of the text can be presented. These give essential contextual information which is important to document at the outset. The first of these concerns the definition and classification of acute repiratory infections adopted in this report; and the second is background information on The Gambia.

1. Definition and Classification of ARI

The International Classification of Diseases and Causes of Death (ICD) classifies diseases according to the biological aetiology of the causes of death, or, where aetiology is not apparent, the anatomical localisation. [1] ARI classified under "diseases of the respiratory system" in the ninth revision are presented in table 1.

Table 1: Classification of diseases of the respiratory system from the International Classification of Diseases (ICD), 9th Revision

I	**Diseases of the respiratory system**		
	Acute Respiratory Infections (code 460-466):		
	(460)		- common cold
	(461)		- acute sinusitis
	(462)		- acute pharyngitis
	(463)		- acute tonsillitis
	(464)		- acute laryngitis and tracheitis
	(465)		- AURI of multiple or unspecified sites
	(466)		- acute bronchitis and bronchiolitis
II	**Pneumonia and Influenza (code 480-487)**		
	(480)		- viral pneumonia
	(481)		- pneumococcal pneumonia
	(482-483)		- pneumonia due to other bacteria and other organisms
	(484)		- pneumonia in infectious diseases classified elsewhere
		(484.3)	+ pneumonia in whooping cough
	(485)		- bronchopnemonia, organism unspecified
	(486)		- pneumonia, organism unspecified
	(487)		- influenza
	Infectious and parasitic diseases		
		052.1	- pneumonia in varicella
		055.1	- pneumonia in measles

Note: Codes 470 - 478 include other respiratory diseases and chronic conditions (deviated septum and polyps and chronic upper respiratory conditions.
Codes 490 - 496 include chronic obstructive pulmonary disease and allied conditions (chronic bronchitis, aemphysema, asthma).
Codes 010 - 018 include respiratory tuberculosis

Under this system the common cold (code 460) is coded separately from acute bronchitis and bronchiolitis (code 466) and influenza and pneumonia (which are considered together in codes 480-7). In addition, the fourth digit of the ICD permits one to specify pneumonia occurring after certain diseases such as measles (484.0), and pertussis (484.3). Earlier revisions of the ICD differ slightly from the ninth revision. For instance, in the eighth revision, pneumonia (480-6) was classified separately from influenza (470-4) and pneumonia after measles or pertussis was not included in the diseases of the respiratory system. However, reasonably complete national registration data is rarely available in Africa and the ICD classification has been little used in African studies of ARI mortality or morbidity.

Traditionally in clinical medical training, ARI have been sub- categorised anatomically into acute upper respiratory infections (those occurring above the level of the epiglottis) and acute lower respiratory infections (those occurring at or below the level of the epiglottis). This has not proven to be useful for two main reasons. Firstly this distinction is an artificial one since many ARI involve multiple areas of the respiratory tract both above and below the epiglottis at the same time. Secondly this classification does not serve to guide the subsequent management of children presenting with symptoms of ARI and has recently been abandoned by WHO.

In this report acute respiratory infections (ARI) are considered to include all infections of the respiratory tract and therefore incorporate all of the ICD codes 460-466 and 480-487 mentioned above and shown in table 1. They range from ear infections , sore throat, common cold, laryngotracheobronchitis (croup), epiglottitis and bronchitis to bronchiolitis and pneumonia. Children with ARI can therefore present with any of the following symptoms: cough, difficulty breathing, sore throat, runny nose, earache or ear discharge. The majority of ARI episodes are due to the common cold (ICD code 460).

The most important objective in the assessment and classification of children with ARI in developing countries is to identify the few children with pneumonia from among the very many with cough due to the common cold. It is therefore necessary to adopt a classification system which recognises children with signs and symptoms that are predictive of the presence of pneumonia. A number of simple clinical signs which identify children with fast or difficult breathing can be used to identify this group of children. However these signs also identify some other children with ARI who have evidence of fast or difficult breathing due to involvement of their lower respiratory tract namely those with bronchiolitis or wheeze associated with viral respiratory infections. Since this group of children with ARI and associated fast or

difficult breathing is broader than simply pneumonia alone, it is termed acute lower respiratory infection (ALRI) throughout this report and is used consistently in this manner (please refer to section 2.5 for precise details of criteria used). It relates to the following ICD codes in the "diseases of the respiratory system" section: 466 (bronchiolitis only) and 480-486. It does not refer to the anatomical ALRI classification and therefore it should be noted that the clinical condition "bronchitis" (which occurs anatomically in the lower respiratory tract but which does not result in fast or difficult breathing) is not included. This nosological approach is now widely adopted and is consistent with the current WHO classification system.

The use of the above clinical criteria for the classification of ALRI is not completely sensitive and specific and so a number of false negative and false positive cases will be included. For the purposes of studying the relationship of a number of possible "risk factors" with incidence of ALRI, it is desirable to improve the specificity of the definition and thus decrease the proportion of false positives. Thus some of for these analyses we considered only ALRI episodes for which there was, in addition, corroborative radiological evidence of ALRI (all children with ALRI were investigated by chest x-ray subject to parental consent).

The term "pneumonia" is used in this report in two main ways. Firstly to refer to the condition of alveolar infiltration identified by specific clinical findings (such as bronchial breathing) or characteristic radiographic pattern and is a sub-group of the ALRI classification. This diagnosis can be established usually only in hospital-based studies in which a more complete assessment is undertaken (including expert paediatric assessment and radiological examination). The other use of the term "pneumonia" is found in the study of mothers knowledge, attitudes and practices in which this term refers to the mothers concepts of this condition (see glossary for a fuller discussion of this issue).

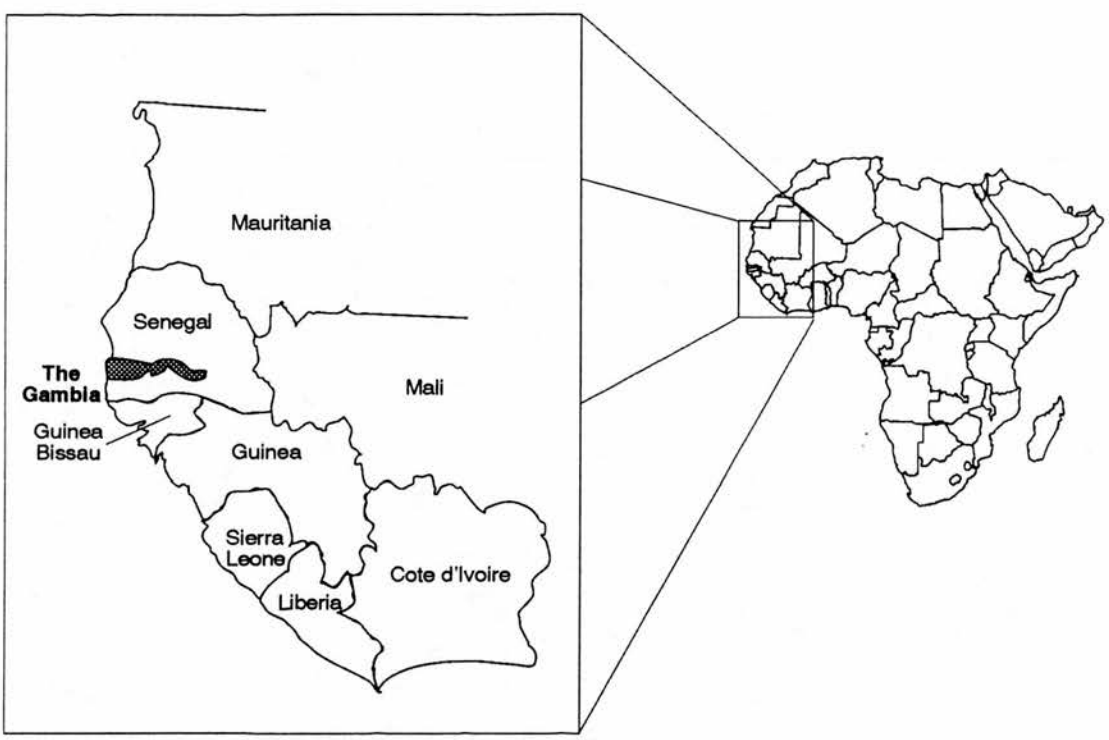
For the purposes of ARI surveillance in this study precise clinical criteria were adopted as the basis of the case definition of ALRI. The clinical diagnosis was based on a set of standardised symptoms and signs, assessed by trained observers in a standardised way. Specific details of these criteria are presented in section 2.5 of the report.

2. The Gambia

Geography

The Gambia lies on the west coast of Africa between latitudes 13°3' and 13°49'N and longitudes 16°48' and 13°47'W. Its total land area of 11,607 square kilometres makes it one of the smallest countries in Africa. It has a short Atlantic seaboard of 48 kilometres from which it extends eastwards on both sides of the Gambia river for a distance of 487 kilometres , forming an enclave within the Republic of Senegal (figure 1).

Figure 1: Map of West Africa



The country is flat and nowhere rises more than 90 metres above sea level. Its main geographical feature, the river after which it is named, is saline for approximately 200 kilometres upstream. Low- lying swamps are found on each side of the river and beyond those the country is mainly sandstone plateau with scattered laterite outcrops. The predominant pattern of vegetation is Guinea savanna and secondary forest, with very little primary tropical forest remaining.

Climate

The climate of The Gambia is characteristic of the sub-sahel with a rainy season which lasts from July to October and a long dry season. Annual rainfall in recent years has been about 600mm. There has been a progressive decline in rainfall over the past 50 years and The Gambia is on the edge of the areas severely affected by the Sahelian drought. Many diseases show a strong seasonal pattern; infant and child mortality are much higher in the rainy season than during the dry season.

Transport and communications

Although used as a major trade route in colonial times, the river Gambia has lost much of its importance as a means of communication in recent years. Most goods are carried along a tarred road which runs along the south bank of the river from the coast to Basse, the main town and administrative centre of upper river division. The laterite roads to individual villages deteriorate during the rains making access possible only by 4-wheel drive vehicles.

The telephone network is currently being up-graded to an nation-wide automatic system. There are plans in the current National Health Development Plan to equip selected health facilities with short wave radios.

Education

The aim of universal primary education is a priority of the Gambian government. In the academic year 1980/81 only 46% of children of primary school age were attending primary school. Primary education is free but not compulsory for children aged 8 years and above. Places in secondary school are awarded on a competitive basis, and it is estimated that 40% of those completing primary school go on to secondary education.

Population

The most recent national census was carried out in 1983. This revealed a total population of approximately 690,000 with an estimated annual growth rate of 3.4%. The population projection for 1988 is 790,000 and for 1993 it is 910,000. The population density of 64 people per square kilometre is very high by African standards. There has been a considerable movement of population from rural areas to the urban and peri-urban areas associated with the capital Banjul. However most of the population still live predominantly in rural villages and hamlets.

Infant and child mortality

Studies carried out in the Gambian village of Keneba during the 1950's and 1960's showed that one half of all children born in this village died before reaching the age of 5 years. In recent years the situation has improved but infant mortality and child mortality remain high in rural areas. Accurate estimates of infant and child mortality rates are difficult to obtain in developing countries which have no national death registration. The official estimates taken from the most recent Gambian Government censuses state that the infant mortality rate was 217 in 1973 and 167 in 1983. Indirect techniques based on the modified Brass method have been used to estimate infant mortality (using information on the proportion of child survival among those ever born by women classified according to either their age or their marriage duration). This substantial reduction in infant mortality over the period 1973-1983 is in keeping with values obtained by direct measurements of infant mortality carried out in defined populations by MRC in recent years. Data from both the Government estimates and MRC community-based studies have consistently shown considerable variation in mortality rates within the country with higher mortality rates being found in districts farthest from the coast and the capital, Banjul.

Economy

The majority of the population live in rural areas growing rice, maize, sorghum and millet for their own consumption, and groundnuts for export. There are no major manufacturing industries and the groundnut crop is the country's main source of foreign currency. The salaried sector is very small, but a large number of people make their living through trade, largely operating outside the formal economy. Tourism is limited to the coastal region and makes a small contribution to the economy. In the peri-urban areas around the capital Banjul, a larger proportion of the population are wage-earners but, even in these circumstances, family income is often supplemented by agriculture or trading.

Health infrastructure

The national health programme is under the administrative control of the Minister of Health, Environment, Labour and Social Welfare. The Director of Medical Services is in charge of the medical and health department and is assisted by an Assistant Director of Medical Services, a Medical Officer of Health, Chief Nursing Officer, Principal Public Health Officer and Chief Pharmacist. A number of specialised units exist at the central level: Health Education, Maternal and Child Health / Family planning, Nutrition, Expanded Programme of Immunisation (EPI), Epidemiology

and Statistics, Diarrhoeal Diseases Control and Acute Respiratory Infection Control, Tuberculosis / Leprosy Control, Vector Control, Health Inspectorate and Central Medical Stores.

Health delivery in The Gambia is on a 3 tier level linked to one another by a referral system. The primary level is the Village Health Services, the secondary level consists of the Health Centres and Dispensaries and the tertiary level the hospitals. Throughout the country there are 316 Village Health Services posts, 14 Dispensaries, 16 Health Centres, 2 Government Hospitals and 3 Private Hospitals. There are also a limited number of clinics run by Non Governmental Organisations.

A major commitment has been made to Primary Health Care (PHC). During the last 8 years a national PHC programme has been in progress which includes provision for a trained village health worker and traditional birth attendant in each village with a population of 400 and above. Village health workers are trained in various aspects of preventative health care and in curative medicine, including the treatment of ARI.

The government spends 2.7% of the gross domestic product on health, amounting to less than $3.5 per capita (1986). In 1984 external aid to the health sector amounted to $4.3 million from all sources. In the period 1980-86 64% of all health expenditure was on primary health care.

1. INTRODUCTION

1.1 Importance of ARI

1.1.1 Acute respiratory infections (ARI), diarrhoeal disease, malaria, and malnutrition are the most common causes of illness and death among children in developing countries. It has been estimated that one quarter to one third of under five child mortality in developing countries is attributable to ARI.[2,3,4] The 1991 WHO global childhood mortality estimates place ARI as the single largest cause of death accounting for an estimated 4.3 million deaths in children under 5 years of age in 1990. The most frequent causes of death from ARI are pneumonia, bronchiolitis and acute obstructive laryngitis. Of these, pneumonia is by far the most important. For children growing up in the developing world today Sir William Osler's words are as true today as they were for children in developed countries in 1901 - "the most widespread and fatal of all acute illnesses, pneumonia, is now Captain of the Men of Death". Given the magnitude of this problem it is truly remarkable that ARI had received so little international attention up until the last 10 years and that so little research has, even today, been undertaken in developing countries to better understand this "most fatal of all acute illnesses".

1.1.2 Community-based studies suggest that the overall incidence of acute respiratory infections is similar among children in developing and industrialised countries (about 2-5 episodes per child per year in rural areas and 5-8 episodes per child per year in urban areas).[5] However, the incidence of acute lower respiratory infections (ALRI), is about 5 times higher among children in developing countries and mortality from ARI is as much as 50 times higher.[6] The reasons for these disparities are not fully understood.

1.1.3 Current knowledge of the epidemiology and aetiology of ALRI in young children in developing countries is predominantly derived from hospital-based studies.[7] Although children hospitalised with ALRI represent an important group with high case-fatality rate, they are nevertheless a highly selected group with respect to all childhood ALRI occurring in a community and also in relation to all ALRI deaths in young children, because only a few such children die in hospital. Thus community-based research is required to complement hospital-based

studies and to set their results in context. This is especially true for populations with few health-care facilities.

1.2 The epidemiology of ARI in Africa

1.2.1 Mortality from ARI

1.2.1.1 Surveys undertaken in various parts of tropical Africa have shown that pneumonia is one of the leading causes of deaths in children admitted to hospitals.[8] There have been few attempts to determine the overall mortality from ARI among children in Africa. A WHO co-ordinated study conducted in 6 African countries in 1970 - 1973 recorded a mortality associated with ARI of 1454 per 100,000 among infants and 467 per 100,000 among children aged 1 - 4 years.

1.2.1.2 Community-based longitudinal studies gathering data on ARI deaths have been carried out in 7 African countries (table 2).

Table 2: Mortality from ALRI among children aged 0 - 4 years in Africa: summary of data from recent studies

Study	Number of deaths	Mortality all causes		Observed % ALRI deaths
		Q/1,000	M/1,000	
Community Studies				
Kenya	557	75.2	16.0	19.5
Morocco	382	101.9	22.2	11.4
Senegal	1593	256.3	64.5	15.8
Tanzania	325	182.2	40.1	35.7
Registration systems				
South Africa				
1968 - 1973	13810	19.5	4.0	18.6
1974 - 1979	11079	16.5	3.4	18.6
1980 - 1985	4647	7.1	1.4	18.5

Q = Probability of dying between 0 and 59 months of age
M = Number of deaths in children age 0 - 4 years/1,000 child years.

Since most of the deaths in children occur outside hospital, investigators have developed methods for interviewing relatives of the deceased child and have attempted to translate this information into a medical diagnosis. This procedure , known as "verbal autopsy" has been recently reviewed. [9] In 6 of these studies (Senegal [10], Kenya [11], Nigeria [12], Gambia [13], Guinea

Bissau [14], Morocco [15]) the ascertainment of ARI deaths was part of an overall assessment of cause-specific mortality and in the seventh (Tanzania [16]) the longitudinal surveillance was aimed specifically at ascertaining deaths due to ARI to assess the impact on ARI mortality of a community-based ARI intervention project. In addition a study of ARI mortality in South Africa was performed based on a review of the national death registration data [17] over the period 1968-85 (table 2).

1.2.1.3 Two African studies have looked at the causes of ARI deaths and found that 90% of these deaths were due to pneumonia.[18,19] This is consistent with South Africa national registration data in which Von Schirnding [17] found that among 3774 "coloured" infants age 0-11 months who died from ARI, 96.3% had a diagnosis of pneumonia recorded on the death certificate. Supporting evidence from studies from other continents have shown that pneumonia is the primary cause of hospitalisation for ARI [20,21,22,23] and that hospital case fatality rates associated with pneumonia are high. [20,21,22,

1.2.1.4 Historically measles has been associated with a high proportion of ARI deaths in young children in developing countries. Three studies in Africa have considered its role in ARI mortality [24] and their results differ widely as shown in table 3. The proportion of ARI deaths associated with measles depends very much on the incidence of measles (a large outbreak of measles occurred during the period of registration of deaths in the Guinea-Bissau study shown in table 3) and the measles immunisation coverage over the period considered. An analysis of data from 16 developing countries [24] showed a mean of 18.6% of ARI deaths were associated with measles, although few studies clearly defined their criteria for considering an ARI death to be associated with measles.

Table 3: Contribution of Measles to ARI mortality in young children in Africa

Study	Age Group (Years)	Number of Measles deaths	% of Measles deaths associated with ARI	Number of ARI deaths	% of ARI deaths due to Measles
Guinea Bissau 1986	0 - 7	62	100	31	92.5
Senegal 1990	0 - 5	78	30	250	9.2
Tanzania 1986	0 - 5			421	25

1.2.2 Morbidity from ARI

1.2.2.1 Eight major longitudinal studies gathering data on ARI incidence have been carried out in Sub-Saharan Africa since 1970.[10,11,12,16,25,26,27,28] Estimates of ARI incidence ranged from approximately 7 to 13 episodes per child per year, With ARI accounting for about 25 - 35% of all illness episodes and 17 - 40% of all health facility attendances in children. However these studies have not yielded estimates of ALRI incidence based on the surveillance of specific and precisely defined clinical signs which can be meaningfully compared with other data which has been collected from other developing countries in recent years.

1.2.3 Aetiology of pneumonia

1.2.3.1 Diagnosis of the cause of ALRI in a child can be difficult, even in hospitals with full laboratory resources. Blood culture is positive in only about 25% of patients with bacterial pneumonia. Children with ALRI rarely produce sputum and the value of sputum examination by conventional bacteriological techniques is in any case uncertain.[29] In many patients a bacteriological diagnosis will be established only if lung puncture is performed.[30] Diagnosis of a viral respiratory infection requires considerable laboratory resources and expertise. It is, therefore, not surprising that there have been few detailed studies of the causes of ARI in African children.

1.2.3.2 Seven hospital studies in Africa have been published which investigated the bacterial aetiology of pneumonia.[31,32,33,34,35,36] Overall, Streptococcus pneumoniae predominated, followed by Haemophilus influenzae. Staphylococcus aureus featured strongly in studies in which patients had received prior antibiotic treatment. There have been very few attempts to study the role of viruses in the aetiology of ARI in Africa. Three studies have found respiratory syncytial virus, parainfluenza and influenza viruses to be the commonest viral agents.[37,38,39].

1.2.3.3 These diagnostic problems are even more acute in community- based studies with no ready access to hospital diagnostic facilities. The scarcity of data on the aetiology of pneumonia in children in communities in developing countries is largely a consequence of the lack of a simple, reliable method for establishing aetiology in paediatric out-patients.

1.3 Magnitude of the ARI problem in The Gambia

1.3.1 Mortality from ARI

1.3.1.1 In 1980 the Medical Research Council (MRC) laboratories in The Gambia were asked by the Gambia Government Medical and Health Department to study the pattern of childhood mortality and morbidity in a rural area of The Gambia prior to the introduction of the primary health care programme. During a 1 year period in 1982 -1983 all deaths in childhood were recorded in a study population of 13,000 subjects using a comprehensive surveillance system, and an attempt was made to establish the cause of death by interviewing the relatives of each deceased child. Twenty-seven (15%) of 184 deaths in children aged one month up to 7 years were attributed to ARI. Acute respiratory infections were the commonest cause of death in children who survived beyond the age of 1 month.[13]

1.3.1.2 The validity of the verbal autopsy technique as a means of determining cause of death was investigated by comparing diagnoses made in children admitted to the MRC hospital with a potentially fatal illness on the basis of the mother's history alone with the diagnoses established after full clinical and laboratory investigation. An overall concordance of 88% was found and all in 17 children with ARI a correct diagnosis was made from the history alone.[40]

1.3.1.3 Deaths from ARI were encountered most frequently in children under 2 years of age and occurred throughout the year. The age specific mortality from ARI in young Gambian children was estimated at 10 per 1000 per year.

1.3.2 Morbidity from ARI

1.3.2.1 Hospital and health centre records show that ARI are second only to fever (usually attributed to malaria) as a cause of sickness in young Gambian children. At the MRC hospital in Fajara pneumonia is the commonest cause of paediatric admission to hospital and ARI account for 30% of paediatric out-patient attendances.

1.3.3 Aetiology of ARI

1.3.3.1 During the past few years the Medical Research Council has undertaken several investigations into the causes of pneumonia in young children. Studies (including bacterial and viral culture of material obtained from lung aspiration) established a bacterial aetiology in two thirds of all cases.[41] Streptococcus pneumoniae and Haemophilus influenzae were the most common causes of pneumonia in young children admitted to the MRC hospital . Studies of the antibiotic sensitivity of isolated Streptococcus pneumoniae and Haemophilus influenzae have shown them to be fully sensitive both to cotrimoxazole and to penicillin. Viral studies have identified respiratory syncytial virus (RSV) to be a significant cause of ALRI in infancy which occurs in short defined outbreaks. RSV was identified in 37% of infants admitted with ALRI to the MRC hospital in Fajara over a one year period in 1987-88. [42,43]

1.4 Response of The Gambian Medical and Health Services

1.4.1 In the past 15 years The Gambia has systematically expanded its basic health services through village health workers and strengthened its health infrastructure. Building on a successful yellow-fever vaccination campaign that followed an outbreak of this disease in the The Gambia in 1978, a nation-wide Expanded Programme on Immunisation (EPI) has been established which has achieved consistently high coverage during the past 8 years. This has significantly reduced the incidence of diseases such as measles and pertussis which had contributed to deaths from ARI. Improvements to the transport fleet and regular vaccine supply have contributed to the continuing improvements.

1.4.2 Accurate estimates of infant mortality rate are notoriously difficult to obtain in developing countries. The Gambian Government census document in 1983 quoted the infant mortality rate as 167 per 1000 live births (an estimate based on a number of surveys throughout The Gambia utilising the modified Brass indirect technique for mortality estimation). More accurate direct estimates in smaller defined areas have been obtained by MRC through intensive community surveillance and these have yielded figures of 142 per 1,000 thousand live births in Farafenni in 1982-3 and 100 per 1,000 in Upper River Division in 1988-9. Thus, despite excellent EPI vaccine coverage infant mortality in The Gambia remains very high and deaths from ARI account for a major proportion of these infant deaths.

Improvements in vaccine coverage with existing vaccines are likely therefore to have only a modest effect on infant mortality. If this is to be reduced further it will be necessary to concentrate on other preventive or case management interventions targeted against the major infectious diseases causing childhood mortality in The Gambia: ARI, malaria, chronic diarrhoea and neonatal sepsis.

1.4.3 An Essential Drugs Committee has completed work on treatment schedules for health centres and dispensaries. This aims to standardise treatment for all common illnesses including ARI. A similar schedule for hospitals is being prepared. A quarterly inventory system has been instituted resulting in regular stock checking.

1.4.4 ARI control as a child survival strategy is accorded high priority by the Ministry of Health. An ARI programme manager has been identified, a national ARI programme which is integrated into the PHC system has been started, and there is considerable interest and determination within the Medical and Health department to intensify these efforts to control ARI.

1.4.5 The Government of The Gambia has embarked on an ambitious primary health care programme which will soon achieve nation-wide coverage for all villages with a population of 400 or more. Case management of ARI in children was identified by the National PHC Programme since its inception, as one of the key activities of village health workers. A manual for training village health workers (VHWs) was issued by the Medical and Health department in 1983. The recognition of symptoms and signs and the treatment of respiratory infections was included in the 8 week VHW training. A long list of symptoms and signs for which antibiotic treatment was recommended was given in the manual and these included the following: "looks ill", fever, sore throat, loss of voice, ear aches, rapid breathing whilst sleeping, chest indrawing and chest pain. The VHWs were supplied with tablets of oral phenoxymethylpenicillin for the treatment of these conditions. Each penicillin container was labelled with a picture representing the symptoms for which it was to be dispensed and the doses for the various age groups.

1.4.6 If most ALRI episodes in young children are caused by S. pneumoniae or H. influenzae then treatment with phenoxymethylpenicillin is not likely to be effective; if they are caused predominantly by viruses it is unnecessary.

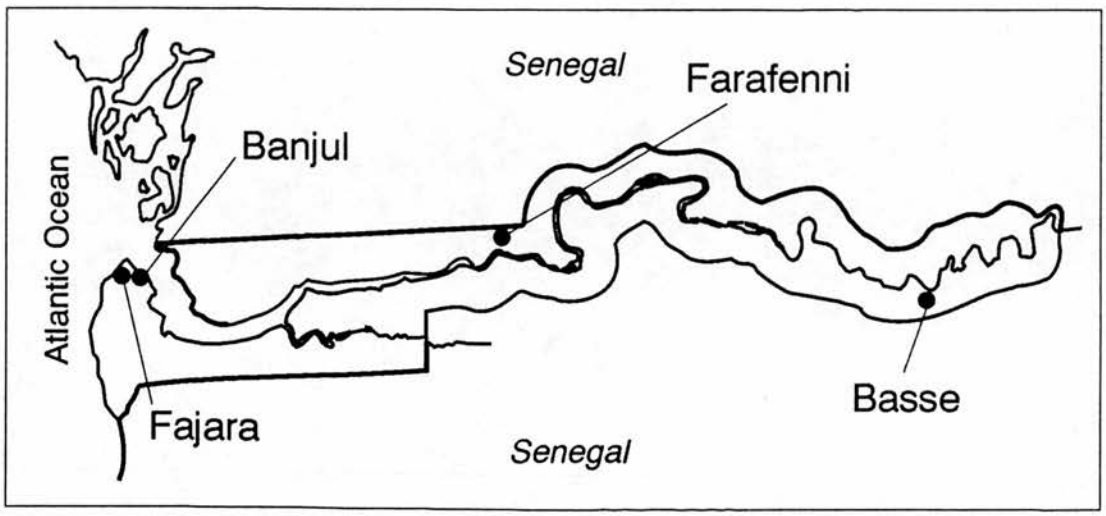
Thus, more information is required on the aetiology of ALRI, and specifically pneumonia (since it is believed that this is the major cause of death as discussed above), in Gambian children before a more rational programme of treatment for primary health care workers can be devised.

1.5 Medical Research Council Laboratories, The Gambia

1.5.1 The MRC Laboratories, The Gambia is one of 56 research units supported by the United Kingdom Medical Research Council. The laboratories in The Gambia, established in 1947 as a nutritional field research station, is one of MRC's oldest units. In the 1950's and 1960's the laboratories, under the directorship of Sir Ian McGregor, gained an international reputation for research in malaria. The laboratories currently have a staff of approximately 400, about 30 of whom are senior scientists or scientific officers. The main research centre, situated on the coast at Fajara near to the capital, Banjul, comprises a 40-bed hospital, out-patient clinic, research laboratories, garage and maintenance areas. There are 3 up-country field stations at Farafenni, Walikunda and Basse (figure 2). A further field station at Keneba is part of the MRC Dunn Nutrition Unit based in Cambridge, England. The main laboratories at Fajara are well equipped for laboratory research in bacteriology, virology, parasitology and immunology. Laboratories at the up-country field stations are equipped more simply.

1.5.2 The MRC laboratories work in close partnership with the Medical and Health Department of the Government of The Gambia. Research policy is decided by the Joint Gambia Government/ MRC Committee which meets twice a year. All research projects must be approved by a Scientific Co-ordinating Committee and by an Ethical Committee which has Gambian medical and lay members.

Figure 2: Map of The Gambia



1.5.3 Basse Field Station

1.5.3.1 Although MRC staff had worked intermittently in Upper River Division for many years, a permanent base in this part of the country was obtained only in 1982 when a new field station was built in Basse (figure 2). This was used initially as a base for studies on the epidemiology of schistosomiasis. Unfortunately, financial constraints made it necessary to run down the operation of the field station in 1984 and for 2 years it had no resident staff. An improvement in the unit's finances made it possible to re-open the field station in 1986.

1.5.3.2 The field station is situated on the bank of the river and comprises domestic accommodation for one senior staff member and 3 visitors, laboratories and a clinic. The laboratories are equipped to undertake bacteriological and immunological studies. In 1986 the facilities were extended to include a clinic with a small routine laboratory, a simple x-ray machine which is adequate for taking chest radiographs in young children and a computer facility with 2 computers. To maintain these laboratory facilities it is necessary for the field station to generate its own electricity by means of 2

diesel generators. Simple vehicle maintenance is also undertaken at the field station.

1.5.4 The Basse ARI Project

1.5.4.1 The general objective of the study was to establish a surveillance system for ALRI capable of identifying young children with ALRI, obtaining appropriate specimens and documenting epidemiological and clinical data in order to determine the importance of ALRI as a cause of morbidity in Gambian children living in an area with few medical resources and to investigate the aetiology of ALRI in this community in as far as this was possible with currently available methods.

1.5.4.2 The study was conceived as a preliminary descriptive study to investigate the epidemiology of acute lower respiratory infections (ALRI) in young children in a rural Gambian community. Results from this study would then help direct further research in ARI undertaken by the MRC unit.

1.5.4.3 However it was recognised that the establishment of the infrastructure necessary to achieve this objective would, in addition, give the opportunity to study a range of related issues surrounding the epidemiology and treatment of ALRI including: an assessment of the validity of the existing World Health Organisation (WHO) clinical criteria for detecting ALRI (to determine whether these should be adopted by the primary health care system in The Gambia), a study of the knowledge, attitudes and practices of Gambian mothers with respect to ARI, and a comparison of two alternative methods of treatment for pneumonia that could be administered through the primary health care system in The Gambia.

1.5.4.4 It was recognised that due to the many problems and difficulties involved in establishing strict surveillance of rural populations in Africa and due to the relatively high level of technical input required in order to undertake bacteriological and virological diagnosis of ALRI in a rural setting remote from hospital laboratories, this study would be the first of its kind in Africa and that therefore the results would be of interest to other African countries. Community-based research in defined populations with few health care facilities was and still is required to complement the predominantly hospital-based studies which had been performed in The Gambia and in other African countries.

1.5.4.5 The study comprised two separate yet linked elements. The community study consisted of, in brief, an active surveillance system for ALRI which was established in 1987 in 7 villages near to Basse in the upper river division of The Gambia. For a one year period all (approximately 500) children under the age of 5 years resident in these villages were visited weekly by an MRC field worker. A morbidity questionnaire was administered and the child's temperature and respiratory rate recorded. In addition, mothers of children who became sick during the period between visits usually sought help from the MRC field worker who was resident in their village. Thus, nearly all episodes of ALRI in these children should have been identified. When a field worker suspected that a child had an ALRI he requested, through a radio link between the villages and the Basse field station, for transport to take the child to Basse for investigation. On arrival at the field station the child was examined by the study physician and, if the diagnosis of ALRI was confirmed, a chest x-ray was taken and microbiological investigations performed.

1.5.4.6 Concurrently a health centre-based study took place on one morning of each week during the one year period of community surveillance. All children under the age of 5 years who lived within a 40 kilometre radius of Basse and who attended the out-patient department of the government health centre in Basse were monitored using identical clinical criteria for the recognition of ALRI. The purpose of this aspect of the study was to increase the number of children with ALRI for investigation and to compare results between the two groups. However few cases (49) of ALRI were identified by this method. This was largely due to the very marked decline in attendances at the health centre which followed the exhaustion in antibiotic supplies to this health centre. This situation persisted for 9 out of the 12 months of study.

2. STUDY METHODOLOGY

2.1 Study Area

2.1.1 The population of Upper River Division is estimated to be 125,000. A high proportion of the population live in large villages but over 300 discrete settlements have been identified. Three main population groups (Mandinka, Fula and Serehuli) are represented each with their own distinct language.

2.1.2 Basse is a busy market town with links with Senegal, Mali and Guinea. It has a health centre with facilities for the admission of about 30 patients and is staffed by one government doctor who is responsible for both the curative and preventative care throughout the division. Families living in this area rely on subsistence farming with some additional support from cash generated from the sale of groundnuts. The level of school education amongst rural women from the study villages is very low with less than 5% having received any primary education.

2.2 Study population

2.2.1 A major goal of the study was to identify and study all episodes of ALRI in young children in a defined population. Since case definition required confirmation of clinical signs by the study physician and further study involved radiological and laboratory investigations it was necessary that all children identified by the field workers as having clinical signs consistent with ALRI be referred to the field station. It was known that the local communities made limited use of fixed health centre facilities in the region. This was in part due to the expense of transport and subsequent medical treatment and in part due to the difficulties which women had in being away from their domestic and farming duties for the lengthy period of several hours which was typically required for a visit to the health centre in Basse. Therefore in order to ensure that all such children were indeed studied, free transport and subsequent treatment was provided. This however dictated that the study site had to be located in reasonably close proximity (10-15 kilometres) to the field station to allow twice daily landrover visits to each study village.

2.2.2 Within this 10-15 kilometre radius from the field station villages and hamlets were chosen to the <u>east</u> of the field station. This decision was reached after discussion with the MRC Director and a Senior Scientist with many years experience working in this region. It was taken based on a

knowledge of the condition of the local roads during past rainy seasons (many laterite roads become impassable at this time) and on a positive decision to try to include communities of different sizes (only the larger settlements have a government health worker) and ethnic group compositions.

2.2.3 Villages to the north could be reached only by a ferry crossing (which was not completely dependable) and by poor quality roads which were difficult to negotiate in the rainy season. There were insufficient villages within a 10-15 kilometre radius to the west and the communities to the south were more typical of a rural town (Basse) rather than the rural villages in which most of the Gambian population live. Therefore communities within a 10-15 kilometre radius to the east were selected.

2.2.4 It was recognised that such a directive method of study population selection serves to limit the confidence with which study findings can be generalised to other areas, however the considerable operational difficulties inherent in this study dictated that this course be followed. Indeed, the logistic and technical problems involved have been the reason why similar community-based studies had not previously been attempted in Africa. The intention was principally to gain an understanding of the epidemiology of ARI in this rural community over a one year period. This information could then be considered together with available hospital-based data in the future planning for services and in directing future research priorities.

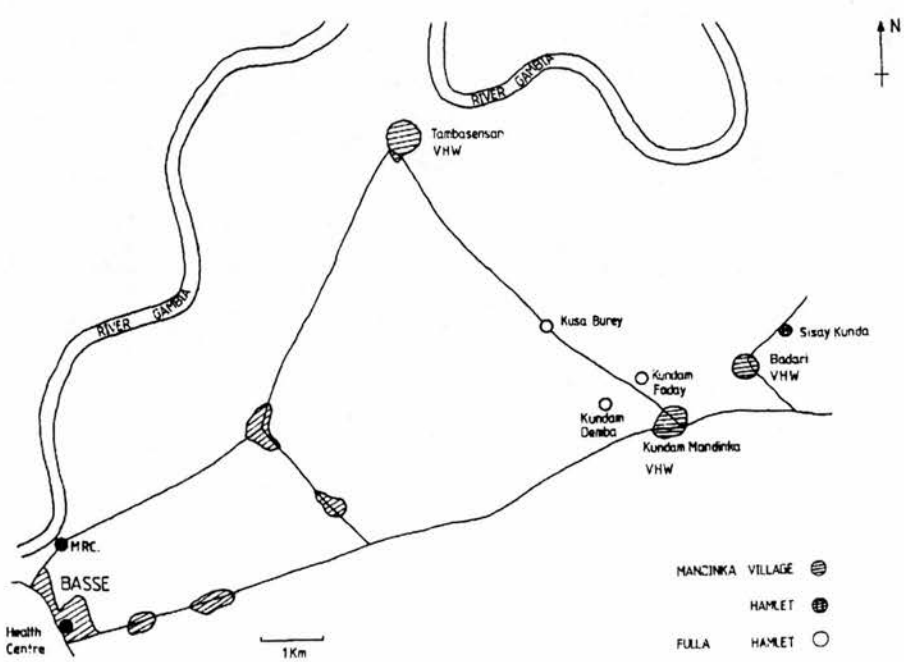
2.2.5 This was principally an observational descriptive study seeking establish the incidence rate of ALRI among young children in this rural community. No similar community-based data were available to guide our study planning. However WHO estimates 300 ALRI episodes per 1,000 children under 5 years of age for resource planning purposes in programme manager's training materials). [44] To estimate a rate of 0.3 episodes/child/year with a 95% confidence interval of 0.275 - 0.325 episodes/child/year would require a study follow up of about 500 child-years ($n=u/e^2$, where u is the rate and e is the standard error and we approximate a 95% confidence interval to equal plus or minus 2 standard errors). Since approximately 16% of the Gambian population are under 5 years of age this would require a total population of about 3,000 people. This size of study population would therefore be expected to result in 150 episodes of ALRI in young children. If 90% of these episodes were

successfully identified then 135 episodes would be available for study. This would allow the ALRI incidence rate to be expressed with reasonable precision. In addition, 135 ALRI episodes is of the same magnitude as previous aetiology studies performed in Fajara which had yielded important clues to the aetiology of ALRI in The Gambia. We considered therefore that this sample size would be adequate for the purposes of the aetiology study if similar isolation and identification rates were found.

2.2.6 It was additionally considered important that the study period consist of at least one complete year since seasonal factors were known to greatly influence the epidemiology of many infectious diseases in The Gambia. Ideally this study would be repeated over a number of years to consider the year to year variation which is known to occur in ARI (since many respiratory viruses are epidemic in behaviour) but this was not financially possible.

2.2.7 The communities which we selected comprised three Mandinka villages (Tambasensan, Kundam Mandinka and Badari), one Mandinka hamlet (Sisekunda), and three Fula hamlets (Kundam Foday, Kusa Burey and

Figure 3: Map showing location of study village and hamlets



Kundam Demba) as illustrated in figure 3. Two other Mandinka villages to the east were excluded since they were less than 5 kilometres from the health centre at Basse and it was considered that many parents in these villages made much more regular use of the health centre. It was therefore likely that a significantly lower proportion of cases of ALRI would be able to be studied fully.

2.2.8 Informed consent was obtained by first explaining details of the proposed study at village meetings (at least two in each village) followed by individual explanations by field workers to each family. The free medical services offered to the study population were not withheld from the few families who declined to take part. Further village meetings were held in each village on at least two further occasions during the study year to allow discussion of the study with the villagers. Emphasis was placed in these meetings on specific practical details of what was proposed rather than general statements of intent. The proportion of children in the study villages whose parents consented for them to take part varied throughout the year but never fell below 90% at any time.

2.2.9 In order to define the study cohort accurately two independent censuses of the villages by different field workers were carried out. Data on the under 5 year old children were compared and any major discrepancies were identified. In these circumstances the field work supervisor checked for the census details a third time. A local events calendar was prepared and used to assist in establishing the date of birth of each child. A final method used to identify errors in recorded dates of birth was used during the cross sectional survey immediately prior to the 1 year surveillance period. Outlying weight for age values were identified and all dates of birth of these children were again re-checked.

2.2.10 All children under 5 years of age who were identified by the initial census and the ongoing recording of vital events and whose parents gave informed consent for them to take part in the study were entered into the study (when children reached their fifth birthday they took no further part in the study). Thus our results (due to this "rolling cohort" design) portray childhood ALRI in a defined community during a one year period rather than in a cohort of specific children.

2.3 Establishment of field work activities

2.3.1 The field station was closed prior to the study commencing so a number of essential activities preceded the start of the project (table 4). These included the interviewing and hiring of field staff, followed by their training in basic epidemiologic techniques such as performing a census, mapping villages, recording of vital events and the principles of population surveillance using structured data forms suitable for direct computer entry.

Table 4: Timetable of field work activities in the establishment of Basse Field Station, April - November, 1986

April	Selection of study villages Village meetings
May	Census of study population Mapping of villages
June	Field worker training Field workers sited in villages Identification of village reporters Ongoing recording of vital events
August	Field worker training - recognition of ALRI Pilot of mobidity questionnaires
September	Surveillance system in operation Patient referrals
November	Cross-sectional survey of cohort (end of wet season)

A series of village meetings were held to select study villages and then a census and mapping of the villages took place. The villages were encouraged to provide a volunteer "reporter" who helped us identify births, deaths, and migratory events (into, out of and between study villages). Considerable effort went into thorough preparation and training at each step and it took 12 months of full time activity before the cohort study commenced in March 1987.

2.3.2 An experienced field worker who had worked for many years at Farafenni field station co-ordinated the census and mapping of the study villages. These communities consist of groupings of family "compounds" which are surrounded by fences. Each of these was mapped and given a unique number. Within each of these compounds individual huts were given a letter and each child was allocated a unique identifying number which comprised a letter (designating the study village), a two figure digit (the compound number), a second letter (corresponding to the child's bedroom)

and finally a two digit personal code number. This number was recorded on the child's "Road to Health Card", was printed on a separate "Basse Study Card" given to the mother, entered into hand written census forms and finally punched into a computer (dBase 3) database.[45]

2.3.3 Field workers were trained in the collection of weekly vital events in the study village. Forms were designed to facilitate the collection of this information and village reporters were identified by the villages and paid a small honorarium to assist the field workers to identify village vital events (births, deaths, children moving to other addresses both within or outwith the study villages and children moving into the study villages). Babies born during the study period were recruited into the study as soon as they were identified usually within 7-10 days of birth. Children moving residence within the study villages were retained in the study cohort and their unique number was not altered. Children moving out of the study villages exited the study unless it was known in advance that they were going to return in the near future. Children moving into the study villages were entered into the study cohort. Vital event forms were delivered weekly to the field station, checked by the field supervisor then entered on the same day into the census database.

2.3.4 A questionnaire was designed to collect morbidity information from the cohort children. This was developed over a period of five months with the fourth version eventually being adopted as the study instrument after extensive pilot testing (see appendix a). The questionnaire asked about the presence of general and respiratory- specific symptoms in the preceding week, the presence or absence of any illness during that time, and whether or not treatment had been sought by the mother.

2.3.5 Each of the five field workers visited approximately 100 children weekly. Once weekly visits were adopted. It is recognised that observed incidence rates tend to increase as the frequency of visiting increases. WHO currently recommend weekly surveillance for studies seeking to establish ALRI incidence rates in a community.[46] A fixed surveillance timetable was adopted, visiting each child on the same day every week as far as possible. This encourages better co- operation from the surveillance population and facilitates data analysis. If a child was not at home on the day of the visit the field worker would ascertain why the child was not present and then return on several occasions thereafter to try to see the child. The field

workers lived in the study villages for 5 days of the week to facilitate their collection of surveillance data. In practice, most contacts with the cohort children took place in the early morning and early evening since the mothers often were away from home and working in the fields during the day. If children missed more than 4 weekly visits a meeting was held with the appropriate field worker and the field worker supervisor to clarify where the child was and to decide what action to take.

2.3.6 The field worker supervisor was allocated a motor cycle to allow him to visit the study villages to check the quality of the work of the other field workers. In addition the study physician made "spot checks" unannounced in the study villages. Frequency distributions of answers to each of the questionnaire items were generated during each of the 3 weeks of pilot surveillance activity in January/ February 1987 in an attempt to identify gross differences in response rates between field workers which would suggest a difference in their approach to the mothers or the way they administered the questionnaire.

2.3.7 Field workers were trained to count the respiratory rate of children and to recognise chest indrawing, nasal flaring and wheeze. This training took place over a period of three months both at the Basse field station and in the study villages during supervisory visits. Respiratory rate counts made by field workers were checked immediately afterwards on over one thousand children. Further training was given to those field workers whose performance was poorest and they were given more attention in the supervisory visits. The cross- sectional survey which took place in November 1986 before the cohort study commenced provided the opportunity to do blind paired (study physician - field worker) observations on about 500 children. Field workers were kept under close supervision until their respiratory rate counts were regularly within 5 counts of the study physician. An outbreak of bronchiolitis in the community immediately before the one year study period enabled the field workers to hear many children with wheeze. Field workers were encouraged to refer any child with noisy breathing if they were unsure whether or not wheeze was present.

2.3.8 It was not possible to train the field workers adequately in the recognition of stridor since, as has been noted in other developing country settings, the incidence of stridor was extremely low in these communities.

2.3.9 An attempt was made to identify the main concepts and linguistic terms used to describe local women's perception of a chest problem or breathing difficulty in young children to guide the formulation of specific questions for the morbidity questionnaire. A convenience sample of fifteen villages in the surrounding 50 kilometres were selected to reflect a the two language groups found in the cohort villages (Mandinka or Fula) and to be similar in size to the cohort villages and hamlets. Field workers visited these villages and held informal discussions with key informants (identified in advance as village health workers, traditional birth attendants, leaders of local women's associations and grandmothers) as well as 4 or 5 village mothers with large families. Discussions with these people were guided by a standard list of topics to be covered in the interview. It was found that 3 major terms were used to describe a chest problem or difficulty breathing. These were chest pain, fast breathing and "open chest" (see glossary). These terms were incorporated into the weekly surveillance questionnaire.

2.3.10 As well as the prospective longitudinal study of the cohort which took place from March 1987 to March 1988, three cross-sectional surveys were performed on the study population. These were carried out in October 1986, April/May 1987 and March 1988. During these surveys an attempt was made to examine all of the study cohort and in each survey over 90% of the children were actually examined. A questionnaire designed to collect data on socio-economic status, parental education and occupation and family size was administered. A clinical consultation was then carried out comprising the recording of clinical history details (immunisation status, birth weight, breast feeding status and hospital admissions) and a clinical examination. Finally a number of laboratory tests were carried out as described in the section on laboratory investigations (see forms in appendix b).

2.4 Data Management

2.4.1 Quality control of data was greatly facilitated by an active data management system involving the processing of all vital event and questionnaire data and provision of feedback to individual field workers within a one-week period. On receipt of handwritten questionnaires, details were checked by a field supervisor then entered each week into computer databases (one of the surveillance data and another containing the census and vital event data) at Basse field station. The data management programme allowed preparation of weekly cohort lists which were updated

on a weekly basis. Field workers were supplied with a computer generated package of labels each containing the unique identifying information for each study child and these were subsequently used to locate and confirm the identity of all children to be studied that week and to attach to the appropriate questionnaire form.

2.4.2 Data processing involved several distinct and important stages:- visual checking of questionnaires by the field supervisor, double punching and verification of data, range and logic checking of the database, the production of a concise weekly data summary table, creation of backup files on both hard and floppy discs (one copy of which was regularly sent to the computer centre in Fajara since this was dust-free and air-conditioned), and follow up of errors or omissions with individual field workers where possible. A simple data base programme written in "dBase 3" [45] enabled this process to take place with minimum operator input. An evaluation of a similar data management system operating in the Farafenni field station has shown that high levels of data accuracy with error rates of 0.29 per 100 items can be achieved [47]. Given the very large volumes of data (approximately 0.1 megabytes per week) generated by prospective longitudinal studies such as this a data management system such as the one described is essential if good data quality is to achieved. An alternative and equally successful methodology is to utilise programmed hand-held computers for data entry in the field. A subsequent study evaluated this system with the same level of field worker and found that it offered a lower error rates and shorter interview times.[48]

2.4.3 Data from the study was entered into "dBase 3+" databases [45] and data management programmes were written in "dBase 3" programming language. The following programmes were used for data analysis: SPSS,[49] EpiInfo,[50] and SAS.[51]

2.4.4 Thus an active surveillance programme was instituted for a period of 1 year from March 1987 to March 1988 in a group of 3 villages and 4 hamlets 10 to 15 kilometres from the MRC field station in Basse (figure 3) and a cohort of approximately 500 children less than 5 years old were visited weekly. During each visit a morbidity questionnaire (appendix a) was administered and the child was examined for signs of ALRI by trained field workers who lived in the study villages.

2.4.5 Three cross-sectional surveys were performed at the start, middle and end of the surveillance period. An attempt was made to examine all cohort children during each of these surveys.

2.5 Diagnosis of ALRI

2.5.1 Acute lower respiratory infection (ALRI) was defined for the purposes of this study as an episode of ARI which was associated with any one of the following signs or symptoms: fast breathing (as defined by WHO at the time of the study - respiratory rate greater than or equal to 50 breaths per minute), chest indrawing, wheeze, stridor, nasal flaring severe systemic upset such as inability to drink or cyanosis. Since stridor was a very uncommon clinical finding, asthma did not appear to be a common condition in this population, and there was no respiratory syncytial virus activity (and hence no major bronchiolitis epidemic) during the one year surveillance period of this study it was considered that this definition of ALRI principally identified episodes of pneumonia.

2.5.2 A new episode was defined as one that began after a one week ARI-symptom free period and an acute (as opposed to a chronic) episode was defined as one that lasted less than 28 days.

2.5.3 Episodes were thus clinically defined on the basis of symptoms recognised by the mother or signs identified by the field worker (and confirmed by the study physician). All children whom the study physician classified as having ALRI were further investigated by chest x-ray (subject to parental consent being given) but subsequent radiographic findings did not alter the initial clinical classification.

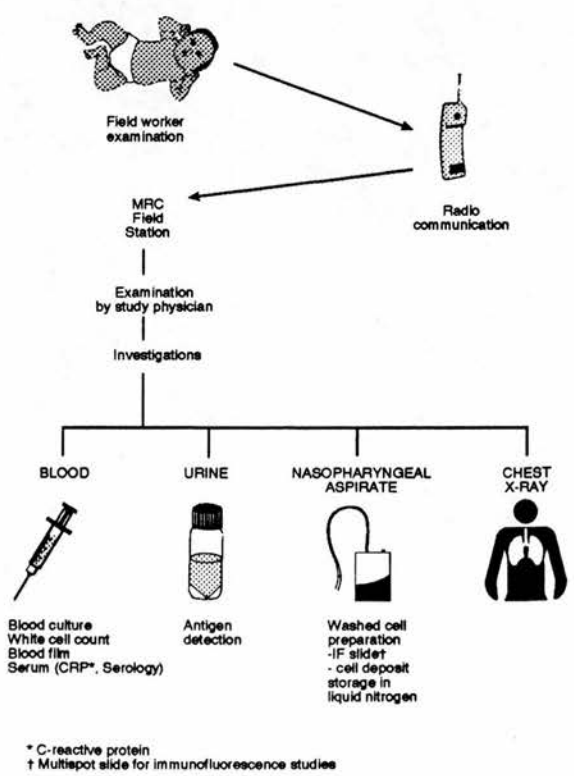
2.5.4 This classification system was chosen for three main reasons. Firstly a clinical classification system was considered to be of primary importance for study since the majority of children in many developing countries have very poor access to radiographic facilities. Secondly WHO had adopted an assessment and classification system based on simple clinical signs alone since the majority of ALRI episodes in developing countries are not managed by doctors. Thirdly the definitions adopted were consistent with those adopted by the hospital-based or urban community-based studies of the epidemiology of ARI which were carried out concurrently in 12 developing countries under the direction and co-ordination of BOSTID (the

Board of Science and Technology for International Development) programme of the United States National Academy of Sciences.

2.5.5 Field workers were trained to record accurately a child's respiratory rate and temperature and to recognise the signs of respiratory distress that defined the presence of ALRI. All children that the field workers considered to have signs of ALRI (as outlined above) were referred to the field station. Other children with respiratory complaints who did not satisfy these criteria but whom a field worker was concerned about were also referred. More than 95% of these children were referred within a 24 hour period, the majority being referred within a period of a few hours. These children were promptly seen on arrival at the field station, examined, entered into the study if appropriate (if the study physician confirmed that signs of ALRI were present), given treatment for the ARI episode and for any other intercurrent illnesses and transported back to their village the same day.

2.5.6 They were fully examined by the study physician. An episode of ALRI was recorded as having occurred if the above findings were confirmed to be

Figure 4: Schematic diagram of referral system



present. It is recognised that this definition incorporates the clinical categories of pneumonia, bronchiolitis, asthma, wheezing associated with viral respiratory infections and laryngotracheobronchitis. However stridor was rarely encountered and no recorded episode of ALRI was considered to be due to laryngotracheobronchitis. In addition, since there was no outbreak of RSV bronchiolitis during the study year and since wheeze was not a common finding, it is therefore likely that most of these episodes represented episodes of pneumonia (although findings from this study raise the possibility that a minority of these episodes may represent episodes of malaria - see section 3.6). Children with these clinical findings had a chest x-ray performed and a blood specimen and naso- pharyngeal aspirate were taken for aetiological studies (figure 4). Further details of these investigations are found below.

2.5.7 A trained field worker also attended the out-patient department of the government health centre in Basse on one morning of each week and recruited all children found meeting the referral criteria and whose parents consented to take part in the study. Of the children who were identified in this manner more than 90% agreed to take part in the study.

2.6 Anthropometric measurements

2.6.1 Cohort children were weighed periodically according to a set schedule. In the first year of life they were weighed every 4 weeks, while older children were weighed every 13 weeks. Call lists for weighing were computer-generated and issued weekly to each field workers for the children assigned to him or her. Heights were recorded during the cross-sectional surveys. Subsequently the data on sex, age, height and weight were used to produce weight-for-age z-scores by comparison with the NCHS (National Child Health Survey) reference population. The nutritional analysis module (EpiNut) from EpiInfo 5 [50] was used to perform the calculations.

2.7 Establishment of laboratory procedures

2.7.1 At the beginning of the project there were no functioning laboratory, radiological, computer or clinical facilities at the Basse field station. Basic laboratory procedures were quickly established by bringing appropriate supplies from the MRC headquarters in Fajara. The establishment of a bacteriological and virological laboratory at Basse was, however, a

considerable challenge in itself considering the difficult conditions, the limited facilities in Basse and the laboratory staff who had little prior experience in the required methods. This period is briefly described since a rural community- based ARI study such as this has not previously been undertaken in a developing country, the challenges are considerable and these issues are rarely described or discussed in publications.

2.7.2 With the assistance of experienced laboratory personnel from Fajara basic methods were established and quality control checks performed. Sheep were purchased locally and were found grazing in the study villages. These served as the source of blood for the blood agar plates which were made regularly in Basse. Problems with suspended Bacillus spp in the air caused considerable initial difficulties with agar plate production, however the enforcement of strict sterile procedures overcame these difficulties. Surveys to study nasopharyngeal carriage of pneumococcus and H. influenzae in the study cohort showed that about 98% carried pneumococcus and over 80% carried H. influenzae at any given time (full details of the results obtained and methods employed have been published elsewhere [52]). Many hundreds of specimens were processed during these surveys under strict quality control. Thus by the start of the surveillance period in March 1987 the laboratory was confident in its ability to grow and identify pneumococcus and H. influenzae, both of which are relatively fastidious organisms.

2.7.3 The procedures used for obtaining and processing naso-pharyngeal specimens are those previously described. [42,43,53,] Many hundreds of specimens obtained in the above surveys were processed and monitored for quality over a period of several months before the techniques were being performed to a satisfactory level. During an epidemic of RSV in November 1986, before the surveillance period started, many isolates of RSV were successfully stored in liquid nitrogen and transported to Fajara where they were subsequently cultured. Since RSV is recognised to be one of the respiratory viruses which is most sensitive to damage from freezing and thawing, it was considered that virological methods were adequate (this is discussed more fully in the results section below).

2.7.4 Computer and radiological facilities were built and Gambian staff trained to run these services. Problems with heat and dust resulted in some problems initially. These were overcome by sealing the windows in the room, wet mopping the floor daily, installing air conditioning, limiting the use of

floppy discs, ensuring that backup procedures were strictly carried out daily and by keeping master copies of all data in the data storage room in Fajara. The high ambient temperature in the hot season also had a marked effect on x- ray processing and ice had to be used when necessary to cool the developing and fixing tanks so that they could be kept near set temperatures so that processing times could be standardised.

2.7.5 The key to success in establishing reliable procedures with predictable quality in these difficult disciplines was the careful attention to every detail at the time of introducing each procedure, a period of quality monitoring by experienced staff (from Fajara), the establishment of regular routines of carrying out each procedure with intermittent quality checks, and the focusing on one procedure at a time ensuring its satisfactory introduction before moving attention to the next new technique.

2.7.6 Finally two points are of particular importance. Firstly there is no substitute for allowing adequate time for each of these steps. It may be of interest to note that a period of 12 months elapsed before we decided to commence the study and that for some months before the surveillance started these laboratory methods were being carried out daily in order to establish set routines. Secondly it would be impossible to set up these laboratory capabilities in a rural area without the excellent logistic back-up from Fajara since many unforeseen problems arise (fuel shortages, supply problems, power cuts, staff sicknesses, vehicle accidents and breakdowns, laboratory equipment failure, computer malfunctions) which require an urgent response if the surveillance is to proceed without interruption. Radio contact was maintained with Fajara and regular calls made daily. The logistic support at MRC Fajara was truly outstanding and a testimony to excellent staff and experience with every type of problem built up over the 40 years of the MRC's operation in The Gambia.

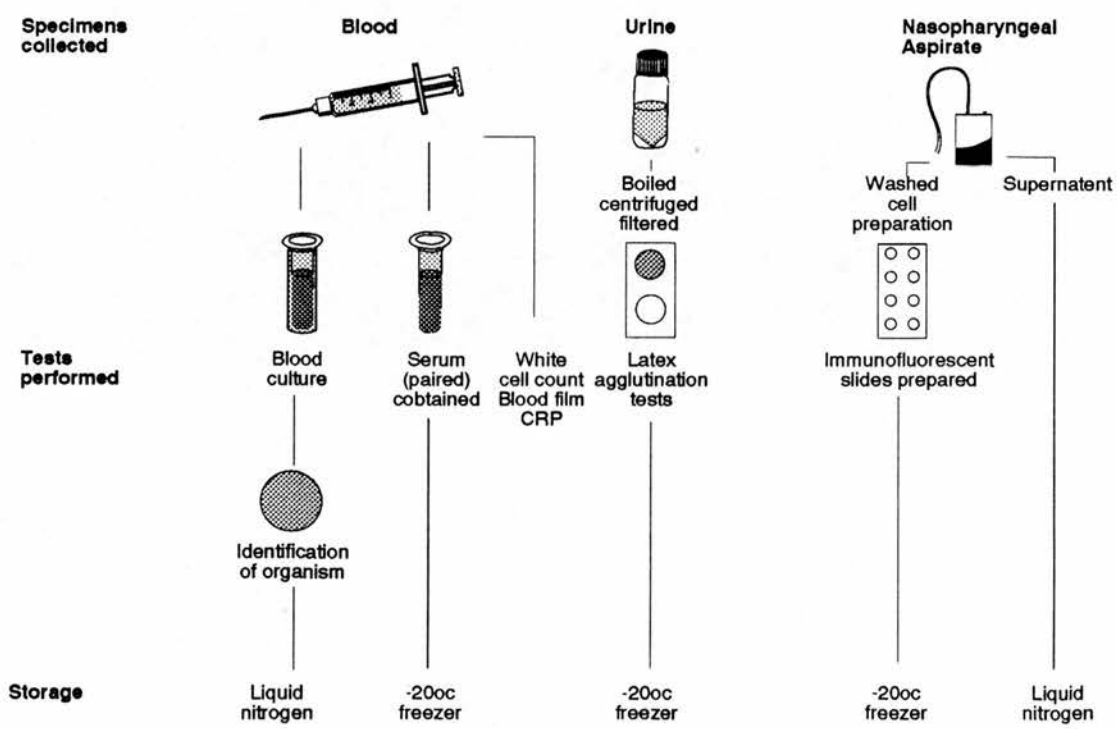
2.8 Laboratory Investigations

2.8.1 In order to investigate whether the pattern of ALRI aetiology described in the MRC hospital studies [41,42,43], was representative of the situation that prevails in a rural area of The Gambia, children with an ALRI identified by the village surveillance were investigated using similar diagnostic techniques to those employed in the hospital studies (with the exception of lung aspirate investigations). Full details of the techniques involved in this

study can be found in the publications related to this study [42,43,54]. The intention in this report is to describe the general principles involved rather than the detailed methodologies whilst at the same time clearly indicating where further details and a fuller discussion can be found.

2.8.2 All children who were identified as having clinical features of ALRI were investigated in an attempt to establish the aetiology of the episode. Following a clinical examination and after obtaining informed consent from the child's guardian, blood was taken for culture, serology, differential white cell count, C reactive protein and for preparation of a thick film which was examined for malarial parasites. Nasopharyngeal aspirates were collected by means of a 8FG nasopharyngeal catheter using the standard technique described by Gardner and McQuillan.[55] Urine specimens were collected by cleaning the child's perineum with isopropyl alcohol then

Figure 5: Specimens collected and investigations performed at Basse Field Station



attaching an adhesive paediatric urine bag. A convalescent finger-prick blood specimen was taken after an interval of 2-3 weeks (figure 5).

2.8.3 A chest x-ray was taken and read by the study physician to guide the immediate treatment of the child. All chest x-rays were later read independently by a paediatric radiologist who had no details of the clinical findings. Abnormal findings were recorded following a pre- arranged coding schedule in which consolidation was recorded as lobar (opacification of an entire lobe), segmental (opacification of a localised area for example a bronchopulmonary segment but occupying less than an entire lobe) or diffuse.

2.8.4 Bacteriology

2.8.4.1 Blood specimens were inoculated into Tryptone Soy Broth and Thioglycollate broth and incubated at 37°C. All broths were subcultured after 24 and 48 hours and at 7 days on to 5% sheep blood agar and enriched chocolate blood agar and incubated overnight at 37°C in candle jars. Bacterial isolates were identified by standard methods.[41,42,43]

2.8.4.2 Urine specimens were collected and processed (boiled for three minutes, spun at 1500 r.p.m. for 5 minutes and filtered through a 0.45 micrometer Millipore nitro-cellulose filter) to remove proteins then each specimen was tested for H. influenzae type b polysaccharide antigen using a commercial latex agglutination test (Biomerieux, Lyon, France) and for the 10 commonest types of S. pneumoniae isolated in the Gambia using a series of type-specific latex tests. These methods have been described in detail in a related publication. [54]

2.8.4.3 Anti-pneumolysin,[56] antibodies were measured by ELISA in the Gambia by Dr Maija Leinonen of the National Public Health Institute, Helsinki, Finland. A two-fold increase or more in antibody titre to pneumolysin between acute and convalescent specimens was taken (from previous evidence [57]) to be evidence of pneumococcal infection. This method has been described in detail by Dr Leinonen [57].

2.8.4.4 Anti H. influenzae and anti Br. catarrhalis antibodies were also measured by ELISA with the use of antigen prepared from the middle ear of children with otitis media as reported previously.[57] A three-fold or greater rise in titre between paired serum specimens has been shown from a previous study to be diagnostic for H. influenzae and Br. catarrhalis.[58]

2.8.4.5 Paired sera were also collected from 58 under five year old children with proven malaria (but no current signs of ALRI) and acted as control sera for

the assessment of the specificity of the pneumolysin enzyme linked immunosorbent assay. Only three (5%) showed a 2-fold or greater response to pneumolysin and none showed a 3-fold of greater response to H.influenzae or Br. catarrhalis.

2.8.5 Virology

2.8.5.1 Portions of nasopharyngeal aspirate for virus isolation were inoculated into cryotubes containing Virus Transport Medium (VTM) consisting of a balanced salt solution, 0.5% Bovine Serum Albumen and antibiotics. Specimens from infants 4 months of age and under were also inoculated into 2-sucrose-phosphate transport medium for the recovery of Chlamydia trachomatis. The cryotubes were snap frozen and stored in liquid nitrogen and transferred to the virus laboratory 250 miles away where they were transferred to a minus 70° C freezer. Each specimen in VTM was then inoculated on to monolayers of secondary rhesus monkey kidney cells, human embryonic lung fibroblasts and HEp2 cells and incubated stationary at 37 degrees or rolling at 33 degrees centigrade. Monolayers were inspected every 2-3 days for a minimum of 14 days for evidence of viral replication; any viral isolates were identified by neutralisation or immunofluorescence (IFA). Subtyping of influenza isolates was performed by the Virus Reference Laboratory, Colindale, London. Washed nasopharyngeal aspirate cell deposits for IFA studies were spotted onto microscope slides, dried, fixed in acetone and stored at -20° C before being transferred to the virus laboratory for immunofluorescent staining using commercially available antisera (Wellcome Research Laboratories, Kent, England). Slides were read using a Leitz Orthoplan UV microscope.

2.8.5.2 Specimens of nasopharyngeal aspirate stored in 2-sucrose- phosphate transport medium for culture of C. trachomatis were treated with cyclohexamide and incubated at 37° C for 48 hours before being stained for the presence of chlamydial inclusions using an immunofluorescent monoclonal antibody culture confirmation preparation (Syva Corporation).

2.8.5.3 Acute and convalescent sera were diluted 1:8 and screened for antibody to Influenza A and B, Parainfluenza 1 and 3, Adenovirus, Respiratory Syncytial Virus (RSV) and Mycoplasma pneumoniae by the Complement Fixation test (CFT). All sera giving 75-100% fixation were titrated from 1:8 to 1:256. A four-fold increase in antibody titre between the acute and

convalescent serum or a consistently high titre of 1:128 or above was considered evidence of infection. These values were selected after analysis of a pool of known "positive" and "negative" sera.

2.8.5.4 Antibody to RSV was also measured by ELISA using partly purified antigen supplied by Dr Olli Meurman, Department of Virology, University of Helsinki. A sonicated extract of a culture of uninfected HEp2 cells was used as control antigen. Each serum was tested in duplicate at 1:100 and 1:1000 dilution. The titre of each serum was calculated by linear regression. The cut-off optical density (OD) value was taken as the mean OD plus or minus 2 standard deviations (based on results of 30 negative control sera assayed in duplicate at 1:100 dilution on 3 separate occasions). A three-fold or greater rise in titre was accepted from previous studies as evidence of recent RSV infection.

2.8.5.5 Antibody to Chlamydia pneumoniae (TWAR) and Chlamydia trachomatis was assayed in The Gambia by Dr Pekka Saikku, Department of Virology, University of Helsinki, Finland using micro- immunofluorescence as previously described. [59]

2.8.5.6 Ninety-six children from the cohort who had minor illnesses but no signs ALRI at the time of the examination nor during the examination in the previous week were studied contemporaneously with the children with ALRI. Specimens of naso-pharyngeal aspirate were taken from these children to act as control data for the virological studies (see section 4.2).

2.9 Malaria surveillance

2.9.1 Axillary temperatures were recorded by means of a digital thermometer at each weekly visit, and also when a child was referred to the project clinician. A thick blood film was taken and examined for malaria parasites if the temperature was found to be 37.5°C or above.

2.9.2 These methods were consistent with those employed at Farafenni field station which had prospectively studied the epidemiology of malaria over several years so that results from different areas of The Gambia could be compared.[60]

2.9.3 The accuracy of all the digital thermometers were confirmed at the start of the study and intermittently thereafter by testing them in a water bath and comparing results to standard temperature reading. A study comparing the

results from the use of digital and mercury thermometers had previously been performed and found that digital thermometer readings accurately reflected results obtained by mercury thermometer but with a shorter time delay required before the final reading could be obtained. This study also established the time at which the temperature reading stopped changing and therefore this time period was utilised during the study (Greenwood BM unpublished, personal communication).

2.9.4 A clinical episode of malaria was defined as occurring in a child with a fever (axillary temperature of 37.5 ^{o} C or above) and a parasite density of of 5,000 per microlitre or above.[61] This latter figure was chosen based on results from a community surveillance of a cohort of children near Farafenni and Walikunda in The Gambia which undertook regular blood film examinations in each cohort child in an attempt to describe the parasitaemia rates in this population in both wet and dry seasons ([60], and Wilkins A, personal communication). These studies established that parasite densities of 5,000 per microlitre or above were consistently found to associated with clinical symptoms of malaria and were not found in "well" children.

2.10 Survey of indoor air pollution

2.10.1 It is estimated that 30% of urban households and 90% of rural households in developing countries rely on biomass fuel as the major, or only, source of domestic energy. These fuels are burned under inefficient conditions producing large quantities of smoke and gaseous products, leading to high levels of indoor air pollution. The health aspects of biomass fuel combustion have recently been reviewed by WHO.[62] There is some evidence from a study in Nepal that domestic smoke pollution from cooking fires is a risk factor for ALRI in young children.[63,64]

2.10.2 In collaboration with staff from the Department of Air Pollution, University of Wagenigen in the Netherlands, (and with support from the WHO Acute respiratory infections and Prevention of Environmental Pollution units) a study was conducted to investigate the levels of indoor air pollutants in the homes of cohort children.[65,66]

2.10.3 The villages in the study area consist of a number of compounds, most of which are inhabited by one family and containing several traditional huts one of which is used as a kitchen. The kitchen huts have dirt floors, mud

walls and thatched roofs with a ventilation gap between the wall and the roof. All cooking is done on traditional three stone fires using wood for fuel. During the dry season about two-thirds of the cooking is done inside, while during the wet season almost all the cooking is performed inside. The wives of the family take turns preparing the food for the whole family. Infants are only found near the fire when carried on the back of their mothers. Older children generally are not allowed to enter the kitchen. During the rainy season, however, older children are sometimes allowed in the kitchen.

2.10.4 The study was carried out in 2 of the Mandinka villages (Tambasensan and Badari) and 1 of the Fula hamlets (Kundam Demba), chosen so that communities of different sizes and ethnic groups could be studied. In each of these communities 6 compounds were chosen at random from the census data. These were studied during both the dry and the wet seasons. Full details of the techniques employed have been published previously. [65,66]

2.10.5 24 hour average measurements

2.10.5.1 In each of the 18 kitchens 24 hour average measurements for suspended particulate matter and nitrogen dioxide were performed twice with an interval between the two measurements of about one week. A pump/filter technique (using Dupont P2500 constant flow pumps) following by accurate weighing was used. The flow of the pumps was checked by a Brooks flowrater at the beginning and end of each sampling period. PAS-6 (filter diameter 30 micrometers) and Casella cyclone (filter diameter 5 micrometers) were used as sampling heads to record respirable and inspirable (able to be inspired into the distal respiratory tract) particles respectively. A sampling height of 80 centimetres corresponding to the breathing height of women during the preparation of a meal was employed.

2.10.5.2 In the filters sampled during the dry season, the amount of polycyclic aromatic hydrocarbons (PAHs) was determined in Wagenigen by the standard Dutch method. The nitrogen dioxide was measured with Palmes diffusion tubes in duplicate pairs.

2.10.5.3 During the 24 hour measuring periods families were continuously observed by field workers to record the presence of the mothers and children aged under five years near the fire. Finally, some characteristics of the kitchens

such as surface area and the presence and size of ventilation openings was recorded.

2.10.6 Daily pollution pattern measurements

2.10.6.1 To observe the variations in concentrations during the day, measurements of carbon dioxide, carbon monoxide and respirable particles (RSP) were carried out together with observations of the activities of mothers and children in three kitchens each hour between 0600 and 2000 hours during the dry season.

2.10.6.2 The carbon dioxide and monoxide concentrations were measured with Drager indicator tubes and a hand operate pump

2.10.6.3 Duplicate measurements allowed the precision of the various measurements to be checked. The coefficients of variation for the measurements of RSP, PAH and NO_2 were about 6%,30% and 6% respectively.

2.11 Survey of maternal knowledge, attitudes and practices

2.11.1 A simple random sample of 150 mothers who had at least one child under the age of 5 years was drawn from the 7 study villages. This was achieved by listing the study children indexed by village and compound number (the unique study number of each child contained these identifiers), excluding siblings so that each mother was represented only once, then sequentially numbering these records and using a table of random numbers to select the mothers to be studied.

2.11.2 Since it was considered possible that participation in the study might have influenced the responses of the women from these rural villages it was decided to select a further sample of 50 mothers from an adjacent village (Dampha Kunda) which had not taken part in this study due to its close proximity to Basse health centre as described in section 2.2 above. Since resources were not available to census this village, a random sample could not be taken. Therefore mothers were selected from compounds chosen from all sections of the village in a systematic manner (the field worker was given written instructions to enter the village and to travel in a set direction visiting every third house which was encountered).

2.11.4 Interviews were conducted with each of the mothers in their native language (Mandinka or Fula). The questionnaire was pilot-tested to confirm that questions were understood by the Gambian women and to determine

the range of responses so that a coding schedule could be produced to guide interpretation and categorisation of responses. The final format of the questionnaire included questions inquiring about age, ethnic group, educational level, place of birth, marital status, parity and socio-economic status (assessed by a score based on household possessions). This was followed by specific questions about perceptions of cause and symptomatic presentation of ARI and in particular "pneumonia" and "open chest"; criteria used to judge if an ARI episode is serious; and the nature of treatment practices including home care for episodes of cough and care-seeking behaviour when further treatment was thought necessary.

2.11.5 The study took the form of a structured interview consisting of open questions. It was considered to be particularly important that mothers be allowed to freely express their responses, and that we should neither limit these by insisting on fixed categories of response nor falsely augment them by prompting, in situations in which no reply was forthcoming.

2.12 Antibiotic Treatment Trial

2.12.1 This trial formed part of the larger community-based study. In The Gambia, as in other developing countries, cotrimoxazole is widely used for the treatment of children with pneumonia but there is little published evidence of its efficacy and no controlled trial of its efficacy for the treatment of ALRI in children in developing countries has been published. As described in section 2.2 above it was estimated that approximately 150 episodes of ALRI would be identified during the one year surveillance period. It was further considered that about 100 of these might be eligible to take part part in a comparative trial of two alternative treatment regimens (see inclusion criteria below). If 50 of these children were allocated to the standard treatment group (cotrimoxazole) this would allow an estimated response rate of 85% among cohort children to be expressed with a 95% confidence interval of 73-94%. If a similar number of episodes were recruited from Basse Health Centre then it would be possible to detect a difference of 15% (90% compared to 75%) with 80% power at a 5% significance level. [67]

2.12.2 It was decided therefore to include children identified by the same standard surveillance procedure conducted on one day each week at Basse health centre to increase the study numbers and thus improve the precision of response rate estimates. It was recognised that the two study populations

would have to be considered separately before any decision could be made on combining the study results.

2.12.3 A child was considered for admission to the trial if he/she were aged 1 month to 4 years of age and had an ARI of less than one week duration together with signs of either chest indrawing or nasal flaring, and had not received antibiotics in the previous two weeks. This group was chosen since it corresponded to the operational classification of "severe pneumonia" found in WHO first-level health worker training materials and thus were considered to be an important group with significant mortality if untreated or inadequately treated.

2.12.4 The project clinician examined each child referred by the field workers from the study villages or the health centre. One hundred and forty three children aged 1 month to 4 years were identified by these study criteria during the period March 1987 to March 1988 and were considered for entry into the trial. One hundred and thirteen were recruited by trained field workers during the active surveillance programme in the study cohort villages; the remaining 30 cases were recruited from the out-patient department of the government health centre in Basse by a field worker who attended on one morning of each week. The same selection criteria were applied in both the community study and the health centre setting.

2.12.5 Nine potentially eligible children were excluded for the following reasons. Five were unable to take oral treatment, 3 had very severe disease (convulsions, drowsiness, or severe dehydration) and the mother of 1 child refused to take part.

2.12.6 The remaining 134 children were assigned sequentially to one of two treatment groups. If the entry criteria were met the child was allocated the next study number. The treatment groups were then assigned in a strict sequential manner (A, B, A, B ,A and so on). Children in group A received a five day course of oral cotrimoxazole. Those in group B received one intramuscular injection of fortified procaine penicillin (procaine penicillin 4 mega-units plus benzyl penicillin 1 mega-unit per vial) together with a five day course of oral ampicillin. Doses were calculated according to current WHO recommendations. All children with fever were given chloroquine. The dispenser, in a separate room in the field station clinic, gave the

appropriate treatment. This was not discussed with the study physician (myself) nor the field staff (who were not present in the field station).

2.12.7 Mothers gave oral consent before allowing their children to take part in the study which was approved by The Gambia Government / MRC ethical committee.

2.12.8 Outcome was assessed in two ways:-

2.12.8.1 Trained field workers visited the homes of the children from the surveillance villages during the first and second weeks after treatment was started and recorded the respiratory rate, the temperature, and the presence or absence of indrawing. They also asked about symptoms of respiratory illness throughout the preceding week. These field workers had no knowledge of the treatment group allocation when making their assessments.

2.12.8.2 Mothers were interviewed by the clinician at two weeks follow up and were asked to score their child's cough, breathing difficulty, fever, and appetite as better, the same, or worse. The same project clinician who made the assessment for study entry examined each child after two weeks and made a clinical assessment of outcome. This was done without referring to the original case-notes of the child which recorded the treatment group. All assessments for study entry and of final outcome were made by the study physician (myself).

2.12.9 Neither the field workers nor the study physician were strictly blind to the treatment allocation in that it was possible for the field workers to ask the mother whether or not her child received an injection. In addition it is possible that mothers (and indeed likely from results of the KAP studies mentioned above) that mothers attached more value to a treatment course that included an injection. These biases would tend to favour treatment group B (procaine penicillin plus ampicillin). In addition it would have been possible for the study physician (myself) to have sought out the child's earlier treatment notes before making the final examination since these notes were always available for consultation in the study clinic.

2.12.10 If a child's condition deteriorated and either the field worker referred the child back for re-assessment or the mother sought further care then the study physician first assessed the child without consulting the record of treatment allocation. If it was clear that the child's condition had

deteriorated sufficiently so as to require a change in treatment or admission to the health centre then all case records were referred to in making further treatment decisions.

3. EPIDEMIOLOGY OF ALRI: INCIDENCE AND CLINICAL FEATURES

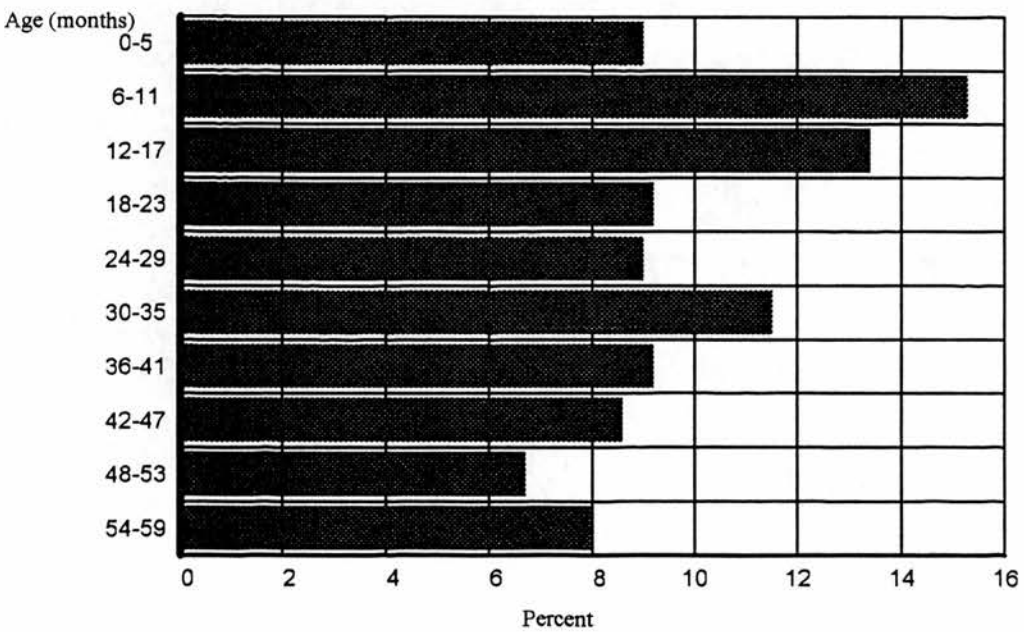
3.1 Description of the study population

3.1.1 As described in section 2.2 a "rolling cohort" study design was implemented which investigated childhood ALRI in a defined community during a one year period. Children entered the cohort as they were born and exited at their fifth birthday. At any point in time approximately 500 children were under surveillance, with a total of 685 children participating in the study cohort at some time during the one year period. In order to describe the study population data is presented here on the 477 children who were examined in the second cross-sectional survey carried out in April/May 1987 shortly after the start of the one year surveillance period. These 477 children is represented about 95% of the study cohort at that time.

3.1.2 Age and Sex

The age distribution of the children is shown in figure 6. The lower than expected proportion in the 0-5 month category can be explained by two

Figure 6: Age distribution of children in cross-sectional survey



factors: the lower than average attendance rate at the cross- sectional survey in this age group and as a consequence of seasonal variation in the birth rate. 45.5% were females and 54.5% were males.

3.1.3 Ethnic Groups

14.3% were Fula and 85.7% were Mandinka, two of the three major ethnic groups in the Upper River Division of The Gambia. No Serehuli were represented in this study. A few members of the Jahanka sub-group of Mandinka were classified as Mandinka.

3.1.4 Education

5.3% of mothers had received no education, 93.4% had attended Koranic school (religious education in Islam only), and a very small minority (1.3%) had ever attended a government school. The education of fathers showed a similar picture with 3.4% having received no education, 94.7% Koranic education and only 1.9% having completed any level of government education. This contrasts markedly with the current levels of primary school attendance.

3.1.5 Occupation

Only 52.5% of fathers and 0.6% of mothers had a source of employment outside of the home. Most families were subsistence farmers working in their own fields, or in the case of the Fula with their own herds of cattle, sheep and goats.

3.1.6 Number of wives in a family

Polygamy is common in this population with about 50% of children coming from families in which their father had more than one wife. The maximum number of wives in a family was five (figure 7).

3.1.8 Number of children born per mother

The distribution of the total number of children born to each mother (live born children ever born to that mother) is shown in figure 8. The median number of children is 5, as is the mode of the distribution. Only 10% of mothers have more than 8 children. The largest number recorded was 15. It is likely that babies who died in early infancy might not have been mentioned by some mothers in this survey.

Figure 7: Distribution of families by number of wives in each family

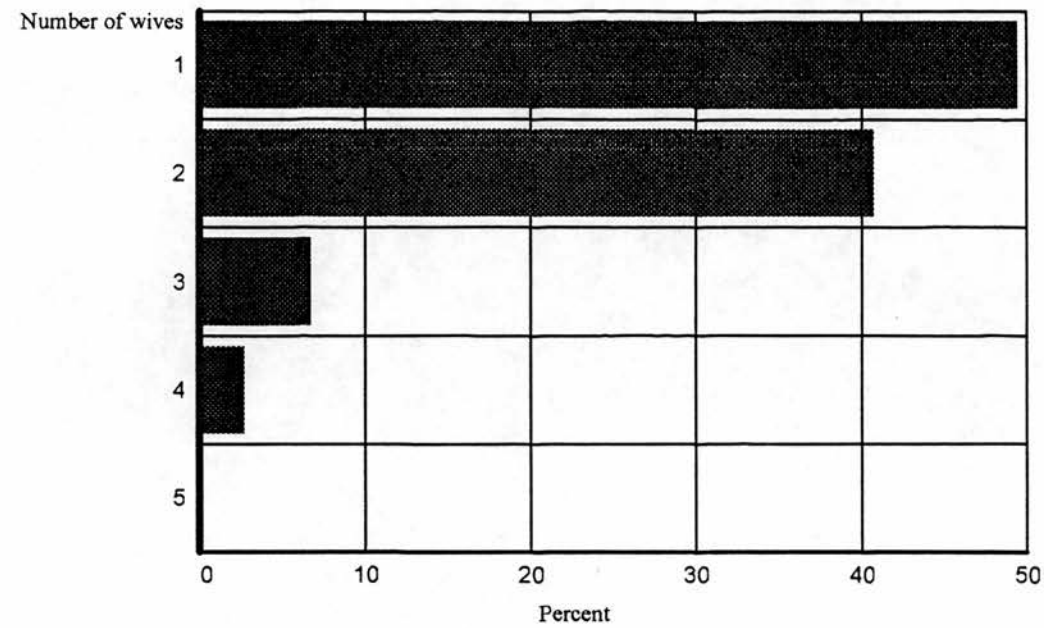
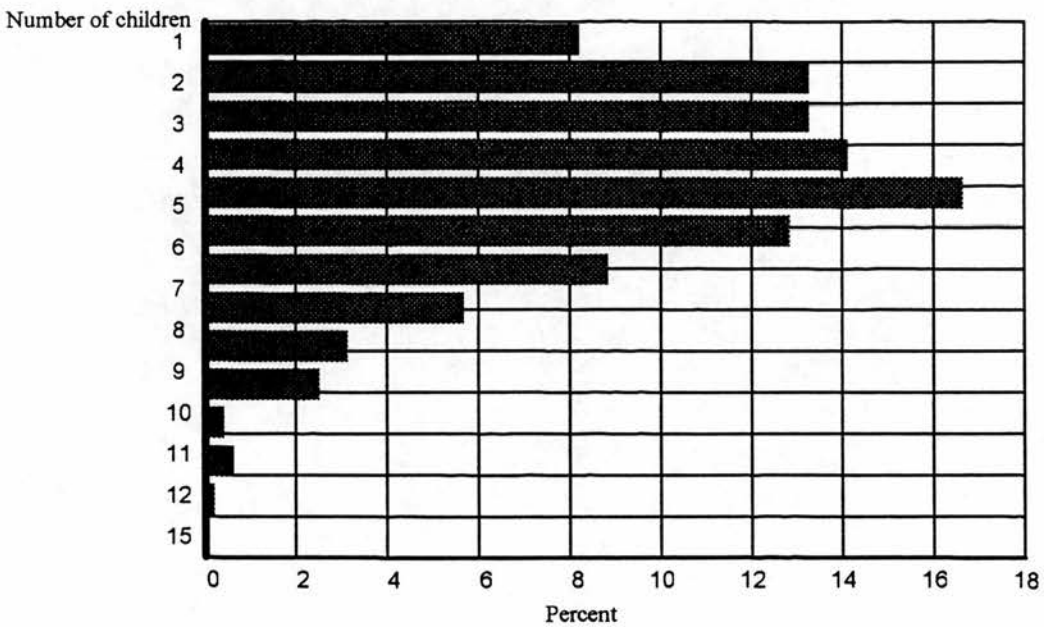


Figure 8: Distribution of mothers by number of children born to each mother

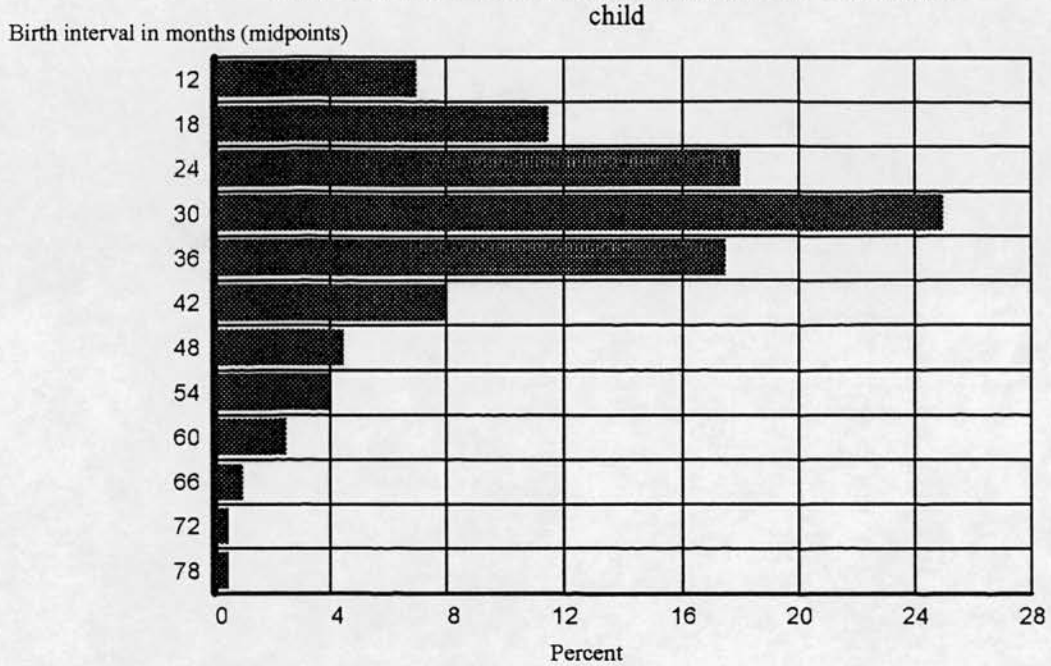


3.1.9 Birth Interval

The distribution of birth intervals between each cohort child and the next eldest child is shown in figure 9. This data was cross-checked with recorded dates of birth. A mean interval of 32 months (median of 31

months) was found which is considerably greater than expected. The distribution is, of course, limited to the left and thus is skewed to the right. The interquartile range (the value for 50% of the population in the centre of the distribution) is from 24 to 37 months.

Figure 9: Distribution of birth intervals: months to next older child



3.1.10 Socio-economic status

This was simply assessed by information collected on the possession of three common items (a mule or horse, a radio, and a corrugated iron roof on the house) in this community. These were chosen from a list of other alternatives because results based on these 3 criteria produces a reasonably good distribution within this population. 83% of families owned a mule or horse, 59% a radio, and 58% a corrugated roof. 30.4% have 1 item, 31.9% have 2 items, and 37.8% have all three items.

3.1.11 Smoking

Smoking was much less common in mothers (2.7% smoked) than in fathers (53% smoked). In addition mothers who smoked did so with less frequency than men (15% of women who smoked used 5 or more cigarettes per day compared to 28% of men who smoked using 10-20 cigarettes per day). No-one claimed to smoke more than 20 cigarettes per day.

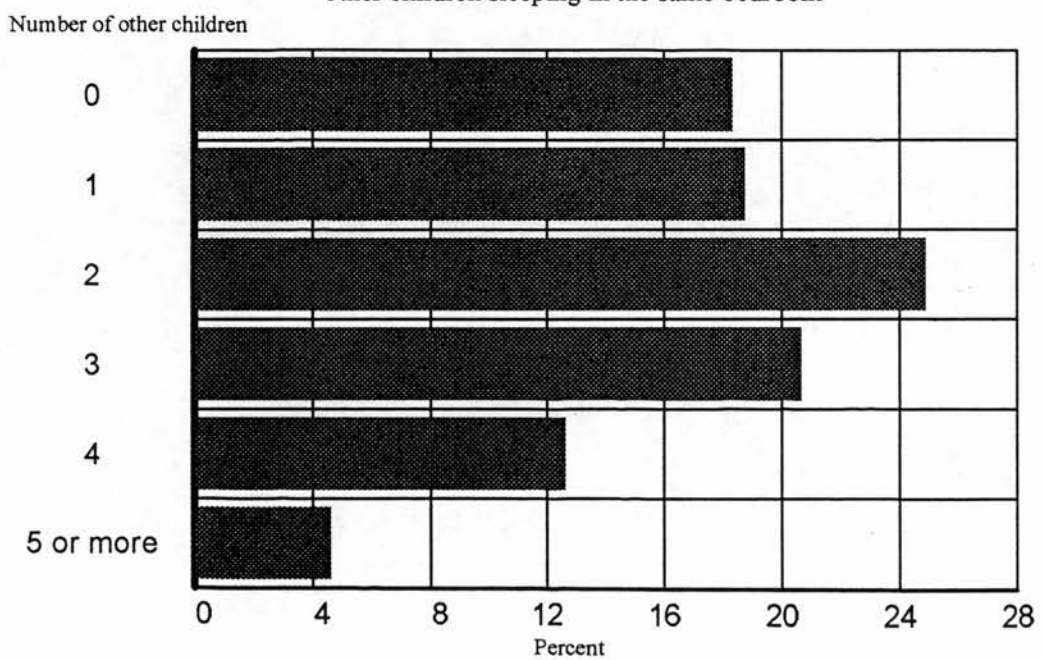
3.1.12 Possession of a "Road to Health" card

73% of children were able to produce a health card on the day of the survey. A further 14.3% were said to have left their health card at home. Data from other sources have shown that more than 90% of Gambian mothers register their child's birth, receive a health card and have their young infant immunised with BCG.

3.1.13 Crowding

It has been postulated that crowding, (often measured by the number of other children in direct contact particularly in enclosed places) is a risk factor for many infectious diseases including ARI. In more developed countries, schools and day-care centres play a central role in this exposure. In this community, close child-to child contact occurs in the house and this can be studied by considering the number of children sleeping in the same bedroom (distribution shown in figure 10). Only 18% of children sleep in a bedroom with no other children, in contrast 37% sleep in "crowded" bedrooms with 3 or more other children.

Figure 10: Crowding: distribution of children by number of other children sleeping in the same bedroom



3.1.14 Use of a bed net at night

63% of children were said to sleep regularly under a bed net. We have previously shown that this practice confers a degree of protection against malaria in this community.[68]

3.1.15 Immunisation history

The proportion of children who had received at least one dose of a recommended vaccine is illustrated in figure 11. These data were checked wherever possible against recorded immunisation data in the child's "road to health" card. The highest coverage is for BCG immunisation. Lowest coverages are shown for measles and yellow fever vaccines as one would expect from the later recommended age of immunisation. In relation to ARI, measles immunisation is particularly important. Levels of measles vaccine coverage have remained relatively stable in recent years (figure 11). The distribution of age at measles immunisation is shown in figure 12.

Figure 11: Percentage of children having received one or more doses of vaccine by age group and vaccine type

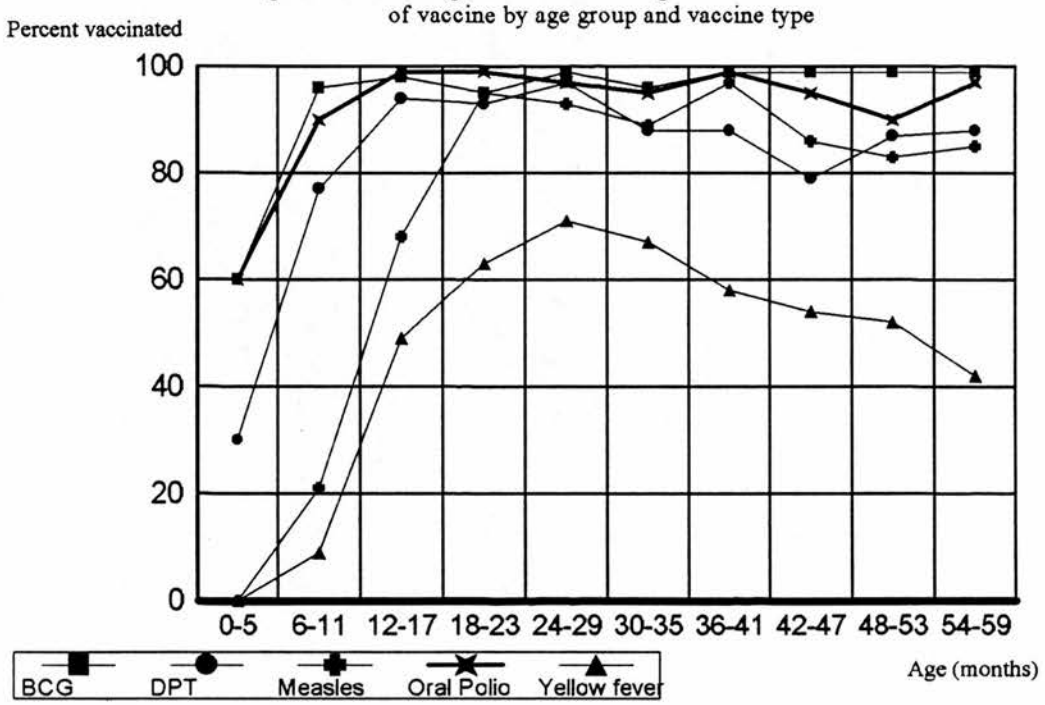
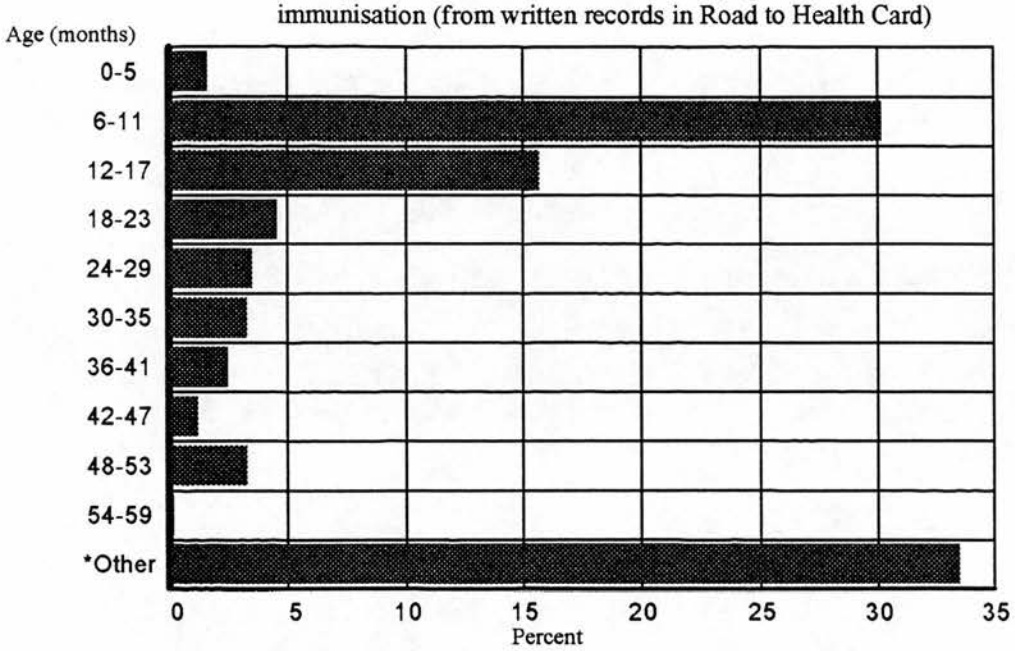


Figure 12: Distribution of children by age at Measles immunisation (from written records in Road to Health Card)

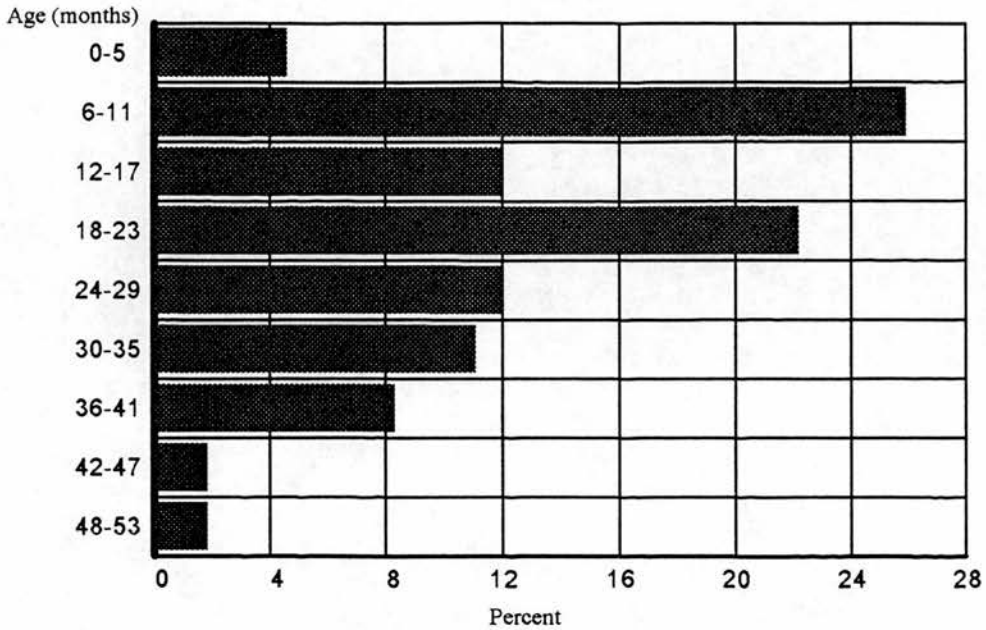


*Never vaccinated or no written record available

3.1.16 Past history of measles

Mothers were asked if and at what age their child had contracted measles in the past (recognition of measles by mothers was thought to be relatively good and a specific term is used by them for measles) and this data is illustrated in figure 13. 31% of cases had occurred in the first year of life (by which time relatively few children had been immunised against measles - see figure 13), and 75% of cases by the 30th month. It would appear that there is still considerable scope for improving the delivery of measles vaccine to young children at the recommended age of 9 months in The Gambia.

Figure 13: Distribution of children with history of previous Measles attack by age at time of occurrence



3.1.17 Breastfeeding

Breastfeeding is almost universal in the first 18 months of life as shown in table 5. Thereafter the proportion falls rapidly with no children older than 3 years being regularly breastfed.

Table 5: Percentage of study cohort children regularly (daily) breastfeeding by age group

Age group (months)	n	Percentage of children regularly breastfed
0 - 5	43	100
6 - 11	73	99
12-17	64	100
18-23	44	68
24-29	43	9
30-35	55	0
36-39	155	0

3.1.18 Introduction of solid foods

The timing of the introduction of solid foods is an important determinant of a child's nutritional status. Mothers of children under 2 years of age (older children were excluded in an attempt to reduce recall errors) were asked about the introduction of solid foods. Among those receiving solid foods at the time of interview, 63.5% were introduced to them in the first 6 months of life and 97.2% had been introduced in the first 12 months of life.

3.1.19 Nutritional status

3.1.19.1 Data (weight, height, age, sex) from the first and second cross-sectional surveys in October 1986 (wet season) and April 1987 (dry season) respectively were compared to NCHS standards and z-scores of the distributions of weight-for-age, height-for-age and weight-for height for each child were calculated. Figures 14 and 15 illustrate the z-scores for the 3 nutritional indices stratified by age group for the wet and dry seasons respectively. Lowest mean values are found in the 12-35 month age range.

Figure 14: Distribution of Z-Score means by age group for 3 anthropometric indicators: dry season

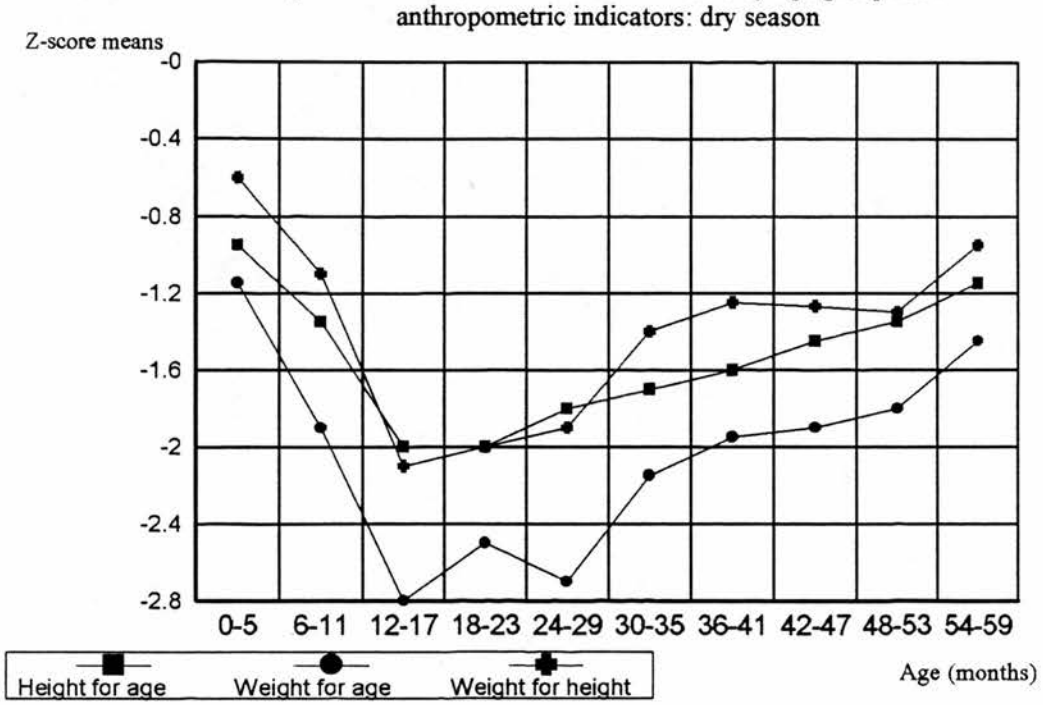
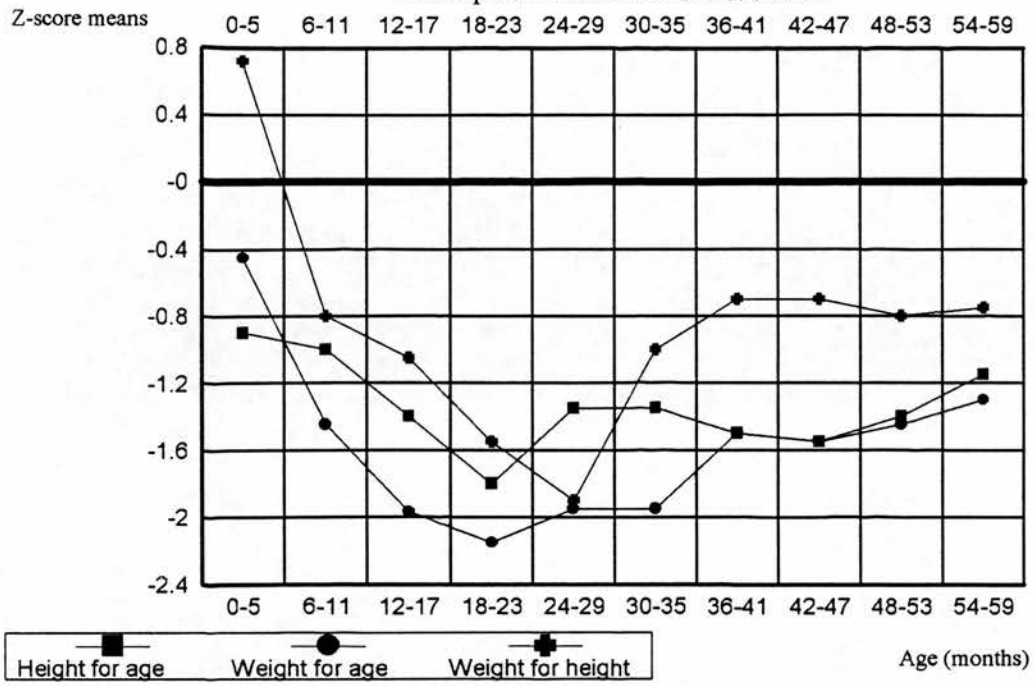


Figure 15: Distribution of Z-Score means by age group for 3 anthropometric indicators: wet season



Nutritional status as reflected by all 3 anthropometric indices are poorer in the wet season than in the dry season.

3.1.19.2 If we define a malnourished child for the purposes of this study (see section 3.7) as one with a z-score of less than minus 2 (these children would appear with a frequency of less than 2.5% in the NCHS population), then figures 16 and 17 illustrate the prevalence of malnutrition as defined by these parameters and reflect the patterns shown in figures 14 and 15. The prevalences in the first six months of life are low (2.3% for the dry season and 16.7% for the wet season).

Figure 16: Prevalence of malnutrition by age group defined by 3 anthropometric indices: wet season

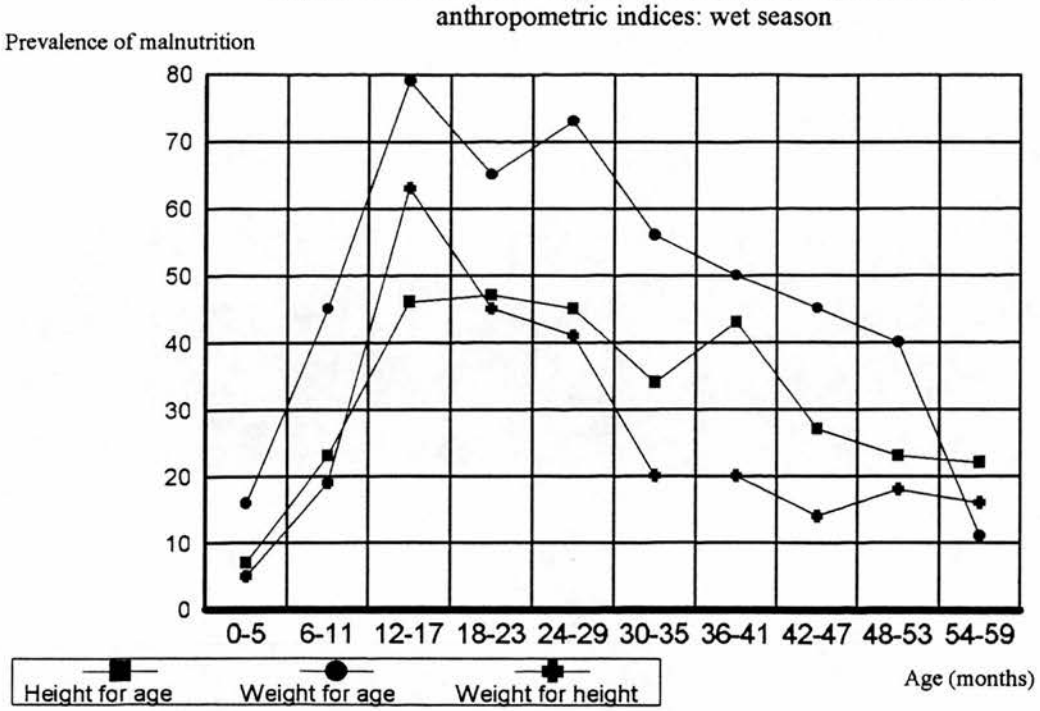
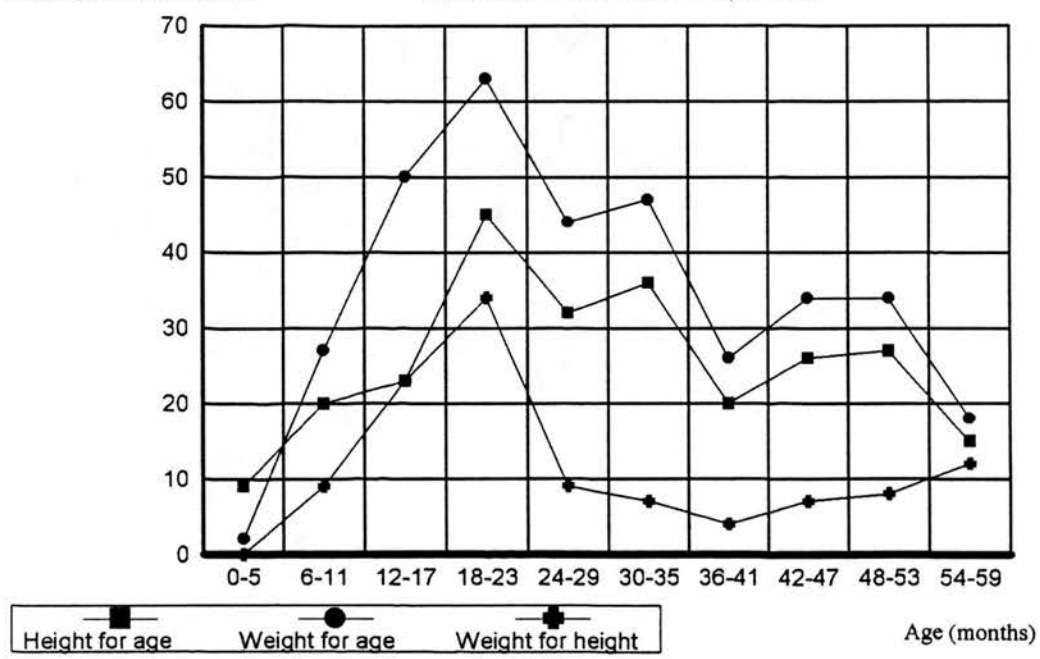


Figure 17: Prevalence of malnutrition by age group defined by 3 anthropometric indices: dry season



3.2 ARI Morbidity Data

3.2.1 A total of 25,028 weekly morbidity questionnaires (copy given for reference in appendix a) were completed on a total of 685 children under the age of five years during the one year surveillance period. Mothers or guardians were asked about nine different symptoms at each interview. The average weekly period prevalence of symptoms reported in any week (based on data from the complete year of observation) was as follows:- blocked or runny nose 52%, fever 34%, cough 20%, diarrhoea 10%, chest pain 8%, vomiting 5%, fast breathing 4%, refusing to breast feed or to eat 2.5%, "open chest" 1%. In addition, mothers were asked whether the child was unwell (recorded in 47% of interviews), suffering from a respiratory illness (18% of interviews) or had another illness (29% of interviews).

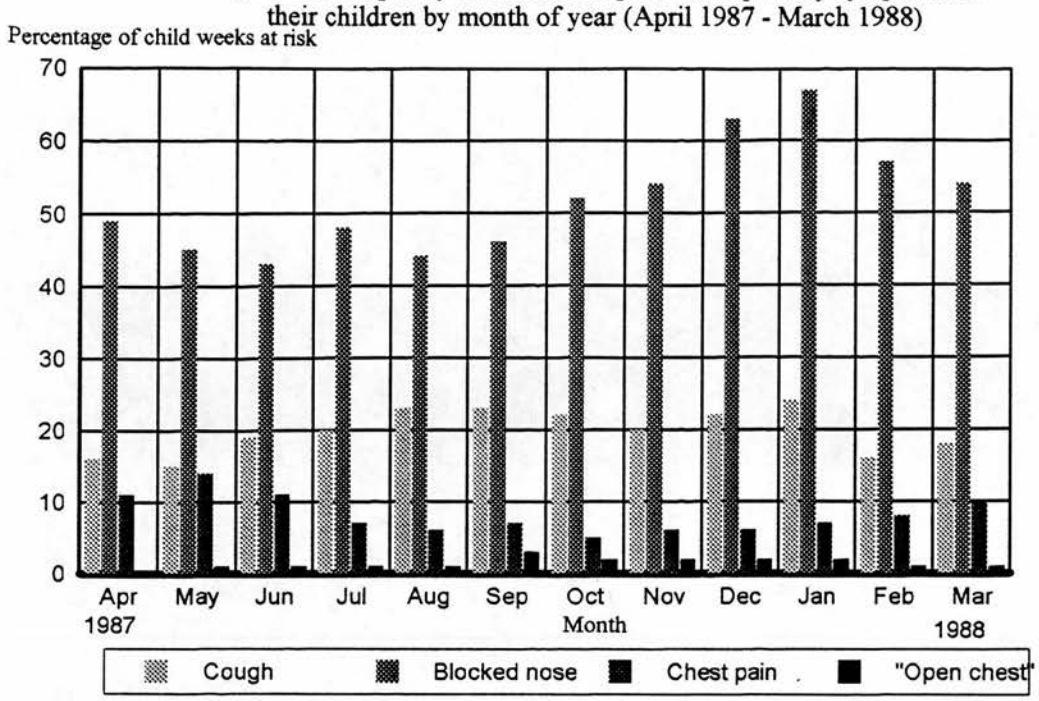
3.2.2 Maternal reports of ARI symptoms found in their children are shown in table 6 by age of the child and expressed as percentage of child weeks at risk. The variation in maternal reports of cough, blocked or runny nose, and "open chest" expressed as percentage child weeks at risk over the course of the one year surveillance period is shown in figure 18.

Table 6: Maternal reports of symptoms of respiratory infections in cohort children during the one year surveillance period

Symptom or sign	0-2 months	3-11 months	12-59 months	0-59 months
respiratory illness	22.1%	19.1%	17.6%	18.1%
other illness	23.2%	34.1%	28.8%	29.2%
cough	22.9%	23.7%	18.9%	19.9%
blocked nose	32.9%	50.8%	53.5%	51.7%
subjective fever	32.3%	42.8%	32.3%	34.0%
chest pain	8.5%	8.8%	7.8%	8.0%
"open chest"	2.2%	2.2%	1.0%	1.3%
refusing food	0.6%	2.1%	2.8%	2.5%
Total child weeks at risk observed	**1615**	**3931**	**19482**	**25028**

Footnote: Results are expressed as percent child weeks at risk in different age groups and for all children under 5 years of age.

Figure 18: Frequency of maternal reports of respiratory symptoms in their children by month of year (April 1987 - March 1988)



3.2.3 Field worker observations of ARI during weekly home visits are shown in table 7 by age of child and expressed as percentage of child weeks at risk.

Table 7: Field workers' observations of respiratory infections in cohort children during one year surveillance period

Symptom or sign	0-2 months	3-11 months	12-59 months	0-59 months
Insuction	3.3%	0.9%	0.5%	0.8%
Nasal flaring	1.6%	0.6%	0.4%	0.5%
Blocked nose	21.1%	50.4%	60.0%	55.8%
Cough observed	10.5%	12.7%	9.8%	10.3%
irritable	1.3%	1.0%	1.1%	1.1%
drowsy unresponsive	1.0%	0.3%	0.2%	0.2%
mean RR/min (sd,n)	41.8 (6.9,1615)	38.5 (6.6,3929)	33.4 (6.4,19477)	34.8 (6.4,25021)
mean temp °C (sd,n)	36.4 (0.5,1615)	36.4 (0.5,1615)	36.4 (0.6,19477)	36.4 (0.6,25021)
Total child weeks at risk observed	1615	3931	19482	25028

Footnote: Results are expressed as percent child weeks at risk in different age groups and for all children under 5 years of age.

3.2.4 Clinical findings recorded by the study physician at 2 cross- sectional surveys of the study cohort in November 1986 (wet season) and May 1987 (dry season) are shown in table 8.

Table 8: Results from two cross-sectional surveys of the study cohort in the wet and dry seasons: Comparison of clinical findings

Patient details	**Wet season (November 1986) (n=441)**	**Dry season (May 1987) (n=487)**
sex = male	224/441 (50.8%)	265/487 (54.4%)
mean age (months) (s.d.,n)	25.6 (sd 16.5, 441)	27.3 (sd 17.4, 441)
Mandinka ethnic group	378/441 (85.7%)	417/487 (85.6%)
Respiratory rates (RR) at rest		
Infants; mean RR (breaths/minute) (s.d.,n)	43.3 (sd 7.8, 87)	41.4 (sd 9.2, 85)
Children 1-4 years; mean RR (breaths/minute)	38.8 (sd 7.7, 295)	33.7 (sd 7.6, 340)
Children 1 - 4 years; percentage of children breathing at 50/m in or above	12/295 (4.1%)	7/340 (2.0%)
Other clinical findings		
Chest indrawing	11/441 (2.5%)	11/487 (2.3%)
Nasal flaring	1/441 (0.2%)	0/487
Audible wheezing	0/441	2/487 (0.4%)
Stridor	0/441	1/487 (0.2%)
Abnormalities on chest ausculation [1]	22/441 (5.0%)	1/487 (0.2%)
Abnormal cervical nodes	72/441 (16.3%)	64/487 (13.1%)
Enlarged spleen	97/417 (23.3%)	48/466 (10.3%)
Enlarged liver	25/422 (5.9%)	1/482 (0.2%)
Skin abnormalities	143/441 (32.4%)	31/487 (6.4%)
Peripheral oedema	10/441 (2.3%)	34/487 (7.0%)

Footnote: [1] Crepitations which didn't clear on coughing, decreased air entry, bronchial breath sounds and (sibilant) rhonchi or wheeze.

3.2.5 ARI are the commonest acute illnesses in childhood world-wide. Due to the fact that ARI symptoms were so prevalent in the study population, it proved

extremely difficult to identify discrete episodes of ARI. Attempts to define an episode were made problematic by the sensitivity of the definitions chosen to minor changes. No attempt is therefore made to report an overall ARI incidence rate in the study population. In these circumstances prevalence data on ARI symptoms may be the most meaningful measure. As can be seen from above the weekly period prevalence of cough was 20% and of reported ARI was 18% in this cohort during the year of observation.

3.2.6 Mothers who reported respiratory illness in their children said that they had sought treatment for this illness in 1357/4540 (30%, 95% confidence interval 29%-31%) of episodes. Mothers of 0-3 months old children who had symptoms of a respiratory illness sought treatment more frequently - in 145/362 (40%, 95% confidence interval 35%-45%) of episodes. These rates of self referral did not vary significantly throughout the year.

3.2.7 During episodes in which the mother considered that her child had a respiratory illness (the 4540 episodes described in table 9), the frequency of reporting of individual symptoms and the frequencies with which these symptoms were associated with self-referral for treatment were calculated (table 9).

Table 9: Analysis of 4540 episodes of ARI (reported by mothers during weekly surveillence) in cohort children during the one year study period

Symptom	Number (percentage) of these episodes when symptom reported		Number (percentage) of episodes when symptom present in which self referral for treatment took place	
	n	%	n	%
blocked nose	3874	(85)	1116	(29)
fever	2454	(54)	993	(40)
cough	2278	(50)	786	(38)
chest pain	942	(21)	480	(51)
diarrhoea	637	(14)	244	(38)
fast breathing	535	(12)	233	(44)
vomiting	531	(12)	276	(44)
open chest	187	(4)	130	(70)
refusal to feed	173	(4)	82	(47)

The commonest symptoms which led mothers to seek treatment for episodes of respiratory illness in their children were blocked nose, fever and cough, with self-referral occurring in 35% (95% confidence interval 33%-37%) of episodes in which cough was reported. Although symptoms related to the chest (chest pain, fast breathing, and "open chest") and to systemic upset (vomiting and refusal to feed) were reported less frequently than cough or fever, their presence was more often associated with self referral for treatment. Thus, mothers sought treatment on 51% (95% confidence interval 48%-54%) of occasions in which they considered chest pain to be present and on 70% (95% confidence interval 63%-76%) of occasions when "open chest" was considered to be present.

3.3 Incidence of ALRI

3.3.1 Two hundred and twenty-two episodes of ALRI (as previously defined in section 2.5) were identified among an average of approximately 491 children (mid-year population) during the one year surveillance period. This corresponds to an annual ALRI incidence rate of 468 episodes per 1000 children aged under 5 per year. 122 children had a single episode, 36 children had 2 episodes, 8 had 3 episodes and 1 child had 4 episodes over the one year period. The male to female ratio was 1.2:1.

3.3.2 In 216 of these episodes a chest X-ray was subsequently performed and in 81 (38%) radiological abnormalities consistent with ALRI were found. Lobar consolidation of at least one entire lobe was present in 25 (12%). These episodes, therefore, can reasonably be considered to be lobar pneumonia and the annual incidence rate of this condition was thus 51 per 1000 children under 5 years of age. Since chest x-rays were only performed on the few children identified by the surveillance as having clinical signs of ALRI and since the clinical criteria used are not 100% sensitive, this incidence rate can be considered to be a minimum figure.

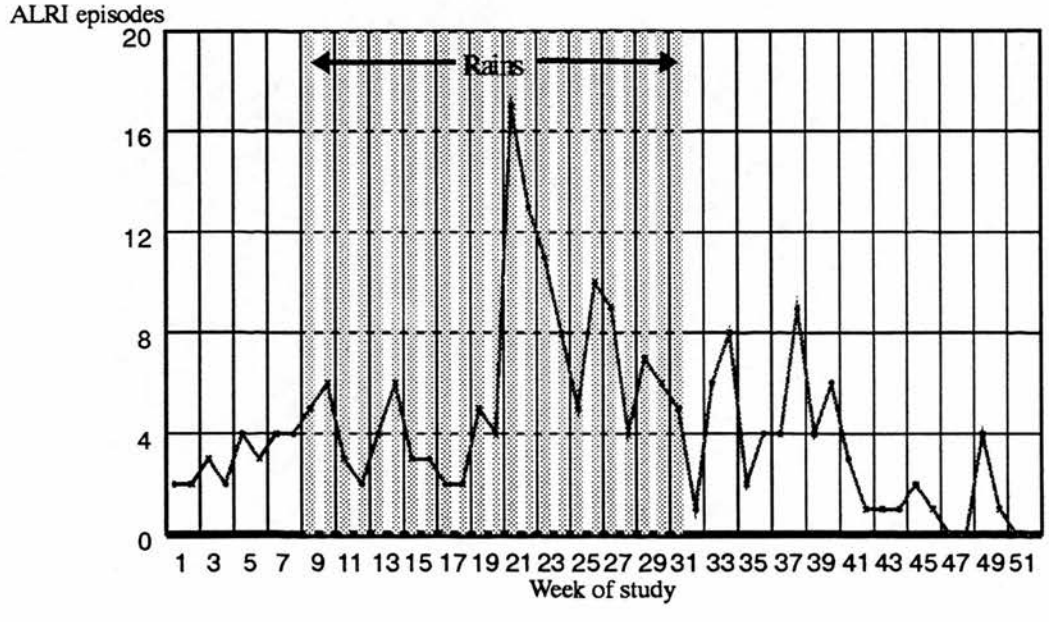
3.3.3 The incidence rate of ALRI episodes over the one year period in different age groups (quoted with the mid-year cohort age distribution as the denominator) was 0.70 (83/119; 95% confidence interval 0.62- 0.78) among infants 0-11 months old, 0.52 (61/118; 95% confidence interval 0.43-0.61) among children 12-23 months old, 0.41 (39/96; 95% confidence interval 0.31-0.51) among children 24-35 months old, and 0.25 (39/158; 95% confidence interval 0.18-0.31) among children 36-60 months old. This

pattern of maximum incidence in infancy with steadily decreasing incidence thereafter is highly significant (chi-squared value for linear trend = 55.9, $p<0.001$). Further analysis showed that within the period of infancy incidence was greatest in the first 6 months of life (see section 3.7).

3.3.4 Fifty percent of children with ALRI had a weight for age less than 80% of the median (NCHS standards) and 8% a weight for age less than 60% of the median. In 138 (62%) of episodes chest indrawing was noted to be present, and in 10 (5%) the child was reported to be unable to take oral fluids reliably.

3.3.5 The weekly incidence of ALRI episodes over the one year period is shown in figure 19. It can be seen that weeks 21-23 in the wet season was the period of maximum incidence. ALRI incidence was significantly higher in the wet season in infants but not in older children (see section 3.7). The epidemic nature of ALRI epidemiology is shown in the variation in weekly episodes over the course of the year ranging from a mean of 3-4 episodes per week in the first 20 weeks of the study to a mean of 14 episodes per week in weeks 21-3.

Figure 19: Weekly incidence of ALRI episodes over one year surveillance period

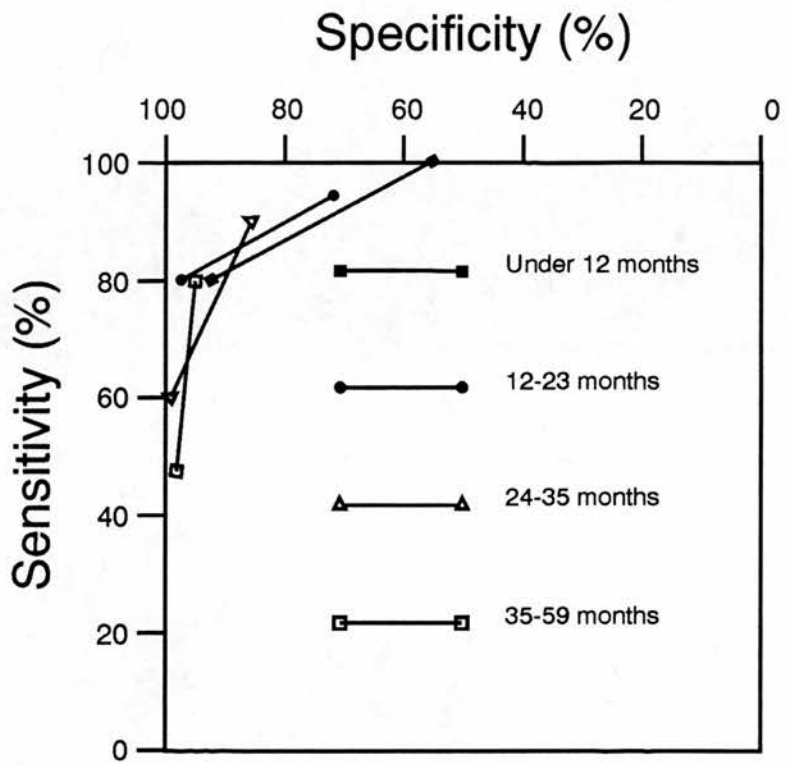


3.4 Respiratory rate criteria for diagnosis of ALRI

3.4.1 The use of simple clinical signs for the detection of ALRI has been adopted in the surveillance programme. However, although recommended by WHO and based on seminal work in Papua New Guinea [69], the validity of this methodology had been little studied in developing countries. In order to evaluate the validity (sensitivity and specificity) of these signs for the identification of ALRI it was necessary to compare them against a standard. The assumption was therefore made that the most useful standard definition of ALRI for this purpose is the clinical judgement of a paediatrician who has access to a chest x-ray. Thus ALRI for the purposes of this analysis was defined as the presence of auscultatory signs of ALRI (bronchial breath sounds, decreased air entry, coarse crepitations which did not clear on coughing or [sibilant] rhonchi), or radiological abnormalities (principally consolidation) consistent with ALRI. One hundred and fifty four of the 222 ALRI episodes identified by surveillance met these criteria. We also recorded the respiratory rate on 4318 (4540 episodes of ARI mentioned in table 9 minus the 222 episodes which were classified as ALRI) occasions when a cohort child reported an ARI but no signs of ALRI were found on examination.

3.4.2 Of the 4318 occasions when respiratory rate was measured in children with an ARI (other than ALRI), 2% (66) of episodes were associated with a respiratory rate above 50/minute, whereas in 13% (533) of the episodes the respiratory rate was either above 50/minute (in infants) or above 40/minute (in 1 - 4 year olds). The sensitivity and specificity of various respiratory rate cut-offs for the prediction of the presence of ALRI (as defined for this analysis by children with the radiological or auscultatory findings mentioned above) is shown in the receiver- operator characteristic (ROC) curves in figure 20. These data suggest that a respiratory rate of above 50 per minute in infants and a respiratory rate above 40 per minute in children 1 -4 years old are the most valid predictors of the presence of ALRI. This was not in agreement with the WHO guidelines at that time which recommended the use of a respiratory rate cut-off of 50/minute for all children under 5 years of age.

Figure 20: The sensitivity and specificity of two respiratory rate thresholds for the diagnosis of ALRI in different age groups: receiver-operator characteristic (ROC) curves

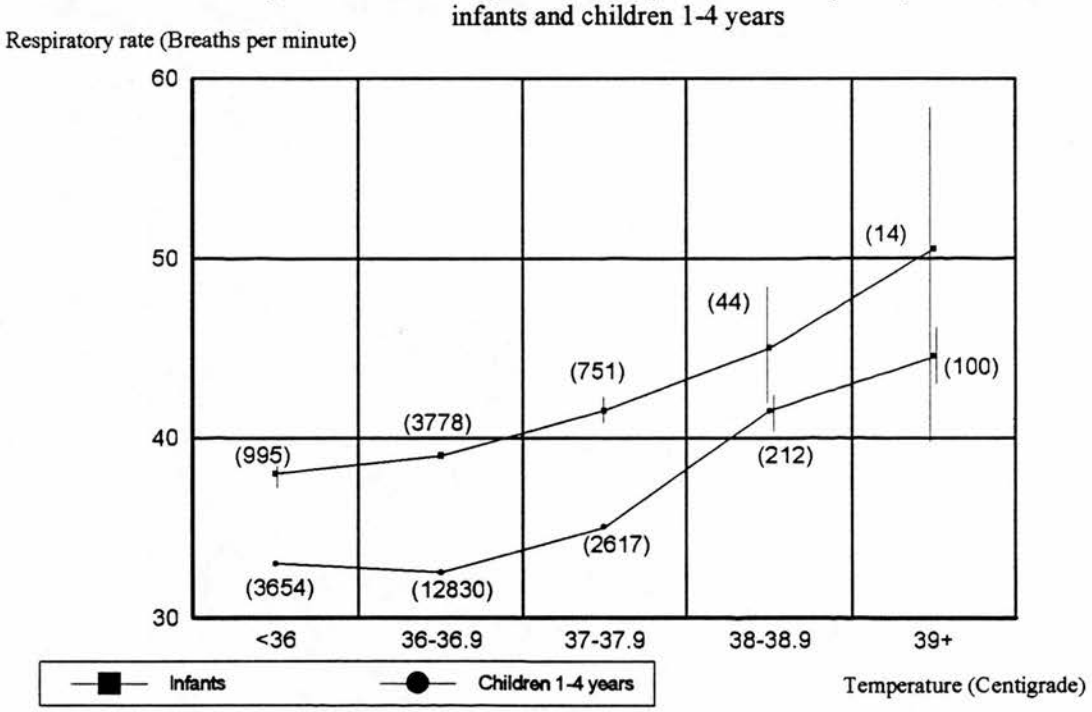


3.4.3 If we consider the maternal reports of whether or not fast breathing was present, the age-specific sensitivities and specificities of reported rapid breathing as a predictor of ALRI were 74% and 86% (year); 79% and 90% (1 year); 79% and 91% (2 years) and 55% and 93% (3-4 years). Mothers therefore appear to recognise respiratory distress in their children, particularly in younger children up to 3 years of age.

3.4.4 A possible confounding factor in the relationship between respiratory rate and ALRI is temperature since many children with ALRI are febrile and it is possible that fever results in a rise in respiratory rate. Since this hypothesis had not previously been studied, the relationship between temperature and respiratory rate was explored in 25,043 observations in 685 children recorded during the one year surveillance. Although these observations are technically not independent, it is suggested that measurements of respiratory rate and temperature carried out at one week intervals on a young child might reasonably be assumed to be independent. In instances in which radiological abnormalities were found, these

observations were excluded from the analysis. The relationships between temperature and respiratory rate for infants (5,542 observations) and for children aged 1-4 years (19,413 observations) are shown in Figure 21. In both groups the mean respiratory rate shows a steady increase with increasing temperature of approximately 2.5 breaths per minute per $1^{o}C$ rise in temperature over the temperature range shown. A similar analysis restricted to children with cough (2,537 observations) showed a similar relationship.

Figure 21:Relationship between temperature and respiratory rate in infants and children 1-4 years



3.5 Clinical signs of lobar pneumonia

3.5.1 In table 10, symptoms and signs at presentation among the 222 episodes of ALRI identified in the study cohort have been compared with the presence or absence of radiological lobar consolidation (only 216 of the 222 episodes were x-rayed). Clinical features that best predicted the presence of lobar pneumonia on chest x-ray were auscultatory findings of bronchial breathing or decreased air entry, respiratory rate above 60/minute, axillary temperature above 38.5^{o} C, grunting, and a history of refusing to breast feed or take solids. Neither the presence of indrawing or nasal flaring, nor

the finding of crepitations on auscultation reliably distinguished those with lobar consolidation. The sensitivities, specificities, positive predictive values and prevalence of some selected symptoms and signs for identifying lobar consolidation were calculated and are shown in table 11.

Table 10: ALRI episodes in cohort children: relationship of reported symptoms and clinical signs on examination to subsequent radiological changes found on chest X-ray

Symptoms (maternal report)	Chest x-ray findings lobar consolidation		X^2	p value
	present n=25	absent n=191		
vomiting	17 (68%)	88 (46%)	3.4	NS
rapid breathing	15 (60%)	135 (71%)	0.7	NS
refusing to eat or breast feed	11 (44%)	42 (22%)	4.7	<0.05
Signs (recorded by study physician)				
chest indrawing	15 (60%)	117 (61%)	0.01	NS
nasal flaring	4 (16%)	26 (14%)	<0.01	NS
respiratory rate >=50/minute	21 (84%)	130 (68%)	2.0	NS
respiratory rate >=60/minute	15 (60%)	52 (27%)	9.6	<0.01
heart rate >160/minute	7 (28%)	30 (16%)	1.6	NS
temperature >37.5 °C	20 (80%)	87 (46%)	9.2	<0.01
temperature >38.5 °C	15 (60%)	35 (18%)	19.3	<0.001
crepitations on auscultation	6 (24%)	62 (32%)	0.4	NS
bronchial breath sounds or decreased air entry	8 (32%)	6 (3%)	25.8	<0.001
rhonchi on auscultation	2 (8%)	40 (44%)	1.6	NS
grunting	3 (12%)	3 (2%)	5.5	<0.025

Footnote: only 216 of the 222 episodes of ALRI were successfully chest x-rayed
: lobar consolidation is defined as confluent consolidation of at least one complete lobe of the lung

3.5.2 In infants, refusal to breast feed (found in 43% of episodes with lobar consolidation compared to 11% of those without) and temperature above 38.5° C (43% versus 11%); and in older children, bronchial breath sounds (39% versus 4%), temperature above 38.5° C (76% versus 23%) and

respiratory rate above 60 per minute (61% versus 21%) were the best discriminatory features.

Table 11: ALRI episodes in cohort children: Sensitivity, specificity and positive predictive value of selected reported symptoms and clinical signs for the prediction of lobar consolidation on chest x-ray

Symptoms	lobar consolidation present n (%) with the symptom or sign (sensitivity)		lobar consolidation absent n (%) without symptom or sign (specificity)		prevalence		positive predictive value
	n	%	n	%	n	%	
vomiting	17	(68)	108	(55)	105	(49)	0.16
refusing to eat or breast feed	11	(44)	154	(78)	53	(25)	0.21
Signs							
chest indrawing	15	(60)	74	(38)	132	(61)	0.11
respiratory rate >=50/minute	21	(84)	65	(33)	151	(70)	0.14
respiratory rate >=60/minute	15	(60)	154	(78)	67	(31)	0.22
temperature >37.5 °C	20	(80)	108	(55)	107	(50)	0.19
temperature >38.5 °C	15	(60)	162	(82)	50	(23)	0.30
grunting	3	(12)	194	(98)	6	(28)	0.09
crepitations	6	(24)	133	(68)	68	(31)	0.57
bronchial breath sounds or decreased air entry	8	(32)	191	(97)	14	(65)	0.50
respiratory rate >=60/minute plus temperature >38.5 °C	11	(44)	177	(93)	25	(12)	0.44

Footnote: only 216 of the 222 episodes of ALRI were successfully chest x-rayed
: lobar consolidation is defined as confluent consolidation of at least one complete lobe of the lung

3.5.3 When multiple episodes of ALRI in the same child were omitted, leaving 162 episodes of which 23 had lobar consolidation, only bronchial breath sounds or decreased air entry (odds ratio 6.6, 95% confidence interval 1.5 - 29.4) and fever above 38.5°C (8.6, 3.1 - 24.1) were independently associated with lobar consolidation after adjusting for other factors.

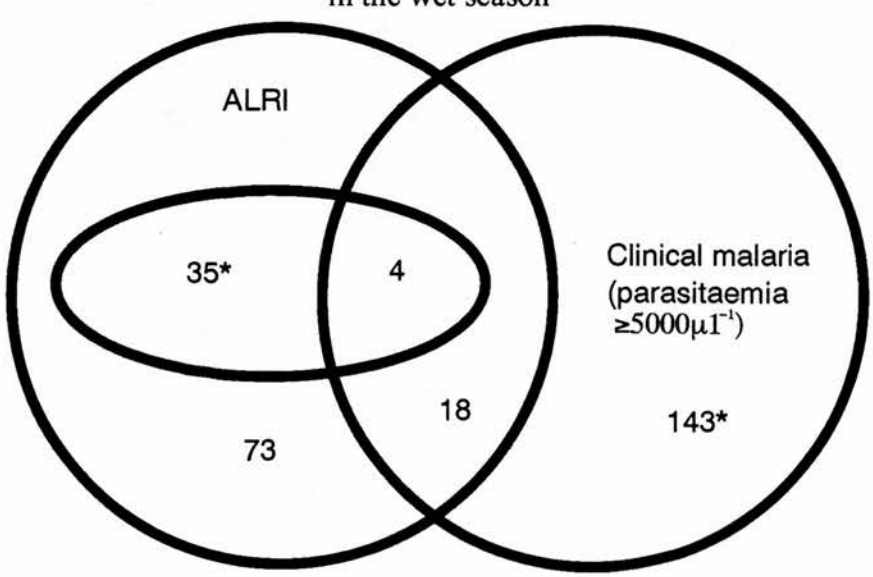
3.6 Respiratory symptoms and signs in children with malaria

3.6.1 ALRI and malaria are two most frequent causes of mortality and morbidity in young Gambian children and yet little is known about their possible interactions. These may be important at the epidemiological, diagnostic and therapeutic level yet had not been previously studied.

3.6.2 Of the children with ALRI and a temperature above 38.5°C only 13/90 (14%) had any malarial parasitaemia. This level of parasitaemia is no higher than would be expected in a group of healthy rural Gambian children with a similar age distribution.[70]

3.6.3 During the one year surveillance period 183 children experienced an clinical attack of malaria (clinical malaria defined as fever together with a parasite density of greater than 5,000 per microlitre as described in section 2.9). 165 (90%) of these presented in a 20 week period in the rainy season. In the same 20 week period, 130 children experienced an attack of ALRI (39 were subsequently found to have radiological abnormalities). The relationship between these two conditions over the 20-week rainy (malaria) season is shown in figure 22.

Figure 22: Occurrence of ALRI and clinical Malaria and distribution of radiological abnormalities found among cohort children during a 20 week period in the wet season



** Nine children had both clinical malaria and radiological abnormalities at different times in the 20 week period.*

3.6.4 Thirteen children had episodes of both ALRI and malaria, as defined above, during the 20-week surveillance over the rainy season. Four of these children had signs defining both clinical malaria and ALRI concurrently. The other nine children experienced an episode of malaria and ALRI at different times during the 20-week period. In each of these latter cases the two episodes were separated by one month or more.

3.6.5 If an episode of malaria and an episode of ALRI were to occur independently in a child experiencing both during the 20-week period, the probability of both occurring in the same week would be 0.05. Thus the probability of observing malaria and ALRI at the same time in 4 of the 13 children who experienced both of these conditions is $^{13}C_4 \times 0.05^4 \times 0.95^9 = 0.0028$. Clinical malaria and ALRI were therefore associated together more often than would be expected by chance. Each of these four children had radiographic abnormalities reported independently (and without any clinical information about the children) by a paediatric radiologist in the United Kingdom. In all four cases these were classified as "interstitial changes". This is significantly greater than the overall prevalence of interstitial changes among the 35 children with radiological abnormalities not associated with malaria was only 10/35 (29%) ($p<0.05$, Fisher exact test).

3.6.6 There are a number of possible explanations for the this finding[61] (see discussion in section 8.4). However one possibility is that malaria causes clinical signs (such as fast breathing) that can be interpreted as ALRI. This possibility has more recently been confirmed by other investigators.[71,72] Since this overlap may result in misdiagnosis and incorrect treatment, the clinical presentations of ALRI and malaria in this study population were considered further. For this comparison, children with ALRI who, in addition, had radiological abnormalities and were febrile were compared to children with malaria (since it would not have been appropriate to compare <u>all</u> children with ALRI if we are postulating that some might have signs that define ALRI due to some consequence of malaria - for example pulmonary parasite sequestration or fast breathing due to fever). Table 7 compares the symptoms and signs in these two groups of children.

3.6.7 During the one year surveillance period among the 222 episodes of ALRI there were 81 episodes associated with fever and radiological abnormalities consistent with ALRI occurring in 68 children. Seventy- one (88%) of these

episodes were not associated with any parasitaemia. Forty four of these episodes occurred in the 20-week rainy season (the time of year during which diagnostic uncertainties between these two conditions would be most relevant.

3.6.8 During the same period of surveillance, a total of 222 episodes of fever (37.5 ^{o}C and over) associated with parasitaemia (5,000 per microlitre or above) were found in 183 children. Clinical signs consistent with a diagnosis of ALRI were observed in 30 cases. 6 of these 30 cases were excluded from this comparison since radiological abnormalities consistent with ALRI were found (the other 24 showed no radiological changes). A total of 153 such episodes occurred over the 20 week period and are presented table 12.

Table 12: Parental smoking and exposure to indoor air pollution (carriage on mothers back while cooking) and subsequent development of an episode of difficult breathing in cohort children

Variable	Level	Log (odds ratio)	odds ratio (95% confidence limits)
Father smoking	none	0	1
	1-5	0.86	2.35 (0.90, 6.14)
	6-10	1.39	3.81 (1.14, 14.11)
	>11	1.64	5.18 (1.57, 9.25)
Carriage on mother's back	no	0	1
	yes	1.03	2.80 (1.29, 6.09)
Ethnic group	other	0	1
	Mandinka	2.60	13.42 (0.96, 188.10)
Village	B	0	1
	D	2.16	8.65
	F	1.34	3.83
	K	4.34	76.84
	R	-3.92	0.02
	S	-0.33	0.72
	T	-0.10	0.90

Footnote:for variables with 2 or more levels, the odds ratio is given relative to the first level.
: difficult breathing refers to the reports made by mothers during weekly surveillance visits.

3.6.9 Measurements of respiratory rate and assessments of the presence of chest indrawing by the project clinician are shown together with the presenting symptoms reported by mothers of the children during weekly field worker surveillance (before the child was referred) in table 12. A greater proportion

of children complaining of cough, chest pain, "open chest", difficult breathing and lack of appetite, and with chest indrawing; and a higher mean respiratory rate were found in the ALRI group. The malaria group recorded more complaints of fever. There was, however, considerable overlap in presenting symptoms such that children with ALRI often present with fever and children with malaria often present with respiratory symptoms. In addition we have already seen in figure 22 that a proportion of children with clinical malaria have raised respiratory rate (thus causing diagnostic uncertainty) and it should be noted that the extent of this overlap in clinical classifications will vary depending on the criteria adopted for the classification of the two syndromes (so, for example, a change in the respiratory rate threshold for the definition of ALRI from 50 to 40 per minute in children 1-4 years of age as was adopted by WHO in 1990 will act to increase this clinical overlap).

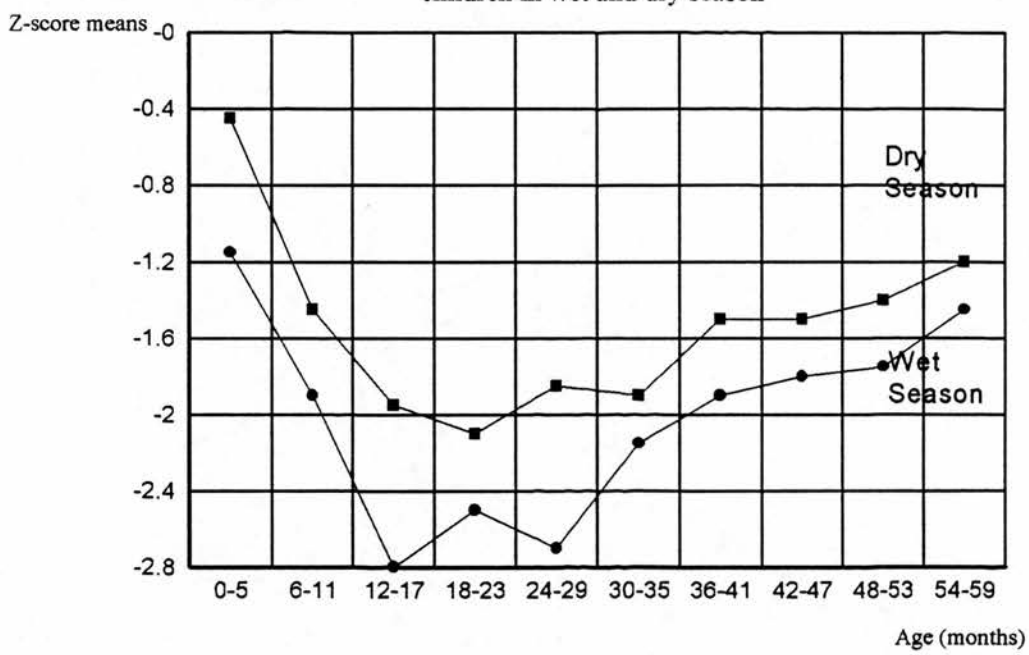
3.7 Relationship between ALRI and nutritional status

3.7.1 An analysis was made of the association between the incidence of ALRI and nutritional status. As described above, anthropometric indices show marked seasonal changes. Breastfeeding is almost universal until 18 months of life and solids are introduced to the great majority of children in the first year of life.

3.7.2 Any assessment of a possible association is complicated by the fact that age, season and nutritional status are all time-dependent factors; and some children had more than one episode of ALRI in the one year period (indeed the ALRI episodes in this study show overdispersion when compared to a Poisson distribution). In order to deal with time-dependent factors the observation time for each child was broken down into a number of smaller units. Infants and children 1-4 years were considered separately. Six month age group categories were formed then the resulting intervals were subdivided so that each new interval started with a new weight measure so that ALRI episodes occurring during that interval are related to the (recent) nutritional recorded its start. Finally the mid-point of these intervals were classified by season. A Poisson regression was performed and Pearson's chi-squared statistic used to test and correct for overdispersion. Fuller details of these methods are presented elsewhere. [73,74]

3.7.3 The observed distributions of weight-for-age z-scores for wet and dry seasons are shown in figure 23. Nutritional groups were defined according to whether they were above or below a z-score of -2. Multiple Poisson regression models were fitted to the data. Basic confounders included in the models were age, sex and ethnic group. Other factors studied were season, parent's education, number of children sleeping in the same bedroom (crowding index), parental smoking, father's occupation, and father's number of wives.

Figure 23: Distribution of weight for age Z-Scores in cohort children in wet and dry season



3.7.4 Table 13 shows the number of episodes observed and the time of follow up for the categories of age and nutritional status. There was no effect of nutritional status on ALRI incidence in either infants or 1-4 year old children as shown in tables 14 and 15. In infants the ALRI incidence fell sharply with age and incidence of ALRI was higher during the wet season. Among older children ALRI incidence once again fell with age but there was no significant seasonal difference in the incidence of ALRI.

Table 13: Number of ALRI episodes and child weeks at risk by nutritional status and age group

Age group (months)	Malnourished children		Normal children	
	No. of episodes	child weeks at risk	No. of episodes	child weeks at risk
0 -11	11	955	56	3431
12 - 35	47	4329	36	4103
0 - 59	3	1644	17	3345
Total	**61**	**6928**	**109**	**10879**

Footnote: "Malnourished" defined here as a weight for age z-score of less than -2

Table 14: Observed association between ALRI and a number of possible risk factors including malnutrition in children aged 1 - 4 years: results of Poisson regression modelling

Risk Factor	Comparison made	Incidence density ratio (IDR)	IDR confidence interval	
			lower bound	upper bound
sex	female/male	1.00	0.65	1.55
ethnic group	Fula/Mandinka	1.06	0.58	1.92
age (months)	24-35/12-23 36-47/12-23 48-59/12-23	0.90 0.43 0.34	0.55 0.22 0.14	1.47 0.86 0.81
nutritional status weight for age Z - score	less than -2/-2 and above	1.03	0.67	1.61
number of wives	>1/1	0.53	0.34	0.82

Footnote: Basic confounders included in the models were sex, ethnic group and age; factors studied were nutritional status, season, parental education, number of children to mother, number of other children in same bedroom, father's smoking habit, father's occupation, father's number of wives.

Table 15: Observed association between ALRI and a number of possible risk factors including malnutrition in infants: results of Poisson regression modelling

Risk Factor	Comparison made	Incidence density ratio (IDR)	IDR confidence interval	
			lower bound	upper bound
sex	female/male	0.66	0.31	1.38
ethnic group	Fula/Mandinka	1.23	0.58	2.65
age (months)	6-11/0-5	0.43	0.26	0.73
nutritional status	less than -2/-2 and above	0.94	0.48	1.84
number of wives	>1/1	1.58	0.94	2.64
season	wet/dry	2.63	1.56	4.44

Footnote: Basic confounders included in the models were sex, ethnic group and age; factors studied were nutritional status, season, parental education, number of children to mother, number of other children in same bedroom, father's smoking habit, father's occupation, father's number of wives.

4. EPIDEMIOLOGY OF ALRI: AETIOLOGY

4.1 Specimens collected

4.1.1 Two hundred and twenty-two episodes of ALRI were identified as previously described during the one year surveillance period of the cohort, and 49 episodes were identified from the surveillance at Basse health centre. Viral culture was performed on specimens from 221 of the 222 cohort cases, all of the cases identified at the health centre and from 96 controls (see section 2.8.5 for details of their selection). Paired sera were available for viral serology from 203 (91%) cohort episodes of ALRI and 39 (80%) health centre patients. Blood cultures were performed in 214 (96%) cases, bacterial serology was performed on paired sera from 192 (86%) cases and urine from 207 (93%) cases was tested for the presence of bacterial antigens. Urine for antigen detection and blood for blood culture was taken from all children with ALRI recruited from Basse health centre.

4.2 Viral Infections

4.2.1 A viral infection was identified in 55 (24.9%, 95% confidence interval 19%-30%) of the ALRI episodes among cohort children (table 16). These figures exclude cytomegalovirus infections since it is not clear that these infections were directly related to the ALRI episode (see section 4.2.10).

Table 16: Episodes of ALRI in study cohort children: Viral infections (excluding CMV)

Viral Aetiology	Culture and/or serology (n=221) %		Culture only (n=221) %		Serology only (n=203) %	
Total positive	55	(24.9)	42	(19)	33	(16.2)
RSV	4	(1.8)	0	(0)	4	(2.0)
Parainfluenza	14	(6.3)	8	(3.6)	10	(4.9)
Adenovirus	18	(8.1)	13	(5.9)	9	(4.4)
Influenza	14	(6.3)	8	(3.6)	12	(5.9)
Other	15	(6.8)	15	(6.8)	Not Determined	
Mixed viral	9	(4.1)*	1	(0.5)*	2	(1.0)

* One triple virus infection

4.2.2 One or more viruses were cultured from 42 specimens (19%, 95% confidence interval 14%-24%) whereas viral serology was positive in 33 (16%, 95% confidence interval 10%-19%) of episodes (in 14 cases the virus infection identified was positive by both techniques). Mixed viral infections, excluding CMV excretion, was identified in 6 subjects. One

patient had 3 respiratory viruses recovered simultaneously: parainfluenza type 1, adenovirus type 5 and a rhinovirus.

4.2.3 Disregarding isolates of non-respiratory viruses such as enteroviruses and herpes simplex, an acute viral infection was identified in 46 (21%, 95% confidence interval 15%-26%) of ALRI episodes. The proportion of ALRI episodes in which a viral infection could be identified tended to increase with the age of the child but this trend was not statistically significant.

4.2.4 No outbreak of RSV infection was observed during the surveillance period although 4 children showed serological evidence of possible recent infection.

4.2.5 Adenoviruses were identified in 18 (8.1%) of the ALRI episodes. 8 (61.5%) of the 13 adenovirus isolates were type 6, 6 of these being isolated during weeks 21-26. A further 3 children with ALRI had a rising titre to adenovirus during this period. Adenovirus was cultured from 5 (5.2%) of 96 control patients, only one of which was adenovirus type 6.

4.2.6 Each of the 13 influenza A infections that were identified in cohort cases occurred in weeks 23-28. 11 influenza A infections were identified by serology and 8 by virus isolation. At least 5 of the isolates were of the H1 N1 subtype and closely resembled influenza A/Taiwan/1/86. Serological evidence of influenza B infection was found in 1 child. No influenza viruses were isolated from any of the 96 control children investigated.

4.2.7 Seven of the 14 parainfluenza virus infections identified in children with ALRI were caused by type 1 virus and 7 by type 3 virus.

4.2.8 The number of episodes of ALRI found by week of study, together with the viral infections identified are shown in figure 24. The majority of viral infections occurred in the rainy season between July and September (weeks 16-28) when the relative humidity was high. Several viruses , notably parainfluenza types 1 and 3, were also recovered during the late dry season. The incidence of ALRI was highest in August (weeks 21-23) when 17, 13 and 11 episodes were identified in successive weeks among cohort children. This appeared to be associated with an increase in the recovery of adenoviruses particularly type 6. Immediately after this period during weeks 23-28 marked activity of influenza A virus was found. Significantly fewer viral infections were identified after the rains had ended (X^2=8.8,

Figure 24a: Episodes of ALRI identified in cohort children and influenza infections by week of study

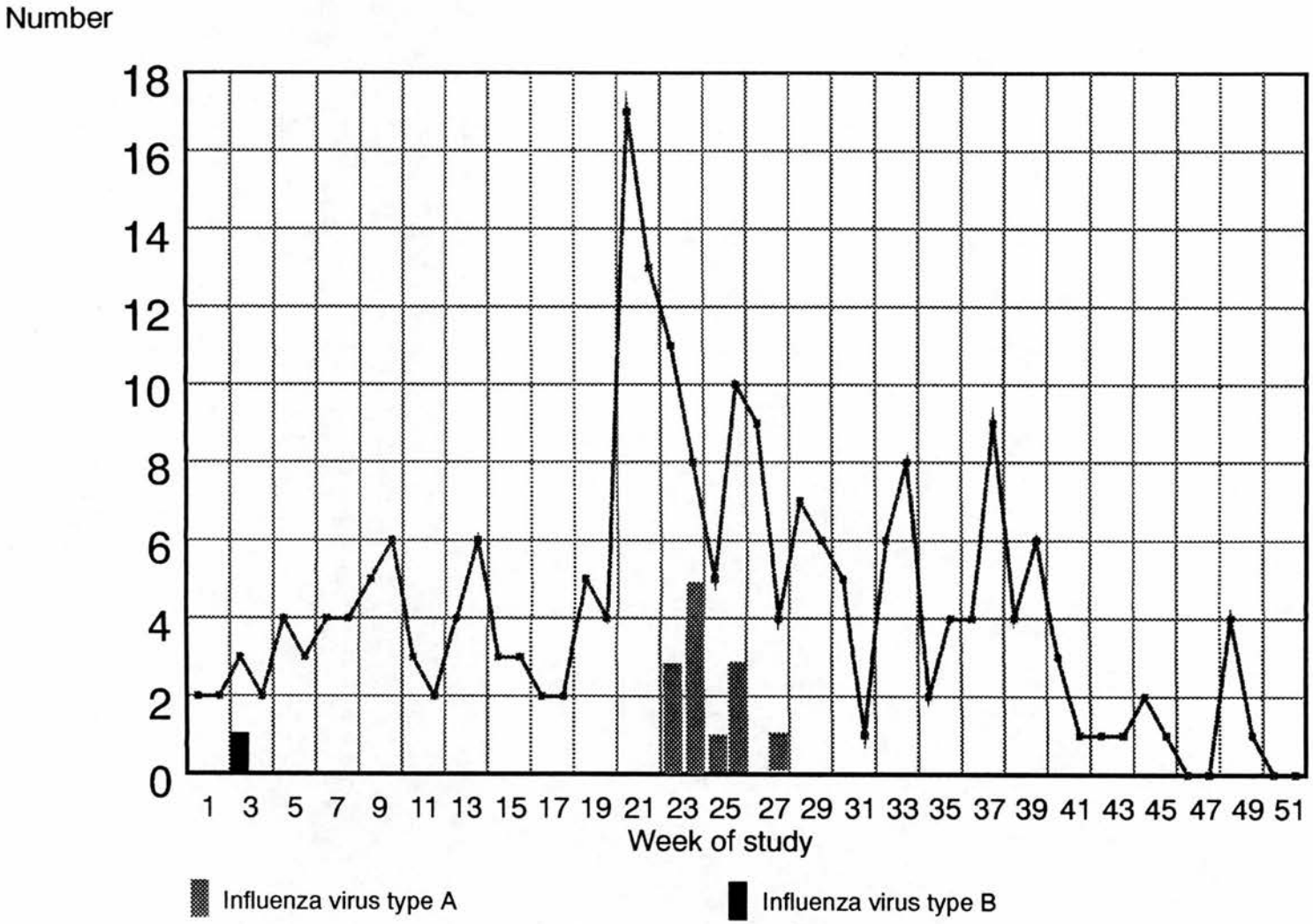


Figure 24b: Episodes of ALRI identified in cohort children and adenovirus infections by week of study

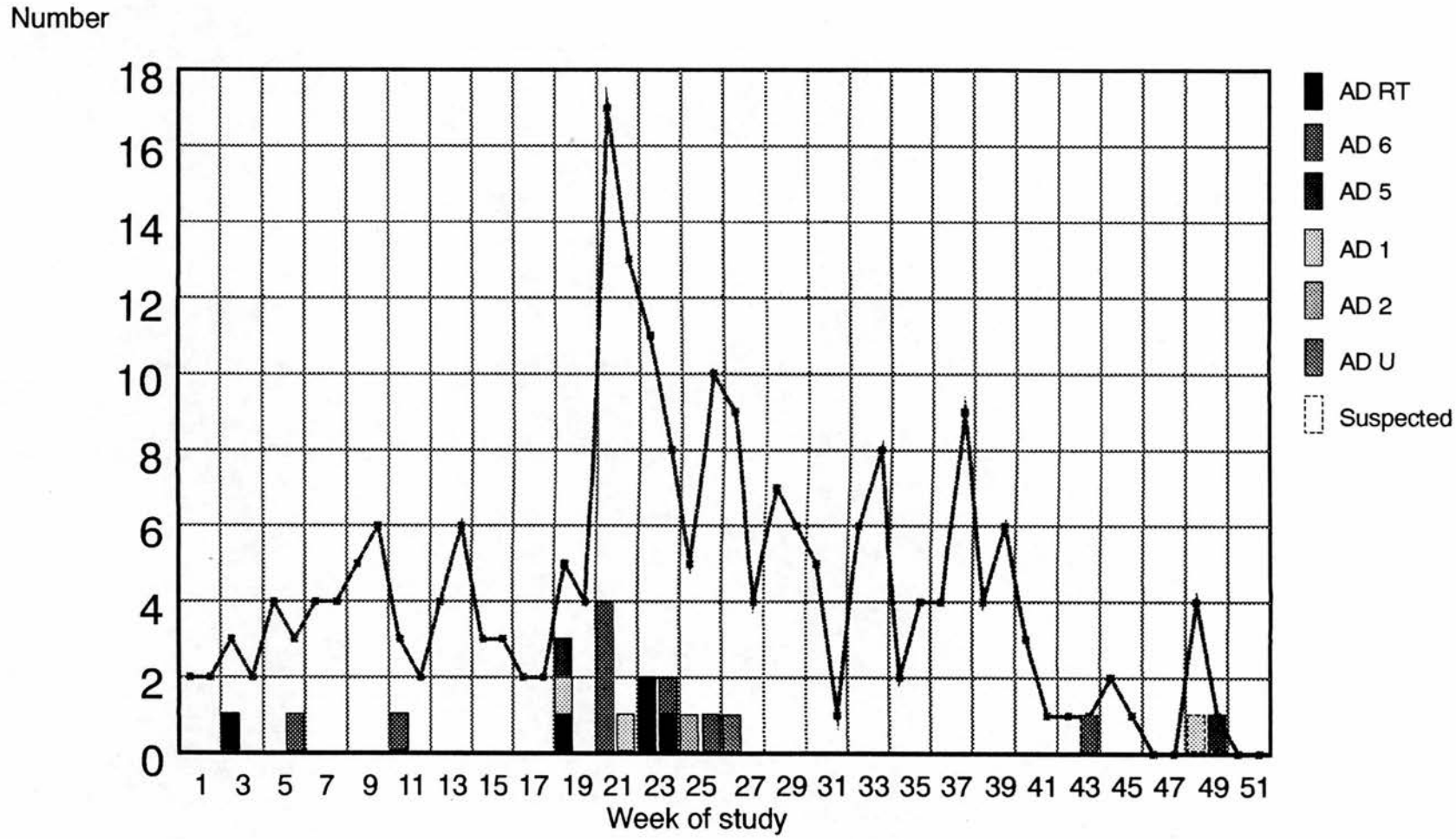


Figure 24c: Episodes of ALRI identified in cohort children and parainfluenza infections by week of study

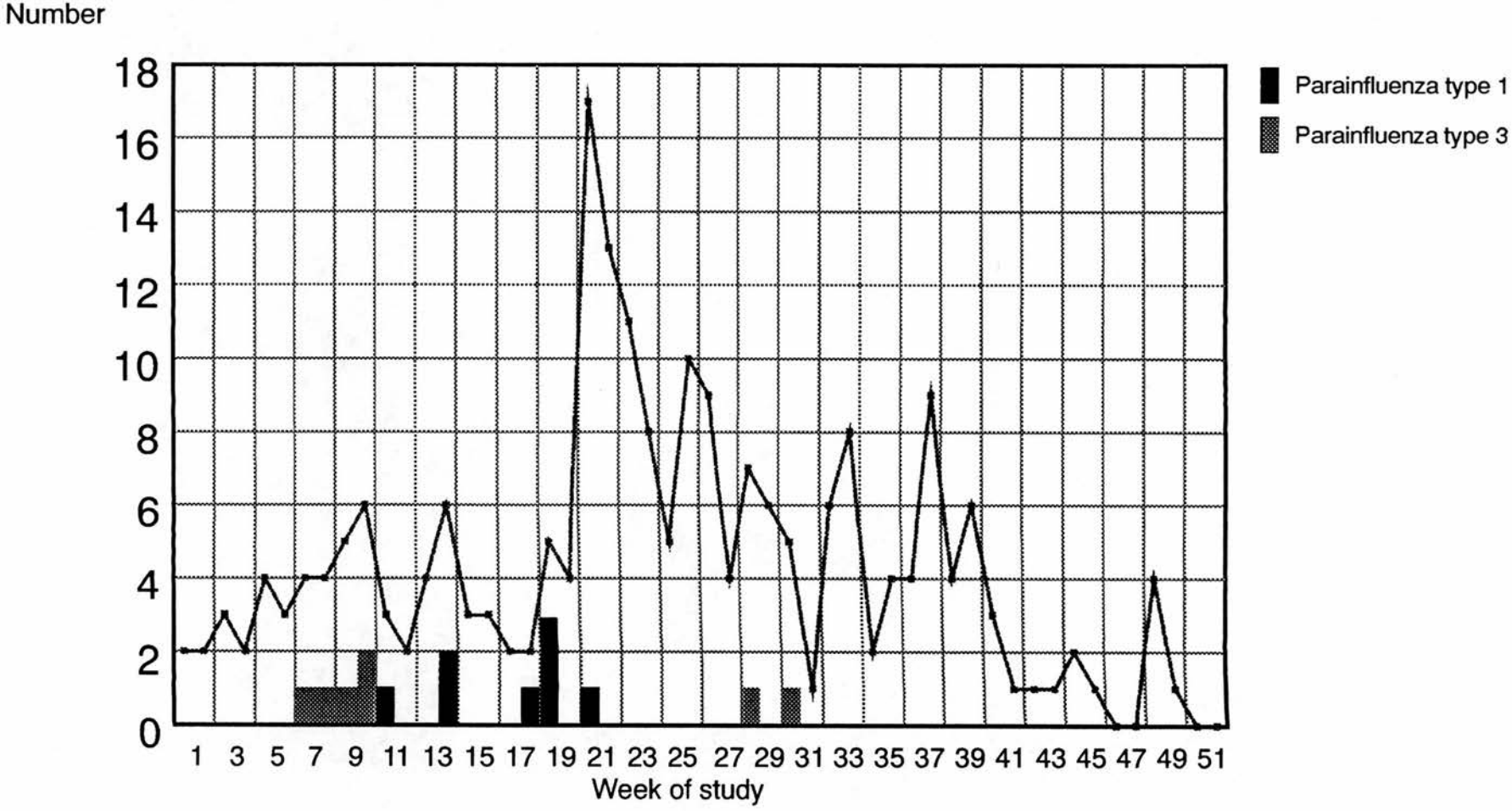


Figure 24d: Episodes of ALRI identified in cohort children and other viral infections by week of study

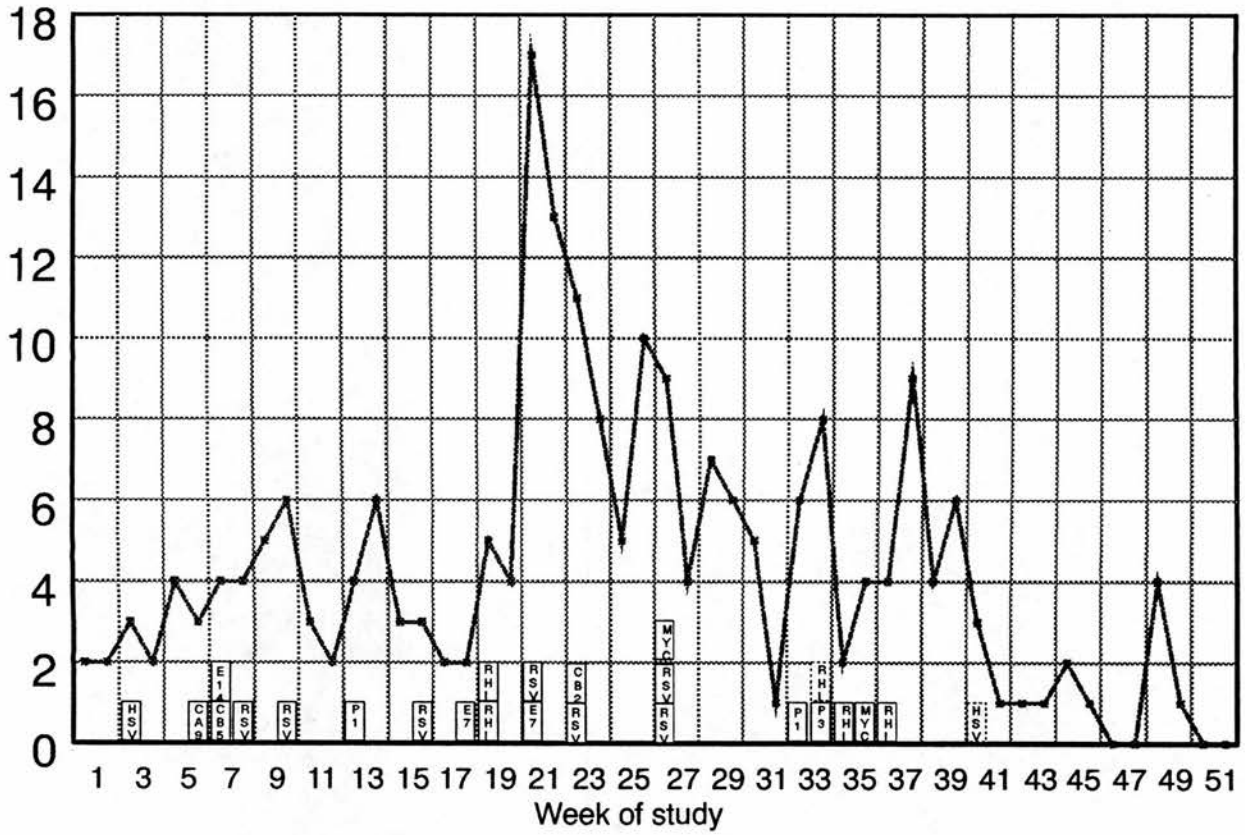
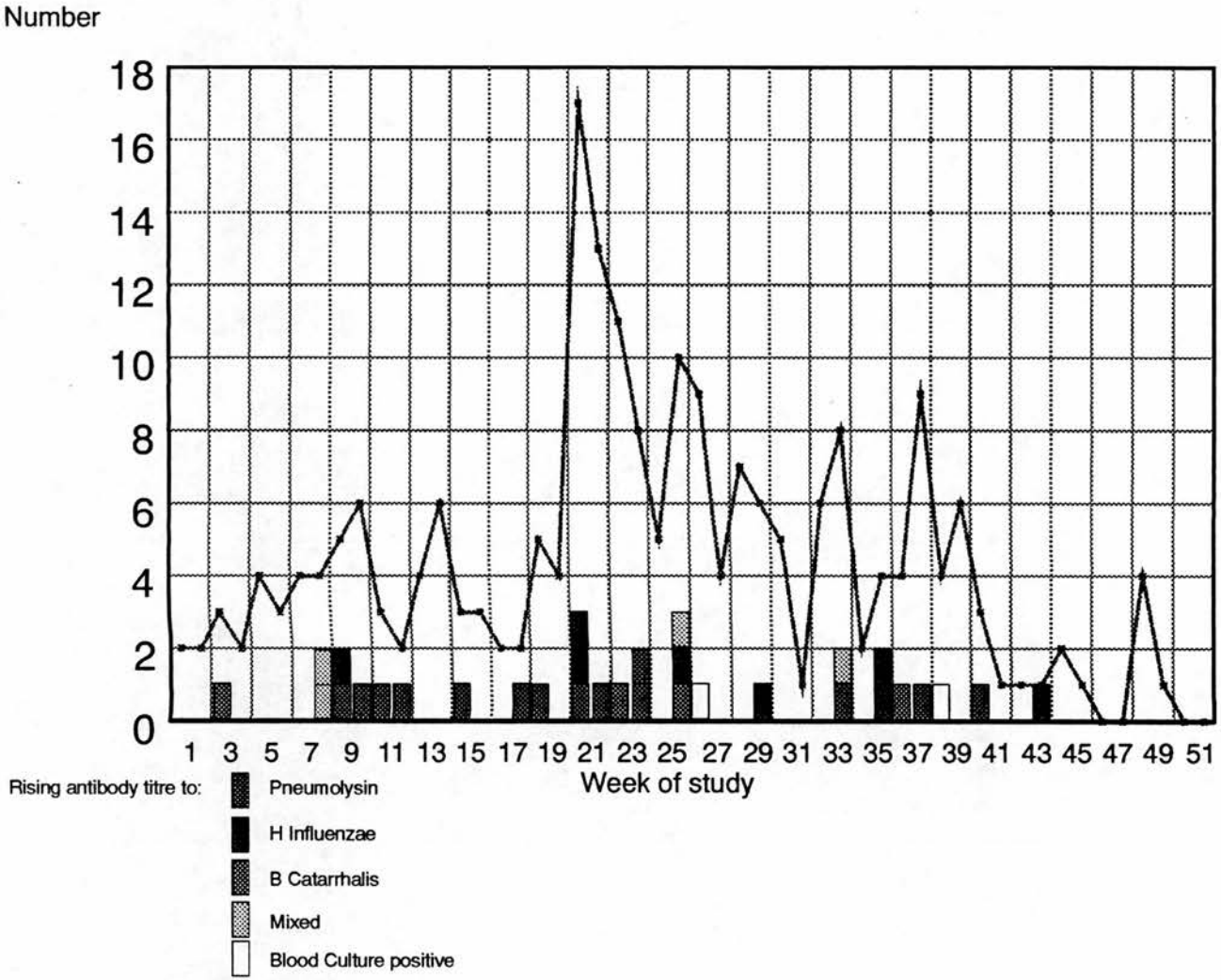


Figure 24e: Episodes of ALRI identified in cohort children and bacterial infections by week of study



$p<0.005$) despite a period when a noticeable rise in the number of episodes of clinical ALRI was observed.

4.2.9 CMV was isolated from 30% of ALRI episodes but also from 30.2% of 96 controls specimens. The highest CMV isolation rates (45%) were in children 12-23 months of age.

4.2.10 In total, viruses other than CMV were isolated from 14 (14.6%, 95% confidence interval 8%-23%) of the 96 cohort control children investigated contemporaneously with the cases of ALRI (table 17). This figure is not significantly different ($X^2=0.6$, n.s.) from the 42 viruses (19%, 95% confidence interval 14%-24%) cultured from children with ALRI.

Table 17: Viral Infections identified by culture in 96 control[1] children from the study cohort

Virus	n	%
RSV	0	0
Influenza	0	0
Parainfluenza	2	2.1
Adenovirus	5	5.2
Other	7	7.2
Mixed viral	0	0
Total positive	14	14.6

Footnote:[1] children with no evidence of ALRI at the time of examination or in preceding 2 weeks

4.3 Bacterial infections

4.3.1 Bacterial infection was detected by blood culture in only 2 of 222 episodes of ALRI among cohort children and in 9 (18%) of 49 episodes among children identified at Basse health centre. The isolates were as follows: E. coli 1 (from cohort child), S. pneumoniae 5 , H. influenzae 1 , Staph aureus 2, Sal. typhi 1, and Sal. spp 1.

4.3.2 A total of 30 (15.6%) of the 192 specimens from ALRI episodes among cohort children showed a rising antibody titre to one or more of the three bacterial antigens tested. 19 had a rising titre to pneumolysin, 10 to H. influenzae and 6 to Br. catarrhalis. In 5 cases a rising titre to more than one agent was found (pneumococcus and H. influenzae 1, pneumococcus and Br. catarrhalis 3, H. influenzae and Br. catarrhalis 1.

4.3.3 Serological evidence of bacterial infection was found in 9 (41%, 95% confidence interval 21%-64%) of the 22 ALRI episodes which were subsequently found to have lobar consolidation on x-ray compared to 21

(12.3%, 95% confidence interval 7%-17%) of 170 ALRI episodes which did not show lobar consolidation (X^2=9.9, p<0.005).

4.3.4 Of the 10 ALRI episodes in cohort or health centre children which showed a significant rising titre to pneumolysin, 7 (70%) were found to have lobar consolidation on x-ray.

4.3.5 Acute and convalescent sera from 58 children with acute malaria (see section 2.8.4.5) were used as controls for the pneumolysin ELISA (the non-specific hypergammaglobulinaemia observed in such patients was considered a good test of the specificity of the antibody assay). A rising titre was observed in only 3 (5%) patients.

4.3.6 18% of urine specimens from both cohort ALRI cases and controls gave a positive reaction when they were tested by the type-specific latex tests for pneumococcal antigen.[54] Detection of pneumococcal antigenuria by the type-specific latex test was therefore not considered to be a reliable indication of pneumococcal infection in this population and the results have not been included in the calculations of the number of ALRI episodes in which a bacterial infection was identified. No H. influenzae type b antigenuria was found in any ALRI episodes in cohort children.

4.3.7 Serological evidence of bacterial infection was found throughout the year though the majority were detected during the mid rainy season when the incidence of ALRI was maximum (figure 24).

4.4 Other infections

4.4.1 Evidence of M. pneumoniae infection was found in 2 cohort children with ALRI. The first was a 16 month old child and the second a 46 month old child. In 23 of the 43 cohort ALRI episodes in children aged 4 months or less specimens were cultured for C. trachomatis. No isolates were obtained. Paired sera from 144 cohort ALRI episodes were screened for antibody to C. trachomatis but no evidence of current infection was found.

4.4.2 Chlamydia pneumoniae (TWAR) infections were identified by immunofluorescence in 4 (2%) of the 189 children with ALRI who were tested. Three were aged 1-2 years and one was 4 years old. In 2 of these cases evidence of a concurrent aetiological agent was found: parainfluenzae type 3 in one and serological evidence of H. influenzae infection in the

other. 14 cases had evidence of previous infection by C. pneumoniae (stable antibody titres of between 32 and 256).

4.4.3 Fifteen (47%) of 32 patients with bacterial ALRI identified by serology or culture also had evidence of viral or mycoplasmal infection. Overall, 1 or more pathogens was identified in 76 (34.2%, 95% confidence interval 28%-41%) of the 222 ALRI episodes in the cohort children.

5. EPIDEMIOLOGY OF ALRI: INDOOR AIR POLLUTION

5.1 Levels of exposure to indoor air pollution

5.1.1 A summary of selected observational data related to the kitchens and families studied in the dry season and the time budgets are given in table 18. The results of the 24 hour suspended particles (RSP) measurements for all 18 kitchens in the dry season is given in table 19. There were no significant differences in the mean RSP measurements between the dry and wet seasons. In both case mean values were about 2,000 micrograms/ m^3, well above acceptable levels (WHO guidelines recommend a maximum of 100-150 micrograms/ m^3). In the dry season values ranged from around 600 to 3,500 micrograms /m^3, whereas in the wet season the range was greater (150 to 6,200 micrograms /m^3). Analysis of log-transformed data from the 2 seasons indicated that only about 30% of the total variance was caused by differences among the kitchens and about 70% was due to differences between days.[65,66] The mean levels of NO^2 recorded were 132 micrograms /m^3 in the dry season and 160 micrograms /m^3 in the wet season.

Table 18: Descriptive study of indoor air pollution in 3 of the study cohort villages: characteristics of kitchens and families studied

Characteristics	Mean	Standard deviation
Door and window area (m^2)	1.2	0.4
Ventilation gap between wall and roof (m^2)	2.9	2.5
Kitchen floor area (m^2)	11.0	3.1
Number of huts in the compound	7.4	5.8
Number of persons in the compound	19.2	13.3
Number of children in the compound participating in the ARI study	2.8	2.2
Burning time of cooking fire (hours)	7.8	2.2
Presence of mother near fire	4.1	1.5
Presence of child near fire (hours) [1]	1.8	1.2

Footnote [1] figures relate only to children who spent time in the kitchen, those that did not enter the kitchen were excluded.

Table 19: Descriptive study of indoor air pollution in the 3 of the study cohort villages: analysis of variance of measurements of suspended particles (RSP) in dry season

	Number	Mean	Standard deviation	Geometric mean[1]	Geometric standard deviation	Minimum	Maximum
All kitchens	36	2013	783	1860	1.5	675	3444
paired observations visit 1	18	2124	767	1992	1.5	1097	3444
visit2	18	1901	806	1736	1.6	675	3361
Tambasensan	12	2264	618	2184	1.3	1205	3444
Kundam-demba	12	1945	942	1733	1.7	675	3427
Badari	12	1828	757	1700	1.5	1026	3361

Footnote:Data from paired measurements in 18 kitchens (in micrograms/m^3)
[1] geometric mean given for comparison since RSP distribution is positively skewed and therefore this mean value is less influenced by very high values.

5.1.2 Analysis of covariance was performed (at the University of Wagenigen) with the logtransformed RSP and NO_2 concentrations as dependent variables in various models with the following characteristics as independent variables: village, burning hours, season, total ventilation area, kitchen area, number of huts in the compound, number of persons in the compound and number of children in the compound. Only burning hours and total ventilation area showed significant relationships with pollution levels. The intercept, regression coefficients, standard errors and confidence levels for the RSP analysis are given in table 20.

Table 20: Descriptive study of indoor air pollution in 3 of the study cohort villages: correlation between suspended particle concentration (RSP) and a number of local factors

	regression coefficient	standard error	confidence level
intercept	2.934	0.104	<0.01
village 1 [2]	0.171	0.095	0.08
village 2 [2]	0.032	0.013	0.61
burning hours	0.058	0.018	<0.01[1]
ventilation area	-0.048	0.018	<0.05[1]

Footnote:Analysis of covariance with logtransformed RSP measurement as dependent variable and the following as independent variables: village (3 levels), visit (2 levels), burning hours, season, total ventilation area, kitchen area, number of huts in compound, number of people in compound, number of children in compound.
: [1] burning hours and total ventilation area showed significant association with RSP levels
:[2] compared to village 3

5.1.3 The daily pollution pattern measurements, in the dry season, showed the highest concentrations under high burning conditions of the cooking fires.

This is important because it is the time when the women and children are likely to be near the fire and thus exposed to peak concentrations. The observations of the fieldworkers during the 24 hour measuring period for each kitchen showed that women spent an average of 4.1 and 3.3 hours attending the fire in the dry and wet seasons respectively. Children were recorded as being present in the kitchen on 61% and 74% of the recording periods (and for an average of 1.8 and 1.5 hours per day) in the dry and wet seasons respectively.

5.2 Exposure to indoor air pollution and ALRI

5.2.1 Although there was very little variation in findings between different houses with all kitchens showing similarly high levels of indoor suspended particles, observation of maternal behaviour patterns identified a subgroup of children with low exposure to indoor smoke. Combustion of biofuels is not generally required for space heating in The Gambia, so smoke exposure is predominantly from cooking fires. Since young children are usually excluded from cooking huts except when carried on their mothers' backs, two groups with substantially different exposure to smoke could be identified: those normally carried and those not normally carried by the mother whilst cooking.[75]

5.2.2 Carriage on the mother's back, together with parental smoking and a number of other factors which might influence incidence or severity of ARI (including age, sex, village of residence, ethnic group, socio-economic score, maternal education, nutritional indicators, vaccination status, number of visits to health clinic for illness episodes, an index of crowding, birth interval, type of mattress, and the presence of various animals kept close to the home) were related to maternal history of difficulty breathing in the subsequent 3 month period among a group of 280 children who were youngest in their family. As mentioned above (section 3.4.3) a maternal history of fast or difficult breathing was found to be predictive of ALRI.

5.2.3 Factors found to show a significant (5% level) association by univariate analysis were considered together in a multiple logistic regression model.[75] Both the carriage on the mothers' back and the number of cigarettes smoked by the father were found to be significantly associated with a subsequent episode of difficulty breathing (only very few mothers reported smoking regularly) as shown in Table 21.

Table 21: Comparison of presenting symptoms and clinical signs in cohort children with fever and either ALRI or Malaria during a 20 week period in the wet season

Signs	ALRI [3] (n=44)	MALARIA [3] (n=153)	Comparison
mean respiratory rate (/min)	60.6 (s.d. 9.6)	43.2 (s.d. 9.6)	$p < 0.001$ [1]
chest indrawing	26/44 (59%)	7/153 (5%)	$p<0.001$ [2]
Reported Symptoms			
cough	31/44 (70%)	48/153 (31%)	$p<0.001$ [2]
blocked nose	31/44 (70%)	96/153 (63%)	n.s.
fever	34/44 (77%)	143/153 (94%)	$p<0.01$ [2]
chest pain	21/44 (48%)	16/153 (11%)	$p<0.001$ [2]
"open chest"	11/44 (25%)	6/153 (4%)	$p<0.001$ [2]
noisy or difficult breathing	20/44 (45%)	18/153 (12%)	$p<0.001$ [2]
refusing food	18/44 (41%)	31/153 (20%)	$p<0.005$ [2]
diarrhoea	8/44 (41%)	25/153 (16%)	n.s
vomiting	16/44 (36%)	48/153 (31%)	n.s

Footnotes: for variable s with 2 or more levels, the odds ratio is given is relative to the first level.
[1] two way analysis of variance allowing for age
[2] mantel-haenszel chi-squared test allowing for age
[3] Comparison groups are (a) ALRI - febrile children with ALRI and radiological abnormalities but not parasitaemia;(b) Malaria - febrile children with parasitaemia but no clinical evidence of ALRI(see text for discussion).

5.2.4 This possible association was then studied further by directly comparing exposure (carriage of a young child on the mother's back) to ALRI episodes identified during the one year surveillance period. Possible risk factors for ALRI were explored in the two cross- sectional surveys at the start and end of the surveillance period. Of the 685 children who were included in the morbidity surveillance at some time, 587 were seen during at least one of the two surveys. The prevalence of various possible risk

factors for ALRI are presented in table 22. Analysis was restricted to episodes of ALRI which were associated with radiological abnormalities. This was done in an attempt to define ALRI more precisely (for example, ALRI clinically defined as in this study will contain some false positive cases and we have suggested above that malarial infection may be one such cause) on the basis that this might aid any understanding of mechanisms of risk association.

5.2.5 A child-weeks at risk approach was adopted with 23,122 child- weeks at risk studied.[75] The first two weeks after any episode of ALRI were omitted from both the numerator and denominator, to ensure that the child had recovered before returning to the cohort. The resulting data set was analysed first by calculating relative rates for each factor, stratifying for sex, age, season and village. The factors showing a significant (5% level) association in this way were considered together using a multiple logistic regression model, to relate the proportion of child weeks with disease to each risk factor, after having adjusted for all of the others. Interactions between variables were assessed by fitting a series of logistic regression models. The results of the multiple logistic regression model are given in table 23 in the form of adjusted odds ratios and 95% confidence limits for each factor which showed a significant relationship with disease risk. Parental smoking increases the risk of ALRI. For girls, but not boys, carriage on the mother's back and being part of a polygamous family increases the risk of ALRI. For boys, being part of a polygamous family has a protective effect.

Table 22: Prevalence of possible risk factors for ALRI among study cohort children: data from two cross-sectional surveys

Risk factor	Frequency (%) in study children (n=587)	n	%
Sex	Male	316	(53.8%)
	Female	271	(46.2%)
Age * at second survey	1 - 11 months	96	(16.4%)
	12 - 59 months	49	(83.6%)
Weight for age (NCHS standards)	<80% median (in both surveys)**	163	(27.8%)
	> = 80% median (in either)	422	(71.8%)
	Unknown	2	(0.3%)
Village+	1	86	(14.7%)
	2	135	(23.0%)
	3	169	(28.8%)
	4	19	(33.6%)
Socioeconomic index ⊕	Low	147	(25%)
	High	368	(62.7%)
	Unknown	72	(12.3%)
Number of wives of father	1	289	(49.2%)
	2 - 5	29	(50.8%)
Birth order	1st - 4th	319	(54.3%)
	5th - 15th	245	(41.7%)
	Unknown	23	(3.9%)
Number of siblings at school	0	173	(29.5%)
	1 - 10	41	(70.5%)
Number of siblings sharing bedroom	0 - 2	383	(65.2%)
	3 - 10	20	(34.8%)
Months to next oldest child	N/A (oldest)	101	(17.2%)
	9 - 30	237	(40.4%)
	31 - 80	235	(40.0%)
	Unknown	14	(2.4%)
Age started solids	1 - 5 months	191	(32.5%)
	6 - 24 months	262	(44.6%)
	Unknown, N/A	13	(22.8%)
Health card	Yes	421	(71.7%)
	No	145	(24.7%)
	Unknown	21	(3.6%)
Clinic visits per year	0	401	(68.3%)
	1 - 5	18	(31.7%)
Vitamin A intake (estimated from dietary questionnaire)	Low/medium	358	(61.0%)
	High	216	(36.8%)
	Unknown	13	(2.2%)
Grass mattress	Yes (in either survey)	531	(90.5%)
	No (in both)**	43	(7.3%)
	Unknown	13	(2.2%)
Carried regularly on mother's back while cooking	Yes (in both surveys)**	214	(36.5%)
	No (in either)	37	(63.5%)
Cigarettes father smokes per day	Does not smoke	283	(48.2%)
	0 - 5	166	(28.3%)
	6 - 10	57	(9.7%)
	11 - 20	81	(13.8%)

Footnote: *Age was included in the analysis as a "dynamic" variable, age at the time of weekly surveillance, categorised into two groups, 0 - 11 months and 12 - 59 months.
**Includes those who were only seen in one survey, ie., the data were missing for the other survey.
+ Ethnic group effects are largely confounded with village. The smaller of the study villages were combined for the analysis.
⊕Derived from number of a list of possible possessions owned.

Table 23: Observed association between episodes of ALRI and a number of possible risk factors: results of multiple logistic regression

Risk factor	Odds ratio (95% CI)
Father's smoking *(11-20/0-10 per day)	1.9 (1.1, 3.4)
Carriage on mother's back when cooking *(yes/no)	
Boys	0.5 (0.2, 1.2)
Girls	1.9 (1.0, 3.9)
Number of wives of father **(2-5/1)	
Boys	0.5 (0.2, 0.9)
Girls	2.4 (1.1, 5.3)

*p<0.05

**p<0.001.

Footnote:Relative rates for a number of possible risk factors (see table 22) were calculated, stratified for age, sex season and village and those showing a significant association in this way were considered in the multiple logistic regression model.

6. MATERNAL KNOWLEDGE, ATTITUDES AND PRACTICES

6.1 Study population

The study populations consisted of women from a number of different tribal groups: 89% were Mandinka, 9% Fula, and 2% were from other ethnic groups. All but 8% had been born and brought up in the district of current residence. 80% of the women were between 20 and 40 years, and about 70% were the "first" wife of their husband. Only 2% had received any primary education and only 6% could read English, French or Arabic. These women came from communities which rely on subsistence farming, with families often owning numerous livestock but having only a small income from the sale of groundnuts and vegetables and hence few household possessions.

6.2 Perception of "open chest" and "pneumonia"

6.2.1 Table 24 shows the frequency of symptoms and signs which mothers reported to be present in "pneumonia" (in practice this clinical condition was described to mothers in terms that were locally understood - see glossary). Fast breathing, difficult breathing and to a lesser extent chest pain (since the term is less specific), are terms that reflect an appreciation of respiratory distress and are therefore the most important symptoms for mothers to recognise and act upon.

Table 24: "Pneumonia" in children: symptoms and signs most commonly reported by mothers		
Symptom/sign	**Mothers from study cohort village (n=150) %**	**Mothers from Dampha Kinda (n=50) %**
Fever	33	42
Chest/side pain	48	56
Cough	15	28
Difficulty breathing	10	20
Fast breathing	3	4
Fresh cold	1	0
Cold feet/hands	15	16
Feeling cold/shivering	15	4
Don't know	18	12
Footnote: The clinical condition of "pneumonia" was described to the mothers in terms that they understood and they were then asked which symptoms and signs were associated with this condition.		

6.2.2 Table 25 shows the frequency of symptoms and signs which mothers reported to be present in "open chest" ("open chest" being the direct translation into English of the Mandinka and Fula terms used by mothers).

Table 25: "Open chest" in children: symptoms and signs most commonly reported by mothers		
Symptoms/sign	**Mothers from study Cohort village (n=150) %**	**Mothers from Dampha Kinda (n=50) %**
Cough	20	10
Fast breathing	14	10
Side/chest pain	43	40
Difficulty breathing	11	12
Fever	10	26
Crying	9	6
Wheeze	1	0
Indrawing	1	0
Jumping chest	9	4
Grunting	3	10
Don't know	31	28

6.2.3 Mothers did not report the presence of nasal flaring and only 1% of mothers referred to chest indrawing as a sign of respiratory distress.

6.2.4 Fast breathing was recognised as a sign of serious illness by 95% of women. Illnesses which were were thought by mothers to cause fast

breathing are shown in table 26. Appropriate responses ("pneumonia", "open chest", chest pain, or asthma) were given by 92/150 (61%, 95% confidence interval 54%-69%) of the mothers in the study cohort villages and 36% (95% confidence interval 23%-51%) of mothers from Dampha Kunda. 35/150 (23%, 95% confidence interval 17%- 30%) of mothers from the cohort villages gave incorrect responses such as fresh cold or cough alone compared to 9/50 (18%, 95% confidence interval 9%-31%) of mothers from Dampha Kunda.

Table 26: Illnesses or conditions which mothers report as causing rapid breathing

Illnesses or conditions	Mothers in study cohort village (%)	Mothers in Dampa Kunda (%)
"Pneumonia"	18	30
"Chest pain"	30	4
"Open chest"	2	0
Asthma	11	2
Coughing	19	16
Fever	7	8
Fresh cold	5	2
Malaria	0	2
Don't know	35	40

Footnote: Illnesses reported are translations of the terms used by the mothers, either direct translations as in "Chest pain" or as an interpretation of the concept expressed by the mother (where no direct translation is possible) as in asthma.

6.2.5 43% of the mothers thought that "pneumonia" was caused by cold weather and 16% that it was caused by getting wet in the cold season. No mothers expressed any ideas relating to either germ theory of disease causation or to the concept of transmission of some infectious agent. In contrast, most mothers thought that "open chest" was caused by some traumatic event e.g. a guardian lifting a child by one arm; or by a child falling or coughing excessively or lifting heavy objects.

6.3 Perceived symptoms of severe respiratory illness

Mothers were asked about which symptoms they considered to be indicative of serious illness in a child with a cough. Only 9% of women from the cohort villages and 6% of women from Dampha Kunda mentioned fast breathing as an important sign. Thus we have seen above (see section 3.4) that mothers' reports of the presence of fast breathing are predictive of the presence of ALRI, but find now that mothers do not appear to consider

this to be an important sign of serious illness in a child with a cough. 40% of women reported that signs of systemic upset in a child with a cough would lead them to believe that the illness was a serious one.

6.4 Home management of ARI episodes

6.4.1 More than 90% of mothers recognised a need for treatment of "pneumonia" in their children. 77% of women replied that "pneumonia" should be treated with either medicines or injections. Many other "Western" and traditional treatments were also mentioned.

6.4.2 About 60% of mothers said that one of their children had had a cough in the last six months. Of these mothers, 50-60% reported that they treated their child's cough at home before seeking advice. Local herbal remedies were the predominant form of home treatment for cough with more than 30 different types of leaves or roots being mentioned; very few other treatments were reported. No adverse practices were identified. This is very different to the picture in urban areas in The Gambia where the most common home treatments include cough syrup, aspirin, paracetamol, mentholatum balms, tepid sponging and a few local dried leaves which are bought in the market (unpublished data).

6.4.3 Those mothers who sought treatment outside the home for the episode of cough mentioned that the severity of the cough (reported by 87% of mothers) and the presence of fever (reported by 61% of mothers) were the major reasons why further advice and treatment were sought. Only 1% of mothers mentioned wheeze as a reason for seeking treatment.

6.4 81% of mothers who sought treatment for an episode of cough in their child did so in the first 3 days of the ARI illness.

6.5 Access to communication channels for Health Education

We attempted to identify routes through which mothers' understanding of ARI and its management might be modified. 41% of mothers had access to a radio and of these 53% listened to health education programmes. 87% of mothers attended meetings (agricultural, political, health, social and general).

7. ANTIBIOTIC TREATMENT OF COMMUNITY-ACQUIRED ALRI

7.1 Description of treatment groups

7.1.1 Children were recruited to the trial from the community-based study and from Basse health centre as described above (see section 2.12). Although 43% of children reported vomiting and 28% reported refusing to breast feed or to take food, only 5 (3%) were excluded from the trial due to an inability to take oral treatment.

7.1.2 Sequential allocation resulted in good matching of the children in the two treatment groups. Sixty six children were allocated to group A (41 boys and 25 girls) and 68 to group B (38 boys and 30 girls). The mean age was 22 months in group A, and 21.8 in group B; with 30% and 36% under the age of one year respectively. There were no statistically significant differences between the two groups in any of the symptoms, signs or laboratory findings considered, including length of illness, mean respiratory or heart rate, mean temperature, presence of auscultatory or radiological changes consistent with pneumonia, or blood culture isolation rate (table 27).

Table 27: Trial of two regimens for the treatment of ALRI: comparison of children recruited by sequential allocation into the two groups (A: Cotrimoxazole and B: Procaine penicillin plus ampicillin)

Centre of recruitment	Group A cotrimoxazole (n=66)	Group B procaine penicillin + ampicillin (n=68)	Difference (difference;95% confidence interval)
M.R.C. field station	53 (80%0	54 (79%)	
Basse health centre	13 (20%)	14 (21%)	
History			
cough reported	66 (100%)	68 (100%)	
mean days of cough	5.4 (sd 5.1)	4.5 (sd 2.6)	-0.89; -2.2 to 0.5
fever reported	63 (95%)	63 (93%)	-2.8; -5.2 to 10.8%
mean days of fever	4.6 (sd 4.0)	4.4 (sd 4.0)	-0.2; -1.5 to 1.2
mean days difficulty breathing	5.3 (sd 7.6)	4.6 (sd 4.3)	-0.7; -2.8 to 1.4
vomiting reported	25 (37%)	33 (49%)	11%; -27.3 to 6.0%
mean days refusing food	1.0 (sd 2.1)	1.3 (sd 2.3)	0.3; -0.4 to 1.0

Footnote: study children comprised those with ARI and either chest indrawing or nasal flaring recruited from the study cohort (n=107) or Basse health centre (n=27)

7.1.3 Children recruited from the health centre had a higher mean respiratory rate per minute, compared with children recruited during community surveillance (62.6 versus 52.4) and a higher mean heart rate per minute (150.1 versus 117.5). A higher proportion of health centre cases had chest

x-ray changes consistent with pneumonia (70.0% versus 28.8%), x-ray changes of lobar consolidation (30.0% versus 8.2%), and a positive blood culture (14.8% versus 0.9%). All these differences are statistically significant at the 5% level. Although all children satisfied the conditions for ALRI severe enough to require hospital admission by WHO criteria (cough with the presence of chest indrawing), those identified at the health centre constituted a more seriously ill group.

7.2 Response to treatment

Only five children (3.7%) were admitted to the health centre, two in treatment group B, and three in group A. Two children died, both in group B, an overall mortality of 1.5%. There were no significant differences between the two groups in terms of final outcome at two weeks follow up as assessed either by the mothers or the clinician. The recordings performed single blind by the field workers in the first week of follow-up showed no significant difference between the 2 groups (table 28). These results held true when the the cohort and health centre cases were analysed separately. The 95% confidence intervals of the differences between all of the parameters assessed include the possibilities of a 10% worse result to a 23% better result in the cotrimoxazole group.

Table 28: Trial of two regimens for the treatment of ALRI: comparison of outcomes at follow-up in the two groups (A: Cotrimoxazole and B: Procaine penicillin + ampicillin)

Mothers' assessment at 2 weeks (n=131)	Group A Cotrimoxazole (n=66)	Group B Procaine penicillin + ampicillin (n=68)	Difference difference; 95% confidence interval	
No continuing problem	56/66 (84.8%)	56/65 (86.2%)	-1.4%;	-13% to 11%
Cough better	62/66 (93.9%)	61/65 (93.8%)	0.1%;	- 8% to 8%
Breathing difficulty better	63/66 (95.5%)	62/65 (95.4%)	0.1%;	- 7% to 7%
Appetite better	65/66 (98.5)	62/65 (95.4%)	3.1%;	- 3% to 9%
Clinician's assessment at 2 weeks (n=131)				
Outcome at two weeks same/worse	5/66 (7.6%)	5/65 (7.7%) [1]	-0.1%;	- 9% to 9%
Incomplete recovery/further treatment given	1/66 (1.5%)	2/65 (3.1%) [1]	-1.6%;	- 7% to 4%
Field workers' assessment in the first week (n=101)[2]				
Reduction in respiratory rate	46/51 (90.2%)	44/50 (88.0%)	2.2%;	- 10% to 14%
Afebrile or reduction in temperature	41/51 (80.4%)	37/50 (74.0%)	6.4%;	- 10% to 23%
Indrawing no longer present	44/51 (86.3%)	41/50 (82.0%)	4.3%;	-10% to 19%

Footnote: [1] We were unable to follow-up 3 children in group B at 2 weeks thus data from these 3 children are not available for presentation here; subsequent follow-up confirmed a successful outcome without requirement for a change in treatment.

[2] field worker observations at seven days (5-9 days) were available only in 101 (75%) of episodes (77% of episodes in Group A and 73% of episodes in group B), the remainder of episodes were followed up either earlier than 5 days or later than 9 days after the start of treatment.

8. DISCUSSION

8.1 Prevalence of ARI

8.1.1 Surveillance of the cohort resulted in data being gathered from a total of 685 children (with an average of approximately 491 children examined each week). In all 25,028 parental interviews followed by examinations of their children took place over the one year period. Symptoms of acute respiratory infections (ARI) were very frequently reported by the mothers of the cohort children. Blocked or runny nose was reported in 52% and cough in 20% of all interviews.

8.1.2 Mothers reported that their children had a new episode of a respiratory illness on 18% of the weeks that they were interviewed. If we assume that these episodes last 4-6 days then this would be consistent with an incidence of ARI of about 10-11 episodes per year. This crude estimate is the best measure of ARI incidence from this study since the weekly morbidity data showed that cough, runny nose and other ARI symptoms were extremely common and the data (daily records of the presence or absence of specific symptoms over the one year period) could not easily be divided up into discrete episodes. Attempts to do this yielded results which were very sensitive to small changes in episode definition and were thus not considered to be useful. In these circumstances prevalence data on ARI symptoms may be the most meaningful descriptors.

8.1.3 Even making allowance for the above difficulties, it is clear that ARI symptoms are very commonly reported in this population as can be seen from the daily reports of cough for each cohort child (see appendix d). Recent reviews of the epidemiology of ARI and WHO publications have suggested that ARI symptoms are equally common in both developing and developed countries. The results from this study do not support these statements. The burden of illness from ARI would appear to be substantially greater in this rural Gambian community than has been described in community-based studies in developed countries.[77,78] Data from Papua New Guinea have also shown very high prevalences of ARI symptoms such as runny or blocked nose. Further work is required to improve available methodologies for the estimation of ARI episodes and further investigation will be required to assess whether these sypmtoms are primarily due to ARI or, in part, as a respponse to some environmental factors (for example smoke exposure).

8.2 Incidence of ALRI

8.2.1 The incidence of acute lower respiratory infections (ALRI), defined as being present if a child with cough also had any one of the following signs or symptoms: fast breathing (as defined by WHO at the time of this study - 50 breaths per minute or above) , chest indrawing, nasal flaring, wheeze, stridor, or severe systemic upset (such as inability to drink), which was documented in the study children was 468 episodes per 1,000 children under 5 years of age per year. Since stridor and wheeze were uncommon in this study population during the period of surveillance it is suggested that these criteria identified a group of children with ALRI principally with the clinical conditions of bronchiolitis and pneumonia. All children with ALRI were examined by chest x-ray and an incidence rate for lobar pneumonia of 50 per 1,000 per year. This can be considered to be a minimum figure for this condition in this population (as discussed in section 3.3.2).

8.2.2 These incidence rates are the first to be published from a rural community based longitudinal study in Africa. Due to the epidemic nature of ARI, estimates from cross-sectional studies are likely to give inaccurate results. These incidence rates are among the highest yet described in any community.[76] and suggest that by the time that rural Gambian children reach the age of 5 years, almost all have had one episode of ALRI severe enough to produce chest x-ray changes and that about one in four has had an episode of lobar pneumonia. The annual ALRI incidence rate of 468/1000 children 0-4 years in this study is more than 10 times greater than incidence rates in developed countries (for example the annual ALRI incidence rates in two classical studies in North Carolina and Washington State in USA were 30-40/1000 children 0-4 years of age).[77,78]

8.2.3 The only other published data on ALRI incidence in a rural developing country community are from the Asaro valley in Papua New Guinea where they found annual incidence rates of 1074/1000 infants and 90/1000 children 1-4 years.[79,80] Our data from Basse show similarly very high incidence rates in infancy 700/1000 infants, but a markedly higher rate of 370/1000 in older 1-4 year old children. These extremely high incidence rates in infancy draw attention to the fact that ALRI is principally a disease of very young children. This is supported by other studies which have shown that about 70% of all ARI mortality occurs in the first year of life. The reason for the difference in rates in 1-4 year old children is not clear

but one possible explanation is that a proportion of the episodes in this age group (in Basse but not in the Asaro valley) represented episodes of clinical malaria associated with fast breathing and thus classified as ALRI (and so increased the observed incidence rate in this age group). Four findings would support this hypothesis. Firstly we have shown that fever is associated with raised respiratory rates. Secondly we have shown that malaria and interstitial infiltrates on chest x-ray are associated and have suggested that this may be due to pulmonary pathology from malaria. Thirdly, the incidence of malaria in the Gambia is much greater in 1-4 year old children compared to infants. Fourthly, malaria is not found in the Asaro valley in the highlands of Papua New Guinea. This hypothesis is currently being further investigated in Basse and data from this study presented at a recent WHO meeting (but as yet otherwise unpublished) would appear to be supportive.[72]

8.2.4 It should be remembered however that substantial year to year variation is likely to exist. This is well illustrated by the fact that there was no epidemic of RSV bronchiolitis during the year of surveillance (an epidemic having occurred immediately before the surveillance began). Annual RSV epidemics have been documented in urban areas in every country which has studied this infection and is always the major viral cause of ALRI. It is likely therefore that the ALRI incidence rate in this area would be greater than the figure found in this study in years in which RSV epidemics occur.

8.2.5 The incidence of ALRI was highest in the first six months of life and fell steadily thereafter. The incidence figure for ALRI in infants was 722 episodes per 1,000 infants per year, whereas the incidence rate in children aged 1-4 years was 374 episodes per 1,000 children aged 1-4 years per year. This age differential is not as marked as that found for mortality from ALRI. The incidence rate in infants was considerably greater in the wet season than in the dry. This difference was less marked (and the difference not statistically significant) in older children.

8.2.6 Inevitably the recorded incidence rates are sensitive to a number of study features. Firstly the definitions used are critically important. Many previous published reports have been of limited interest since subjective signs such as "wet cough" and "breathing difficulty " were employed to define episodes of ALRI. This study defined ALRI precisely by a set of relatively objective and reproducible clinical signs. These were the same as those

adopted by the BOSTID group of investigators [81] in their multicentre study in several developing countries and is consistent with the classification system adopted by WHO (who term this group "pneumonia" since this term is more easily understood by mothers and health workers alike). Since all episodes of ALRI identified by the field workers were confirmed by the study physician it is likely that the ALRI incidence rate is a minimum figure (there may have been other children not identified by the field workers whom the study physician had no opportunity to examine). This effect may, however, be small since in this community that made little use of government health facilities at the time of the surveillance (due to a shortage of drugs in the Basse health centre) it is likely that any child with ALRI who was missed would simply be identified at a later stage when more obviously ill.

8.2.7 Secondly, this study set out to specifically study ALRI. It is known that the frequency of home visiting effects recorded incidence rates with increasing frequency of visits yielding higher incidence rates by as much as a factor of 2. A recent WHO meeting to discuss these methodological issues, however, endorsed the weekly visiting schedule which we adopted as being the most useful for longitudinal studies of ARI.[46]

8.2.8 Thirdly, recorded incidence rates are considerably lower in studies which ascertain cases in clinic rather than home settings due to the fact that a proportion of mothers will choose not to attend for clinic treatment. Home visiting is clearly more labour intensive but preferable.

8.2.9 Fourthly, most longitudinal studies exhibit the phenomenon of incidence rates falling over time. It is not clear whether this is due to a real decrease in incidence or to field worker or maternal fatigue with the study. This effect however is generally seen most clearly in studies lasting 2 or 3 years and in less obvious in shorter studies such as the present one.

8.3 Clinical features and diagnosis of ALRI

8.3.1 In Africa, most children who present to health services with ALRI are first seen by a peripheral health worker. It is, therefore , very important that staff in this category can diagnose ALRI in children and manage the episode correctly. The two major issues faced by peripheral health workers are firstly the identification of children with respiratory symptoms who require antibiotic treatment and secondly the identification of more severely ill

children who require immediate referral to a health centre or hospital for in-patient treatment. For this purpose, WHO had devised a set of management criteria for ALRI based on the recognition of simple clinical signs such as raised respiratory rate and chest indrawing.

8.3.2 WHO recommended that children with ARI who have chest indrawing should be referred for hospital treatment and those who have no chest indrawing but who are breathing fast (greater that 50 per minute for children under 5 years of age) should be given out-patient antibiotic treatment. In addition, children with ARI who are unable to take oral fluids reliably should be referred for in-patient treatment. [82] These recommendations represent the result of a consensus of informed opinion reviewing a small number of predominantly hospital-based studies.[69,83]

8.3.3 However, it has been pointed out that clinical experience of hospital practice is not an adequate basis for the development of primary health care plans.[84] Community studies are therefore required to assess the validity of WHO criteria. To validate these guidelines for The Gambia, clinical observations made by field staff on children with an ALRI seen in their village during the community survey were compared with the results of examination of these children by a paediatrician and with chest x-ray findings. These analyses confirmed that a respiratory rate of 50 or more per minute was a valid (sensitive and specific) indicator of ALRI in children under one year of age but that a respiratory rate of 40 per minute or more had a better discriminatory value for older children. This is in agreement with data presented from South India.[85] Thus, the adoption of simple clinical signs have been found to be both sensitive and specific indicators of the presence of ALRI in young children. Subsequent to this study and responding to the findings from Vellore, India and Basse, WHO set up two studies in Swaziland and the Philippines which confirmed the improved sensitivity and specificity of the 50/40 criteria over the original criteria.[86] These have now been adopted as the revised WHO recommendations. It should be noted that neither this nor the South India study had the power to consider the under 2 months age group. This group requires separate investigation since different respiratory rate thresholds will apply to this group.

8.3.4 The value of simple clinical signs in predicting <u>severe</u> illness requiring hospital treatment was investigated also. Chest indrawing (intercostal,

subcostal or lower chest wall) was found in 62% of all episodes of ALRI in this study. It was clear from this finding that there are insufficient rural paediatric in-patient facilities in The Gambia to admit all children with ALRI who show chest indrawing defined in this way, as was recommended in WHO guidelines at that time. This finding was subsequently confirmed by other investigators [86] and WHO changed the definition of indrawing so that it was more precisely defined as lower chest wall indrawing (and not intercostal indrawing). This has meant that children with minor degrees of intercostal indrawing, not uncommon in thin children or in those with blocked noses, are no longer misclassified as requiring hospital admission.

8.3.5 The presence of lobar pneumonia (x-ray opacification in at least one entire lobe considered to be due to consolidation) was considered to be an objective indicator of severe disease. The results of this investigation confirmed that bronchial breath sounds or decreased air entry on auscultation, and the presence of grunting are very specific signs of lobar consolidation. However, their low sensitivity (especially in infants), and the fact that they are difficult signs to teach to non-medical staff limit their practical usefulness. In infants, a high fever (greater than 38.5^{o} C), vomiting, and refusal to breast feed were the signs that best predicted the presence of lobar consolidation. In 1-4 year old children the most valid signs were a high fever (greater than 38.5^{o} C) and a respiratory rate above 60/minute, with the presence of both signs together further increasing the positive predictive value. It is recognised that lobar pneumonia does not include all forms of ALRI which have high mortality and thus could be called severe. Nevertheless in the pre-antibiotic era this condition had a high mortality in children. With the current availability of pulse oximetry enabling the identification of children with ALRI who have significant oxygen desaturation the consideration of the clinical presentation of children with severe ALRI should be extended to include children with desaturation since they also show increased mortality. This issue merits further additional study so that the group of children with ALRI who have the highest case fatality rates can be more accurately identified.

8.3.6 Mortality is particularly high in the first two months of life. This study yielded little useful information on this important group (due to small numbers in this age group in the study cohort). This group will require separate independent study as a specific group in its own right.

8.4 ALRI and malaria

8.4.1 We found that malaria and ALRI occurred together more often than would be expected by chance.[61] There are several possible explanations for this finding. Clinical malaria may predispose some children to ALRI, perhaps by influencing immune mechanisms. However, other studies in The Gambia[87] have not a reduction in respiratory symptoms among a group of children substantially protected from malaria by means of chemoprophylaxis. Conversely, ALRI may predispose to malaria, or allow subclinical parasitaemias become patent. However we have shown here that children with ALRI do not have parasitaemia more often than other children. Thirdly, malaria may itself may, in some cases, present with respiratory signs and symptoms. The first published recognition of this association came from this study[61], however other investigators have since confirmed this finding and provided further more complete evidence to support this hypothesis.[71,72]

8.4.2 Isolated case reports of acute pulmonary oedema associated with malaria have been made on several occasions[88,89], mostly in non-immune adults. Increased cytoadherence between parasitised red blood cells and pulmonary endothelial cells has been suggested as a cause of respiratory distress in malaria. [90] The occurrence of pulmonary complications in semi-immune African children is less certain. Nevertheless interstitial changes similar to those reported by Godard and Hansen [89] were found in all 4 children in this study who had clinical malaria and ALRI simultaneously. Similar changes were seen in only 10/35 (29%) of children with ALRI associated with radiological abnormalities not associated with malaria ($p<0.005$, Fisher exact test).

8.4.3 In the absence of information on the incidence of radiological abnormalities in normal Gambian children some caution is needed in assessing the likely significance of our findings, but a growing body of opinion now supports such an association as recently discussed at a WHO meeting to better understand these issues.[72]

8.4.4 We have compared the clinical presentations of children with malaria and those who were febrile due to ALRI. There is considerable overlap in the clinical pictures such that the clinical presentation alone would not greatly assist a rural health worker to distinguish between these two important conditions.

8.4.5 It will be important to study this relationship once again in the light of the above change (see section 8.3.3) in WHO guidelines since there will be a higher proportion of children aged 1-4 years with malaria who have a respiratory rate above 40 breaths per minute. There are a number of mechanisms by which malaria might raise the respiratory rate including by means of fever, low haematocrit, acidosis or due to sequestration of malaria parasites in pulmonary blood vessels. This study has presented evidence for a modest effect of temperature on respiratory rate (a rise of about 2.5 breaths per minute for each rise in 1^0C). It will be important to study the inter- relationships of these factors in more detail.

8.4.6 Finally the results of this and subsequent (unpublished) work in The Gambia together with findings in Malawi [71] gave fresh impetus to the issue of the antimalarial efficacy of cotrimoxazole. Evidence is accumulating that this drug is an effective antimalarial in young children.[72] This is important since this antimicrobial drug is effective against the major two bacterial causes of pneumonia in The Gambia.

8.4.7 These findings are important since cough and fever are two of the most common presenting symptoms in young children and malaria and ALRI are the two most common causes of death in young children in The Gambia. It will be important in African settings that peripheral health workers be trained to manage these children correctly based on clinical signs only and without recourse to laboratory investigations (often not available outside hospitals) and that management guidelines ensure adequate treatment of both conditions in situations where it is very difficult to tell them apart. In a child presenting with ALRI and fever a 5 day course of cotrimoxazole will give adequate treatment of both conditions.

8.5 ALRI and nutritional status

8.5.1 Protein-calorie malnutrition is a condition resulting from inadequate intake or utilisation of calories or protein in the diet. However, diets deficient in calories or protein are also commonly deficient in vitamins and minerals, and these specific deficiencies may in themselves have an effect on disease outcomes such as ALRI. Such malnutrition can be assessed in various ways. In this study anthropometric indices were used with measurements compared to a well- nourished international reference population (NCHS). Weight-for-age z- scores (the difference between the child's measurement

and th NCHS median value is divided by the standard deviation for the NCHS population) were used to define nutritional status when exploring the relationship with ALRI incidence. However this classification, although the most frequently used historically, does not distinguish between acute or present and chronic or past malnutrition. Finally since it has been shown that an episode of ALRI results in weight faltering in Gambian children, [91] any observed association between nutritional status and ALRI incidence will be complex to interpret.

8.5.2 We were unable to show any effect of nutritional status on the incidence of ALRI. At first this may seem surprising since the much higher incidence of ALRI in developing countries than that in developed countries might have reasonably been assumed to be, at least in part, due to nutritional differences between these two groups.

8.5.3 Observational studies have consistently demonstrated a relationship between anthropometric indices of child growth and mortality risk, with very high risks in children of poor nutritional status and with the data remaining consistent even after accounting for confounding, self selection biases and reverse causality.[92,93,94,95,96] A more limited series of studies suggests that this is also the case for ARI-specific mortality.[97,98]

8.5.4 However community-based studies do not demonstrate an important effect on ALRI incidence. Only studies from the Philippines[81], Papua New Guinea[99], Guatemala[100], and Uruguay[101] have adequately defined nutritional status, the presence or absence of ALRI and evaluated their association. A prospective community-based study in Philippines reported that children between -2 and -3 z-score weight-for-age had a relative of 1.2 for ALRI. In Papua New Guinea, children 0-17 months old had a relative risk of 0.8 whilst older children had a relative risk of 2.3. Similarly in Uruguay children 0-17 months had no increase in risk whilst children 18-35 months had a relative risk of 2.7. The Guatemala study observed no increased risk for ALRI among children below the 10^{th} centile weight-for-age.

8.5.5 The data from the Basse study taken together with data from the above published studies show that malnutrition appears to have a strong influence on ALRI severity (hospital admission rates and case fatality rates[102,103]) and mortality but a more uncertain and weaker influence on ALRI

incidence.[104] It is possible therefore that the major effect of malnutrition on ALRI mortality may be mediated through increasing the severity and case fatality rate of ALRI episodes in children rather than by greatly increasing the risk that young children will have an episode of ALRI.

8.5.6 These results, however, should be interpreted carefully since we are using anthropometric indices as a measure of nutritional status and it is known that these are crude measures of undernutrition. These indices describe a range of nutritional problems and the mechanism of any increased risk with respect to undernutrition is not well understood. It is therefore still possible, indeed likely, that some specific aspect of undernutrition may be an important determinant of ALRI incidence but this is not clearly shown in crude analyses making use of weight-for-age indices. Finally, it is possible that, had sufficient data been available to permit an adequate analysis using weight-for-height z-scores, an association between ALRI incidence and wasting may have been found.

8.6 Aetiology of ALRI

8.6.1 It is now recognised that most children dying from ARI in developing countries have bacterial pneumonia. However almost all of the studies that have reported on the aetiology of pneumonia have been hospital-based.[30,31,32,33,34,35,41] It is important that these findings be repeated in community settings. This will be important both to support the current strategy of early antibiotic treatment of pneumonia, and to provide data for the design of vaccine trials of the new generation protein conjugate vaccines against pneumococcus and Haemophilus influenzae type b.[105,106]

8.6.2 Such epidemiological studies are severely limited by the insensitivity of currently available methods of bacterial diagnosis. Since bacterial and viral ALRI cannot be distinguished on clinical or radiological grounds, laboratory confirmation of bacterial ALRI is required. Culture of pharyngeal swabs is misleading and the insensitivity of blood culture in the diagnosis of bacterial infection of the lower respiratory tract is well described. Children hospitalised with severe pneumonia have detectable bacteraemia in only 10 - 30% of cases; in less severe pneumonia which is treated on an out-patient basis the yield is much less.

8.6.3 Clearly, alternative techniques to blood culture are required. Methods commonly employed are measurement of the serological response to

bacterial invasion and detection of bacterial antigen in body fluids. While these techniques have yet to be demonstrated to be reliable enough for clinical management of out-patients, aetiological studies using these techniques have suggested that bacterial pneumonia in children may be more frequent than previously suspected. [107,108,109, 110,111]

8.6.4 The two most common bacterial respiratory pathogens are S. pneumoniae and H. influenzae.[41] Detection of the capsular polysaccharide antigens of these two organisms using counterimmunoelectrophoresis or latex agglutination in serum and urine of patients with ALRI has received most attention. The majority of studies have been in hospitalised patients with severe pneumonia to allow the sensitivity and specificity of the methods to be assessed by comparison with the results of culture proven bacterial pneumonia. While the detection of Haemophilus influenzae type b antigen has been shown to be fairly accurate the occurrence of both false positive and false negatives are common in tests for pneumococcal antigen.[107,108,109,110,111] Careful specimen preparation by boiling and filtering has been shown to reduce the incidence of false positive reactions.[112] We have demonstrated (not described in this report) that the use of individual type-specific latex preparations may enhance the sensitivity of the latex test for pneumococcal antigen to around 75% in patients with severe pneumonia.[54] An antibody test to pneumococcal pneumolysin (a haemolytic protein of pneumococci) has recently been shown to detect approximately 80% of pneumococcal infections in adults.[113] The sensitivity of the assay in children is unknown although we have found a rising titre to pneumolysin in 11 (79%) of 16 culture proven cases of pneumococcal pneumonia in children (unpublished data).

8.6.5 This study represents the first community based study of the aetiology of ALRI in a rural area of a developing country. Aetiological data from such areas are important since the majority of deaths from ALRI occur in rural areas. The results of the study highlight the difficulty of establishing the aetiology of pneumonia in paediatric community studies. Although a virus was cultured from 19% (95% confidence interval 14%-24%) of ALRI episodes occurring in cohort children, a virus was also recovered from 14.6% (95% confidence interval 8%-23%) of 96 control children. Furthermore no particular group of viruses was recovered significantly more often from children with ALRI than from control children. However

the marked rise in ALRI incidence from an average of 3-4 per week to a mean of 14 per week in weeks 21-23 is likely to be attributable, at least in part, to the increased activity of one or more viruses such as influenza A virus or adenovirus type 6.

8.6.6 The process of freezing specimens for virus isolation prior to culture may have had some effect on the virus isolation rate but it is unlikely that this was responsible for the notable absence of RSV infections during the study period. The good agreement between the serology and virus isolation results with respect to the epidemiological and temporal succession of respiratory virus infections suggests that the culture results are an accurate representation of the incidence and pattern of respiratory virus infection that occurred in the study villages during the surveillance period. Moreover, during an outbreak of RSV infection which occurred 6 months before formal surveillance of the cohort began, RSV was isolated using identical culture techniques from 25 (81%) of 31 children identified as being infected with the virus by indirect immunofluorescence. Since RSV is considered to be a particularly labile virus, it is likely that culture for the other respiratory viruses during the study was of similarly high sensitivity.

8.6.7 The absence of an outbreak of RSV infection during the one year surveillance (and for a one year period following this) is of interest. Seasonal epidemics of RSV infection, predominantly in the winter and early spring months, are well recognised in temperate climates. While non-epidemic years have been observed, these are unusual. It is possible that the epidemiology of RSV infection is different in urban and rural areas. This phenomenon has been described for measles virus. [114] Regular annual outbreaks of RSV activity has been almost universally described from many studies in urban areas. Our results suggest that more isolated rural communities may only experience activity every 2 or 3 years. It has been suggested that the force of infection and the size of the infecting dose are important determinants of mortality from measles.[115,116] If this were true for RSV infection it may be that irregular epidemics could lead to more serious disease in the epidemic years in rural communities. The epidemiology of RSV is not well described in rural communities in developing countries and merits further study.

8.6.8 A high proportion (about 30%) of both cases of ALRI and controls were found to be excreting CMV from their respiratory tract so it is not possible

to ascribe a specific aetiological role to this virus with respect to ALRI. Similar results have been reported previously from The Gambia and other countries where the seropositivity rate in mothers is high. [117,118,119,120]

8.6.9 Neither M.pneumoniae nor C. trachomatis appeared to be important causes of ALRI in this population. Using both culture and serological techniques we found no evidence of C. trachomatis infection in any of the 29 infants under 4 months of age examined. However it is possible that a greater number of M. pneumoniae infections would have been identified in older children if a combination of both culture and serological techniques had been used.[121]

8.6.10 The limited data on infection by C. pneumoniae, a recently described Chlamydia organism, has indicated that the agent is associated with outbreaks of pneumonia in young adults [122] and military recruits [123]. However C. pneumoniae can also cause pneumonia in young children, particularly in developing countries where there is some evidence that the organism causes infection at an earlier age. [124] In this study C. pneumoniae was identified by serology in 4 (2%) of the 189 ALRI episodes tested. In 2 of the episodes C. pneumoniae was the only agent identified. The remaining ALRI episodes were subsequently found to have consolidation on chest x-ray and were associated with a parainfluenza type 3 infection and a rise in H. influenza antibody. This is consistent with the observation [123] that C. pneumoniae infections alone tend to cause a mild illness but in combination with other infections more serious and possibly more prolonged illness may result.

8.6.11 In this study a pathogen was identified in 76 (34.2%, 95% confidence interval 28%-41%) of ALRI episodes among cohort children. Evidence of infection with a bacterial pathogen, most commonly Streptococcus pneumoniae or Haemophilus influenzae was obtained in 32 (14.4%) of these episodes. Viral agents were cultured from 42 (19%) of ALRI episodes but also from 14 (14.6%) of control specimens.

8.6.12 Mixed infections with bacteria and viruses were frequently found (47% of episodes of ALRI in cohort children in which a bacterial aetiology was identified also showed evidence of concurrent viral infection). This is consistent with the hypothesis that an initial viral infection may predispose to subsequent bacterial infection and underlines the fact that the recovery of

a respiratory virus in a child with ALRI does not rule out the possibility of a concurrent bacterial infection.

8.6.13 The overall level of diagnosis in this community-based study was lower than that achieved in the hospital studies. [41,42,43] Whether the large group of children in whom no diagnosis was made (66%) had a viral or bacterial infection is a matter for speculation. It is possible that many of these children did have a bacterial infection but that, because of the very active surveillance system employed, they were identified and treated too early in the course of their disease for the relatively insensitive microbiological techniques currently available to identify their nature.

8.6.14 While only 2 of 222 episodes of ALRI among cohort children were associated with a positive blood culture, 9 (18%) of the 49 episodes identified at Basse health centre showed significant bacteraemia (bacteraemia due to an organism known to cause pneumonia). These latter results are in agreement with other studies of the bacterial aetiology of pneumonia and suggest that the blood culture techniques used were satisfactory.

8.6.15 It seems likely that these children presenting to the health centre had their disease for longer than the children detected during the intensive village surveillance. This is supported by the finding that the health centre children, had a higher mean respiratory rate (63 versus 52) and a higher mean heart rate (150 versus 117) and a greater proportion had radiologically proven ALRI (30 % versus 8%). These differences are all statistically significant at the 5% level. The mean age of these children was not significantly different to that of the children with ALRI identified by village surveillance and they were from the same 2 ethnic groups (Mandinka and Fulla). The field workers who worked in the village surveillance and at the health centre out-patients were trained in the same way and used identical selection criteria for case recognition. The fact that their parents had actively sought treatment at the health centre in Basse (compared to the child being identified as ill by regular surveillance) is also consistent with the suggestion that these children represent a different illness group - those with more severe illness. Thus cohort children with ALRI were perhaps investigated at an earlier stage of illness when bacteraemia may be uncommon and a bacterial aetiology difficult to establish with current methods.

8.6.16 This may in part be an explanation for the failure of the pneumococcal type-specific latex agglutination test in the cohort study though it does not explain the high rates of (false) positivity found in the control specimens. An alternative explanation is that bacterial growth during transport and storage led to false positive reactions which were not found previously in a study of hospital patients in The Gambia.[54]

8.6.17 Other alternative methods to blood culture for the detection of bacterial ALRI are antibody assays for bacterial protein antigens. Among the ALRI episodes in cohort children that were associated with a subsequent finding of x-ray consolidation, 7 (70%) of the 10 episodes in which a rising titre to pneumolysin was detected had a lobar consolidation pattern (the classical pattern of pneumococcal infection).

8.6.18 Whilst the serological techniques used for diagnosis of bacterial infection cannot give as certain a bacterial diagnosis as blood culture, indirect evidence in support of the results obtained can be found in the observation ALRI episodes in which lobar consolidation was present yielded a significantly higher rate of bacterial detection (9/25 or 36%) than the other ALRI episodes (23/197 or 13%, $p<0.05$). In addition the mean CRP level among the group of bacterial infections was considerably higher (112 mg/l, s.d. 98, n=32) than that found in the group of viral infections (44mg/l, s.d. 70, n=42). Since lobar consolidation and very high CRP values are known to be associated with bacterial infection these findings give some corroborative support to the findings of the serological results.

8.6.19 The positive blood cultures from the health centre study (6/9 of which were positive for S. pneumoniae or H. influenzae) together with the serological results suggest that these two bacteria are the major causes of bacterial pneumonia in rural communities as well as in urban hospital patients. However the possibility that other bacteria, which rarely give rise to positive blood culture and for which there is no serological test, are also important cannot be excluded.

8.7 ALRI and indoor air pollution

8.7.1 The health aspects of biomass fuel combustion have recently been reviewed by WHO.[125] Biomass fuels are used as the major or only source of fuel in 30% of urban and 90% of rural households in developing countries.[126] These fuels are usually burned under inefficient conditions producing large

quantities of smoke and gaseous products. The poor ventilation found in many kitchens compounds this problem. There is very little data from developing countries which relates smoke exposure to incidence or severity of ALRI in young children . However there is evidence from one study in Nepal that domestic smoke pollution from cooking fires is a risk factor for ALRI in young children.[63,64]

8.7.2 Levels of indoor air pollutants

8.7.2.1 In rural areas of The Gambia, cooking is usually done in a separate kitchen and fires are lit within living rooms for only a very short period during the coldest time of the year, if at all. Many kitchens are poorly ventilated. To determine whether exposure to kitchen smoke might be one reason the high incidence of ALRI in Gambian children, a study was undertaken in conjunction with scientists from the University of Wagenigen, The Netherlands to measure the extent to which rural Gambian children are exposed to kitchen smoke and to determine some of its physical and chemical characteristics.

8.7.2.2 Very high levels of respirable suspended particles (RSP) were recorded (mean 2,000 micrograms/ m^3), well in excess of WHO recommended levels (100-150 micrograms/ m^3). Several kitchens studied had no or only a small gap between the wall and the roof. Since we found that that total ventilation area showed a significant association with RSP concentrations it would be advisable to have a larger gap to improve ventilation. For example, in Tambasensan, when the ventilation area is increased from 1 m^3 (small gap) to 6 m^3 (large gap) the RSP concentration is reduced from 3318 to 1910 micrograms/ m^3.

8.7.2.3 It was shown that women spend an average of 3-4 hours per day in the kitchen when cooking and that pollution levels are highest at the time of cooking. Children were found to spend an average of 1.5- 1.8 hours per day in the kitchen at cooking times.

8.7.2.4 PAH (polycyclic aromatic hydrocarbon) concentrations were also very high and this is also of concern since there is evidence that these compounds are carcinogenic to experimental animals[127] and can cause cancer in humans.[128] The levels shown in this survey can therefore be considered a potential hazard to the exposed population.

8.7.3 Exposure to indoor air pollution and ALRI

8.7.3.1 A study of the possible relationship between ALRI episodes and exposure to smoke showed an association between father's smoking habits and increased incidence of ALRI in children. Due to the much greater contact between mothers and their children it would have been expected that maternal smoking would have had a larger effect. However, only 3% of mothers in our study reported regular smoking, so we were unable to investigate this. In this community maternal smoking is unlikely to be an important risk factor. This association with father's smoking is of concern since studies in developed countries have shown an increased incidence of ARI [62,129,130] and a substantial negative effect on the rate of increase of FEV_1 (forced expiratory volume) among children of parents who smoke.[131]

8.7.3.2 We were able to show a significant association between smoke exposure and ALRI, but only in girls. As described above this exposure occurs through the carriage of the youngest child on the back of the mother whilst cooking (because no other child-minder is available to look after the child). This behaviour appears to be consistent over a period of time and only changes when another child is born or the child grows too old. Misclassification of these smoke exposure groups may have occurred but is likely to have been uniform for all subjects and therefore tended to decrease any observed association.

8.7.3.3 The difference between boys and girls and of family structure is unexplained, but the size of the difference between the sexes suggests that this is unlikely to be a chance finding. In our study, girls over one year old were more likely to be carried on their mother's back while cooking than boys (37% girls, 28% boys: chi- squared=4.8,$p<0.05$). This is not due to weight differences (older girls tend to be heavier than boys), but may reflect differences in maternal behaviour. It is possible that girls are carried for longer periods of time than boys. It will be necessary to perform more detailed studies, including direct observation of the behaviour of mothers in order to investigate this unexpected finding.

8.7.3.4 There are recognised problems in interpreting data from such "risk factor" studies. Measurement errors with misclassification of exposure groups (due to limitations in sampling methods, poor recall of activity patterns by mothers, and the use of inappropriate proxy measures of exposure) may cause difficulties. In addition bias and confounding can be particularly

problematic in studies considering environmental risk factors which show weak association with health outcomes.[132]

8.7.3.5 In this study the exposure information was based on data collected from simple questionnaire surveys. It is likely that maternal recall of past events is subject to substantial error. If these errors are uniform for all subjects this will act to reduce the size of any observed associations. It is possible that an episode of ALRI may selectively alter maternal recall. This effect should be limited, however, in this study since risk factor data for the majority of children was collected before the surveillance period began. Nevertheless we were unable to confirm the accuracy of our exposure data (for example by cotinine or carboxyhaemoglobin measurements) or the validity of the proxy measures used (for vitamin A status, socio-economic status and crowding).

8.7.3.6 It is difficult, therefore , to predict the possible health effects that might be expected by decreasing such smoke exposure. Many causal mechanisms, each with distinct sets of component causes, probably exist for ARI. Such inter-relationships between risk factors may make it very difficult to quantify the effect of each individual factor and very dangerous to predict the effect on disease outcome of changing one of these factors. Furthermore, in these circumstances it is possible that no component cause in any of the mechanisms will appear to be strongly related to ARI.[133] It is now recognised that there are particular problems in interpreting data from such studies. The effect of confounding and other biases may lead to serious misinterpretation of results.[134] Measurement errors as described above and consequent misclassification of subjects by exposure, may be particularly problematic in this type of study.

8.7.3.7 The two most important sources of potential confounding in this study are environmental tobacco smoke since the monitoring techniques used do not distinguish RSP from biomass combustion and tobacco smoke. However it can be calculated from the emission factors for biomass combustion (about 2g/kg) and sidestream tar (about 20g/kg) and the weight of material burned that the RSP from the cooking fire is roughly equivalent to 15-30 packets of 20 cigarettes.[135] The second possible source of confounding is housing characteristics (such as poor ventilation) which may result in high smoke exposures but also be associated with crowding or otherwise increase the

transmission of pathogens. Both of these factors were held in the analyses as independent factors so that any possible interactions could be identified.

8.7.3.8 High risk or high disease incidence populations are generally unsuitable for "risk factor" studies in circumstances in which there is a weak association of a risk factor with disease outcome but may be particularly suitable for assessment of preventive measures[133]. Intervention studies are the most likely to give useful information on the importance of air pollution in relation to other risk factors. However such studies will be difficult to perform since reductions in indoor air pollution at a community level will be hard to achieve and verify. Furthermore, the problem of pollution from biofuel combustion has many facets affecting rural community development, housing design and energy utilisation as well as health, so that cost benefit analyses of interventions will be complex to assess.[136] In 1992 WHO Programmes of the Control of ARI and for the Prevention of Environmental Pollution met with external experts met to discuss this issue. It concluded that the data from Nepal and this study, together with what is known from developed country studies were of sufficient importance and concern that intervention studies should be carried out in a number of different sites. The methodological issues involved in the design of these studies are complex and cannot easily be briefly summarised in this report. A full discussion of the issues is to be presented in detail in the meeting report.

8.7.3.9 Until the results from these studies are known it would seem to be prudent for national ARI programmes to stress the detrimental effects of parental smoking and indoor air pollution. Improving ventilation in cooking and living areas may be feasible in some communities. It may be possible to educate mothers to discourage young children from entering smoky kitchens and to limit the smoke exposure of infants by allowing other adults or older siblings to care for their youngest child whilst they are cooking.

8.8 Maternal knowledge, attitudes and practices

8.8.1 Improved case management strategies to reduce ARI mortality place emphasis on rapid access to appropriate antibiotic treatment for children who have ALRI. The role of the mother in recognising that her child has ALRI and in seeking treatment from the primary health care services is critical to the success of this strategy. Furthermore, since the majority of

cases of ALRI in children will be treated as out-patients the mother will be responsible for administering the antibiotic treatment and ensuring that other beneficial supportive measures are adopted.

8.8.2 Community education must be based on an understanding of health knowledge and behaviour among mothers in individual developing countries. Currently, however, there are few data either describing mothers' perception of ARI or assessing the feasibility of educating semi-literate or illiterate mothers to identify ALRI and to seek help at an early stage of the illness. Review of ALRI intervention studies suggest that the impact on mortality will be measurably reduced if national ARI programmes depend on passive case finding (self referral to village health workers or health clinics) rather than active case finding through population surveillance.[16,137,138,139]

8.8.3 The mother's perception of severe symptoms in her child is a major factor determining whether or not she attends a health clinic[140,141]. However little is known about the observations and criteria used by parents to determine whether an ARI episode is serious, and how these in turn relate to the WHO classification of ARI. Similarly the bases of parental judgements involved in deciding whether or not to seek care when signs ARI are perceived are largely unknown. These questions are particularly pertinent to ARI control activities since, in rural communities, approximately 50% of deaths from ALRI in young children occur within 3 days of onset of symptoms.[16] This emphasises the need for early recognition of pneumonia by mothers and a decision by the mother or guardian to seek treatment.

8.8.4 One of the greatest challenges facing national ARI control programmes is the development of effective communications strategies aimed at teaching communities to recognise the signs and symptoms of ARI in young children, to give supportive home care for children with coughs and colds and to seek appropriate care for the more serious ALRI. There is a growing recognition that to achieve this, programmes first need to understand local beliefs and practices concerning the management of ARI in children. Particularly useful is knowledge of locally recognised illnesses which involve ARI signs and symptoms, their perceived causes and preferred treatments as well as constraints to prompt careseeking from qualified health workers.

8.8.5 To find out more about mothers' attitudes to ARI in the The Gambia, groups of rural women were asked about the causes of ALRI, its symptoms and signs and about how they manage this illness. Most women had little understanding of the germ theory concept of infection or had concepts of transmission of infection from one child to another. However, they were better at describing the signs and symptoms of ALRI. Several categories of ALRI are recognised and given specific names in local languages.

8.8.6 The findings suggest that mothers recognise chest indrawing but have no specific expression to describe it's presence, or only recognise it together with other related signs (which comprise "open chest"). This has important implications for the strategy adopted in community education activities since it would be important to build on this traditional concept of respiratory distress rather than displacing it with a term, such as "chest indrawing" that is not understood as a separate condition and which has no linguistic equivalent in the major Gambian languages.

8.8.7 The frequent reporting of chest pain as a symptom of ARI suggests that the entry point to ARI case management should be a history of cough or chest pain rather than a history of cough exclusively (as is currently recommended in ARI training in The Gambia). Inquiry into maternal ideas of causes of ARI have given insight into the concepts of the aetiology of respiratory illness that exist in this rural area of The Gambia that will be of importance when designing communication messages on ARI for this population.

8.8.8 Although the mothers in the study villages did not count the respiratory rate of their children (nor would it be possible to teach them to do this since many cannot count and most do not possess a watch), they nonetheless were able to recognise the presence of fast breathing. This may have been recognised as simply a departure from the normal appearance of the child breathing. Mothers reports of fast breathing were found to be predictive of the presence of ALRI. This recognition of fast breathing by mothers has also been commented on in studies in India [85] and Papua New Guinea.[69]

8.8.9 However the presence of fast breathing was considered to indicate severe illness by only 9% of mothers. It is therefore important to attempt to change mothers' attitude to this recognition of fast breathing by educating them that this is an important sign of ALRI and therefore a sign which should

alert them of the need to seek care from a health worker. In addition, if mothers can learn to appreciate the relevance of the health worker counting the respiratory rate of a child they will be more likely to accept that decisions regarding antibiotic treatment are based on this criterion. This may help to limit the community pressure on the VHW to prescribe antibiotics to all children with cough.

8.8.10 About 40% of mothers correctly reported that signs of systemic upset are indicators of the presence of "pneumonia". This recognition may be particularly relevant to the management of neonatal sepsis. There has been an increasing awareness that children under 2 months of age form a particularly high mortality group and that presentation of illness is not sharply delineated into clinical conditions of for example pneumonia and meningitis. Guidelines for the management of sepsis in this age group rely more on recognition of signs of systemic upset that predict the presence of sepsis. It might therefore be possible to build on the existing community awareness of the significance of these factors.

8.8.11 The pattern of local treatment that was given as home-care for children who had a cough seemed to reflect the immediate availability of local remedies (such as local leaves and herbs). We identified no adverse local practices.

8.8.12 Mothers showed no understanding of either germ theory of disease causation nor concepts of transmission of some infectious agent. Most mothers thought that "pneumonia" was caused by cold weather or getting wet in the cold season, and that "open chest" was caused by a traumatic event. The idea of cold predisposing to ARI is common in many societies however there is no sound evidence that it predisposes to either the common cold or ALRI, nor that it is associated with increased mortality outside the neonatal period. In contrast there is considerable evidence that hypothermic babies have increased mortality and randomised controlled trials of temperature control by use of incubators (and much less rigorous studies relating to the "kangaroo method" of temperature control) are consistent with a causal relationship between chilling and mortality in low birth weight infants, but the evidence related to impact on ALRI specifically is inadequate. Biological plausibility is supported by animal studies, but the effects on cellular function are seen only at very low temperatures. A fuller discussion of these issues has been presented elsewhere.[142]

8.8.13 In this poorly educated rural population in which traditional medical beliefs and practices are widely prevalent, mothers recognise ALRI as a severe disease and have cultural concepts of fast and difficult breathing which, although they do not directly equate with the clinical signs of indrawing or nasal flaring, are predictive of ALRI. Mothers can be encouraged to seek treatment when such symptoms or signs are present. Community education should play a key role in national ARI programmes and a local review of maternal perceptions of ARI must be an integral part of such an approach. The results suggest that an education programme based on promoting the recognition of local concepts of chest illness or difficult or fast breathing would encourage appropriate care-seeking by mothers of children with ALRI. The encouragement of such self-referral should facilitate early treatment and hence make an important contribution to the strategy of reducing mortality from ALRI by improved case management.

8.9 Treatment of community acquired ALRI

8.9.1 We compared two strategies in the out-patient management of children with community acquired ALRI. These were chosen after consultation with the Gambian Government and reflected treatment practices commonly found in The Gambia. One group received a 5 day course of oral cotrimoxazole. The other group received a single dose of fortified procaine penicillin (procaine penicillin 3 mega-units plus benzyl penicillin 1 mega-unit per vial) together with a 5 day course of oral ampicillin. The second treatment group reflects a common practice of administering a single dose of intramuscular procaine penicillin combined with a course of oral antibiotics. This has the advantages of ensuring reliable antibiotic administration on the day of presentation (thought to be important as many of these children are reported to be vomiting or taking oral fluids poorly), whilst not requiring repeated visits to the health centre for a course of injections.

8.9.2 The comparative efficacy of these two regimes is important for two reasons. Firstly, a course of oral cotrimoxazole can be administered by all grades of health worker including village health workers with minimal training.[143,144,145,146] Secondly, the cost of treatment with cotrimoxazole is considerably cheaper than that with ampicillin. Current prices quoted by 'Equipment for Charity Hospitals Overseas' (ECHO), a major supplier of medical drugs to developing countries, give a 5 day course of

cotrimoxazole for a 1 - 4 year old child (5 tablets) as £0.05, whereas an equivalent 5 day course of ampicillin would cost £0.41 (capsules) or £0.94 (syrup). A single dose of fortified procaine penicillin plus needle and syringe would cost an additional £0.08.[147]

8.9.3 We found no significant difference in outcome (judged both by mothers assessments and the findings of the study physician) between the two groups at two week follow up. This study was not a randomised double-blind controlled trial, however strict sequential allocation of treatment groups greatly limited the opportunity for the introduction of selection bias in the treatment allocations. This is confirmed by the comparison of the two groups shown in table 27. Neither the mothers nor the physician were strictly blind to the treatment allocation however any bias introduced would very likely have been towards favouring the procaine penicillin/ampicillin group since it is known that mothers in The Gambia, as in many developing countries prefer their children to receive treatment by injection. However cotrimoxazole was found to be equally efficaceous despite this potential bias.

8.9.4 Subsequent to this study, data from Malawi[71] were published demonstrating that cotrimoxazole was highly effective in rapidly clearing P. falciparum parasitaemia and symptoms of clinical malaria in young children. Since we have shown that there is a clinical overlap in the presentation of ALRI and malaria, it is possible that some children who participated in this treatment trial had malaria (with respiratory signs of consistent with ALRI) and responded to differentially to treatment in the two groups (since ampicillin has no known antimalarial action) thus favouring the cotrimoxazole group. It is not possible to consider this issue further with the existing data set but this issue should be considered in any similar future trial of treatment for ALRI which take place in a malarious area.

8.9.5 Adverse reactions to cotrimoxazole are uncommon. The two serious forms of adverse reactions, exfoliative dermatitis and bone marrow depression, occur very rarely. The estimated incidence of fatal reactions in Sweden and in Britain was less than 1 in 100,000 children in both cases. [148,149]

8.9.6 There are two major concerns surrounding the widespread use of cotrimoxazole as a first-line treatment against ARI in developing countries.

Firstly, it is as yet unknown whether the widespread use of cotrimoxazole will induce resistance to antimalarials such as the sulphadoxine plus pyrimethamine combination. Secondly, widespread use of cotrimoxazole might lead to selection of strains of S. pneumoniae and H. influenzae with reduced sensitivity. A recent report from North Carolina, USA has linked the increasing use of cotrimoxazole as a treatment for otitis media with the finding of an increasing proportion of pneumococci showing reduced sensitivity to cotrimoxazole.[150]

8.9.7 Training health workers to identify reliably children with ARI who require antibiotic treatment reliably is, therefore, of key importance in preventing over-use of antibiotics and the emergence of resistance. The adoption of validated clinical signs for the diagnosis of chest infections may substantially reduce the overall use of antibiotics in the community, whilst still reliably identifying the children who require antibiotic treatment.[85] Intermittent surveillance of the antibiotic sensitivity of S. pneumoniae and H. influenzae isolates should be implemented to monitor any changes in sensitivity patterns and so direct the choice of antibiotic. Guidelines for this surveillance are now available in a manual from WHO and a Gambian MRC investigator has been involved in the development of this manual.

8.9.8 We have found that early identification of pneumonias using simple clinical signs, followed by prompt treatment with oral cotrimoxazole is an effective intervention against community-acquired pneumonia. In developing countries where most strains of S. pneumoniae and H. influenzae are found to be sensitive, a strong case can be made for cotrimoxazole as a first line treatment in the management of young children with pneumonia. The efficacy of cotrimoxazole in this situation had not been previously studied, however our findings have been recently confirmed by other investigators in Zimbabwe. [151] Young infants in the first two months of life were not included in this study since the absorption of cotrimoxazole in sick young infants in unknown and it's use is not recommended by some authorities. [152] Optimum methods for treating neonates with severe pneumonia need to be studied and better defined.

8.9.9 The use of cotrimoxazole by village health workers as part of a health education and improved case management intervention in rural Bagamoyo district in Tanzania resulted in a reduction of the ARI specific mortality rate from 14.3 to 10 per 1000, a reduction of 30.1%.[16]

9. CONCLUSIONS

9.1 Prevalence of ARI

9.1.1 Symptoms of acute respiratory infection were very frequently reported with runny nose reported as present in 52% and cough (see appendix c) in 20% of the weekly interviews. Mothers reported that their children had a new episode of ARI on 18% of the weeks interviewed. ARI symptoms are therefore considerably more common in this population than similar reports of ARI symptoms from community-based studies in developed countries. The results of this study are supported by findings in Papua New Guinea and challenge the position taken in recent reviews of the epidemiology of ARI and WHO publications which have suggested that ARI symptoms are equally common in both developing and developed countries. Since this issue is of importance in the understanding of the pathogenesis of ALRI it merits further investigation.

9.2 Incidence of ALRI

9.2.1 The incidence rate of ALRI in rural Gambia is amongst the highest yet described in any community study. The annual ALRI incidence rate was 468/1000 children 0-4 years which is approximately ten times the corresponding figure found in developed country studies. The annual incidence rate lobar pneumonia was 50/1000 0-4 year old children.

9.2.2 The incidence of ALRI is highest in infants (700/1000 infants compared to 370/1000 in 1-4 year old children). This picture is different to that found in Papua New Guinea in which the ALRI incidence in infants is about 12 times higher than that in older children. One explanation may be due to an elevated observed incidence in 1-4 year olds in this population due to the clinical overlap with malaria in this age group (there being no malaria transmission in the highlands of Papua New Guinea).

9.3 Clinical features and diagnosis

9.3.1 Taken together with data from other recently published studies in India and Papua New Guinea and with data from more recent studies in Swaziland, the Philippines and Lesotho, the results of this study support the use of simple clinical signs, and in particular measurement of the respiratory rate, as a valid method of making a diagnosis of ALRI in young children. A respiratory rate cut-off of 50 per minute in infants 2-11 months of age, and

40 per minute in children 1 - 4 years was found to be the most valid (in terms of sensitivity and specificity) in this population. WHO guidelines (which recommended the use of 50 per minute for all children 2 months to 4 years of age at the time of the study), were revised in 1990 to adopt the above thresholds.

9.3.2 Chest "indrawing" was found very frequently (in 62% of all episodes of ALRI identified in this study) and therefore, without further qualification, was not a useful indicator of severe episodes requiring hospital admission. WHO guidelines for the identification of ALRI episodes requiring hospital admission (which included both subcostal and intercostal indrawing at the time of the study) were revised in 1990 so that only subcostal indrawing was recommended as a sign of ALRI requiring hospital admission.

9.3.3 This study generated little data on young infants less than two months of age. Further research is required into the clinical presentation of ALRI and bacterial sepsis in the 0 - 2 month old infant. (The author participated in the design of a multicentre study to address this issue; The Gambia was selected as one of the 5 developing country sites and the study is currently underway there with support from WHO).

9.3.4 In The Gambia most children who present to the health services with ALRI are first seen by a peripheral health worker. It is therefore very important that these health workers are able to recognise ALRI and manage it correctly. Implementation research is urgently required to assess the feasibility of teaching Gambian village health workers to make a diagnosis of ALRI by counting the respiratory rate. ARI intervention studies in India (Haryana and Maharastra), Nepal (Kathmandu valley and Jumla), Bangladesh, Indonesia, Tanzania and the Philippines have shown that similar groups of community based health workers can be successfully trained to perform this task. (The author participated in the design of a study carried out in 1991 by UNICEF which began to investigate this issue utilising electronic sounding timers which have a one minute alarm and which have been developed by WHO for use in developing country settings).

9.4 ALRI and malaria

9.4.1 Malaria and ALRI occurred together more often than would be expected by chance. It is suggested that malaria may cause (and may indeed present

with) respiratory signs and symptoms. Since cough and fever are the two most common presenting symptoms in young children in The Gambia; and since ALRI and malaria are the two most important causes of death in young children it is great importance that this interaction be fully investigated so that peripheral health workers (with no access to laboratory investigations) are able to ensure adequate treatment of both conditions. (This issue was investigated in more depth in Basse in 1990-2. The author acted as chairman at a WHO meeting in 1991 to recommend clinical guidelines for children (in malarious areas) presenting with fever and signs of ALRI, and to identify priority areas for further research on this subject).

9.5 ALRI and malnutrition

9.5.1 The higher incidence of ALRI in developing countries than developed countries is generally considered to be, in part, due to nutritional factors. This study was unable to demonstrate an association between the anthropometric index weight-for-age and incidence of ALRI. This association is particularly difficult to explore at the present time when the specific elements of malnutrition which might influence ALRI pathogenesis are not clearly known. Nevertheless a literature review revealed a limited number of other developing country studies which have studied this association. The Basse data are generally consistent with those from these other studies and suggest that the major effect of protein-calorie malnutrition on ALRI mortality may be mediated through increasing the severity and case fatality rate of ALRI episodes rather than by greatly increasing the risk of ALRI episodes in young children.

9.6 Aetiology

9.6.1 Data are presented which are consistent with the contention that bacteria are frequent causes of ALRI in young children. This had been previously shown in urban hospital studies, however these data suggest that this may also be true in rural areas. Streptococcus pneumoniae was the commonest bacterial cause of ALRI identified.

9.6.2 The aetiology of ALRI in Gambian children has now been studied in urban and rural communities with the most sensitive diagnostic tools currently available. Further advances in our understanding in this area must await the development of improved methods of bacterial and viral diagnosis. These are urgently required for the epidemiological study of bacterial ALRI.

Community based studies of S. pneumoniae and Haemophilus influenzae type b infection are particularly required to give baseline information for the design and planning of vaccine efficacy trials against these agents.

9.6.3 The aetiology of a substantial proportion of ALRI episodes remains unknown. It is possible that malaria was responsible for some of these episodes, however the majority are likely to represent microbiological agents which are as yet unknown or for which current diagnostic methods are insensitive or cannot be applied in community- based studies.

9.6.4 A respiratory syncytial virus epidemic occurred each year during the period 1986-89 in an urban area of The Gambia (Bakau). In Basse however no RSV activity was found during the one year surveillance period. This raises the possibility that the micro- epidemiology may be different to that in urban areas (as is the case for measles infections). This merits further study since effective protein subunit vaccines against RSV may become available in the next 10 years and the field testing of these vaccines will require to be undertaken in developing country settings in which the epidemiology of RSV infection is well characterised.

9.6.5 There are two important groups of children who require further study since they have not been adequately represented in the above studies and because they represent high mortality groups. These are the severely malnourished child and the neonate. The aetiology of ALRI may be different in these groups from the general pattern and thus alternative forms of treatment may be required. (Studies to investigate these two groups are currently underway in The Gambia with the support of WHO).

9.7 ALRI and air pollution

9.7.1 Very high levels of a number of indoor air pollutants were recorded in Gambian kitchens. The behaviours of some mothers in carrying young children on their backs when cooking exposes these young children to this air pollution and was associated, in this study, with increased incidence of ALRI. A similar study in Nepal has also shown this association between smoke exposure in children and ALRI. It would therefore seem prudent for the Gambian ARI programme to inform Gambian mothers that this practice may be harmful.

9.7.2 The best way to further explore this association would be by the creation of a low-exposure group by means of an intervention study. This issue was

discussed at a recent WHO meeting in 1992 and the detailed design of such studies was started. A number of interventions relating to the improvement of ventilation or of cooking stoves have already been devised. Technical support to research studies seeking to explore this issue is available from a number of sources. An important first stage in these studies should be to show that a low exposure group can be established and maintained over time and that this reduction in exposure can be adequately documented. The second stage would then be to implement the intervention in a population and to investigate the relationship between reduction in domestic smoke pollution and outcome measurements (for example ALRI incidence or mortality from ARI).

9.8 Maternal knowledge, attitudes and practices

9.8.1 Rural Gambian mothers recognise fast breathing in their children and have traditional concepts of difficulty breathing which are reasonably predictive of ALRI. This recognition of fast breathing has been commented upon in studies in India and Papua New Guinea also and is essentially qualitative since it does not require a formal count of the respiratory rate to be made by the mother. Indeed Gambian mothers do not possess watches and in many cases have a low level of numeracy so attempts to teach them to count the respiratory rate more formally should be avoided. However most mothers did not consider the presence of fast breathing to indicate a severe illness.

9.8.2 The study found that mothers appeared to recognise the presence of chest indrawing but had no specific expression to describe it's presence, or only recognised it together with other related signs (which comprise "open chest"). Health education should focus on these traditional concepts of respiratory distress rather than introducing foreign ideas such as "chest indrawing". The objective should be to encourage parents to seek care for an episode of ARI when they consider such fast or difficult breathing to be present.

9.8.3 Further studies to investigate the knowledge, attitudes and practices of mothers with respect to ARI are important before the Gambian ARI programme is fully implemented. An important element of a control strategy based on improved case management of ARI will be health education and in particular education to teach mothers and other care-takers to recognise the dangers of ALRI in young children. In order to be

effective, health education must emphasise interaction between health workers and families and must be based on an understanding of the mother's ability to recognise the signs of ALRI, of the popular perceptions concerning the cause and treatment of ARI and of the patterns of health seeking behaviour for ARI at the household level. (An ethnographic study was carried out in The Gambia in 1991 using the "focused ethnographic survey instrument" developed by WHO for this purpose and with assistance from personnel from Johns Hopkins University, Baltimore, USA).

9.9 Treatment of community-acquired ALRI

9.9.1 Two treatment regimens for the out-patient treatment of ALRI were compared. Oral cotrimoxazole was found to be effective and early diagnosis and treatment of ALRI with cotrimoxazole resulted in satisfactory outcome in over 90% of cases and very few children required referral for hospital care. This finding is important since cotrimoxazole is cheap and a course of oral cotrimoxazole can be administered by all grades of health worker in The Gambia. In addition it has been shown that it is an effective antimalarial agent in young children and so children with presenting with fever and signs of ALRI can be safely treated with cotrimoxazole by village health workers. It may be difficult to distinguish between these two conditions in some children but a five day course of cotrimoxazole should ensure adequate treatment of both conditions.

9.9.2 Further research is required to look at compliance with the recommended cotrimoxazole regimens and to investigate the possible further simplification of regimens such as a daily instead of twice daily schedule for cotrimoxazole, or 3 day instead of 5 days treatment course. (The author developed a draft study protocol to investigate this issue in 1989 during a 3 week period as temporary adviser to the WHO ARI programme). In addition, optimum methods for treating young infants (less than two months of age) need to be studied and better defined.

9.10 Closing remarks

9.10.1 An infant mortality rate of 80 per 1,000 live births was recorded in the study villages during this one year period of intensive surveillance. Although this is lower that other recorded estimates of infant mortality rates in rural Gambian communities there is, unfortunately, no reliable concurrent mortality data from the surrounding villages for the period of

the study and so it is not possible to make a meaningful statement about any mortality reduction in the study villages which may have accompanied the community surveillance.

9.10.2 Government estimates of infant mortality in upper river division based on indirect methods were 199 in 1983 and 120 to 160 per 1,000 live births in 1986-7. The most reliable mortality estimates, based on population censuses and longitudinal recording of vital events in defined populations in rural areas of The Gambia, were measured in Farafenni in 1982-3 when an infant mortality of 142 per 1,000 live births was found [28] and in upper river division subsequent to the Basse ARI study when an infant mortality rate of about 100 was recorded.

9.10.3 In developing countries in which there is good coverage with EPI (expanded programme of immunisation) vaccines, further substantial reductions childhood mortality is unlikely to occur due to further improvements in EPI vaccine delivery. This situation has already been noted in Farafenni, another rural Gambian community.[13]

9.10.4 Data from this and other related Gambian studies have underlined the importance of two bacteria (S. pneumoniae and H. influenzae) and respiratory syncytial virus as the major causes of ALRI in The Gambia. It is likely therefore that the new protein- polysaccharide vaccines against S. pneumoniae and H. influenzae (and in the longer term the protein subunit vaccine against RSV infection) will be of major public health significance in The Gambia. Since these vaccines will require to be field tested in developing country settings with known epidemiology it is important that studies to better define the epidemiology of these aetiological agents be undertaken. (Such studies are currently underway in The Gambia supported by the United States Agency for International Development in upper river division (surveillance of S. pneumoniae infections) and WHO (surveillance of H. influenzae infections in western division)).

9.10.5 A number of factors which are likely to be important determinants of ALRI mortality in The Gambia were identified in this study : malnutrition(23% of children with ALRI in the Basse study were less than 70% and 8% were less than 60% of the median weight for age values of the NCHS standards); low birth weight (20% of children born in the study villages during the surveillance period had a birth weight less than 2.5 kilograms); exposure to

parental smoking (51% of fathers of cohort children smoked regularly); exposure to biomass smoke pollution (all houses studied had very high level recorded of particulates, NO2 and aromatic polycyclic hydrocarbons); and low levels of maternal education (less than 3% of mothers of cohort children had received any primary school education).

9.10.6 Significant and substantial reductions in the levels of these risk factors will probably only take place after improvements in general socio-economic conditions. In the meantime The Gambian ARI programme should stress the importance of childhood vaccination with EPI vaccines, emphasise the dangers to children resulting from parental smoking and outdoor air pollution, and support the nutritional and educational messages of the Maternal and Child Health and Family Planning programmes.

9.10.7 However at this time when the economic conditions in many African countries is actually deteriorating it is important to institute some measures to control the high level of ARI mortality: this can be achieved by improving the case management of ARI. The Basse study resulted in an ARI intervention which consisted of the recognition of illness (principally ALRI by fast breathing or chest indrawing, and malaria by the presence of fever) by standard clinical signs which can be taught to non-medical health workers; and management of ALRI episodes with simple oral antibiotics, chloroquine for the presumptive treatment of fever and oral rehydration salts in the treatment of diarrhoea. Very few (less than ten) children required referral to hospital for further care.

9.10.8 A number of ARI intervention studies have shown substantial reductions in infant and under 5 mortality rates. Nine studies in seven developing countries have shown reductions in ARI mortality of 20 - 70% (with reductions of more than 50% in 5 of the studies). Reductions in overall infant and childhood mortality were also recorded. These studies have shown that it is possible to train village health workers to recognise episodes of ALRI (by the use of simple clinical signs) and to treat the majority of identified episodes with oral antibiotics. The challenge for The Gambia will be to attempt to reach the coverage levels achieved in these intervention study settings by training and supplying with cotrimoxazole health staff at all levels.

9.10.9 The results of this study suggest that a significant proportion of ALRI episodes are bacterial in origin; that simple signs (which can be taught to all categories of health workers) are valid predictors of the presence of ALRI; and that oral cotrimoxazole can be used to successfully treat the majority of cases of community-acquired ALRI. These findings lend support to the Gambian Government's initiative in establishing an improved ARI case management intervention in The Gambia. Our experience, taken together with achievements recorded in other developing country settings, suggests that the use of simple clinical signs in health worker training together with a regular antibiotic supply and health education to promote early care-seeking has the potential to have a considerable impact on childhood ARI mortality in both urban and rural areas of The Gambia.

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APPENDICES

a. WEEKLY MORBIDITY QUESTIONNAIRE

b. CROSS-SECTIONAL SURVEY QUESTIONNAIRES

c. DAILY REPORTS ON PRESENCE OF COUGH IN COHORT CHILDREN OVER 1 YEAR SURVEILLANCE PERIOD

d. GLOSSARY

e. LIST OF PUBLICATIONS BY AUTHOR RELATED TO THESIS

f. COPY OF SELECTED PUBLISHED ARTICLES

a. WEEKLY MORBIDITY QUESTIONNAIRE

Form ARI/WM4 Serial no.:

Week no.: |_._|

A.R.I. STUDY
WEEKLY MORBIDITY FORM

Day of week: _____

Day last seen: _____

CHECK THE CHILD'S IDENTITY
AND THEN
STICK THE LABEL IN THIS BOX

DATE: |_._/_._/8.7|

Make sure that the child is settled, then record the following:-

(If the child is not settled, wait until later to record the data)

1. RESPIRATORY RATE (count over one minute) |_|_|_|

2. Can you see INSUCTION? (Y for YES, N for NO) |_|

3. Can you see NASAL FLARING? (Y for YES, N for NO) |_|

4. Can you see RUNNING/BLOCKED NOSE? (Y for YES, N for NO) |_|

5. Does the child have a COUGH? (Y for YES, N for NO) |_|

6. Was the child SETTLED when you made the recordings?
(Y for YES, N for NO, S for SLEEPING) |_|

7. TEMPERATURE (Axillary, °C) |_|_|.|_|

8. WEIGHT (only if child is due for weighing today) |_|_|.|_|

9. GENERAL BEHAVIOUR (note your observations - don't ask respondee)
W - well, behaves normally, interested in what is happening
I - irritable, not interested in what is happening
D - drowsy, no response to what is happening |_|

10. Have you heard WHEEZE? (Y for YES, N for NO) |_|

11. Have you heard STRIDOR? (Y for YES, N for NO) |_|

12. Was a blood film taken? (Y for YES, N for NO) |_|

If so, what was the result? (F = P. falciparum, M = P. malariae, O = P. ovale, N = none) |_|

13. Was the child referred as an ARI case? (Y for YES, N for NO) |_|

If so, what was the result? |_|

14. Was the child referred for another sickness? (Y or N) : :

If so, what was the diagnosis? : :

QUESTIONS ABOUT THE CHILD

Try to ask the mother if possible, consider coming back later if the mother is not there.

15. Is the mother the respondent? (Y for YES, N for NO : :

If NO, say who is _____

16. Is the child with the respondent? (Y for YES, N for NO) : :

If NO, say where he/she is _____

17. Ask the mother if the child has been well in the last week:
W - well
R - unwell, respiratory illness
U - unwell, any other illness : :

If unwell, was treatment sought? (Y for YES, N for NO) : :

If yes, state where e.g. traditional, VHW, health centre, MRC

_____

18. Is the child breast fed every day?
A - breast feeding only
B - breast feeding every day plus solids
C - not breast fed every day, but at least once a week
D - no breast feeding : :

HEALTH - record any of the following symptoms since the last questionnaire
(Y for YES, N for NO, D for DON'T KNOW, in each box)

(day 1 = today, 2 = yesterday, etc.)	1	2	3	4	5	6	7	8	9	10
RECORD DAY OF THE WEEK										
19. COUGH - (S if only at night)										
20. BLOCKED/RUNNY NOSE (nuntu sasa)										
21. FEVER										
22. CHEST PAIN (sise deemengaw)										
23. OPEN CHEST (sise yello)										
24. NOISY OR FAST BREATHING										
25. REFUSING FOOD/BREAST										
26. DIARRHOEA										
27. VOMITING										

28. FIELDWORKER: : :

b. CROSS-SECTIONAL SURVEY QUESTIONNAIRES

Form ARI/QF1 XS no. ¦ . . ¦

A.R.I. STUDY
CROSS-SECTIONAL SURVEY - QUESTION FORM

CHECK THE CHILD'S IDENTITY
AND THEN
STICK THE LABEL IN THIS BOX

DATE: ¦ . / . / 8. 6¦

EDUCATION

Did the mother receive any education? Y/N . . . . . ¦ ¦

If YES, state highest level
{1 = primary, 2 = secondary, 3 = further} . . ¦ ¦

Did the father receive any education? Y/N . . . . . ¦ ¦

If YES, state highest level
{1 = primary, 2 = secondary, 3 = further} . . ¦ ¦

OCCUPATION

Does the mother have a job outside the compound? Y/N . . ¦ ¦

If YES, specify . . . . . ¦ ¦

Does the father have a job other than farming? Y/N . . . ¦ ¦

If YES, specify . . . . . ¦ ¦

FAMILY

How many wives does the father have? . . . . . ¦ ¦

SCHOOL

How many children in the household attend school? . . . . ¦ ¦

MORTALITY

Total number of children born to the mother . . . . . ¦ . ¦

Total number of children died under 1 month of age . . . . ¦ ¦

Total number of children died between 1 month and 5 years . ¦ ¦

SMOKING

Does the mother smoke regularly (more than once a day)? Y/N ¦ ¦

If YES, how many per day? . . . . . ¦ . ¦

Does the father smoke regularly (more than once a day)? Y/N ¦ ¦

If YES, how many per day? . . . . . ¦ . ¦

FIRE

Where is the cooking usually done? . . . . . ¦ ¦

Is there ever a fire in the house? Y/N . . . . . ¦ ¦

If YES, specify when . . . . . ¦ ¦

is there provision for a smoke outlet? Y/N . ¦ ¦

Does the mother carry any children on her back when cooking? ¦ ¦

What is the main fuel used for cooking?
{G = gas, W = wood, C = charcoal, K = kerosene} ¦ ¦

Is a fire ever used for heating in the compound? Y/N ¦ ¦

If YES, specify . . . . . ¦ ¦

MALARIA

Has the child normally slept under a bed net during the rains? ¦ ¦

Interviewer: ¦ ¦

Form ARI/LF1 XS no. ¦ . . . ¦

A.R.I. STUDY
CROSS-SECTIONAL SURVEY - LABORATORY FORM

CHECK THE CHILD'S IDENTITY
AND THEN
STICK THE LABEL IN THIS BOX

DATE: ¦ . / . / 8. 6¦

SPECIMENS COLLECTED

1. BLOOD

Slide 1:	Thin film Y/N	¦ ¦
Slide 2:	Thick film Y/N	¦ ¦
Capillary:	PCV/genotype Y/N	¦ ¦
Pipette:	W.C.C. Y/N	¦ ¦
Microtainer:	Serum for storage Y/N	¦ ¦
Venepuncture:	Blood culture Y/N	¦ ¦
	Isolate in liquid N_2 Y/N	¦ ¦
	Isolate on Bijou slope Y/N	¦ ¦

2. URINE

Universal:	Stored at -20°C Y/N	¦ ¦

3. CHEST X-RAY

CXR:	*If done,* record film number	¦ . . ¦

4. NASO-PHARYNGEAL ASPIRATE

NPA:	Was NPA successful? Y/N	¦ ¦
Nasal wash:	Was nasal wash taken? Y/N	¦ ¦
I.F. slide:	Viral antigens, stored at -20°C Y/N . . .	¦ ¦
NUNC:	Viral culture, stored in liquid N_2? Y/N . .	¦ ¦
BACTERIOLOGY:	Bacteriology plates innoculated? Y/N . . .	¦ ¦

RESULTS

THICK FILM — Malaria parasites present? Y/N . . . . . | |

If YES, how many fields/100 positive for –

P. falciparum . . . . . | . . |

P. malariae . . . . . | . . |

P. ovale . . . . . | . . |

Density of parasitaemia (no. per HPF) . | . . |

THIN FILM — Malaria parasites present? Y/N . . . . . | |

If YES, which species? {F, M, V} . . | | | |

Differential white count performed? Y/N . . | |

If YES, record % N . . . . . | . |

% L . . . . . | . |

% E . . . . . | . |

% B . . . . . | . |

% M . . . . . | . |

Other white cell abnormalities? Y/N . . . | |

If YES, specify . . . . . | |

Any red cell abnormalities? Y/N . . . . . | |

If YES, specify . . . . . | |

P.C.V. — Measured? Y/N . . . . . | |

If YES, record result . . . . . | . |

N.P.A. — Was it plated out for bacteriology? Y/N . . | |

If YES, pneumococci isolated (provisional) Y/N | |

confirmed with optochin Y/N . . . | |

Pen G sensitivity (mm diameter) . | . |

haemophilus isolated (provisional) Y/N | |

confirmed with X/V/XV Y/N . . . | |

Pen G sensitivity (mm diameter) . | . |

other organisms grown? Y/N . . . | |

If YES, specify . . . . . | |

Technician: . . . . . | |

Form ARI/C1-1 XS no. |___.___|

A.R.I. STUDY
CROSS-SECTIONAL SURVEY - CLINICAL FORM 1

CHECK THE CHILD'S IDENTITY
AND THEN
STICK THE LABEL IN THIS BOX

DATE: |__./__./8.6|

EXAMINE THE HEALTH CARD

Number of visits to clinic since November 1985 . . . . . |__|

Number of A.L.R.I. episodes noted . . . . . |__|

Courses of treatment given . . . . . Chloroquine . . . |__|

Antibiotics . . . |__|

Antibiotics for ARI |__|

Number of hospital admissions . . . . . |__|

Note diagnosis: . . . . . |__|

EXAMINE THE CHILD

Is the child settled? Y/N . . . . . |__|

Respiratory rate (per minute) . . . . . |___|

Indrawing seen? Y/N . . . . . |__|

Flaring seen? Y/N . . . . . |__|

Other signs of respiratory distress (note) . . . . . |__|

Wheeze heard? Y/N . . . . . |__|

Stridor heard? Y/N . . . . . |__|

Nasal discharge? Y/N . . . . . |__|

Heart rate (per minute) . . . . . |___|

Heart sounds normal? Y/N . . . . . |__|

If NO, comment . . . . . |__|

Chest Auscultation normal? Y/N . . . . . |__|

If NO, comment . . . . . |__|

Chest Percussion normal? Y/N . . . . . |__|

If NO, comment . . . . . |__|

Other Chest abnormalities? Y/N . . . . . |__|

Specify . . . . . |__|

Cervical nodes normal? Y/N . . . . . |__|

If NO, comment . . . . . |__|

Size of spleen (cm) . . . . . |__.__|

Size of liver (cm) . . . . . |__.__|

Other abdominal abnormalities? Y/N . . . . . |__|

If YES, specify . . . . . |__|

Skin rash present? Y/N . . . . . |__|

If YES, specify . . . . . |__|

Eye abnormality? Y/N . . . . . |__|

If YES, specify . . . . . |__|

Oedema present? Y/N . . . . . |__|

Ears normal? Y/N . . . . . |__|

If NO, specify LEFT . . . . . |__|

RIGHT . . . . . |__|

Clinician . . . . . |__|

Form ARI/C2-1 XS no. |___.___|

A.R.I. STUDY
CROSS-SECTIONAL SURVEY - CLINICAL FORM 2

CHECK THE CHILD'S IDENTITY
AND THEN
STICK THE LABEL IN THIS BOX

DATE: |__./__./8.6|

TEMPERATURE Axillary °C . . . . . |__.__|

WEIGHT kg . . . . . |__.__|

LENGTH cm . . . . . |__.__|

Does the child have a health card? Y/N . . . . . |__|

If NO, why? {L = lost, N = never had, H = at home} . . . |__|

VACCINATION HISTORY

Is this from the health card? Y/N . . . . . |__|

If NO, say who is giving information: . . . . . |__|

B.C.G. Y/N . . . . . |__|

D.P.T. (record number of doses) . . . . . |__|

O.P.V. (record number of doses) . . . . . |__|

Yellow Fever Y/N . . . . . |__|

Measles Y/N . . . . . |__|

If YES, record age in months at vaccination: . . . |__.__|

BIRTH WEIGHT

Is it recorded on the health card? Y/N . . . . . |__|

If YES, specify (kg) . . . . . |__.__|

WEIGHTS Make a note of all recorded weights in the last year

	Date	Weight (kg)
1.	¦ . / . / . ¦	¦ . : ¦
2.	¦ . / . / . ¦	¦ . : ¦
3.	¦ . / . / . ¦	¦ . : ¦
4.	¦ . / . / . ¦	¦ . : ¦
5.	¦ . / . / . ¦	¦ . : ¦

PAST MEDICAL HISTORY

Measles? Y/N . . . . . ¦ ¦

If YES, who made the diagnosis? . . . . . ¦ ¦

number of months since measles . . . . . ¦ . ¦

Previous hospital admission with chest infection? Y/N . ¦ ¦

Previous chest infection on health card? Y/N . . . . . ¦ ¦

Previous record for admission with malnutrition? Y/N . . ¦ ¦

Other relevant comments on the health card? Y/N . . . ¦ ¦

If YES, specify . . . . . ¦ ¦

Was the child born more than one month early? Y/N . . . ¦ ¦

Is there a weight recorded below 2.5 kg? Y/N . . . . ¦ ¦

Is the child being breast-fed every day? Y/N . . . . ¦ ¦

If NO, how long did daily breast feeding last? (months) . ¦ . ¦

At what age were solid foods introduced? (months) . . . ¦ . ¦

Is this the oldest child of the mother? Y/N . . . . . ¦ ¦

If NO, how many months older is the next child? . . . ¦ . ¦

how many months older is the next but one? . . . ¦ . ¦

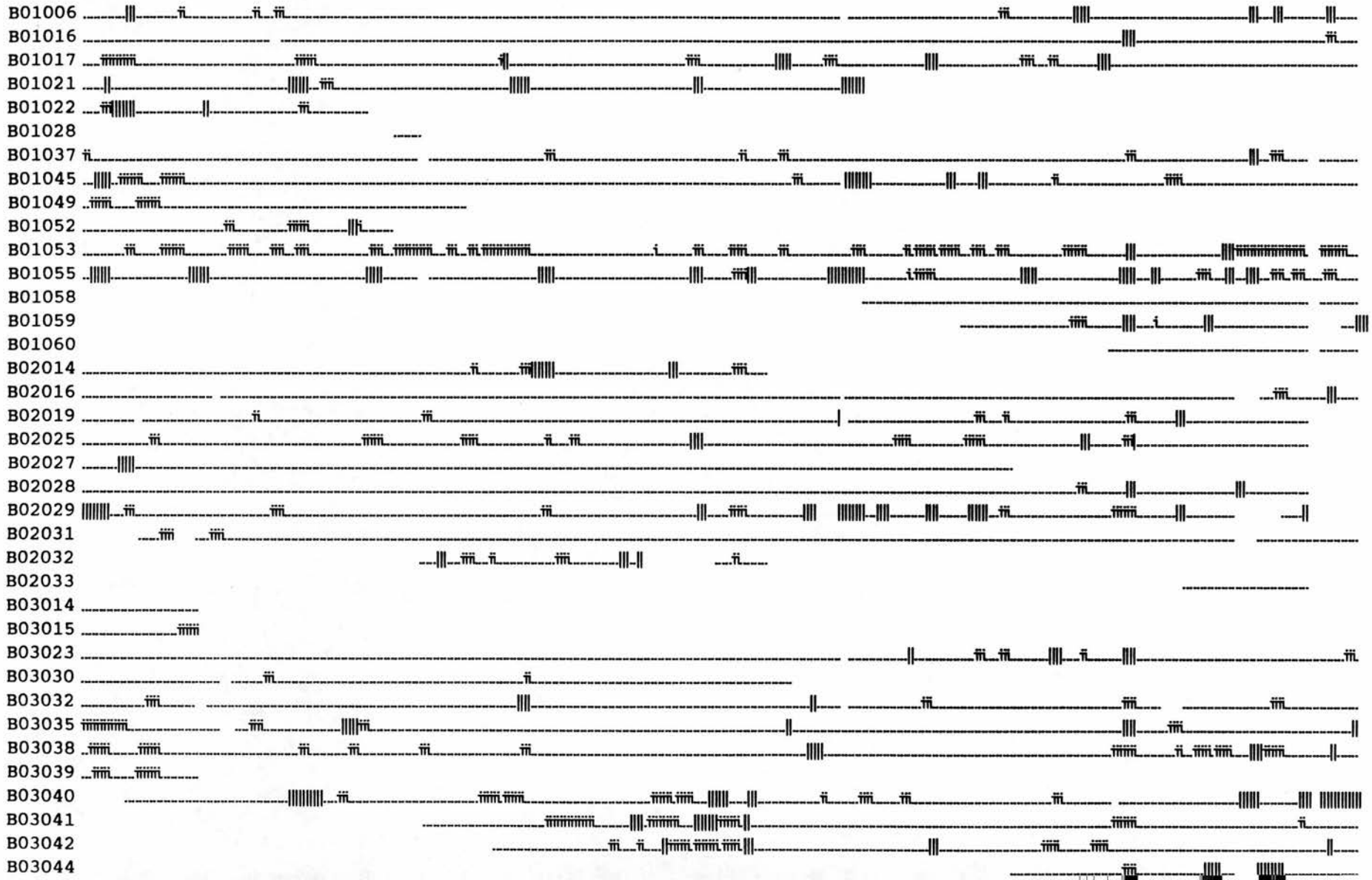
Clinician . . . . . ¦ ¦

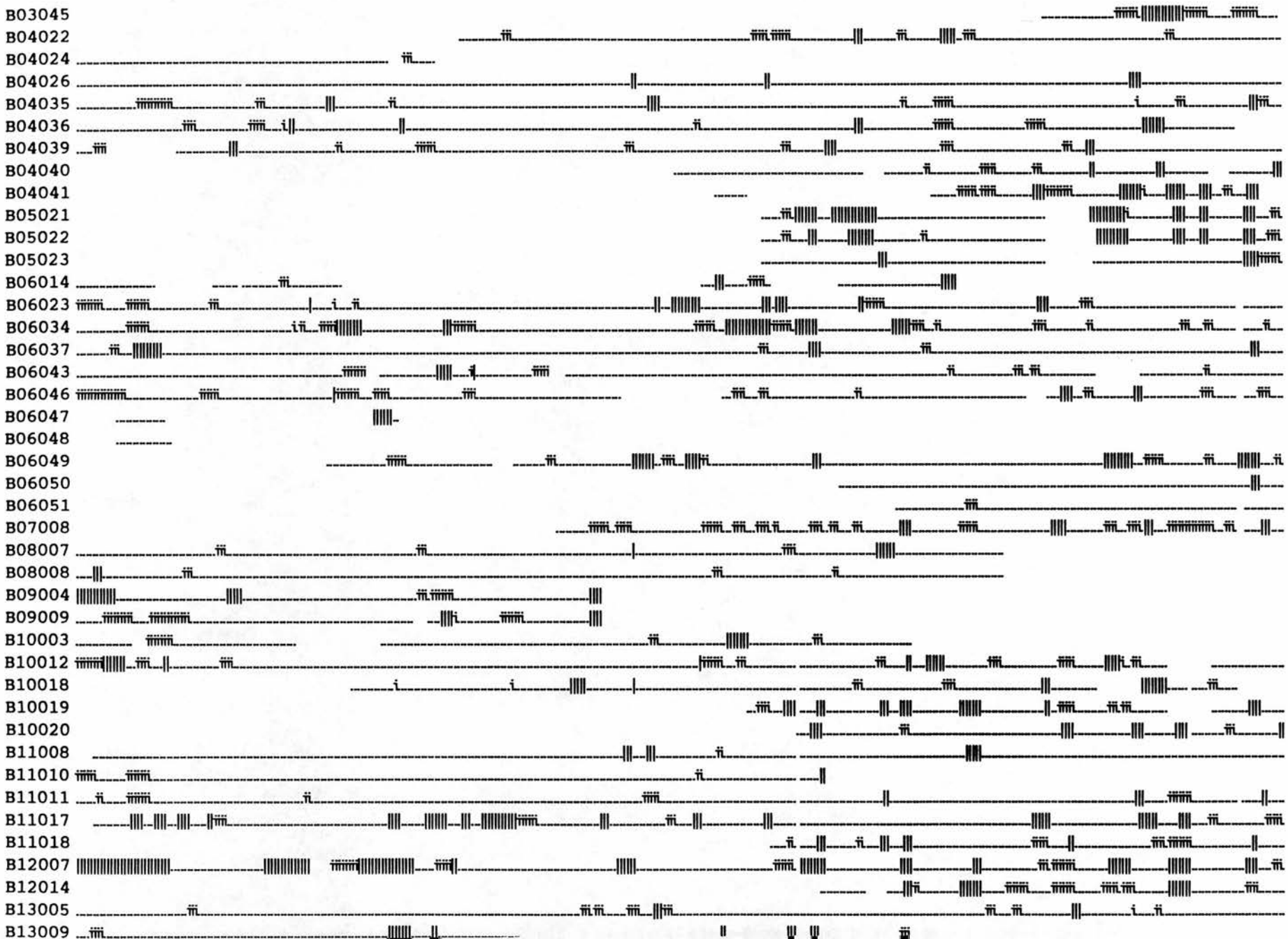
c. DAILY REPORTS ON PRESENCE OF COUGH IN COHORT CHILDREN OVER 1 YEAR SURVEILLANCE PERIOD

COUGH

_____ = days without cough ‾‾‾‾‾‾‾‾‾ = days with cough when sleeping |||||||||||||||= days with cough

APRIL 1987 MARCH 1988

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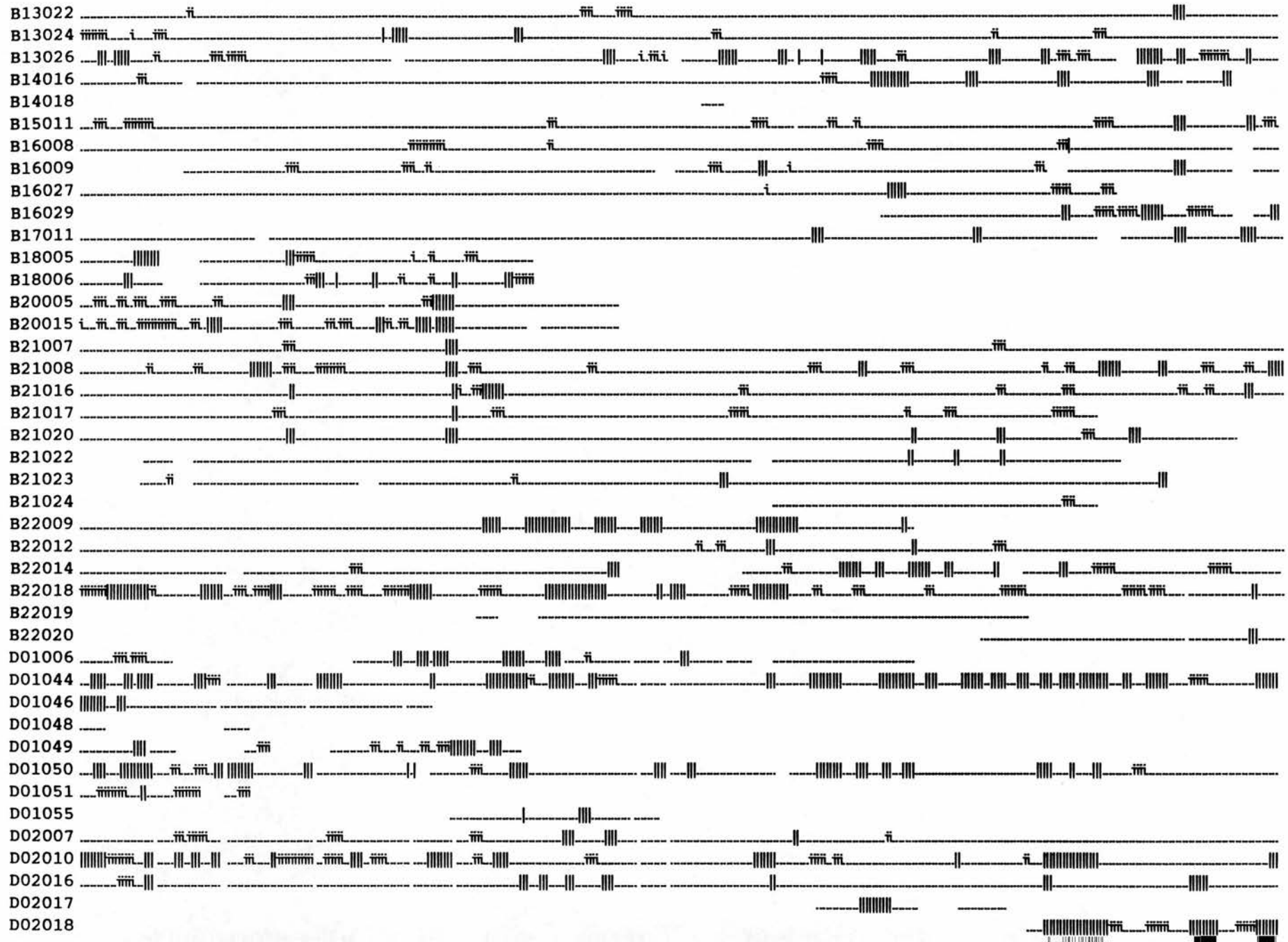
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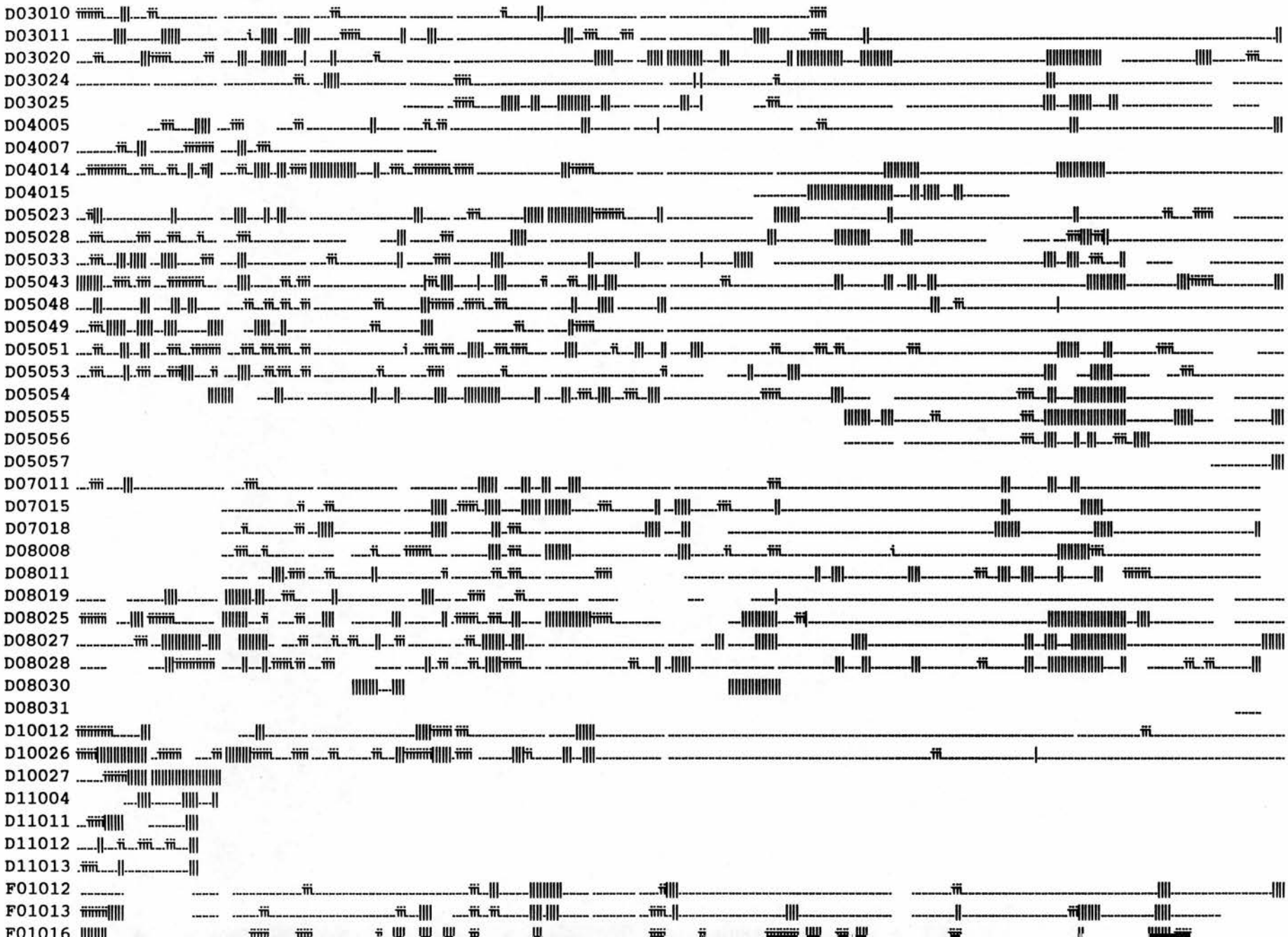
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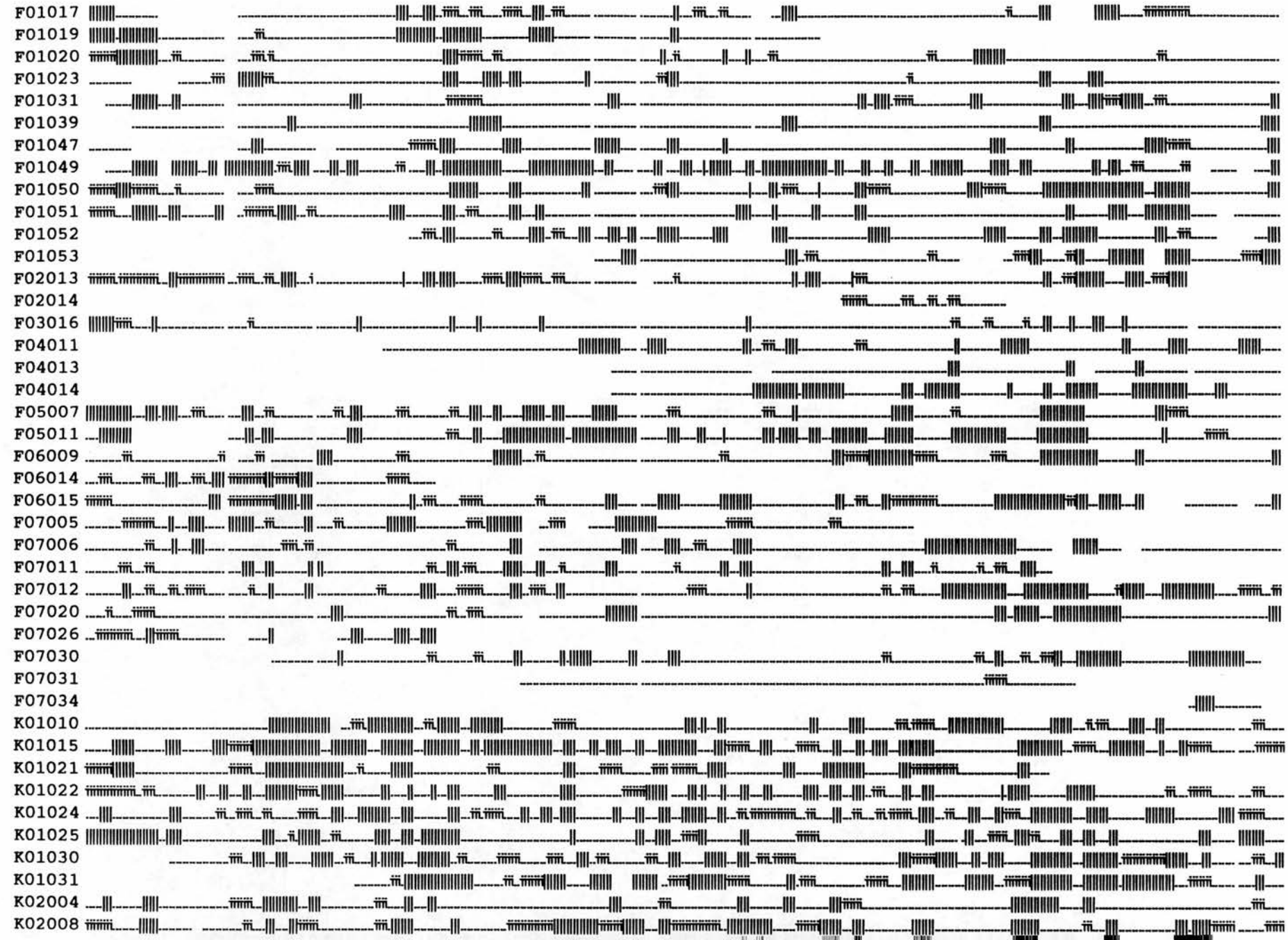
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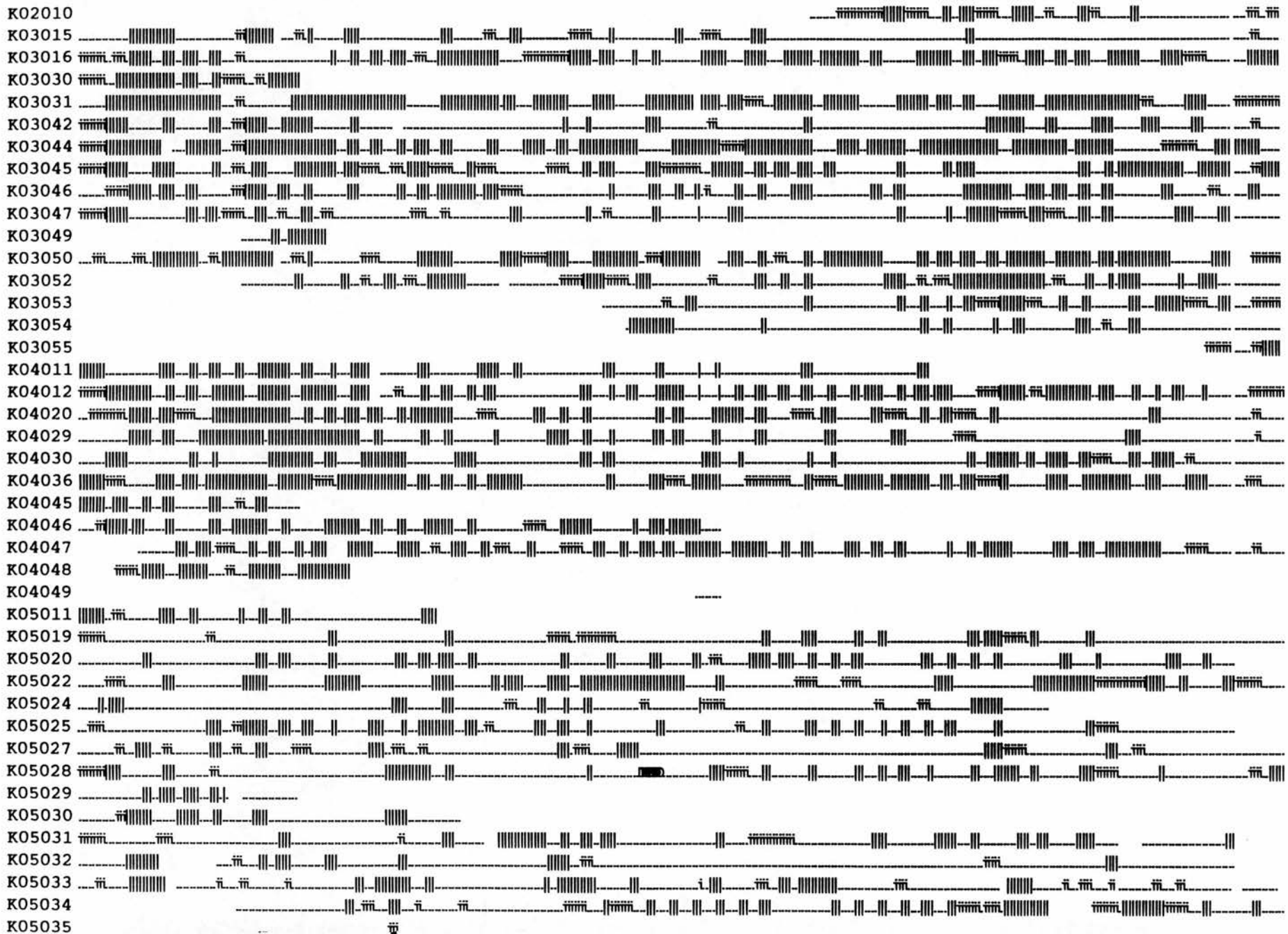
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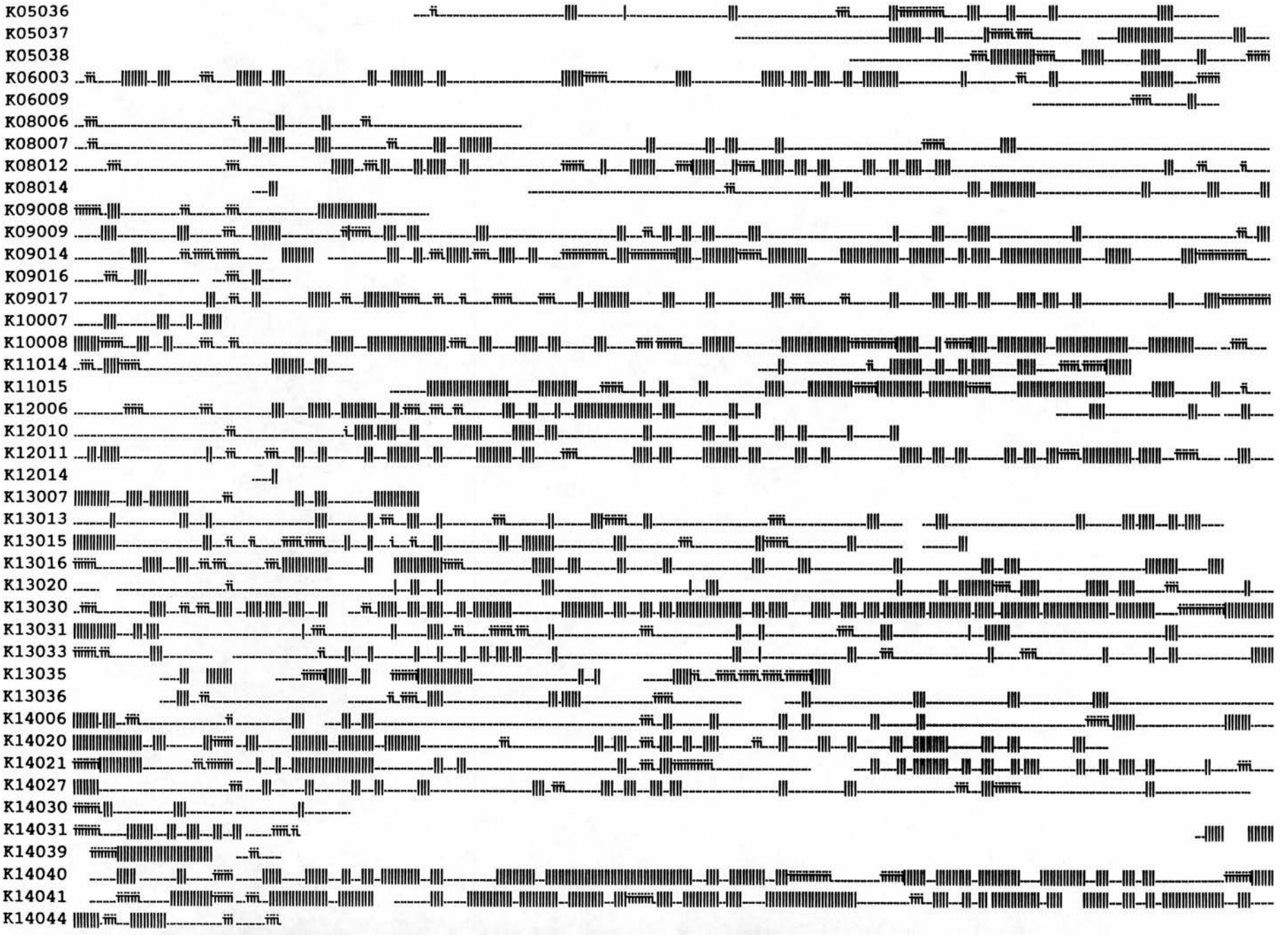
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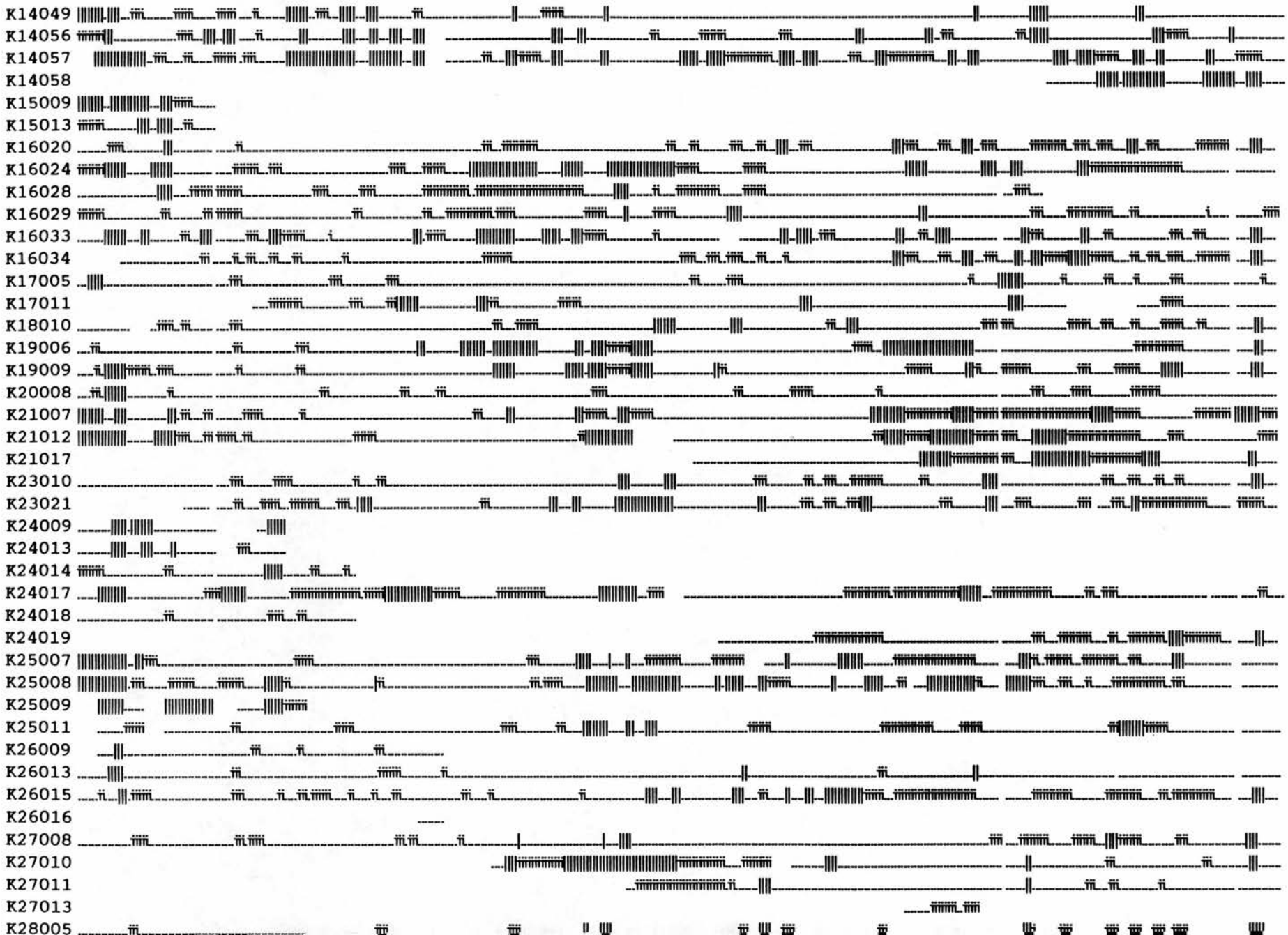
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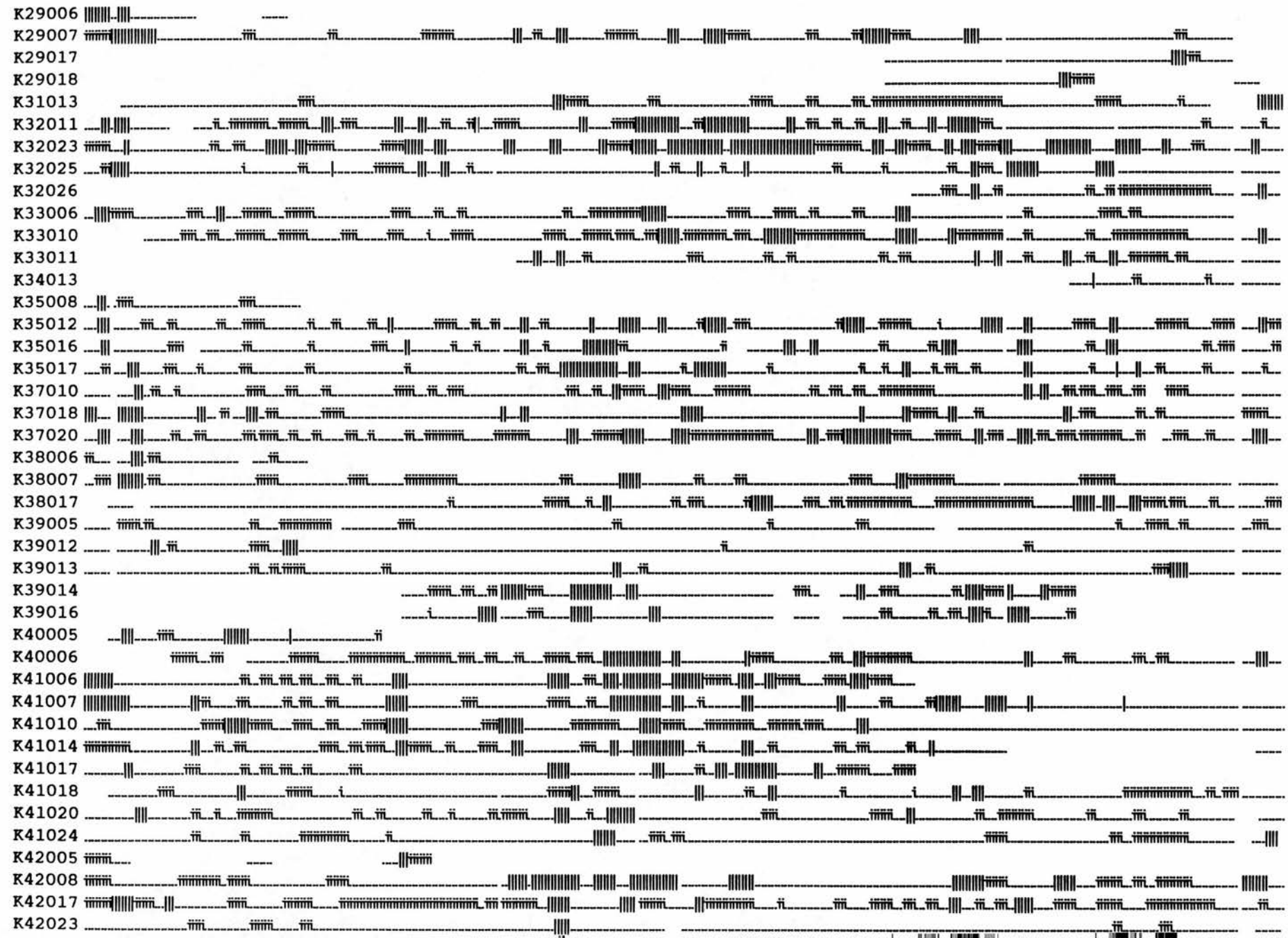
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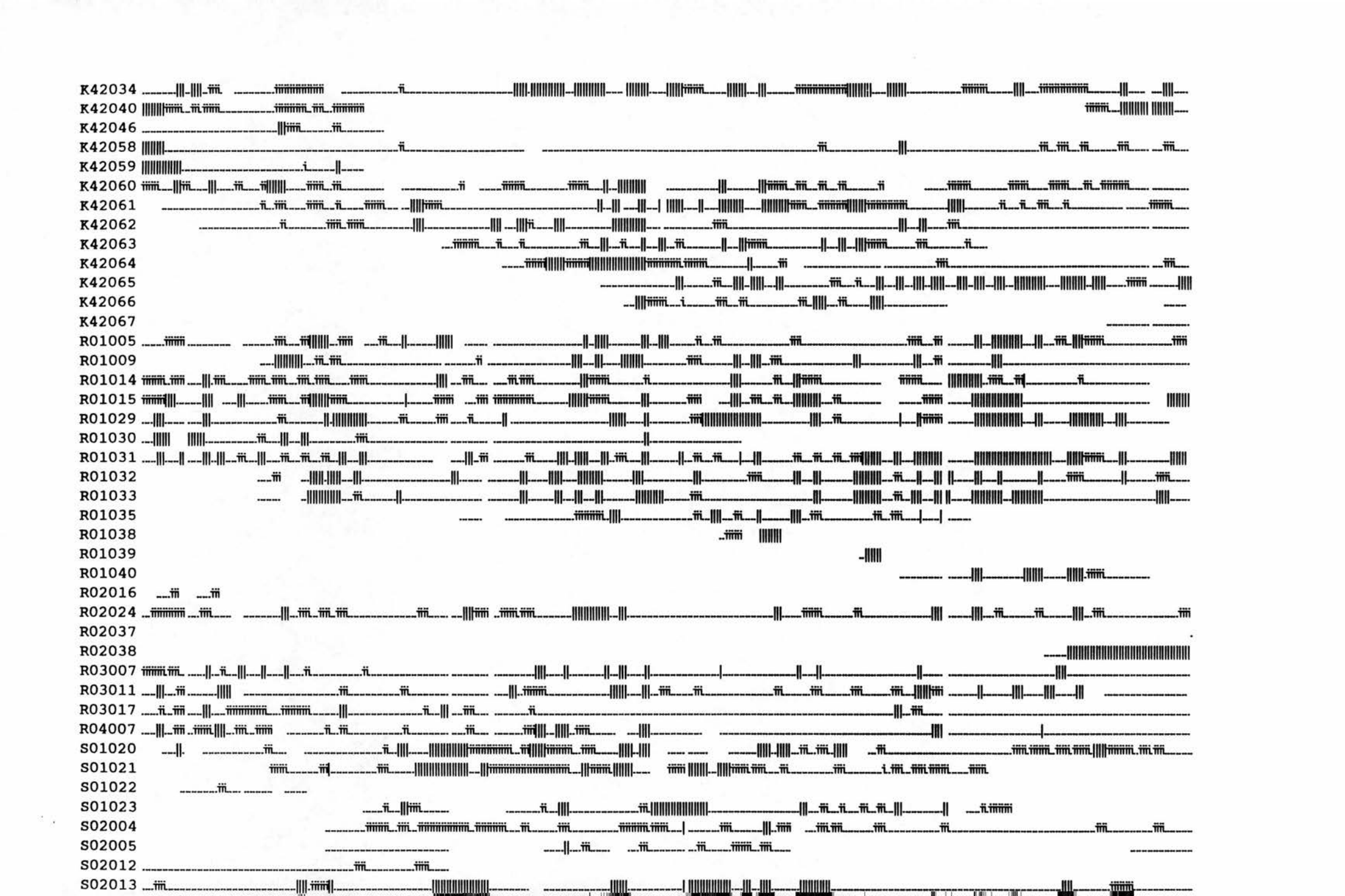
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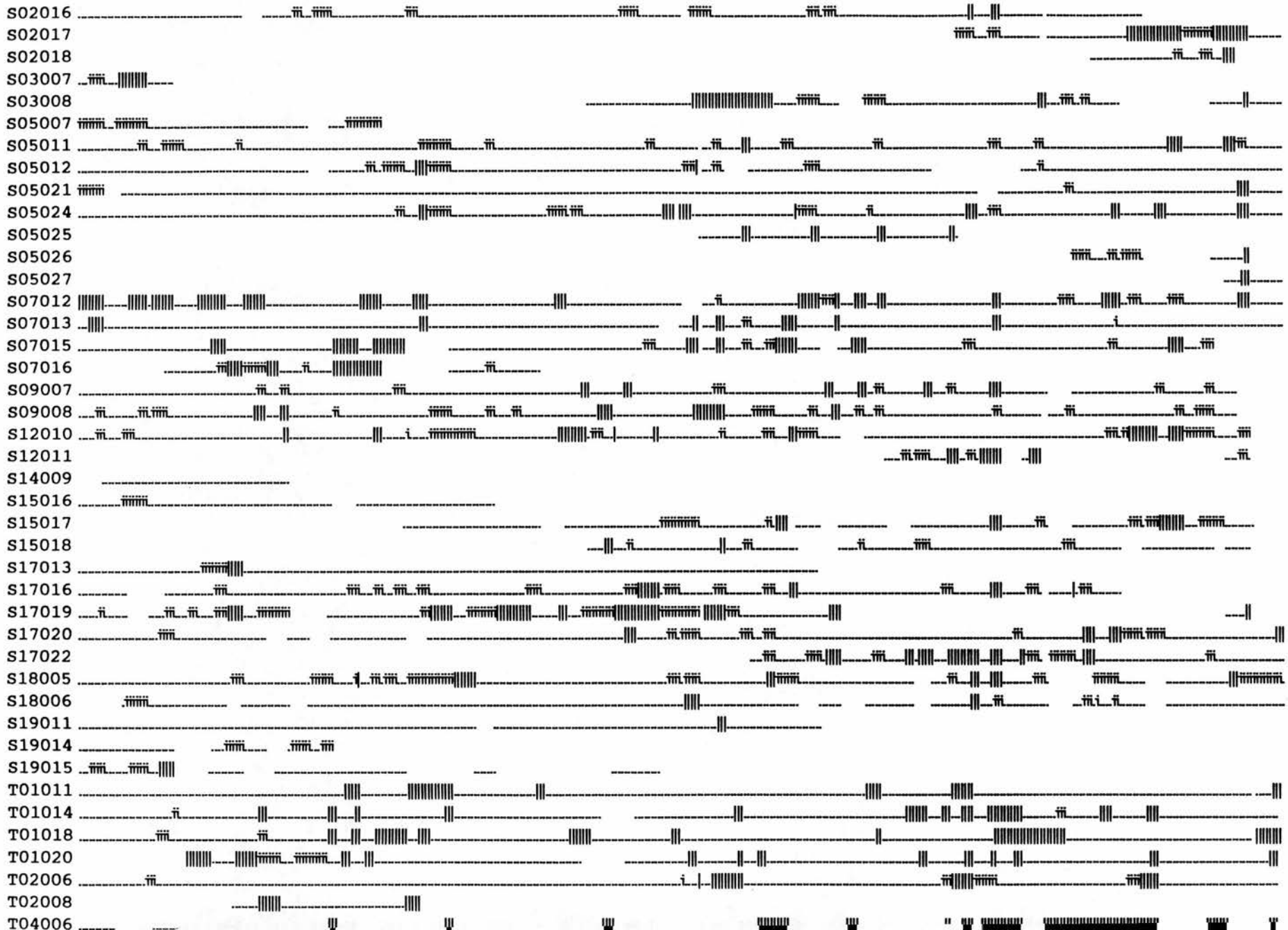
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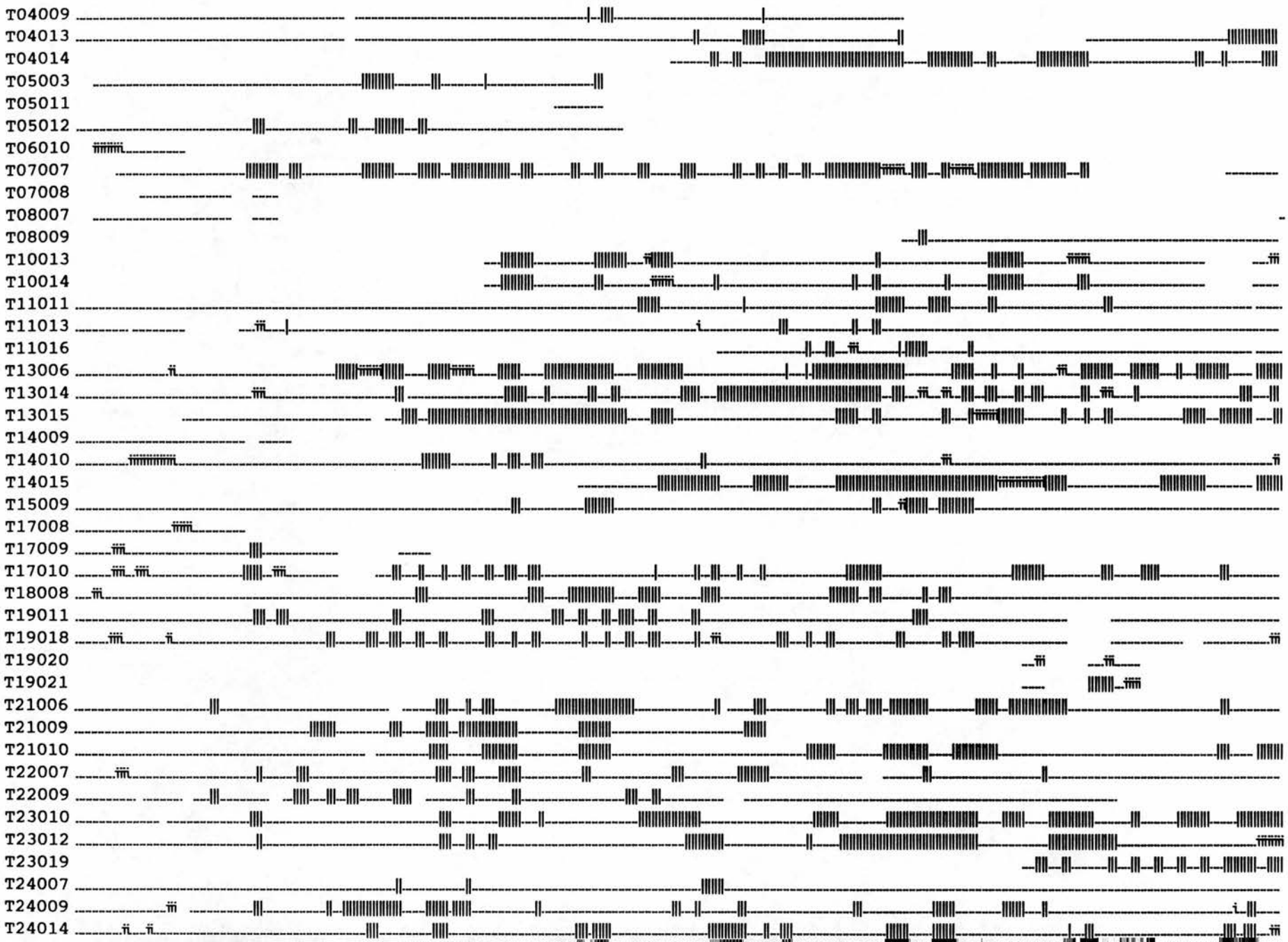
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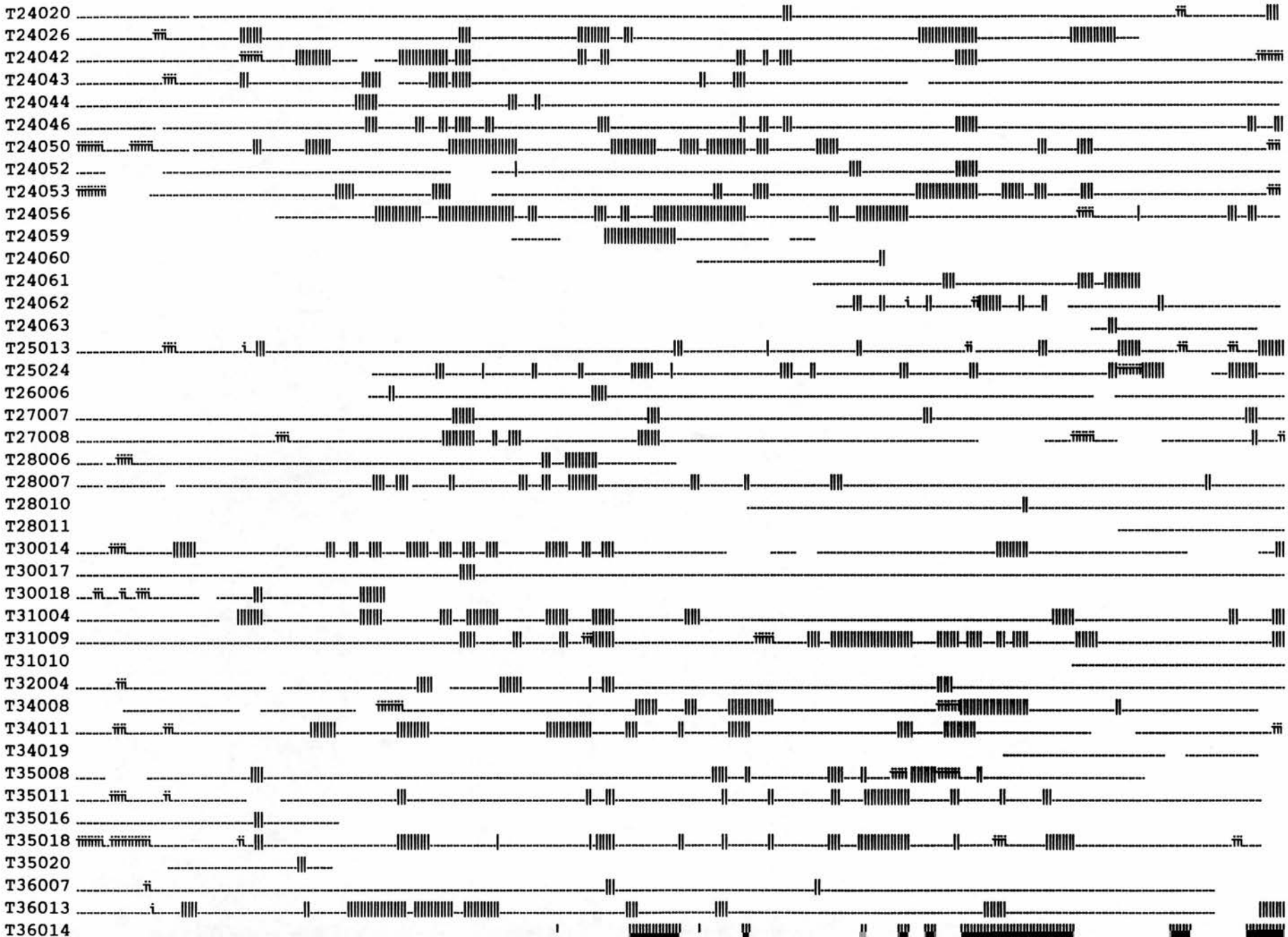
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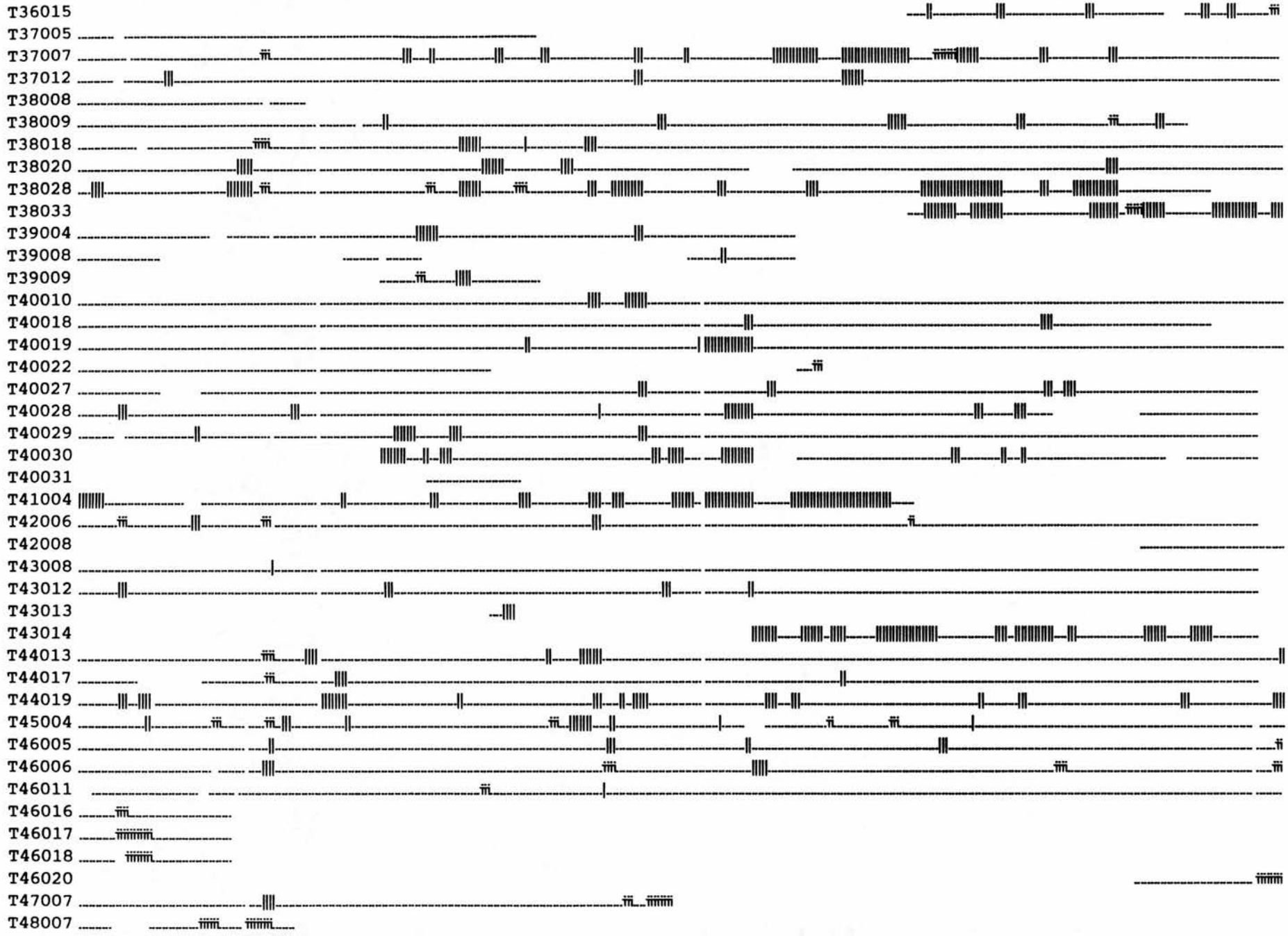
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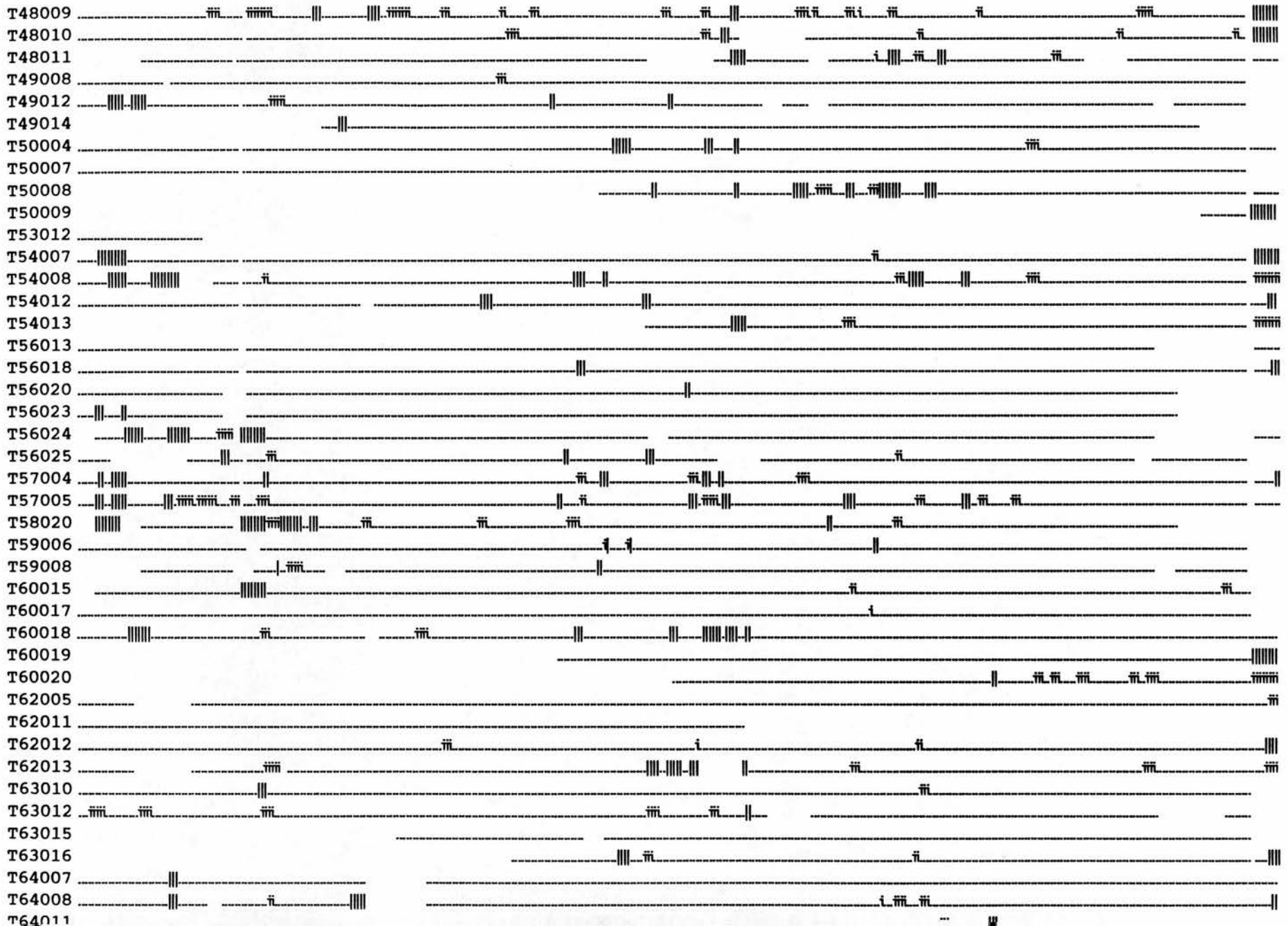
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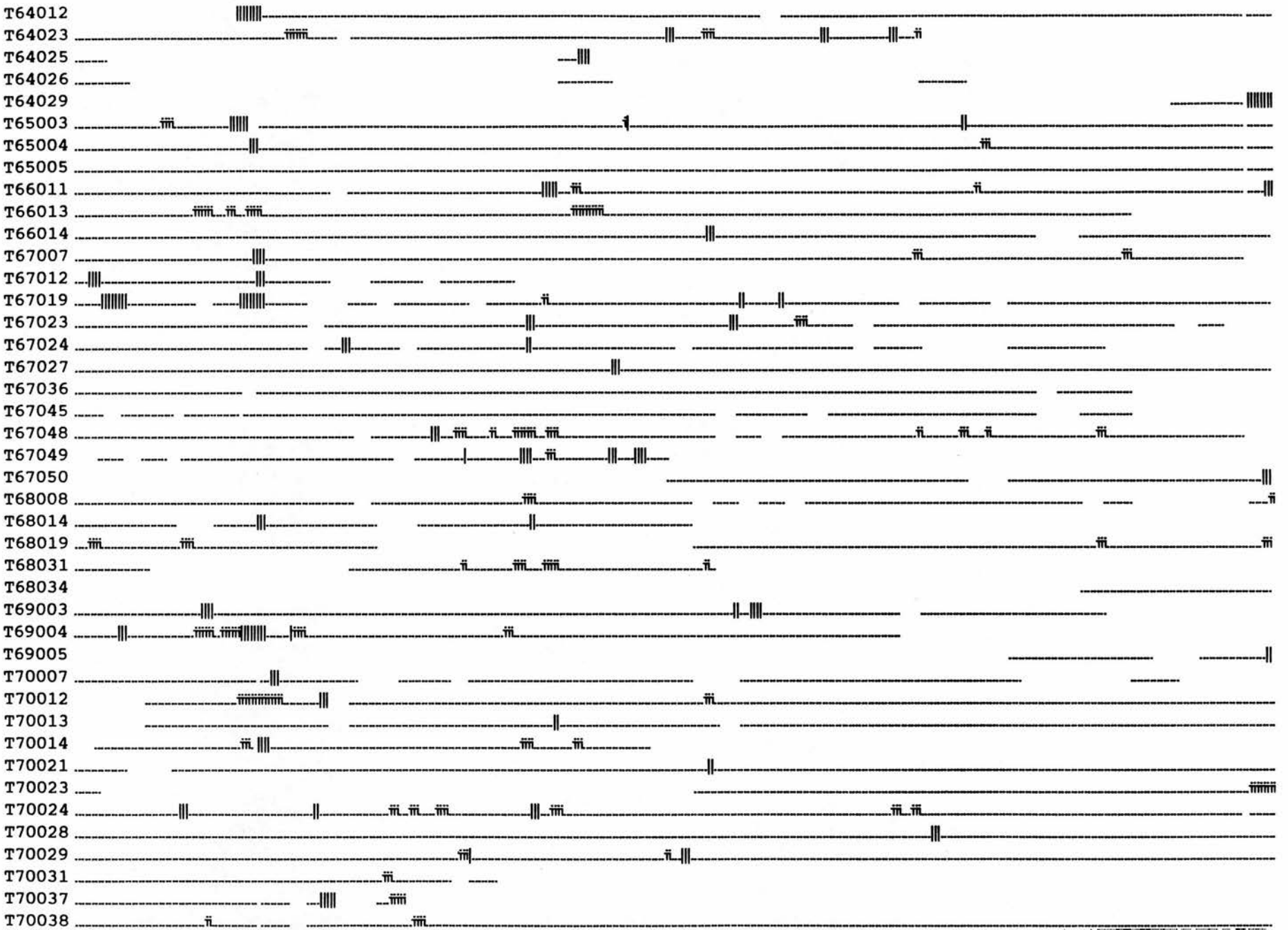
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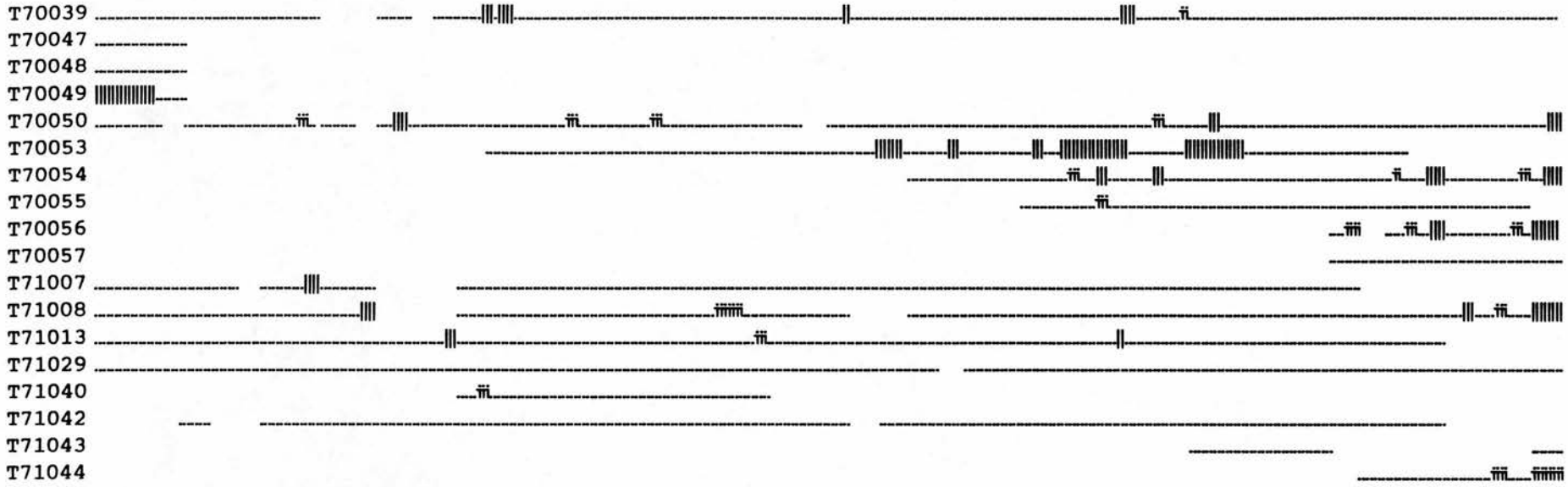
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d. GLOSSARY

GLOSSARY

Definitions

"Open chest"

This is a literal translation of the Mandinka word "sise yelo" which represents a collection of chest symptoms (with features of pneumonia) whose presence in a child are interpreted as severe ARI. The presence of "sise yelo" is determined usually by a "sisebulandila".

"Sisebulandila"

This the name for a particular type of local healer who is experienced in assessing the presence or absence of "sise yelo". He establishes whether or not the condition is present by comparing the distance measured from one shoulder tip to the other via the top of the child's head with the circumference of the chest at nipple level. If the latter distance is the greater then the child's chest is said to be "open". The Sisebulandila then "closes" the chest by tying the cloth with which he made the measurement tightly around the chest and praying over the child.

"Chest pain"

This is a literal translation of a local expression frequently used by mothers to describe difficulty breathing in their child. The exact nature of the perceived breathing difficulty is not clear. However mothers consistently report that the symptom is present if the child cries when being lifted by the chest.

"Pneumonia"

Many Gambians are familiar with the English word "pneumonia" and take it to have the same meaning as the Mandinka word "sumaya kurango" (literally "cold weather disease"). Throughout the study where the mother was not familiar with the English word we used the expression "sumaya kurango".

"Jumping chest"

This is a literal translation of the Mandinka phrase "sise jankaro" which describes a chest sign which mothers report when they are aware of the child's prominent apex beat visible through the chest wall of an unwell and thin child.

Marabout

Marabouts are Muslim men with several years Islamic education and training and who are considered to have the power to seek out the cause of a variety of social, financial and medical problems and to find their solution. They also provide amulets or charms to protect against future dangers. Almost all rural Muslim infants have these amulets tied around their chest or arms. The work of the marabout is based to some extent on Islamic medical traditions, but they also provide a wide range of other services and are consulted by non- Muslims as well as Muslims.

e. LIST OF PUBLICATIONS BY AUTHOR RELATED TO THESIS

LIST OF PUBLICATIONS BY AUTHOR RELATED TO THIS THESIS.

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f. COPY OF SELECTED PUBLISHED ARTICLES

Child Health

TRIAL OF CO-TRIMOXAZOLE VERSUS PROCAINE PENICILLIN WITH AMPICILLIN IN TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA IN YOUNG GAMBIAN CHILDREN

H. CAMPBELL
I. M. FORGIE
N. LLOYD-EVANS[1]
P. BYASS
K. P. O'NEILL
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Medical Research Council Laboratories, Fajara, The Gambia; and Gambia Government MRC Joint Research Unit,[1] Fajara

Summary 134 Gambian children under 5 years of age with severe pneumonia (as defined by the World Health Organisation classification of acute respiratory infections) were given either oral co-trimoxazole for 5 days, or a single intramuscular dose of fortified procaine penicillin and 5 days of oral ampicillin. At 2 weeks, there was no significant difference in outcome between the two groups. Co-trimoxazole is much less expensive than ampicillin or procaine penicillin, requires only twice-daily administration, and can be given by health-care staff with little training. The results support the use of co-trimoxazole as the antibiotic of first choice in outpatient management of young children with pneumonia in developing countries.

INTRODUCTION

MORE than four million children under the age of 5 years die of pneumonia every year.[1] In 1982–83, an investigation[2] of the causes of death in children under 5 years in Farafenni, a rural area of The Gambia, showed that chest infections were the commonest cause of death in children after the neonatal period. The annual mortality rate attributed to chest infections in this age-group was approximately 10 per 1000 children. A study[3] at the Medical Research Council (MRC) hospital in Fajara, The Gambia, indicated that *Streptococcus pneumoniae* (isolated in 53% of cases) and *Haemophilus influenzae* (isolated in 20% of cases) were the pathogens most frequently identified in patients with clinical or radiological evidence of pulmonary consolidation. All the *Strep pneumoniae* and *H influenzae* isolates were fully sensitive to penicillin, ampicillin, and co-trimoxazole, and the *H influenzae* isolates were all β-lactamase negative.

Because the high frequency of bacterial infections may explain, at least in part, the high mortality of acute respiratory infections in developing countries, the World Health Organisation (WHO) scientific working group on acute respiratory infections[4] has emphasised the need for early use of appropriate antimicrobial drugs in the treatment of children with clinically diagnosed pneumonia. In The Gambia, as in other developing countries, co-trimoxazole is widely used for the treatment of pneumonia in children but there is little published evidence of its efficacy. We report a controlled trial of co-trimoxazole given for 5 days, compared with a regimen of one intramuscular injection of fortified procaine penicillin with a 5-day course of oral ampicillin, in the treatment of children who had community-acquired pneumonia.

PATIENTS AND METHODS

The trial formed part of a larger community-based study of pneumonia in young children in a rural area of The Gambia, 350 km from the capital, Banjul.

143 children, aged 1 month to 4 years, who presented with signs of severe pneumonia between March, 1987, and March, 1988, were considered for entry into the trial. 113 were recruited by trained field workers during an active surveillance programme in 7 villages which were 10 to 15 km from the MRC Basse field station; the other 30 cases were recruited from the outpatient department of the government health centre in Basse. Admission to the trial was considered if the child had an acute respiratory illness for less than 1 week with signs of respiratory distress (intercostal indrawing or nasal flaring), and had not received antibiotics in the previous 2 weeks. 9 children with severe pneumonia were excluded: 5 were unable to take tablets, 3 had very severe disease (convulsions, drowsiness, or severe dehydration), and the mother of 1 child refused to take part. After assessment by the project clinician, the remaining 134 children were assigned sequentially to one of the two treatment groups. Mothers gave oral consent before their children were entered into the study, which had been approved by the Gambia Government and MRC joint ethical committee.

The WHO recommends inpatient treatment for young children with severe pneumonia who show indrawing of the intercostal spaces. However, because of the shortage of inpatient treatment facilities (there are only 10 paediatric beds at Basse health centre) only 5 children, who had striking evidence of systemic upset or who were severely malnourished, were admitted; the others were managed as outpatients. Children in group A received a 5-day course of oral co-trimoxazole. Those in group B received a single

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intramuscular injection of fortified procaine penicillin (procaine penicillin 4 megaunits plus benzylpenicillin 1 megaunit per vial) and a 5-day course of oral ampicillin. Doses were calculated according to current WHO recommendations.[5] All children with fever were also given chloroquine.

Samples of blood, urine, and nasopharyngeal aspirate were collected from each child. A chest radiograph was assessed independently by a paediatric radiologist. Details of the laboratory methods and findings will be published separately.

Outcome was assessed in two ways. Firstly, trained field workers visited the homes of the children from the surveillance villages in the first and second weeks after treatment was started, and recorded respiratory rate, temperature, and the presence or absence of intercostal indrawing. They also recorded symptoms of respiratory illness in the preceding week. The field workers had no knowledge of the treatment group allocation at the time of assessment. Secondly, mothers were interviewed by the clinician after 2 weeks and were asked to score their child's cough, breathing difficulty, fever, and appetite as better, the same, or worse. At this visit, the project clinician examined each child and made a clinical assessment of outcome, without reference to the original casenotes which recorded the treatment group. All assessments for study entry and of final outcome were made by the same clinician.

95% confidence intervals of differences in means or proportions between the two groups have been compared.

RESULTS

43% of mothers reported vomiting and 28% reported refusal to feed, but only 5 children were excluded from the trial because of inability to take oral treatment. Sequential allocation resulted in good matching of the children in the two treatment groups. 66 were allocated to group A (41 boys and 25 girls), and 68 to group B (38 boys and 30 girls). The mean age was 22 months in group A, and 21·8 in group B; 30% and 36% were under the age of 1 year, respectively. There were no significant differences between the two groups in any of the symptoms, signs, or laboratory findings (eg, length of illness, mean respiratory or heart rate, mean temperature, presence of auscultatory or radiological changes consistent with pneumonia, and blood culture isolation rate). Children recruited from the health centre had a higher mean respiratory rate compared with children recruited from community surveillance (62·6 *vs* 52·4 per min) and a higher mean heart rate (150·1 *vs* 117·5 per min). A higher proportion of health centre patients had radiological changes consistent with pneumonia (70·0% *vs* 28·8%), and of lobar consolidation (30·0% *vs* 8·2%), and were more likely to have a positive blood culture (14·8% *vs* 0·9%). These differences are significant: all children in this study satisfied the WHO classification for severe pneumonia, but the group identified at the health centre were more seriously ill.

COMPARISON OF CHILDREN WITH SEVERE PNEUMONIA TREATED WITH ORAL CO-TRIMOXAZOLE (GROUP A) AND CHILDREN TREATED WITH PROCAINE PENICILLIN PLUS ORAL AMPICILLIN (GROUP B)

—	Group A (n = 66)	Group B (n = 68)	Difference (95% CI)
Mothers' assessment at 2 wk			
No continuing problem	56/66 (84·8%)	56·65 (86·2%)	−1·4% (−13, 11)
Cough better	62/66 (93·9%)	61·65 (93·8%)	0·1% (−8, 8)
Breathing difficulty better	63/66 (95·5%)	62·65 (95·4%)	0·1% (−7, 7)
Appetite better	65/66 (98·5%)	62·65 (95·4%)	3·1% (−3, 9)
Clinician's assessment at 2 wk			
Outcome same or worse	5/66 (7·6%)	5/65 (7·7%)	−0·1% (−9, 9)
Incomplete recovery: further treatment given	1·66 (1·5%)	2·65 (3·1%)	−1·6% (−7, 4)
*Field workers' assessment in first wk**			
Reduced respiratory rate	46·51 (90·2%)	44·50 (88·0%)	2·2% (−10, 14)
Afebrile or reduced temperature	41·51 (80·4%)	37·50 (74·0%)	6·4% (−10, 23)
Indrawing ceased	44/51 (86·3%)	41·50 (82·0%)	4·3% (−10, 19)

*Excludes cases recruited at Basse health centre.

Only 5 children (3·7%) were admitted to the health centre, 2 from treatment group B, and 3 from group A. 2 children died, both in group B—an overall mortality of 1·5%. There were no significant differences between the two groups in terms of final outcome at 2 weeks follow-up when assessed either by the mothers or the clinician. The single-blind recordings by field workers in the first week of follow-up also showed no significant differences between the groups (see table). The results were similar when the village and health-centre patients were analysed separately.

DISCUSSION

Early use of antibiotics has been recommended to prevent deaths from community-acquired pneumonia;[6,7] evidence from a few studies has supported this policy.[8,9] WHO guidelines propose three alternative first-line outpatient treatments for children with pneumonia: procaine penicillin, co-trimoxazole, and ampicillin or amoxycillin. We have compared the efficacy of co-trimoxazole against ampicillin plus a single intramuscular injection of fortified procaine penicillin. Gutman[10] has suggested that co-trimoxazole should not be used in neonates. Furthermore, the absorption of oral co-trimoxazole in sick neonates is unknown: children under the age of 1 month were therefore excluded from this study.

Strict sequential allocation of children to the two groups resulted in good matching for reported symptoms, signs on examination, and laboratory findings at presentation. Outcome in the two groups was similar; children who were treated with co-trimoxazole seemed to recover as well as those given penicillins. This finding is important because a course of oral co-trimoxazole can be administered by all grades of health worker, including village health workers with little training, and a course of co-trimoxazole is only 12·5–20% of the cost of ampicillin.[11,12]

Co-trimoxazole is effective in vitro against most bacteria that are known to cause community-acquired pneumonia in young children, including *Strep pneumoniae* and *H influenzae*. It is also active against chlamydia and pneumocystis, which may cause pneumonia in early infancy.[13] It is cheap, requires only twice daily administration, and is well tolerated. The use of co-trimoxazole by village health workers as part of a health education and improved case management project in the rural Bagamoyo district of Tanzania[9] resulted in a 30% reduction of the specific mortality rate from acute respiratory infections. Adverse reactions are uncommon, and the two most serious—exfoliative dermatitis and bone marrow depression—are very rare. The incidence of fatal reactions in both Sweden and in Britain has been estimated at less than 1 in 100 000 children.[14,15]

Two major concerns might arise from widespread use of co-trimoxazole as a first-line treatment against acute respiratory infections in developing countries. Firstly, widespread use of co-trimoxazole might induce resistance to

antimalarials, such as sulphadoxine with pyrimethamine. Secondly, widespread use of co-trimoxazole could lead to selection of strains of *Strep pneumoniae* and *H influenzae* with reduced sensitivity. A report from North Carolina has linked the increasing use of co-trimoxazole for otitis media with an increasing proportion of pneumococci with reduced sensitivity to co-trimoxazole.[16] It is therefore essential to train health workers to identify those children with acute respiratory infections who require antibiotic treatment. Use of validated clinical signs for the diagnosis of chest infections can substantially reduce the overall use of antibiotics in the community, whilst the children who require antibiotic treatment can still be reliably identified.[17] Intermittent surveillance of the antibiotic sensitivities of *Strep pneumoniae* and *H influenzae* isolates should be used to monitor changes in sensitivity patterns.

We have found that early identification of pneumonia from simple clinical signs, followed by prompt treatment with oral co-trimoxazole, is effective against community-acquired pneumonia. In developing countries, where most strains of *Strep pneumoniae* and *H influenzae* are found to be sensitive, a strong case can be made for use of co-trimoxazole as a first-line treatment in the management of young children with pneumonia.

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Point of View

MEMORIES: A NEGLECTED CONCEPT IN CARE

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IT is surprising sometimes how a series of chance events, comments, or ideas set off a train of thought that leads to a rethinking of the patterns of care provided for patients, families, and staff. A few lines from a television programme and a comment from a relative and a patient, occurring within a few hours of each other, occasioned my review of the concept of memories. As usual, the concept is not new, but its importance in the provision of care is perhaps sufficiently neglected for us to remind ourselves of the implications of memory. Neither is it a surprising concept. Talk to any group of patients, relatives, friends, or colleagues about an event involving medical care and the phrase, "I remember . . . ", occurs very frequently. What was new for me was the implication behind the statement, for the quality of care delivered. Nor is the recognition of importance of memories a new one. Their psychological significance is well recognised, and for professionals our experience and recollection of events, people, or incidents affect our clinical practice and are an important stimulus to learning. These random thoughts, therefore, led me to take a closer look at "memories" in clinical care.

The first thought which struck me was that memories are uniquely related to the individual and sometimes bear little relation to what actually happened. They are often intensely personal and tiny details of what happened, of which others may have taken little or no notice, may stand out. It is not possible to predict what will be remembered by any individual, and this idiosyncrasy is crucial to the concept of memory and its place in the provision of care. The link with learning is relevant here too. Faced with almost any critical situation, (a sick child, a patient in coronary care, a postoperative problem), a group of medical students will, individually, recollect and learn different aspects from these cases. So it is with patients and relatives. The personal, individual view predominates. Inevitably, if one sees patients who are ill or dying many of the events remembered are related to those surrounding the period of the last illness. The lessons learned, however, are applicable to all aspects of medicine and all episodes of care.

The second thought was that memory covered several different, though related, activities. There is the memory of the doctor and what he or she said or did; the memory of the team; of the place of care—ward, room, house; and memories of the patient and the family and their response to the illness. It is not difficult for the doctor or nurse to remember particular places, rooms or their furnishings associated with a particular patient, long after the patient has gone. It is not difficult to recollect how a doctor dealt with a member of the family. Specific memories are important, as is their impact. For example, one nurse recalled the arrangement of flowers outside a particular ward which reminded her of a funeral parlour. She could not enter the ward without thinking about this. In contrast, other nurses felt that the area was welcoming and friendly. The memory of the kindness of a nurse, a smile, a handshake, a word of thanks, a telephone call can often be instantly recalled.

days and at 6 weeks, but not beyond this age. Colostrum may therefore be especially beneficial for the infant's cell-mediated immune response. In infants who received BCG after 1 month of age, only 6 were still breast-feeding, 3 of whom stopped within 1 month of immunisation: the low numbers may explain the similar PPD SI responses for formula-fed and breast-fed infants who were vaccinated later. Breast-fed infants who had a BCG vaccination in the first week of life had a higher lymphocyte response to PPD than formula-fed infants. Therefore the response to BCG immunisation at birth may be enhanced by breast-feeding. The numbers of children were too small to determine if duration of breast-feeding affected response to PPD. There was no correlation between maternal PPD immunity and the lymphocyte response to PPD of the breast-fed infants and, like Keller et al,[7] we found no evidence for passive transfer of PPD immunity by breast-feeding. There was no change in the immune response to candida and SK antigens, which may induce a later immune response as exposure to environmental organisms increases.[11]

Does colostrum contain a substance that enhances the infant's immune system response to various antigens? Our findings, like those of Stephens and colleagues,[10] indicate that breast-fed infants do have an enhanced immune response during the first few weeks of life.

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ASSESSMENT OF CLINICAL CRITERIA FOR IDENTIFICATION OF SEVERE ACUTE LOWER RESPIRATORY TRACT INFECTIONS IN CHILDREN

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Summary 222 acute lower respiratory tract infections (LRI), as defined by the World Health Organisation, were identified during one year's surveillance of a cohort of 500 Gambian children aged 0 to 4 years. Symptoms and signs at presentation were related to radiological evidence of lobar consolidation, indicating severe LRI. In infants, a fever of greater than 38·5°C, refusal to breast-feed, or the presence of vomiting were the best predictors of severe LRI. In children aged 1 to 4 years, a fever of greater than 38·5°C or a respiratory rate greater than 60/min were the most accurate clinical signs for severe LRI. Chest indrawing did not discriminate severe LRI. These community-based findings differ from results of hospital-based studies.

Introduction

ACUTE lower respiratory infections (LRI) are an important cause of death and illness in young children in developing countries.[1] The age-specific mortality from LRI in young Gambian children has been estimated at 10 per 1000 each year.[2] One of the main objectives of the World Health Organisation's acute respiratory infections programme is to improve case detection and patient management by primary health-care workers,[3] and so reduce mortality. The village health workers (VHWs) need to identify those children with respiratory symptoms who require antibiotic treatment, and to decide which children require immediate referral for inpatient treatment. Simple clinical signs have been identified that can predict the need for antibiotic treatment.[4,5] WHO recommends that children with LRI who are unable to take oral fluids reliably, or who show chest indrawing, should be referred for inpatient treatment; in areas in which wheeze is common, WHO recommends that children with wheeze should be referred only if they are unable to drink or have a respiratory rate above 70/min.[6] These recommendations have been made from the results of predominantly hospital-based studies.[7,8] However, clinical experience of hospital practice alone is insufficient to plan primary health care programmes.[9] When used in the community and among health-centre outpatients, WHO criteria can fit children with substantially different severities of illness.[10] For one year we monitored the occurrence of LRI in a cohort of approximately 500 rural Gambian children under the age of 5 years. Presenting symptoms and signs of infection were compared with radiological evidence of lobar consolidation in one or more lobes, to identify the clinical features that might best be used in the community to discriminate between mild and severe LRI. Radiological evidence of lobar consolidation was used to indicate the severity of infection because it can be assessed objectively.[11] A study in Fajara, a peri-urban area of The Gambia, showed bacterial infection in 69% of children who were seen in an outpatient department and who had lobar consolidation (blood culture was positive in 27%).[12] Similarly, we have found bacteraemia in 5 of 14 children with both LRI and lobar consolidation on radiography who attended Basse health centre, but in only 4 of 36 who did not have consolidation. Children with lobar consolidation are probably more severely ill, and most have pneumococcal or *Haemophilus influenzae* infection,[13] and the observer variation that occurs in X-ray reporting is likely to be substantially less for the presence or absence of a striking

abnormality such as lobar consolidation than for less obvious changes.

Patients and Methods

The study was done in a rural area of The Gambia, 350 km from the capital, Banjul. A cohort of approximately 500 children under 5 years of age was surveyed for one year; they lived in 7 villages, 10–15 km from the Medical Research Council (MRC) field station in Basse. Children were visited weekly and examined for signs of LRI by trained field workers, who lived in the study villages and were frequently asked to see children who became ill between the weekly visits.

Field workers were trained to record accurately a child's respiratory rate and temperature, and to recognise signs of respiratory distress. All children with a respiratory rate above 50 /min, chest indrawing, nasal flaring, wheeze, stridor, or severe systemic upset (such as an inability to drink) were referred to the project clinician. Other children with an acute respiratory infection that did not satisfy these criteria, but whom a field worker thought might have LRI, were also referred.

All children referred were examined by the project clinician, and samples of blood were collected. A chest radiograph was assessed independently by a paediatric radiologist. Radiographs were identified by code and included films from children without a clinical diagnosis of LRI; clinical details were not made available to the radiologist.

Axillary temperature was recorded at each weekly visit, and also when a child was referred to the project clinician. A thick blood film was examined for malaria parasites if the temperature was 37·5°C or greater.

χ^2 tests with Yates' continuity correction were used to calculate the differences in distribution of clinical signs and symptoms between groups with and without radiological evidence of lobar consolidation. Signs and symptoms which were significant on univariate analysis were considered together by use of multiple logistic regression. Sensitivity, specificity, and positive predictive value were calculated by standard methods.

Results

222 episodes of LRI among 491 children (mid-year population) met WHO criteria (cough with respiratory rate above 50/min, indrawing, wheeze, or stridor). The age distribution (mid-year cohort age distribution used as the denominator) was 83/119 aged 0–11 months; 61/118 aged 12–23 months; 39/96 aged 24–35 months; and 39/158 aged 35–60 months. Half had a weight less than 80% of the median for age (NCHS standards), and 8% weighed less than 60% of the median. In 138 (62%) episodes chest indrawing was noted, and in 10 (5%) the child was reported to be unable to take oral fluids reliably. A chest radiograph was done in 216: 81 (38%) showed radiological changes consistent with LRI and 25 (12%) showed lobar consolidation.

Table I shows the symptoms and signs at presentation compared with radiological changes. Clinical features that discriminated best between children with radiological signs of lobar consolidation and those with less severe changes or normal radiographs were auscultatory findings of bronchial breathing or reduced air entry, respiratory rate above 60/min, axillary temperature above 38·5°C, grunting, and a history of refusing to breast-feed or take solids. Intercostal indrawing, nasal flaring, and crepitations heard on auscultation did not reliably distinguish those with lobar consolidation. Table II shows the sensitivity, specificity, positive predictive value, and prevalence of selected symptoms and signs.

In infants, refusal to breast-feed (found in 43% with lobar consolidation *vs* 11% without) and temperature above 38·5°C (43% *vs* 11%) were the best predictors for severe LRI. In older children, bronchial breath sounds (39% *vs* 4%), temperature above 38·5°C (76% *vs* 23%), and respiratory rate above 60 /min (61% *vs* 21%) were the most accurate. When multiple episodes of LRI in the same child were omitted there were 162 episodes, 23 of which had lobar consolidation. Only bronchial breath sounds or decreased air entry (odds ratio 6·6, 95% CI 1·5–29·4) and fever above 38·5°C (8·6, CI 3·1–24·1) were independently associated with severe disease after adjustment for other factors.

Only 13 (14%) of 90 children with LRI and a temperature above 38·5°C had malarial parasites in the thick blood film. This level of parasitaemia is no higher than would be expected in a group of healthy rural Gambian children with a similar age distribution.[14]

TABLE I—RELATION OF SYMPTOMS AND SIGNS TO RADIOLOGICAL CHANGES

—	Lobar consolidation: Present n = 25	Lobar consolidation: Absent n = 191	p
Symptoms			
Vomiting	17 (68%)	88 (46%)	NS
Rapid breathing	15 (60%)	135 (71%)	NS
Refusing to feed	11 (44%)	42 (22%)	<0·05
Signs			
Chest indrawing	15 (60%)	117 (61%)	NS
Severe chest indrawing	2 (8%)	12 (6%)	NS
Nasal flaring	4 (16%)	26 (14%)	NS
RespR > 50 /min	21 (84%)	130 (68%)	NS
RespR > 60 /min	15 (60%)	52 (27%)	<0·01
HR > 160 /min	7 (28%)	30 (16%)	NS
T > 37·5°C	20 (80%)	87 (46%)	<0·01
T > 38·5°C	15 (60%)	35 (18%)	<0·001
Crepitations	6 (24%)	62 (32%)	NS
BB or RAE	8 (32%)	6 (3%)	<0·001
Rhonchi	2 (8%)	40 (44%)	NS
Grunting	3 (12%)	3 (2%)	<0·025

RespR = respiratory rate; HR = heart rate; T = temperature; BB = bronchial breathing; RAE = reduced air entry; NS = not significant.

TABLE II—SENSITIVITY AND SPECIFICITY OF SYMPTOMS AND SIGNS IN PREDICTION OF LOBAR CONSOLIDATION

—	Lobar consolidation: Present (n = 25) % with sign (*Sensitivity*)	Lobar consolidation: Absent (n = 191) % without sign (*Specificity*)	Prevalence (%)	Positive predictive value
Symptoms				
Vomiting	68	54	49	0·16
Refusing feed	44	78	25	0·21
Signs				
Chest indrawing	60	39	61	0·11
RespR > 50 /min	84	32	70	0·14
RespR > 60 /min	60	73	31	0·22
T > 37·5°C	80	54	50	0·19
T > 38·5°C	60	82	23	0·30
Grunting	12	98	3	0·50
Crepitations	24	68	31	0·09
BB or RAE	32	97	6	0·57
RespR > 60 /min and T > 38·5°C	44	93	12	0·44

Abbreviations as for table I.

Discussion

In rural areas of developing countries, the case-fatality rate from LRI in children is most likely to be reduced if primary health-care workers can identify the most serious forms of LRI, and deal with them appropriately. Accurate guidelines to enable differentiation of children with LRI who can be safely treated with antibiotics as outpatients

from those who require immediate referral must be based on symptoms and signs that can readily be assessed.

Our results confirm that bronchial breath sounds or decreased air entry on auscultation, and the presence of grunting, are very specific signs of lobar consolidation. However, their usefulness is limited by the low sensitivity (especially in infants), and they are difficult signs to teach to non-medical staff. Intercostal indrawing and nasal flaring were not satisfactory predictors of lobar consolidation, even when we considered only those children with LRI who showed striking indrawing (7%), or excluded children with wheeze (8%). In infants, a high fever (above 38·5°C), vomiting, and refusal to breast-feed were the best predictors for lobar consolidation. In children aged 1 to 4 years the best predictors were a high fever (greater than 38·5°C) and a respiratory rate above 60/min; the presence of both signs together further increased the positive predictive value.

High fever, together with systemic upset or irritability and signs of consolidation (in older children), has been used to indicate bacterial pneumonia.[15,16] High fever alone has been used to indicate bacteraemia.[17-19] However, fever was not considered to be a useful indicator for the management of LRI in children in Papua New Guinea:[20] Shann et al,[7] measured forehead (not axillary) skin temperature and used "the need for inpatient treatment" (criteria for admission undefined) as their indicator of severity. Different populations were being studied (hospital outpatients in Papua New Guinea, and children identified by community surveillance in Basse) and, because fever often prompts mothers to take their children to the health services,[20] mothers may have tended to take febrile children with mild LRI to the health centre or hospital more often than non-febrile children with mild LRI. Furthermore, a different incidence of other febrile communicable diseases (especially malaria) may have interfered with the diagnosis of pneumonia and the assessment of its severity, or have coexisted in some children; only 14% of episodes of LRI in our study were associated with malarial parasitaemia. Both factors would tend to confound the relation between fever and severity of LRI.

We have found previously that a respiratory rate above 50/min and the presence of indrawing are satisfactory indicators of LRI (defined by clinical criteria) in young children.[5] However, current WHO criteria for recognition of severe LRI did not reliably identify children with lobar consolidation in this study, and there are insufficient rural paediatric inpatient facilities in The Gambia to admit all children with LRI who show indrawing (62% of all cases in this study; an annual incidence of 29 per 100 children aged 0 to 4 years). The results of hospital-based studies should be interpreted with caution when VHW training and national respiratory infection programmes are set up. Such programmes must adopt policies that take into consideration the health resources available to implement them. In rural areas of many developing countries the referral systems are poorly developed and paediatric inpatient facilities limited, and much of the primary care must be devolved to VHWs. The advice that such workers are given should come from community-based studies; ideally the recommended criteria for antibiotic treatment or referral should be validated locally before adoption.

We thank Dr Hilton Whittle, Ms Joanna Armstrong, and the MRC Basse field station staff.

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References at foot of next column

Preliminary Commun

RADIOIMMUNOIMAGING FOR DIAGNOSIS OF BONE MARROW INVOLVEMENT IN BREAST CANCER AND MALIGNANT LYMPHOMA

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Summary Granulopoietic bone-marrow was scintigraphically imaged in 15 patients with carcinoma of the breast and known skeletal metastases, 10 patients with malignant lymphomas, and 15 controls without suspected malignant disease, with a technetium-99m labelled murine monoclonal IgG_1 antibody directed against nonspecific cross-reacting antigen (NCA-95) and carcinoembryonic antigen. Immunoscintigraphy revealed more lesions than did bone scanning in both patient groups. This method offers a sensitive, cost-effective, and easy-to-perform whole body technique for evaluating metastatic spread.

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Ursodeoxycholic acid has no definite side-effects in patients without gallstones and none were observed. It is a promising first-line treatment of symptoms, and may slow or halt the progression of disease, but did not improve steatorrhoea.

Patients with primary biliary cirrhosis would probably appreciate a trial of ursodeoxycholic acid as single therapy since it will control symptoms in many of them.

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EPSTEIN-BARR VIRUS INFECTION AND THYROID DYSFUNCTION

SIR,— Epstein-Barr virus (EBV) is a herpes virus that can establish persistent infection. It is cytotropic for B lymphocytes and pharyngeal and cervical epithelial cells.[1] Infection of B lymphocytes results in their transformation and immortalisation and can lead to potent polyclonal activation of antibody production.[2] Epithelial cells provide a reservoir for viral persistence after primary infection.[3] EBV is the cause of infectious mononucleosis. During acute infection many organs may be affected but to date there is no evidence that the thyroid gland is involved.

A 13-year-old boy with a glandular-fever-like illness was admitted to hospital with an enlarged liver and spleen and abnormal liver function tests. A 'Monospot' test was positive. Tests for hepatitis B surface antigen and hepatitis A IgM antibody were negative. He was treated symptomatically and discharged after 4 days. 6 weeks later at outpatients he gave a 5-day history of diarrhoea, and a small diffuse goitre was found. Juvenile thyrotoxicosis was diagnosed on the basis of a free thyroxine (T4) of 61·2 pmol/l and a thyrotropin-stimulating hormone (TSH) of 0·6 mU/l, and treatment began. 2 days later the patient was admitted in thyrotoxic crisis which required intensive medical management. He also had a lower-respiratory-tract infection. Once stabilised he was discharged on medication.

An 18-year-old woman presented with a 5-day history of neck swelling. She had a small diffuse goitre. She was clinically euthyroid but had gross hypothyroidism (total T4 26 nmol/l, free T4 2·7 pmol/l, and TSH 238 mU/l). Thyroid microsomal antibodies were just positive (titre 6400). 4 months later her goitre had disappeared, she remained euthyroid, and thyroid function had returned to normal. However, her thyroid microsomal antibody titre had risen to 25 600.

A 50-year-old woman presented with a 4-month history of hypothyroid symptoms. Admission to hospital had been precipitated by a 2-day history of increasing tenderness in her neck. She had a diffuse tender goitre and clinical signs of hypothyroidism; serum T3 0·49 nmol/l, free T4 1·94 pmol/l, TSH above 50 units/l. Her thyroid microsomal antibody titre was very high (102 400). She was discharged on replacement therapy.

Antibodies to EBV viral capsid antigen (VCA) and early antigen (EA) were determined by indirect immunofluorescence tests. The P3HR-1 cell line was used to detect VCA specific IgG, IgA, and IgM. Sera were pretreated to remove any rheumatoid factor.[4] In addition EBV specific VCA-IgM was assayed with the DuPont ELISA kit. EBV-EA specific IgG and IgA were detected in Raji cells treated with 12-O-tetradecanoylphorbol-13 acetate.[5] The results are shown in the table.

All three patients were positive for EBV VCA-IgM by both the ELISA and immunofluorescence tests, indicating recent infection with this virus. These results are unlikely to be a non-specific response to their endocrine abnormality because a further eight patients with a range of thyroid conditions were EBV VCA-IgM negative. The EBV antibody profiles of the three patients are consistent with recent infection.

If EBV is causing thyroid dysfunction in these patients then it may be through direct infection of the gland or by immune-mediated pathways. In patient 1 EBV infection preceded the onset of severe thyrotoxicosis. The interval of 6 weeks between the glandular fever and the onset of thyrotoxicosis would support an immunological mechanism. The immune response to the virus may give rise to antibodies cross-reacting with thyroid tissue, or the virus may be transforming and switching on a B-cell clone which recognises thyroid epitopes. Alternatively the virus may persistently infect thyroid epithelial cells and produce an altered "self" image to the immune system, resulting in a damaging response. Whatever the mechanism, the thyroid could become the target for an autoimmune process. Recognition of EBV involvement in other patients will depend on whether the initial infection is symptomatic and on the interval between it and the onset of thyroid dysfunction. If thyroid dysfunction occurs beyond a 3–4 month period, VCA-IgM will become negative, and the temporal relation will be missed.

EBV ANTIBODY TITRES OF PATIENTS WITH THYROID DYSFUNCTION

Date	EBV-VCA			EBV-EA	
	IgM*	IgG	IgA	IgG	IgA
Case 1					
July 26, 1988	+	640	ND	ND	ND
Oct 21, 1988	−	640	ND	640	ND
Case 2					
Aug 1, 1988	+	1280	10	160	ND
Oct 21, 1988	+	1280	ND	80	ND
Dec 16, 1988	−	1280	ND	160	ND
Case 3					
Aug 12, 1987	+	2560	40	320	ND

Titres are expressed as reciprocals.
*EBV-VCA IgM screened at titre of 10 by immunofluorescence and 40 by ELISA. ND = not detected at a titre of 10.

We thank Dr C. Russell (Tyrone County Hospital) and Dr T. Robinson (Craigavon Area Hospital) for their cooperation.

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CLINICAL SIGNS OF PNEUMONIA IN CHILDREN

SIR,—Dr Shann (March 25, p 673) criticises our study of clinical criteria for the identification of severe disease, and hence need for referral, among Gambian children with clinical signs of acute lower respiratory infections. He correctly points out that to study simple clinical symptoms and signs that may be used to predict pneumonia, then all patients should be equally available for the measurements that define outcome, otherwise serious bias may result. Other important considerations would be precise definitions and blind assessment of an objective outcome of pneumonia (eg, radiological evidence scored by an independent observer on a standard classification). These points have been discussed[1] and are important when evaluating studies of this type.[2-4] We have previously reported such a study[4] and our findings were in broad agreement with Shann's calculations; for example, with respect to the sensitivity and negative predictive value of indrawing as a predictor. We concluded that our findings supported the current WHO recommendations for the identification of lower respiratory infection and hence the need for antibiotic treatment.

The report which Shann criticises is not, as he suggests, a study of clinical symptoms and signs for the prediction of pneumonia in the community, and therefore his comments, which are sound, are not

relevant. Since our previous findings supported the currently recommended criteria for recognition of lower respiratory infection in children outside the extended neonatal period, we further analysed the data relating to children selected by these criteria—ie, those who would be identified by trained health workers as having lower respiratory infection. Our report therefore only considered this group and the results do not relate directly to the community base. The group of children with respiratory infections who did not meet WHO criteria, and whom our field workers did not judge to have lower respiratory infection, were indeed studied but were not featured in this report. Our intention was to consider, in a group of children with signs, which symptoms and signs predicted more severe disease and the need for referral. In the absence of any generally agreed objective definition of severity we chose radiological consolidation in at least one complete lobe as the severity outcome. We look forward to the results of pulse oximetry studies in the hope that identification of hypoxia may be a valid and objective measure of severity to complement radiological criteria.

We affirm our support for the currently recommended WHO approach to simplified case management but re-emphasise our concerns. Case management guidelines for acute respiratory infection that are to be implemented within primary health care systems must be assessed at the community or first referral levels and not solely at hospital level. Chest indrawing (defined as any intercostal or subcostal indrawing in a settled child) is a common finding in Gambian children with lower respiratory infection; thus it would not be practical to refer for inpatient treatment all children who have indrawing so defined. The presence of such indrawing among those with signs of lower respiratory infection in the Basse community study was not found to predict lobar consolidation; it remains to be seen if, in developing countries, it is a good predictor of hypoxia (such studies should define indrawing precisely by site and degree). Finally we believe that, although current case management guidelines reflect the relevant available data from early seminal studies, it will be important for several more rigorous studies to review these preliminary findings. Such studies should consider a variety of different epidemiological situations and should follow a common protocol that addresses the methodological issues.

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MORBIDITY OF VERY-LOW-BIRTHWEIGHT INFANTS

SIR,—The birthweight distribution of infants below 1500 g in the most recent report from the Netherlands (Feb 4, p 253) is such that the results of the study are not generalisable, certainly not to the United States. The evidence indicates that birthweight-specific mortality and morbidity rates have been understated, leading the project group to overemphasise the importance[1] of tertiary care and maternal transport systems.[2]

For comparison with birthweight distribution in the Netherlands the table contains data for white livebirths in the USA below 1500 g in 1983;[3] also included are states whose low birthweight rates (below 2500 g) were less than 5%. (Black livebirths below 1500 g have not been included as the incidence of black births in this weight group is three times greater than whites; 35% of all births less than 1500 g in the USA are blacks.) Recent, geographically defined population studies from England[4] and Canada[5] have also been included.

Although the rates of livebirths 1000–1499 g were similar in all areas except Merseyside (where it was higher), the rates below

BIRTHWEIGHT DISTRIBUTION BELOW 1500 GRAMS

Area	Livebirths	Birthweight (g)		
		< 500	500–999	1000–1499
Netherlands	170 000	5 (0·003%)	287 (0·17%)	805 (0·47%)
USA (white)	2904 250	2521 (0·09%)	10 050 (0·35%)	14 301 (0·49%)
Iowa	41 592	30 (0·07%)	105 (0·25%)	185 (0·44%)
Minnesota	61 161	56 (0·09%)	189 (0·31%)	262 (0·43%)
Oregon	37 094	23 (0·06%)	128 (0·34%)	163 (0·44%)
Washington	60 509	52 (0·08%)	173 (0·28%)	260 (0·43%)
Wisconsin	65 748	67 (0·10%)	220 (0·33%)	279 (0·42%)
Merseyside	60 771	9 (0·01%)	202 (0·33%)	392 (0·64%)
Newfoundland				
Labrador	19 690	..	55 (0·28%)	86 (0·44%)

1000 g varied and were much lower in the Netherlands, especially below 500 g. Furthermore, among births 500–749 g, there were 66 births (0·04%) in the Netherlands compared with 79 (0·12%) in the Mersey area. It can be assumed that all infants below 500 g did not survive and very few infants 500–749 g did so.

The importance of these small numbers of births in determining mortality and morbidity rates is underscored by pointing out that in the Netherlands 0·65% of all births accounted for 24% of all deaths in the first year of life. For 1983, with figures such as these, the Netherlands scored seventh, ahead of Canada and the UK and well ahead of the USA in an international rating of infant mortality rates.[6]

We agree that geographically defined population studies are indispensable for the evaluation of care of the newborn; the development of tertiary referral centres, maternal transport systems, and an absence of controlled trials of neonatal care[7] have made this so. However, the livebirths below 1000 g appear to be under-reported in the latest Netherlands' study, invalidating the results. Two facts might explain the under-reporting; 35% of all births in that country were home deliveries[8] and the Netherlands has no established national system for collecting the vital statistics of birthweights.

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AMINOPHYLLINE REVERSAL OF DIAZEPAM INTOXICATION

SIR,—Dr Appel and colleagues (Feb 18, p 392) report a patient with chronic obstructive pulmonary disease who was admitted with bradyphrenia, dyspnoea, anisocoria, and psychomotor slowness. His home medication included diazepam 2 mg twice daily and ipratropium bromide by aerosol four times daily. The patient's neurological deterioration was related to central hypoxia and the use of diazepam. The benzodiazepine antagonist flumazenil was administered to counteract the effect of diazepam. In addition intravenous aminophylline (720 mg over 24 h) was administered to relieve respiratory distress. Treatment resulted in rapid clinical improvement, with complete clearance of all symptoms for the next 48 h, which Appel et al attribute to flumazenil. However, the half-life of flumazenil is 0·7–1·3 h, due to its rapid hepatic elimination, and the duration of its action is 2–3 h,[1] whereas

containing molecule such as CHFClCHFCl has a tropospheric life time of 5 years, compared with 380 years for CF_3CF_2Cl, 77 years for CCl_3F (CFC-11), and 139 years for CCl_2F_2 (CFC-12). Perhaps only 1% of all halothane used eventually reaches the stratosphere, with a life time of about 3 years (ICI Pharmaceuticals, personal communication).

The efficiency with which ozone is depleted by various chlorofluorocarbons varies.[1] CFC-11 and CFC-12 have a relative depletion efficiency of 1·0 compared with 0·1 for methylchloroform, a value similar to that for halothane. The annual global production of CFC-11 and CFC-12, which it is estimated are responsible for 70% of all ozone destruction,[1] is of the order of 630 000 tonnes (1 tonne = 1000 kg) whilst total CFC production is nearly 1 million tonnes annually. Annual global production of halothane is only 1000 tonnes. It is unlikely therefore that halothane can be responsible for any more than one-thousandth of 1% of all ozone destruction, and probably a great deal less. (The relative damage to the ozone layer by halothane is calculated by multiplying the relative stratospheric life time by the function that reaches the stratosphere, the relative ozone depletion efficiency, and relative production—ie, 0·03 × 0·01 × 0·1 × 0·001 = 0·00003%.) We are assured by ICI Pharmaceuticals that for these reasons halothane is not included amongst the compounds listed under the Montreal Protocol.[2]

Although production figures are less readily available for enflurane and isoflurane the same arguments apply. We estimate that the global production of enflurane and isoflurane is 5400 tonnes, on the basis of extrapolation from our hospital consumption.

In the operating theatre we use many CFC-containing products:

Product	*Propellant*	*Product*	*Propellant*
'Dispray 1'	CFC	'Sprilon 2'	CFC
'Dispray 2'	CFC	'PR Spray'	CFC
Betadine dry powder	CFC	'Opsite'	CFC*
'Rikospray'	CFC	Betadine	Nitrogen

*Soon to be replaced by butane.

Rather than drawing attention to volatile anaesthetic agents by making statements that cannot be realistically substantiated, clinicians could make a positive contribution to the environment by avoiding ozone-damaging propellants.

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INDOOR AIR POLLUTION IN DEVELOPING COUNTRIES AND ACUTE RESPIRATORY INFECTION IN CHILDREN

SIR,—Prof Pandey and colleagues (Feb 25, p 427) report that our study in the Gambia failed to show a relation between acute respiratory infections (ARI) and indoor pollution (despite the high levels of indoor particulate concentrations), since all the sites studied showed similarly high levels. However, observation of maternal behaviour has enabled us to identify a subgroup of children with low exposure to indoor smoke. Combustion of biofuels is not generally required for space heating, so smoke exposure is mostly from cooking fires. Since young children are usually excluded from cooking huts except when carried on their mothers' backs, two groups with different exposure to smoke can be identified: those normally carried and those not normally carried by the mother while cooking. We therefore related carriage on the mother's back, together with parental smoking and several other factors that might influence incidence or severity of ARI (including age, sex, village of residence, ethnic group, socioeconomic score, maternal education, nutritional indicators, vaccination status, number of visits to health clinic for illness episodes, an index of crowding, birth interval, type of mattress, and the presence of various animals kept close to the home), to maternal history of difficulty in breathing in the subsequent three-month period among 280 children who were the youngest in their family. We have shown that a maternal history of fast[1] or difficult (unpublished) breathing is predictive of lower respiratory infection.

ADJUSTED ODDS RATIOS* FOR SUBSEQUENT DEVELOPMENT OF AN EPISODE OF DIFFICULTY IN BREATHING

Variable	Level	Odds ratio (95% confidence interval)
Father smoking	None	1
	1–5	2·35 (0·90, 6·14)
	6–10	3·81 (1·14, 14·11)
	>11	5·18 (1·57, 9·25)
Carriage on mother's back	No	1
	Yes	2·80 (1·29, 6·09)

*By multiple logistic regression for the change in deviance for each factor, after allowance for all other factors found to be significantly associated on univariate analysis.

Carriage on the mother's back and the number of cigarettes smoked by the father were significantly associated with a subsequent episode of difficulty in breathing (only 1% of mothers reported smoking regularly; table). Our results therefore support Pandey and colleagues' findings in Nepal.

However, we urge caution in the extrapolation of such results. It is probably too simplistic to "discount the many possible confounding factors" and extrapolate findings to calculate possible health effects that can be expected by decreasing such smoke exposure. In these circumstances it is possible that no cause will be strongly related to ARI.[2] There are particular problems in interpreting data from such studies.[3] Measurement errors (due to limitations in sampling methods, poor recall of activity patterns by mothers, and the use of inappropriate proxy measures of exposure), and consequent misclassification of subjects by exposure, may cause difficulties. Pandey and colleagues' predicted health effects should thus be read with caution.

Populations at high risk or with high disease incidence are generally unsuitable for such studies (showing weak association of risk factor to disease outcome) but may be especially suitable for assessment of preventive measures.[2] We agree with Pandey et al that intervention studies are the most likely to give useful information on the importance of air pollution in relation to other risk factors. However, such studies will be difficult since reductions in indoor air pollution at a community level will be hard to achieve and verify. Furthermore pollution from biofuel combustion has many facets affecting rural community development, housing design, and energy utilisation as well as health, so that cost-benefit analyses of interventions will be complex.

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INCREASED RISK OF BREAST CANCER AFTER LOW-DOSE IRRADIATION

SIR,—There may be an alternative explanation to that which Professor Modan and colleagues propose (March 25, p 629) for the apparently increased risk of breast cancer in women exposed to low-dose irradiation of the scalp at age 5–9 years.

It is likely that the thymus gland was also irradiated. This could have led to an increased susceptibility to cancer at sites not necessarily directly receiving irradiation, in turn manifest as increased risk of a malignancy such as breast cancer as the population ages. The population at risk is at present aged from about 35 to 49, and hence is only just into the "age dependent"

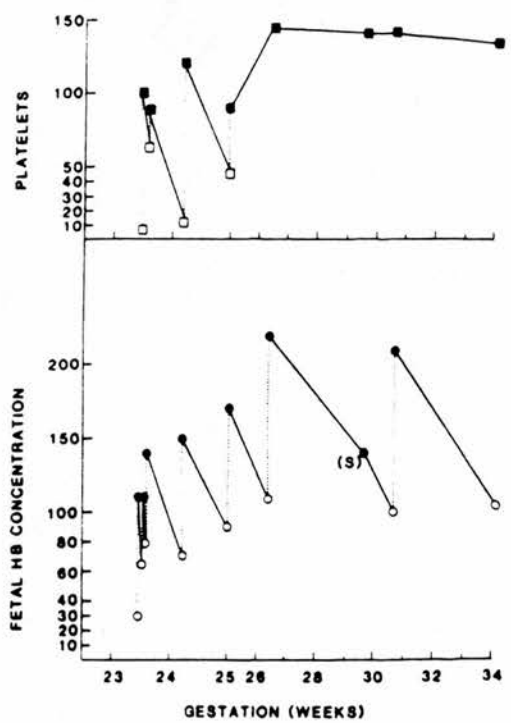
SCHEDULE OF INTRAUTERINE PROCEDURES

IVT	Gestation (wk day)	Transfusion volume (ml)		
		Platelets	Blood*	Total
1	23 4	0	20	20
2	23 4	8	12	20
3	23 5	6	20	26
4	24 2	6	25	31
5	25 0	8	30	38
6	26 3	0	55	55
7	30 4	0	90	90

*Group O, rhesus negative, hepatitis and HIV negative, haemoglobin Hb 300 g/l.

time ultrasound showed a large intra-amniotic "cloud" of blood, the fetus had stopped moving, the fetal heart rate had increased to 165/min, and BPS was 2/10. Backbleeding after an uneventful second IVT lasted 240 s. Fetal Hb, 112 g/l after the first IVT, fell to 66 g/l before the second, a loss of at least 40% of the circulating red cells over 90 min.

The third IVT was done 18 h later, at which time sedation was necessary because of an extremely active fetus. Backbleeding lasted 196 s. The pre-transfusion platelet count suggested that the levels sustained by the transfusions probably ensured adequate haemostasis. The fourth IVT 4 days later was also fortified with platelets. Vigorous fetal movement necessitated the use of pancuronium. The pre-transfusion platelet count fell significantly from the post-transfusion value of 4 days earlier. With this transfusion the bleeding time was 230 s. Platelet fortification of the transfusion was also used with the fifth IVT, before which the fetus appeared able to maintain a modest but haemostatic platelet count. Further platelet supplements were deemed unnecessary. The final IVTs were complicated by emergence of two new maternal alloantibodies to Fy^a and Jk^b. These may have reduced the lifespan of the transfused red cells, but there was no clinical evidence of accelerating fetal disease. Bleeding time was 140 s in both instances.



Fetal platelet counts ($10^3/\mu l$) and Hb concentrations (g/l).

Dotted lines = increases achieved by transfusions; solid lines = changes between procedures. Open symbols = pretransfusion; closed symbols = post-transfusion. Note that left-hand abscissa is expanded. (S) = fetal blood sampling without transfusion at 29½ weeks to determine effect on donor red-cell lifespan by new antibodies.

Fetal condition improved progressively over the 72 days from first intrauterine transfusion to delivery at 34 weeks of a healthy girl, 2200 g, Hb 105 g/l (100% donor in origin). Apgar scores were 7 and 8 at 1 and 5 min, respectively. She received two blood transfusions (one simple, one exchange for increased serum bilirubin) and one platelet transfusion. The baby was discharged from the intensive care nursery at age 7 days.

Serious thrombocytopenia in severe neonatal erythroblastosis, especially in extreme hydrops, often requires platelet transfusions.[3] The mechanism of this thrombocytopenia is uncertain but may include bilirubin toxicity[5] (fetal bilirubin, in our case maximum 71 mg/l, was modest) or a combination of reduced production and increased destruction.[6] The occurrence of thrombocytopenic haemorrhage in the fetus is probably masked by the lethal consequences of haemolysis and hepatic failure. Puncturing the cord is another matter.

It may not be possible to estimate accurately the volume lost due to massive bleeding, but without platelet infusion this haemorrhage would probably have ended in fetal death. The platelet deficit persisted initially but further bleeding was averted by giving platelets as well as blood.

We now give platelets at first IVT of all fetuses at risk of severe thrombocytopenia—those with severe signs of hydrops.. Donor blood is usually diluted with saline to render it injectable. When platelet concentrate transfusion is required, platelet is substituted for saline to give more than 10^8 platelets per µl of transfusate. Giving blood and platelets together avoids problems of multiple infusions. The platelet count in the first fetal blood sample determines whether platelets are given at the next transfusion, and so on. When the fetus maintains platelets at 20 000–30 000/µl, life-threatening haemorrhage is unlikely and further supplement is unnecessary. Normal haemostasis must be assured by monitoring backbleeding. At our institution, of the 30 alloimmunised fetuses treated with IVT since 1986, only 1 moribund fetus has died.

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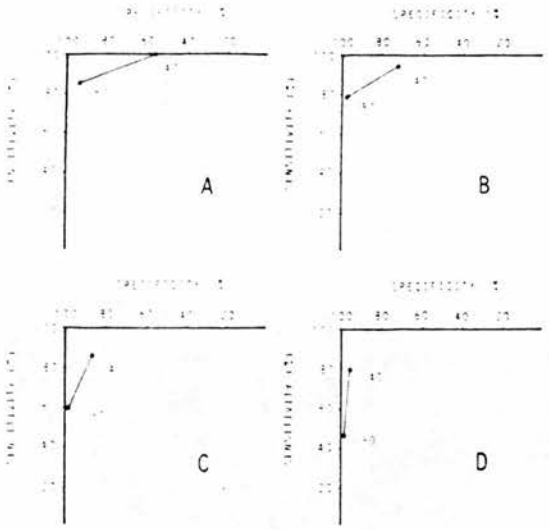
SIMPLE CLINICAL SIGNS FOR DIAGNOSIS OF ACUTE LOWER RESPIRATORY INFECTIONS

SIR,—Dr Cherian and colleagues (July 16, p 125) stress that studies are required to validate the usefulness of simple clinical criteria for the diagnosis of acute lower-respiratory-tract infections (LRI) in the community. We have completed a one year community-based study of acute respiratory infections in a cohort of about 500 children under the age of 5 years in a rural area of The Gambia (Basse).

During this study 154 children were investigated who had auscultatory signs of LRI, radiological abnormalities consistent with LRI, or both. We recorded the respiratory rate on 4208 occasions when 702 study children reported upper respiratory tract illness (URI) which was not accompanied by any signs of LRI. This was assessed by trained field workers and, in selected cases in whom the diagnosis was not certain, by the project clinician.



Specificity and sensitivity with respiratory rates 40/min or 50/min as indicators of LRI.

A = < 12 months; B = 12–23 months; C = 24–35 months; D = > 35 months.

In agreement with the hospital-based study in Vellore, the results of our community-based study in Basse suggest that, considered alone, a respiratory rate of 40 min is a better predictor of LRI in children over 1 year of age than 50 min (figure). However, our data suggest that, in contrast to Cherian's findings, a respiratory rate of 40/min continues to be a useful predictor of LRI even in children over 3 years old (sensitivity 79%, compared with 56% in Vellore).

The sensitivity of a respiratory cut-off of > 50/min can be increased, even in older children, if combined with an assessment of indrawing. This combination of signs was very sensitive and specific in all age groups (table).

The age specific sensitivities and specificities of a history of rapid breathing given by the mother, as opposed to an observed increase in respiratory rate, as a predictor of LRI were 74% and 86% (below 1 year), 79% and 90% (1 year), 79% and 91% (2 years), and 55% and 93% (above 3 years). This merits further consideration as an indicator to be used by health staff with little training.

Our findings accord with those of Cherian et al in that in older children, but not in infants, a respiratory rate above 40/min is a better cut-off for the diagnosis of LRI than a cut-off over 50/min,

PRESENCE OR ABSENCE OF RESPIRATORY RATE ABOVE 50/MIN AND OF CHEST INDRAWING IN INFANTS AND CHILDREN WITH URI AND LRI

	LRI		URI	
Clinical sign	No	No with sign	No	No without sign
0–11 mo				
RR > 50 min		45 (85%)		850 (94%)
Indrawing	53	30 (57%)	902	878 (97%)
Either		49 (92%)		845 (94%)
12–23 mo				
RR > 50 min		33 (79%)		1104 (97%)
Indrawing	42	23 (55%)	1138	1117 (98%)
Either		39 (95%)		1092 (96%)
24–35 mo				
RR > 50 min		18 (60%)		902 (99%)
Indrawing	30	20 (69%)	910	899 (99%)
Either		26 (90%)		896 (98%)
> 35 mo				
RR > 50 min		14 (48%)		1248 (99%)
Indrawing	29	23 (79%)	1258	1247 (99%)
Either		29 (100%)		1238 (98%)

the sensitivity of the latter dropping to 48% in the (lower risk[1]) over-3-year group. However, in many circumstances it would be difficult to implement a screening programme based on age-dependent criteria. A balance has to be made between greater sensitivity on the one hand and simplicity and ease of implementation on the other, so that recommendations are suitable for use by village health workers. The current World Health Organisation policy of giving antibiotics to infants and children with a respiratory rate above 50 min or with indrawing is still appropriate.

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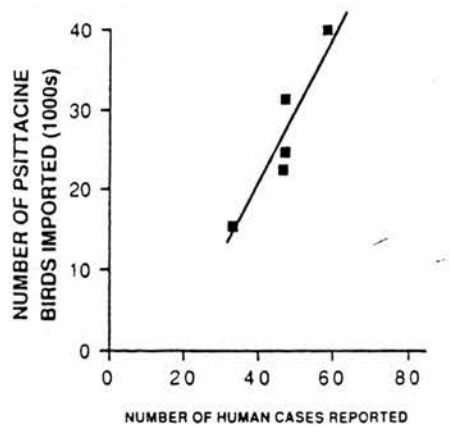
RESPIRATORY TRACT CHLAMYDIAL INFECTION AND IMPORTATION OF PSITTACINE BIRDS

SIR,—Dr Forsey (April 9, p 830) and Dr Puolakkainen and colleagues (July 30, p 287) comment on our study[1] of the relation between human respiratory tract chlamydial infection in Cambridge and the importation of psittacine birds into Britain. The figure shows that, between 1982 and 1986, the numbers of cases of human respiratory tract chlamydial infection in Cambridge correlated closely with the numbers of psittacine birds imported into Britain. We accept that some of our cases may have been the result of infection with TWAR strains of chlamydia but it is unlikely that most were, because of the striking correlation with the numbers of imported psittacine birds. Furthermore over 20% of our cases have had relevant contact with such birds.



Correlation between importation of psittacine birds into Britain (1982–86) and respiratory tract chlamydial infection.

We are now examining serum samples in this series for evidence of TWAR infection. In the meantime experience in Finland, where importation of psittacine birds is strictly limited and where the prevalence of high complement fixation (CF) titres indicating recent infection with chlamydia is less than 2%, hardly justifies Puolakkainen and colleagues' statement that "infections contracted from psittacine birds cannot be considered a major source of chlamydial CF antibody in man". If anything the Finnish experience supports our belief that the correlation between human respiratory tract chlamydial infections and the importation of psittacine birds is more than fortuitous.

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LETTERS to the EDITOR

WHO guidelines on detecting pneumonia in children

SIR,—Dr Harari and colleagues (Oct 12, p 928) revive a discussion published in *The Lancet* in 1988 on the need for age-specific respiratory rate thresholds in guidelines for the detection of children with pneumonia in developing countries. In 1989, the WHO Programme for the Control of Acute Respiratory Infections (WHO/ARI) altered its recommendations for clinic-based health workers,[1,2] on the basis of clinic-based[3-5] and community-based studies.[6] Children under 5 with cough or difficult breathing should be treated for possible pneumonia if they have fast breathing or lower chest wall indrawing. "Fast breathing" is ≥60/min for infants less than 2 months old; ≥50 for aged 2–11 months; and ≥40 for those 1–4 years old. Harari et al used a broader definition of chest indrawing (including intercostal indrawing) and included 5-year-olds, and may have underestimated the benefit of a lower respiratory rate threshold at age 1–4 years. A key issue raised by their paper is the balance between the need to detect and treat a high proportion of cases of pneumonia (sensitivity) and concerns about specificity and positive predictive value (proportion of treated children who do have pneumonia).

In Harari and colleagues' study, the protocol based on chest indrawing or fast breathing with a threshold of 40/min for children aged 1–5 when compared with a threshold of 50 increased sensitivity for children aged 2 months to 5 years by 9% with a 6% loss of specificity. A similar analysis, with lower chest wall indrawing only (the definition in WHO training material) in children aged 2 months to 4 years, showed a gain in sensitivity of 16% with a loss in specificity of 14% in the Philippines and an 8% gain and a 9% loss respectively, in Swaziland.[4] In Harari and colleagues' study, if we consider separately the 1–5 year group, the gain in sensitivity from use of 40 rather than 50/min is more striking (17%), a result comparable with that found in other studies. Sensitivity was greatly improved when the threshold was ≥40/min:

Study	Sensitivity (%) ≥50	≥40	Specificity (%) ≥50	≥40
Clinic-based studies				
India[3]	57	71	96	87
Lesotho (doctors)*	19	54	91	69
Philippines[1]	52	78	85	75
Papua New Guinea[5] (1984)†	57	74	89	73
Papua New Guinea (Harari et al) (1990)‡	54	71	85	73
Community-based study				
The Gambia[6]	64	87	98	82

*Redd S. et al (unpublished).
†>50 and >40, not ≥50 and ≥40.
‡Also included 5-year-olds.

This increase in sensitivity is worth the small loss in specificity. Many clinicians and other WHO/ARI staff insist on adequate sensitivity in a protocol guiding the management of the leading killer of young children. A sensitivity of only 63% seems unacceptable since 37% of children with pneumonia who present to a clinic will not be treated.

The WHO protocol and training material are designed for clinics, health centres, or outpatient departments. Children are brought in because the mother is worried; maternal recognition of fast breathing has predictive value for pneumonia. In these settings, the prevalence of pneumonia among children presenting with cough or difficult breathing may be as high as 30%. We do not think it advisable, in a clinic which is often some distance from the home, to apply guidelines with a sensitivity of only 50–60% in the interest of improving specificity by 5–10%. The health worker often has only one opportunity to treat the child, and mothers tend to seek care from non-medical sources if the child gets worse after he or she has been sent home without antibiotic treatment.

Some degree of overtreatment is unavoidable in any safe empirical treatment protocol, and it is small in comparison with the current rates of antibiotic treatment. In some countries, antibiotic use for acute respiratory infections has fallen with the implementation of ARI control activities.[7]

As the prevalence of disease falls in children examined, the positive predictive value of cough with fast breathing or chest indrawing will fall, even if sensitivity and specificity remain the same. This increase in false positives applies especially if at a routine home visit children are found who are not sick enough for the mothers to seek care. In this setting it would be feasible to ask the health worker to re-examine a child with a respiratory rate of 40–49/min the next day. This would allow two respiratory rate thresholds to be used (60 for infants under 2 months and 50 for those aged 2 months to 4 years), a simpler protocol for health workers operating in a setting of much lower disease prevalence. Training material for community-based practitioners are being developed by WHO/ARI.

Children with apparent radiological pneumonia can be found in the absence of clinical disease—and acutely ill children with fever, fast breathing, and auscultatory signs may have a normal chest radiograph at first but would be considered by paediatricians to need antibiotic treatment. The variability in interpretation of radiographs is also striking. Thus it is hard at this time to consider radiography as the gold standard.

Continued discussion about respiratory rate thresholds must not divert attention from the efficacy of the WHO guidelines and the need to implement them in developing countries with high infant mortality rates.[8] Pneumonia is the leading killer of children under 5. Death can be prevented in most cases of bacterial pneumonia by early treatment with antibiotics. WHO and UNICEF are collaborating with ministries of health to implement national control programmes; this involves training in both clinical and programme management and the provision of inexpensive antibiotics. 55 countries have adopted the WHO protocol with age-specific respiratory rate thresholds and 21 countries have begun training clinic-based health workers. Experience to date in training first-level health workers indicates that the protocol can be applied successfully in diverse settings.

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SIR,—Dr Harari and colleagues conclude that rapid breathing should be defined as ≥50/min to diagnose pneumonia irrespective of the age of the child. Previous studies[1-3] have shown a threshold of 50 to be less sensitive in identifying pneumonia in children 12 months and older compared with younger children. These studies

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Etiology of acute lower respiratory tract infections in children in a rural community in The Gambia

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Approximately 500 children younger than 5 years old resident in 7 villages in a rural area of The Gambia were monitored closely for 1 year for episodes of acute lower respiratory tract infection (ALRI). Each episode was investigated with antigen detection techniques and antibody assays as well as culture for bacteria and viruses. A pathogen was identified in 76 (34.2%) of 222 cases with clinical signs of ALRI and in 34 (42%) of the 81 cases who, in addition, had radiologic evidence of ALRI. Evidence of infection with a bacterial pathogen, most commonly *Streptococcus pneumoniae* or *Haemophilus influenzae*, was obtained in 32 (14.4%) cases with clinical signs of ALRI (23.5% of those with radiologically proved pneumonia). Viral agents were cultured from 42 (19%) of 221 cases but also from 14 (14.6%) of 96 controls some of whom had minor symptoms of upper respiratory tract infection. In the absence of an outbreak of respiratory syncytial virus the viral agents recovered most often were influenza A and adenoviruses.

INTRODUCTION

In developing countries acute respiratory infections, diarrheal disease, malaria and malnutrition are the commonest causes of death among young children.[1] Mortality from acute respiratory infections is 30 to 70 times higher than in developed countries[2] and it has been estimated that up to one-third of all deaths in children less than 5 years are attributable to acute respiratory infections as an underlying or contributing cause.[3] In addition infections of the lower respiratory tract, particularly pneumonia, are recognized as an important cause of morbidity and are a leading reason for hospitalization and attendance at health clinics.[4] Previous studies in a Gambian hospital have shown *Streptococcus pneumoniae* and *Haemophilus influenzae* to be common bacterial pathogens in infants[5] and children[6]; respiratory syncytial virus was also shown to be a frequent pathogen in infants.[5]

Current knowledge of the etiology of acute lower respiratory infections (ALRI) in young children in developing countries is predominantly derived from hospital-based studies.[7] Although children hospitalized with ALRI represent an important group with high case fatality, they are nevertheless a highly selected group with respect to all childhood pneumonias occurring in a community and also in relation to all severe pneumonias in young children, because only a few such children die in hospital. Thus community-based research is required to complement hospital-based studies and to set their results in context.[8] This is especially true for populations with few health care facilities.

The scarcity of data on the etiology of ALRI in children in communities in developing countries is to an extent a consequence of the lack of simple, reliable methods for establishing the etiology of respiratory infections in pediatric outpatients.[9] The etiologic diagnosis of bacterial pneumonia in young children is difficult because sputum is unavailable and blood cultures have a sensitivity of only 10 to 30%.[10] Lung puncture is a more sensitive method but it is an invasive procedure reserved only for those patients with severe disease who can be kept under close observation. Cultures of throat swabs are not suitable because of the high carriage rate of bacterial respira-

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Key words: Acute respiratory infections, pneumonia, children, *Streptococcus pneumoniae*, *Haemophilus influenzae*, respiratory syncytial virus, *Chlamydia trachomatis*, *Chlamydia pneumoniae*.
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tory pathogens in healthy children. Obtaining laboratory confirmation of the diagnosis of viral respiratory infection in patients in the field is also difficult. The lability of viruses during transportation to the laboratory may make culture unreliable and serology may not be helpful in infants because of their low immunocompetence and the presence of maternal antibody. Moreover specimens from asymptomatic control patients are required to help assess the importance of viral infections in different populations.

The purpose of the present study was to determine the incidence of ALRI in young children in a rural Gambian community and to identify the important etiological agents. In an effort to increase the sensitivity of our diagnostic methods we used antigen detection procedures and antibody assays for the diagnosis of both bacterial and viral infection in conjunction with more traditional culture techniques for bacteria and viruses.

PATIENTS AND METHODS

Study area. The Gambia is a small West African republic with a population of approximately 800 000. Most of the population live in the large periurban area on the coast near the capital Banjul, the rural area inland being much less densely populated. This study was undertaken in a rural community near Basse, a busy market town located in the far eastern part of the country, 350 km from Banjul. The country has a subtropical climate with a rainy season from June to October followed by a long dry season. In general the incidence and severity of disease are at their greatest in the rainy season. In common with other developing countries in West Africa most of the population of The Gambia endure a very low standard of living with poor sanitation and crowded living conditions, often with several children sleeping in the same bed. Houses in urban areas are constructed from cement blocks and have corrugated iron roofs whereas houses in rural areas tend to be built with mud bricks and have a thatched roof. The laterite roads to individual villages deteriorate during the rains making access possible only by four-wheel drive vehicles. Basse has a health center with facilities for the admission of about 30 patients. The health center is staffed by one government doctor who is responsible for both curative and preventative health care throughout the area. The infant mortality rate is about 140/1000 with diarrhea, malaria and ALRI being the major causes of death. Breast-feeding is universal and continues in nearly all children up to the age of 18 months and often beyond to the birth of the next child. The staple diet of older children and adults is rice.

This study was approved by the Medical Research Council/Gambian Government Ethical Committee. A measles vaccination campaign in November, 1986, resulted in high coverage in the study area and no cases of measles were observed during the study period.

Patients and controls. During a 1-year period (March, 1987, to March, 1988) approximately 500 children ages less than 5 years living in 3 villages and 4 hamlets near the town of Basse were monitored weekly for signs of ALRI by trained field workers living in the villages. All children with cough and a raised respiratory rate (abve 50/minute), chest indrawing, nasal flaring, wheeze or stridor or with evidence of severe systemic upset such as inability to drink (and who had not received antibiotic treatment in the previous 2 weeks) were referred to the project clinician at the Medical Research Council field station at Basse for further investigation. Further details of the study population, ALRI surveillance methods and case definitions have been presented elsewhere.[11]

Controls consisted of children from the cohort who presented with minor illnesses but who had no signs of ALRI. They were studied contemporaneously with children with ALRI. Nasopharyngeal aspirates were collected from these control children, all of whom were matched within 1 year of age of a case (within 6 months for infants).

Investigations. After informed consent had been obtained from the child's guardian, blood was taken for culture and serology and a thick film prepared and examined for malaria parasites. A nasopharyngeal aspirate and a urine specimen were also collected and chest radiology was performed. A convalescent finger prick blood specimen was taken after an interval of 2 to 3 weeks.

Chest roentgenograms were interpreted by a pediatric radiologist who had no details of the clinical findings. Abnormal findings were recorded according to a prearranged coding schedule.

Children with ALRI were normally treated either with oral trimethoprim-sulfamethoxazole or fortified procaine penicillin plus oral ampicillin.[12]

Virology. Portions of nasopharyngeal aspirate for virus isolation were inoculated into a cryotube containing virus transport medium. Specimens from infants up to 4 months old were also inoculated into 2-sucrose-phosphate transport medium for the recovery of *Chlamydia trachomatis*. Cryotubes were snap frozen and stored in liquid nitrogen before transportation to the virus laboratory 350 km away where they were transferred to a −70°C freezer. Each specimen in virus transport medium was inoculated onto monolayers of secondary rhesus monkey kidney cells, human embryonic lung fibroblasts and HEp2 cells and incubated stationary at 37°C or rolling at 33°C. The monolayers were inspected every 2 to 3 days for a minimum of 14

days for evidence of viral replication; any isolates were identified by neutralization or immunofluorescence. Subtyping of influenza isolates was performed by the Virus Reference Laboratory, Colindale, London, United Kingdom. Cells in the remainder of the nasopharyngeal aspirate were washed free of mucus, spotted onto microscope slides, dried, fixed in acetone and stored at −20°C before being transferred to the virus laboratory for immunofluorescent staining with the use of commercially available antisera (Wellcome Research Laboratories, Kent, England). Specimens of nasopharyngeal aspirate stored in 2-sucrose-phosphate transport medium for culture of *C. trachomatis* were centrifuged onto monolayers of McCoy cells. The monolayers were treated with cyclohexamide and incubated at 37°C for 48 hours before being stained for the presence of chlamydial inclusions using an immunofluorescent monoclonal antibody culture confirmation preparation (Syva Corp.).

Acute and convalescent sera were screened for complement-fixing antibody to influenza A and B, parainfluenza 1 and 3, adenovirus, respiratory syncytial virus (RSV) and *Mycoplasma pneumoniae* at a dilution of 1:8. Sera giving 75 to 100% fixation were titrated from 1:8 to 1:256. A 4-fold increase in antibody titer between the acute and convalescent serum or a consistently high titer of 1:128 or above was considered evidence of infection. Antibody to RSV was also measured by enzyme immunoassay with the use of partially purified antigen supplied by Dr Olli Meurman, Department of Virology, University of Turku, Turku, Finland. A sonicated extract of a culture of uninfected Vero cells was used as control antigen. Each serum was tested in duplicate at 1:100 and 1:1000 dilution. The titer of each serum was calculated by linear regression. The cutoff optical density (OD) value was taken as the mean OD ± 2 SD of 30 negative control sera assayed in duplicate at 1:100 dilution on three separate occasions. A 3-fold rise in titer or greater was accepted as evidence of recent RSV infection.

Antibody to *Chlamydia pneumoniae* and *C. trachomatis* was assayed by Dr. Pekka Saikku, Department of Virology, University of Helsinki, Helsinki, Finland, using microimmunofluorescence as described previously.[13]

Bacteriology. Blood specimens were inoculated into tryptone soy broth and thyoglycollate broth and incubated at 37°C. All broths were subcultured after 24 and 48 hours of culture and at 7 days onto 5% sheep blood agar and enriched chocolate blood agar and incubated overnight at 37°C in candle jars. Bacterial isolates were identified by standard methods. Specimens of urine and serum were collected and processed as described previously.[14] Each urine was tested for *H. influenzae* type b polysaccharide antigen using a commercial latex agglutination test (Slidex méningite-kit®, Biomérieux, Charbonnières-les-Bains, France) and for the 10 commonest types of *S. pneumoniae* isolated in The Gambia with a series of type-specific latex tests as reported previously.[14]

Anti-pneumolysin antibodies were measured by enzyme immunoassay as described previously.[15] A 2-fold increase or more in antibody titer to pneumolysin between acute and convalescent specimens was taken to be evidence of pneumococcal infection. Anti-*H. influenzae* and anti-*Moraxella catarrhalis* antibodies were also measured by enzyme immunoassay with the use of antigen prepared from noncapsulated strains of bacteria isolated from the middle ear of children with otitis media as reported previously.[16] A 3-fold or greater rise in titer between paired serum specimens was considered to be diagnostic for *H. influenzae* and *M. catarrhalis* infections. The diagnostic criteria for bacterial antibody assays were assessed by testing paired sera from 40 Gambian children with acute malaria; only one (2.5%) showed a 2-fold or greater response to pneumolysin but none showed a response to *H. influenzae* or *M. catarrhalis*.

RESULTS

Cases and controls. During the 1-year surveillance period 222 episodes of ALRI were identified among 491 village cohort children giving an ALRI annual incidence rate of 452/1000 children younger than 5 years of age. Chest roentgenograms were done in 216 cases; 81 (38%) had radiologic changes consistent with ALRI (incidence rate, 165/1000 children/year). Consolidation of at least 1 lobe was present in 25 (12%) (incidence rate, 51/1000 children/year). One hundred twenty-two children had a single episode of ALRI, 36 children had 2 episodes, 8 had 3 episodes and 1 child had 4 separate episodes of ALRI during the study period. The male:female ratio was 1.2:1. Viral culture was performed on 221 cases while paired sera for viral serology was obtained from 203 (91%) cases. Blood cultures were done on 214 (96%) cases, bacterial serology was performed on paired sera from 192 (86%) cases and urine from 207 (93%) cases was tested for the presence of bacterial antigens.

Ninety-six control children who had no clinical signs of ALRI were studied contemporaneously with the cases. None of these control children had clinical signs of ALRI although some had symptoms of mild upper respiratory tract infection.

Viral infections. A viral infection, excluding cytomegalovirus (see below), was identified during 55 (24.9%) of 221 episodes of ALRI in village children and during 19 (23.4%) of 81 episodes of radiologically proven ALRI (Table 1). Respiratory viruses accounted for 46 (20.8%) of the viral infections identified, the remaining 9 infections being associated with enteroviruses and herpes simplex (4%). The proportion of viral diagnoses was 25% in children age under 12

TABLE 1. Episodes of ALRI identified by community surveillance: viral infections (excluding CMV)

Viral Etiology	Episodes of Clinical ALRI			Episodes of Radiologically Confirmed ALRI			Episodes of Lobar Pneumonia		
	Culture and/or serology (n = 221)	Culture only (n = 221)	Serology only (n = 203)	Culture and/or serology (n = 81)	Culture only (n = 81)	Serology only (n = 73)	Culture and/or serology (n = 25)	Culture only (n = 25)	Serology only (n = 23)
Total positive	55 (24.9)*	42 (19)	33 (16.2)	19 (23.4)	15 (18.5)	13 (17.8)	4 (16.0)	2 (8.0)	3 (13.0)
RSV	4 (1.8)	0 (0)	4 (2.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Parainfluenza	14 (6.3)	8 (3.6)	10 (4.9)	5 (6.2)	3 (3.7)	4 (5.5)	1 (4.0)	0 (0)	1 (4.3)
Adenovirus	18 (8.1)	13 (5.9)	9 (4.4)	7 (8.6)	5 (6.2)	5 (6.8)	0 (0)	0 (0)	0 (0)
Influenza	14 (6.3)	8 (3.6)	12 (5.9)	4 (4.9)	1 (1.2)	4 (5.5)	2 (8.0)	0 (0)	2 (8.7)
Other	15 (6.8)	15 (6.8)	ND	6 (7.4)	6 (7.4)	ND	2 (8.0)	2 (8.0)	ND
Mixed viral	9 (4.1)†	1 (0.5)†	2 (1.0)	3 (3.7)	0 (0)	0 (0)	1 (4.0)	0 (0)	0 (0)

* Numbers in parentheses, percent.
† One triple virus infection.
ND, not determined.

months, 17% in those age 12 to 23 months, 33% in those age 24 to 35 months and 42% in those age 36 to 60 months. One or more viruses were cultured from 42 cases (19%); 33 cases (16.2%) were identified by serologic techniques and in 14 cases a virus infection was identified by both techniques.

Adenoviruses were identified in 18 (8.1%) of the 221 episodes of ALRI. Eight (61.5%) of the 13 adenovirus isolates were type 6, 6 of these being isolated during Weeks 21 to 26. A further 3 children with ALRI had a rising titer to adenovirus during this period. Adenovirus was cultured from 5 (5.2%) of 96 control patients; only 1 was adenovirus type 6.

Each of the 13 influenza A infections that were identified in village children with ALRI occurred in Weeks 23 to 28. Eleven influenza A infections were identified by serology and 8 by virus isolation. At least 5 of the isolates were of the H_1N_1 subtype and closely resembled influenza A/Taiwan/1/86. Serologic evidence of influenza B infection was found in 1 child. No influenza viruses were isolated from any of the 96 control children investigated ($P = 0.11$, Fisher's exact test).

Seven of the 14 parainfluenza virus infections identified in children with ALRI were caused by type 1 virus and 7 by type 3 virus.

No outbreak of RSV infection was observed during the surveillance period although 4 cases had serologic evidence of recent infection. Mixed viral infections, excluding CMV, were identified in 9 subjects (4%). The proportion of viruses isolated in cases of radiologically proved ALRI was similar to that found where the diagnosis was made clinically but fell markedly in cases of lobar pneumonia (Table 1).

Viruses, other than CMV, were isolated from 14 (14.6%) of the 96 control subjects investigated contemporaneously with the cases of ALRI (Table 2). This figure is not significantly different from the number of viruses cultured from children with ALRI (42 viruses isolated from 221 cases, 19%, chi square = 0.6, not significant).

CMV was isolated from 29.9% of children with ALRI but also from 30.2% of 96 control patients. CMV isolation results have therefore been excluded from calculations of the total number of patients in whom a virus infection was identified. The highest CMV isolation rates were in children ages 12 to 23 months (45%).

The number of episodes of ALRI found by week of study, together with the viral infections identified, is shown in Figure 1. The majority of viral infections occurred in the rainy season, particularly between July and September (Weeks 16 to 28) when the relative humidity was high. The highest weekly incidence of ALRI (Weeks 21 to 23) coincided with the recovery of adenoviruses, particularly type 6. Infections with influenza A were identified in Weeks 23 to 28, immediately after the peak incidence of ALRI had occurred. Significantly fewer viral infections were identified in the period following the rains (chi square = 8.8, $P < 0.005$) despite up to 9 episodes of ALRI per week being observed.

Bacterial infections. Positive blood cultures were obtained during only 2 (1%) of the 222 episodes of ALRI in village children. *Escherichia coli* and a *Salmonella* species were isolated (recorded as "other bacteria" in Table 3). Thirty (15.6%) of the 192 cases tested had a rising titer to one or more of the bacterial antigens to which antibody was measured. Nineteen episodes of ALRI were associated with a rising titer to pneumolysin, 10 to *H. influenzae* and 6 to *M. catarrhalis*. In 5 cases a rising titer to more than 1 agent was found (pneumolysin and *H. influenzae* 1; pneumolysin and *M. catarrhalis* 3; *H. influenzae* and *M. catarrhalis* 1). Serologic evidence of bacterial in-

TABLE 2. Viral infections identified by culture in 96 control children from the village cohort

Virus	n = 96	%
RSV	0	0
Influenza	0	0
Parainfluenza	2	2.1
Adenovirus	5	5.2
Other	7	7.2
Mixed viral	0	0
Total positive	14	14.6

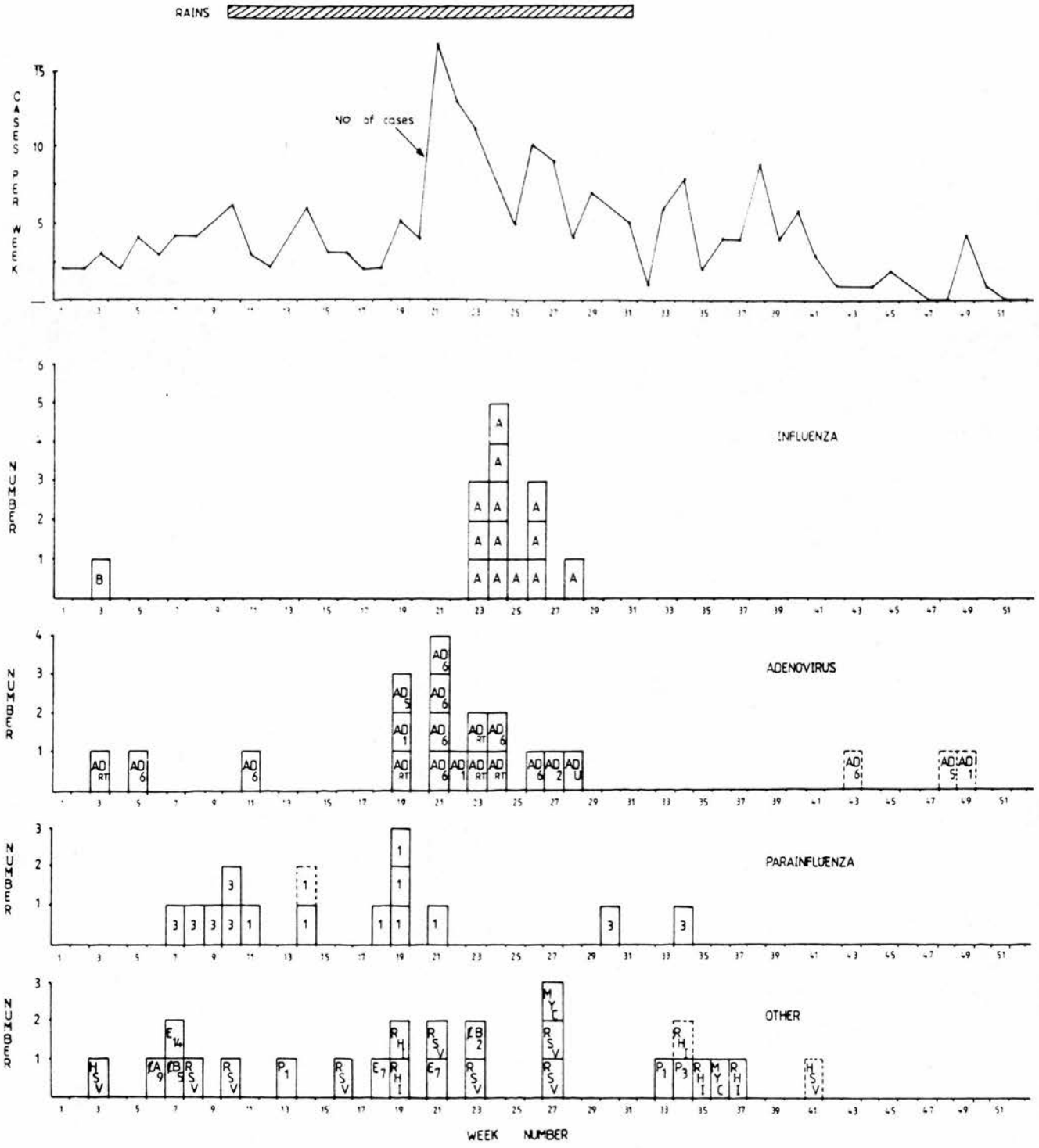

FIG. 1. Episodes of ALRI identified in Basse village cohort children and associated viral infections by week of study. *A*, influenza virus type A; *B*, influenza virus type B; *1*, parainfluenza virus type 1; *3*, parainfluenza virus type 3; *AD*, adenovirus; *RHI*, rhinovirus; HSV, herpes simplex virus; *CA*, Coxsackie A virus type; *CB*, Coxsackie B virus type; *P*, polio virus; *E*, ECHO virus; *MYC*, *Mycoplasma pneumoniae*.

fection was found in 9 (41%) of the 22 cases with lobar pneumonia who were investigated compared with 21 (12.3%) of 170 cases of ALRI who did not have lobar pneumonia (chi square = 9.9, $P < 0.01$).

Eighteen percent of urines from both cases and controls gave a positive reaction when they were tested by the type-specific latex tests for pneumococcal antigen. Detection of pneumococcal antigenuria by the type-specific latex test was therefore not considered to be a reliable indication of pneumococcal infection in this population and the results have not been included in calculations of the number of cases in whom

TABLE 3. Episodes of ALRI identified by community surveillance: bacterial infections

Bacterial Etiology	Episodes of Clinical ALRI			Episodes of Radiologically Confirmed ALRI			Episodes of Lobar Pneumonia		
	Culture and/or serology (n = 222)	Culture only (n = 222)	Serology only (n = 192)	Culture and/or serology (n = 81)	Culture only (n = 81)	Serology only (n = 69)	Culture and/or serology (n = 25)	Culture only (n = 25)	Serology only (n = 22)
Total positive	32 (14.4)*	2 (0.9)	30 (15.6)	19 (23.5)	2 (2.5)	17 (24.6)	9 (36.0)	0 (0)	9 (40.9)
Pneumococcus	19 (8.6)	0 (0)	19 (9.9)	10 (12.3)	0 (0)	10 (14.5)	7 (28.0)	0 (0)	7 (31.8)
Haemophilus influenzae	10 (4.5)	0 (0)	10 (5.2)	6 (7.4)	0 (0)	6 (8.7)	1 (4.0)	0 (0)	1 (4.5)
Moraxella catarrhalis	6 (2.7)	0 (0)	6 (3.1)	2 (2.5)	0 (0)	2 (2.9)	1 (4.0)	0 (0)	1 (4.5)
Other bacteria	2 (0.9)	2 (0.9)	ND	2 (2.5)	0 (2.5)	ND	0 (0)	0 (0)	ND
Mixed bacterial	5 (2.3)	0 (0)	5 (2.6)	1 (1.2)	0 (0)	1 (1.4)	0 (0)	0 (0)	0 (0)
Mixed viral-bacterial	15 (6.8)	1 (0.5)	13 (6.8)	5 (6.2)	1 (1.2)	3 (4.3)	2 (8.0)	0 (0)	1 (4.5)

* Numbers in parentheses, percent.
ND, not determined.

bacterial infection was identified. No *H. influenzae* type b antigenuria was found in any of the episodes of ALRI in cohort children.

Serologic evidence of bacterial infection was found throughout the year. Fifteen cases of lobar pneumonia occurred in the dry season (Weeks 1 to 12 and 31 to 52) compared with 10 in the wet season (Weeks 13 to 30).

Other infections. Evidence of *M. pneumoniae* infection was found in two children from the cohort with ALRI. The first was a 16-month-old child and the second a 46-month-old child. Twenty-three of the 43 cases 4 months old or less were cultured for *C. trachomatis*. No isolates were obtained. Paired sera from 144 cases of ALRI were screened for antibody to *C. trachomatis* but no evidence of current infection was found.

C. pneumoniae infections were identified in 4 of the 189 cases of ALRI tested by microimmunofluorescence. Three cases had a rising titer to *C. pneumoniae* and one had a constant higher titer (>512). On radiograph 2 of the children with *C. pneumoniae* infection had radiologic changes. The cases were 22, 47, 14 and 22 months old, respectively. Fourteen cases had evidence of previous infection by *C. pneumoniae* (stable antibody titers between 32 and 256).

Fifteen (47%) of 32 patients with bacterial ALRI identified by serology or culture also had evidence of viral or a mycoplasmal infection. Overall 1 or more pathogens were identified in 76 (34.2%) of the 222 cases with clinical signs of ALRI and in 34 (42%) of the 81 who, in addition, had radiologic evidence of ALRI.

DISCUSSION

Although lower respiratory tract infections are known to be common in children in developing countries few data are available on their incidence in defined populations. By active surveillance we have found an incidence rate of 452 episodes of ALRI/1000/year in children under the age of 5 years in a rural community in The Gambia using simple clinical criteria such as a raised respiratory rate, chest indrawing and wheezing. The incidence rate for radiologically proved pneumonia was 165 episodes/1000/year. In contrast the annual incidence of ALRI in the same age group in North Carolina and Washington State is 30 to 40 episodes/1000/year.[17,18] Thus the incidence of ALRI in The Gambia is about ten times higher than that found in the United States and other developed countries. This high rate of morbidity is reflected in the high mortality from respiratory disease in The Gambia. In another rural area Greenwood et al.[19] found respiratory infections to be the leading cause of death in young children surviving the neonatal period. High incidences of ALRI have also been reported from Papua New Guinea where rates of 1074/1000 infants/year and 90/1000 children ages 1 to 4 years have been recorded.[20,21]

The results of this study highlight the difficulty of establishing the etiology of pneumonia in pediatric community studies. Although a virus was cultured from 19% of the 221 cohort cases of ALRI investigated a virus was also recovered from 14.6% of 96 controls. Furthermore no particular group of viruses was recovered significantly more often from cases compared with controls. Other cohort children with ALRI did show a rise in specific viral antibody but paired sera were not available from control children for comparison. However, the marked rise in the incidence of ALRI episodes from an average of 3 to 4/week in the first 20 weeks of study to a mean of 14/week in Weeks 21 to 23 is likely to be attributable, at least in part, to the increased activity of one or more viruses such as influenza A virus or adenovirus type 6.

The process of freezing specimens for virus isolation before culture may have had some affect on the virus isolation rate but it is unlikely that this was responsible for the notable absence of RSV infections during the study period. Good agreement was found between the virus isolation and serology results with respect to the epidemiologic and temporal succession of respiratory virus infections, suggesting that the culture results are an accurate representation of the incidence

and pattern of respiratory virus infections that occurred in the Basse village cohort during the surveillance period. Furthermore RSV was isolated by identical culture techniques from 25 (81%) of 31 children shown to be infected with the virus by indirect immunofluorescent staining of cells from nasopharyngeal aspirates during an outbreak of RSV infection which occurred 6 months before formal surveillance of the cohort began. Thus the absence of RSV infection during the study period may be because, like measles,[22] epidemics of RSV infection are less frequent in remote rural areas than in urban areas.

A high proportion of both cases of ALRI and controls were found to be excreting CMV from their respiratory tract (around 30%); therefore it is not possible to ascribe a specific etiology of ALRI to this virus. Similar results have been reported previously from The Gambia and other countries where the seropositivity rate in mothers is high.[23-26]

Neither *M. pneumoniae* nor *C. trachomatis* appeared to be important causes of ALRI in this population. Using culture and serologic techniques we found no evidence of *C. trachomatis* infection in any of the 29 infants less than 4 months of age who were examined. However, it is possible that a greater number of *M. pneumoniae* infections would have been identified in older children if a combination of both culture and serologic techniques had been used.[27]

The limited data on infection by *C. pneumoniae*, a recently described *Chlamydia* organism, has indicated that the agent is associated primarily with outbreaks of pneumonia in young adults[28] and military recruits.[13] However, *C. pneumoniae* can also cause pneumonia in young children, particularly in tropical countries where there is some evidence that the organism causes infection at an earlier age than in children in temperate climates.[29] In this study *C. pneumoniae* infection was diagnosed by serology in 4 (2%) of the 189 children with ALRI who were tested. In 2 of the cases, neither of whom had radiologic evidence of ALRI, *C. pneumoniae* was the only agent identified. The remaining cases had radiologically proved pneumonia and were associated in one case with parainfluenza type 3 infection and in the other with a rise in *H. influenzae* antibody. This is consistent with the observation of Kleemola et al.[13] that, as in adults, *C. pneumoniae* infection alone tends to cause a mild pneumonia but in combination with other infections more serious, and possibly more prolonged, illness may result.

Bacteremia was detected in only 2 (1%) of 222 cases of ALRI but this was not caused by poor culture methods; during the same study period we isolated respiratory pathogens from the blood of 9 (20.5%) of 44 pediatric patients with ALRI attending a nearby health center (unpublished data). The latter patients were recruited during weekly visits to the outpatient department of the health center and were recruited according to selection criteria identical to those used to detect cases of ALRI in the village cohort. Two-thirds of the bacterial isolates from health center patients were *S. pneumoniae* and *H. influenzae*. A fundamental difference between children with ALRI from the village cohort and the health center cases is that the former were identified and referred for treatment by active surveillance. Thus cohort cases were investigated at an earlier stage of disease when bacteremia may be uncommon. This may in part be an explanation for the failure of the pneumococcal type-specific latex agglutination test in village cohort children although it does not explain the high rates of positivity found in the controls. An alternative explanation is that bacterial growth during transport and storage led to positive reactions that were not found previously in a study of hospital patients.[14]

Alternative methods to blood culture for the detection of bacterial ALRI include assays for the detection of antibody to bacterial protein antigens. Among radiologically proved pneumonias in the Basse village cohort 7 (70%) of the 10 patients with ALRI in whom a rising titer to pneumolysin was detected had lobar pneumonia. Although the serologic techniques used for diagnosis of bacterial infection cannot give as certain a diagnosis as blood culture the proportion of village cohort cases with radiologically proved lobar pneumonia in whom a bacterial infection was detected was significantly higher than in cases who had only clinical signs of ALRI ($P < 0.05$). This suggests that bacterial infections were often associated with the more severe forms of ALRI found among the village cohort children. Moreover the patients from the health center who were studied tended to be more severely ill than village cohort patients (with a significantly higher rate of radiologically proven ALRI and lobar pneumonia) thus providing further evidence that the more severe forms of ALRI observed among children in the Basse community were associated with an increased proportion of bacterial infection.

If bacterial infection is indeed as common as these findings suggest, the results of our study would support the use of antibiotics by village health workers in such rural communities where the incidence of ALRI in young children is high and access to health care facilities is limited.

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Indoor Air Pollution Exposure and Lower Respiratory Infections in Young Gambian Children

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Armstrong J R M (Medical Research Council Laboratories, Fajara, Banjul, The Gambia) and Campbell H. Indoor air pollution exposure and lower respiratory infections in young Gambian children. *International Journal of Epidemiology* 1991; **20**: 424–429.

In a rural population-based cohort study of approximately 500 Gambian children under five years old followed for one year, incidence of acute lower respiratory infections (ALRI) was related to various risk factors including parental smoking and regular carriage on the mother's back while cooking, a proxy measure for exposure to smoke from cooking fires. Two statistical analyses using a 'child-weeks at risk' approach were carried out, including and excluding multiple disease episodes in the same child. Weekly surveillance for ALRI found 75 episodes in 62 children. Stratified analyses using both approaches suggested father's smoking, and, for girls only, carriage on the mother's back while cooking and being part of a polygamous family were the main risk factors associated with infection: when multiple episodes occurring in the same child were excluded, not having a health card was an additional risk factor in children over a year old. Multiple logistic regression modelling of data from both approaches, including each of these risk factors and sex, age, village and season, suggested father's smoking, carriage on the mother's back while cooking and being part of a polygamous family increase risk of ALRI, the latter two for girls only. The analysis excluding multiple episodes in the same child also suggested that not having a health card is a risk factor for children aged 1–5 years. The difficulties in interpreting these findings are discussed.

Acute respiratory infections (ARI), and in particular pneumonias, are an important cause of morbidity and mortality in young children in developing countries.[1] The strategy of improved case management has been shown to reduce mortality from ARI.[2] However, it can be expected to have little impact on death from very severe pneumonia, which often has a fulminant course uninfluenced by antibiotic treatment, and a limited effect on morbidity from ARI. Therefore, it is important to assess the significance of a number of potential risk factors for ARI and to assess the effectiveness, cost and feasibility of interventions which seek to reduce their effect. Such an approach[3] may identify interventions that prove useful in ARI control.

Biomass fuels such as wood, agricultural waste and manure are derived from vegetable material of recent origin. The health aspects of biomass fuel combustion have recently been reviewed by the World Health Organization (WHO).[4] There is some evidence that domestic smoke pollution from cooking fires is a risk factor for acute lower respiratory infections (ALRI) in young children.[5–7]

It is estimated that about 30% of urban households and 90% of rural households in developing countries rely on biomass fuel materials as the major, or only, source of domestic energy[8] for cooking and sometimes also for domestic heating. These fuels are usually burned under inefficient conditions producing large quantities of smoke and gaseous products, leading to high levels of indoor air pollution. The poor ventilation found in many kitchens in developing countries compounds this problem. Many children are carried on their mother's back or lap during cooking and hence are exposed to these toxic emissions from early infancy.

There are reports from a number of studies documenting representative levels of air pollution in rural households and the physical and social factors that lead to these exposures.[6,9] However, there are relatively few data from developing countries which relate smoke exposure to incidence or severity of lower respiratory infections in young children. We have previously reported the very high indoor particulate

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concentrations found in rural Gambian kitchens.[10,11] Since young children are usually excluded from cooking huts except when carried on their mothers' backs, two groups with substantially different exposure to smoke can be identified: those normally carried and those not normally carried by the mother whilst cooking.[5] Therefore, we related carriage on the mother's back, together with parental smoking and a number of other factors which might influence incidence or severity of ALRI to the incidence of clinical and radiological lower respiratory infection occurring in a rolling cohort of approximately 500 children over a one-year surveillance period.[12]

METHODS

Study Population

A community-based study of pneumonia in young children was undertaken in a rural area of The Gambia, 350 kilometres from the capital Banjul. An active surveillance programme was instituted for a period of one year in a group of seven villages located 10 to 15 kilometres from the Medical Research Council (MRC) field station in Basse. A cohort of approximately 500 children under five years old were visited weekly and examined for signs of ALRI by trained field workers. The criteria for the diagnosis of ALRI have been described previously.[12] An episode was only considered to represent an ALRI if both clinical and radiological signs were present. X-rays were independently assessed by two clinical investigators.

At the start of the study, the cohort consisted of all under five year old children in the study villages. Children were added to the cohort at birth and dropped from surveillance as they reached the age of five years. Two cross-sectional questionnaire surveys recording possible risk factors for ALRI were carried out, at the beginning and end of the study. These risk factors and basic demographic variables are shown in Table 1, with their frequency of occurrence in the cohort children. Of the 685 children who were included in the morbidity surveillance at some time during the year, 587 were seen during at least one of these surveys, but because this was a 'rolling cohort', and as some children were away from home for periods of time, many were in the cohort for less than 52 weeks.

The weekly morbidity surveillance of cohort children found 75 episodes of ALRI, as confirmed by X-ray changes, in 62 children during the year.

Statistical Analysis

A 'child-weeks at risk' approach was adopted: the total number of child-weeks of disease in each risk factor category was related to the total number of child-

TABLE 1 *Risk factors and their frequency of occurrence*

Risk factor	Frequency (%) in study children (n=587)	
Sex	Male	316 (53.8%)
	Female	271 (46.2%)
Age* at second survey	1–11 months	96 (16.4%)
	12–59 months	491 (83.6%)
Weight for age (NCHS standards)	<80% median (in both surveys)**	163(27.8%)
	>=80% median (in either)	422 (71.8%)
	Unknown	2 (0.3%)
Village†	1	86 (14.7%)
	2	135 (23.0%)
	3	169 (28.8%)
	4	197 (33.6%)
Socioeconomic index‡	Low	147 (25.0%)
	High	368 (62.7%)
	Unknown	72 (12.3%)
Number of wives of father	1	289 (49.2%)
	2–5	298 (50.8%)
Birth order	1st–4th	319 (54.3%)
	5th–15th	245 (41.7%)
	Unknown	23 (3.9%)
Number of siblings at school	0	173 (29.5%)
	1–10	414 (70.5%)
Number of siblings sharing bedroom	0–2	383 (65.2%)
	3–10	204 (34.8%)
Months to next oldest child	N/A (oldest)	101 (17.2%)
	9–30	237 (40.4%)
	31–80	235 (40.0%)
	Unknown	14 (2.4%)
Age started solids	1–5 months	191 (32.5%)
	6–24 months	262 (44.6%)
	Unknown, N/A	134 (22.8%)
Health card	Yes	421 (71.7%)
	No	145 (24.7%)
	Unknown	21 (3.6%)
Clinic visits per year	0	401 (68.3%)
	1–5	186 (31.7%)
Vitamin A intake (estimated from dietary questionnaire)	Low/medium	358 (61.0%)
	High	216 (36.8%)
	Unknown	13 (2.2%)
Grass mattress	Yes (in either survey)	531 (90.5%)
	No (in both)**	43 (7.3%)
	Unknown	13 (2.2%)
Carried regularly on mother's back while cooking	Yes (in both surveys)**	214 (36.5%)
	No (in either)	373 (63.5%)
Cigarettes father smokes per day	Does not smoke	283 (48.2%)
	0–5	166 (28.3%)
	6–10	57 (9.7%)
	11–20	81 (13.8%)

*Age was included in the analysis as a 'dynamic' variable, age at the time of weekly surveillance, categorized into two groups, 0–11 months and 12–59 months.

**Includes those who were only seen in one survey, i.e. the data were missing for the other survey.

†Ethnic group effects are largely confounded with village. The smaller of the seven study villages were combined for the analysis.

‡Derived from number of a list of possible possessions owned.

weeks at risk in that category. The first two weeks after any episode of ALRI were omitted from both numerator and denominator, to ensure that the child had recovered before being returned to the cohort. The resulting data set was analysed first by calculating relative rates for each factor, stratifying for sex, age, season and village. The factors found to show a significant association in this way were then considered together using a multiple logistic regression model, to relate the proportion of child weeks with disease to each risk factor, after having adjusted for all the others. Interactions between variables were assessed by fitting a series of logistic regression models.

Two analyses were carried out:

(i) including all episodes of ALRI in every child, together with disease-free periods between multiple episodes in the same child. This gave 23 122 child-weeks at risk and 75 child-weeks with disease.

(ii) excluding all weeks of observation for any child after the first (or only) episode of ALRI. This gave 21 600 child-weeks of observation and 62 child-weeks with disease.

Age was included as a 'dynamic' variable, age at the time of weekly surveillance, categorized into two groups, 0–11 months and 12–59 months. In this way a child would move from the first to the second category on reaching its first birthday.

RESULTS

Approach (i)

The overall disease rate was 3.2 episodes per 1000 child-weeks at risk. Rates by sex, age, village and season are given in Table 2.

For each risk factor in turn, estimates of common relative rate across the strata were found and homogeneity across strata was checked. This initial analysis showed that the risk of disease was related to father's smoking, to carriage on the mother's back while cooking and to family structure (one or more wives), but for the latter two variables only in female children. Multiple logistic regression was then carried out on these variables together with sex, age, village and season.

TABLE 2 *Disease rates per 1000 child-weeks at risk, by sex, age, village and season—approach (i)*

Sex	Males	3.3
	Females	3.2
Age (months)	<12	4.0
	12–59	3.0
	12–23	3.3
	24–35	4.0
	36–47	3.3
	48–59	0.9
Village	1	2.1
	2	3.4
	3	4.1
	4	3.1
Season	Dry	2.7
	Wet	4.2

The risk from smoking did not increase in a linear way with number of cigarettes smoked, though the rate was consistently higher in the children of relatively heavy smokers (11–20 cigarettes per day) than in children of light smokers and non-smokers. For this reason the smoking variable was reclassified into two groups, 0–10 cigarettes per day and 11–20 cigarettes per day.

The results of the multiple logistic regression modelling are given in Table 3 in the form of adjusted odds ratios and 95% confidence limits for each factor which showed a significant relationship with disease risk. Parental smoking increases risk of ALRI. For girls, but not boys, carriage on the mother's back and being part of a polygamous family increases risk of ALRI. For boys, being part of a polygamous family has a protective effect.

Approach (ii)

The overall disease rate was 2.9 episodes per 1000 child-weeks at risk. The rates by age, sex, village and season are given in Table 4.

Stratified analysis suggested the same risk factors as with approach (i), with the addition of possession or not of a health card among children over 12 months old. The smoking variable was again reclassified into two groups, for the same reasons as before.

The results of the multiple logistic regression are shown in Table 5. Parental smoking increases the risk of ALRI, though this result is of borderline significance. For girls, but not boys, carriage on the mother's back and being part of a polygamous family again increase risk of ALRI. In children aged 1–5 years, not having a health card is associated with an increased risk of ALRI. However, for some of these effects the confidence interval for the odds ratio is very wide, reflecting the relatively small number of child-weeks at risk in the relevant category.

TABLE 3 *Results of multiple logistic regression, approach (i)*

Risk factor	Odds ratio (95% CI)
Father's smoking* (11–20/0–10 per day)	1.9 (1.1, 3.4)
Carriage on mother's back when cooking* (yes/no)	
Boys	0.5 (0.2, 1.2)
Girls	1.9 (1.0, 3.9)
Number of wives of father*** (2–5/1)	
Boys	0.5 (0.2, 0.9)
Girls	2.4 (1.1, 5.3)

*$p<0.05$.
***$p<0.001$.

TABLE 4 *Disease rates per 1000 child-weeks at risk, by sex, age, village and season—approach (ii)*

Sex	Males	2.7
	Females	3.0
Age (months)	<12	3.6
	12–59	2.6
	12–23	2.6
	24–35	3.3
	36–47	3.3
	48–59	0.9
Village	1	2.0
	2	3.4
	3	3.3
	4	2.8
Season	Dry	2.6
	Wet	3.4

DISCUSSION

The problems inherent in studies which investigate the relationship between illness episodes and possible risk factors are well described. These are particularly important when considering environmental risk factors which often show weak association: bias and confounding may make interpretation of results difficult. Environmental factors are often interrelated so that it is difficult to quantify the effect of each individual factor. Indirect measurements are often used as a proxy for measurement of true exposure, and misclassification of exposure groups may result.[13]

In this report the information on exposure was based on data collected from simple questionnaire surveys. It is likely that maternal recall of past events or activities is subject to substantial error. If these errors are uniform for all subjects then this will act to reduce the size of any observed associations. However it is possible that an episode of lower respiratory infection in a child may selectively alter maternal recall and lead to false associations. We were unable to confirm the accuracy of our exposure data independently. Techniques now exist to estimate cumulative dose of smoke exposure by urinary cotinine (a metabolic product of nicotine whose excretion is related to frequency of cigarette smoking) and carboxyhaemoglobin measurements: such methods might eliminate the need for indirect measures of smoke exposure. Proxy measures were also adopted for assessment of vitamin A status, socioeconomic status and crowding and may have limited validity as indicators of these risk factors.

Because of the rolling cohort nature of the data, and the highly mobile population, it would be difficult to analyse these data on a truly individual basis rather than as 'child-weeks at risk': either approach (i) or approach (ii) is necessary. The former is appropriate in giving overall disease rates in this cohort. However, the assessment of risk factors by including multiple episodes in the same child in the analysis, as with approach (i), assumes that episodes are independent observations, randomly distributed throughout the cohort. This assumption may be tested by investigating the distribution of ALRI episodes: there were 75 episodes in 685 children (623 children were disease-free, 51 had one episode, 9 had two episodes and 2 had three episodes), giving a mean number of episodes per child as 0.109 in the period observed. This distribution is more widely dispersed than Poisson (chi-squared test = 36.8 on 2df, $p<0.001$) and thus it would appear that individual episodes are not independent: some children are more likely to have repeated episodes than others. Though the validity of this test may be questionable since not all children were followed up for an equal length of time, it seems reasonable if we assume that length of follow-up is unrelated to disease. The effect of approach (i) is to overemphasize the risk factors of those children who had repeat episodes, whereas approach (ii) might be expected to underestimate them. As multiple episodes are not independent, approach (ii) would seem the better of the two when making inferences relating risk factors to disease, as we would otherwise be biasing the risk factor analysis towards those children who did have more than one episode.

Studies in developed countries have shown an increased incidence of ARI in children of mothers who smoke compared to children of those who do not, with most of the effect being observed during the first two years of life.[14–16] The fact that relatively low levels of direct tobacco exposure in children and adolescents have a measurable effect on pulmonary function is emphasized by the finding that such exposure has a substantial negative effect on the rate of increase in FEV_1 (forced expiratory volume) during childhood growth.[17]

We found that the incidence of lower respiratory

TABLE 5 *Results of multiple logistic regression—approach (ii)*

Risk factor	Odds ratio (95% CI)
Father's smoking (*) (11–20/0–10 per day)	1.8 (1.0, 3.4)
Carriage on mother's back when cooking** (yes/no)	
Boys	0.5 (0.2, 1.3)
Girls	6.0 (1.1, 34.2)
Number of wives of father** (2–5/1)	
Boys	0.5 (0.2, 1.0)
Girls	14.4 (2.3, 90.2)
Health card* (no/yes)	
<12 months	0.2 (0.0, 1.7)
12–59 months	15.1 (1.3, 169.2)

(*)$p<0.10$.
*$p<0.05$.
**$p<0.01$.

infection in Gambian children is related to their father's smoking habits. Due to the much greater contact between mothers and their children it would be expected that maternal smoking would have a larger effect. However, only 3% of mothers in our study reported regular smoking, so we were unable to investigate this. In this community maternal smoking is unlikely to be an important risk factor.

We were able to show a significant association between smoke exposure and incidence of ALRI, but only in girls. Since combustion of biofuels is not generally required for space heating in rural Gambian populations, smoke exposure is predominantly from cooking fires. Young children are usually excluded from cooking huts except when carried on their mothers' backs. Some mothers regularly carry their youngest child on their back whilst cooking because no other child minder is available to care for the child. This behaviour appears to be consistent over a period of time and changes only when another child is born or the child grows too old. Though the proportion of mothers carrying their children was highest for infants (58%), 31% of four and five-year-old children in our study were still regularly carried by their mothers while cooking. Thus there are two groups of children with substantially different exposure to smoke: those regularly carried and those not regularly carried by the mother whilst cooking. Misclassification of smoke exposure groups may have occurred but is likely to have been uniform for all subjects and hence will have tended to decrease any observed association with ALRI. Approach (ii) would suggest that the strength of the association between smoke exposure and the incidence of ALRI in girls is of greater magnitude than that of parental smoking.

However these results should be interpreted in the light of the methodological problems discussed and bearing in mind that no allowance has been made in significance levels for the multiple comparisons that have been carried out. Future studies should attempt to define groups with substantially different exposure more clearly and make independent measurements of some index of exposure in order to minimize misclassification.

The difference between boys and girls with respect to the effects of carriage on the mother's back and of family structure is unexplained, but the size of the difference between the sexes suggests that this is unlikely to be a chance finding. In our study, girls over one year old were more likely to be carried on their mother's back while cooking than boys (37% girls, 28% boys: chi-square = 4.8, $p<0.05$): this is not due to weight differences between boys and girls as older girls were, if anything, heavier for their age than the older boys. However, how such differences in maternal behaviour might result in girls having an increased risk of ARI while being carried is unclear. It is possible that older girls, in addition to being more likely to be carried than boys, are carried for longer periods of time. Further more detailed studies, including direct observation of the behaviour of mothers in cooking huts, are needed to investigate this unexpected finding.

We found a weak association indicating an increased risk of ALRI in children over 12 months old without a health card. Not having a health card is likely to reflect maternal education level, socioeconomic status, and attitude to and availability of medical services, so that a link between this and disease might have been expected in all under-fives rather than just the older group.

Our data suggest that there may be a link between ALRI in young Gambian children and paternal smoking and exposure to the smoke of cooking fires. It is thus likely to be important for national ARI programmes to consider attempts to reduce these risks through parental education, and by improving methods of cooking. However, the cost and feasibility of suitable interventions should be further studied. Given the methodological difficulties inherent in such studies this may be best achieved by an intervention study which creates a low smoke exposure group.

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NAI than reflex anal dilatation is of child sexual abuse.[4]

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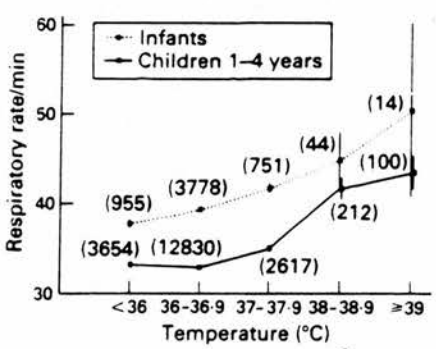
Effects of body temperature on respiratory rate in young children

SIR,—Dr Simoes and colleagues have reported studies of variability in measurements of respiratory rate in young American children, but did not consider possible effects of body temperature on these measurements.[1] Previous work suggested a weak association between body temperature and respiratory rate in young infants studied in Australia and Britain.[2] Current World Health Organisation guidelines for the management of acute respiratory infections in children recommend that young children with cough or difficult breathing and raised respiratory rate should be treated for pneumonia irrespective of temperature.

In a community study of acute respiratory infections undertaken at the MRC Laboratories in the Gambia, weekly measurements of temperature and respiratory rate were made on a population including approximately 500 children under the age of 5 years, over a one year period. This study is described in detail elsewhere.[3] Although these repeated observations are technically not independent, we consider that measurements of respiratory rate and temperature carried out not more than once weekly on a young child may reasonably be assumed to be independent. A total of 25 025 observations on 685 young children were made. In 70 instances abnormalities on chest radiography were found and these observations have been excluded from the following analysis. The relationships between temperature and respiratory rate for infants (5542 observations), and for children aged 1 to 4 years (19 413 observations), are shown in the figure. In both groups, mean respiratory rate shows a steady increase with increasing temperature of appoximately 2·5 min °C over the temperature range shown. A similar analysis restricted to children with cough (2537 observations) showed a similar relationship (data not shown).



Relationships between respiratory rate and temperature in young Gambian children. Vertical bars represent 95% confidence intervals of the mean, and numbers of observations for each point are shown in parentheses.

The data presented, in accordance with experimental results on the effects of temperature on breathing,[4] suggest that raised respiratory rates may be partly attributable to increases in body temperature. We earlier reported that in children with cough or difficult breathing respiratory rate is a valid predictor of the presence of clinical or radiological pneumonia.[3] The findings presented here do not challenge this, but they suggest that this relationship between fever and respiratory rate may account for some of the false positive diagnoses of pneumonia in children with cough or difficult breathing, fever and raised respiratory rate. This issue may be of particular importance in areas in which malaria is prevalent as it has been shown that there may be a very substantial overlap of clinical presentation in children with malaria and pneumonia.[5] The possible effect of this phenomenon on the specificity of raised respiratory rate as an indicator for pneumonia needs further investigation.

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Consumer safety and child choking attacks

SIR,—From time to time you publish letters which do not have any direct relevance to immediate past publications and it would be helpful if such letters indicated their origin. One such letter recently published gives no explanation as to why Drs Matthes, Sibert, and Levene were concerned about possible inhalation of foreign bodies from toys.[1] Those paediatricians who help local authority consumer protection departments by assessing or commenting on the safety of toys will be aware there has been a recent increase in the vigilance of trading standards officers regarding choking hazards to children because of a number of deaths. Dr Levene chaired a working party under the auspices of the Child Accident Prevention Trust, which found little published evidence of any serious hazard from the inhalation or ingestion of hair plucked from toys.[2] This report is being used by manufacturers to defend their products against legal action even though safer alternative materials are available.

The recent letter refers to a survey of paediatricians and ear, nose, and throat surgeons throughout Wales seeking to identify their awareness of choking hazards to young children from hair or other small objects. It is gratifying that they knew of no such hazard but we suggest that the wrong people were asked the wrong questions. The children who died in Leeds (from obstructive inhalation after ingestion of hair from a toy donkey) and in Birmingham (after inhalation of a small piece of plastic from inside a novelty chocolate egg) were unknown to paediatricians or ear, nose, and throat surgeons because casualty doctors and pathologists dealt with them.

Life is full of hazards and it would be impossible to ever legislate them all away. Even if this could be done it would then so grossly distort normal childhood experience as to be unacceptable. There are, however, measures that can be taken to control unnecessary hazards and we are of the opinion that inappropriately long hair that is inadequately fixed to a fur fabric is not suitable for the exterior decoration of any toy. It is to be expected that young children will pluck or suck the hair and may then inhale or ingest with the risk of asphyxiation or bezoar formation. Small pieces of plastic that may occlude the airway are also inappropriate in toys intended for young children.

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Coroners' records of accidental deaths

SIR,—Dr Levene has demonstrated the potential of using coroners' records as a source of data relevant to child accident prevention studies.[1] In a similar retrospective study in this district using the coroner's records we discovered 69 children aged under 15 years who had died as a result of an accident between the years 1980–9 inclusive. Road traffic accidents represented the commonest fatal accident with falls, drownings, and asphyxia accounting for the remainder. Head injury was the commonest reported cause of death. Most deaths occurred within 2 km of the child's home while children were playing without supervision. We encountered an association between social class and incidence of accidents with 10 times as many accidents occurring in classes IV and V than in I and II. There was, in addition, a clustering of cases in areas with high deprivation scores.

This information was of great use to us in planning local child accident prevention strategy as it enabled us to target limited resources to areas where they were needed most. However, as in Dr Levene's case, we were made aware of the limitations of using coroner's records alone for this purpose. We discovered that inquisitions relate to deaths occurring to children who died within the boundaries of our district only. During the period of our study we became aware that several local children had died while visiting other districts but this information would not

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Coincidence of malaria parasitaemia and abnormal chest X-ray findings in young Gambian children

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Summary

Weekly surveillance of Gambian children aged less than 5 years for both acute lower respiratory infections (ALRI) and clinical malaria showed a high rate of coincidence between abnormal chest X-ray findings and high levels of malaria parasitaemia. Generalized interstitial X-ray changes were particularly associated with these cases of malaria parasitaemia. It is suggested that such ALRIs in these children may be attributable to malaria.

Introduction

Both acute lower respiratory infections (ALRI) and malaria are major causes of childhood mortality and morbidity in many developing countries (Greenwood *et al.* 1987). However, potential interactions between the two disease complexes have not been investigated extensively.

Patients and methods

In a community-based study of respiratory disease in the eastern region of The Gambia, all children under 5 years old living in seven rural villages were closely monitored for respiratory complaints and febrile illnesses. Children with clinical evidence of lower respiratory infection (cough and either a respiratory rate of 50 min^{-1} and over, or any chest indrawing) were referred to a clinician for further investigations, including chest X-rays (all read blind by an experienced paediatric radiologist) and thick blood films. Thick blood films were also made for all children found to have axillary temperatures of 37.5°C and over during weekly surveillance visits.

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Results

During the 1-year study period, the mean under-5 population in the study villages was 482. In this population, 183 children experienced a clinical attack of malaria associated with a parasite density of 5000 μl^{-1} and over, of which 165 (90%) presented in a 20-week period in the rainy season. In this same period, 130 ALRI episodes meeting the WHO criteria were detected, with abnormal chest X-ray findings occurring in 39 cases (30%). Four children had malaria parasites at a density of 5000 μl^{-1} and over at the time of their respiratory episode. A further nine children experienced an episode of malaria and a respiratory illness associated with an abnormal chest X-ray at different times during the 20-week period. In each of these cases the two episodes of illness were separated by 1 month or more (Figure 1).

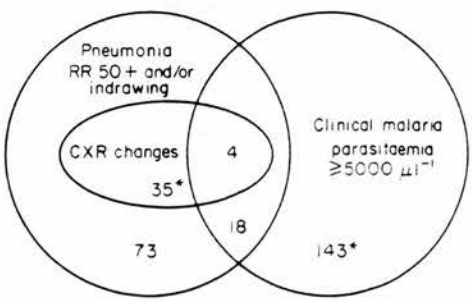

Figure 1. Occurrence of pneumonia, chest X-ray changes and clinical malaria among a population ($n = 482$) of rural Gambian children aged less than 5 years during a 20-week period in the wet season. *Nine children had both CXR changes and clinical malaria at different times.

If an episode of malaria and an episode of respiratory illness associated with an abnormal chest X-ray were to occur independently in a child experiencing both during a 20-week period, the probability of both occurring in the same week would be 0.05. Conversely, the probability of separate occurrence would be 0.95. Thus, the probability of observing malaria and an abnormal chest X-ray at the same time in four of the 13 children who experienced both these conditions is $^{13}C_4 \times 0.05^4 \times 0.95^9 = 0.0028$. We conclude therefore that malaria parasitaemia of 5000 μl^{-1} and over was associated more often with abnormal chest X-ray findings in this group of children than would be expected by chance.

There are several possible explanations for this finding. Clinical malaria may predispose some children to ALRIs, perhaps by influencing immune mechanisms. However, Greenwood *et al.* (1989) did not find a reduction in respiratory symptoms among a group of children substantially protected from malaria by means of chemoprophylaxis. Conversely, ALRIs may predispose to malaria, or allow sub-clinical parasitaemias to become patent. Thirdly, malaria itself may, in some cases, present with respiratory signs and symptoms. Isolated case reports of acute pulmonary oedema associated with malaria have been made on several occasions (Brooks *et al.* 1968; Godard & Hansen 1971), mostly in non-immune adults. Increased cytoadherence between parasitized red blood cells and pulmonary endothelial cells has been suggested as a cause of respiratory distress in malaria (Corbett *et al.* 1989). The occurrence of pulmonary complications in semi-immune African children is less certain, although Edington (1954) reported pulmonary abnormalities at autopsy in Ghanaian children who had died of cerebral malaria. Nevertheless, interstitial changes similar to those reported by Godard and Hansen (1971) were found in all four of our children who had clinical malaria and X-ray changes simultaneously. Similar changes were seen in only 10/35 (29%) of abnormal chest X-rays not associated with malaria ($P < 0.02$, Fisher's Exact test).

In the absence of information on the incidence of chest X-ray changes in normal Gambian children some caution is needed in assessing the likely significance of our findings. However, our data suggest that lower respiratory disease and malaria do not behave independently in rural Gambian children and that a small proportion of episodes of clinical malaria are associated with chest X-ray changes of an interstitial nature.

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Acute lower respiratory infections in Gambian children: maternal perception of illness

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Summary. A study of mothers' perceptions of childhood acute respiratory infections (ARI) was performed in a rural Gambian population. A total of 25 046 interviews were recorded over a 1-year period with mothers from three villages and four hamlets, and these were analysed together with the results of surveillance of their children for episodes of ARI. Mothers recognized acute lower respiratory infection as a severe disease and recognized fast and difficult breathing as features which discriminated it from upper respiratory infections (sensitivity 73%, specificity 73%). They sought treatment for their children on 51% of occasions when chest pain was reported and on 70% of occasions when 'open chest' was reported. We conclude that even in poorly educated populations in which traditional medical beliefs and practices are widespread, it may be possible to educate mothers to identify lower respiratory infections and to seek early treatment. Community education should play a major role in all national ARI programmes and may be a critical determinant of the success of case management strategies in preventing ARI-related mortality in children.

Introduction

Acute lower respiratory infections (ALRI) are a major cause of morbidity and mortality in young children in developing countries. In 1982–83 an investigation of causes of death in children under 5 years of age undertaken in a rural area of The Gambia, using a post-mortem questionnaire, suggested that chest infections were the most common cause of death in children surviving the neonatal period.[1]

The development and distribution of effective vaccines against respiratory pathogens, specifically *Streptococcus pneumoniae*, *Haemophilus influenzae* and respiratory syncytial virus, may prove to be the most effective method of reducing deaths from ALRI in the long term. However, a joint UNICEF-WHO statement has highlighted two control measures which might produce an immediate impact on mortality.[2] These are the adoption of appropriate case management for ARI within the primary health care structure and health education to promote appropriate child-care practices related to ARI at the family and community levels. Two key determinants of the success or otherwise of case-management strategies in reducing mortality from ALRI are likely to be the capacity of mothers and peripheral health workers to discriminate between different severities of ARI (mild ARI requiring supportive care, moderate ARI requiring antibiotic therapy, and severe ARI requiring referral for in-patient treatment) and the ease of access to effective treatment.

Community health education is of central importance to effective case management since it has the potential to establish

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productive contact between the health services and the community, to increase the capability of families to recognize signs of ALRI in children and to encourage appropriate and early care-seeking behaviour. The fact that in some rural communities 50% of ALRI deaths occur within 3 days of onset of symptoms emphasizes the need for early recognition of ALRI and early treatment.[3] A recent review of seven ALRI intervention trials in developing countries has confirmed that it is possible to implement a case-management system operated by semi-literate peripheral health workers.[4] Reduction in mortality from ALRI was found to be greatest in those studies in which active case finding in the home was employed. It would be difficult to sustain this level of active surveillance within the primary health care structures of most developing countries, but the impact of a passive case finding approach is limited by the proportion of disease episodes for which mothers seek treatment from peripheral health workers. Therefore, in developing countries which have high ALRI-specific mortality rates, it is important to understand both maternal perception of ARI in young children and the factors which determine whether the mother of a child with ALRI seeks treatment. Effective health education can only be provided on the basis of an accurate understanding of the prevailing knowledge, attitudes and practices of a population. The recent proposals for the introduction of a national ARI programme in The Gambia, and the lack of published data from developing countries relating to these issues prompted us to study the behaviour of mothers with respect to childhood ARI in a rural Gambian community.

Patients and methods

Study area

A community-based study of pneumonia in young children was undertaken in a rural area of The Gambia, 350 km from the capital, Banjul. An active surveillance programme was instituted for a period of 1 year in a group of seven villages 10–15 km from the Medical Research Council field station in Basse.[5] Families living in this area rely on subsistence farming with some additional support from cash generated from the sale of groundnuts. The level of school education amongst rural women from the study villages is very low with only 20 417 (5%) having received any primary education and 1 417 secondary education. A cohort of approximately 500 children less than 5 years old were visited weekly. At any particular time this cohort included all children up to the age of 5 years residing in the study area. Our results hence portray childhood ALRI in a defined community during a 1-year period, rather than in a cohort of specific children. During each visit a morbidity questionnaire was administered and the child was examined for signs of ALRI by trained field workers who lived in the study villages. The questionnaire asked about the presence of general and respiratory-specific symptoms in the preceding week, the presence or absence of any illness during that time, and whether or not treatment had been sought by the mother. A key informant interview survey, using the main local languages (Mandinka and Fula), in 15 neighbouring villages together with a pilot study of mothers had identified three concepts that described local women's perceptions of chest disease or breathing difficulty. These were chest pain, fast breathing and 'open chest', the latter being a widely understood condition which is stated to be present if a measurement from one shoulder of the child, over the head to the other shoulder is exceeded by the circumference of the child's chest. Each community is able to identify individuals who are experienced in performing this assessment, although most mothers also claim to be able to recognize the condition of 'open chest' independently. There was no local word to describe chest indrawing although this idea is probably incorporated in the above three concepts.

iagnosis of ALRI

eld workers were trained to record accutely a child's respiratory rate and temperare and to recognize signs of respiratory stress. All children with a raised respiraty rate (above 50/min), chest indrawing, sal flaring, wheeze, stridor or with severe stemic upset, such as an inability to drink, ere referred to the project clinician. Other ildren with respiratory complaints who d not satisfy these criteria but whom a field orker thought might have ALRI were also ferred. All children referred were fully amined by the project clinician, bled for tiological studies and X-rayed. Chest X-ys were read independently by a paediatric diologist who assessed whether or not diological changes consistent with a clini-l diagnosis of ALRI were present.

nalysis of reported symptoms

ghty-one discrete episodes of ALRI associed with confirmatory radiological changes ere identified during the 1-year study. hree cases for whom morbidity data at the ne of the chest X-ray were not available ere excluded from analysis giving 78 cases ' radiologically proven ALRI. From the) 046 morbidity records, 78 children with ı upper respiratory infection (either stated have respiratory disease or cough on the ıy of the interview by the mother, but ithout any of the features of ALRI) and 78 ell children (stated to be well and without cough on the day of the interview) were lected. These two groups of children were ıosen by indexing the morbidity database ing (week + village + age + sex) as a compote key, and then selecting the records near-t to that of an ALRI case of a child with ırrent upper respiratory infection and to ıat of a well child. For each of the 78 ALRI ıisodes, a 7-day period of morbidity records om the day before presentation to 8 days :fore presentation was examined. Corresonding 7-day periods for the other two oups were also considered, and for all 234 ıild-weeks observation the presence of each of nine symptoms on at least 1 day in the 7-day period, or their total absence, was noted.

Results

Overall results of morbidity assessments

A total of 25 046 weekly morbidity questionnaires were completed on approximately 500 children under the age of 5 years during a 1-year surveillance period. Mothers or guardians were asked about nine different symptoms at each interview. The overall frequency of symptoms reported was as follows: blocked or runny nose, 48%; fever, 24%; cough, 19%; diarrhoea, 10%; chest pain, 7%; vomiting, 5%; fast breathing, 4%; refusing to breastfeed or to eat, 2%; 'open chest', 1%. In addition, mothers were asked whether the child was unwell (reported in 47% of interviews), suffering from a respiratory illness (18% of interviews) or had another illness (29% of interviews).

Comparison of matched groups

Morbidity data were compared for three groups of children—78 cases of radiologically proven ALRI, 78 with an upper respiratory infection (URTI), and 78 with no respiratory symptoms. The three groups were matched exactly for the week of study and village of origin. The mean (SD) ages of the children were 24.1 (15.1) months in the ALRI group, 24.0 (14.8) months in the upper respiratory infection group, and 25.3 (14.6) months in the well group. The proportion of boys in the groups were 57, 50 and 60%, respectively. The frequency with which mothers reported specific symptoms in the three groups of children is shown (Table I). When the ALRI and URTI groups are compared, highly significant increases in reports of chest pain, 'open chest', fast breathing, refusal to feed and vomiting are found among children with ALRI. Episodes in which the mother reported that the child had chest pain, fast breathing, 'open chest' or a combination of these symptoms were much more

TABLE I. Differences in frequencies of reported symptoms between groups of children with subsequent clinical and radiological ALRI, upper respiratory infection (URTI), and no respiratory illness

	Group			Comparison URTI ALRI		
	Well ($n=78$)	URTI ($n=78$)	ALRI ($n=78$)	χ^2	p	Odds ratio (95% CI)
Symptom						
Cough	0	65	65	0.05	NS	1.0
Blocked runny nose	24	60	57	0.14	NS	0.8
Fever	6	55	54	0.0	NS	0.9
Chest pain	0	21	52	23.2	<0.001	5.4 (2.6–11.5)
'Open chest'	0	3	16	8.6	<0.005	6.5 (1.6–29.3)
Fast breathing	0	14	38	15.3	<0.001	4.3 (1.9–9.6)
Refusal to feed	0	7	23	9.3	<0.003	4.2 (1.5–11.8)
Diarrhoea	3	15	11	0.4	NS	0.7
Vomiting	2	12	26	5.9	<0.01	2.7 (1.2–6.4)

likely to be associated with a clinical and radiological diagnosis of pneumonia than when these symptoms were absent (odds ratio 4.6, 95% confidence interval 2.2–9.6). Analysis of all 25 046 interviews showed that the presence of one or more of these three symptoms predicted the finding of clinical and radiological ALRI with a sensitivity of 73% (57/78) and a specificity of 89% (22 180/24 968). These findings were equally valid in the high-risk under-1-year-old group (sensitivity 79%, specificity 86%) as in older children. When the 4540 interviews in which the mother considered that a child had a current respiratory illness were considered alone, the specificity dropped to 73%.

Frequency of self-referral for treatment

Mothers who reported respiratory illness in their children said that they had sought treatment for this illness in 30% (1357/4540) of episodes. Mothers of 0–3-month-old children who had symptoms of a respiratory illness sought treatment more frequently—in 40% (145/362) of episodes. These rates of self-referral did not vary significantly throughout the year. The frequency of reporting of individual symptoms and the frequency with which these symptoms were associated with self-referral for treatment during episodes in which the mother considered that her child had a respiratory illness are shown in Table II. The commonest symptoms which led mothers to seek treatment for episodes of respiratory illness in their children were blocked nose, fever and cough, with self-referral occurring in 38% of episodes in which cough was reported. Although symptoms related to the chest (chest pain, fast breathing and 'open chest') and to systemic upset (vomiting and refusal to feed) were reported less frequently than cough or fever, their presence was more often associated with self-referral for treatment. Thus, mothers sought treatment on 51% of occasions in which they considered chest pain to be present and on 70% of occasions when 'open chest' was considered to be present. The rate of self-referral when at least one of the symptoms of chest pain, fast breathing or 'open chest' was reported was 145/362 (40%) in 0–3-month-old children and 1357/4540 (30%) overall.

Discussion

Improved case-management strategies to reduce ARI mortality place emphasis on rapid access to appropriate treatment for children

TABLE II. Symptoms reported by mothers, and associated self-referral, in 4540 episodes of reported respiratory illness among a cohort of 500 Gambian children under 5 years of age during 1 year

	Episodes when symptom reported		Number of self-referrals for treatment when symptom present	
	No.	(%)	No.	(%)
Symptom				
Blocked nose	3874	(85)	1116	(29)
Fever	2454	(54)	993	(40)
Cough	2278	(50)	786	(38)
Chest pain	942	(21)	480	(51)
Diarrhoea	637	(14)	244	(38)
Fast breathing	535	(12)	233	(44)
Vomiting	531	(12)	276	(44)
'Open chest'	187	(4)	130	(70)
Refusal to feed	173	(4)	82	(47)

who have an ALRI. The role of the mother in recognizing that her child has a chest infection and in seeking treatment from the primary health care services is critical to the success of this strategy. Furthermore, since the majority of cases of ALRI in children will be treated as out-patients the mother will be responsible for administering the antibiotic treatment and ensuring that other beneficial supportive measures are adopted.

Community education must be based on an understanding of health knowledge and behaviour among mothers in individual developing countries. Currently, however, there are few data either describing mothers' perception of ARI or assessing the feasibility of educating semi-literate or illiterate mothers to identify ALRI and to seek help at an early stage of the illness. Review of ALRI intervention studies suggest that the impact on mortality will be measurably reduced if national ARI programmes depend on passive case-finding (self-referral to village health workers or health clinics) rather than active case-finding through population surveillance.

Data from two earlier studies indicate that rural mothers can recognize fast breathing in their children.[6,7] We are concerned, however, about the considerable potential for bias in these two previous studies. The groups interviewed (children with upper and lower respiratory infections) were managed very differently: comparisons were made between paediatric in-patients who had been X-rayed and children in out-patient departments who had not. Such a comparison allows the potential for recall bias which may exaggerate the differences between groups. Thus, the mothers of children with more severe disease may have assigned more significance to past symptoms whilst searching for an explanation for the illnesses of their children than mothers of less severely ill children and their accuracy of recall may have differed from that of mothers whose children were treated as out-patients.[8] This could result in over-optimistic estimates of the ability of mothers to discriminate lower from upper ARI. Neither of these studies adopted an objective diagnostic criterion of ALRI such as radiological changes assessed by a single independent investigator. Nevertheless, their finding that maternal perception of fast breathing is a valid predictor of ALRI is a very important observation with regard to the planning of national ARI programmes. The current study defined ALRI by radiological as well as

by clinical criteria and attempted to limit recall bias by considering only morbidity data collected in the villages by field workers well known to the families and by excluding the symptom reports for the day of referral to the clinic. Reporting of morbidity was documented before management decisions were made and had no direct treatment implications.

A pilot questionnaire enquiring about maternal attitudes to ARI identified fever and cough as the commonest symptoms that mothers associate with ALRI. However, these symptoms, which are intuitively plausible as factors associated with ALRI, were not found more frequently in the ALRI group than in children with an upper respiratory infection. In contrast, features recognized by mothers as fast breathing, chest pain and 'open chest' were reported much more frequently by mothers of children with ALRI, indicating that these symptoms could be used in educational campaigns aimed at increasing self-referral of children who need antibiotic treatment.

It is difficult, except by indirect means, to assess maternal behaviour when a child becomes ill with an ARI. However, we were able by analysis of data from 25 046 interviews with the cohort mothers to study which symptoms brought about care-seeking behaviour most frequently. Of the symptoms considered, 'open chest', fast breathing, refusal to feed and chest pain were those that most frequently resulted in treatment being sought. In 70% of episodes in which mothers perceived that their child had 'open chest' and in 51% of episodes in which chest pain was reported, treatment was sought. Similarly, high rates of self-referral for these symptoms were found among mothers of children in the at-risk 0–3-month age group as among the study group overall. Thus, many mothers recognized features of respiratory infections in their children that were associated with radiologically confirmed ALRI and sought treatment when these were present.

We conclude that in this poorly educated rural population in which traditional medical beliefs and practices are widely prevalent, mothers recognize ALRI as a severe disease and have cultural concepts of fast and difficult breathing which, although they do not directly equate with the clinical signs of indrawing or nasal flaring, are predictive of ALRI. Mothers can be encouraged to seek treatment when such symptoms or signs are present. We suggest that community education should play a key role in national ARI programmes and that a local review of maternal perceptions of ARI must be an integral part of such an approach. Our findings, although influenced by the fact that the population was aware that the primary focus of the study was to identify and investigate ALRI, suggest that an education programme based on promoting the recognition of local concepts of chest illness or difficult or fast breathing would bring about appropriate care-seeking from mothers of children with ALRI. The encouragement of such self-referral should facilitate early treatment and hence make an important contribution to the strategy of reducing mortality from ALRI by improved case management.

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Serologic Responses to an *Haemophilus influenzae* Type b Polysaccharide-*Neisseria meningitidis* Outer Membrane Protein Conjugate Vaccine in Very Young Gambian Infants

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ABSTRACT. Recent studies in the United States and Europe have shown that *Haemophilus influenzae* type b polysaccharide-protein conjugate vaccines can induce protective antibody levels in young infants, but it was not clear that this would be the case in African infants, to whom *H influenzae* vaccines must be given at a very early age to prevent disease caused by *H influenzae*. Therefore, antibody responses to an *H influenzae* type b polysaccharide-*Neisseria meningitidis* outer membrane protein conjugate vaccine were measured in very young Gambian infants. In the first group (n = 85), to whom the vaccine was given at the ages of 1 and 3 months, the geometric mean antibody level rose from a prevaccination level of 0.23 μg/mL to a postvaccination level of 1.27 μg/mL, and in the second group (n = 56), vaccinated at the ages of 2 and 4 months, the prevaccination level of 0.16 μg/mL rose to a postvaccination level of 1.59 μg/mL. These two final postvaccination levels did not differ significantly, and interpolation suggests that similar antibody levels were present in both groups of infants at the age of 3 months. This is the age by which protection would need to be achieved to protect against *H influenzae* meningitis in The Gambia and in other countries where the infection has similar epidemiologic characteristics. No significant side effects of vaccination were noted. *Pediatrics* 1990;86:102–107; *Haemophilus influenzae type b, conjugate vaccine, immunization, The Gambia, infants.*

ABBREVIATIONS. MSDRL, Merck Sharp & Dohme Research Laboratories; PRP, polyribosyl ribitol phosphate; EPI, Extended Programme for Immunization; DTP, diphtheria-tetanus-pertussis; CI, confidence interval.

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Acute bacterial meningitis is an important cause of mortality and severe morbidity in children throughout tropical Africa.[1] Major epidemics of meningococcal disease in the African "meningitis belt"[2] attract world-wide attention. However, these epidemics occur against a background of endemic meningitis, which is many times higher than that seen in industrialized societies. Thus, the incidence of endemic meningitis in tropical Africa is approximately 20 to 30 per 100 000 population per year, compared with figures of 3 to 5 per 100 000 in Europe and the United States.[1] In developing countries mortality from endemic meningitis (30% to 50%) is much higher than in industrialized societies.

Hospital studies in tropical Africa have identified pneumococcus and *Haemophilus influenzae* as the most important causes of endemic meningitis.[1] Among 2415 cases of meningitis in patients of all ages seen in Dakar, Senegal, *H influenzae* was isolated from 27% of patients.[3] Figures from 25% to 50% have been found in smaller African studies.[1] In The Gambia, *H influenzae* accounts for approximately 25% of hospitalized pediatric meningitis cases (D. Brewster, personal communication). During 2 years of intensive surveillance, 77 cases of *H influenzae* type b meningitis were identified in the western part of The Gambia, giving attack rates of approximately 60 per 100 000 per year in children younger than 5 years and 300 per 100 000 in infants.[4] Although a small number of African cases of *H influenzae* meningitis have been caused by non-b serotypes,[5] the vast majority have been caused by *H influenzae* type b.[4,6]

the community served by this health center, the only major health facility in the area, were eligible for the study. A weekly computerized call list system was implemented as previously described,[16] so that field workers could visit mothers in their homes before the day of the clinic, asking them to attend with their children on the day of vaccination.

Side effects surveillance was carried out by field workers making home visits during the week after vaccination, with comparable surveillance of control subjects who had received only EPI vaccines. Children were examined for the presence of pain, swelling, or redness at the vaccination site, their axillary temperature measured, and the mothers' opinions sought with regard to symptoms observed since vaccination. The field workers were also asked to make a subjective assessment of whether the child was experiencing any systemic side effects after vaccination. It was not possible for the field workers to be blind in this assessment as no placebo vaccination was given.

Serology

Antibody levels were assayed by MSDRL on code-numbered serum samples, the key to which was not available to any member of MSDRL staff when the assays were done. Total antibodies to PRP (anti-PRP) were measured by a standardized radioimmunoassay procedure (Dr C. Frasch, Center for Biologics Evaluation and Research, Bethesda, MD, unpublished data). The procedure uses extrinsically labeled [^{125}I]-PRP in a Farr-type assay to detect anti-PRP. The lower limit of sensitivity of the assay is 0.125 μg/mL. This assay procedure as performed by MSDRL showed the best correlation with the assay used by the Finland National Public Health Institute.[17]

Analysis

To evaluate serologic responses to vaccination, comparisons were made of geometric mean antibody levels and of response rates; response was defined as doubling antibody levels or as attaining levels of more than 0.15 or 1 μg/mL. Levels below the sensitivity of the assay were taken as 0.125 μg/mL. Ninety-five percent confidence intervals (CIs) of geometric means, proportions, and their ratios or differences were used for comparisons.

Ethical Approval

The study was approved by the Gambian Government/Medical Research Council Ethical Committee and met the requirements of the US Investigational New Drug Regulations.

RESULTS

A total of 99 children were recruited to group A, 95 to group B, and 90 to group C. Full compliance with the vaccination schedule and blood sampling was achieved by 85 infants in group A (immunized with two doses of vaccine at 1 and 3 months) and by 56 in group B (immunized at 2 and 4 months). The reason for the difference in compliance between the two groups is unclear; however, the generally high level of mobility in the population probably accounts for most of the noncompliance, and this effect may increase with age.

Mean antibody levels before and after vaccination in the different groups are shown in Fig 2 and summarized in Table 1. In all vaccinated groups, mean levels were significantly higher than in the corresponding age-matched control subjects (Fig 2). Table 1 also shows antibody responses in terms of the proportions of children with doubling levels after vaccination and of those whose levels exceeded 0.15 and 1 μg/mL. No child in group C had an antibody level of more than 1 μg/mL, while 27% had levels of more than 0.15 μg/mL at 3 months, 27% at 4 months, and 25% at 5 months.

Children in group A showed significantly higher prevaccination antibody levels, both in terms of mean level and the proportion exceeding 0.15 or 1 μg/mL, than children in group B. This was associated with a lower mean level after their first dose, and in significantly lower proportions with doubling levels and with levels exceeding 1 μg/mL after the first vaccination than seen among children in group B. However, after the second dose there were no significant differences between the two groups in

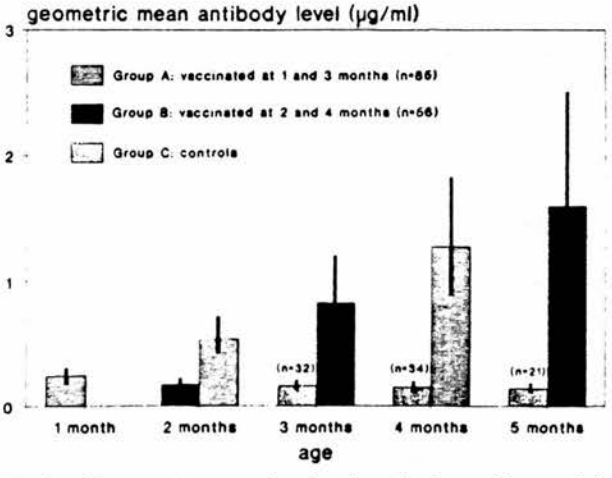

Fig 2. Geometric mean levels of antibody to *Haemophilus influenzae* type b polysaccharide in two groups of Gambian infants immunized at different ages (antibody levels measured prevaccination, after 1 dose, and after 2 doses) and in control infants, by age. Vertical bars represent 95% confidence intervals.

TABLE 1. Serologic Responses to *Haemophilus influenzae* Type b Conjugate Vaccine in 85 Gambian Infants Vaccinated at 1 and 3 Months of Age (Group A) and in 56 Similar Infants Vaccinated at 2 and 4 Months of Age (Group B)*

Responses	Group A (n = 85)	Group B (n = 56)	Comparison (B vs A)
Geometric mean antibody levels, μg/mL			
Prevaccination	0.24 (0.19, 0.29)	0.16 (0.14, 0.18)	0.69 (0.54, 0.87)
1 mo after first dose	0.53 (0.41, 0.70)	0.82 (0.57, 1.18)	1.54 (0.98, 2.40)
1 mo after second dose	1.27 (0.89, 1.81)	1.59 (1.01, 2.49)	1.25 (0.70, 2.20)
Proportions with more than twofold rise in level, %			
1 mo after first dose	43.5	67.8	24.3 (8.1, 40.5)
1 mo after second dose	49.4	51.8	2.4 (−14.5, 19.2)
Overall change after 2 doses	70.6	73.2	2.6 (−17.7, 12.5)
Proportions with levels >0.15 μg/mL, %			
Prevaccination	42.4	21.4	−20.9 (−36.0, −5.9)
1 mo after first dose	72.9	78.6	5.6 (−8.7, 19.9)
1 mo after second dose	83.5	83.9	0.4 (−12.0, 12.8)
Proportions with levels >1 μg/mL, %			
Prevaccination	14.1	3.6	−10.6 (−19.4, −1.7)
1 mo after first dose	32.9	51.8	18.8 (2.4, 35.3)
1 mo after second dose	54.1	60.7	6.6 (−23.2, 10.0)

* 95% confidence intervals are shown in parentheses.

mean level, proportion with doubling levels, or proportions with levels exceeding 0.15 or 1 μg/mL.

Titers of less than 1 μg/mL in both postvaccination samples were found in 32 (37.6%) of 85 children in group A, compared with 16 (28.6%) of 56 children in group B (difference 9.1%, 95% CI −6.6% to 24.8%). Six children (4.3%), 4 from group B and 2 from group A, had no measurable antibody level (>0.125 μg/mL) at any time.

Ten children not included in the above analyses failed to attend for their second dose but were tested successfully 3 months after first vaccination. Of three vaccinated at 1 month, one had a level exceeding 1 μg/mL 3 months later, whereas five of seven given one dose of vaccine at the age of 2 months had a level that exceeded 1 μg/mL at the 3-month follow-up.

Observations for side effects were made after a total of 293 vaccinations, comprising 88 first vaccinations at 1 month, 79 first vaccinations at 2 months, 73 second vaccinations at 3 months, and 53 second vaccinations at 4 months. Observations were also made on 108 control children who did not receive *H influenzae* type b vaccine. Children were visited an average of 3.6 times in the week after vaccination. Findings are presented per child-vaccination in Table 2. Side effects were mild. A small proportion of children had a local reaction at the vaccination site, which was more marked after the first than after the second dose. The size of swelling and redness observed at the site of vaccination exceeded 2 cm in only one case. Observations of the vaccination site were not relevant in control subjects, who received no placebo injection. Fever was also noted more frequently after the first vaccination than the second, although not more frequently than in the control subjects, 5.6% of whom (6/108) showed a raised axillary temperature sometime during the week-long observation period. Mothers complained of subjective fever significantly more often in vaccinees than in control subjects (68% compared with 43%) but reported diarrhea, vomit-

ing, and wheezing significantly more often in control subjects. There were no differences in occurrence of side effects with age of vaccination, and there were no correlations between the incidence of side effects and prevaccination antibody levels.

DISCUSSION

Previous studies in the United States with the *H influenzae* type b conjugate vaccine used in the present study have shown that it is immunogenic when given to infants and that it induces priming of the immune response.[11,12,18] However, the immune response to vaccines, particularly polysaccharide vaccines, is influenced both by genetic and environmental factors such as malaria and malnutrition, and it cannot be assumed that a vaccine found to be effective in American infants will necessarily be immunogenic in infants in tropical Africa. Nevertheless, previous studies in this community have shown infants younger than 6 months to be relatively healthy and well-nourished.[19] It is, therefore, reassuring to find that the vaccine tested produced a prompt rise in antibody level 1 month after first immunization as noted in previous studies and that two doses of vaccine produced antibody levels only slightly lower than those obtained in US infants.

The level of antibody required for protection against disease caused by *H influenzae* type b is not well defined, although serologic studies in Finland suggest that antibody levels of 1 μg/mL or more are protective.[20] It is, therefore, of some concern that only about 50% of vaccinated Gambian children had reached this antibody level by the age of 3 months. However, studies in hypogammaglobulinemic children suggest that lower levels of antibody may give protection, and only 34% of children in the successful Finnish trial (83% efficacy) of an *H influenzae* type b polysaccharide-diphtheria toxoid conjugate vaccine achieved an antibody level of 1 μg/mL.[15] A level of 0.15 μg/mL at the time of exposure may be protective,[21] and this level was achieved by more than 80% of our infants at the age of maximum risk of disease caused by disease *H influenzae* type b. The six children (4.3%) who failed to show any response after two doses of vaccine are a matter of concern as it is conceivable that they would be those most at risk, for genetic or other reasons, from disease caused by *H influenzae* type b.

The age at which protective antibody levels can be achieved after immunization is of crucial importance to the control of *H influenzae* type b meningitis in Africa. In The Gambia approximately 40% of cases occur in infants aged 3 to 5 months. It is thus crucial to achieve protective antibody levels in most children by the age of 3 months. Comparing our two vaccination regimens, antibody levels 1 month after first vaccination were lower in infants immunized at 1 month than in those immunized at 2 months, but interpolation suggests that similar levels of antibody were achieved by the age of 3 months. It is probable that the earlier vaccination regimen gave enhanced antibody response only between the ages of 6 and 10 weeks, a period of low incidence of disease caused by *H influenzae* type b.

Introduction of a new vaccine into the EPI programme requires that it not disrupt existing vaccination schedules, in view of logistic and economic constraints. In The Gambia, children are seen at 1 month for the administration of BCG and at 2, 3,

TABLE 2. Incidence of Side Effects During the Week After Administration of First (at 1 to 2 Months) and Second (at 3 to 4 Months) Doses of *Haemophilus influenzae* Type b Conjugate Vaccine in Gambian Infants*

Side Effects	First Vaccination (n = 167)	Second Vaccination (n = 126)
Local reactions		
Pain	10 (6.0%)	2 (1.6%)
Swelling	4 (2.4%)	3 (2.4%)
Redness	2 (1.2%)	2 (1.6%)
Axillary temperature >37.5°C†	5 (3.0%)	1 (0.8%)
Side effects noted by field worker‡	3 (1.8%)	1 (0.8%)

* Values are given as number (%) of infants.
† Temperature >37.5°C was also found in 6 (5.6%) of 108 control infants who received diphtheria-tetanus-pertussis but not *H influenzae* type b vaccine.
‡ No side effects were noted by field workers in any of 108 control infants.

and 4 months for immunization with DTP. Thus, a possible schedule for an *H influenzae* type b conjugate vaccine in The Gambia would be with DTP, ideally as a combined vaccine. However, before DTP and *H influenzae* type b vaccines can be given together it is essential to establish that there are no mutual adverse reactions. Studies to investigate this are now being planned.

Our finding that very young African infants respond well to an *H influenzae* type b conjugate vaccine should encourage the development of conjugate vaccines against the pneumococcus, which is responsible for many deaths in young children throughout the developing world.

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THE TENTATIVE NATURE OF SCIENTIFIC TRUTH

. . .Scientific truth consists of what has not yet been disproved; it is at best a dense mosaic of approximations.

Chargaff E. *Voices in the Labyrinth*. New York: The Seabury Press; 1977.

Submitted by Student

Carriage of *Haemophilus influenzae* in healthy Gambian children

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Abstract

1240 throat samples were processed during different seasons in 11 different communities of The Gambia (West Africa). The carriage rate for *Haemophilus influenzae* type b ranged from 0 to 33%, but often attained 10% or more, higher than that reported from other open communities. The duration of carriage was short (less than 3 months) and *H. influenzae* b was found in only 10% of the carriers isolated during the previous or the following survey. Children less than 5 years old carried *H. influenzae* b in their throat significantly more often than children older than 14 years ($P<0{\cdot}05$). A high carriage rate did not correlate with the wet or dry season. The carriage rate of children in rural areas was similar to that of children in urban areas. Children in day-care centres or nurseries had a surprisingly low carriage rate (2%). The carriage rate of *H. influenzae* b was compared to the presence of *H. influenzae* subspecies in a random sample, which revealed that *H. influenzae* subspecies was found in 90% of the children under 5 years old. Encapsulated strains of *H. influenzae* were found in 25% of the same sample, two-thirds of which were not type b. All capsule types were represented. No meningitis cases occurred in the survey populations. We conclude that the prevalence of *H. influenzae* b in open Gambian communities is similar to that in closed communities elsewhere, but that the kinetics are different from those in closed communities, as persistance of infection in Gambian children is short-lived.

Introduction

The epidemiology and frequency of invasive disease due to *Haemophilus influenzae* type b varies in different parts of the world. The higher the incidence, the younger the age of children affected. It is not clear how carriage of *H. influenzae* b in the throat is related to disease. During outbreaks the carriage rate is usually high (GINSBURG *et al.*, 1977; MELISH *et al.*, 1976; GLODE *et al.*, 1976); in a non-epidemic situation, it is usually less than 5% (TURK & MAY, 1967). However, a low carriage rate may be found in populations with an extremely high incidence of invasive disease (COULEHAN *et al.*, 1984; WARD *et al.*, 1981). Conversely, a high carriage rate can be found in closed institutions without any invasive disease (TURK & MAY, 1967; MURPHY *et al.*, 1985). Day-care centres in the United States appear to create a distinct epidemiological situation in which children who are susceptible to *H. influenzae* b infections are brought close together. In these circumstances, rapid transmission is possible, secondary cases may occur, and high carriage rates have been found (GINSBURG *et al.*, 1977; MELISH *et al.*, 1976).

The incidence of *H. influenzae* meningitis in The Gambia is high and comparable to that in the United States, but the peak is lower–5 months of age (H. A. Bijlmer *et al.*, in preparation). In order to gain more information about the prevalence of *H. influenzae* b in the normal population of The Gambia, in particular in children under 5 years of age, several village surveys were undertaken in different seasons to investigate the carriage rate of *H. influenzae*, in particular type b, in healthy children. In addition, a random sample of children, aged 3–5 years, was examined in 4 different day-care centres or nurseries. The target populations were chosen with the following objectives: (i) to assess *H. influenzae* b carriage rates in several, geographically well separated rural communities; (ii) to analyse age differences in carriage; (iii) to record seasonal differences in carriage; (iv) to assess loss, persistence or acquisition of infection in the same communities; (v) to compare urban with rural communities; and (vi) to assess carriage rate in day-care centres and nurseries. This study was part of a survey on the overall epidemiology of *H. influenzae* meningitis in The Gambia.

Materials and Methods

Geography

The Gambia is a small country in West Africa. It stretches over a distance of 350 km along the Gambia river, but is nowhere more than 40 km wide. The capital, Banjul, and the densely populated surrounding areas are near the coast. Inland there are few large towns and mainly small, rural villages. The Gambia has two distinct seasons. The dry season lasts from November to June, during which virtually no rains fall. In the second half of June the rain starts; it usually stops around the end of October.

Survey populations

(i) Brefet, a rural village 60 km from the coast, is 5 km from the main road and has 246 inhabitants. Surveys were done on 4 occasions over a period of one year: survey I in the early dry season, survey II in the late dry season, survey III just after the rainy season, and survey IV in the same period as survey II but one year later. Initially the entire population was sampled in order to obtain an impression of the prevalence of *H. influenzae* b in a whole community. In the following surveys the target population was restricted

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either to children under 15 years of age or to children under 5 years of age. Refusals never exceeded 5% of the target population.

(ii) Basse area. Five different villages near the town of Basse, 300 km from the coast, with a total population of 283 children under 5 years of age was surveyed. Survey I was undertaken just after the rainy season, survey II in the late dry season. All children under 5 years of age were examined except in one village in which some of the children were missed during the first survey for logistic reasons. The age distribution in the missed group was similar to that of the children who were seen. Additionally, in one of the villages in which the children under 5 years of age had an unusually high carriage rate of *H. influenzae* b, the whole population of 71 inhabitants was examined. Refusals did not exceed 6% of the target population in any village. During the second survey a sample of 99 children distributed equally over 5 age groups between zero and 5 years of age was examined for *H. influenzae* non-type b in the naso-pharynx.

(iii) Brikama/Lamin. Brikama and Lamin are 2 urban areas near the coast. In parallel with a pilot pneumococcal vaccine study, throat swabs were taken from 130 children in defined age-groups: 2, 4, 6 and 9 months and more than 5 years old. The survey was done just after the rainy season.

(iv) Day care centres/nurseries. Throat swabs were taken from 165 children, aged 3–5 years, from 4 different urban day-care centres or nurseries: 2 in Banjul and 2 in Bakau on the coast. This survey was done in the late dry season.

The aim of the study and the procedure were explained to all people who were going to be examined and informed consent was obtained from them or their guardians before examination. The project was approved by the Gambian Government/Medical Research Council Ethical Committee.

Table 1 shows the number of people examined and the timing of the surveys.

Table 1. Number of persons examined and dates of the surveys

Locations	1986 Dry season Feb.	1986 Dry season May	1986 Rainy season	1987 Dry season Nov.	1987 Dry season Dec.	1987 Dry season May	1987 Dry season Jun.
Brefet	217	51	—	—	112	53	—
Basse area	—	—	—	233	—	279	—
Brikama/Lamin	—	—	—	—	130	—	—
Day-care centres and nurseries	—	—	—	—	—	—	165

Sampling method

Throat swabs were taken in the surveys done in Brefet, Birkama/Lamin, and all day-care centres/nurseries. In the Basse area approximately half the specimens were obtained by means of naso-pharyngeal aspirates, which were being collected for virological studies, the other half by throat swabs. As some of the specimens were obtained by means of naso-pharyngeal aspirate, and some by throat swabs, we cultured a small sample of 20 specimens obtained by both methods simultaneously. The same 2 subjects were positive for *H. influenzae* b by both methods. This observation, combined with the expected carrier rate of 10%, indicated that we could not expect to detect a difference in rate of 10% or less between the 2 methods of collection without sampling almost the entire population simultaneously.

Culture

Naso-pharyngeal aspirates and throat swabs were immediately inoculated on antiserum-agar plates, selective for *H. influenzae* b. On return to the laboratory the inoculum was plated out further and incubated overnight in a candle jar at 37°C. After first inspection, plates were kept for 24 h at 4°C to allow optimal visualization of the antiserum-antigen complex, and re-examined the next day. Colonies with a halo of precipitate were subcultured on to chocolate agar and tested for X factor dependency (delta-amino laevulinic acid test) (KILIAN, 1974) and V factor dependency (satellite test). Selective antiserum agars were a combination of the usual antiserum-containing agar (RODRIGUES *et al.*, 1972) and a mixture of antibiotics as used in chocolate agar, selective for *H. influenzae* (CHAPIN & DOERN, 1983). Briefly, the antiserum agars were clear plates of brain heart infusion broth and Noble agar supplemented with levinthal base, plus 0·8 ml anti-*H. influenzae* b antiserum per 10 ml for specificity, and bacitracin, vancomycin and clindamycin for selectivity in a concentration of 3250 iu, 2·5 mg and 0·5 mg/650 ml medium respectively. Control plates with a known *H. influenzae* b strain were included. Anti-*H. influenzae* b antiserum Burro 132 was kindly supplied by Dr J. B. Robbins, and sheep anti-*H. influenzae* b antiserum was raised by repeated immunization with strain 760705 as described previously (SEVERIN, 1972). These antisera gave similar results. To assess the prevalence of *H. influenzae* of all types in the naso-pharynx, naso-pharyngeal aspirates and swabs were cultured on chocolate agar with the same selective antibiotics as the antiserum agar plates. Four

Table 2. Prevalence of *H. influenzae* type b in Brefet village

Age (years)	Survey/Season I Early dry No. examined	I Early dry No. positive	II Late dry No. examined	II Late dry No. positive	III Post-rainy No. examined	III Post-rainy No. positive	IV Late dry No. examined	IV Late dry No. positive
0–4	54	2(4%)	51	0	56	7(13%)	53	0
5–9	36	0	ND[a]		36	3(8%)	ND	
10–14	18	0	ND		20	1(5%)	ND	
>14	109	0	ND		ND		ND	

[a] = not done.

colonies were picked from each plate and tested for X and V factor dependancy. Serotypes were assessed by latex agglutination (SEVERIN, 1972) using antisera types a to f.

Results

Brefet

H. influenzae b was not found in adults in this village, which is representative of rural Gambia (Table 2). The age range for carriage of *H. influenzae* b was from 0–10 years. Carriage was more frequent in younger than in older children, 13% in those aged 0–4 years compared with 5% in those aged 10–14 years old. The proportion of carriage seen in children 0–5 years in survey III (after the rainy season) was significantly higher than the proportion of carriage in surveys II or IV (χ^2, 2 df, $P<0{\cdot}05$). All 11 strains of *H. influenzae* b isolated in survey III were found in 4 out of 13 compounds. Most compounds had more than one house and all 11 strains were found in 7 of 33 houses: 3, 2, 2, 1, 1, 1, 1 strains per house, respectively. The 2 children that had *H. influenzae* b in survey I were negative in survey II, III and IV. No case of meningitis occurred in the village.

Table 3. Prevalence of *H. influenzae* type b in children under five years old in the Basse area

	Survey/Season			
	I		II	
	Post-rainy		Late-dry	
Village	No. examined	No. positive	No. examined	No. positive
Badari	72	2(3%)	70	6(8%)
Kumdam Demba	31	4(13%)	31	1(3%)
Kumdam Foday	30	1(3%)	23	0
Kumdam Mandinka	88	14(16%)	142	17(12%)
Kusa Bure	12	4(33%)	13	3(23%)
Total	122	25(11%)	279	27(10%)

Basse area

Although Brefet village was considered representative of a rural community, further studies were carried out in children under 5 years old in 5 more rural villages, situated 400 km inland in a rural area, to confirm the findings in Brefet. Survey I was carried out just after the rainy season, survey II in the late dry season. The results of these surveys are shown in Table 3. The difference in the number of subjects studied between the first and second surveys in Kundam Mandinka was due to the fact that swabbing started on the second day of continuing respiratory diseases survey in this village. The sex ratio of those examined was 1:1. The overall rate of carriage of *H. influenzae* b in both Basse surveys was the same (10–11%). No seasonal effect was seen, but a significant heterogeneity in carriage rates between villages was present (Fisher's exact test, $P<0{\cdot}05$). Of 18 positive children seen in the first survey, only 3 were positive in the 2nd survey. In contrast, 17 new positive cases were found in the 2nd survey which had been negative in the first. Clustering was not evident due to small numbers. An exceptionally high rate of carriage was found in the small village Kusa Bure (33%). To find out whether carriage was restricted to the few 5-year-old children in this village, an additional survey was made of the whole village one week after the first survey (Table 4). Two of the children under 5 years old who were carrying *H. influenzae* b abundantly in their throat during the first survey appeared to have lost the organism before the second survey, i.e. within one week. One carrier under 5 years old in the second survey was not swabbed the first time. The carriers were evenly distributed over all 4 compounds. Carriage was not restricted to children under 5 years old in this village, but occurred in the age groups below 10 years, with only an occasional adult carrier. The drop in the overall *H. influenzae* b infection rate to 8% in the second survey was due to the lower carriage rate in adults.

Table 4. Prevalence of *H. influenzae* type b in the whole population of Kusa Bure

Age (years)	No. examined	No. positive
0–4	16*	3(19%)
5–9	17	2(12%)
10–14	9	0
>14	29	1(3%)
Total	71	6(8%)

* Including one pair of twins (1 day old) and 2 children not examined previously explain the apparent discrepancy with the numbers shown in Table 3, survey II.

Brikama/Lamin

To answer the question of whether the carriage rate in a rural area was significantly different from that in an urban area, throat swabs were taken from 130 non-related children from Brikama and Lamin, 2 towns near the coast. These healthy children were selected from among children attending a mother and child (MCH) clinic, in order of arrival, divided into 5 different age groups for the purpose of a pilot vaccination trial. The carriage rate in this urban area was similar (10%) to that found in the rural populations in Brefet and Basse in the same season. No obvious difference in age-specific prevalence was seen in this group. The youngest carrier was 2 months old.

Day-care centres/nurseries

Day-care centres and nurseries are pre-school institutions attended by children from 3–8 years old. Many children sit together in small classes, and sometimes the whole school of several hundred children is situated in only one big space. Four different centres were surveyed in late dry season, although the last school was examined after the first rain had fallen. Only 3 out of 165 children, in 3 schools, were positive (2%).

The effect of age

Carriage rates in children aged 0–4 years and in children older than 14 years differed significantly (χ^2, 1d.f., $P<0{\cdot}05$) in the 2 village surveys. The same was true for the 0–9 years group, compared to the group older than 9 years (χ^2, 1d.f., $P<0{\cdot}05$). No significant difference could be shown between the 0–4 years and 5–9 years age groups, or between those 0–4 and 10–14

years old, perhaps due to small numbers. The youngest carrier was 2 months old.

Carriage of H. influenzae *other than type b*

In the second Basse area survey, 99 naso-pharyngeal aspirates were examined for *H. influenzae* of all types: 89 (90%) were positive. Twenty-five strains (28%) were capsulated: 3 type a, 11 type b, 3 type c, 2 type d, 4 type e and 2 type f.

Discussion

TURK & MAY (1967) stated that the carriage of *H. influenzae* b in healthy children was in the range of 2–4%, non-encapsulated *H. influenzae* strains being present in 50–80% of these children. In Alaskan eskimos and Navajo Indians, who have an exceptionally high rate of *H. influenzae* b invasive disease, the carriage rate in healthy children was reported as 5% and 0–9% respectively (COULEHAN *et al.*, 1984; WARD *et al.*, 1981), similar to the rates found in populations with a low incidence of *H. influenzae* b disease. The situation is different in closed communities. In day-care centres small epidemics of *H. influenzae* b disease have occurred with a carriage rate of up to 56% among classmates, which persisted for many months in spite of attempts to eradicate infection (GINSBURG *et al.*, 1977). However, the carriage rate of *H. influenzae* b in children in an orphanage in Thailand did not rise above 17% during an outbreak of meningitis (SIMATHIEN *et al.*, 1980). In contrast, high rates of carriage have been found in closed institutions without the occurrence of meningitis (MURPHY *et al.*, 1985).

Non-encapsulated *H. influenzae* subspecies are common in temperate and non-temperate zones of the world: KUKLINSKA & KILIAN (1984) mapped in great detail the oral bacterial flora in 10 healthy children in Denmark and found unencapsulated *H. influenzae* in 8 of 10 children, usually many different biotypes simultaneously. In Papua New Guinea, GRATTEN *et al.* (1985) found *H. influenzae* in the throat of more than 95% of the children from 3 months of age onwards, usually in conjunction with purulent nasal discharge.

In our surveys 1240 throat samples were processed from 11 different populations over various seasons. The results indicated that the carriage rate of *H. influenzae* b in healthy children under 5 years of age, living in The Gambia, was variable (0–16%), but distinctly higher than that generally reported elsewhere in the world in open communities. The very high rates of 23% and 33% in Kusa Bure were surprising, but the number of children in that village was low.

The seasonal effect that seemed so obvious in Brefet–low carriage rates in the dry season–was not confirmed in Basse area villages. One of the 5 villages followed the same pattern as Brefet, 2 villages maintained a high rate of carriage, one went from low to higher and one was low in both seasons. We conclude that carriage of *H. influenzae* b in The Gambia does not follow a consistent seasonal fluctuation. This is in keeping with the observation that no seasonal peaks have been observed in the incidence of meningitis due to *H. influenzae* b in The Gambia (H. A. Bijlmer *et al.*, in preparation).

No difference in carriage rate was observed between children living in a rural area and children from an urban area, examined in the same season. This is not surprising as the living conditions in terms of crowding are not essentially different between urban areas and rural villages.

Children carried *H. influenzae* b in their throats more often than adults ($P<0{\cdot}05$). Similar observations were made by GRANOFF & DAUM (1980) and MICHAELS & NORDEN (1977) in longitudinal studies with one or more cases of meningitis. The duration of carriage of *H. influenzae* b appeared to be short: more than 90% of the children with a strain were either negative in the previous survey or negative in the next survey. The weekly turnover, calculated on the basis of these small numbers, would be about 20%. So there seems to be a high transmission rate and a short duration of carriage. This is different from observations made in closed communities (GINSBURG *et al.*, 1977; GLODE *et al* 1976; WARD *et al.*, 1978), where carriage of *H. influenzae* b tends to persist for months after an index case of meningitis. Whether carriage of short duration is related to host factors or specific subtypes of *H. influenzae* b is not yet clear. Although the crowded conditions in the day-care centres and nurseries create an ideal environment for rapid transmission, carriage in this group (aged 3–5 years) appeared to be extremely low (2%) in a point-prevalence survey. The low prevalence of carriage parallels the low incidence of meningitis due to *H. influenzae* b in that age-group in The Gambia; the majority of cases occurs before that age (H. A. Bijlmer *et al.*, in preparation). However, the surveys in the 4 schools were made just before end of the last term. The introduction of the microorganism, with subsequent rapid transmission, could have occurred in the first few months of a new school year. We conclude, tentatively, that school-aged children in The Gambia, even the lowest ages, are not an obvious risk group for *H. influenzae* meningitis.

The carriage rate of *H. influenzae* subspecies in the throat (90%) in our study is in accordance with the observations of KUKLINSKA & KILIAN (1984) and GRATTEN *et al.* (1985). Encapsulated strains were present in 28% of a random sample of the Basse area children; 16% were capsulated types other than type b, and all polysaccharide types were present. The prevalence of capsulated non-type b strains in the throat may have been higher than we observed as we did not search for these capsulated types by means of the antiserum plate technique, which we used for type b, a method which is more sensitive. Although encapsulated *H. influenza* non-type b strains appear to be rather common in the healthy community, they rarely cause meningitis in The Gambia (H. A. BIJLMER *et al.*, in preparation). No case of meningitis was recorded in the period following the surveys (3–11 months). So the high carriage rate of *H. influenzae* b did not mean that meningitis due to that organism was imminent. From these data we conclude that the conditions in rural and urban Gambian communities create an environment which facilitates rapid transmission of *H. influenzae* b, predominantly in villages and rural communities and not in day-care centres or nurseries. Although many of these acquisitions are of very short duration, this results in a relatively high carriage rate compared to that in other open communities.

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Announcement

7th Asian Congress of Paediatrics

The Seventh Asian Congress of Paediatrics will be held in Perth, Western Australia, from May 5 to 10, 1991. This Congress will be held jointly with the Annual Scientific Meeting of the Australian College of Paediatrics. There will be joint meetings with other societies including the Royal Australasian College of Physicians, the Australian Association of Paediatric Surgeons and the Asia-Pan Pacific Society for Paediatric Gastroenterology and Nutrition.

Further information can be obtained from:
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Latex agglutination test for diagnosing pneumococcal pneumonia in children in developing countries

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Abstract

Objective—To prepare and assess the sensitivity and specificity of a latex agglutination test specific for the serotype of antigen in diagnosing pneumococcal pneumonia in Gambian children.

Design—Comparison of agglutination test specific for serotype with culture of blood and lung aspirates, countercurrent immunoelectrophoresis, and commercial latex agglutination tests in diagnosing pneumococcal pneumonia. Cross reaction studies and investigation of 102 control children to determine specificity of agglutination test specific for serotype.

Setting—General medical ward of Medical Research Council laboratories, The Gambia.

Patients—101 Gambian children aged between 2 months and 10 years admitted with severe pneumonia.

Interventions—Serum samples were boiled and treated with edetic acid, and urine samples were boiled and concentrated 25 times before testing.

End point—A latex agglutination test specific for the serotype of pneumococcal antigen that is sensitive and highly specific for detecting pneumococcus in the urine of patients with pneumococcal pneumonia.

Measurements and main results—Concentrated urine samples from 16 of the 21 children (76%) with pneumococcal pneumonia established by results of culture of blood or lung aspirates gave a positive result with the agglutination test specific for serotype, whereas only four of the 102 urine samples obtained from control children without pneumonia gave positive results. The serotypes of antigens detected in the urine of children with pneumococcal pneumonia and the serotypes of pneumococci isolated from cultures of blood or lung aspirates were the same in all cases.

Conclusions—When performed on urine samples the agglutination test specific for serotype has a high specificity and is more sensitive than culture of blood or lung aspirates, commercial agglutination tests, or countercurrent immunoelectrophoresis in identifying pneumococcal pneumonia. It is easy to use and should be especially useful in communities with limited laboratory facilities.

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Introduction

Acute respiratory infections are responsible for a high proportion of deaths during childhood in many developing countries and are a common cause of admissions to hospital.[1,2] They cause about four million of the 15 million deaths that occur in children under the age of 5 each year.[3] Hospital based studies have shown that the pneumococcus is the single most important cause of severe respiratory infections in children in developing countries.[2,4] Little work, however, has been done in rural areas because of the difficulty of diagnosing a bacterial cause of pneumonia.

Children with pneumonia rarely produce sputum, and culture of sputum is usually unhelpful for diagnosis because of contamination by potential pathogens resident in the upper respiratory tract. Cultures of blood from patients with pneumococcal pneumonia grow pneumococcus in only 10-30% of cases. Higher rates of isolation are observed in cultures of material obtained by lung aspiration, but this method can occasionally cause haemoptysis or a pneumothorax so should be done only in selected patients.

Capsular polysaccharide antigens have been detected in serum and urine samples from about 40% of patients with pneumococcal pneumonia by countercurrent immunoelectrophoresis.[5-7] Particle agglutination tests, which are more suitable for use in developing countries than countercurrent immunoelectrophoresis, have generally been even less satisfactory. A high percentage of positive results was found by both methods among a group of elderly patients with pneumococcal pneumonia.[8] Studies in children, however, in which latex reagents coated with an antiserum containing antibodies to all known pneumococcal polysaccharide antigens (Omniserum, Statens Seruminstitut, Copenhagen) were used to detect pneumococcus, have given positive results for serum in only about 20% of patients with pneumococcal pneumonia and even poorer results for urine.[9-11] Because of these disappointing results we prepared a series of 10 latex reagents, each coated with antiserum to a single capsular polysaccharide. We investigated the sensitivity and specificity of a test that used these reagents to diagnose pneumococcal pneumonia in Gambian children in whom a bacterial cause had been firmly established by culture of lung aspirates or blood, or both.

Patients and methods

We investigated 101 Gambian children aged 10 and under (range 2 months to 10 years) with pneumonia acquired in the community who had been admitted to a ward at the Medical Research Council laboratories. All of the children had severe or very severe acute respiratory infections according to the World Health Organisation's classification, and nearly all had radiological evidence of consolidation. Controls comprised 70 children aged 10 and under seen during the course of community studies undertaken in two rural areas of The Gambia and 32 children who presented with minor complaints at the outpatient clinic. All controls were examined by a doctor; none had any clinical features of a lower respiratory tract infection.

Blood from all patients was cultured on plates. Lung aspirates were obtained from 42 children with radiological evidence of consolidation.[12] No complications occurred. Urine samples were collected and stored in

sterile containers that contained thiomersal as a preservative. Urine and serum samples were stored for up to 20 months at −20°C before testing. Serum samples were tested for antigen by various methods. Unprocessed samples were tested by countercurrent immunoelectrophoresis. Serum diluted in a buffer and absorbent solution was tested by the Bactigen test (Wampole Laboratories, New Jersey). Serum boiled with edetic acid to destroy rheumatoid factors and to release antigen bound in protein complexes was tested by the Bactigen test and by a latex agglutination test specific for the serotype of the antigen.[13]

Urine samples were centrifuged at 1500 rpm for five minutes, boiled for three minutes, and filtered through a nitrocellulose filter with pores of diameter 0·45 μm (Millipore, Massachusetts) before testing.[14] Unconcentrated urine samples and samples that had been concentrated 25 times in a miniconcentrator (Amicon, Massachusetts) were tested by the Bactigen test, Slidex méningite test (BioMerieux, Lyons), and a latex agglutination test specific for serotype.

Blood was cultured in trypticase soya broth and thioglycollate broth (Oxoid, Basingstoke, United Kingdom). Lung aspirates were stained by Gram's method, cultured on agar containing 5% sheep blood and on enriched chocolate agar, and incubated overnight at 37°C in a candle jar. Lung aspirates were also tested for antigen countercurrent immunoelectrophoresis and latex agglutination. Isolates of *Streptococcus pneumoniae* obtained from cultures of blood or lung aspirates were characterised by standard methods and serotyped by Neufeld's reaction, countercurrent immunoelectrophoresis, and latex agglutination with monospecific antiserum to capsular polysaccharide (Statens Seruminstitut, Copenhagen). Countercurrent immunoelectrophoresis was carried out in 0·7% agarose containing pneumococcal antiserum (Omniserum) in a phosphate buffer containing glycine pH 8·6. All latex agglutination testing was done by two observers who were unaware of the results of other assays.

A latex agglutination test specific for serotype of antigen was developed as follows. Suspensions of latex were coated with monospecific antiserum (Statens Seruminstitut, Copenhagen) to 10 of the serotypes of pneumococci (types 1-6, 8, 14, 18, 19) that most commonly cause invasive pneumococcal disease in The Gambia.[15] Antiserum was diluted to an optimum concentration, which had been established in preliminary studies, in saline buffer containing glycine and added to an equal volume of suspension of latex (particle size 0·81 μm) (Difco, Michigan). The mixture was incubated at 37°C for two hours with shaking every 30 minutes. Two volumes of 0·1% bovine serum albumin in saline buffer containing glycine were then added to the suspension of latex and antiserum and the mixture left overnight at 4°C. The sensitivities of individual latex suspensions to their corresponding solutions of purified pneumococcal polysaccharides (Pneumovax 23, Merck Sharp and Dohme, Pennsylvania) were determined. Each latex reagent detected the appropriate pneumococcal polysaccharide at a concentration of ≥2·5 μg/l. The specificity of each latex reagent was investigated by testing it against a suspension of American collection of type cultures standard strains of *Escherichia coli* (10415), *Staphylococcus aureus* (6571), and *Pseudomonas aeruginosa* (10662) in physiological saline and against suspensions of Gambian isolates of *Klebsiella pneumoniae*, *Salmonella typhi*, other salmonella species, *Streptococcus viridans*, and *Haemophilus influenzae* type b. None of the latex reagents gave agglutination with suspensions of these bacteria.

Results

A bacterial cause for pneumonia was established in 38 of the 101 children in the study: 21 cultures grew *Str pneumoniae*, six grew *H influenzae* type b, one grew *Str pneumoniae* and *H influenzae* type b, four grew *Staph aureus*, and six grew other bacteria. Sixteen diagnoses were based on the results of blood culture alone, 17 on the results of culture of lung aspirates alone, and five on the results of both types of culture. Pneumococcal infection or infection with *H influenzae* was suggested by the results of tests for antigens in 22 patients with cultures that yielded negative results, taking the total number of cases of pneumonia probably caused by bacteria to 60. Pneumococcal pneumonia was diagnosed in 22 patients by growth of *Str pneumoniae* in cultures: 10 in cultures of lung aspirates alone, nine in cultures of blood alone, and three in both types of culture.

The table gives the results of the tests for bacterial antigens in the 101 patients with pneumonia and the controls. The sensitivity of each test was assessed in patients with cultures that yielded positive results. The specificity of each test was assessed in children with pneumonia in whom infection with another bacterium was definitely diagnosed and controls who were healthy at the time the samples were taken.

Tests on serum samples were highly specific, but their sensitivity was too low for them to be useful clinically. When the Bactigen latex agglutination test was used on untreated serum samples positive results were obtained in 10 of 19 patients with pneumococcal pneumonia but also in six of 15 patients with other forms of pneumonia amd 27 of 57 patients with cultures that yielded negative results, which suggests that the test was giving false positive results.

No positive results were obtained when urine from patients with pneumococcal pneumonia was tested by

Results of tests for pneumococcal capsular polysaccharide antigens in serum and urine from children with pneumonia and controls. Values in parentheses are sensitivities and specificities defined in relation to findings in patients with pneumonia from whom another bacterium was isolated† and findings in controls‡*

Test	Patients: Cultures grew *Str pneumoniae* (sensitivity*) (n=22)	Patients: Cultures grew other bacteria (specificity†) (n=16)	Patients: Cultures yielded negative results (n=63)	Controls (specificity‡) (n=102)
		Serum samples§		
Countercurrent immunoelectrophoresis	3/21 (14)	0/15 (100)	2/58	3/30 (90)
Bactigen latex agglutination	2/19 (11)	0/15 (100)	4/57	
Latex agglutination specific for serotype	3/16 (19)	0/14 (100)	3/51	0/30 (100)
		Urine samples‖		
Countercurrent immunoelectrophoresis	9/22 (41)	0/16 (100)	5/57	3/90 (97)
Bactigen latex agglutination	0/21 (0)	2/15 (87)	3/57	6/87 (93)
Slidex méningite latex agglutination	0/21 (0)	0/16 (100)	2/53	2/94 (98)
Latex agglutination specific for serotype	16/21 (76)	2/15 (87)	20/54	4/102 (96)

Differences between total numbers of subjects and specific numbers for each test reflect missing or inadequate samples.
§Boiled and treated with edetic acid before testing.
‖Concentrated 25 times by ultrafiltration before testing.

commercial latex agglutination tests (latex coated with Omniserum), but a latex agglutination test specific for serotype gave a positive result in 16 of 21 patients. Pneumococcal capsular polysaccharide antigen was detected by the type specific latex test in concentrated urine from nine of 12 patients with blood cultures that yielded positive results and from nine of 13 patients with cultures of lung aspirates that yielded positive results, eight of whom did not have bacteraemia. Unconcentrated urine samples were also tested by the latex test specific for serotype. Positive results were obtained in 11 of 22 samples from patients with cultures that grew pnemococcus, in one of 15 samples from patients with other forms of bacterial pneumonia, and in one of 101 samples from controls, giving a sensitivity of 50% and specificities of 93% and 99% respectively.

The serotype of the pneumococcus was determined in 20 of the 22 patients with cultures that grew pneumococcus (in 16 by Neufeld's reaction in bacteria cultured from blood or lung aspirates and in four by latex agglutination of lung aspirates that did not grow bacteria when cultured). Pneumococcal antigen was detected in the urine of 14 of these patients by the latex agglutination test specific for serotype. In each case the antigen detected in urine corresponded with the serotype of the pneumococcus identified in the blood or lung aspirate (six type 1, three type 5, two type 6, two type 14, and one type 19).

Pneumococcal capsular polysaccharide antigen was detected in the urine of 20 patients with cultures that yielded negative results by the agglutination test specific for serotype. Ten patients had other evidence to suggest pneumococcal infection: four had pneumococcus of the same serotype detected by latex agglutination tests on lung aspirates, five had pneumococcal antigen detected either in their urine or serum by countercurrent immunoelectrophoresis, and one had the appropriate capsular polysaccharide antigen detected in his serum by the agglutination test specific for serotype.

Discussion

We found that commercial tests for detecting antigens gave positive results for only a small proportion of patients with pneumonia whose cultured blood or lung aspirates grew pneumococcus. An antigen assay that used latex reagents coated with individual antisera to 10 pneumococcal serotypes was much more successful and gave positive results for urine from 76% of patients (16/22) whose cultures grew pneumococcus. The serotype of the polysaccharide antigen found in urine and the serotype of the pneumococcus obtained from blood or the lung aspirate were the same in all cases.

Our findings suggest that pneumococcal capsular polysaccharide antigen is present in the urine of nearly all patients with pneumococcal pneumonia (we tested against only the 10 most common serotypes so we would expect our test to give positive results in only about 80% of cases) and that latex reagents coated with Omniserum are unable to detect type specific antigens in urine, perhaps because the concentration of specific antiserum coated on each latex particle is too low.

A small number of positive results for pneumococcal polysaccharide capsular antigen were obtained with urine samples from patients with other forms of bacterial pneumonia and from healthy children. Cross reactions between pneumococcal capsular polysaccharide antigens and antigens of other bacteria are well recognised and may be expected to cause occasional diagnostic problems. In this study a positive result for polysaccharide of serotype 2 was obtained in a patient with *H influenzae* type b infection and a positive result for polysaccharide of serotype 19 was obtained in a patient with *Str viridans* infection. These may have been false positive results, but these children may have had mixed infections. The small proportion of positive results of latex agglutination tests on urine of apparently healthy children is worrying. The reactions possibly occurred because of excretion of antigens after a past infection or because of heavy nasopharyngeal colonisation with pneumococci, which is almost universal in Gambian children (NL-E, unpublished work).

For the latex agglutination test specific for serotype of the antigen to be used successfully to diagnose pneumococcal infections the serotypes of the pneumococci responsible for invasive disease being studied must be known. Though the relative importance of different serotypes varies from region to region, there may be large areas – for example, west Africa – where a similar distribution of serotypes is seen.[15] We chose to make 10 reagents for our study, which covered about 80% of the serotypes of pneumococci responsible for invasive disease in The Gambia. In some locations it may be possible to use fewer latex preparations, whereas in others, or when a higher degree of sensitivity is required, more preparations may be required.

Coating suitable latex reagents with type specific antiserum, which is produced commercially, is not difficult and should be within the scope of any moderately well equipped laboratory. Once prepared the latex reagents are stable for long periods. The latex agglutination test is simple to carry out and requires a minimum of equipment and technical skill and is thus suitable for use in laboratories in developing countries. The use of 10 latex reagents, as opposed to the smaller number provided in commercial kits, adds a little to the time needed to do a test. We calculate the cost of the reagents needed to do one agglutination test specific for serotype to be about 10 pence. Filtration through a millipore filter and concentration of urine with a microconcentrator adds substantially to the cost of each test (an additional £2.50), but cheaper effective methods of concentrating urine for the latex agglutination test could probably be devised.

Investigation of the epidemiology of pneumococcal infection has been seriously hindered by the lack of a diagnostic test that can be used in community studies. Our preliminary results with a latex agglutination test specific for serotype performed on urine are encouraging. We found this simple, non-invasive test to be more sensitive than culture of blood or lung aspirates. The test may be of value in diagnosing pneumococcal pneumonia, especially in communities with limited laboratory facilities. It should be a useful tool for evaluating interventions directed against this disease. An evaluation of the effectiveness of such a test in developed countries where pneumonia is still an important cause of childhood deaths[16] and where proof of a pneumococcal cause is invariably difficult would also be interesting.

The test could also have broader clinical applications. It might be used to detect pneumococcal infection in those who are particularly susceptible, such as the elderly and those with sickle cell disease, the nephrotic syndrome, and asplenia, and after an antibiotic has been given, such as in partially treated meningitis.

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Incidence of AIDS and excess of mortality associated with HIV in haemophiliacs in the United Kingdom: report on behalf of the directors of haemophilia centres in the United Kingdom

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Abstract

Objective—To estimate the cumulative incidence of AIDS by time since seroconversion in haemophiliacs positive for HIV and to examine the evidence for excess mortality associated with HIV in those who had not yet been diagnosed as having AIDS.

Design—Analysis of data from ongoing national surveys.

Setting—Haemophilia centres in the United Kingdom.

Patients—A total of 1201 men with haemophilia who had lived in the United Kingdom during 1980-7 and were positive for HIV.

Intervention—None.

End points—Diagnosis of AIDS; death in those not diagnosed as having AIDS.

Measurements and main results—Estimation of cumulative incidence of AIDS and number of excess deaths in seropositive patients not diagnosed with AIDS. Median follow up after seroconversion was 5 years 2 months. Eighty five patients developed AIDS. Cumulative incidence of AIDS five years after seroconversion was 4% among patients aged <25 at first test positive for HIV, 6% among those aged 25-44, and 19% among those aged ≥45. There was little evidence that type or severity of haemophilia or type of factor VIII or IX that had caused HIV infection affected the rate of progression to AIDS. Mortality was increased among those who had not been diagnosed as having AIDS, especially among those with "AIDS related complex." Thirteen deaths were observed among 36 patients diagnosed as having AIDS related complex against 0·65 expected, and 34 deaths in 1080 other patients against 22·77 expected; both calculations were based on mortality rates observed in haemophiliacs in the United Kingdom in the late 1970s.

Conclusions—Rate of progression to AIDS depended strongly on age. There is a substantial burden of fatal disease among patients positive for HIV who have not been formally diagnosed as having AIDS.

Introduction

The proportion of people positive for HIV who proceed to develop serious disease as a result is still uncertain. In this paper information from a recent survey of seroprevalence in haemophiliacs in the United Kingdom was combined with information on the development of AIDS to estimate the cumulative incidence of AIDS by time since seroconversion and its relation with the age of the patient, the type and severity of haemophilia, and the type of factor VIII or IX that gave rise to infection with HIV. In addition, information about mortality was used to assess the evidence for excess mortality among those known to be seropositive for HIV but not diagnosed as having AIDS.

Patients and methods

Information on the numbers of male patients registered with haemophilia A or B who had lived in the United Kingdom in the period 1980-7 and had been tested and found to be seropositive for HIV was obtained from a recent survey of seroprevalence.[1] Information on the dates of the first seropositive test and of the latest seronegative test, if known, were also obtained from this source. Information on patients with AIDS was obtained from an ongoing survey carried out by the United Kingdom haemophilia centre directors' AIDS committee since 1983 and supplemented by information from the Communicable Disease Surveillance Centre at Colindale. Information on the type of factor VIII or IX received by the patients during 1980-7 was obtained from the ongoing national survey carried out in Oxford on behalf of the haemophilia centre directors. Information received by August 1988 has been included in the present report although, to ensure that reporting is as complete as possible, a cut off date of 31 December 1987 has been used in the analyses presented here. Additional information has been sought from the certified causes of death of haemophiliacs positive for HIV who have died. In a few instances in which a diagnosis of AIDS had not been recorded at the haemophilia centres the certified cause suggests that death may have been due to AIDS. It has not been possible to validate this suggestion and so these have not been included as deaths from AIDS in the analysis. They are, however, described in our discussion of the results.

For haemophiliacs positive for HIV the exact date of seroconversion is unknown, and so it has been estimated from the date of the earliest seropositive test and the date of the latest seronegative test, if known. If

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Etiology of acute lower respiratory tract infections in Gambian children: I. Acute lower respiratory tract infections in infants presenting at the hospital

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Ninety infants less than 1 year of age with pneumonia and 43 control infants were investigated for viral and chlamydial infection with the use of culture and serology and for bacterial infection with the use of blood cultures, lung aspirates, antibody assays and antigen detection procedures. One or more potential pathogens were identified in 62 (69%) cases with pneumonia and in 12 (28%) controls. Infection by respiratory viruses was identified in 42 (49%) cases and in 8 (19%) controls. Respiratory syncytial virus was the commonest pathogen identified and was found in 32 cases (37%). Bacterial infections were also common, being found in 27 (30%) cases and 3 (7%) controls, and predominantly involved *Streptococcus pneumoniae* (20%) or *Haemophilus influenzae* (11%). Bacterial infections were associated with raised white blood cell counts and were identified more often by antigen detection procedures (68%) than by culture of blood or lung aspirates (34%) or by serology (33%). Mixed viral-bacterial infections were identified in 13 cases (15%). Infection with *Chlamydia trachomatis* was diagnosed in 2 infants with acute lower respiratory tract infection and in 1 control infant.

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Key words: Acute respiratory infections, pneumonia, infants, *Streptococcus pneumoniae*, *Haemophilus influenzae*, respiratory syncytial virus, *Chlamydia trachomatis*, *Chlamydia pneumoniae*.
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INTRODUCTION

In developing countries acute respiratory infections (ARI) are a leading cause of severe morbidity and death throughout childhood, especially in children less than 1 year of age (infants). It is estimated that about 2.5 million infants die every year from ARI in devel-

oping countries with mortality rates approximately 10 to 30 times greater than in developed countries.[1,2] In a rural area of The Gambia, with an infant mortality rate of 142/1000 live births per year, postmortem questionnaires suggested that ARI was the most frequent cause of death in young children who survived the neonatal period.[3] ARI accounted for 19% of the deaths that occurred after the neonatal period and exceeded deaths attributed to malaria (17%) and acute diarrhea (11%). A high proportion of ARI deaths occurred in children younger than 1 year.

Factors that are thought to contribute to the increased susceptibility to respiratory pathogens of infants in underdeveloped countries include poor nutrition, indoor air pollution, overcrowding, low immunocompetence and high nasopharyngeal carriage rates of potential pathogens. It is unlikely that the socioeconomic disadvantages that underlie these problems will improve greatly in the foreseeable future and strategies to reduce mortality and morbidity due to ARI must, therefore, focus on identifying the agents responsible for these infections and finding ways of treating and preventing them.

Study of the etiology of pneumonia in infants has been made a priority in the World Health Organization's ARI research program, particularly infants less than 3 months of age, because the etiology of infections in this age group may differ from that in older children.[4] However, few etiologic studies in infants have been done. Respiratory viruses, and respiratory syncytial virus in particular, are recognized as a major cause of acute lower respiratory tract infections (ALRI) in the first year of life in industrialized countries. In developing countries evidence from lung aspirate studies suggests that bacteria, particularly *Streptococcus pneumoniae, Haemophilus influenzae* and *Staphylococcus aureus*, are also responsible for many pneumonias in young children.[5] In a previous hospital-based study of pneumonia in Gambian children of all ages bacteria were cultured from lung aspirates from 11 of 15 infants.[6] However, although lung aspirate studies can give a positive etiologic diagnosis in up to 70% of cases they are suitable only for infants with obvious consolidation. Infants with lesser radiologic changes can be severely ill yet cannot be investigated by needle aspiration. The etiology of lower respiratory infections in this group is, therefore, more obscure.

There is evidence that more unusual organisms may play an important etiologic role in pneumonia in infants, either in combination with bacteria and viruses or as primary pathogens themselves. *Chlamydia trachomatis* is now well-recognized as a cause of afebrile pneumonitis in young infants, particularly in the United States. Stagno et al.[7] have suggested that cytomegalovirus (CMV), *Pneumocystis carinii* and *Ureaplasma urealyticum* may also be important causes of pneumonia in infants less than 3 months of age. In a study of 94 children hospitalized with pneumonia in Papua New Guinea, where all but 3 of the children were younger than 24 months, Shann et al.[8] found serologic evidence of infection by *P. carinii, C. trachomatis* and *Mycoplasma pneumoniae*. Thus the spectrum of pathogenic agents associated with pneumonia in infants may be more diverse than in older children, perhaps reflecting infants' susceptibility to organisms normally considered to be of low pathogenicity.

During the past 3 years detailed studies of the etiology of pneumonia have been undertaken in Gambian children presenting to the Medical Research Council (MRC) Hospital, Fajara, using bacteriologic, virologic and serologic techniques. In this paper we report our findings in a group of infants with pneumonia; a subsequent paper[9] describes our findings in an older group of children presenting to the same hospital.

MATERIALS AND METHODS

The Gambia. The Gambia is a small West African republic with a population of approximately 800 000, the majority of whom live in the large periurban area on the coast near the capital Banjul. The country has a subtropical climate with a rainy season from June to October followed by a long dry season. In general the incidence and severity of disease in children are at their greatest during the rainy season. In common with other developing countries in West Africa most of the population of The Gambia endure a very low standard of living with poor sanitation and crowded living conditions, often with several children sleeping in the same bed. The infant mortality rate is about 140/1000 with diarrhea, malaria and ALRI being the major causes of death. Most of the limited health resources are directed toward a primary health care system based on 40 health centers distributed throughout the country and through which a well-developed immunization program operates. Breast-feeding is universal and continues in nearly all children up to the age of 18 months and often beyond to the birth of the next child. The staple diet of older children and adults is rice.

Patients and controls. Infants admitted to the MRC hospital, Fajara during normal working hours between June, 1987, and May, 1988, who had clinical signs and symptoms of ALRI were enrolled into the trial. Any infant with either (1) indrawing or (2) a respiratory rate greater than 50/minute *plus* cyanosis *or* nasal flaring *or* inability to breast-feed was included. Radiologic findings were not used as entry criteria.

From November, 1987, to March, 1988, the MRC ward was partially closed for renovation so that only very seriously ill children could be admitted because of the limited space available. During this period many

infants who fulfilled the study criteria and who normally would have been admitted were included in the trial and treated as outpatients under daily supervision. The study was undertaken 1 year after a mass vaccination campaign against measles and no measles virus activity was noted during the study period.

After informed consent had been obtained from the child's guardian a standard clinical history and examination were carried out. The weight, pulse, temperature, respiratory rate and auscultatory chest signs of each infant were recorded. The presence of cyanosis, dehydration, indrawing (intercostal recession) or nasal flaring was also noted. A control group of infants were studied simultaneously to establish baseline values and to help interpret the findings of the various microbiologic techniques used. Control infants were selected only on the basis of age (within 3 months of the case), the absence of clinical signs and symptoms of ALRI and the geographic proximity of their dwelling place with respect to that of the case. All were examined in a fashion identical to that of cases. Some control infants had mild symptoms of upper respiratory tract infection.

Investigations. On admission a chest roentgenogram was taken from each case, and a urine sample and a nasopharyngeal aspirate were collected. Chest roentgenograms were examined by the project clinician without knowledge of the patient's identity and abnormal radiologic findings were recorded according to a prearranged coding schedule. Only two infants met the criteria for lung aspiration which included informed parental consent and an obvious accessible area of consolidation confirmed by radiologic examination. Marasmic children and those on antibiotics or with wheeze were excluded. Venous blood was collected for culture, hemoglobin estimation, differential white blood cell (WBC) count and C-reactive protein (CRP) concentration and a blood film was prepared and examined for malaria parasites. Serum was taken at the time of the acute infection and approximately 2 weeks later for serologic studies.

Controls were investigated in a manner similar to that for cases except that chest radiographs and blood cultures were not done and convalescent serum samples were not collected.

Virology. Portions of nasopharyngeal aspirate for virus and *C. trachomatis* isolation were inoculated into cryotubes containing virus transport medium and 2-sucrose-phosphate *Chlamydia* transport medium, respectively, and stored at −70°C. Each specimen in virus transport medium was inoculated onto monolayers of secondary rhesus monkey kidney cells, human embryonic lung fibroblasts and HEp2 cells and incubated stationary at 37°C or rolling at 33°C. The monolayers were inspected every 2 to 3 days for a minimum of 14 days for evidence of viral replication and any isolates were identified by neutralization or immunofluorescence. Specimens of nasopharyngeal aspirate stored in 2-sucrose-phosphate transport medium for culture of *C. trachomatis* were centrifuged onto monolayers of McCoy cells. The monolayers were treated with cycloheximide and incubated at 37°C for 48 hours before being stained for the presence of chlamydial inclusions using an immunofluorescent monoclonal antibody culture confirmation preparation (Syva Corp.). Cells in the remainder of the nasopharyngeal aspirate were washed free of mucus, spotted onto microscope slides, dried, fixed in acetone and stored at −20°C before being stained by immunofluorescence using commercially available antisera (Wellcome Laboratories, Kent, United Kingdom).

Acute and convalescent sera were screened for antibody to influenza A and B, parainfluenza 1 and 3, adenovirus, respiratory syncytial virus (RSV) and *M. pneumoniae* by the complement fixation test at a dilution of 1:8. Sera giving 75 to 100% fixation were titrated from 1:8 to 1:256. A 4-fold increase in antibody titer between the acute and convalescent serum or a consistently high titer of 1:128 or above was considered evidence of infection. Antibody to RSV was also measured by enzyme-linked immunoassay (EIA) with the use of partially purified antigen supplied by Dr. Olli Meurman, Department of Virology, University of Turku, Finland.[10] A sonicated extract of a culture of uninfected Vero cells was used as control antigen. Each serum was tested in duplicate at 1:100 and 1:1000 dilution. The titer of each serum was calculated by linear regression. The cutoff optical density (OD) value was taken as the mean OD + 2 SD of 30 negative control sera from children ages 6 to 16 months and assayed in duplicate at 1:100 dilution on 3 separate occasions. A 2-fold rise in titer or greater was accepted as evidence of recent RSV infection.

Antibody to *C. trachomatis* and *C. pneumoniae* strain TWAR was assayed by Dr. Pekka Saikku, Department of Virology, University of Helsinki, Helsinki, Finland, using microimmunofluorescence as described previously.[11]

Bacteriology. Blood specimens were inoculated into tryptone soy broth and thioglycollate broth and incubated at 37°C. All broths were subcultured after 24 and 48 hours of culture and at 7 days onto 5% sheep blood agar and enriched chocolate blood agar and incubated overnight at 37°C in candle jars. Bacterial isolates were identified by standard methods. Specimens of urine and serum were processed as described previously[12] and tested for pneumococcal and *H. influenzae* polysaccharide antigen with commercial latex agglutination tests (Bactigen*; Wampole Laboratories, Cranbury, NJ: Slidex méningite-kit*; Biomérieux, Charbonnieres-les-Bains, France) and by counterimmunoelectrophoresis with omniserum (Statens Serum Institute, Copenhagen, Denmark). Type-specific latex tests for the 10 commonest types of *S.*

pneumoniae isolated in The Gambia were also used to test urine as reported previously.[12]

Antibodies to pneumococcal pneumolysin, to *H. influenzae* and to *Moraxella catarrhalis* were measured using EIAs as described previously.[13-15] A 2-fold increase or more in antibody titer to pneumolysin between acute and convalescent specimens was taken to be evidence of pneumococcal infection. Antibodies to *H. influenzae* and *Moraxella catarrhalis* antigen were also measured by EIA using antigen prepared from noncapsulate strains of bacteria isolated from the middle ear of children with otitis media as reported previously.[13] A 3-fold or greater rise in titer between paired serum specimens was considered to be diagnostic for *H. influenzae* and *Moraxella catarrhalis* infections. The diagnostic criteria for bacterial antibody assays were assessed by testing paired sera from 40 Gambian children with acute malaria; one (2.5%) showed over a 2-fold response to pneumolysin but none showed a response to *H. influenzae* or *Moraxella catarrhalis*.

Other investigations. Differential white blood cell counts were performed by standard methods and C-reactive protein levels were measured in acute phase sera by immunoturbidometry using a Cobas Mira® automatic analyzer (Roche Diagnostica, Basel, Switzerland).

RESULTS

Cases and controls. Ninety infants with ALRI (51 male, 39 female) and 43 control infants (18 male, 25 female) were investigated during the 1-year period from June, 1987, to the end of May, 1988. Thirteen (14%) cases were ages 0 to 2 months, 27 (30%) ages 3 to 5 months, 13 (14%) ages 6 to 8 months and 37 (41%) ages 9 to 11 months. Sixty-two (69%) infants with ALRI were investigated during the 6 dry season months (December to May) compared with 28 investigated during the 6-month period June to November which includes the rainy season and the first month after the rainy season when humidity is still high.

Clinical presentation and course. Clinical findings in cases and controls on presentation are summarized in Table 1. Abnormal auscultatory signs were found in 64% of cases compared with 2% of controls. Radiologic changes consistent with ALRI were found in 73% of cases and 28% had lobar pneumonia. Twelve infants (13%) had very severe pneumonia as defined by World Health Organization criteria (indrawing plus cyanosis or inability to drink). A significantly higher proportion of cases were below the third percentile for weight for age using NCHS standards compared with control infants (chi square, 6.9, $P < 0.01$). Most infants who could take oral fluids reliably were treated orally with trimethoprim-sulfamethaxozole with additional supportive therapy as required. More severely ill infants such as those with cyanosis or inability to drink or who were clinically toxic or less than 3 months of age were given parenteral fluids and antibiotics (generally benzyl penicillin or chloramphenicol).

TABLE 1. Clinical details of 90 infants with ALRI presenting at hospital and 43 controls

	Cases	Controls
Total no. (%)	90	43
Age (months)	7 ± 3*	7 ± 4
Sex (M:F)	51:39	18:25
Weight (kg)	6.2 ± 1.8	7.3 ± 1.8
Weight (% < 3rd percentile)	21 (23)	2 (5)
Temperature (°C)	38.4 ± 1.0	37.3 ± 0.3
Pulse rate	156 ± 23	133 ± 15
Respiratory rate	69 ± 15	40 ± 12
Respiratory rate above 50/minute	84 (93)	5 (11.6)
Indrawing	82 (91)	0
Flaring	49 (54)	0
Cyanosis	2 (2)	0
Inability to drink	11 (12)	0
Bronchial breathing	7 (8)	0
Crepitations	30 (33)	0
Diminished air entry	10 (11)	0
Wheeze	26 (29)	1
Normal breath sounds	32 (36)	42 (98)
Chest radiograph	n = 78	ND
Abnormal	57 (73)	
Consolidation	22 (28)	
Death	6	0

*Mean ± SD.
ND, not done.

Six infants died giving a case fatality rate of 6.6%. *H. influenzae* type b was cultured from the blood of two of these infants. A tentative diagnosis of RSV infection was made in a third infant who developed clinical bronchiolitis and died at the time of an RSV outbreak. However, virologic investigations were not performed on this infant. No etiologic diagnosis was established in the remaining three infants who died, one of whom was not investigated for viral infection.

Etiology. *Bacterial infections.* Blood cultures were done on 81 (90%) infants with pneumonia and serologic tests for bacterial infection were performed on 67 paired serum specimens (74%). Urine and serum was available for testing for bacterial antigens from 80 patients (89%). The commonest bacterial agents identified were *S. pneumoniae* and *H. influenzae* found in 18 (20%) and 10 (11%) cases, respectively (Table 2). In 14 infants with ALRI bacteria were the only pathogens identified. Seventeen infants had a history of recent antibiotic therapy before presentation. A bacterial diagnosis was made in 6 (35%) of these infants, 1 by blood culture and 5 by antigen detection or serology. Of the 73 infants with no such history on presentation a bacterial diagnosis was made in 21 (29%), 9 by culture and 12 by indirect means.

Six of the *S. pneumoniae* cases were identified by culture (five blood culture, one lung aspirate) all of whom had antigenuria detected by latex agglutination or counterimmunoelectrophoresis (CIE) (Table 2). A further nine pneumococcal infections were diagnosed by detection of capsular polysaccharide in urine (two

TABLE 2. Methods by which infection with respiratory pathogens were identified in hospitalized infants with severe ALRI

Pathogen	No. with Evidence of Infection	Culture	Serology	Antigen Detection	Immunofluorescence
Bacteria					
Streptococcus pneumoniae	18	6 (33)*	4 (22)	15 (83)	ND
Haemophilus influenzae	10	3 (30)	4 (40)	4 (40)	ND
Moraxella catarrhalis	2	0	2 (100)	ND	ND
Salmonella spp.	1	1 (100)	ND	ND	ND
Tuberculosis	1	1 (100)	ND	ND	ND
Chlamydiae					
Chlamydia trachomatis	2	2 (100)	2 (100)	ND	ND
Chlamydia pneumoniae	1	0	1 (100)	ND	ND
Viruses					
RSV	32	29 (91)	16 (50)	ND	30 (94)
Influenza	1	1 (100)	0	ND	0
Parainfluenza	3	3 (100)	0	ND	1 (33.3)
Adenovirus	4	3 (75)	2 (50)	ND	1 (25)
Rhinovirus	5	5 (100)	ND	ND	ND
Enterovirus	3	3 (100)	ND	ND	ND
Herpes simplex	1	1 (100)	ND	ND	ND
Cytomegalovirus	37	37 (100)	ND	ND	ND

* Numbers in parentheses, percent.
ND, not done.

TABLE 3. Etiologic diagnoses established in 90 infants with severe ALRI by age and in controls

Pathogen	Cases					Controls (All ages)
	0–2 months	3–5 months	6–8 months	9–11 months	All ages	
	n = 13	*n = 27*	*n = 13*	*n = 37*	*n = 90*	*n = 43*
Any bacterium	2 (15)*	7 (26)	3 (23)	15 (41)	27 (30)	3 (7)
Streptococcus pneumoniae	1 (8)	4 (15)	3 (23)	10 (27)	18 (20)	2 (4.6)
Haemophilus influenzae	1 (8)	5 (19)	0 (0)	4 (15)	10 (11)	1 (2)
Other bacterium	0 (0)	2 (7)	0 (0)	2 (5)	4 (4)	0
	n = 13	*n = 6*	*n = 13*	*n = 34*	*n = 86*†	*n = 42*
Any respiratory virus	8 (62)	12 (46)	5 (38)	17 (50)	42 (49)	8 (19)
RSV	5 (38)	10 (38)	4 (31)	13 (38)	32 (37)	2 (5)
Influenza	0 (0)	(0)	0 (0)	1 (3)	1 (1)	2 (5)
Parainfluenza	2 (15)	0 (0)	0 (0)	1 (3)	3 (3)	0
Adenovirus	0 (0)	1 (4)	0 (0)	3 (9)	4 (5)	3 (7)
Rhinovirus	1 (8)	3 (12)	1 (8)	0 (0)	5 (6)	2 (5)
Other virus	0 (0)	1 (4)	2 (15)	1 (3)	4 (5)	2 (5)
Chlamydia trachomatis	2 (15)	0 (0)	0 (0)	0 (0)	2 (2)	1 (2.4)
Chlamydia pneumoniae	0 (0)	1 (4)	0 (0)	0 (0)	1 (1)	0 (0)
Any potential pathogen found	12 (92)	17 (63)	8 (62)	25 (68)	62 (69)	12 (28)
Cytomegalovirus	0 (0)	14 (54)	7 (54)	16 (47)	37 (43)	14 (33)

* Numbers in parentheses, percent.
† Four patients were not investigated for viral infection.

by CIE on urine, seven by the pneumococcal serotype-specific latex agglutination test). Only four cases had a rising titer to pneumococcal pneumolysin, one of whom also had antigen detected in the urine. The proportion of infants with evidence of pneumococcal infection increased with each quarter of infancy (Table 3) but the differences were not statistically significant.

H. influenzae infection was diagnosed by blood culture in three cases of whom one also had antigen detected in the serum by CIE; four cases were diagnosed by serology alone and four cases solely by detection of *H. influenzae* type b antigen in body fluids (two by CIE on serum and urine, two in urine by commercial latex agglutination kits) (Table 2). Two children had a seroresponse to *Moraxella catarrhalis* both of whom had evidence of infection by other bacteria. Of the two remaining infants in whom a bacterial infection was diagnosed one had *Salmonella typhi* isolated from the blood and one had a massive pericardial effusion from which *Mycobacterium tuberculosis* was subsequently isolated.

Three control infants had evidence suggesting a bacterial infection. Pneumococcal antigen was detected in the urine of 2 infants both of whom had a virus infection (one RSV and one ECHO type 6) and *H. influenzae* type b antigen was found by latex agglutination in the urine of a third infant. None of the remaining 36 urine and serum specimens from control infants tested for bacterial antigens were found to be positive.

Viral infections. Eighty-six (96%) of the 90 cases were investigated for evidence of viral infection. Infection by one or more respiratory viruses was identified in 42 infants with ALRI (48.8%). RSV was the commonest virus identified, accounting for 32 (37%)

cases (Table 2). Other respiratory virus infections included rhinovirus (isolated from 5 cases), adenovirus (4 cases), parainfluenza (3 cases) and influenza virus (1 case). In addition enteroviruses were isolated from 3 cases and herpes simplex from 1 case. Overall a viral infection, other than CMV (see below), was identified in 45 infants with ALRI (52%). In 32 infants with ALRI a virus was the only pathogen found.

The way in which diagnosis of viral infections was established is shown in Table 2. Thirty (94%) of the RSV positive cases were identified by immunofluorescence, the virus was isolated from 29 (91%) cases and 2 infections were diagnosed by serology alone. Serology was, however, insensitive with the CFT and EIA methods each detecting rising antibody titers to RSV in only 12 infants. Agreement between the two methods was found in 8 cases; in 4 cases with positive EIA results no rising titer to RSV was detected by complement fixation. In 4 cases with a rise in complement-fixing antibody titer alone 2 gave a nonspecific EIA reaction.

Infection with RSV was found in approximately the same proportion of infants in each quarter of infancy (Table 3). In 21 infants with ALRI RSV was the only pathogenic agent identified. Infections by respiratory viruses other than RSV were found in 37.5% of infants younger than 3 months and 21.7% of infants ages 3 to 11 months. This difference is not significant.

Forty-two of the 43 control patients were investigated for evidence of viral infection. A respiratory virus infection was identified in 8 controls (19%) comprising adenovirus (3), RSV (2), rhinovirus (1), influenza A (1) and a mixed influenza B/rhinovirus infection (Table 3). An enterovirus was isolated from a further 2 control infants.

CMV was recovered from 37 (43%) infants with ALRI of whom 18 (49%) had, in addition, evidence of infection by other organisms. The virus was also isolated from 14 (33%) control infants. CMV was not recovered from any infant younger than 3 months of age.

The viral infections identified in cases and controls by month, including the outbreak of RSV infection between December, 1987, and February, 1988, are shown in Figure 1.

Chlamydial infections. C. trachomatis was isolated from 2 infants with pneumonia ages 4 and 6 weeks. The same infants were also found to have serologic evidence of infection. None of the remaining 71 paired serum specimens that were tested had evidence of a serologic response to *C. trachomatis* infection. However, *C. trachomatis* was isolated from the nasopharyngeal aspirate of 1 control infant age 4 weeks (2%).

C. pneumoniae infection was diagnosed by rising titer and the presence of specific IgM antibody in one 5-month-old infant with ALRI.

Mixed infections. Overall a respiratory pathogen was found in 62 (69%) of the 90 infants with ALRI who were investigated. Mixed bacterial-viral infections were found in 13 (14.5%) cases (*S. pneumoniae*/RSV (5), *S. pneumoniae/H. influenzae*/RSV (1), *S. pneumoniae*/adenovirus/rhinovirus (1), *S. pneumoniae*/adenovirus (1), *S. pneumoniae/H. influenzae*/adenovirus (1), *S. pneumoniae*/enterovirus (2), *Salmonella* spp./RSV (1) and *H. influenzae/Moraxella catarrhalis*/RSV (1)). In contrast 32 (37%) infants had evidence of a viral infection only, 14 (15.5%) had evidence only of a bacterial infection (though 2 of these cases were not investigated for viral infection) and 3 infants had evidence of chlamydial infection alone. No pathogen was found in the remaining 28 cases studied, 2 of whom were not investigated for viral infection.

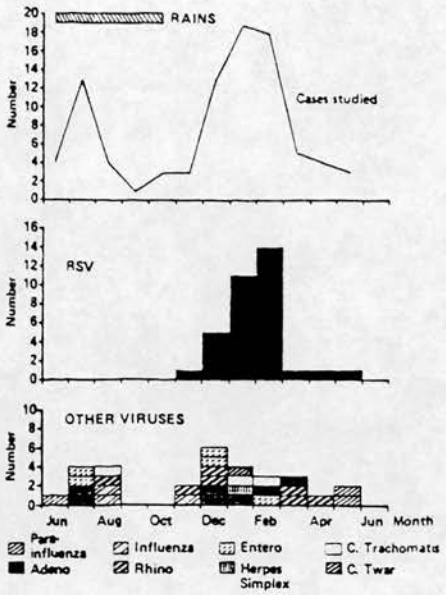

FIG. 1. Seasonal distribution of the infants with acute lower respiratory tract infections investigated together with the viral and chlamydial infections identified.

Clinical features and etiology. A comparison of the clinical findings in cases of viral and bacterial etiology is shown in Table 4. Cases with evidence of pneumococcal or *H. influenzae* infection either alone or combined with viral infection were considered together and compared with cases in whom only a virus or only RSV infection was identified. The remaining group comprised those cases in whom no etiologic diagnosis was made. No significant differences were found in mean temperatures, respiratory rate or pulse rate between cases with viral infection alone compared with cases with pneumococcal or *H. influenzae* infection. However, the mean WBC was significantly higher and the mean hemoglobin concentration was significantly lower in infants with evidence of infection by either of these bacteria than in infants with evidence of viral infection alone (Student *t* test, $P < 0.001$ and $P < 0.05$, respectively). These significance values increased when infants with evidence of infec-

TABLE 4. Comparison of clinical, radiologic and laboratory findings in infants with ALRI caused by different etiologic agents

	Cases with Evidence of Infection by Different Etiologic Agents			
	A virus as only pathogen identified	RSV as only pathogen identified	All Pn- or Hi-positive cases	Cases in which no pathogen identified
Total no.	32	21	25	26
Mean age (months)	6 ± 3[a]	6 ± 3	7 ± 3	7 ± 3
Sex (M:F)	15:17	9:12	14:11	17:9
Weight (kg)	6.1 ± 1.8	6.0 ± 1.8	6.8 ± 1.8	6.2 ± 1.9
Temperature	38.1 ± 0.9	37.9 ± 0.8	38.8 ± 1.0	38.4 ± 1.0
Respiratory rate	69 ± 16	65 ± 15	69 ± 14	70 ± 15
Indrawing	32 (100)[b]	21 (100)	22 (88)	21 (81)
Flaring	15 (47)	7 (33)	18 (72)	13 (50)
Cyanosis	1 (3)	0	1 (4)	0
Bronchial breathing	0	0	3 (12)	2 (18)
Crepitations	10 (31)	6 (29)	11 (44)	8 (31)
Diminished air entry	1 (3)	0	4 (16)	3 (12)
Wheeze	18 (56)	13 (62)	4 (16)	4 (15)
Chest roentgenogram				
Adequate	29	19	21	24
Abnormal	22 (76)	13 (62)	16 (71)	17 (71)
Consolidation	4 (14)	1 (5)	10 (48)	6 (25)
Hemoglobin	11.2 ± 2.3	11.6 ± 2.0	9.7 ± 2.0	10.2 ± 1.8
WBC ($\times 10^3$ cells/mm^3)	12.9 ± 4.5	13.0 ± 5.1	24.1 ± 13.1	18.0 ± 9.0
WBC count >15 × 10^3 cells/mm^3	8/30 (26)	6/31 (28)	15/22 (68)	13/23 (56)
WBC count >20 × 10^3 cells/mm^3	1/30 (3)	1/21 (5)	10/22 (45)	7/23 (30)
CRP (mg/l)	42 ± 55 (n = 16)	26 ± 30 (n = 8)	87 ± 79 (n = 19)	81 ± 86 (n = 17)

[a] Mean ± SD.
[b] Numbers in parentheses, percent.
Pn, pneumococcus; Hi, *Haemophilus influenzae*.

ion by the pneumococcus or *H. influenzae* were compared with infants in whom RSV was the only pathogen identified. The difference in mean temperature between the latter two groups was also significant (Student t test, $P < 0.005$).

Among the clinical signs that were recorded wheeze was found to be more common in infants with viral infections alone than in those with a bacterial infection (chi square, 8.0; $P < 0.01$). Conversely nasal flaring was associated more often with infants who had evidence of pneumococcal or *H. influenzae* infection than cases in whom RSV was the only pathogen identified (chi square, 5.4; $P < 0.05$).

Lobar consolidation and a WBC count greater than or equal to 15 × 10^3/mm^3 were found more frequently in cases with evidence of pneumococcal or *H. influenzae* infection than in cases in whom a virus was the only pathogen identified (chi square, 5.34; $P < 0.05$, and chi square, 7.27; $P < 0.01$, respectively). When cases with a WBC count greater than or equal to 20 × 10^3/mm^3 were analyzed the latter significance value rose to $P < 0.001$ (Fishers exact test). The positive predictive value of a WBC count of 20 × 10^3/mm^3 or above was 52%.

Although mean CRP levels were higher in infants with bacterial infection and in infants in whom no pathogen was identified, compared with those with viral infection alone the differences did not achieve statistical significance (Mann-Whitney U test).

DISCUSSION

In this study of hospitalized infants with moderate to severe ALRI drawn from a periurban area in The Gambia over a 1-year period viral infections were common. Respiratory virus infections were identified in 19% of the healthy controls studied and 47% of infants with ALRI. Similar results were found by Mufson et al.[16] in Chicago; they identified a virus in 291 of 746 (39%) hospitalized infants with ALRI less than 18 months of age and 9 of 54 controls (17%). In industrialized countries respiratory viruses are reported to be the main cause of ALRI among young children.

RSV in particular is considered to be the most important respiratory pathogen in infancy and annual epidemics of RSV infection in the winter and early spring months are well-recognized in temperate climates. The available evidence suggests that RSV is also a major pathogen in tropical climates although the epidemiology of the virus in such areas is less well-defined.[17-21] In The Gambia we observed RSV to be active during the late rainy season (September/October) immediately before the start of this study. However, during the study period an outbreak of RSV occurred in the dry season during the coolest months of the year (December to February). Evidence of infection with RSV was found in more than one-third of the cases investigated but in only 2 (4.6%) of 43 control infants. Thus although asymptomatic virus infections were found in a high proportion of control infants, infection with RSV was almost always associated with disease. This contrasts with, for example, rhinoviruses and adenoviruses which were isolated, albeit in low numbers, from approximately equal proportions of cases and controls. Asymptomatic virus-positive individuals were not, however, followed up to

determine whether they later developed clinically apparent disease.

Because a large proportion of the infants studied presented to the MRC hospital between December, 1987, and February, 1988, during the outbreak of RSV infection it is possible that other viruses such as influenza and parainfluenza are underrepresented. Glezen and Denny[22] have commented that a type of interference phenomenon is often observed among major viral respiratory pathogens so that when one major virus is epidemic others tend to be inactive. In addition, because only infants with severe ALRI presenting to the MRC Laboratories were studied, it is possible that other infants with less severe disease which is associated with infection by other viruses were missed.

CMV has been implicated as a cause of pneumonitis in the neonatal period. Stagno et al.[7] in a prospective study of 104 hospitalized infants between 1 and 3 months of age with pneumonitis isolated CMV from 21 (20%) and from 3 (3%) of 97 control infants hospitalized for reasons other than pneumonia. In the present study CMV was not isolated from any of the 14 infants with ALRI who were less than 3 months of age or from any of the 4 control infants in the same age group. CMV was, however, frequently isolated from older sick infants and controls. Excretion of CMV in the respiratory secretions of a high proportion of young children is well-documented.[23]

As might be expected in a study of infants the majority of viral infections were identified by culture of infectious agents rather than by serologic techniques. Rises in complement-fixing antibody were found only in 14 infants: 12 (37%) of 32 infants infected with RSV and 2 infants with adenovirus infections. The insensitivity of the complement fixation technique in detecting RSV infections, in particular, in this age group is well-recognized.[24, 25] In an attempt to overcome this an EIA test for RSV-specific IgG antibody was developed but this was not found to be appreciably more sensitive than the complement fixation test. Assay for RSV-specific IgM antibody might have allowed additional serologic diagnoses to be made.

In contrast to respiratory viruses bacteria are thought to be an infrequent cause of ALRI in developed countries, although recent studies have suggested that the incidence might be higher than previously suspected.[26] Evidence from studies using lung aspirates in developing countries, however, have indicated that bacterial infection of the lower respiratory tract in young children is common.[5] Although only 2 infants in the present study had suitable clinical signs for lung aspiration to be performed we found evidence of bacterial infection in 27 (30%) cases and 3 (7%) controls using blood culture, antigen detection methods and bacterial serology. Although inevitably there is some uncertainty about the reliability of diagnosing bacterial infections on the basis of antigen detection or serologic tests, culture-proved bacterial infection was found in 12% of cases compared with the 4.4% found by Mufson et al.,[16] and bacteria were the only infectious agents identified in 14 (52%) of the 27 bacteria-positive cases. These observations support the view that bacterial infections are more common among infants in developing countries than industrialized countries and that cases may often be primarily of bacterial origin and not simply secondary bacterial invasion after viral infection. Moreover WBC and CRP levels were raised in many of the infants in whom no etiologic diagnosis was established suggesting that many of these infants had a bacterial rather than a viral infection. This may reflect the relative insensitivity of presently available techniques for the laboratory diagnosis of bacterial respiratory infections in young children compared with the techniques available for the laboratory diagnosis of viral respiratory infections.

In the United States *C. trachomatis* is reported to be the commonest cause of pneumonia in the first 3 months of life.[27] However, little is known about the prevalence of extraconjunctival chlamydial infection in African infants. Though the number of young infants investigated in this study is too small to draw firm conclusions the data would appear to suggest that in The Gambia, as in industrialized countries, *C. trachomatis* infection is confined to the first few months of life. The organism was isolated from 2 (14%) of the 14 infants younger than 3 months of age with ALRI and 1 of the 4 control infants investigated in this age group. All 3 isolates were from infants ages 6 weeks or less. Serologic evidence of recent *C. trachomatis* infection was found only in the 2 cases from whom the organism was isolated.

Culture of *M. pneumoniae* was not attempted. Although some *M. pneumoniae* infections may therefore have been missed such infections are reported to be uncommon in infants.[16, 28, 29] Investigations for other organisms suggested to be potentially important causes of ALRI in infants such as *Ureaplasma urealyticum, Pneumocystis carinii* and *Legionella pneumophila* were not performed.

Few clinical signs or symptoms were found that could reliably differentiate bacterial from viral pneumonia. The presence of wheeze was significantly associated with viral infection while nasal flaring was commoner in bacterial infection. In contrast to some previous studies we found a markedly raised WBC count (20×10^3 cells/mm^3 or above) to suggest bacterial infection.

Nearly one-third of the infants with moderate to severe pneumonia seen in this study had laboratory evidence of bacterial infection, despite a major viral pathogen, RSV, being active during the study period.

Because only minor clinical differences on presentation were found in infants with viral or bacterial infection prompt treatment with antibiotics which cover the bacterial and chlamydial agents implicated in the etiology of ALRI in this age group is appropriate for all Gambian infants with moderate or severe ALRI.

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production of various chemical messengers, including interferon, interleukin-1, and tumour necrosis factor. In this respect, the enterotoxins resemble another toxin produced by *S aureus*—namely, toxic shock syndrome toxin-1 (TSST-1)—and this may explain the recent observations[17] that SEA, SEB, and SEC produced by clinical strains of *S aureus* can induce toxic-shock-like illness. These new observations may well contribute to our understanding of the biochemical nature of the toxins action. For example, it is possible that T-cell activation accompanied by secretion of lymphokines is responsible wholly or partly for some of the pathological effects caused by these toxins in man, including vomiting, diarrhoea, and shock.

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CLINICAL PRACTICE

Antibody persistence in Gambian children after high-dose Edmonston-Zagreb measles vaccine

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Measles antibody concentrations in Gambian children immunised at 4 months of age with a high-dose Edmonston-Zagreb (EZ) measles vaccine or at 9 months with conventional Schwarz vaccine were measured 5 months after vaccination, and at 18 and 36 months of age. Schwarz vaccinees produced, on average, a 2·4-fold higher concentration of measles haemagglutinin inhibiting (HAI) antibody than EZ vaccinees, but at 36 months of age 82 of 93 (88%) EZ vaccinees and 83 of 87 (95%) Schwarz vaccinees had measles plaque-neutralising antibody concentrations above the assumed protective level of 200 mIU/ml ($p > 0·1$). HAI antibody concentrations 5 months after vaccination were inversely related to the presence of maternal antibody at vaccination, but above protective levels; at 18 and 36 months of age there was no relation to antibody concentration at vaccination, and decay of HAI antibody between 18 and 36 months of age was similar for EZ and Schwarz vaccinees.

Lancet 1990; **336**: 1046–48.

Introduction

After successful trials among young infants in West Africa[1-3] and Mexico,[4] the global advisory group of the Extended Programme of Immunisation (EPI) and the World Health Organisation (WHO) recommended vaccination at 6 months of age with high-dose Edmonston-Zagreb (EZ) vaccine in countries where measles is common before the age of 9 months.[5] However, there is concern that the duration of antibody response after early immunisation—especially in infants who have maternal antibody at vaccination—may be less than after vaccination at a later age. We describe the persistence of measles antibody at 36 months after immunisation with high-dose EZ vaccine at 4 months of age.

Subjects and methods

The study area, the children recruited, and the design of the trial have been described previously.[1] Briefly, children were vaccinated

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TABLE I—MEASLES HAI ANTIBODY CONCENTRATIONS AFTER VACCINATION WITH EZ VACCINE AT 4 MONTHS OF AGE OR SCHWARZ MEASLES VACCINE AT 9 MONTHS

Vaccine	Measles HAI antibody concentration (mIU/ml)		
	5 months after vaccination	At age 18 months	At age 36 months
EZ	650 (529–799) *n = 111*	1392 (1054–1840) *n = 105*	1104 (840–1440) *n = 94*
Schwarz	1600 (1260–2031) *n = 105*	3200 (2046–4257) *n = 100*	2728 (1942–3832) *n = 89*

Values shown as geometric mean (95% CI).

TABLE II—PERSISTENCE OF MEASLES HAI ANTIBODY CONCENTRATIONS IN RELATION TO ANTIBODY CONCENTRATIONS AT EZ VACCINATION AT 4 MONTHS

Pre-vaccination	9 months	18 months	36 months
< 100	987 (687–1417) *n = 33*	1387 (848–2268) *n = 34*	1425 (903–2247) *n = 30*
100–400	749 (538–1401) *n = 42*	1541 (905–2623) *n = 37*	1094 (682–1755) *n = 31*
> 400	353 (253–494) *n = 28*	1645 (848–3189) *n = 25*	930 (442–1955) *n = 23*

Values shown as geometric mean (95% CI) mIU/ml

at 18 weeks of age with 40 000 plaque forming units (PFU) of EZ vaccine or at 9 months with 6000 tissue culture infectious units ($TCID_{50}$) of Schwarz vaccine. Capillary blood was taken 5 months after vaccination (aged 9 and 14 months, respectively) and at 18 and 36 months of age.

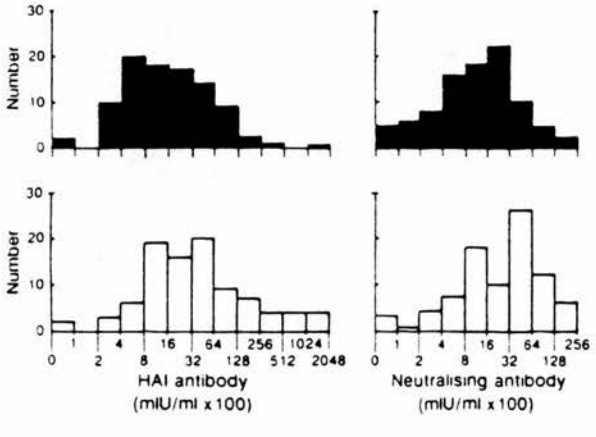
The measles haemagglutination inhibition (HAI) test used in this study has also been described in detail elsewhere.[6] The starting serum dilution was 1 in 2 which detected 100 mIU/ml of HAI antibody. Schwarz virus at a dose of 30 PFU, Vero cells grown in 24-well plates, and 0·75% carboxymethyl cellulose overlay were used in a conventional plaque neutralisation test (Pnt) to measure neutralising antibody, with a starting serum dilution of 1 in 10, which detected 100 mIU/ml of neutralising antibody.

The study was approved by The Gambia Government/Medical Research Council ethics committee.

Results

Measles HAI antibody concentrations at different times after vaccination are shown in table I. Children vaccinated with EZ vaccine had, on average, a 2·4-fold lower mean HAI antibody response than children vaccinated with Schwarz vaccine ($p < 0·01$; t test, at each interval). Analysis of individual changes in antibody titres between 18 and 36 months showed no significant difference between the groups: the mean (SD) $\log_2$ fall in antibody titre was 0·49 (2·40) for 81 EZ vaccinees and 0·33 (2·33) for 85 Schwarz vaccinees. 2 children in each group had no detectable HAI antibody.

The figure shows the distribution of both HAI and Pnt antibodies at 36 months of age. The geometric mean (95% CI) concentration of Pnt antibody was 992 (768–1282) mIU/ml for 93 EZ vaccinees and 2088 (1593–2738) mIU/ml



Distribution of measles haemagglutinin inhibiting (HAI) and plaque neutralising antibody concentrations at 36 months of age after EZ (filled columns) or Schwarz (empty) vaccine.

for 87 Schwarz vaccinees ($p < 0·001$; t test). 5 of the EZ group and 3 of the Schwarz group had no detectable Pnt antibody; 11 and 4, respectively, had a Pnt concentration below 200 mIU/ml ($p > 0·1$; χ^2 test).

HAI antibody concentrations in EZ vaccinees were also analysed in relation to antibody concentrations (< 100, 100–400, > 400 mIU/ml) found at vaccination (table II). (This analysis was not possible for Schwarz vaccinees because few had detectable antibody before vaccination.) At 9 months (5 months after vaccination), there were significant differences between the groups: subjects with the highest prevaccination antibody concentrations (> 400 mIU/ml) had the lowest post-vaccination levels ($p < 0·001$; analysis of variance [ANOVA]). At 18 and 36 months of age there were no significant differences between the groups ($p > 0·10$, ANOVA).

There was no significant difference between the mean (SD) weights of 98 EZ and 97 Schwarz vaccinees at 36 months of age (13·0 [1·4] kg and 12·9 [1·6] kg, respectively). 0 of 119 EZ-vaccinated children were known to have died compared to 4 of 120 Schwarz-vaccinated children ($p = 0·07$; Fisher's exact test, 1-tailed), and 2 and 7, respectively, contracted measles during an outbreak in the first half of the study ($p = 0·08$; Fisher's exact test, 1-tailed).[1] Thereafter no case of measles was seen among vaccinees or among other children who lived in the village.

Discussion

This study again shows that antibody responses to high-dose EZ vaccine given at 4 months of age are lower than those elicited with a conventional dose of Schwarz vaccine given at 9 months.[3,4] In EZ vaccinees, HAI antibody concentrations 5 months after vaccination were inversely related to prevaccination antibody levels, but by 18 months of age a further rise in antibody titre was observed—perhaps as a result of boosted exposure to measles virus—and there was no relation to prevaccination titres. More importantly, antibody decay between 18 and 36 months of age was similar for both vaccines, and was not influenced by prevaccination antibody concentrations in the EZ group. During this part of the study no confirmed case of measles was reported in the study area, so rates of antibody decay are unlikely to have been influenced by exposure to measles in either group.

At 36 months of age, 88% of EZ and 95% of Schwarz vaccinees had Pnt antibody concentrations above the assumed protective level of 200 mIU/ml.[4] Although these results are encouraging, assessment of the long-term clinical efficacy of high-dose EZ vaccine given at 4–6 months of age—especially in the absence of natural boosting of immunity once measles virus has been controlled—awaits the results of long-term trials, which are already under way in West Africa and elsewhere.

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EPIDEMIOLOGY

Evaluation of prevalence of "doping" among Italian athletes

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To evaluate knowledge of, attitudes to, and use of illegal drugs and other forms of "doping" in sport 1015 Italian athletes and 216 coaches, doctors, and managers (technicians) were interviewed after selection on a quota basis. Overall, 30% of athletes, managers, and coaches and 21% of doctors indicated that athletic performance can be enhanced by drugs or other doping practices. Over 10% of athletes indicated a frequent use of amphetamines or anabolic steroids at national or international level, fewer athletes mentioning blood doping (7%) and beta-blockers (2%) or other classes of drugs. These proportions were 2–3 times higher for occasional use than for frequent use. Estimates by managers and coaches were much the same as those of athletes when allowance was made for larger random variation. 62% of athletes who acknowledged doping reported pressure to do so from coaches and managers. According to over 70% of athletes access to illegal substances was not difficult. Both athletes and technicians awarded higher scores to risk than to efficacy for any substance, although 42–67% of athletes and technicians regarded amphetamines and anabolic steroids as efficacious. 82% wanted stricter controls not only during competitions but also during training.

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Introduction

The public's attention has been directed lately to the use of illegal substances or drugs in sport. Most of this attention has arisen because of specific anecdotal episodes and vehement commentaries in the medical press, and in the absence of any data on the prevalence of drug-taking in sport.[1-9]

In 1988 the Italian National Olympic Committee (CONI) and National Research Council (CNR) appointed an independent committee to specifically conduct a survey on the knowledge about and attitudes of Italian athletes to "doping" practices. We report the main results of this survey.

Subjects and methods

The survey was undertaken during the summer of 1989 by the DOXA Institute, the Italian branch of the Gallup International Research Institutes. The population sample was selected on a quota basis—ie, by requiring interviewers to select, on the basis of sex, age, and type of sport, the athletes or technicians (doctors, coaches, managers) to be questioned. Thus, the sampling frame included definition of the number of individuals to be interviewed within each geographical area, sex and age group, and type and level of competition. Individual subjects were not identified. This sample definition was not modified subsequently. The starting point for recruitment of athletes was the training site (eg, gymnasiums, stadiums, sportsgrounds).

Trained interviewers identified and questioned the subjects selected with two similarly structured questionnaires—one for athletes and one for technicians. Subjects were asked about the role in athletic performances of diet, other energy providing substances, and six categories of drugs (amphetamines, anabolic steroids, beta-blockers, diuretics, vasodilators, narcotics); treatments such as blood doping; the prevalence of doping practices; and the availability, desired side-effects, and the reasons for use of drugs and other substances. For example, the interviewer asked "I am now going to show you a list of substances. For each one please tell me whether you know it (ie, whether you have heard mention of it),

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