Child mortality after high-titre measles vaccines: prospective study in Senegal

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The use of Edmonston-Zagreb high-titre (EZ-HT) vaccine at age 6 months has been recommended for countries in which measles before the age of 9 months is a substantial cause of death, but little is known about the long-term effects of high-titre live measles vaccines given early in life. In a randomised vaccine trial in a rural area of Senegal, children were randomly assigned at birth to three vaccine groups: EZ-HT at 5 months (n=336); Schwarz high-titre (SW-HT) at 5 months (n=321); and placebo at 5 months followed by standard low-titre Schwarz vaccine at 10 months (standard: n=358). All children were prospectively followed for 24–39 months in a well-established demographic surveillance system. Child mortality after immunisation was significantly higher in the two groups which received high-titre vaccines than in the group given the standard vaccine. The relative risk of death was 1·80 (95% confidence interval [CI] 1·18–2·74; p=0·007) in the EZ-HT group and 1·51 (0·97–2·34; p=0·07) in the SW-HT group compared with the standard group. The three vaccine groups were comparable as regards various social, family, and health characteristics, and there was no difference in mortality between children who received the standard vaccine and those who were eligible for the trial but did not take part for various reasons. The higher risk of death in the two high-titre vaccine groups remained significant in multivariate analyses. These findings suggest a need to reconsider the use of high-titre measles vaccines early in life in less developed countries.

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Introduction

Measles is a leading cause of child mortality and morbidity in less developed countries.[1,2] It is rare in infants under 4 months old owing to the protection afforded by transplacentally acquired maternal antibodies. In less developed countries the majority of infants become susceptible shortly after the age of 4 months. Measles case-fatality rates are highest at younger ages, especially between 4 and 12 months.[3]

In developed countries low-titre, live, attenuated measles vaccines are safe, immunogenic, and effective when given in the second year of life. In less developed countries, the profile of maternal antibodies differs somewhat,[4,5] and the usually recommended age for vaccination is 9 months.[6] However, this strategy leaves open a window of high risk of death from measles between the ages of 4 and 9 months.

The live Edmonston-Zagreb (EZ) vaccine[7] produces a better immunological response than standard vaccines even when given as early as 4 months of age.[8-10] Two possible explanations for the better performance of this vaccine are the strain and the titre, often 10–100 times higher than that of standard vaccines. Several vaccine trials have compared the immunological responses and adverse reactions after Edmonston-Zagreb vaccines of low, medium, and high titres with those of other measles vaccines of the same titres in children younger than 9 months.[11-16]

The use of Edmonston-Zagreb high-titre vaccine has been recommended "at age 6 months in countries in which measles before the age of 9 months is a significant cause of death".[17] However, little is known about the long-term effects of high-titre live measles vaccines given early in life.

Subjects and methods

The study area was located near Niakhar, in the department of Fatick in central Senegal. It included 30 villages, inhabited by about 25 000 people of Sereer origin. A comprehensive demographic surveillance system based on yearly censuses and weekly visits to households to register vital events was in progress before the study started and has been maintained since.

A randomised vaccine trial of the efficacy, safety, and immunogenicity of two high-titre live measles vaccines, Edmonston-Zagreb (EZ-HT) and Schwarz (SW-HT), was carried out in 1987–89.[18] Although the primary objective of the study was clinical efficacy, a mortality surveillance was set up both to check safety and to evaluate the vaccination strategy. In addition to the routine surveillance system, independent checks on child deaths were made in October, 1990, and February, 1991. More details on the study area and on the data collection system can be found elsewhere.[19-21]

The study was approved by the Ministère de la Santé Publique, Dakar, Senegal; by ORSTOM authorities (Institut Français de Recherche pour le Développement en Coopération, Paris); and by the ethical committee of the British Medical Research Council, Fajarah, The Gambia. Oral informed consent was obtained from the parents of the participants; 20% of parents refused to allow their children to participate. During the 3 years of the project, vaccination was available to everyone, and free drugs and medical services were provided to all children and adults of the study population. As a consequence, overall mortality was substantially lower than during the 3 preceding years (1984–86).

Three measles vaccines were supplied by the manufacturers: EZ-HT (batch 81/3; titre 5·4 $\log_{10}$ plaque-forming units [pfu]; Institute of Immunology, Zagreb, Yugoslavia); SW-HT (batch 0980; titre 5·4 $\log_{10}$ pfu; Institut Mérieux, Lyon, France), and a Schwarz standard vaccine (titre 3·7 $\log_{10}$ pfu, Institut Mérieux). A placebo produced by Institut Mérieux as a standard vaccine preparation without the active particles was also used. The titre of the vaccines monitored throughout the project remained stable.

The study was carried out within the framework of the National Expanded Programme for Immunisation of Senegal. Children were vaccinated at ages 3, 5, and 10 months. At each session they received an injection of diphtheria, pertussis, tetanus vaccine and inactivated poliomyelitis vaccine; in addition they received BCG at 3 months and yellow fever vaccine at 10 months. High-titre measles vaccines were given only at 5 months (mean 22 [SD 2] weeks), and the standard measles vaccine was given at 10 months (after placebo at 5 months). By age 10 months all children who came to the three

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TABLE I—ENROLMENT, DURATION OF FOLLOW-UP, LOSS TO FOLLOW-UP, AND MORTALITY IN STUDY POPULATION

—	Trial participants			Non-participants
	EZ-HT	SW-HT	Standard	
No assigned at birth	526	527	539	(−189)*
No enrolled at 5 mo	336	321	358	388
Person-months of follow-up	9522	9208	10 416	10 551
Mean (SD) duration of follow-up (mo)	28·3 (9·7)	28·6 (9·9)	29·1 (9·2)	27·2 (9·8)
No of non-accidental deaths during follow-up	50	42	32	35
No lost to follow-up	22	15	23	43

*Deaths and outmigrants before 5 mo.

TABLE II—SURVIVAL AFTER 5 mo BY VACCINE GROUP

Months of follow-up after vaccination (age)	Survival (SE) per 1000 survivors at 5 mo			
	Trial participants			Non-participants
	EZ-HT	SW-HT	Standard	
0 (5)	1000·0	1000·0	1000·0	1000·0
6 (11)	969·9 (9·4)	946·8 (12·6)	963·5 (9·9)	976·2 (7·9)
12 (17)	932·8 (13·8)	927·8 (14·5)	943·4 (12·3)	943·6 (12·0)
18 (23)	904·7 (16·3)†	902·0 (16·7)†	937·6 (12·9)	935·2 (12·8)
24 (29)	876·3 (18·3)*	889·0 (17·7)	922·8 (14·3)	912·2 (14·8)
30 (35)	859·8 (19·4)*	870·4 (19·2)†	910·6 (15·3)	901·2 (16·0)
36 (41)	831·8 (22·5)*	858·6 (20·7)†	906·3 (15·9)	901·2 (16·0)

Significance of difference from standard group: *$p<0.05$, †<0.10 (both two-tailed).

sessions were completely vaccinated. Children who missed a session could come later to complete their vaccination series.

At birth, children were randomly assigned by means of a computer random generator to one of three vaccine groups: EZ-HT vaccine at 5 months; SW-HT vaccine at 5 months; or placebo at 5 months and standard measles vaccine at 10 months (standard schedule). Some children born during the study period did not take part in the study because the parents refused, the 5 months vaccination was missed, or vaccination was contraindicated. These non-participants were eligible for regular vaccinations, including measles at 9–10 months, and were included in the surveillance for survival in the same way as the participants.

Criteria for inclusion in the study were: birth to a resident mother between Feb 1, 1987, and May 31, 1988; clinic attendance at 5 months for vaccination and parental agreement to participation; absence of any contraindication to measles vaccination (evolving infectious disease, history of convulsion, previous measles infection, or previous measles vaccination); and no revaccination with another measles vaccine between 5 and 10 months of age.

Investigators and field workers were unaware which type of measles vaccine had been given until the code was broken in June, 1989. Furthermore, the code was not revealed to the field workers who routinely recorded deaths or to the two physicians who reviewed the verbal autopsy questionnaires until the review was completed. Physicians and nurses who were treating patients in the local dispensaries knew nothing about vaccine assignment, because there was no mention of the type of measles vaccine on the health cards or on the dispensary register.

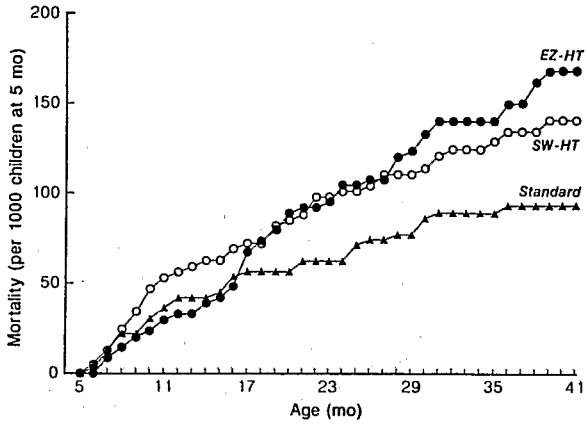

Fig 1—Cumulative mortality from 5 to 41 months, according to vaccine group.

Survival of children was analysed in a monthly life-table (Kaplan-Meier product limit estimates). Multivariate analyses were carried out with linear logistic regressions on age-specific death rates. Proportional hazard models were also tried, but they did not fit the situation well, because of the very strong seasonal pattern of mortality among children. Standard testing procedures were applied, and two-tailed tests were used.

Results

1015 children were included in the vaccine trial: 336 in the EZ-HT group, 321 in the SW-HT group, and 358 in the standard group; 388 children assigned at birth did not take part in the study (table I). By October, 1990, there was an excess of non-accidental deaths in both groups vaccinated with the high-titre vaccines (table I). There was only 1 accidental death—among the non-participants.

In a life-table analysis, children who received the EZ-HT vaccine at 5 months had significantly higher mortality at 41 months than children in the standard group (table II, fig 1): the relative risk of death was 1·80 (95% confidence interval [CI] 1·18–2·74; $p=0.007$). Children who received the SW-HT vaccine at 5 months also had a higher mortality than children in the standard group (relative risk 1·51 [95% CI 0·97–2·34]; $p=0.07$). There was no significant difference

TABLE III—COMPARISON OF VACCINE GROUPS ACCORDING TO CHARACTERISTICS OF FAMILY AND INFANT AT 5 mo

—	Mean (SD)			
	Trial participants			Non-participants
	EZ-HT	SW-HT	Standard	
Age of mother (yr)	27·7 (6·5)	28·1 (7·8)	28·0 (7·3)	28·6 (7·0)
% of literate mothers	3·7 (1·2)	3·8 (1·2)	3·2 (1·0)	3·6 (1·1)
No of residents in compound	23 (14)	23 (18)	23 (18)	23 (19)
Distance to dispensary (km)	3·8 (2·3)	3·9 (2·5)	3·9 (2·6)	4·1 (2·3)
Mortality of older siblings of same mother (per 1000 livebirths)	313 (25)	309 (26)	313 (25)	297 (23)
% outmigrant children	6·5 (1·3)	4·7 (1·2)	8·9 (1·3)	11·1 (1·6)
Death rate in compound of residence (per 1000)	17·6 (20)	17·9 (25)	17·3 (23)	20·0 (25)
Infant at 5 mo				
Age at vaccination (wk)	21·6 (2·1)	21·6 (2·0)	21·5 (1·9)*	
Weight (kg)	6·45 (1·00)	6·46 (1·00)	6·40 (0·90)	
Height (cm)	63·0 (26·0)	63·3 (26·0)	63·2 (24·0)	
Left upper mid-arm circumference (mm)	132 (13)	132 (13)	132 (13)	

*With placebo vaccine; standard Schwarz vaccine given at 10 mo.

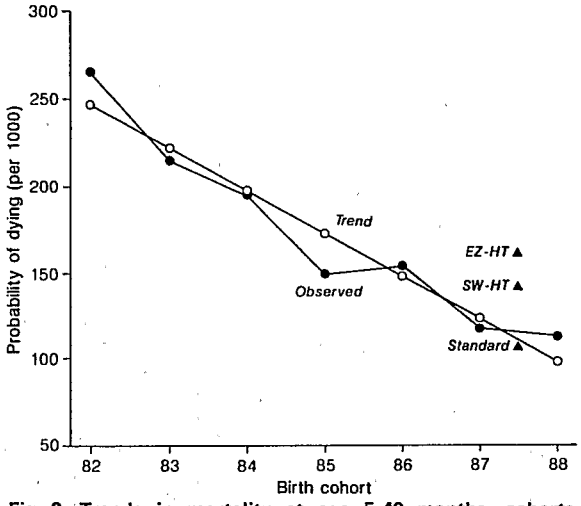

Fig 2—Trends in mortality at age 5–40 months, cohorts 1982–88.

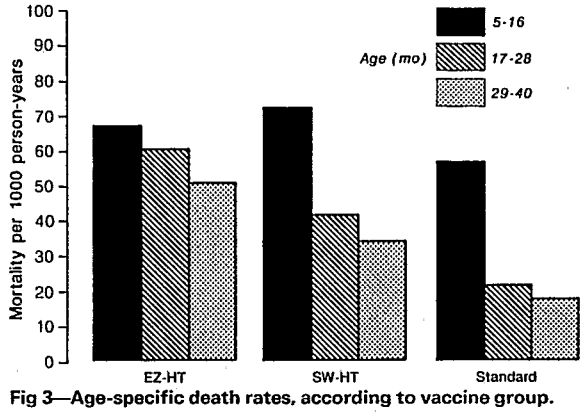

Fig 3—Age-specific death rates, according to vaccine group.

in cumulative mortality at 41 months between the EZ-HT and SW-HT groups (168 *vs* 141 per 1000 between 5 and 41 months) or between the standard group and the non-participant group (93 *vs* 99 per 1000).

Analyses to determine whether the vaccine groups were comparable showed that they were similar for the variables listed in table III and mortality in the randomised groups from birth to 4 months. Children in the non-participant group were also from families with a similar background. Children in the three vaccine groups were similar at 5 months in average age at vaccination, weight, height, and arm circumference (table III).

To exclude the possibility that mortality in the standard vaccine group was abnormally low, the mortality rates in the vaccine groups were compared with the rate predicted from trends in mortality since 1982 (fig 2). Extension of the trends predicts a mortality of 91 per 1000 during the study period compared with the 93 per 1000 found in the standard group.

There was no significant difference within the study group in mortality by sex: the relative risk of death (female/male) was 1·20 in the EZ-HT group ($p=0·497$), 1·14 in the SW-HT group ($p=0·636$), 0·64 in the standard group ($p=0·195$), and 1·16 among the non-participants ($p=0·640$). Baseline data, going back to 1963, in the same population showed no difference in mortality by sex beyond the neonatal period.

The effect of various correlates of mortality was investigated in linear logistic regressions, which allowed a better fit of the mortality pattern with strong seasonal variation and changes with age. Periods of exposure to mortality were divided into 4-month periods corresponding to the three seasons of the year: July to October (rainy), November to February (dry, cool), and March to June (dry, hot). Separate models were tested for each vaccine group. Results of the effects of the vaccines (relative risks) remained stable with control for all other variables that were available: age, sex, age at vaccination, season, season of vaccination, measles antibody titre at 5 months, and seroconversion between 5 and 10 months of age. Odds ratios associated with high-titre vaccines remained stable in the various multivariate analyses. In the final model, the odds ratios were 1·71 ($p=0·019$) for EZ-HT and 1·49 ($p=0·093$) for SW-HT (table IV). The coefficient of the rainy season was always high and significant and was greater in the two HT-vaccinated groups than in the standard group. Sex, titre of antibodies at 5 months, and seroconversion between 5 and 10 months of age were not significant variables in any group.

The same multivariate analyses by vaccine group showed that the coefficient of age in the EZ-HT group was close to zero: this finding shows that mortality remained consistently high in the second and third year after the EZ-HT vaccine, whereas in other groups death rates declined substantially with age as would be expected (fig 3). The lack of decline in mortality rates with age of children is a cause for concern.

The finding of excess mortality in the vaccinated groups was possible for two reasons: the incidence of measles was low during the study period (69 cases among the study children), otherwise there might have been measles deaths between 5 and 10 months in the standard group (who received the placebo at 5 months); and the measles case-fatality rate was also low as a result of intensive medical care provided during the project. The only child who died from measles was away from the study area and was a non-participant in the study.

Only verbal autopsies were available to evaluate causes of death. Few children died in hospital. Most of the deaths were apparently from common diseases of childhood (table V). In the EZ-HT vaccine group 9 deaths were attributed to kwashiorkor and 5 to viral diseases other than measles. 5 of 6 dysentery deaths and 8 of 10 deaths due to acute respiratory infections were in the SW-HT group. The only accidental

TABLE IV—RESULTS OF MULTIVARIATE LOGIT ANALYSIS OF DEATH RATES

Covariate	Estimate (SE)	*t* test	p (two-tailed)
Model 1: all combined			
Vaccine: EZ-HT	0·5382 (0·2295)	2·3449	0·0192*
Vaccine: SW-HT	0·3994 (0·2376)	1·6806	0·0932†
Model 2: by vaccine			
Age (EZ-HT)	−0·0071 (0·0135)	−0·5287	0·5974 (NS)
Age (SW-HT)	−0·0383 (0·0166)	−2·3120	0·0214*
Age (standard)	−0·0405 (0·0190)	−2·1307	0·0338*

Standard = reference.
*$p<0·05$; †$p<0·10$.

TABLE V—DISTRIBUTION OF DEATHS BY REPORTED CAUSE

Probable cause	Trial participants			Non-participants
	EZ-HT	SW-HT	Standard	
Diarrhoea, dysentery	24	21	17	21
Malaria	8	6	7	2
Malnutrition	10	4	5	4
Acute respiratory	0	8	0	2
Measles	0	0	0	1
Other infectious diseases	5	1	1	3
Accident	0	0	0	1
Unknown	3	2	2	2
Total	50	42	32	36

death and the only death attributed to measles were among the non-participants. The frequency of other diseases and unknown causes of death was similar in the four groups.

Discussion

The demographic surveillance system developed in Niakhar is an unusually reliable system of data collection that is unique in tropical Africa. Weekly visits to households ensure accuracy of dates of births and deaths, and yearly updating of maternity histories and full-scale census taking by roll call from computer printouts guarantees the complete recording of vital events.

Differences in mortality among the groups were tested by eight statistical procedures (life-table, death rate, probability of death, age-standardised death rates, linear logistic regression, proportional hazards, log-rank tests, and simulations). They showed a consistent level of significance of mortality differences from the standard vaccine group ($p = 0{\cdot}007$ to $0{\cdot}024$ for the EZ-HT group and $p = 0{\cdot}041$ to $0{\cdot}102$ for the SW-HT group).

The consistency of the data, both in the groups vaccinated with high-titre vaccines and in the groups not given the high-titre vaccines, was striking. The probability of concurrent occurrence of at least 50 deaths in the EZ-HT group and at least 42 deaths in the SW-HT group was very low ($p < 0{\cdot}0001$).

Since the goal of the study was to compare two strategies—vaccination at 5 months with high-titre vaccines versus vaccination at 10 months with a standard vaccine—survival after 10 months was also investigated. The two groups receiving the high-titre vaccines at 5 months had a similar excess mortality between 10 and 41 months over that in the standard vaccine group. Relative risks of deaths were 2·50 (95% CI 1·52–4·13; $p = 0{\cdot}0004$) in the EZ-HT group and 1·73 (1·00–2·98; $p = 0{\cdot}56$) in the SW-HT group.

The fact that children who migrated out of the study area were removed (censored) at the time of their move did not affect the results. An attempt to find those who died after outmigration showed that their inclusion would not have affected the results. There were 11 deaths—3 in the EZ-HT group, 1 in the standard group, and 7 in the non-participant group, which included most of the outmigrants. The difference between the EZ-HT and the standard group would have been even larger (20 deaths) if deaths among migrants had been included.

Later cohorts also were vaccinated with the EZ-HT vaccine at 5 months: those born between June, 1988, and January, 1989, were randomised and those born between March, 1989, and May, 1990, were not randomised. It is too early to judge the mortality of those cohorts, but mortality in the EZ-HT group, although lower than in previous cohort, has not declined with age.

The prevalence of HIV infection was low in the study area: only 2 of 401 project children sampled at age 3 months had HIV antibodies, and neither died. A seroprevalence of 0·5% was found among pregnant mothers of the study area. Thus, HIV infections could not have had a role in this study.

Since the high-titre vaccines produced by two different companies had similar effects, it is unlikely that the excess mortality was due to a production defect such as contamination. Furthermore, both vaccines had high immunogenicity, high efficiency, and only mild side-effects.[18]

It is beyond the scope of this paper to document biological plausibility. However, previous studies suggest that interaction of live measles vaccines with child immunity is possible. Short-term effects of live virus vaccines on child immunity have been observed.[22-26] In a study in the Niakhar area, a low response to yellow fever vaccination was found when it was given in association with the EZ-HT vaccine (personal communication, Dr J-P. Gonzalès). The wild measles virus has severe adverse short-term effects on immunity and nutritional status of children, in particular on nitrogen metabolism[27] and vitamin A.[28] In addition, the wild measles virus can have long-term effects, such as subacute sclerosing panencephalitis.[29]

There was no reason to suspect excess mortality after measles vaccines in the study area: earlier findings there and in a nearby area[30] showed that survival was better among children vaccinated with a standard measles vaccine, even when it was given before 6 months of age. This finding suggests that the high titre may be the main cause of the effect.

Excess mortality became significant for the first time in the spring of 1990, several months after the last child completed the vaccination series. This effect is partly due to the sample size, because the number of deaths was too small before that time for a significant relative risk to show, and partly because most excess deaths were concentrated in the high mortality age group, which lies from 18 to 41 months in this population.

A quick cost-benefit analysis suggests that the strategy of using high-titre vaccines early in life is not worth while: between 48 (SW-HT) and 75 deaths (EZ-HT) per 1000 children reaching age 5 months seemed to be associated with the use of high-titre vaccines. This number exceeds by far the reduction in mortality expected from the early vaccination, estimated to be 4 per 1000 children reaching age 5 months (incidence of 42/1000 between 5 and 10 months multiplied by case-fatality rate of 10%).

If these findings are confirmed in other settings, other strategies to reduce mortality from early measles should be developed. The low titre AIK-C vaccine seemed to produce a good immunogenic response at 6 months among Togolese children.[15] In Niakhar, the standard measles vaccines were safe, even when given at 4–6 months, and may well prevent deaths from measles. Since most complications of measles occur during the second and third weeks after onset, early treatment is possible. A systematic treatment of complications in the Niakhar study reduced the case-fatality rate among children below 3 years of age by 78%.

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Intestinal permeability, mucosal injury, and growth faltering in Gambian infants

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There is controversy over whether children in developing countries can catch up on their growth rates after bouts of diarrhoea. A factor influencing catch-up growth is the extent and duration of mucosal injury. To explore the relation between intestinal disease and growth performance, a non-invasive test of intestinal integrity, the lactulose:mannitol permeability test, was done regularly on children aged 2–15 months, whose growth was monitored over a mean of 7·5 months. The study revealed persistent abnormalities in the small bowel mucosa of 2–15 month old Gambian infants and a negative correlation between these abnormalities and growth. Up to 43% of observed growth faltering can be explained on the basis of these long-term intestinal lesions.

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Introduction

Whether diarrhoeal disease is responsible for the progressive deterioration of nutritional status so regularly observed in infants in developing countries remains a strongly debated issue.[1-4] That episodes of diarrhoea cause short-term faltering in both height and weight development is accepted. What is disputed is whether children are able to catch up with their expected growth trajectory after such episodes.

It is important to the argument that diarrhoea be regarded as a symptom, not a disease. Just as the pathophysiology of diarrhoea varies with precipitating agents, so will the impact of the illness on weight and height growth and the extent of mucosal injury. Episodes associated with a systemic inflammatory reaction can be expected to result in severe growth faltering during the acute phase of the illness, but in the absence of intestinal injury, catch-up growth could be rapid. In contrast, if the diarrhoea is accompanied by damage to the mucosa of the small intestine then full catch-up growth cannot be expected until such injury has been repaired.

Little is known about the time taken for restoration of normal mucosal structure and function following injury mainly because of difficulties in measuring intestinal status. Until recently mucosal damage could be assessed only by endoscopy and/or biopsy of the small intestine, but the introduction of non-invasive techniques for estimating specific aspects of mucosal function and integrity has enabled repeated measurements to be made even under field conditions.[5-7] Here we describe the use of one such method, the dual-sugar intestinal permeability test,[8] to assess small intestinal mucosal status of rural Gambian infants aged 2–15 months at risk of malnutrition. In this test, a low lactulose:mannitol ratio suggests mucosal normality

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