SCREENING FOR CONGENITAL HEART MALFORMATIONS IN CHILD HEALTH CENTRES

BEVOLKINGSONDERZOEK NAAR AANGEBOREN HARTAFWIJKINGEN OP CONSULTATIEBUREAUS

Bert: Nee Ernie, we moeten nog even geduld oefenen.
Ernie: Dat is goed Bert, ga jij maar geduld oefenen, dan ga ik op mijn trompet oefenen.
(Op verzoek van Toon en Bart)

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PART I

INTRODUCTION

CHAPTER 1

Introduction

1. Introduction

1.1. The necessity of screening evaluation studies

The importance of evidence based medicine is frequently emphasised[1]. Politicians, urged by an increasingly critical general public, and the medical profession itself, demand that the effectiveness of medical interventions be thoroughly substantiated. As Archibald Cochrane already explained two decades ago, evidence based medicine is of even greater importance in preventive health care, like mass screening, than in curative medicine[2]. Curative interventions are applied by doctors at the request of patients, who come to them for help themselves. If these doctors act according to the best available medical knowledge, possible failure cannot in all fairness be held against them. Physicians, who do the best they can, are not responsible for the imperfections of medical science. Mass screening, however, is offered, unasked for, to formerly healthy people. These people are invited to submit themselves to medical examinations and potentially to extensive diagnostic and therapeutic procedures for disorders, of which they were hitherto wholly unaware. If such a programme fails to generate provable benefits at least on a population level, it is entirely reasonable to lay this at the door of those offering the programme. Cochrane compares doctors who offer mass screening to the population with propagandists or even evangelists, who have to live up to their promises, including the achievement of better health as a result of participating in their programme.

In addition to the demand for effectiveness, adequate efficiency is also considered to be a compulsive condition for carrying out a screening programme[3]. Generally unfavourable effects of health interventions, accompanying its favourable effects, should be restricted as much as possible. In mass screening, however, this is not straightforward. Dependent on the incidence of the disorder involved and the screening test properties, false positive and false negative test results, resulting in unfavourable side effects, will always arise. False positive test results occur when screening wrongly indicates participants to have a condition that leads to an adverse outcome. When such errors are immediately recognised by the subsequent (mostly clinical) gold standard examination, the unfavourable consequences for participants may be limited to unnecessary effort and anxiety. In several cases, however, conditions will be revealed, in which it is uncertain whether deterioration or spontaneous regression may take place. In such cases, it would be a sensible policy to postpone intervention until it has been established beyond all doubt that the condition will deteriorate if not treated. However, if delaying treatment is considered to increase the risk of an adverse or even fatal outcome unjustifiably, intervention will follow without delay. Hence over-treatment may occur as an unfavourable effect for screening participants.

False negative test results may lead to false reassurance and consequently under-treatment.

These unfavourable effects should be amply counterbalanced by the benefits of the screening.
Another efficiency aspect is that of the costs and potential savings as a result of mass screening. Governments and health insurance organisations, responsible for the optimal use of usually limited health budgets, insist on the most advantageous cost-effectiveness ratio's possible in preventive health care[4].
Many mass screening programmes, however, were introduced before these perceptions became widely accepted. As a result, solid evaluations of the effectiveness and efficiency of these programmes are frequently lacking, all the more because such evaluations become more difficult to perform, the more widely implemented and accepted by the population the programme is. Concrete examples are certainly also to be found among the many screening activities performed within the scope of child health care programmes, in for example the Netherlands. The Dutch programme was started at the beginning of the twentieth century[5]. Right from the beginning, a complete periodical medical examination of preferably all children in the population was part of this programme, with as objective the detection of diseases in an early stage, as to prevent adverse outcomes of these disorders by early intervention. Whether such adverse outcomes are really reduced by these activities, and at what costs in terms of unfavourable effects and financial expenditure, has barely been subject to any evaluation until today[6,7].

1.2. Screening for congenital heart malformations in child health centres

The stethoscope makes the doctor. For many people the use of the stethoscope is emblematic for a well-performed medical examination. Parents visiting child health centres with their babies or toddlers would probably feel cheated, if the physician failed to use the stethoscope. Possibly this is the most important reason that periodical auscultation of healthy young children is one of the most consistently applied mass screening activities in any country with a preventive health system like that in the Netherlands. Virtually the only logical justification for routine auscultation of healthy children, however, is the possibility of detecting formerly unnoticed congenital malformations of heart and great vessels[8]. The main objective of such a detection strategy is obviously the prevention of haemodynamic complications by early therapeutic intervention[9]. Just as for most other routine medical examinations of healthy young children, the question of whether this intended health outcome is truly realised has hitherto insufficiently been evaluated. Nor has any evaluation been made of the efficiency aspects of such screening.
Furthermore it should be underlined that although auscultation is probably applied consistently by most child health centre physicians, this does not necessarily mean that screening for congenital heart malformations is always optimally performed. In addition to auscultation, other routine physical and anamnestic investigations may also help to detect formerly unnoticed circulatory disorders in children. Whether or not

these investigations are properly performed may be decisive for the success of the screening programme. Whether or not the screening programme is attended at the right ages may be an additional decisive factor. Finally, the course and the duration of the referral procedure from the child health centre via the general practitioner and the paediatrician to the paediatric cardiologist may be relevant for the ultimate success of the screening programme. All these factors may be susceptible to improvement

1.3. This thesis

The objective of this thesis is to clarify the effectiveness and the efficiency of screening for congenital heart malformations in Dutch child health centres and the possibilities to optimise this prevention programme. To this end the following main questions will be addressed.

1. Does screening for congenital heart malformations, as actually performed in Dutch child health centres, prevent adverse outcomes of these disorders in the short and long run? What would be the answer to this question, if all children were optimally screened?
2. Will screening for congenital heart malformations as actually performed in Dutch child health centres, considering its test properties and the proportions of false positive and false negative test results, lead to unfavourable effects? What would be the answer to this question, if all children were optimally screened?
3. What costs and savings are involved in the management, including screening in child health centres, of relevant congenital heart malformations?
4. What costs are made per child benefiting from the screening programme as actually performed? What would be these costs, if all children were optimally screened?
5. What measures will have to be taken to optimise the effect of screening for congenital heart malformations in Dutch child health centres?

In Part II the background of the study will be clarified.
In order to place the study in a broader context, the state of the art of evaluating preventive interventions within the scope of Dutch preschool child health care will be clarified in chapter 2.
In chapter 3, the characteristics of congenital heart malformations that determine the potential impact of screening for these disorders in child health care will be explored.
Chapter 4 offers a review of the scarce data found in the international medical literature on evaluation of screening for congenital heart disease in the neonatal period and the first years of life.
Since the results presented in part III are merely based on a patient follow-up study, in chapter 5 the merits and shortcomings of such a study design for evaluating screening programmes like the one under discussion will be clarified.
Part III is dedicated to the main study.

In chapter 6, the potency of the current screening programme to prevent congenital heart malformations from being diagnosed "too late", i.e. after haemodynamic complications have already occurred, is investigated. The same potency is estimated, assuming all children were adequately screened according to established guidelines. Also in this chapter, the test-properties and the proportions of false positive and false negative test results will be estimated for the current programme as well as for an imaginary programme in which all children are adequately screened.
In chapter 7 several factors determining the effectiveness of the screening programme as established in chapter 6, will be identified. The topics addressed will include:

- the impact of the screening attendance by the parents and the performance by the physician,
- the interaction between the adequacy of screening and the severity of the disorder in determining the actual age of the diagnosis,
- the impact of the referral interval between detection and diagnosis.

On the basis of the outcomes of these investigations, recommendations for the optimisation of the screening policy will be formulated.
The conclusions drawn in chapters 6 and 7 are based on the presupposition that haemodynamic complications can be averted in patients diagnosed "in time". In chapter 8 it will be investigated whether this is true for a follow-up period of two years. As an ultimate test for the effectiveness of the screening, the question of whether adequately screened patients are less likely to develop complications than inadequately screened patients during these two years will be investigated as well. Finally in this chapter, the potential impact of the screening programme on the general and functional health will be explored as well as, albeit not decisively, on mortality from congenital heart malformations.
In chapter 9 an economic evaluation will be carried out of the management of congenital heart malformations that can be detected by screening at child health centres and estimations of costs per child benefiting from screening will be estimated.
In Part IV, chapter 10, first the conclusions of Part II will be summarised. Subsequently, answers to the five main questions mentioned above will be formulated based on the results presented in Part III. In conclusion, the extent to which the proposed objective of this thesis, i.e. to clarify the effectiveness and the efficiency of this prevention programme and the possibilities to optimise it, has been fulfilled, will be evaluated.

1.4. Key concepts

All explored variables are defined in detail in the methods sections of the various chapters. For the convenience of the reader, three key concepts, which are important for the thesis as a whole, are here shortly clarified in advance.

The observation by a paediatric cardiologist, whether a patient was diagnosed *"too late"* or *"in time"* to prevent haemodynamic complications, is used as a proximal measure of the effectiveness of the screening programme. It is important to notice that the classification "too late" in itself does not imply any judgement on the question, whether or not a timely diagnosis would have been possible or should have been accomplished. The used terms could easily be interpreted as some kind of moral opinion, which is not the case. Neither does this definition imply any information on the actual age at the time of diagnosis. A congenital heart malformation can be diagnosed "too late" very early in life and "in time" at a rather advanced age.

The conclusion, whether a patient was *"adequately"* or *"inadequately"* screened, based on the information acquired from the parents and the physicians involved, is used as exposure measure. Screening is only classified as adequate if three conditions are fulfilled:

- the parents visited the child health centre following a standard visit schedule,
- the physician performed the complete screening protocol and
- the child was referred as soon as a positive test result was found.

All other cases were classified as "inadequate screened"

As will be clarified in chapter 5, *severity* of the disorder is an important confounder in the effect evaluation of this screening programme. Disorders will be classified in four degrees of severity by paediatric cardiologists. Severity depends on the size and the nature of the malformation involved and is supposed to give an indication on the velocity of the natural course of the disorder and not on the actual clinical situation of the child.

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PART II

BACKGROUND

CHAPTER 2

Towards evidence-based preschool child health care

Abstract.

Objective
In this chapter, a recent inventory of the specific preventive interventions performed within the scope of the Dutch preschool Child Health Care programme is presented, including vaccinations, screening and health education. The methodology for scientific evaluation of these preventive interventions is discussed. Activities of which the effectiveness has already been convincingly demonstrated are indicated and plans for an extensive research programme are presented.

Highlights
Effectiveness and efficiency should preferably be established in Randomised Controlled Trials (RCT). If this is not feasible, researchers should stay as near as possible to the theoretical points of departure of an RCT. In some cases, judgement on the merits of the prevention programme must be based on incomplete data.
In comparing different interventions, unambiguous cost-effectiveness measures such as costs per gained quality adjusted life year (QALY) should be used. This measure however does not include the intergenerational effects that are always present in Child Health Care. Alternative cost-effectiveness measures should therefore be developed for this specific sector.
Definitions of preventive interventions and their intended health outcomes are not always straightforward, notably where the psychosocial and pedagogical aspects are concerned.
From an effect-evaluation point of view, the difference between "screening" and "surveillance" is not very essential.
Definitions of the intended health outcomes of all preventive interventions are presented. Only a small minority of all activities proved ultimately to be sufficiently evaluated.

Conclusion
Preschool Child Health Care in the Netherlands is a very popular preventive programme, which is generally considered as a precious achievement. Its scientific foundation, however, is far from complete. Four key organisations in Dutch Public Child Health Care have jointly set up a development project with the purpose to formulate a comprehensive research agenda for Child Health Care effect-evaluations for the next 10 years.

2. Towards evidence-based preschool child health care

2.1 Introduction

The Netherlands has an extremely popular and ambitious programme for preventive Child Health Care[1,2]. Several authors, however, have emphasised that many of the preventive activities undertaken have long dispensed with any scientific evaluation of their effectiveness and efficiency, an omission, which urgently demands correction[3-5]. In other countries, similar conclusions have been drawn[6,7]. The government, responsible for an optimal use of available budgets, also insists on a prevention programme that is evidenced based. Consequently, the necessity of an extensive research programme for the evaluation of preventive Child Health Care activities is generally recognised by policy makers and the profession.

This chapter will first describe Dutch preschool preventive Child Health Care and present a recent inventory of the specific activities performed within this health system. Next, the methodology for scientific evaluation of these preventive interventions is discussed and clear definitions of their intended health outcomes are formulated. We subsequently indicate activities of which the effectiveness has been already convincingly demonstrated in monographs or survey publications. Finally our plans for an extensive research programme on preventive Child Health Care in the Netherlands are presented.

2.2 The Dutch system

Dutch preventive Child Health Care is divided into preschool Child Health Care, covering the first four years of life and carried out by private organisations for Home Care, and school health care, covering ages from 4 until approximately 19 years and implemented by the municipal health authorities. The focus of this chapter is on the former.

Home Care organisations receive announcements of all registered new-borns within two days after birth. Next, the families are visited at home by a Child Health Care nurse, who invites the parents to participate in the Child Health Care programme. More than 95 % of all parents comply with this invitation. Generally blood for phenylketonuria (PKU) and congenital hypothyroidism (CHT) screening is also sampled during these home visits. Moreover all parents are offered the so-called "Growth Book", an elaborate booklet, including growth charts, extensive health education and formats to register specific health information concerning their child[8]. Subsequently during the first year the programme comprises approximately 10 visits to a Child Health Centre, including generally 5 consultations by the Child Health Care physician and 5 by the Child Health Care nurse. Over the following 3 years parents and children visit the Child Health Care-physician 3 times and the Child Health Care nurse 5 to 6 times. If necessary, extra consultations and home visits will be arranged. In addition many Home Care organisations organise health-education courses for parents of young children[9]. All activities are financed by an obligatory national insurance system.

In this programme parents and children are offered the following preventive activities:

- vaccinations,

- anamnestic and physical examinations for the early detection of health risk factors, including various formal screening programs.
- health education.

A broad definition of "health" is used, covering somatic, psychosocial and pedagogical aspects.

In addition to these preventive activities, which are actively offered by the Child Health Care workers, parents may also specifically ask for help with their child's health problems. In this respect the Child Health Centre plays a part complementary to the general practitioner. If medical treatment is necessary, parents and children will be referred to the general practitioner.

2.3 Inventory of Dutch preschool Child Health Care activities

In February 1998 the Dutch minister of Health installed a working party with the assignment to establish a common core of basic prevention tasks for Child Health Care in the Netherlands. The resulting list is presented in Table 2.1. in a condensed format. All preschool activities aiming at a specific health outcome, with which parents and children are directly confronted in practice, are mentioned. The working party also inventoried the school Child Health Care activities and a variety of other Child Health Care tasks such as providing epidemiological data, organising the required infrastructure, advising about environmental health threats, stimulating collaboration within a social and public health network and policy making. For an enumeration of these tasks we refer to the working party's final report[10].

2.4 Methodology for evaluation of Child Health Care activities

Effectiveness

Prevention is aimed at the reduction of the incidence of adverse health outcomes. The most elementary measure, therefore, of the intended effect of a preventive intervention on a personal level is the Odds Ratio for reaching the adverse health outcome depending on whether or not being exposed to that intervention. An Odds Ratio distinctly smaller than 1, and preferably close to 0 (zero), points to a preventive intervention that may be considered to achieve its intended effect. On a population level the Potential Impact Factor (PIF) may serve as a useful measure. The PIF is the decrease of the incidence of adverse health outcomes as a result of the preventive intervention actually performed, as a proportion of the incidence without preventive intervention[11,12].

Efficiency

In addition to the intended favourable effects, evaluation of preventive interventions should also establish potential unfavourable effects, such as adverse side effects of diagnostic or therapeutic procedures and the unnecessary burdening of healthy people. Vaccinations may evoke complications. In screening programmes, unfavourable effects are for the most part related to false-negative test results (false reassurance and under-treatment) and false-positive test results (unnecessary anxiety and over-treatment). Health education may unintentionally lead to an exaggerated preoccupation with risk avoiding behaviour. Finally, the costs of a preventive intervention and the

possible savings (in terms of treatment costs prevented etc) must be taken into consideration.

Study design

From a methodological point of view, the only study design, which will yield reliable, unbiased data for the evaluation of a preventive intervention, is a Randomised Controlled Trial (RCT). If, however, a prevention programme has already been implemented on a large scale in a population, it is almost impossible to conduct an RCT. Definite faith in the benefits of the programme, although based on merely circumstantial evidence, means that considerable outcry from the public and the professional field will be ensuing, if the programme is withheld from persons, who would normally have had the opportunity to participate. In these cases, researchers will find themselves caught between relaxing the methodological rigour to a certain extent or having no research results at all. In these situations, however, researchers should remain as close as possible to the theoretical points of departure of an RCT.

When an RCT for an already existing prevention program is not feasible, reliance must be placed in observational studies, meticulously considering possible sources of confounding. Several study designs may apply, such as follow-up studies with a (possibly historical) reference group, case-reference studies and, as far as screening is concerned, a combination of separate evaluations of test properties and therapeutic interventions. Inevitably, in some cases the conclusion will be that further effect evaluations are not feasible, and that the merits of the prevention programme will have to be judged on the basis of incomplete data.

Comparable outcome measures

In an aggregate effect evaluation of a preventive programme all intended and unintended effects and costs and savings are inventoried and weighted as advantages and disadvantages. Ideally an unambiguous final measure for cost-effectiveness will be developed, as to enable the comparison of different interventions. A recent and influential book on the standardisation of cost-effectiveness studies recommends expressing all results from economic evaluation studies as costs per gained quality adjusted life year (QALY)[13]. However, the technique of cost-effectiveness was clearly developed for a clinical setting, and it is doubtful whether this can simply be generalised to Child Health Care. In particular, the problem of intergenerational effects remains unsolved[14,15]. This is very clearly demonstrated in a 'worked example' in the book by Gold et al[16]. It is a meticulous assessment of all the costs and effects of supplementing folic acid for the prevention of neural tube defects: it includes, for example, the costs of the extra time parents need to care for a child with such a disorder. However, the prime reason why a woman probably would take folic acid, that parents simply want a healthy child, is not included in the evaluation because this would not affect the quality of life of the child and thus its QALY's[16]. When intergenerational effects are present, as is always the case with Child Health Care, researchers cannot blindly follow present cookbook methods for economic evaluation, but should present results in a way that is relevant for this specific health care sector.

This may lead to other outcome measures than costs per QALY gained. Such measures, however, have yet to be developed.

Practical considerations
Besides these methodological considerations, several more practical conditions must be fulfilled. Effect evaluations of Child Health Care prevention programmes should include many aspects, which often exceed the domain of one organisation or of one sector of the health system. The screening programmes are a good example: the actual screening tests are executed at the Child Health Centres, the referral to the specialists is the responsibility of the general practitioners, while the final diagnosis and the actual intervention in the natural course of the disorder involved will generally be performed by hospital specialists. If opinions on the screening programme strongly diverge among different professionals, an evaluation study will not be successful. An obvious example is the distraction test (Ewing screening) for hearing loss: many general practitioners are not convinced that a positive screening outcome should imperatively lead to referral to an otolaryngologistic or audiologic centre[17].
Some prevention programmes deal with relatively rare disorders. In these cases effect evaluation is only possible if a large population is included, which calls for collaboration between various organisations in several geographical regions. This can lead to a complicated study design and considerable communication problems.

Definition of interventions
For evaluation of a preventive intervention, a clear definition of the activity is indispensable. There are, however, no protocols available for various Child Health Care activities, or different protocols are used in different regions. For example it is broadly agreed that psychosocial and pedagogical problems in families should be identified as early as possible. There are, however, no generally accepted methods available that have proven to be effective. Some efforts to develop reliable methods for this purpose have been reported[18-21]. Considering the problems in this field, such as for instance the large social and cultural differences between the many different ethnic populations in our big cities, these are rather arduous endeavours.
Also, drawing a clear-cut distinction between different forms of preventive activities is not always easy. Again, the efforts in the psychosocial and pedagogical field provide a good example. Health education on these topics is in principle offered equally to all parents. In practice, most efforts will be aimed at parents with specific problems. Hence this may be considered as a mixture of screening and health education.
An invariably recurring controversy in the field of early detection refers to the distinction that is often made between the concepts of "screening" and "surveillance"[2, 22-26]. Screening is generally associated with clearly defined, preferably simple, tests with distinct cut-off-points for referral. The most straightforward example is the PKU/CHT blood sample screening. Surveillance generally refers to a longitudinal process, in which the child is observed several times, as a result of which the observer may conclude that further action is indicated. A good example is the early detection of developmental retardation, in which use is made of the "Van Wiechen-check list" in the Netherlands. Although an extensive protocol for the use of this instrument is

available, the decision to refer depends on so many different data, that a distinct cut-off point cannot be defined. From an effect-evaluation point of view the difference between screening and surveillance is not very essential. In both procedures decisions are made, which on the one hand may lead to a reduction of adverse outcomes and on the other hand to unintended effects. These decisions can be evaluated; the effects can be inventoried, quantified and weighted as advantages and disadvantages of the prevention programme.
In the second column of Table 2.1. we indicated whether a well-defined national protocol is available (+) or not (-) for the relevant activity[27].

Definition of intended health outcomes.
The intended final health targets for various activities in Child Health Care are not clear. Effect evaluation, however, is only possible if these outcomes can be specified in dichotomous or quantifiable entities. Reverse definitions are convenient for this purpose: the reduction of the adverse outcome to be avoided by the preventive intervention. Defining somatic outcomes will generally not be very complicated. Defining targets in psychosocial and pedagogical prevention programmes, however, is less straightforward. Table 2.1. presents what we think are the intended health outcomes of the core list of preventive interventions.

Table 2.1.
Preschool Child Health Care preventive interventions inventoried by the ministerial working party.

I	*II*	*III*	*IV*
<u>Vaccinations</u>			
DPT-IPV-cocktail	+[28]	Diphtheria	+
		Pertussis	+
		Tetanus	+
		Poliomyelitis	+
"Hib-vaccination"	+[28]	Haemophilus Influenza type B	+
MMR-cocktail	+[28]	Mumps	+
		Measles	+
		Rubella	+
Gammaglobuline and vaccination in children born from carrier-mothers	+[28]	Hepatitis B	+

Legends:
I Preventive interventions
II Availability of national protocols (+/-)
III Adverse health outcomes to be reduced
IV Effectiveness convincingly established in monographs or key publications(+/-).

Table 2.1. Continuation

I	*II*	*III*	*IV*
Early detection of:			
Phenylketonuria and Congenital Hypothyroidism.	+[46]	Clinical appearance of these disorders: Mental retardation.	+
Heredity-determined disorders in the child's family and parental consanguinity	-	Avoidable complications of the disorders involved.	-
		Consequences avoidable by timely genetic counselling.	-
Down's Syndrom	-	Unnecessary developmental retardation and emotional harm.	-
Diverging skull size	+[47]	Death, motor handicaps and lost of intelligence because of hydrocephalus	-
Loss of hearing	+[48]	Period before starting adequate training of children with perception deafness.	-
		Episodes of conduction deafness.	-
		Language development retardation	-
Eye conditions and loss of vision	+[49]	Amblyopia at age 7.	-
		Not corrected refraction deviation.	-
		Loss of vision because of structural eye-conditions	-
		Death from retinoblastoma	-
Cleft palate	-	Feeding problems and complications because of aspiration of food.	-
Torti Collis	-	Irreversible asymmetric position anomaly.	-
Congenital heart malformations	-	Hypoxemia and heart failure	-
		Endocarditis correlated with (dental) surgery	-
Asthma	-	Lack of breath.	-

Legends:
I Preventive interventions
II Availability of national protocols (+/-)
III Adverse health outcomes to be reduced
IV Effectiveness convincingly established in monographs or key publications(+/-).

Table 2.1. Continuation

I	*II*	*III*	*IV*
Early detection of:			
Fistulae, Hernia (inguinal and umbical), Hydrocele	-	Infections, constriction and other related complications	-
Position of testicles	+[8,50]	Infertility, Testicular cancer Disturbance of psycho-sexual development Unnecessary surgery	- - - +
Congenital foot anomalies	-	Irreversible position anomalies Limping	- -
Congenital hip anomalies	+[51]	Limping Surgery for hip dislocation Juvenile Coxarthrosis.	- - -
Cow-milk allergy	+[52]	Episodes of symptoms Over-treatment	
Growth abnormalities	+[47]	Avoidable adverse biometric outcomes	-
Psychomotor developmental retardation using the "Van Wiechen schedule".	+[53]	Period before starting adequate developmental training. Insufficient utilisation of healthy rest-functions	- -
Language developmental retardation	-	Language development retardation.	-
Psycho-social and pedagogical problems	-	Behavioural disorders Disturbed child-parent relationship. Developmental retardation Child abuse	- - - -
Child abuse	-	Irreversible consequences of child abuse	-

Legends:

I Preventive interventions

II Availability of national protocols (+/-)

III Adverse health outcomes to be reduced

IV Effectiveness convincingly established in monographs or key publications(+/-).

Table 2.1. Continuation

<u>Health education on:</u>			
Nutrition	-	Premature abandoning breastfeeding	-
		Malnutrition	-
		Over-nutrition	-
		Vitamin deficiencies	
		• Vitamin K: subarachnoidal haemorrhage	+
		• Vitamin D: Rachitis	+
		Eating problems	-
Physical care	-	Skin disorders	-
		Infections	-
Sleeping position	+[27]	Sudden Infant Death Syndrome	+
Dental care	+[27]	Caries	+
Accident prevention	+[54]	Injuries, permanent handicaps and death.	-
Pedagogy: strengthening parental competence, clarifying developmental phases and maturation, stimulating playing, games and mingling with peers.	-	Behavioural disorders	-
		Disturbed child-parent relationship.	-
		Developmental retardation	-
		Child abuse.	-

Legends:
I Preventive interventions
II Availability of national protocols (+/-)
III Adverse health outcomes to be reduced
IV Effectiveness convincingly established in monographs or key publications(+/-).

2.5 Activities already convincingly evaluated.

Preventive interventions for which the effectiveness and efficiency have already convincingly been established, may be excluded from further evaluation studies. First and foremost the effectiveness should be established. Information on the efficiency of preventive interventions is of relatively limited relevance if there is no evidence that they are indeed able to decrease adverse health outcomes. To avoid unnecessary efforts in coming evaluation studies on preschool Child Health Care, we verified on which activities mentioned in the table convincing data on favourable effects are available in monographs and review publications. In the fourth column of the table such activities were marked by (+) and all others by (-). We also verified the extent to which the efficiency aspects (unfavourable effects and costs) of these interventions had been assessed.

Only a small minority of all activities turned out to have been sufficiently evaluated. Decreases of adverse health outcomes after introduction of the preventive interventions are convincingly reported for vaccinations[28, 29], prevention of unnecessary surgery due to pseudo-cryptorchism[30, 31], prevention of Sudden Infant Death by health education on sleeping position[32] and caries prevention by health education on fluoride

application[33, 34]. Unfavourable effects and costs, although not thoroughly evaluated in all cases, seem to remain within reasonable limits. In the case of vaccination recurrences of adverse health outcomes after interruption of the preventive programme are reported[35, 36]. As far as the two screening programmes for PKU and CHT are concerned, solid evaluations of the test properties and the effectiveness of the therapeutic interventions as well as reports on an impressive decrease of the incidence of adverse outcomes after the introduction are available. All authors are convinced that this positive yield exceeds by far the negative impact of false-positive and false-negative test-results and that the costs are low compared to the financial burden of treatment and care of children with mental retardation as a result of these disorders[37-40]. The biological background of vitamin D and K deficiencies as decisive etiological factors for rickets and intra-cranial haemorrhages are undisputed[41, 42]. In a vitamin D health education programme in Glasgow aimed at a high-risk population the decrease of rickets was considerable[43, 44]. The beneficial effects of both parenteral and oral administration of Vitamine K in the prevention of intra-cranial haemorrhages were established in a study with a case referent design[45]. Efficiency evaluations on these health education programmes, however, are lacking.

2.6 Present research plans.

Four key organisations in Dutch Public Child Health Care, i.e. National Society of Municipal Health Departments, National Centre of Preschool Child Health Care, TNO-Health and Prevention and Department of Public Health of Erasmus University Rotterdam have jointly set up a development project. The purpose of this project is to formulate a comprehensive research agenda for Child Health Care effect-evaluations for the next 10 years. Criteria for establishing priorities in this agenda are

- the nature, severity and extent of health problems involved,
- the knowledge of favourable and unfavourable effects of the preventive activity involved,
- the costs and attainable savings of the preventive activity involved and
- public support for the preventive activity involved.

First, an extensive expert consultation and literature investigation, covering monographs and review publications as well as the original studies, will be carried out. If possible, formal meta-analyses will be performed. Of every activity inventoried by the ministerial working party, a short epidemiological review of the disorders involved will be drawn up and the following questions will be investigated:

- What is presently known about this activity's favourable and unfavourable effects?
- Which needs and opinions about this activity exist among the public, Child Health Care workers and authorities?
- Given the present knowledge and conditions, will scientific research contribute to better evidence about the intervention's effectiveness and efficiency?
- What are the estimated costs and attainable savings involved?

2.7 Discussion.

Although the importance of effect evaluation in Child Health Care cannot be emphasised enough, it is also sensible to underline its possible limitations. Obviously,

deciding about the activities of which the effectiveness can either be clearly established or rejected is relatively simple. However, for several well-established preventive activities, it will be very difficult to reach an unambiguous conclusion, since applying the necessary methodology is not feasible[5]. This will possibly also be the case for in particular the social and supportive parts of the Child Health Care programme, which defy an exact description of the activity and the intended health outcomes.

It would be wrong to equate such activities mindlessly with those of which the effectiveness can scientifically be rejected. Moreover, even here "soft" evaluation may be feasible and quality improving. The primary aim of the proposed research programme, however, is to define an effective and efficient core programme to act as a "carrier" for other important aspects, which are more difficult to assess.

Because of limited funds, establishing priorities in the public health programme might be necessary. However, since unambiguous final measures for cost-effectiveness in Child Health Care are lacking, comparison with other health facilities is no straightforward task, the more so since such evidence is lacking in many other areas of health care as well. The development of such measures is an important scientific challenge.

Preschool Child Health Care in the Netherlands is a very popular preventive programme, which is generally considered as a precious achievement. The scientific foundation of this preventive programme, however, is far from complete. In the following years we hope to provide frequent reports on the progress made in underpinning child health care activities.

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CHAPTER 3

Characteristics of congenital heart malformations

Abstract

Objective
This chapter describes the characteristics of congenital heart malformations that determine the potential impact of screening for these disorders in child health care.

Highlights
Secondary prevention programmes like screening cannot prevent congenital heart malformations themselves. That would require primary prevention strategies, aimed at etiologic factors. Since most of these factors are not well understood, such strategies are generally not yet feasible. Nevertheless, given the clinical qualities of congenital heart malformations, screening in child health care may potentially pay a substantial contribution to the optimal management of these disorders. Timely detection and subsequent intervention might prevent deterioration of these patients' condition and even death. The screening programme at the Dutch child health centres, however, has an important limitation that a neonatal screening is lacking. As the first screening is scheduled at 1 month of age, this programme will fail to cover those severe, fast-deteriorating conditions, which become symptomatic before that age. Whether screening might have favourable consequences in the long run for a substantial number of patients is not easy to answer. Current therapeutic interventions are so effective, that the final outcome in a majority of the patients, even in those in whom hemodynamic complications did occur, may be quite favourable.

Conclusion
The main purpose of child health care screening for congenital heart malformations is to prevent or to shorten episodes of heart failure and hypoxemia.

3. Characteristics of congenital heart malformations

3.1. Introduction

In this chapter, we will describe the characteristics of congenital heart malformations that determine the potential impact of screening for these disorders in child health care. The foetal pathogenesis of these disorders, their natural course after birth and the prevalence of cardiac malformations at birth will be presented. Subsequently we will indicate how modern diagnostic and therapeutic procedures have changed the prognosis of congenital heart disease during the last decades. Finally we will discuss how all this may influence the potential outcome of a child health care screening programme.

3.2. Pathogenesis during foetal life

Congenital heart malformation comprises a long list of different disorders, which occur as a singular condition or in combinations[1]. The prevalence distribution of various types of cardiac malformations is reported with remarkable similarity as Hoffman concluded from an extensive review[2]. These data are summarised in table 3.1, second column.

Table 3.1.

Prevalence distribution in most frequent congenital heart malformations and hospital mortality provided the application of current surgical and catheter interventions.

Types	*Prevalence distribution*	*Hospital mortality*
Ventricular Septal Defect (VSD)	28 %	2-5 %
Atrial Septal Defect (ASD)	10 %	0-1 %
Pulmonary Stenosis (PS)	10 %	0-1 %
Patent Ductus Arteriosus (PDA)	10 %	0-1 %
Fallot's Tetralogy (4F)	10 %	1-5 %
Aortic Stenosis (AS)	7 %	0-5 %
Coarctation of the Aorta (CoA)	5 %	0-10 %
Transposition of the Great Arteries (TGA)	5 %	2-3 %
Miscellaneous disorders, including combinations, pulmonary or aortic valve atresia and univentricular hearts	15 %	5-70 %

Congenital heart malformations originate from abnormal organogeneses during the embryological period, of which the etiology is generally not well understood. Buskens provides a solid review on the possible etiology of congenital heart disease[3]. Although adverse influences of genetic factors, toxic factors and intra-uterine infections are established, most cases are attributed to miscellaneous, in fact unknown, causes (see table 3.2).

Table 3.2.
Factors to which the etiology of congenital heart malformations is attributed

Factors	*Percentage*
Genetic factors (chromosomal, micro-deletions)	approx. 6-10 %
Toxic factors (vitamin A derivatives, drugs for epilepsy, alcohol)	approx. 1 %
Intra-uterine infections (Rubella, CMV, Toxoplasmosis.	approx. 1 %
Miscellaneous factors (interaction genetic an environmental factors)	approx. 90 %

Besides divergent organogenesis, development of parts of the cardiovascular system may also be merely delayed[4]. Therefore many anomalies, such as a ventricular septal defect or a persisting patent ductus arteriosus may still spontaneously resolve in the course of time.
The incidence of divergent and delayed organogeneses of the cardiovascular system is probably rather high, as may be concluded from high prevalence figures in autopsy series on spontaneous abortions and stillbirths (> 10 %)[5, 6]. Probably many pregnancies in which the development of the cardiovascular system is abnormal will result in premature termination without producing a viable child. Obviously the most severe cases will have the least chance to survive. There are, however, some important exceptions. In foetal life, gas-exchange takes place via the placenta and shunts are present between the pulmonary and systemic circulation. With these features even very severe abnormalities such as pulmonary or aortic valve atresia do not result in circulatory problems in utero. When at birth the functional circulatory and ventilatory adaptations occur, these malformations will, however, result either in severe hypoxemia or low systemic output yet within a few days. Another example is the transposition of the great arteries, which also may be of little consequence during pregnancy. After birth, however, these patients may only survive if substantial shunts exist, such as an atrial septum defect or a patent ductus arteriosus, which enables mixing between both parallel-situated circulations.
It can be concluded that as a result of all divergent and delayed organogeneses of the cardiovascular system during foetal life, eventually at birth a varied assembly is presented of very ill, barely surviving infants, living "time-bombs" with few symptoms, who may, however, suddenly deteriorate, patients with less severe slowly deteriorating disorders and children with moderate or even trivial disorders.

3.3. Natural course after birth

Congenital heart malformations may cause more or less severe deviations from the normal blood circulation. Clinically such deviations may in principle lead to three sorts of haemodynamic complications[1]:

1. Heart failure resulting from increased volume-load (left-right shunts) or pressure-load (constrictions or secondary pulmonary hypertension)
2. Hypoxemia because of insufficient oxygen-carbon dioxide exchange in the lungs, resulting from insufficient inflow of blood (circulation anomalies or constrictions), or inadequate mixing or secondary lung pathology.
3. A combination of both.

Whether and when the natural course of a congenital heart malformation may lead to these complications, depends mainly on the nature and the size the defect. Large and complicated disorders will often deteriorate virtually immediately after birth. But even these disorders may go unrecognised for a considerable period of time. To illustrate this a few examples will be given:

A child with a transposition of the great arteries may not only, as indicated above, survive after birth, but may also be apparently asymptotic, as long as substantial shunts between both circulation systems are functioning well. In such cases, a cardiac murmur, however, will probably be audible at auscultation. As soon as the patent ductus arteriosus closes, which in some cases may be delayed by several weeks, the patient will quickly become hypoxemic with a potentially fatal outcome.

In another relatively complicated hypoxemic disorder, Fallot's tetralogy, the child may remains asymptomatic for a much longer period and deteriorates more slowly and virtually unnoticed. Fallot's tetralogy includes the following four abnormalities: ventricular septal defect, pulmonary stenosis, right ventricular hypertrophy and overriding of the aorta. The pulmonary stenosis is the decisive characteristic as far as the hypoxemia is concerned. In case of a relatively mild stenosis, hypoxemia may only become manifest after several months or even 1 or 2 years, when due to growth the stenosis becomes relatively more severe. Hypoxemic spells may then acutely compromise the child's condition. In a Fallot's tetralogy a cardiac murmur is always manifest from birth.

In an isolated ventricular septal defect, the symptoms predominantly depend on the magnitude of the inter-ventricular shunt, which is subsidiary to the size of the defect and its tendency to close or not. Shortly after birth there may be pressure equilibrium between both ventricles, because of still existing high pulmonary vascular resistance. In this period the disorder will be hard to discover, as not even a cardiac murmur will be audible at auscultation. In the first weeks the pulmonary vascular resistance will decrease resulting in a left-right shunt, which will also make a cardiac murmur manifest. Subsequently, longstanding pulmonary over-perfusion may increase the pulmonary vascular resistance and eventually lead to reversal of the shunt direction and hypoxemia.

From a screening evaluation point of view it is essential to distinguish three potential outcomes of the natural course of congenital heart disease:

1. The disorder resolves without any therapeutic intervention because of spontaneous regression.
2. Small stable disorders remain without any haemodynamic consequences in the short or long run.
3. Haemodynamic complications occur: heart failure and hypoxemia.

Patients with small stable disorders may be at risk for endocarditis as a complication of surgical and dental interventions[7, 8].

The prognosis of untreated hemodynamic complications is virtually always adverse at the short or longer term and may imply reduced exercise tolerance, irreversible pulmonary hypertension and death.

3.4. Prevalence

Buskens underlines the potential confusion in terminology between "incidence" and "prevalence"[9]. With good reason he rejects the use of "incidence" as a measure of occurrence of congenital heart malformations at birth and advocates the term "birth prevalence". He emphasises that birth prevalence is a function of the occurrence of malformations, or incidence, during pregnancy and survival characteristics of the foetuses. The incidence is an important measure for those investigators who focus on the etiology of the disease, the teratogenic capacity of risk factors and eventually on the possibilities of primary prevention. It may also be of concern for those who focus on prenatal screening. As Buskens concludes, the real incidence of congenital heart malformations is unknown. As for investigators who focus on the evaluation of screening in child health care, however, the birth prevalence is the only measure that matters. Actually attention should be predominantly aimed at clinically significant disorders, i.e. disorders which, if untreated, will lead to haemodynamic complications.

Both Buskens[9]and Hoffman[2] provide extensive reviews of publications in which the birth prevalence of congenital heart disease is established. A broad variability of outcomes is reported, varying from 2 to 12 per thousand[10, 11]. Closer examination of these data however reveals that this variability is mostly to be attributed to differences in methodology and selection of research populations. Buskens observed differences in duration of follow-up, methods of establishment (routine examination versus cases only), diagnostic procedures (invasive only versus non-invasive included, no ultrasound versus ultra-sound included), study population (only live born versus stillborn included) and inclusion definitions (insignificant minor anatomical variations like bicuspid aortic valve included or not). Generally, 8 per thousand may be considered an adequate estimation of the birth prevalence of congenital heart malformations, if minor anatomical variations are excluded. Studies distinguishing between clinically significant disorders (i.e. leading to haemodynamic complications if not treated) and insignificant disorders yield a stable estimate of 4 significant cardiac malformations per thousand live births[2]. Trends in time or geographical variations could not be established. The above estimation on the birth prevalence of significant malformations also applies in the Netherlands, as evidenced by recent hospital based data[12].

3.5. Diagnostic procedures

Recent achievements in diagnostic procedures for congenital heart disease are impressive[13]. Today ultra-sound and diagnostic catheter techniques enable paediatric cardiologists to ascertain malformations of the cardiovascular system with utmost adequacy[14, 15]. Since these techniques provide the actual visualisation of the disorders, assessment of the impact and the prognosis in the short and the long run has been remarkably facilitated and improved. Moreover the non-invasive character of ultra-sound diagnostic procedures has caused a minimisation of diagnostic risks[15].

3.6. Therapy

In addition to the advancements made in the diagnostic procedures, the success rates for interventions for congenital heart disease have also improved enormously over the last decades. The possibilities of cardio-surgical[16] and catheter intervention techniques[17, 18] in particular have progressed spectacularly. This has resulted in a sharp decrease of the mortality of most congenital heart malformations[9]. The present hospital mortality figures for these disorders are summarised in table 3.1, third column.

3.7. Discussion

Secondary prevention programmes like screening cannot prevent congenital heart malformations themselves. To realise a reduction of the incidence of abnormal organogeneses, and consequently of the birth prevalence of these disorders, primary prevention strategies, aimed at etiological factors, should be resorted to. Although avoiding some specific intra-uterine infections and toxic factors and genetic counselling for certain chromosomal disorders may yield some preventive effect, generally spoken primary prevention strategies are not yet feasible, since most aetiological factors are not well understood[9].

Given the clinical qualities of congenital heart malformations, however, screening in child health care may potentially pay a substantial contribution to the optimal management of these disorders. Timely detection and subsequent intervention might prevent deterioration of these patients' condition and even death. The screening programme at the Dutch child health centres, however, has an important limitation that it lacks a neonatal screening[19]. Since the first screening is scheduled at the age of 1 month, this programme will fail to cover those severe, fast-deteriorating conditions, which become symptomatic before that age. At the other hand, relatively frequent malformations as, for example, ventricular septal defects may not be detectable shortly after birth an can still be timely discovered at the age of 1 month.

Whether screening might have favourable consequences in the long run for a substantial number of patients is not easy to answer. Current therapeutic interventions are so effective, that the final outcome in a majority of the patients, even in those in whom hemodynamic complications did occur, may be quite favourable.

The conclusion of this chapter is that the main purpose of child health care screening for congenital heart malformations is to prevent or to shorten episodes of heart failure and hypoxemia. Prevention of endocarditis related to surgical and dental procedures in these patients may possibly be an additional benefit.

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CHAPTER 4

Evaluation of screening for congenital heart malformations in preventive child health care: a virtually unexplored research field

Abstract

Objective
This chapter describes the evaluation of screening for congenital heart malformations in child health care during the neonatal period and the first years of life, based on the available international literature. The study is aimed at both the test properties and the occurrence of favourable and unfavourable effects of this screening.

Methods
Using Medline, a complete search of papers published from 1968 until November 1998, was performed. One hundred and eight publications matched with the search criteria of which only 2 specifically concerned the subject of discussion.

Results
In a retrospective study restricted to a number of relatively rare, very severe disorders the sensitivity of the neonatal clinical screening was estimated at 0.31, that of the screening at the 6 weeks of age at 0.69. The overall sensitivity of the programme was estimated at 0.43. In a prospective 2 year screening survey on newborn patients with Down's syndrome, the sensitivity of clinical screening in the first week was estimated at 0.53 and the specificity at 0.94. Neither the reduction of adverse outcomes as a result of screening, nor the occurrence of unfavourable effects of screening is estimated in the reviewed publications.

Conclusion
Although screening for congenital heart malformations is broadly advocated and actually applied on a large scale, effect evaluation of these activities is a virtually unexplored research field.

4. Evaluation of screening for congenital heart malformations in preventive child health care: a virtually unexplored research field.

4.1. Introduction

As already noticed in chapter 1, probably as a result of the prevailing expectations of parents, auscultation of healthy young children is one of the most applied mass screening activities in any country with a preventive child health care system. The only logical justification of routine auscultation of healthy babies, however, is the possibility to detect formerly unnoticed congenital malformations of heart and great vessels. The main objective of such a detection strategy is obviously to prevent haemodynamic complications by early therapeutic intervention.

Several authors advocate screening for congenital heart malformations as part of the child health care programme in an implicit way [1-3]. In England as well as in the Netherlands, such a screening programme is officially recommended [4-6]. Since in the Netherlands about one third of all children is born at home, one third in an out-patient setting and only one third in a clinical setting[7, 8], there is no formal paediatric neonatal examination. The first screening is recommended at the age of 1 month at the first visit to the child health centre. Three extra examinations are recommended during the first year and another three in the age period from 1 to 4 years[9]. (See Table 4.1).

Table 4.1.
Dutch protocol for screening for congenital heart malformations at child health centres [9].

Examination and definition of positive result	
Examination	*Positive result*
History: • routine question babies: Is he/she drinking the (breast-) feeding well? • routine question toddlers: How does he/she react on physical exercise	Clues for reduced exercise tolerance (in babies notably during feeding): • exhaustion • perspiration • laboured breathing • not finishing feeding, although still impressing as hungry
Biometry	Insufficient weight gain: • serious bending away of weight growing curve • weight beneath 3rd percentile
Inspection	Central Cyanosis

Table 4.1. Continuation

Examination and definition of positive result	
Examination	*Positive result*
Auscultation of the thorax • 2nd intercostal space, left and right parasternal • 4th intercostal space, left parasternal and at mid-clavicular line ("apex") In case of perceived murmur: • on the back left beneath the scapula • at the jugular left and right checking for thrills with the palm of the hand.	Non suspect murmurs Suspect murmurs
Palpation of the abdomen	Liver more than 2 cm beneath the rib cage.
Distinction between suspect and non suspect murmurs	
Characteristics non suspect murmur	*Characteristics suspect murmur*
Systolic murmur without any diastolic component Short (early-systolic) ejection sound Soft: < grade III/VI Well locatable without diffusion No thrill Louder in exercise or anxiety Louder sitting upright than laying down No other abnormal cardiac sounds	Diastolic sounds Pan-systolic sounds Late systolic sounds Loud: III/VI or louder Jugular diffusion Thrill Continuous sounds Sounds audible at the backside
Loudness of murmurs	
I/VI	Soft: only just audible with stethoscope
II/VI	Soft: audible with stethoscope without any doubt
III/VI	Loud, no thrill perceivable
IV/VI	Loud, precardial thrill perceivable
V/VI	Very loud: audible with the stethoscope without completely touching the thorax
VI/VI	Very loud: audible without stethoscope
Referral criteria	**Screening schedule**
Central cyanosis Suspect murmur Liver more than 2 cm beneath the rib cage Combination of 2 or3 of the following findings • Clues for reduced exercise tolerance • Insufficient weight gain • Non suspect murmur	1 month 3 months 12-14 months 24 months 36 months 45 months

The importance of evidence-based medicine is frequently emphasised[10]. Evidence-based medicine probably is even more important in the mass screening programmes, actively offered to the general population than in the curative care offered to patients who seek help themselves[11]. In the Netherlands, a project has been launched, with as objective to collect and review literature able to underpin the various activities within the national preventive child health care programme. This chapter presents the results of this project with respect to screening for congenital heart malformations. The

chapter proposes to clarify the state of the art in evaluation of the favourable and unfavourable effects of this screening, based on the available international literature.
Screening programmes are aimed at detecting disorders at an early stage in order to reduce adverse health outcomes by timely therapeutic intervention. The effectiveness of such programmes depends on the potential of the screening-tests to discover pre-symptomatic conditions and on the potential of the subsequent therapeutic intervention to prevent adverse outcomes. When evaluating the effect of a screening programme, the most elementary measure is the odds ratio for the occurrence of the adverse health outcome involved, depending on whether or not being screened[12]. Considering the natural course of congenital cardiovascular disorders, the adverse outcomes which screening aims to avert are, in the first place, episodes of heart failure or hypoxemia. Endocarditis as a complication of surgical and dental interventions may be defined as a secondary potentially adverse outcome.
Next to the intended favourable effects, screening may also have unfavourable consequences for participants, mainly arising from false-positive test results (unnecessary anxiety and over-treatment) and false-negative test results (false reassurance and under-treatment). The proportions of false test results depend on the test properties (notably sensitivity and specificity) and the prevalence of the disorder involved.
In advance it is essential to emphasise the broad variation in rate of natural course of congenital heart malformations. Three groups can be observed. Firstly complex disorders that rapidly deteriorate in the first days of life, due to the closure of the ductus arteriosus(i.e. pulmonary atresia, hypoplastic left heart). In these patients either the pulmonary system or systemic circulation depends on the blood flow through the ductus. Only prompt neonatal screening can possibly pay a positive contribution to the management of these disorders. A second group consists of disorders that may gradually result in cardiac failure or hypoxemia during the first months of life (i.e. large ventricular septal defects, Fallot's tetralogy). A third group consists of disorders that have not any direct consequences but may result in cardiac dysfunction later in life (i.e. atrial septal defect, ventricular septal defect and coarctation of the aorta). In these last two groups a longitudinal screening programme, in which tests are periodically repeated, may be useful.
In principle, screening programmes should be evaluated by comparing preferably randomly assigned screening and non-screening groups. Test properties as well as the effects of screening should be established. In this chapter, literature on both these aspects, as far as available, will therefore be reviewed.

4.2. Methods

In order to inventory data on evaluations of screening for congenital heart disease in child health care we performed a complete search of papers published from 1968 until November 1998, using Medline. We looked for combinations of "congenital heart

disease", "congenital heart defect" and "congenital heart malformations" with "screening" or "early detection" as words or phrases to be searched in titles or abstracts. One hundred and eight publications matched these criteria, of which only 2 were specifically concerned with screening for congenital heart disease during the neonatal period or the first years of life[13, 14]. One was a general review of several preschool-screening activities [15]. Four dealt with the screening of school children (over 4 years of age) [16-19] and 39 with prenatal ultrasound screening for congenital heart disease. In the other 64 publications the observed combination of words or phrases was coincidence.

4.3. Results.

Test properties.

Abu-Harb e.a. [13] retrospectively documented the contribution of screening by clinical examination at the ages of 24 hours and 6 weeks to the detection of congenital heart disease in 120 patients, consecutively presenting in one health region with either hypoplastic left heart syndrome, interruption of the aortic arch, coarctation of the aorta or aortic valve stenosis. The sensitivity of the neonatal screening for these particular disorders was 0.31 and of the screening at 6 weeks 0.69. In these calculations only the children who were actually screened, were taken into account in the denominator, leaving out children who were diagnosed or who died before the screening age. The screening programme as a whole detected 51 of the total research population of 120 patients, yielding an overall sensitivity of 0.43. Since false-positive test results were not taken into consideration, no other test properties were established. As the authors emphasise, the study is aimed at relatively rare, acutely life-threatening conditions. This is also illustrated by the fact that most patients became symptomatic or died early in life: 10 % before the first screening, 5 % after a negative test result at 24 hours, but still before discharge from the hospital after birth, and 48 % before the second screening.

Tubman e.a. [14] performed a prospective 2 year screening survey on 81 newborn patients with Down's syndrome. Neonatal (first week) screening methods consisting of clinical examination, or consisting of chest radiography or electrocardiography were compared using echocardiography as the gold standard. The sensitivity of clinical examination was 0.53, of chest radiography 0.44 and of electocardiography 0.41. Figures for specificity were 0.94, 0.98 and 1.00 respectively, and for the predictive value of a positive test result 0.86, 0.94 and 1.00.

The publications on the screening of school children solely reported frequencies of positive test results, as to indicate possible prevalence rates. In only one study was the yield of positive test results compared to an estimation of the real prevalence [20]. For this study the estimated sensitivity was 0.83.

Effects

In the reviewed publications neither the reduction of adverse outcomes as a result of screening, nor the occurrence of unfavourable effects of screening are estimated. Abu-Harb e.a., however, conclude that in the light of the poor sensitivity, screening is not advisable. Tubman e.a. emphasise that their study did not determine whether earlier detection and subsequent management of congenital heart disease had any effect on morbidity or outcome. They considered this to be an important but peripheral issue that could be investigated only by a randomised controlled trial, if such a trial is ethically justified.

4.4. Discussion

Testproperties

Data on test properties of child health care screening programmes for congenital heart disease are very incomplete. Abu-Harb e.a. only included a group of relatively rare, but very severe, disorders in their study. They argue that, if screening tests perform as poorly as demonstrated in these life threatening, conditions, they will probably perform even worse in less severe disorders. This is probably true for the sensitivity of the separate screening tests but not necessarily true for the overall sensitivity of the screening programme as a whole. Precisely because of the severity of the disorders involved some patients failed to reach the first screening before becoming symptomatic, and many patients failed to make it to the first follow-up screening. The programme as a whole, therefore, suffered from this lack of opportunity to perform well. In less rapidly progressing disorders, screening programmes with a longitudinal character, such as for instance the Dutch programme, may be able to detect disorders still before deterioration as a result of repeated examinations, yielding a considerable better overall sensitivity. In the Abu-Harb study, too, the best results were reached in the relatively less severe and less rare disorders (coarctation of the aorta and aortic valve stenosis), to which the relatively better result of the 6 week screening (sensitivity = 0,69) is wholly attributable. Tubman e.a. mention the lack of a follow-up screening in their study as a possible cause of the relatively low sensitivity and assume that a second examination at for instance at the age of 1 month might have revealed a substantial number of extra positive test results, notably in patients with rather slowly evolving symptoms.

Favourable effects

Data on the favourable effects of preschool screening for congenital heart disease are completely lacking. Abu-Harb's claim that a poor sensitivity in itself leads to the conclusion that screening is not advisable may be rejected. If intervention in participants with true positive test results leads to prevention of adverse outcomes in a substantial proportion of the children, compared to the situation without screening, poor sensitivity figures do not preclude the screening programme from generating

welcome benefits. However, it is doubtful whether screening is a very suitable strategy for the management of very severe cases. Such disorders will frequently lead to adverse outcomes anyhow, whether detected early by screening or not.
Tubman e.a. concluded from their study, that echocardiography should be applied as neonatal screening for all children with Down's syndrome. Although it is quite remarkable to declare the referee of the game (echocardiography as gold standard) to be the winner of the match, this might very well be true. Convincing proof, however, is lacking.

Unfavourable effects
To what extent screening generates unfavourable effects is not clear. The major message from the Abu-Harb study is a warning against false reassurance in the (within this particular group of very serious disorders) frequent cases with false-negative test results. Whether these patients truly suffered from unfavourable consequences such as delayed diagnosis and therapy, however, was not established. Tubman e.a. reported rather favourable figures for specificity and the predictive value of a positive test result, implying a low false-positive rate. Since echocardiography is used as gold standard, we are not informed about the possible number of false-positive test results, were echocardiography itself used as a screening (as is suggested by the authors), and the appearance of clinically significant disorders as gold standard. Potentially routine neonatal echocardiography may detect numerous cases of a still open ductus arteriosus or oval foramen, which may be closed in the first weeks of life. Furthermore false-positive test results are likely to be numerous in a longitudinal programme like the Dutch one. Erroneous clinical signs, notably innocent murmurs, occur often in young children[21, 22]. So unnecessary efforts and anxiety resulting from false-positive test results seem inevitable in screening for congenital heart malformations. Over-treatment as was suggested in a 1967 publication[23] nowadays is unlikely. Over-treatment resulting from screening is notably a problem in diseases, which proceed in disguise, such as cancer[24]. In congenital heart disease, current diagnostic procedures enable paediatric cardiologist to visualise the malformation completely. Consequently, the natural course can be monitored adequately and interventions can be postponed until deterioration can be foreseen with substantial accuracy.

General discussion
To summarise we may conclude that there is an enormous paucity of studies on this subject. This may be not be easily remedied. Tubman e.a. were right to emphasise the ethical problems that a randomised controlled trial may invoke. If a screening programme is already being performed on a large scale, it is almost impossible to organise such a study because of considerable public and professional objections. Failing a randomised trial observational studies must be relied upon, meticulously considering possible sources of confounding. Several study designs may contribute,

such as follow-up studies with a possibly historical or geographical reference group, and case-referent studies. An important condition is to ensure that such a study is aimed at a population in which the actual performance of the screening programme varies, or at two or more different populations with different screening programmes, as to make it possible to compare research groups with different screening exposures.

4.6. Conclusion

Although screening for congenital heart malformations is broadly advocated and actually applied on a large scale, effect evaluation of these activities is a virtually unexplored research field. In the light of need for evidence based medicine, this omission should be rectified.

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CHAPTER 5

Patient follow-up screening evaluations. Examples with regard to congenital hip dislocation and congenital heart disease.

Abstract

Objective
When screening is established practice and circumstantial evidence points to at least some effectiveness of early intervention, assessment of favourable effects of screening programmes by Randomized Controlled Trials (RCT's) is often not feasible and observational studies will have to be considered. This chapter is concerned with the place of patient follow-up studies in this armoury of designs.

Argumentation
For assessing favourable effects of screening for many conditions, the use of the patient follow-up study design is very problematic, or even unacceptable. The most important objections against this design, especially in cancer screening evaluation, are resulting from *lead time bias, length bias, selection bias* and *over-treatment.* However, for the evaluation of screening for congenital heart disease and congenital hip dislocation, these objections may be overcome:
Lead time bias will be of little importance, as the ages of onset of congenital heart disease and congenital hip dislocation are fixed, namely at birth, and their ultimate outcomes may be expected within relatively short time. Length-bias may largely be avoided by correction for severity of the disorder, i.e. its tendency to rapid deterioration, which can be adequately estimated by modern diagnostic procedures. As in most observational studies stringently guarding selection bias is one of the most arduous problems in patient-follow-up screening evaluations. However, in these screening programmes, exposure to screening probably predominantly depends on whether or not screening is well performed by the child health centre physician. Variation in this performance will not automatically lead to selection bias. Over-treatment can be avoided by the policy of "watchful waiting", which in these disorders can be applied with little risk for fatal outcomes.
The results of two pilot studies suggest that both screenings probably yield considerable benefits

Conclusion
For congenital hip dislocation and congenital heart disease a patient follow-up study, can be an efficient alternative to more customary designs for screening evaluation. More elaborate studies following this design for these conditions are feasible.

5. Patient follow-up screening evaluations. Examples with regard to congenital hip dislocation and congenital heart disease.

5.1. Introduction.

Although the basic concept of screening is deceptively simple, there is a general consensus that assessing the favourable effects of any screening programme is fraught with pitfalls and requires a very strict methodology[1]. From a theoretical point of view the most appropriate design for such studies is the *randomised controlled trial* (RCT), which in principle is the only option to avoid virtually all types of contamination[2]. Unfortunately, many forms of screening already have an established place in health care without ever having been subjected to a randomised trial. Examples are to be found in occupational health, cervical cancer screening, the periodic examinations during pregnancy and child health care. If a screening programme is already performed on a large scale in a population, it is almost impossible to organise an RCT for the evaluation of such a programme. Definite faith in the benefits of screening among many professionals and the public, will, although based on merely circumstantial evidence, lead to strong resistance, if the screening is withheld from persons who normally would have had the opportunity to participate. When an RCT for assessing favourable effects of an already existing screening program is not feasible, one has to rely on less decisive observational studies, meticulously considering possible sources of confounding. The most common observational designs for this purpose are the *population follow-up study* and the *case control study*. This chapter, however, is mainly concerned with the merits and shortcomings of the *patient follow-up study*, which may be considered as an alternative in particular for the case control study.

For many conditions, especially for cancer, the use of the patient follow-up study design for assessing favourable effects of screening is very problematic, or even unacceptable. However, for the evaluation of screening for some disorders with specific characteristics, this design may, under a number of strict conditions, be useful. This may particularly be the case for evaluation of screening for some congenital disorders within the framework of child health care.

After a short description of the patient follow-up study design for assessing favourable effects of screening, we will first discuss the most important objections against this kind of studies, notably as far as cancer screening is concerned. Next we will demonstrate why these objections may play a less prominent role, or may be relatively easily be remedied, in assessing favourable effects of screening for certain conditions in child health care, in particular congenital heart malformations and congenital hip dislocation. Finally we will present two pilot screening evaluations, in which for both these conditions the patient follow-up study design was actually applied.

5.2. The design

In a screening evaluation following the patient follow-up study design, a representative group of patients is followed from diagnosis until the outcome of treatment is known. Retrospectively the exposure to screening will be established. If the odds for reaching an adverse outcome are more favourable for well-screened patients (the screening group) than for patients not or scarcely exposed to screening (the non-screening group), the screening is considered to be effective.

5.3. Objections against patient follow-up studies in cancer screening

Lead-time bias.

Considering the nature of most cancers, the follow-up time after diagnosis, in which the outcome of the treatment is supposed to be established in patient follow-up screening-evaluations, is not fixed. Because for most cancers the adverse outcome to be prevented is death, whether or not patients will survive a period of for example five years after diagnosis, will usually be taken as outcome measure. Since the age of onset of cancer in relation to the age of screening may vary considerably, the screening-group may contain a large proportion of patients with disorders in an early stage. Many of these patients will, regardless of being treated or not, probably not die within 5 years, but may despite receiving treatment still die after five years. In the non-screening group such patients will be virtually absent. This will lead to an overestimation of the proportion of patients with favourable outcomes in the screening-group and consequently to overestimation of the potential favourable effects of screening.

Length bias.

Patients with rapidly deteriorating cancers are more likely to reach an adverse outcome than patients with slowly progressing diseases, while they have also less chance of being screened during the short preclinical detectable phase. In a comparison of screen-detected with non-screen-detected patients this will lead to an overrepresentation of such patients in the non-screen-detected group and consequently to overestimation of the favourable effects of (detection by) screening. This kind of contamination is called "length bias". In a patient follow-up study in which exposure to screening rather than detection by screening is the subject of the comparison, length bias is not a compulsive problem. However, when rapid progression is one way or the other connected with a decreased participation in the screening programme, overestimation of favourable effects of screening as a result of differences in natural course will also occur in this design.

Selection bias

People who have a better chance of being diagnosed in time and treated with favourable outcomes without screening anyway, may also be the better screened. For example, people who are watchful as far as their health is concerned and who are

assertive in acquiring treatment, probably scrupulously attend the screening programme. This will also lead to an overestimation of the effectiveness of screening.

Over-treatment

Another obvious problem in the patient-follow-up study design is the potential presence among those who were apparently treated successfully, of persons who were wrongly indicated as a patient by screening in the first place. This is a problem much wrestled with in cancer screening: The natural course of anomalies found by cancer screening may vary considerably. Many conditions may be regressive and resolve spontaneously or may be slowly progressive and never become a real problem. Generally speaking it would be a sensible policy to postpone treatment of screen-detected disorders until the disease has progressed up to a stage in which a favourable outcome can no longer be expected. This may be feasible for disorders of which the prognosis is relatively easy to establish, yet in many cancers the natural course is quite unpredictable and a policy in which treatment is postponed may easily lead to fatal outcomes. In these cases therapeutic interventions will therefore be applied without delay. Hence over-treatment must be considered as an inevitable disadvantage of screening for many cancers, of which cervical cancer and prostate cancer are the most clear examples[3, 4]. In the light of the possible benefits of screening such a disadvantage may be acceptable. However, in a patient follow-up cancer screening evaluation, this may also lead to overestimation of the favourable effects of screening since in such a study favourable outcomes in over-treated screening participants will contribute to the observed positive effect of the screening.

5.4. Status of these objections in screening for congenital heart malformations and congenital hip dislocation.

Lead-time

The most important differences of these conditions compared to cancer are that their ages of onset are fixed, namely at birth, and that their ultimate outcomes may be expected within relatively short time.

Both congenital hip dislocation and congenital heart malformations are in principle present at birth. An untreated dislocation will almost inevitably arrive at the adverse outcome, i.e. limping, shortly after the age of 1 year. In most untreated clinically significant congenital heart malformations the adverse outcomes, i.e. heamodynamic complications such as heart failure and hypoxemia, will occur even before the age of 1 year. As a result lead-time bias will, contrary to the situation in a patient follow-up assessment of favourable effect of cancer screening, be of no importance in evaluating the screening programmes for these congenital conditions.

Length bias.

In patient follow-up studies for the disorders under discussion length bias may not be ruled out. Screening examinations for congenital heart malformations for example are scheduled relatively close together in the first months of life. Patients with severe

disorders may deteriorate rapidly and consequently fail to attend the screening examination. If such a patient is nonetheless diagnosed shortly after the age at which a screening examination was scheduled, inclusion in the non-screening arm of a patient-follow-up study is possible, resulting in an overestimation of the favourable effects of screening. This might be neutralised by correcting the analysis for severity of the disorder. Reliable assessment of severity, i.e. the tendency to a rapid deterioration, is obviously a requirement for such a solution. In cancer, which often is a condition developing, as it were, in disguise, such an assessment will not be straightforward. However, in congenital heart disease, current diagnostic procedures enable paediatric cardiologists to visualise the malformation completely, considerably facilitating the estimation of the nature of the disorder[5] .

Selection bias.

As in most observational studies stringently guarding selection bias is one of the most arduous problems in patient-follow-up screening evaluations. Nevertheless, in an observational evaluation of child health care screening, selection bias may play a somewhat less important role than in similar evaluations of cancer screening. Selection bias is related to the extent to which, and the reason, people comply with the invitation for the screening. However, in the screening programmes under discussion, exposure to screening does not exclusively depend on the attendance of the parents to the child health centre, but also on whether or not screening is well performed by the child health centre physician. As we will see in Chapter 7 performance of the doctor is actually the predominant determinant of screening exposure. Variation in this performance will not automatically lead to selection bias.

Over-treatment

As clarified above, postponing treatment until the disorder reaches a stage in which spontaneous regression is judged to be impossible is the obvious strategy to prevent over-treatment. This policy of "watchful waiting" enables researchers to exclude screening participants wrongly picked out as "patients" from a patient follow-up screening evaluation. Contrary to many forms of cancer, in which predicting the natural course is very hazardous, this is relatively straightforward for the congenital conditions under discussion. While many cancers develop on a cellular level, these conditions are generally relatively large anatomical malformations. As in congenital heart disease, congenital hip dislocations may nowadays also be completely visualised, with the help of for example ultrasound technology[6]. Consequently the natural course of both conditions can be monitored adequately and interventions can be postponed until deterioration can be foreseen with substantial accuracy.

5.5. Pilot studies.

As during the preparation of our child health care evaluation programme we perceived that congenital heart disease and congenital dislocation of the hip may have the specific characteristics for applying a patient follow-up screening evaluation, we

decided to conduct, two small-scale pilot studies with such a design on these diseases. Both studies were primarily aimed at establishing the feasibility of more elaborate studies in classifying patients suitably as "adverse outcome acquired" or not, and as "adequately screened" or not. In both studies assessment of final outcomes, which is preferably carried out prospectively following diagnosis, were recorded retrospectively by analysis of clinical files.

Congenital heart disease

About 0,8 % of all children are born with congenital heart disease. Large anatomical anomalies, in which spontaneous recovery is quite inconceivable, are treated immediately after diagnosis by medication and catheterisation or surgery. In all other cases, the natural course of the disorders is surveyed until spontaneous regression occurs, i.e. the disorder disappears or proves to be hymodynamically insignificant, or until the adverse outcome of the disease (heart failure or hypoxemia) is judged to be inevitable unless treatment is started[7].

After the neonatal check-up by the doctor or midwife who assisted birth, which is not standardised in the Netherlands, the circulatory system of children in the Netherlands is screened during recurrent physical examinations in the child health care programme.

During 1993 in the Sophia Children Hospital in Rotterdam a patient follow-up study was carried out, comprising 42 children with congenital heart disease. Children were classified in the adverse outcome category if periods of (nearly) heart failure or hypoxemia had occurred. Children who were successfully treated at least as soon as the onset of heart failure or hypoxemia was judged to be inevitable were classified in the non-adverse outcome category. Children were classified as "adequately screened" if they had at least been exposed to all scheduled screening tests in the child health care programme until being diagnosed and if all these screening tests had been performed adequately, i.e. in accordance with the guidelines of the child health care authorities. The number of children in each of the four categories and the odds ratio for reaching the adverse outcome depending on whether or not being adequately screened are presented in Table 5.1.

Table 5.1.

2 x 2 -table for analysis of a pilot patient follow-up study for the evaluation of child health care screening for congenital heart disease.

	Heart failure or hypoxemia	*No complications*	*Total*
Adequately screened	3	16	19
Inadequately screened	17	6	23
Total	20	22	42

Odds ratio for heart failure or hypoxemia depending on whether or not adequately screened.
3:16 / 17:6 =0.07 (CI: 0,01-0,31)

Congenital hip dislocation

About 1 % of all children are born with a hip dislocation or a dislocatable hip. In the absence of (early) intervention this disorder will develop into a permanent anomaly, which finally results in limping, in only 0,08 - 0,16 % of all children[8]. Neonatal screening by the Barlow and Ortolani methods is applied, for instance in the United Kingdom and Scandinavia[9]. Splinting for 4 to 6 weeks starting as soon as possible after birth is often considered an effective and little taxing intervention. However, as in 90 % of the cases the disorder will be regressive, the number of children apparently treated successfully, but actually wrongly picked out as a patient by screening will be substantial. Therefore at first sight this programme appears to be a poor candidate for evaluation with a patient follow-up study design.

Some authors, however, advise to postpone intervention until approximately the 5th month[8]. If the disorder still exists at that age it can safely be considered as an anomaly that will not recover without treatment. Splinting at that age will generally still be successful, though more taxing than in the very young children. Surgery however will be avoided, as will over-treatment.

As in Great Britain screening and intervention are applied on a large scale soon after birth, evaluation by an RCT is problematical[9]. Since in Great Britain the mere existence of congenital dislocation after the age of 1 month is considered the adverse outcome to be avoided, in that country a patient follow-up study, as presented in this chapter will be of no use. If, for instance, the need for surgery would be considered as the adverse outcome to be avoided, such study would become a possibility.

In the Netherlands there is no neonatal screening-programme for congenital hip dislocation. Instead, children are screened much later during recurrent physical examinations in the child health care programme, which include assessment of the abduction range of the hips and the length of the legs[10]. In the Sophia Childrens Hospital in Rotterdam, treatment policy is expectant: splinting is postponed until spontaneous recovery has become very unlikely. Under these circumstances the need for surgery is a useful definition for the adverse outcome, and the patient follow-up design a possible option for screening evaluation.

In 1992 a pilot study was carried out in the Sophia Children Hospital, comprising 60 children with a congenital hip dislocation[11]. All these children had progressive disease: pathologic changes progressed up to a stage in which spontaneous recovery of the dislocation was judged to be impossible, before treatment was applied. Children were classified in the adverse outcome category if surgery was needed and in the no adverse outcome category if they were successfully treated by non-invasive methods. Children were classified as "adequately screened" if until the definite diagnosis they had been at least exposed to all scheduled screening tests in the child health care programme and if all these screening tests were performed adequately, i.e. in accordance with the guidelines of the child health care authorities. All other children were classified as

"inadequately screened". The results and the estimated odds ratio are presented in Table 5.2.

Table 5.2.

2 x 2 -table for analysis of a pilot patient follow-up study for the evaluation of child health care screening for congenital hip dislocation.

	Necessity for surgery	*Conservative intervention possible*	*Total*
Adequately screened	6	13	19
Inadequately screened	26	15	41
Total	32	28	60

Odds ratio for necessity for surgery depending on whether or not adequately screened.
6:13 / 26:15 =0.27 (CI: 0,08-0.85)

The results of these pilot studies support the idea that systematic screening in child health care can prevent episodes of heart failure and hypoxemia in children with congenital heart disease and surgical intervention for congenital hip dislocation

5.6. Discussion

The first question to be answered here is whether it is worthwhile to apply second-best evaluation designs in situations where an RCT is not feasible because of established practice and circumstantial evidence for at least some effectiveness of the intervention. In our opinion the answer depends on the quality of the circumstantial evidence and the chance of further improving the intervention. Since review of the available literature reveals large gaps in our knowledge of the effectiveness of screening protocols in child health care[12, 13], we believe that observational trials for evaluation of the benefits of these screenings are justified.

We believe that for at least congenital hip dislocation and congenital heart disease a partly retrospective partly prospective patient follow-up study can be an efficient alternative for more customary designs for screening evaluation like the population follow-up study and the case control study.

In terms of efficiency a patient follow-up study offers the advantage of the availability of a study group directly from the patient population of for instance an academic hospital providing specialised medical care to a large area. Thus the laborious collection of data in the general population, necessary in a population follow-up study, can be avoided, which, if not based on randomisation, may be cursed with sources of contamination just as much as a patient follow-up study.

Case-control studies provide another relatively efficient alternative for assessing favourable effects of screening. In such a study the case group consists of patients who have reached the adverse outcome of the condition. The exposure to screening in this

group is retrospectively compared with that in a control-group. In order to minimise bias, this control-group should be sampled directly from the total population that generated the cases: the source population[2, 14]. In practice complying with this condition may not be easy. To form a sample from the source population, reliably presenting the average exposure to screening in that population may, especially if data concerning this population are not easily available, be more problematic than gathering complete data of relevant patients from a circumscribed area in a well-defined time window, as required in a patient-follow-up study.

In screening-evaluations by case-control studies one has to deal with the so-called "healthy-screenee-bias". Once a disease is diagnosed the patient is thereafter no longer screened, while "healthy" non-patients are screened again and again. Since the control group (almost) exclusively consists of "healthy" non-patients this phenomenon will, if the total number of applied screening tests is used in establishing the screening history, lead to an overestimation of the effectiveness of screening[14]. To avoid this bias controls are matched with cases for age, and assessment of exposure to screening in a control is exclusively aimed at the period up to the age that the matched case was diagnosed. Matching for other variables may be hazardous, since it may introduce new sources of confounding. In Dutch child health care, for instance, differences in exposure to screening within the population are probably strongly connected with policy differences in child health centres. Matching, for example, for living area may easily lead to matching for child health centre as well. Should there be a real effect of screening, this would lead to an underestimation of the average exposure in the source population, and consequently to an underestimation of the favourable effect of screening.

As the study group in patient follow-up studies is exclusively comprised of patients, a "healthy screenee bias", as in case-control studies, is impossible. Nevertheless, the total number of applied screening tests cannot be used to establish the screening history in patient follow-up studies in child health care either. Cases diagnosed early in life may have a better change of being successfully treated, but will be exposed to fewer screening tests than those who are diagnosed later. Therefore the use of the total number of applied screening tests as a measure for screening history may lead to underestimation of the effectiveness of screening. To avoid this bias in establishing the screening history the proportion of scheduled screening examinations that have actually been carried out until the age of the definite diagnosis can be used.

Patient follow-up studies (as well as case-control studies) aim exclusively at estimating the intended favourable effects of screening and not at weighing advantages and disadvantages (e.g. arising from false positive and false negative tests). This requires additional data collection, which not always have to be very difficult.

A remarkable characteristic of case-control screening evaluations is the fact that although such studies are aimed at assessing benefits of a screening not a single person who does benefit from screening is actually included in the study. The case group

consists of people with adverse outcomes of the condition, the control group consists of people who do not have the condition at all. As a result, in case-control screening evaluations, only the prevention process as a whole starting from exposure to screening can be evaluated. The contribution of separate factors, such as the influence of delay between a positive screening test and adequate diagnosis and intervention, which may be of crucial importance for the effectiveness of the prevention programme, cannot be evaluated. In a patient follow-up study, however, this is straightforward.

If in a case-control screening evaluation a truly representative sample can be taken from the source-population (the population to be judged by the study), selection bias will be avoided more successfully than in a patient-follow-up study in which correction for such contamination is not straightforward. The patient-follow-up study, however, is for both screening programmes under discussion the more feasible design, may provide more supplementary information, and may still provide useful information on the screening effectiveness. The results of the pilot trials, presented in this chapter, indicate that studies following this design are feasible and that both screenings possibly might yield considerable benefits. The odds ratios presented are very low. One is tempted to conclude that, even if selection bias does play an important role, there must be also a real effect of screening. Nevertheless one should be very cautious in drawing such conclusions from these results. Larger and more elaborate studies, in which the follow-up of the outcome after diagnosis is recorded prospectively and in which further attention is paid to the problems and pitfalls mentioned in this chapter, are necessary. As far as congenital heart malformations are concerned such efforts are presented in Part III of this thesis.

As far as the discussion on the definition of the adverse outcome of congenital hip dislocation is concerned some final remarks might be serviceable. Different choices on this subject made in Britain and in the Netherlands are above all of consequence for the intervention strategies applied in both countries. Therefore the problem may essentially be reduced to the ethical issue, of whether or not a less taxing intervention associated with extensive over-treatment (the British situation) is to be preferred over a more taxing intervention associated with less over-treatment (the Dutch situation). However, it would be an overestimation of the quality of decision making in both countries to assume that these differences are the result of diverging ethical considerations instead of more or less coincidental historical processes.

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PART III

MAIN STUDIES

CHAPTER 6

Test-properties and effectiveness of screening for congenital heart malformation in child health centres.

Abstract

Background
Although screening for congenital heart malformations is part of the child health care programme in several countries, evaluations of these activities have virtually never been published. This report is concerned with the evaluation of this screening at the Dutch child health centres .

Methods
All consecutive patients, aged between 32 days and 4 years, presented at the Sophia Children's Hospital Rotterdam throughout a period of two years, with a congenital heart malformation were included in this study. Paediatric cardiologists established whether or not these patients were diagnosed after hemodynamic complications had already developed (diagnosed "too late"). Parents and child health centre physicians were interviewed in order to establish the screening and detection history. Test properties were established for all patients with a congenital heart malformation (n=290), intended effects of screening were established in patients with clinically significant malformations (n=82).

Results:
The sensitivity of the actual screening programme was 0.57 (95%CI: 0.51-0.62), the specificity 0.985 (95%CI: 0.981-0.990) and the predictive value of a positive test result 0.13 (95%CI: 0.10-0.19). Sensitivity in a sub-population of patients adequately screened was 0.89 (95%CI: 0.74-0.96).
Adequately screened patients were less likely to be diagnosed "too late" than inadequately screened patients (OR=0.20 95%CI: 0.04-1.05). The actual risk of being diagnosed "too late" in the study-population (48 %) was only slightly less than the estimated risk for patients not exposed to child health centre screening (58% 95%CI: 43%-72%). Adequately screened patients however were at considerably less risk (17% 95%CI: 4%-48%)

Conclusion:
Screening for congenital heart malformations in child health centres contributes to the timely detection of these disorders. The actual yield, however, is far from optimal, and the screening programme should be improved.

6. Test-properties and effectiveness of screening for congenital heart malformation in child health centres.

6.1 Introduction

In several countries, periodic health examinations are part of the preventive child health care programme[1-5]. In the Netherlands, this programme is executed at the child health centres. These examinations generally include routine medical check-ups of heart and circulation, aimed at the early detection of congenital heart malformations. Evaluations of these screening activities however have virtually never been published[2, 6].

Screening evaluation aims at establishing both favourable and unfavourable effects of screening. Unfavourable effects are mainly due to false-negative and false-positive test results, the numbers of which are determined by the test properties. Favourable effects are defined as the reduction of adverse outcomes of diseases as a result of early detection and subsequent intervention[7].

Approximately half of all cases of congenital heart disease are detected soon after birth by neonatal examinations or due to the onset of symptoms. The remaining patients initially go unrecognised[8]. Child health centre screening is merely aimed at the latter; the first examination is scheduled at the age of 1 month.

Since many of these disorders spontaneously resolve and have no hemodynamic impact in the short or long run[9], the intended effects of screening will only occur in clinically significant congenital heart malformations, which give rise to progressive disease.

The adverse outcomes to be prevented are haemodynamic complications, notably heart failure and hypoxemia. Disorders should be detected "in time", i.e. before these complications occur. Children who have already developed hemodynamic complications at the first cardiological consultation, have been diagnosed "too late", even if these complications are still reversible by therapy. Since haemodynamic complications can be prevented with the help of modern interventional paediatric cardiology[10, 11] and cardiac surgery[12-16] in most patients who are diagnosed "in time", reducing the number of patients diagnosed "too late" may be considered the target of the screening programme.

Compared to patients with moderate disorders, patients with severe disorders may be more at risk for developing complications. These patients are also less likely to have undergone screening prior to the development of complications due to rapid deterioration. In an observational evaluation of screening this may give rise to length bias, leading to an overestimation of the favourable effects of screening. This requires adjustment for confounding[17].

Official guidelines for screening at the Dutch child health centres, regarding procedures and ages of investigation are defined by the Dutch National Association

for Home Care[18]. There is, however, a substantial variation in the actual performance[19].

The purpose of this chapter is:

1. To estimate the test properties of the child health centre screening programme for congenital heart malformations, as actually performed in the south west of the Netherlands, and the maximum attainable sensitivity were all patients to be adequately screened according to the guidelines.
2. To estimate the effect of the present screening programme on the proportion of patients with clinically significant malformations arriving "too late" in a paediatric cardiology department, and the potential effect were all patients to be adequately screened, according to the guidelines.
3. To inventory the actual deviations from the guidelines in the present screening programme.

6.2 Methods

Study group

All patients who fulfilled the following conditions, were included in this study:

- First cardiological consultation at the Sophia Children's Hospital took place between 11-04-1994 and 11-04-1996.
- Children were aged between 32 days and 4 years.
- Children were resident in the south-west of the Netherlands, more specifically the area from which, by national agreement between paediatric centres, all children with cardiovascular disorders are referred to the Sophia Children's Hospital.
- Parents were informed and consented to their children's participation in the study.
- Children presented for the first time with a congenital anatomical heart malformation.

As illustrated in Table 6.1, the study group thus comprised 290 patients.

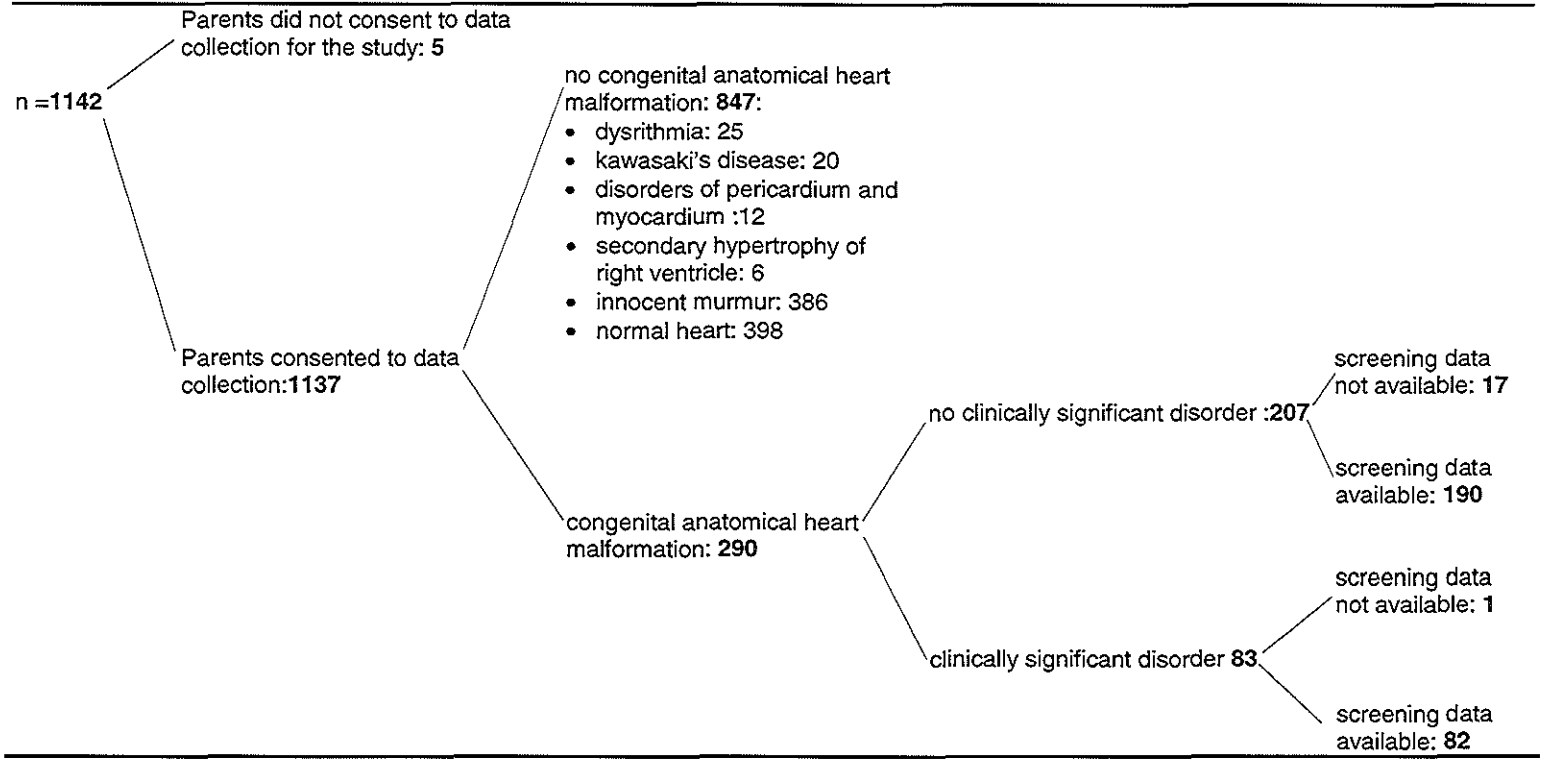
The intended effects of screening can only be established in patients with clinically significant congenital heart malformations. A malformation was defined as clinically significant when it was decided to perform a therapeutic intervention within 9 months after the first cardiological consultation. Eighty-three patients satisfied this condition, of whom 82 were included in the analysis. (Table 6.1).

Data collection and definition of variables:

To establish whether patients were diagnosed "too late" or "in time" a questionnaire was filled in by the paediatric cardiologist in charge at the first cardiological consultation, in which the following aspects were examined :

Table 6.1.

Patients (32 d. - 4 y). first seen at the dept. of paediatric cardiology between April 10th 1994 and April 10th 1996



- Extent of heart failure, resulting from pressure- or volume-load ("none", "moderate", "serious", "very serious").
- Degree of hypoxaemia ("none", "moderate", "serious", "very serious").
- Risk of deterioration.
- Estimated duration of symptoms.

Another paediatric cardiologist was asked to give a second opinion by filling in an identical questionnaire independently. In the event of differences between the answers of the two physicians, a third colleague was asked to make the final judgement.
Diagnosis is considered to have been established "too late" if

- heart failure or hypoxemia was classified as "serious" or "very serious", or
- heart failure or hypoxemia was classified as "moderate", the risk for deterioration was considered realistic and the symptoms were estimated to have existed for over 1 month.

All other disorders were considered to have been diagnosed "in time".

To make it possible to adjust for length bias paediatric cardiologists were also asked to appraise the severity of the disorder by opting for one of four qualifications: "trivial", "moderate", "severe", and "very severe".

In order to establish whether or not their child's disorder was detected as a result of the child health centre screening programme, parents were interviewed by a nurse at the first cardiological consultation. If necessary, additional information was collected from child health centre physicians, general practitioners and clinical specialists. Disorders were assumed to have been detected by the physician who was the first to initiate a referral for a cardiovascular disorder. Patients were classified as having been detected by a child health centre physician or not.

In order to establish the screening history, the child health centre physicians of all patients were approached for an interview. The first author, who was not informed about the nature and severity of the disorder, performed all interviews. Questions were asked about the doctor's normal screening routine and about the actual procedure in this particular case.
A screening history was classified as "adequate" if:

- until the first cardiological consultation the child health centre was visited at least according to the "standard visit schedule", which entails: one visit before the age of 35 days, one in the age interval between 35 and 95 days (first DPTP-Hib-vaccination), one in the age interval between 3 and 14 months (MMR-vaccination) and subsequently one visit every year until the age of 4, and

- during all these visits the child health centre physician at least performed auscultation of the thorax, judged skin colour, size of the liver and weight gain and asked questions aimed at assessing the child's exercise tolerance, and
- the child was referred as soon as one of the following symptoms was found :
  - heart murmur classified by the child health centre physician as "suspect"
  - central cyanosis
  - enlarged liver
  - combination of heart murmur classified by the child health centre physician as "non suspect" and weight gain classified by the child health centre physician as "insufficient"
  - combination of heart murmur classified by the child health centre physician as "non suspect" and anamnestic clues for exercise intolerance.
  - combination of weight gain classified by the child health centre physician as "insufficient" and anamnestic clues for exercise intolerance

Screening history was either classified as "adequate" or as "inadequate". For "inadequate" screened patients the reasons for this classifications were specified.

To determine screening test properties additional data were collected:
- all referrals for congenital heart malformation by Rotterdam child health centre physicians were registered during the second half of 1996.
- figures on births in Rotterdam and the south west of the Netherlands including Rotterdam were acquired from Statistics Netherlands.

Analysis.
It is our opinion that it is essential for patients, parents and their physicians to be informed of any congenital heart malformation present, even if the disorder should eventually prove to have no hemodynamic consequences. Therefore test properties were established for all 290 patients with a congenital heart malformation. To establish the intended effects of screening, however, the analysis was restricted to the 82 patients with clinically significant disorders.
With regard to the latter, logistic regression was used to derive odds ratios, including 95 % confidence intervals, for being diagnosed "too late" depending on whether or not being screened adequately and on whether or not being detected by child health centre screening. In both analyses, correction for severity was applied in order to adjust for length bias.
To appreciate the effects of screening the proportions of patients diagnosed "too late" and "in time" in an imaginary population not exposed to screening are estimated. We assume that these proportions will be appropriately estimated by the proportions "too

late" and "in time" among patients with clinically significant disorders, who were **not** detected by a child health centre physician, corrected for severity. (In this imaginary population a distribution of severity similar to the complete study group may be expected). This estimate was compared to the proportions of diagnoses made "too late" and "in time" in the complete study population (i.e. exposed to screening as it was actually performed) and in the sub-population with a adequate screening history. (Proportions in this sub-population (n=12) could not be corrected for severity, since numbers of patients were too small)

6.3 Results.

Patient inclusion

As shown in Table 6.1, of all 1142 patients, aged between 32 days and 4 years, who were examined during the study by a paediatric cardiologist in the Sophia Children's Hospital for the first time, 290 appeared to have a congenital heart malformation. The screening history of 272 of these patients could be documented. Eighty-three patients were eventually diagnosed as having a clinically significant disorder, of whom in 82 the screening history could be collected. The findings of the two paediatric cardiologists were identical in 79 cases. A third opinion was necessary in 3 cases. Forty-nine patients (60 %) suffered from large left-to-right shunts. Cyanotic heart disease was found in 15 patients (18 %) and disorders resulting in increased pressure-load were seen in 7 patients (9 %). The remaining 11 patients (13 %) had miscellaneous malformations.

Test properties.

Of 290 patients 164 had been detected by a child health centre physician. In 36 (out of 272) patients all requirements for adequate screening had been met. Thirty-two of these were detected by a child health centre physician. The number of referrals for congenital heart malformation by Rotterdam child health centre physicians in 6 months was 60. The numbers of births in the south-west of the Netherlands and Rotterdam during 1994-1995 were 75441 and 14524 respectively. Hence the number of child health centre referrals throughout a period of 2 years in the area under discussion is estimated as 75441/14524x4x60=1247. On the basis of these figures, test properties are calculated and subsequently presented in Table 6.2. The sensitivity of the actual screening programme was 0.57, the specificity 0.985 and the predictive value of a positive test result 0.13. Sensitivity in the adequately screened sub-population was 0.89.

These data also allow to calculate the incidence rate of congenital heart malformations in children aged from 1 month until 4 years, which is 0.38 %.

Table 6.2.

Calculation of incidence of cases of congenital heart malformation diagnosed between 32 day and 4 years, the test properties of the actual child health centre screening activities during two years in the south-west of the Netherlands and the sensitivity of this screening in a subset of adequately screened patients.

(Numbers between parentheses indicate adequately screened patients)

	Congenital heart malformation		*Total*
	+	-	
Screening +	164 (32)	1083	1247
Screening -	126 (4)	74068	74194
Total	290 (36)	75151	75441
incidence:		290/75441=	3,8 per 1000 children
sensitivity :		164/290=	0.57 (95%CI: 0.51-0.62)
specificity :		74068/75151=	0.985 (95%CI: 0.981-0.990)
predictive value positive test :		164/1247 =	0.13 (95%CI: 0.10-0.19)
sensitivity if adequately screened:		32/36 =	0.89 (95%CI: 0.74-0.96)

Table 6.3.

Classification of the 82 patients with clinically significant disorders diagnosed "too late" and "in time" in categories "adequately screened" and "inadequately screened", and "detected and not detected by child health centre".

	"too late"	*"in time"*	*Total*
Adequately screened	2 (17%)	10 (83 %)	12 (100 %)
Inadequately screened	37 (53 %)	33 (47 %)	70 (100 %)
Total	39 (48 %)	43 (52 %)	82 (100 %)
Detected by child health centre	16 (36 %)	29 (64%)	45 (100 %)
Not detected by child health centre	23 (62 %)	14 (38 %)	37 (100 %)
Total	39 (48 %)	43 (52 %)	82 (100%)

Odds Ratios:

for being "too late" depending on whether or not adequately screened.

2:10 / 37: 33 = 0.18 (95%CI: 0.04 - 0.87)

= 0.20 (95%CI: 0.04 - 1.05) corrected for severity

for being "too late" depending on whether or not detected by child health centre screening

16:29 / 23:14 = 0.34 (95%CI: 0.14 - 0.83)

= 0.39 (95%CI: 0.15 - 1.00) corrected for severity

Effectiveness

For the 82 patients with a clinically significant disorder, distributions of screening and detection history in relation to the outcome measures (diagnosed "too late"/ "in time") are shown in Table 6.3.

Of these 82 patients, not surprisingly none was qualified as having a "trivial" disorder. Twenty-nine (35%) of these patients proved to have a moderate, 40 (49%) a severe and 13 (16%) a very severe disorder. Table 6.3 shows that adequately screened children were less likely to be diagnosed "too late" than inadequately screened ones. This was also the case for patients detected by child health centre physicians compared to patients detected otherwise. After correction for severity, both odds ratio's hardly increased, although both confidence intervals now just include 1.00.

In an imaginary population not exposed to child health centre screening, the estimated percentage of children diagnosed "too late" and "in time", based on proportions among children **not** detected by child health centre physicians after correction for severity, are 58% and 42% respectively.

As summarised in Table 6.4, the risk of being diagnosed "too late" in a population exposed to child health centre screening as actually performed in the present study population, is not much lower than the estimated risk for patients in a population not exposed to child health centre screening. In an adequately screened population, however, patients would probably be at considerably less risk of being diagnosed "too late".

Table 6.4.

Proportions of patients diagnosed "too late" and "in time" in populations subjected to different screening expositions

	"too late"	*"in time"*
Imaginary population not exposed to child health centre screening	58 % (CI: 43 – 72)	42 % (CI: 28 - 57)
Population exposed to child health centre screening as actually performed	48 %	52 %
Population exposed to adequate screening	17 % (CI: 4 – 48)	83 % (CI: 52 –95)

Inventory of deviations from guidelines.

Only 12 patients with clinically significant disorders (15 %) qualified as having been screened adequately according to the guidelines (Table 6.5.). Four children (5%) visited the child health centre at recommended ages and were correctly screened by the child health centre physician, but were not referred in spite of a positive test. The other

children were either not screened at recommended ages (10; 12%), or not correctly screened by the child health centre physician (22; 27%) or both (34; 41%), including the 7 children who never have visited the child health centre.

Table 6.6.
Causes of deviation from guidelines for screening procedures

Screening history	
Adequately screened:	
• screening at recommended ages, correctly performed and referred in case of a positive test result	12 (15%)
Inadequately screened:	
• screening at recommended ages, correctly performed but ***not referred in spite of a positive test result***	4 (5%)
• screening ***not at recommended ages***, though correctly performed	10 (12%)
• screening at recommended ages, but ***not correctly performed***	22 (27%)
• screening both ***not at recommended ages*** and ***not correctly performed***	34 (41%)
Total	82 (100%)

6.4 Discussion

The incidence of congenital heart malformations in the Netherlands is estimated at 0.8%[9]. Half of these cases are likely to be diagnosed before the age of 1 month[8]. These data coincide with the incidence rate of 0.38% for congenital heart malformations in children aged from 1 month until 4 years found in this study.

Considering Table 2, we estimate that under the actual screening regime in the south-west of the Netherlands, over a period of two years 126 patients with a congenital heart malformation will not be detected by child health centre physicians but by others (false-negatives). 1082 children will be referred for a congenital heart malformation by child health centre physicians, although further clinical assessment will fail to reveal such disorders (false-positives). If all children were screened adequately, it is estimated that the number of false-negatives would be reduced to (4/36)x290=32. Whether such an improvement will change the false positive rate is difficult to predict and no estimates can be based on the present data. Distress caused by false-positive test results is generally considered to be less severe than distress and adverse health effects caused by false-negative test results[7]. For this reason and in the light of the substantial reduction in numbers of false-negatives, a considerable increase in the number of false-positives would be required to neutralise the positive effects of such a change in policy. If for example the relation between the harm caused by false-negative and false-positive test results is expressed as a ratio of 10:1, the number of

false-positives will almost have to be doubled to 1082+((126-32)x10)=2022 to neutralise the effect of the reduction of false-negatives.

From a methodological point of view the most appropriate design to evaluate potential benefits of screening is a Randomised Controlled Trial (RCT). Should practical and ethical grounds render a RCT not feasible for evaluating a screening programme, which is already established and running, observational designs must be resorted to, meticulously considering possible sources of confounding[7].
A patient follow-up design is used in our study, in which the determinants (screening and detection history) are established retrospectively and the outcome measure (in time/too late) prospectively. In order to use this design, it is essential that treatment for the disorder under discussion can be safely postponed until the disease has progressed up to a stage in which spontaneous resolution can no longer be expected. Consequently, overestimation of the positive effects of screening as result of over-treatment of regressive disorders can be avoided. The management approach in modern paediatric cardiology is cautiously expectant. The decision to treat is always postponed until hemodynamic complications are judged to be inevitable in the short or longer run. Given the nature of the disorders under discussion (relatively large anatomical defects) and the extensive research data on the natural history, paediatric cardiologists may be assumed to be sufficiently reliable in their prognosis of the natural course[20-23].
The differences between adequately and inadequately screened patients may partly be induced by selection bias. If we presume that after correction for severity this bias will be of little consequence, we may conclude that adequately screened children are better off than those inadequately screened and that increasing the proportion of adequately screened children will reduce the incidence of haemodynamic complications from congenital heart malformations. Inadequate screening is a result of both insufficient attendance by parents and incorrect performance by child health centre physicians. We are convinced that both aspects can be improved by health education and management provisions.

6.5 Conclusion.

The present study indicates that systematic screening for congenital heart malformation in Child health centres in the Netherlands contributes to the timely detection and treatment of these disorders. The actual yield of the programme, however, is far from optimal, and the screening attendance and performance should be improved. Optimisation of screening participation and performance may improve screening considerably, resulting in timely treatment of most patients.

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CHAPTER 7

Factors that determine the effectiveness of screening for congenital heart malformations in child health centres

Abstract.

Background
Children with a clinically significant congenital heart malformation who are adequately screened at child health centres, have better chances of favourable outcomes than inadequately screened children. The actual yield of current screening activities, however, is far from optimal. In this study factors that determine the effectiveness of screening for congenital heart malformations at child health centres are identified and recommendations for the optimisation of the screening programme are formulated.

Methods
Eighty-two consecutive patients, aged between 32 days and 4 years, presented at Sophia Children's Hospital Rotterdam during a period of two years with a clinically significant congenital heart malformation were included in this study. Paediatric cardiologists established whether these patients were diagnosed before or after hemodynamic complications had developed ("in time" versus "too late"). Parents and child health centre physicians were interviewed in order to establish the screening, detection and referral history.

Results
Incomplete performance of the screening examination by child health centre physicians has a more significant impact on the occurrence of delayed diagnoses than failure of parents to adhere to the complete visit schedule. Adequate screening advances detection of congenital heart malformations. In 25% of the patients diagnosed "too late" the occurrence of complications was preceded by a prolonged interval between detection and diagnosis, which was predominantly caused by delay on the part of general practitioners and general paediatricians. Screening is probably neither effective in swiftly deteriorating nor in slowly progressive diseases, but may be quite successful in a relatively large group of patients with disorders progressing at a medium pace. In only 7 out of 39 patients diagnosed "too late", no avoidable cause for an adverse outcome could be indicated at all. This suggests that a considerable improvement of the prevention of complications of congenital heart malformations can be acquired.

Conclusion
To optimise the yield of the screening programme an improvement of the performance of the child health centre physicians and co-operation of all other physicians involved in reducing the time between referral and diagnosis are required.

7. Factors that determine the effectiveness of screening for congenital heart malformations in child health centres.

7.1 Introduction.

Screening for congenital heart malformations is common practice in child health care in several countries[1-3]. Evaluations of this practice, however, are scarce. In Chapter 6 we estimated the test properties of such a screening programme in the south-west of the Netherlands and we demonstrated that adequately screened patients have a better chance of being diagnosed "in time", i.e. before hemodynamic complications arise, than inadequately screened patients. The actual yield of the present screening programme, however, is far from optimal[4]. In this chapter several factors determining screening effectiveness are identified and recommendations for the optimisation of the screening policy are formulated. Four topics will be addressed:

Contribution of screening attendance and performance.

The adequacy of the screening is determined by both the attendance of the parents and the performance of the physicians. We will estimate the contribution of these two factors to the effectiveness of the screening programme separately. We will subsequently demonstrate how the different elements of the screening protocol contributed to the referral of the patients.

Interaction between adequacy of screening and severity of the disorder.

Adequate screening is supposed to lead to diagnosis before the occurrence of complications as a result of advancing the detection of the disorder[5]. However, for congenital heart malformations, severity of the disorder is probably the most important factor affecting both the risk of complications and the age at first referral and diagnosis[6]. We will clarify the influence of adequacy of screening as well as severity of the disorder on the outcome of the screening process.

Interval between referral and diagnosis.

The interval between first referral and diagnosis of a disorder may also be related to the outcome of the screening process. A prolonged interval due to delay on the part of either doctor or patient could increase the probability of an adverse outcome[7]. However, if disorders are detected after complications have already occurred, the physicians involved will be inclined to speed up referral procedures. Hence, in such cases adverse outcomes will be accompanied by short intervals. We will evaluate to what extent both interactions occurred in our study population. We will subsequently demonstrate how patients' and doctors' delay contributed to the duration of these intervals.

General impact of screening.
We will estimate to what extent the screening programme could be indicated as a possible cause of diagnosis before ("in time"), and inadequate screening as a possible cause of diagnosis after the occurrence of complications ("too late").

7.2 Methods

Subjects:
This study comprised all patients presented at the Sophia Children's Hospital Rotterdam, who met the following conditions:

- First cardiological consultation took place between 11-04-94 and 11-04-96.
- Children were resident in the south-west of the Netherlands, more specifically the area from which by national agreement between paediatric centres all children with cardiovascular disorders are referred to Sophia Children's Hospital.
- Children were aged between 32 days and 4 years.
- They had clinically significant congenital malformations of the heart or great blood vessels. Malformations were indicated as clinically significant if they were qualified for therapeutic intervention within 9 months after the first diagnosis by the paediatric cardiologist.
- Parents had been informed and consented to their children's participation in the study.

Parents of 1142 children were approached. In five cases parents refused to participate. Of all remaining children 82 met all other conditions.

Data collection and definition of variables:
In order to establish the screening history, the child health care physicians of all the patients were approached for a structured interview. The first author, who was not informed about the nature and severity of the disorder, performed all interviews. Questions were asked about the doctor's normal screening routine and subsequently about the actual procedure in this particular case.
Screening history was classified as *"adequate"* if:

- Prior to the first cardiological consultation the standard visit schedule had been *attended in full*, which includes at least: one visit before the age of 35 days, one in the age interval between 35 and 95 days (first DPTP-Hib-vaccination), one in the age interval between 3 and 14 month (MMR-vaccination) and subsequently one visit every year until the age of 4 years, and
- During all these visits the child health centre physician *performed a complete examination*, comprising at least: auscultation of the thorax, judgement of skin colour, size of the liver and weight gain, asking questions

aimed at assessing the child's exercise tolerance, and referral of the child as soon as one of the following symptoms or comninations was observed :

- heart murmur classified by the physician as "suspect"
- central cyanosis
- enlarged liver
- combination of heart murmur classified by the physician as "non-suspect" and weight gain classified by the physician as "insufficient"
- combination of heart murmur classified by the physician as "non-suspect" and anamnestic clues for decreased exercise tolerance.
- combination of weight gain classified by the physician as "insufficient" and anamnestic clues for decreased exercise tolerance

Screening history was either classified as "adequate" or as "inadequate".
In order to establish when and how their child's disorder was detected, and the course of the referral procedure, parents were interviewed by a nurse at the first cardiological consultation. If necessary, additional information was collected from child health centre physicians, general practitioners and specialists.
The first referral was considered to have taken place as soon as any physician started referral for congenital heart disease for the first time. The first cardiological consultation was taken as date of diagnosis. An interval between first referral and diagnosis of 4 weeks or less was considered acceptable. Longer intervals were classified as "prolonged".
Before diagnosis by the paediatric cardiologist, the child may already have been examined by three other physicians: the child health centre physician, the general practitioner and the (general) paediatrician. The interval between first referral and diagnosis is therefore subdivided in three subintervals: between referral by the child health centre physician and the visit to the general practitioner, between the visits to the general practitioner and the paediatrician and between the visits to the paediatrician and the paediatric cardiologist. In the Netherlands patients themselves determine whether and when they visit the general practitioner. The general practitioner determines whether and when a clinical specialist should be consulted. The specialist may subsequently call in the help of a super-specialist, like a paediatric cardiologist. So the first subinterval is related to delay on the part of the patient the other two subintervals are mainly related to doctor's delay.
To establish whether diagnosis took place after or before hemodynamic complications had occurred ("too late" versus "in time"), two paediatric cardiologists each independently filled in a questionnaire addressing the following aspects:

- Extent of heart failure, resulting from pressure- or volume-load ("none", "moderate", "serious", "very serious").
- Degree of hypoxaemia ("none", "moderate", "serious", "very serious").
- Risk of deterioration.
- Estimated duration of symptoms.

In cases where the answers of these two doctors failed to agree a third colleague was asked to make the final judgement.
Diagnosis was counted as having been established after the occurrence of complications ("too late") if

- heart failure or hypoxemia was classified as "serious" or "very serious", or
- heart failure or hypoxemia was classified as "moderate" with a considerable risk for deterioration and the symptoms estimated to exist for over 1 month.

All other disorders were considered to have been diagnosed "in time".

In the same questionnaire paediatric cardiologists were asked to rank the severity of the malformation as "moderate", "severe" or "very severe".

To estimate the general impact of the current screening activities, patients were classified into four categories:

- *"Too late", not due to an incompletely attended or performed screening*: first referred before reaching first screening age or between screening ages after a completely performed screening with a negative test result. (This implies that for this analysis we consider a false negative test result after a completely performed screening examination, as a result of the test properties inherent to this kind of screening, and at present not amenable to further improvement)
- *"Too late", possibly due to an incompletely attended or performed screening*: first referred as a result of screening, which, however, was delayed due to incomplete attendance, or after an incompletely performed screening with a negative test result.
- *"In time", possibly due to screening*: first referred as a result of screening followed by a visit to the paediatric cardiologist within 28 days.
- *"In time", probably not due to screening*: first referred by others or as a result of screening followed by a visit to the paediatric cardiologist after 28 days.

Analysis
The influence of performance and attendance to the effect of screening are expressed in odds ratios established by logistic regression (see **Results**). Since severity of the disorder may induce length-bias, leading to overestimation of favourable effects of screening[4], these outcomes will be corrected for severity.

Geometric means of ages at first referral and diagnosis are established in several sub-groups and p-values for differences between these sub-groups are calculated on the basis of rank numbers. To evaluate the extent of differences, rates of geometric means are calculated, including 95% confidence intervals. Both distributions of age at first referral and diagnosis are non-normal, which can only partly be adjusted by using a logarithmic scale. Therefore the 95% confidential intervals, as calculated for the rates of geometric means, will not concur completely with the p-values calculated on the basis of rank numbers. As far as age distributions are concerned the latter must be considered as the most reliable in assessing the significance of differences between two groups[8]

7.3 Results:

Contribution of screening attendance and performance

Table 7.1 shows that incomplete screening examination by the child health centre physicians will significantly reduce the chance of being diagnosed "in time", if the parents visited the child health centre according to schedule (OR=0.13 95%CI: 0.02-0.69).

Table 7.1.

Influence of attendance by parents (a) and screening performance by child health centre physicians (p) on whether or not patients with congenital heart malformations were diagnosed "in time".

	in time	*too late*	*total*	*Odds Ratio's for being "in time". Category 1 is the reference value (95%CI)*	*Corrected for severity (95%CI)*
1. a+ p+	10	2	12	1.00	
2. a + p-	10	16	26	0.13 (0.02-0.69)	0.14 (0.02-0.85)
3. a- p+	3	3	6	0.20 (0.02-1.82)	0.26 (0.02-2.74)
4. a- p-	20	18	38	0.22 (0.04-1.15)	0.24 (0.04-1.30)
				Corrected for attendance	
1. p+	13	5	18	1.00	
2. p-	30	34	64	0.32 (0.10-1.04)	0.32 (0.09-1.10)
				Corrected for performance	
1. a+	20	18	38	1.00	
2. a-	23	21	44	1.20 (0.48-3.00)	1.19 (0.45-3.16)

Legends:
a+ = the standard CHC visit schedule was *attended* completely
a- = the standard CHC visit schedule was *attended* incompletely
p+ = performance by CHC-physicians of a complete investigation .
p- = performance by CHC-physicians of an incomplete investigation.

Incomplete examination seems to reduce this chance even regardless of whether the visits were made according to schedule (i.e. unchanged compared to the current practice), although in this case the odds ratio just lacks statistical significance (OR=0.32 95%CI: 0.10-1.04).
Incomplete attending by parents will not significantly reduce the chance of being diagnosed in time, neither if the physician performed complete examinations, nor regardless whether the physician did so. In the former case the odds ratio is low but evidently lacks statistical significance (OR=0.20 95%CI: 0.02-1.82); in the latter the odds ratio exceeds 1, also lacking statistically significance (OR=1.20 CI: 0.48-3.00). Correction for severity of the disorder yielded no relevant change in the results.
All 41 patients, detected at the child health centre through a test result, which rated positive according to our definition, presented with a cardiac murmur audible at auscultation of the thorax. Thirty-nine murmurs were indicated as "suspect" of which 10 were combined with other positive test results such as central cyanosis (5) insufficient weight gain (6) clues for exercise intolerance (6) and an enlarged liver (1). Two murmurs were indicated as "non suspect", of which one was combined with insufficient weight gain and one with clues for decreased exercise tolerance. Child health centre physicians referred four patients after an observation, which rated negative according to our definition (only a murmur classified by the physician as "non-suspect" or only anamnestic clues for decreased exercise tolerance).

Interaction between adequacy of screening and severity of the disorder.
In Table 7.2. the differences in age at first referral and diagnosis are indicated between patients with moderate and (very) severe disorders, between adequately and inadequately screened patients and patients diagnosed "in time" and "too late".
Severe and very severe congenital heart malformations were on average referred at a significantly earlier age than moderate ones (2.3 versus 6.4 months). A similar difference was found for the ages at diagnosis (3.4 versus 7.4 months).
Adequately screened patients were on average referred at a significantly earlier age than inadequate screened ones (2.1 versus 3.7 months). This difference increased after correction for severity. They were also on average diagnosed at an earlier age (3.0 versus 4.8 months), although this difference was not statistically significant. After correction for severity however, the difference increases and only just lacks statistically significance.
Patients diagnosed "too late" were on average referred at an earlier age than patients diagnosed "in time"(2.8 versus 4.1). This difference is not statistically

Table 7.2.

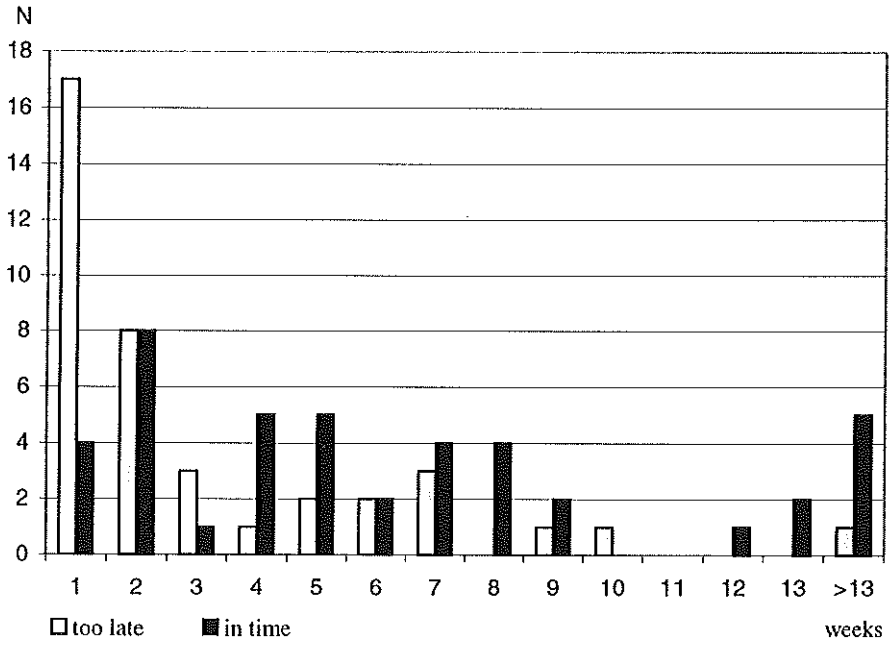
Ages at first referral and diagnosis.

	N	*geometric means in month*	*p-value difference 1 and 2 based on rank number*	*rate of geometric means (2/1) including 95%CI*	*standardised geometric means after correction for severity in month*	*p-value difference 1 and 2 based on rank number corrected for severity*	*rate of geometric means (2/1) including 95%CI corrected for severity*
Age at First Referral							
1 moderate	29	6.4	0.0014	0.38 (0.22-0.63)			
2 (very) severe	53	2.3					
1 adequately screened	12	2.1	0.048	1.76 (0.82-3.75)	1. 9	0.017	1.93 (0.94-3.78)
2 inadequately screened	70	3.7			3.7		
1 "in time"	43	4.1	0.32	0.68 (0.40-1.16)	3. 5	0.98	0.89 (0.51-1.52)
2 "too late"	39	2.8			3. 1		
Age at Diagnosis							
1 moderate	29	7.4	0.0076	0.45(0.28-0.72)			
2 (very) severe	53	3.4					
1 adequately screened	12	3.0	0.17	1.59 (0.82-3.10)	2.7	0.061	1.80 (0.96-3.40)
2 inadequately screened	70	4.8			4. 9		
1 "in time"	43	5.9	0.058	0.58 (0.63-0.92)	5.2	0.33	0.72 (0.45-1.16)
2 "too late"	39	3.4			3.8		

significant. After correction for severity, the difference decreased considerably. No reversal however was seen. As for the age at diagnosis the same trend is visible, although less outspoken.

Interval between first referral and diagnosis
In Figure 7.1. the distribution of the duration of the interval between first referral and diagnosis is shown for patients diagnosed "too late" and "in time". Most patients diagnosed "too late" visited the paediatric cardiologist rather soon after first referral.

Figure 7.1
Intervals between detection and diagnosis of patients, with congenital heart malformations diagnosed too late and in time by durations in weeks.



Forty-six percent of all patients diagnosed "too late" were examined by a paediatric cardiologist within 1 week and 66 % within 2 weeks after referral. However 25 % of the children diagnosed "too late" (n=10), arrived at the Sophia Children's Hospital after a prolonged interval (> 4 weeks).
Table 7.3. shows that the interval between the referral by the child health physician and the visit to the general practitioner contributed on average 5.4 days (15 %) to the total interval between first referral and diagnosis. The intervals between the visits to the general practitioner and the paediatrician and

Table 7. 3.

Mean duration in days of the interval between first referral and diagnosis of congenital heart malformations. Specification for sub-intervals between referral by the child health centre physician (CHC) and the first visit to the general practitioner (GP), between the first visits to the GP and the paediatrician and between the first visits to the paediatrician and the paediatric cardiologist."

	N	*child health centre - general practitioner*		*general practitioner - paediatrician*		*paediatrician – paediatric cardiologist*		*total*	
too late									
interval < 2 wk	25	0.0	1%	1.5	34%	2.8	65%	4.3	100%
interval 2-4 wk	4	0.0	0%	6.3	35%	11.5	65%	17.8	100%
interval 4-8 wk	7	1.4	4%	8.3	21%	29.7	75%	39.4	100%
interval > 8 wk	3	19.0	22%	33.0	38%	36.0	41%	88.0	100%
total	**39**	**1.7**	**9%**	**5.6**	**30%**	**11.1**	**60%**	**18.4**	**100%**
in time									
interval < 2 wk	12	0.3	4%	2.3	34%	4.3	63%	6.9	100%
interval 2-4 wk	6	1.3	6%	5.0	23%	15.8	71%	22.2	100%
interval 4-8 wk	15	3.0	7%	17.3	41%	21.7	52%	42.1	100%
interval > 8 wk	10	31.9	23%	38.4	28%	67.8	49%	138.1	100%
total	**43**	**8.7**	**17%**	**16.3**	**32%**	**26.8**	**52%**	**51.8**	**100%**
too late + in time									
interval < 2 wk	37	0.1	2%	1.8	34%	3.3	64%	5.2	100%
interval 2-4 wk	10	0.8	4%	5.5	27%	14.1	69%	20.4	100%
interval 4-8 wk	22	2.5	6%	14.5	35%	24.3	59%	41.2	100%
interval > 8 wk	13	28.9	23%	37.2	29%	60.5	48%	126.5	100%
total	**82**	**5.4**	**15%**	**11.2**	**31%**	**19.3**	**54%**	**35.9**	**100%**

between the visits to the paediatrician and the paediatric cardiologist contributed on average 11.2 days (31%) and 19.3 days (54%) respectively. The proportion of these contributions was not correlated with the duration of the total interval. Doctor's delay was also much in evidence in the 10 children diagnosed "too late" after a prolonged interval (4-8 + >8 weeks).
Delay on the part of the patients was only seen to make a substantial contribution in those cases in which the total interval was longer than 8 weeks, but still less than the delay after visits to the general practitioner and the paediatrician.

General impact.
Table 7.4. shows, that for 11 out of 39 patients diagnosed "too late", this adverse outcome could not be attributed to an incomplete attendance or incomplete examination by the child health centre physician. On average, these patients were detected at 2.0 months and diagnosed at 2.9 months. Four were confronted with a prolonged referral interval. Conversely, in the other 28 patients diagnosed "too late" the adverse outcome could possibly be attributed to inadequate attendance or screening performance, although prolonged interval between referral and diagnosis also occurred in 6 cases.

Table 7. 4.
General impact of screening.

	N	*n: interval >28 d*	*geometric mean age at detection*	*geometric mean age at diagnosis*
1. "too late" not due to incomplete attendance or performance of the screeningprogramme.	11	4	2.0	2.9
2. "too late" possibly due to incomplete attendance or performance of the screeningprogramme	28	6	3.1	3.6
3. "in time" possibly due to screening.	12	0	1.8	2.4
4. "in time" probably not due to screening	31	27	5.6	8.3

These 28 patients were on average detected and diagnosed later (respectively at 3.1 and 3.6 months) than the 12 patients diagnosed "in time", in whom this favourable outcome might be attributed to the screening (respectively 1.8 and 2.4 months). Differences in ages at referral or diagnosis between these relatively small groups are not statistically significant. In 31 patients, screening had not evidently contributed to the timely detection. These patients were referred at the average age of 5.6 months and diagnosed at 8.3 months. The majority (n=27) had a prolonged interval between first referral and diagnosis.

7.4 Discussion and conclusions.

From a methodological point of view the most appropriate design to evaluate potential benefits of screening is a Randomised Controlled Trial (RCT). Should practical and ethical grounds preclude a RCT of a screening programme already established and running, observational designs must be resorted to. In this project we used a partly retrospective, partly prospective patient-follow-up study. The most important condition for using such design is that treatment for the disorder under discussion can safely be postponed until the disease has progressed up to a stage in which spontaneous resolution can no longer be expected. Consequently, overestimation of screening effectiveness as a result of overtreatment of regressive disorders can be avoided. In Chapter 5 we discussed the applicability of this design for the evaluation of the screening programme presently under discussion.

Contribution of screening attendance and performance

A combination of a completely fulfilled screening protocol by child health centre physicians and attendance according to schedule by parents is the best guarantee for a timely diagnosis. A complete screening examination, however, is apparently the most significant determinant.

Detection by screening is predominantly a result of discovering heart murmurs by auscultation of the thorax. Most physicians, including those who do not perform all required tests, usually do perform auscultation. Probably physicians who are aware of what a complete screening examination entails and who are used to act accordingly, are also more aware of all possible implications of congenital heart disease and therefore more competent in discovering and interpreting murmurs at auscultation, than less skilled and meticulous colleagues.

Optimal training of child health centre physicians is probably the most important condition for improvement of the yield of the screening programme for congenital heart malformations. In the Netherlands, child health centre physicians, unlike School Health Care physicians, are not fully trained in social

paediatrics[9]. In the 10-days course, which trainee MD's are obliged to follow in order to be appointed as child health care physician, only one lecture is dedicated to paediatric cardiology[10]. Apparently this is not sufficient.
Health education aimed at optimising attendance by parents may also help to improve the yield. Parents should be stimulated to visit the consulting hours in time. Such measures, however, should not be expected to boost the yield of the programme to any major extent.

Interaction between adequacy of screening and severity of the disorder
An adequate screening programme is expected to advance the age of referral and diagnosis, to enable the necessary intervention procedure to be carried out before complications occur. Furthermore, patients with severe disorders are more likely to be detected at an early age as well as more likely to develop early complications than patients with less severe disorders. In our study population severity is obviously the most predominant determinant of the age at referral and diagnosis, as well as of the risk of complications. The result is that paradoxically patients diagnosed "too late" are on average referred and diagnosed at an earlier age than patients detected "in time", undoubtedly because of overrepresentation of rapidly deteriorating disorders among patients who were diagnosed "too late". As these differences are minimised after correction for severity, the operational definition for severity provides a useful, but not absolute indicator for speed of progression. After total correction for speed of progression, an inversion of the observed correlation would be expected.

Interval between first referral and diagnosis
Complications, already existing at the first visit to the paediatric cardiologist, are mostly found after short intervals. In these cases, physicians probably accelerated procedures, reacting to already emerging complications. Yet in a minority of at least 10 out of 39 patients who were diagnosed "too late" prolonged intervals between detection and diagnosis may also have contributed to the delayed diagnoses. Prolonged intervals are mostly due to delayed referrals from the GP to the paediatrician and prolonged review periods by this paediatrician before referral to the paediatric cardiologist.
Hence avoiding delay on the part of general practitioners and paediatricians may contribute to the improvement of the prevention programme. In principal general practitioners are neither better equipped for, nor more experienced in detection of congenital heart malformation than child health centre physicians. This implies that after a child health centre physician has referred a child with a positive screening test, the general practitioner, who is in the Netherlands the official "gatekeeper" for hospital and outpatient care[11], is confronted with a

very difficult task. Leaving the general practitioner out the referral sequence for these particular diseases appears to be recommendable. Such an arrangement, however, would be contrary to the conventions of the Dutch health system[10].
General paediatricians should certainly be competent to anticipate the course of congenital heart disease adequately, using ultrasound and ECG facilities. Considering the large numbers of false-positive screening test results and of children with non-progressive disorders[4], it is also very advisable that they do so , if only to prevent overburdening of high care centres. Nevertheless in some of our cases children arrived "too late" at the paediatric cardiologist after a long review period with the general paediatrician.

General impact of screening.
Since patients diagnosed "too late", not due to adequate screening, are detected and diagnosed at a rather early age, accelerated deterioration is probably the predominant cause for the occurrence of complications in these cases. In 4 of these cases, however, a prolonged referral interval may also have played a role. This may also be the case in 6 patients in whom the delayed diagnosis could possibly be attributed to inadequate screening. Patients diagnosed "too late" possibly because of inadequate screening seem to be referred and diagnosed at an older age than those patients whose timely diagnosis may have been due to the screening programme. The patients in whom screening did not contribute to avoiding complications probably had slowly progressive disorders. Apparently in most of these cases neither a delayed detection and diagnosis nor a prolonged interval between the two had an unfavourable effect on the outcome.
These findings suggest that screening for congenital heart malformations, although neither effective in swiftly deteriorating diseases nor in slowly progressive ones, is quite successful in the relatively large middle group of patients with disorders progressing at a medium rate.
In only 7 out of 39 patients diagnosed "too late", no avoidable cause for an adverse outcome could be indicated at all. This suggests that a considerable improvement of the prevention of complications of congenital heart malformations can be acquired. The most important condition for this potential improvement is, however, that performance of child health care physicians and all other physicians who consecutively play a part in this prevention programme be optimised.

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CHAPTER 8

Two-year follow-up effect evaluation of screening for congenital heart malformations in child health centres.

Abstract

Objective

The chance of diagnosing patients with congenital heart malformations "in time" is increased by adequate screening at child health centres. This is concluded from the screening evaluation study based on the clinical judgement of paediatric cardiologists at the first cardiological consultation presented in Chapter 6. In this chapter the follow-up results of this study are presented, using occurrence and duration of haemodynamic complications, health status and mortality as outcome measures

Methods

The initial patient follow-up study, including 82 patients, was extended by 2 years. Data on complications and mortality were gathered by investigation of hospital files. General and functional health status were assessed by the Dutch versions of the "RAND general health rating index for children" and the 'Functional Status II(R) questionnaire'.

Results

Patients diagnosed "in time" proved less likely to develop heart failure (OR: 0.30, 95%CI: 0.11 - 0.76) and hypoxemia (OR: 0.03, 95%CI: 0.004 - 0.27) than patients diagnosed "too late". No preventive effect of adequate screening versus inadequate screening was found for heart failure. For hypoxemia, however, such an effect is evident (OR: 0.00, 95%CI: 0.00 – 0.78). There are no significant differences in general or functional health status after two years between patients diagnosed "in time" and "too late" nor between "adequately" and "inadequately" screened patients. In one out of six deceased patients death might have been prevented by screening.

Conclusion

Timely diagnosis of congenital heart disease leads to fewer haemodynamic complications during the 2 years following the diagnosis. Adequate screening is effective in preventing hypoxemia. Screening has no influence on the ultimate health status 2 years after diagnosis. Death might occasionally be prevented by screening.

8. Two-year follow-up effect evaluation of screening for congenital heart malformations in child health centres.

8.1. Introduction

Effect evaluations of screening for clinically significant congenital heart malformations in preventive child health care are very scarce. In Chapter 6, however, we demonstrated that patients with these disorders are significantly more likely to be diagnosed "in time" after adequate screening at a child health centre than similar patients who were not or inadequately screened[1]. This evaluation was based on the clinical judgement of the paediatric cardiologist at the first cardiological consultation. In this chapter we present the follow-up results of this study with respect to a period of two years after that consultation. As outcome measures we used occurrence and duration of haemodynamic complications, health status and mortality. Since death was relatively rare in the study group, a valid evaluation of the influence of screening on mortality was not possible. Mortality was therefore evaluated in a descriptive way. We addressed the following questions:

1. What differences in occurrence and duration of episodes of heart failure and hypoxemia were seen, during the two-year follow-up period, between patients diagnosed "in time" and "too late", and between adequately and inadequately screened patients?
2. What were the differences in health status after 2 years between these categories?
3. How many children participating in this study died since the first cardiological consultation; were these deaths connected with the congenital heart malformations and was inadequate screening a possible cause of these deaths?

8.2. Methods

Subjects

The study comprised all patients presented at the Sophia Children's Hospital Rotterdam, who met the following conditions:

- First cardiological consultation took place between 11-04-1994 and 11-04-1996.
- Children were resident in the south-west of the Netherlands, more specifically the area, from which by national agreement between paediatric centres all children with cardiovascular disorders are referred to Sophia Children's Hospital.
- Children were aged between 32 days and 4 years (the first screening age at the child health centre is 4 weeks, the last 3 years and 9 months).

- They had clinically significant congenital malformations of the heart or great blood vessels. Malformations were indicated as clinically significant if they were qualified for therapeutic intervention within 9 months after the first diagnosis by the paediatric cardiologist.
- Parents had been informed and consented to their children's participation in the study.

Data collection and definition of variables in the initial study:
"Too late" or "in time"
To establish whether diagnosis took place "too late" or "in time", two paediatric cardiologists each independently filled in a questionnaire at the first visit to the department of paediatric cardiology addressing the following aspects:

- Extent of heart failure, resulting from pressure- or volume-load ("none", "moderate", "serious", "very serious")
- Extent of hypoxaemia ("none", "moderate", "serious", "very serious")
- Risk of deterioration.
- Estimated duration of symptoms.

In cases where the answers of these two doctors failed to agree a third colleague was asked to make the final judgement. Diagnosis was counted as having been established "too late" if

- heart failure or hypoxemia was classified as "serious" or "very serious", or
- heart failure or hypoxemia was classified as "moderate" with a considerable risk for deterioration and the symptoms were estimated to have been present for over 1 month.

All other disorders were considered to have been diagnosed "in time".

Screening history
In order to establish the screening history, the child health care physicians of all the patients were approached for a structured interview. The first author, who was not informed about the nature and severity of the disorder, performed all interviews. Questions were asked about the doctor's normal screening routine and subsequently about the actual procedure in this particular case.
Screening history was classified as *"adequate"* if:

- Prior to the first cardiological consultation the standard visit schedule had been attended in full, which includes at least: one visit before the age of 35 days, one in the age interval between 35 and 95 days (first DPTP-Hib-vaccination), one in the age interval between 3 and 14 month (MMR-vaccination) and subsequently one visit every year until the age of 4 years, and

- During all these visits the child health centre physician performed a complete examination, comprising at least: auscultation of the thorax, judgement of colour, size of the liver and weight gain, asking questions aimed at assessing the child's exercise tolerance, and referral of the child as soon as one of the following symptoms or combinations was observed :
  - heart murmur classified by the physician as "suspect"
  - central cyanosis
  - enlarged liver
  - combination of heart murmur classified by the physician as "non-suspect" and weight gain classified by the physician as "insufficient"
  - combination of heart murmur classified by the physician as "non-suspect" and anamnestic clues for decreased exercise tolerance.
  - combination of weight gain classified by the physician as "insufficient" and anamnestic clues for decreased exercise tolerance

Screening history was either classified as "adequate" or as "inadequate".

Data collection and definition of variables during the two-year follow-up period:

Occurrence of complications

In order to establish the occurrence of episodes of heart failure and hypoxemia during the two years following the first visit to the paediatric cardiologist, the medical files of all patients were examined. A patient was considered to have gone through an episode of heart failure when treatment with diuretics was considered to be necessary and through an episode of hypoxemia when symptoms like cyanosis of skin or mucosa were observed.

Duration of complications

The duration of each episode in days was calculated from the onset even if this dated from before the first visit to the paediatric cardiologist. In that case it had to be estimated partly on the basis of the medical history.

Health status

At least two years after the first visit to the paediatric cardiologist, a paediatric nurse (I Juttmann-Punt) gathered data on the health status of each child, in a telephone interview of one of the parents. Two health status measures were used:

1. The Dutch version of the "RAND general health rating index for children", a questionnaire to measure the general health of children, as perceived by the parent, from 0 to 12 years. This questionnaire contains 7 questions, which

are presented in Appendix 1. (original US version) The result is presented in a score from 0 (minimal general health) to 32 (optimal general health).

2. The Dutch version of the Functional Status II (FSII-R), a questionnaire to measure the functional health status of children from 0 to 12 years, especially covering behavioural aspects. The outcome of this instrument indicates the decrease in functional health status, specifically attributable to the disease involved (in this case the congenital heart malformation). The questionnaire contains 14 questions, which are presented in Appendix 2. (original US version) Whenever the answer to a question indicates a decrease in functioning, an extra question is asked, to establish whether this decrease is considered by the parent to have been caused by the heart malformation. If such is not the case, the answer to the question will be considered to indicate a normal functioning. The result is presented in a score from 0 (minimal functional health status) until 100 (optimal functional health status).

Both measures were originally developed in the United States of America[2-6]. Both have recently been adapted into Dutch, following a standard procedure and validated in several Dutch patient groups and the general population by Post e.a[7, 8]. To facilitate the appraisal of the results of the present study, the Dutch norm scores for the general population as well as for children with asthma will be presented along with these results.

Mortality

In order to establish whether the death of a child was related to the congenital heart malformation and whether such deaths possibly resulted from inadequate screening, the clinical information was re-evaluated by a social paediatrician (RE Juttmann) and a paediatric cardiologist (M Witsenburg).

Adjustment for length bias.

Evaluation of the effects of screening for congenital heart malformation has to deal with length bias[1, 9]. Compared to patients with moderate defects, patients with severe defects may be more at risk for developing complications or permanent impairment. These patients are also less likely to be diagnosed "in time" and to have undergone adequate screening before complications develop. In an observational evaluation of screening this may give rise to overestimation of the favourable effects of screening. To enable adjustment for length bias, paediatric cardiologists ranked the severity of the malformation as "moderate", "severe" or "very severe" at the first cardiological consultation.

8.3. Results.

Inclusion of the study group.

The initial study comprised 82 children. Six of these children had died since the first visit to the paediatric cardiologist. Detailed information from the written medical files of two of the deceased children was not available, so they had to be excluded from the evaluations on heart failure and hypoxemia, leaving a study group of 80 for this part of the study. However, since specific information on circumstances and causes of their deaths could be acquired from the computerised paediatric cardiological file, all deceased children could be included in the mortality evaluation.

Parents of all surviving children were approached by telephone for the health status interview. Sixty-one cases could be included. (forty-five mothers and sixteen fathers, total 81 %) One family refused to co-operate, two families had emigrated to another country, 10 families had moved to addresses unknown at the hospital or by the general practitioner, one family had no telephone and one family had an unlisted telephone number.

Occurrence of complications

Heart failure data are summarised in Table 8.1. During the follow-up period patients with disorders diagnosed "in time" needed significantly less diuretic treatment for heart failure than patients whose disorders had been diagnosed "too late". Patients who were adequately screened paradoxically seemed to need diuretic treatment for heart failure more frequently than inadequately screened patients. These odds ratios, however, lack statistical significance.

Table 8.1.

Odds ratios for developing heart failure during two years following the first visit to the paediatric cardiologist, depending on whether or not having been diagnosed "in time", and depending on whether or not having been screened adequately

	heart failure +	-	*total*	*Odds ratio*	*95% CI*	*Odds ratio corrected for severity*	*95%CI*
"in time"	19	23		0.30	0.11 - 0.76	0.32	0.12 – 0.90
"too late"	28	10	80				
adequately screened	7	4		1.27	0.34 - 4.74	1.37	0.34-5.57
inadequately screened	40	29	80				

The results concerning hypoxemia are summarised in Table 8.2. Of all the patients who developed symptoms of hypoxemia during the follow-up period, only one had a disorder diagnosed "in time" and none was adequately screened. Obviously, children with disorders diagnosed "in time" or adequately screened are therefore less likely to develop symptoms of hypoxemia than children who had been diagnosed "too late" or inadequately screened. For the comparison between adequately and inadequately screened children, however after correction for severity, power is insufficient to show statistical significance.

Table 8.2.
Odds ratios for developing hypoxemia during two years following the first visit to the paediatric cardiologist, depending on whether or not having been diagnosed "in time", and depending on whether or not having been screened adequately.

	hypoxemia		*total*	*Odds ratio*	*95% CI*	*Odds ratio corrected for severity*	*95%CI*
	+	-					
"in time"	1	41		0.03	0.004 - 0.27	0.04	0.004-0.34
"too late"	16	22	80				
adequately screened	0	11		0.00	0.00-0.78	0.00	0.00-1.47
inadequately screened	17	52	80				

Duration of episodes of complications
The mean total duration of episodes of heart failure was 187 days (min: 17, max: 793). Limited for episodes for which hospitalisation was necessary the mean duration was 43 days (min: 4, max: 112). The mean total duration of episodes of hypoxemia was 194 days (min: 3, max: 730). Limited for episodes for which hospitalisation was necessary the mean duration was 24 days (min: 3, max: 66). There were no statistically significant differences between patients diagnosed "in time" and "too late", nor between adequately and inadequately screened children.

Health status
The results of the health status interviews are presented in Table 8.3. The average general health status as reported by parents in the total study population, measured by the RAND-questionnaire is 24.0 in a scale from 0 (minimal general health) to 32 (optimal general health).

Table 8.3.
Results of health status interviews and health status norm scores for the Netherlands

		RAND: general health perceived by parents Range: 0 (minimal) -32 (optimal)			**FSII-R:** functional health attributable to congenital heart malformation Range: 0 (minimal) - 100 (optimal)		
	N	*Mean*	*SD*	*Median*	*Mean*	*SD*	*Median*
Interviews							
"'in time"	29	23.5	4.0	23.3	94.6	9.8	98.3
"too late"	32	24.5	3.8	24.7	94.0	10.6	98.1
adequately screened	8	21.9	4.2	21.5	96.0	8.8	98.0
inadequately screened	53	24.3	3.7	23.9	94.0	10.3	98.1
moderate	20	24.6	4.2	25.0	92.9	11.4	97.5
severe	31	23.7	3.9	23.6	94.6	8.6	98.1
very severe	10	24.0	3.9	23.8	96.1	12.4	96.1
Total	61	24.0	3.9	23.8	94.3	10.1	98.3
Norm scores *							
General Population	79	26.4	4.0	27.0	95.4	9.1	100.0
Children with asthma	124	22.4	5.4	23.0	87.5	16.2	92.9

* Based on Post e.a. [7] and Post e.a. [8]

This score is approximately halfway between the mean RAND norm scores for healthy children (26.4) and children with asthma (22.4) in the Netherlands.
The average disease-related functional health status in the study population, as reported by parents, measured by the FSII-R questionnaire was 94.3 in a scale from 0 (minimal functional health status) to 100 (optimal functional health status). This score virtually equals the mean score among healthy children (95.4) and exceeds the mean score in the asthma group (87.5).
Neither measure reveals significant differences between patients diagnosed "in time" and "too late" or between "adequately" and "inadequately" screened patients. Nor does either measure show significant differences between patients with moderate, severe or very severe malformations, although the mean FSII-R score seems to increase with severity.

Mortality
The results of the mortality evaluation are presented in Table 8.4. Patients are indicated with their unique study identification number.
In three of the six deaths the congenital heart malformation was the immediate cause of death. In one of these three cases (700), the congenital heart malformation was part of a syndrome (Pseudo Trisomy 18) incompatible with life. Another of these patients (79), had very complicated multiple malformations, which, although detected and diagnosed before the first occurrence of complications, slowly deteriorated, ultimately resulting in death after 3 years and 7 months and in spite of 2 surgical interventions. This was also the only child who had been diagnosed "in time" and yet developed symptoms of hypoxemia during the follow-up period. Only in one case (759) could death possibly be attributed to inadequate screening. This child was first screened at the age of 41 days, while screening at 4 weeks (at the latest at 35 days) is recommended. Even though on that occasion the child presented with an obvious central cyanosis, and the Child Health Centre-physician declared the screening test to be "positive", the child was not referred because of a coming control visit to the paediatrician, who had performed the neonatal investigation. During this visit 8 days later this paediatrician had the child transferred to Sophia Childrens'Hospital without delay. Although in this case again, the patient had a very complicated heart malformation, with hindsight we believe that after a timely and rapid referral, immediate surgical intervention might have provided a reasonable chance for survival.
In three patients, congenital heart disease was not the immediate cause of death. In two of these cases (712 and 811) children died because of other fatal disorders. In one case (86) the patient died, after an adequate screening, timely diagnosis and initially successful surgical intervention, from endocarditis.

Table 8.4.
Characteristics deceased patients

No	*Congenital Heart Malformation*	*severity*	*comorbidity*	*adequately screened?*	*1th referral by CHC?*	*age at diagnosis*	*in time/ too late*	*age at death*	*death by CHM?*	*death avoidable by screening?*
79	Tricuspidal atresia Ventricular septal defect Wolff-Parkinson-White syndrome Mitral valve insufficiency	vs		no p-	yes	36 d	in time	3y 7m	yes	no
86	Aortic valve stenosis Preductal aortic coarctation	s	Endocarditis	yes	yes	41 d	in time	1y 5m	no	no
700	Pulmonalis atresia Tricuspidal atresia Ventricular septal defect Underdeveloped right ventricle Mono-atrium with total anomalous connection of pulmonary veins	vs	Pseudo Trisomy 18	no a-	no	36d	too late	41 d	yes	no
712	Atrium septal defect Small muscular ventricular septal defect	m	Carbohydrate deficient glycoprotein syndrom Congenital liver cirrhosis	no a-	no	48 d	in time	2y 6m	no	no
759	Partial anomalous connection of pulmonary veins Patent oval foramen Pulmonary valve and trunk atresia with confluent pulmonary arteriae Coronary fistula to right ventricle	vs		no a- p-	no	49 d	too late	62 d	yes	yes
811	Atrial septum defect II Left aortic arch with vascular ring and right ligamentum arteriosum	s	Cornelia de Lange- or Rubinstein-Taybi syndrom	no a-	no	46 d	in time	9m	no	no

Legenda:
m = moderate
s = severe
vs = very severe
a- = insufficient attendance by parents
p- = inadequate performance by child health centre physician
CHC = Child health centre
CHM = Congenital heart malformation

8.4. Discussion

Methodology

From a methodological point of view a patient follow-up study, of the kind used in this project, is not the most appropriate design to evaluate potential benefits of screening. Generally a Randomised Controlled Trial (RCT), with "screening" offered in the one arm and "no screening" in the other, is considered to be the optimal choice for such study[10]. However, should practical and ethical grounds preclude an RCT of a screening programme already established and running, observational designs must be resorted to, meticulously considering possible sources of confounding[11]. The most important condition for using a patient follow-up study is that treatment for the disorder under discussion must be able to be postponed safely until the disease has progressed up to a stage in which spontaneous resolution can no longer be expected. Consequently, overestimation of screening effectiveness as a result of over-treatment of regressive disorders can be avoided. We discussed the applicability of this design for the evaluation of the screening for congenital heart disease in Chapter 5.

The measurement of child health status by questionnaire is a relatively recent development. Although we used validated standard measures, relatively few data are available about the power of these measures to adequately detect relatively small differences between relatively healthy groups of children. However, given the fact that the measures discriminated well between healthy children and children with asthma, we think we can trust our results.

Results

Judgement by paediatric cardiologists is generally reliable in predicting, whether or not haemodynamic complications can be prevented by therapeutic interventions. During a follow-up period of 2 years, complications were more successfully prevented in patients who were, according to the paediatric cardiologist, diagnosed "in time", than in patients diagnosed "too late". Since adequately screened children are more likely to be diagnosed "in time" than inadequately screened children, these study results indicate that screening is effective in preventing these complications. The ultimate test for this, however, is the assessment of the effect of screening itself on the occurrence of hymodynamic complications. No preventive effect of adequate versus inadequate screening could be demonstrated for heart failure. For hypoxemia, however, such an effect appears to be evident. Generally spoken, hypoxemia is the more serious of both complications. Heart failure will, if treatment is chronically postponed, deteriorate and in several cases eventually lead to hypoxemia.

Screening, however, had no consequences for the ultimate general and functional health status of surviving patients with congenital heart malformations. After the correction of their defect, patients with clinically significant congenital heart malformations apparently do quite well, regardless of their screening and detection history or even the severity of their malformation. After two years, during which these patients were generally treated with surgery or catheter intervention, their general health status seemed to be slightly less than normal and their functional health status seemed to be satisfactory, compared to data from the validation studies of the Dutch version of the used questionnaires[7, 8]

We evaluated screening for congenital heart malformations at the outcome level and found some evidence for a positive, though not protracted, effect of screening. However, important benefits of screening may also be found at the level of so called process-measures[12]. For example, children with cardiac malformations and their parents may go through a less stressful procedure around the time of diagnosis and treatment if the disorders are screen-detected than in cases in which the disorder is detected due to parents' worries about symptoms. Such process-evaluation was not subject of our study, but might be advisable in future studies.

8.5. Conclusion

Timely diagnosis of congenital heart disease leads to fewer, though not to shorter episodes of haemodynamic complications during 2 years following the diagnosis. Adequate screening at child health centres is effective in preventing episodes of hypoxemia, which in a serious expression may last from several days to approximately 2 months. There is, however, no long-term effect of screening on the general and functional health status of patients with congenital heart malformations. Once their malformations have been corrected by modern paediatric cardiological and surgical management, the health of these patients seems generally to be quite satisfactory. Whether adequate screening may also substantially contribute to mortality reduction could not be established. In one out of six deceased patients, we consider death to have been preventable by adequate screening. We conclude that screening for congenital heart malformations occasionally may prevent death.

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CHAPTER 9

Costs and savings in secondary prevention of complications of congenital heart disease in child health centres

Abstract

Objective
This chapter evaluates the economic aspects of screening for congenital heart malformations at child health centres.

Methods
The study applies for the south-west of the Netherlands for two years, encompassing a population in which 75441 children were born. Estimates of the costs are mostly based on Dutch health care fees.

Results
The costs expended on relevant conditions amount to over 5 million Dutch guilders, of which 79 % are attributable to diagnosis and therapy, 13 % to the screening and 8 % to referrals resulting from screening. An average saving of Dfl 5649,- may be expected from preventing a disorder to be diagnosed "too late". As it is performed today the costs per child benefiting from screening are estimated at Dfl 121100,-. Were all children to be screened adequately, these costs would decrease to some Dfl 25265,-.

Conclusion
The expenditures on preventing complications of congenital heart malformations, amounting to over 20% of all costs made on relevant disorders, are currently not being optimally utilised. Improving screening procedures will, apart from better effectiveness, also upgrade the relation between the costs and the yield.

9. Costs and savings in secondary prevention of complications of congenital heart disease in child health centres

9.1. Introduction

Screening children for clinically significant congenital heart malformations between 1 month and 4 years of age at child health centres can be effective in preventing heamodynamic complications. This was concluded from the patient follow-up study in the south-west of the Netherlands presented in Chapter 6, in which the chance of these disorders being diagnosed too late to prevent heart failure or hypoxemia has been estimated for populations exposed to different screening regimes[1]. In this paper we will evaluate the economic aspects of this programme for secondary prevention, considering both costs and savings. In particular savings on the costs of urgent symptomatic treatment in paediatric intensive care units may be achieved by detecting congenital heart malformations before haemodynamic complications arise.

The questions addressed in this chapter are:

1. What health care costs are made for congenital heart malformations diagnosed between the ages of 1 month and 4 years? What expenditures are due to:
   - diagnosis and therapy for patients with clinically significant as well as clinically insignificant malformations,
   - screening tests in the whole population and,
   - referral procedures resulting from these screening tests?
2. To what extent do diagnostic and therapeutic costs for patients with a clinically significant congenital heart disease diagnosed "too late" differ from those for such patients diagnosed "in time"? How do costs of hospitalisation in paediatric intensive care units contribute to these differences?
3. What are the costs due to the preventive programme for each patient potentially benefiting from this programme as actually performed? What would they be if all patients were adequately screened following recently established guidelines[2] ?

9.2. Methods

Costs and saving will be calculated for a period of two years using data from children born in the south-west of the Netherlands (n=75441). All costs are calculated based on the price level of 1996.

Costs of diagnosis and therapy

To estimate diagnostic and therapeutic expenditures on patients with congenital heart malformations we used data from the study population of the patient follow-up study mentioned in the introduction[1]. All patients, who fulfilled the following conditions, were included in that study:

- First cardiological consultation at the Sophia Children's Hospital took place between 11-04-1994 and 11-04-1996.
- Children were aged between 32 days and 4 years.
- Children were resident in the south-west of the Netherlands, more specifically the area from which, by national agreement between paediatric centres, all children with cardiovascular disorders are referred to the Sophia Children's Hospital.
- Parents were informed and consented to their children's participation in the study.
- Children presented for the first time with a congenital anatomical heart malformation.

The study group thus comprised 290 patients. A malformation was defined as clinically significant when a decision to perform a therapeutic intervention was made within 9 months after the first cardiological consultation. Eighty-three patients satisfied that condition and 207 patients did not.

Estimates of the costs for the 83 patients with a clinically significant malformation were based on examination of hospital files of 80 patients. The hospital files of the other three patients were not available for analysis. Estimates of the costs for the 207 patients with clinically insignificant malformations were based on examination of hospital files of a random sample of 40.

These data were gathered for the two years following the first visit to the paediatric cardiologist. The following information was registered:

1. Out-patient Visits
2. Hospitalisation days at
   - Medium Care units
   - Intensive Care Units
3. Diagnostic procedures
   - X-thorax
   - electrocardiogram
   - twenty four hour electrocardiogram
   - ultra-sound investigation
   - transeosophagial ultra-sound investigation
   - diagnostic catheterisations.
4. Therapeutic procedures
   - surgical operations
   - interventional catheterisations
   - diuretic medication days.

Costs of medical procedures are based on Dutch health care fees[3,4]. In the Netherlands, an extensive fee system exists for the reimbursement of specialist costs and hospital costs in medical procedures. Costs of out-patient visits, intensive and medium care hospitalisation days are based on departmental data from the Sophia Children's Hospital, including employee salaries, consumables and supplies, housing and

maintenance, and overhead costs. Since both direct and indirect costs are included, these are integral unit costs. Costs of medication are based on the Dutch Pharmacotherapeutic Manual[5].

Costs of screening.
In the Netherlands, six screening examinations are recommended in the first four years of life[2,6]. In a window of two years, therefore, children undergo an average of 3 screenings. The screening is an integrated part of the periodical examination by the child health centre physician. During these fifteen minute visits doctors assess health chances since the previous visit, perform a physical examination, evaluate findings with the parents and contribute their part to the health education programme. We estimate the cardiovascular examination to take 1 minute of each visit. The health care costs were calculated on the basis of child health centre physicians' salaries[7] and the costs of overhead and accommodation established by the Rotterdam Homecare Foundation. (In the Netherlands, preschool child health care is part of private organisations for homecare) The total population screened during two years in the south west of the Netherlands is calculated on the basis of population statistics acquired from Statistic Netherlands.

Costs of referrals
We considered the consequences of a referral by a physician for a potential congenital heart malformation to be on average:

- one visit to the general practitioner
- one visit to a paediatrician
- one electrocardiogram and
- an ultra-sound investigation in one out of three cases.

The costs are calculated on the basis of fees[3,4]. The number of referrals in the south-west of the Netherlands during two years was estimated by the registered referrals for congenital heart malformations by Rotterdam child health centre physicians during the second half of 1996.

Differences between "too late" and "in time"
To determine whether patients were diagnosed "too late" or "in time" a questionnaire was filled in by the paediatric cardiologist in charge at the first cardiological consultation, in which the following aspects were assessed:

- Extent of heart failure, resulting from pressure- or volume-load ("none", "moderate", "serious", "very serious")
- Degree of hypoxaemia ("none", "moderate", "serious", "very serious")
- Risk of deterioration.
- Estimated duration of symptoms.

Another paediatric cardiologist was asked to give a second opinion by filling in an identical questionnaire independently. In case of differences between the answers of the two physicians, a third colleague was asked to make the final judgement.
Diagnosis is considered to have been established "too late" if

- heart failure or hypoxemia was classified as "serious" or "very serious", or
- heart failure or hypoxemia was classified as "moderate", the risk of deterioration was considered realistic and the symptoms were estimated to have existed for over 1 month.

All other disorders were considered to have been diagnosed "in time".
Whether a patient with a clinically significant congenital heart disease is diagnosed "too late" or "in time" is to a large extent determined by the severity of the disorder. Since severe disorders may generate more costs than moderate ones, this may lead to overestimation of the potential correlation between a delayed diagnosis and costs. To make it possible to adjust for this length bias paediatric cardiologists were also asked to appraise the severity of the disorder by opting for one of four qualifications: "trivial", "moderate", "severe" and "very severe".
The mean difference in costs of patients diagnosed "too late" and those diagnosed "in time" is calculated, broken down into intensive care costs and all other costs. Estimates are corrected for severity and 95% confidential intervals are calculated by means of linear regression analysis

Costs per patient benefiting from screening.
The number of children potentially benefiting from a prevention programme for congenital heart malformations, can be estimated as the difference between the numbers of patients diagnosed "too late" in a population exposed to the programme and in a population not exposed. The estimates of these numbers in the present study are based on the results of the patient follow-up study mentioned in Chapter 6. In this study the chance of congenital heart malformations being diagnosed too late to prevent haemodynamic complications has been estimated at 58 % for a population not exposed to screening. For a population exposed to screening as actually performed in the south-west of the Netherlands this chance has been estimated at 48 % and for a population adequately screened according to recent guidelines[2] at 17%. The number of children benefiting from the actual screening regime in two years in the south-west of the Netherlands is, therefore, estimated at (0.58-0,48) x 83 = 8. Were all patients to be screened in accordance with the guidelines this number would rise to an estimated (0.58-0.17) x 83 = 34
The costs of the screening programme are defined as the costs for all screening tests and for the referrals of patients with false-positive test results. The latter number was the total number of referrals in two years minus the number of patients with true positive referrals. To calculate the mean outcome of costs and savings for one child benefiting from screening, savings per child (the difference between average costs for

patients diagnosed "too late" and "in time") are subtracted from the costs per child. Finally, we estimated the results, for the case when intensification of the screening regime would increase the number of false-positives to 200% or to 400% respectively.

9.3. Results

The diagnostic and therapeutic expenditures on patients are specified in Table 9.1. In a period of two years, in the south-west of the Netherlands, almost over four million Dutch guilders were expended on diagnosis and therapy for patients with congenital heart malformations diagnosed between the ages of 1 month and 4 years. Costs of clinically insignificant disorders (4%) are modest compared to costs of clinically significant disorders (96%). Costs of out-patient visits (5 %) and diagnostic procedures (9%) are relatively small compared to those of hospital admissions (45 %) and therapeutic interventions (42%), including cardiac surgery.

Table 9.1.

Costs of diagnosis and therapy of patients with congenital heart malformations diagnosed between 1 month and 4 years of age throughout a period of two years in the south-west of the Netherlands in Dutch guilders

	clinically insignificant disorders, n=207			*clinically significant disorders n=83*			*total*	*%*
	average costs per patient	*(SD)*	*total costs*	*average costs per patient*	*(SD)*	*total costs*		
out-patient visits	492	(335)	101844	1225	(630)	101675	203519	5%
hospital admissions				22393	(26046)	1858619	1858619	45%
diagnostic procedures	240	(199)	49680	3698	(2783)	306851	356531	9%
therapeutic procedures				20753	(9831)	1722499	1722499	42%
total	732	(514)	151524	48069	(31186)	3989644	4141168	
%			4%			96%		100%

The total health care costs for these patients are summarised in Table 9.2. These costs amount to over 5 million Dutch guilders. Thirteen percent of all costs are to be attributed to the child health centre screening tests; eight percent to referrals resulting from screening.

Table 9.2.
Total costs of congenital heart malformations diagnosed between 1 month and 4 years of age in a period of two years in the south-west of the Netherlands in Dutch guilders.

	n	*mean costs for each patient*	*total costs*	*%*
costs of screening	75441	9,12	688022	13%
costs of referrals	1247	336,10	419116	8%
costs of diagnosis and therapy of clinically insignificant disorders	207	732.00	151524	3%
costs of diagnosis and therapy of clinically significant disorders	83	48068.00	3989644	76%
total			5248306	

As demonstrated in Table 9.3, the average costs for a patient diagnosed "too late" exceed by far the average costs for a patient diagnosed "in time". The difference is to a large extent to be attributed to the costs of hospitalisation in intensive care units. Restricted to intensive care costs the difference is statistically significant. After correction for severity, however, the 95% confidence interval just exceeds 0. The difference in the remaining costs is not statistically significant and is almost entirely to be attributed to an overrepresentation of severe and very severe disorders among patients diagnosed "too late". We conclude that after correction for severity a mean saving of Dfl 5649,- may be expected from preventing a disorder to be diagnosed "too late".

Table 9.3.
Comparison diagnostic and therapeutic costs of patients diagnosed "too late" and "in time" in Dutch guilders.

	too late	*in time*	*difference*	*(95%CI)*	*difference corrected for severity*	*(95%CI)*
n	38	42				
mean costs for each patient:						
• total costs	54035	42670	11365	(24904/ -2173)	5749	(19650/ -8061)
• intensive care costs	13465	5277	8188	(14590/ 1786)	5649	(12085/ -771)
• all other costs	40569	37393	3177	(1247/ -6131)	100	(9871/ -9670)

In table 9.4 the outcome of costs and savings due to the preventive programme for each patient benefiting from this programme is calculated. Health care expenditures to be attributed to the programme as actually performed in the south-west of the Netherlands for each child benefiting from it are estimated at Dfl 121100,-. Were all children to be screened according to guidelines this amount would reduce to Dfl 25265,-. If, as a result of intensifying the screening strategy, the number of false positive referrals were to double, this amount would increase to Dfl 35962,- , while a quadruple number of false-positive referrals would cause this amount to rice to Dfl 57354,-.

Table 9.4.
Costs and savings due to screening for each patient benefiting from screening in the present programme and if all patients were to be adequately screened in accordance with the guidelines (Dutch guilders)

	total costs	*costs for each child benefiting from screening*	
		actual screening n= 8	*adequate screening n=34*
costs screening tests	688022	82894	20218
costs false positive referrals	363996	43855	10696
savings intensive care		-5649	-5649
total		121100	25265
total if false positive referral = 200%			25265+10696=35962
total if false positive referral = 400%			25265+3x(10696)=57354

9.4. Discussion.

The establishment of fees for medical procedures in the Netherlands is the result of a continuous process of negotiations between professional organisations, health insurance organisations and the government agency for health care fees, which will not automatically correspond with real unit costs. Our establishment of costs for diagnostic and therapy procedures should therefore be considered the best possible estimation with the available data, rather than a precise assessment. Screening costs, however, are established on the basis of real salaries and overhead costs.

Although the costs per screening are modest, because of its mass character the total costs of the CHC-screening for congenital heart disease are substantial. When establishing these costs, we included costs to be attributed to the infrastructure. It

should be noticed that this infrastructure comprises a well-established health care system, also facilitating a lot of other highly appreciated child health care activities.
Differences in costs between patients diagnosed "too late" and "in time" are nearly entirely attributable to differences in intensive care hospitalisation days. Since we are exclusively dealing with patients with clinically significant disorders this finding is not surprising. All these children had major malformations, the vast majority of which required surgery or intervention cathetherisation. Such measures give rise to medium care hospitalisations, extended out-patient surveillance and repeated diagnostic procedures in all cases. Children diagnosed "too late", however, will have gone through periods of heart failure and hypoxemia more often. This will sometimes involve very serious symptoms. During such periods, these children will require treatment in intensive care units.
Improving the actual screening practice by increasing the test sensitivity to an optimal level will undoubtedly bring down the expenditures per patient benefiting from screening. Even if such a policy substantially increases the number of referrals on the basis of false-positive test results, these costs will still be less than the actual expenditures. In Chapter 7 we formulated several suggestions for such improvement, specially aiming at upgrading the performance of the physicians involved. The present results support these suggestions, especially since such an improvement will not necessarily generate extra costs.
Finally, it must be debated whether spending about Dfl 25000, - to prevent patients with congenital heart malformations from being diagnosed "too late" is worthwhile. The answer to this question is not straightforward. To answer this question, we must at least clarify the actual benefits gained by this screening programme and compare the costs and these benefits with those of other child health facilities.
The benefits gained by this screening can be expressed in terms of differences in mortality, morbidity and health status in the short and long run between patients diagnosed "in time" and "too late". These aspects were investigated in the extra 2 year follow-up study presented in Chapter 8.. This showed that for approximately Dfl 25000 per patient the main benefit of this screening programme is the prevention of episodes, varying from several days to 2 months, of serious hemodynamic complications, especially hypoxemia, for which often treatment in a paediatric intensive care unit is necessary.
Comparison of these costs and benefits with those of other child health care activities is difficult. Cost-effectiveness evaluations in child health care are very scarce. One of the few examples is the analysis of screening for perceptive hearing defects by the distraction test (Ewing screening)[8]. The diagnosis of such defects may be advanced by 1.5 years as a result of the screening, for approximately Dfl 65000 per patient. For this amount a substantial and possibly irreversible backlog in language development may be prevented.

Comparison of this example with the outcome of our study illustrates how difficult interpretations of these cost-effectiveness analyses are. Which of both preventive programmes is most worthwhile? It is generally recommended that all results from economic evaluation studies be expressed as costs per gained quality adjusted life year (QALY)[9]. However, this technique of cost-effectiveness evaluation was clearly developed for a clinical setting, and cannot simply be generalised to child health care. For instance, the problems of intergenerational effects are still unsolved. Only consequences for the patients themselves are taken into account, while in child health care it is essential to take consequences for the parents into consideration as well [10,11]. Moreover discounting long survival periods yields considerable problems for which there are no straightforward solutions. Hence researchers in the child health care field cannot easily follow present standard procedures for economic evaluation, but should present results in a way that is relevant for this specific health sector. This may lead to other outcome measures than costs per QALY gained. Such measures, however, have yet to be developed, presenting an important scientific challenge for research workers in this sector.

9.5. Conclusion

The considerable expenditures on the early detection of congenital heart malformations, amounting to over 20% of all cost made on relevant disorders, are presently not optimally spend in the south west of the Netherlands. Improvement of the performance of the programme will, apart from better effectiveness, also upgrade the relation between the costs and the yield of the screening programme.

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PART IV

CONCLUSIONS

CHAPTER 10

Conclusions

10. Conclusions

10.1. Conclusions on Background (Part I)

Preschool Child Health Care in the Netherlands is a very popular preventive programme, which is generally cherished as a precious achievement. Its scientific foundation, however, is far from complete. Four key organisations in Dutch Public Child Health Care have jointly set up a development project with as purpose to formulate a comprehensive research agenda for Child Health Care effect-evaluations for the next 10 years. Anticipating this project, this thesis is specifically aimed at the evaluation of screening for congenital heart malformations.

Secondary prevention programmes like screening cannot prevent congenital heart malformations themselves. To realise a reduction of the incidence of abnormal organogeneses and consequently the birth prevalence of these disorders, primary prevention strategies, aimed at etiological factors, should be resorted to. Since most of these factors are not well understood, such strategies are not yet feasible. Nevertheless, given the clinical qualities of congenital heart malformations, screening in child health care may potentially pay a substantial contribution to the optimal management of these disorders. Timely detection and subsequent intervention might prevent deterioration of these patients' condition and even death. The screening programme at the Dutch child health centres, however, has an important limitation that a neonatal screening is lacking. As the first screening is scheduled at 1 month of age, this programme will signally fail to cover those severe, fast-deteriorating conditions, which become symptomatic before that age.

Whether screening might have favourable consequences in the long run for a substantial number of patients is difficult to say. Current therapeutic interventions are so effective that the final outcome in a majority of the patients, even in those in whom hemodynamic complications did occur, may be quite favourable. To prevent or to shorten episodes of heart failure and hypoxemia must be considered to be the main purpose of child health care screening for congenital heart malformations. Prevention of endocarditis in surgical and dental patients may possibly be an additional benefit.

Although screening for congenital heart malformations is broadly advocated and actually applied on a large scale, effect evaluation of these activities is hitherto a virtually unexplored research field.

In screening evaluation the randomised controlled trial (RCT) is the only design to avoid virtually all sorts of bias. Whether second-best evaluation designs are worthwhile in situations where established practice and circumstantial evidence pointing towards at least some effectiveness of the intervention have rendered a randomised trial not feasible, depends on the quality of the circumstantial evidence and the chance of further improving the intervention. Since review of the available literature reveals large gaps in our knowledge of the effectiveness of screening

protocols in child health care, we believe that observational trials for evaluation of the benefits of these screenings are justified.
There are serious objections to the use of a patient follow-up design for screening evaluation studies, as is especially demonstrated for cancer screening. However, in child health care, circumstances and characteristics of disorders differ so much from those in cancer screening programmes that under strict conditions a patient follow-up design might be applicable. In screening for congenital hip dislocation and congenital heart disease, this design could therefore be an efficient alternative to the more customary designs for screening evaluation, such as a population follow-up study and a case control study.
A patient follow-up study offers the advantage of the availability of a study group directly from the patient population of for instance an academic hospital providing specialised medical care to a large area. The laboriously collection of data in the general population necessary in a population follow-up study can thus be avoided. A population follow-up study not based on randomisation may, moreover, be cursed with sources of contamination just as much as a patient follow-up study.
In principle bias may be avoided more successfully in a case-control evaluation of favourable effects of screening, than in a patient-follow-up study, even if the latter is conducted for the specific disorders and considering conditions and pitfalls as described in this paper. The patient-follow-up study, however is the more feasible design, may provide more supplementary information, and may still provide useful information on the screening effectiveness. Patient follow-up studies, as well as case-control studies, aim exclusively at estimating the intended favourable effects of screening and not at weighing advantages and disadvantages as arising from false positive and false negative tests. This requires additional data collection, which does not have to be very difficult.
The results of pilot trials for congenital hip dislocation and congenital heart disease suggest that more elaborate studies following this design are feasible and that both screenings might yield considerable benefits.

10.2 Answers to main questions.

Question 1:
Does screening for congenital heart malformations, as actually performed at Dutch child health centres, prevent adverse outcomes of these disorders in the short and long run? What would be the answer to this question, if all children were optimally screened?
Answer
By screening at child health centres, the number of patients diagnosed "too late", i.e.. after haemodynamic complications have already occurred, and the incidence of episodes of hypoxaemia during two years following diagnosis, can be reduced. Screening as actually performed at child health centres in the south-west of the

Netherlands, however, will only lead to a small reduction in the number of patients diagnosed "too late", i.e. from 58 % in an unscreened population to 48 %. Adequate screening, on the other hand, may reduce this percentage to 17%. Long-term effects of screening on the general and functional health status of these patients are unlikely. Death may be occasionally prevented by screening.

Question 2:
Will screening for congenital heart malformations as actually performed at Dutch child health centres, considering the test properties and proportions of false-positive and false-negative test results, lead to unfavourable effects? What would be the answer to this question, if all children were optimally screened?
Answer:
The predictive value of a positive test result of the present screening is low (0.13), leading to a substantial proportion of false positive test results. Converted for the Netherlands as a whole, this would amount to almost 3 thousand children each year. Unnecessary anxiety, particularly for the parents of these children, is therefore inevitable, although reassurance by means of simple non-invasive diagnostic procedures is relative straightforward. Considering the present state of paediatric care, over-treatment of children with false positive test results is unlikely.
Also, the sensitivity of the present screening is rather low (0.57). A low sensitivity leads to a substantial proportion of false negatives. Of the 39 patients in this study who were diagnosed "too late" to prevent complications, 23 had failed to be detected by the screening programme. Whether delayed diagnoses and consequently delayed treatment were also to be attributed to false reassurance of the parents of these children is not certain. However, reducing of the number of children with false negative test results by improving the sensitivity, will in any case serve to reduce unfavourable side-effects resulting from such test results. This may be achieved if all children were adequately screened (sensitivity=0.89). Whether such an improvement will also change the false-positive rate is difficult to predict and no estimates can be based on the present data. Distress caused by false-positive test results is generally considered to be less severe than distress and adverse health effects caused by false-negative test results. For this reason and in the light of the substantial reduction in numbers of false-negatives, a considerable increase in the number of false-positives would be required to neutralise the positive effects of such a change in policy. If for example the relation between the harm caused by false-negative and false-positive test results is expressed as a ratio of 10:1, the number of false-positives will almost have to be doubled to neutralise the effect of the reduction of false-negatives.

Question 3:
What costs and savings are involved in the management, including screening at child health centres, of relevant congenital heart malformations?

Answer:
In a window of two years, the total costs for these conditions in the south west of the Netherlands in a population in which 75441 children were born, amount to over 5 million Dutch guilders. Of these costs 79 % are to be attributed to diagnosis and therapy, 13 % to the screening and 8 % to referrals resulting from screening. Costs for patients diagnosed "too late" exceed those for patients diagnosed "in time", which is mainly attributable to hospitalisation in intensive care units. On average a saving of Dfl 5649,- may be expected from preventing a disorder to be diagnosed "too late".

Question 4:
What costs are made per child benefiting from the screening programme as actually performed? What would be these costs, if all children were optimally screened?
Answer:
Costs of screening as actually performed per child benefiting from it are estimated at Dfl 121100,-. Were all children to be screened adequately, these costs are estimated at Dfl 25265,-. These results provide an extra motivation for complying with recommendations aimed at the improvement of this screening programme. The considerable expenditures on prevention of complications of congenital heart malformations, amounting to over 20% of all costs made on relevant disorders, are currently not being optimally spent. Improvement of the programme will, apart from better effectiveness, also upgrade the balance between costs and yield.
There is no straightforward answer to the question of whether amply 25 thousand guilders to prevent potential episodes of serious hemodynamic complications is worthwhile, compared to the results of other child health care activities, as unambiguous outcome measures are lacking.

Question 5
What measures will have to be taken to optimise the effect of screening for congenital heart malformations at Dutch child health centres?
Answer:
Optimising the training of child health centre physicians is probably the most important condition for improvement of the yield of the screening programme for congenital heart malformations. Only in 22 % of all cases did the doctors perform the screening protocol completely according to the guidelines.
In the Netherlands, child health centre physicians, unlike school health care physicians, are not fully trained in social paediatrics. In the 10-days course, which trainee MD's are obliged to follow in order to be appointed as child health care physician, only one lecture is dedicated to paediatric cardiology. Apparently this is not sufficient. A more extensive and recurrent training programme, possibly using simulation techniques and other advanced didactical devices is necessary.

In a minority of at least 10 out of 39 patients who were diagnosed "too late", prolonged intervals between detection and diagnosis may also have contributed to the delayed diagnoses. Prolonged intervals are mostly due to delayed referrals from the GP to the paediatrician and prolonged review periods by this paediatrician before referral to the paediatric cardiologist. Hence, avoiding delay on the part of these physicians may contribute to the improvement of the prevention programme. In principle general practitioners are neither better equipped for, nor more experienced in detection of congenital heart malformation than child health centre physicians. This implies that after a child health centre physician has referred a child with a positive screening test, the general practitioner, who is in the Netherlands the official "gatekeeper" for hospital and outpatient care, is confronted with a very difficult task. Leaving the general practitioner out the referral sequence for these particular diseases, appears to be recommendable. Such an arrangement, however, would be contrary to the conventions of the Dutch health system.

General paediatricians should certainly be competent to anticipate the course of congenital heart disease adequately, using ultrasound and ECG facilities. Considering the large numbers of false-positive screening test results and of children with non-progressive disorders, it is also very advisable that they do so, if only to prevent overburdening of high care centres. Nevertheless in some of our cases children arrived "too late" at the paediatric cardiologist after a long review period with the general paediatrician.

Health education aimed at optimising attendance by parents may also help to improve the yield. Parents should be stimulated to visit the consulting hours in time. Such measures, however, should not be expected to boost the yield of the programme to any major extent

10.3 Conclusion on the purpose of the thesis

This thesis has helped to clarify the effectiveness and the efficiency of screening for congenital heart malformations at Dutch child health centres and the possibilities to optimise this prevention programme. The main conclusion is that adequate screening is an effective prevention strategy for complications of congenital heart malformations, particularly hypoxemia. Since the size of the study group was rather small the effect size is difficult to estimate. As to acquire a more precise estimation, larger studies with the same objective may be justified. .

Since actually only a minority of the children is adequately screened, the efficiency of the current prevention programme is limited. Optimisation of the programme is feasible by a better screening performance of child health centre physicians and by more alert referral practices by general practitioners and specialists. This will also lead to a better balance between costs and yield.

Summary

Summary

Chapter 1

The objective of this thesis is to clarify the effectiveness and the efficiency of screening for congenital heart malformations at Dutch child health centres and the possibilities to optimise this prevention programme. To this end the following main questions will be addressed.

1. Does screening for congenital heart malformations, as actually performed at Dutch child health centres, prevent adverse outcomes of these disorders in the short and long run? What would be the answer on this question, if all children were optimally screened?
2. Will screening for congenital heart malformations as actually performed at Dutch child health centres, considering its test properties and the proportions of false positive and false negative test results, lead to unfavourable effects? What would be the answer on this question, if all children were optimally screened?
3. What costs and savings are involved in the management, including screening at child health centres, of relevant congenital heart malformations?
4. What costs are made per child benefiting from the screening programme as actually performed? What would be these costs if all children were optimally screened?
5. What measures will have to be taken to optimise the effect of screening for congenital heart malformations at Dutch child health centres?

Chapter2

In this chapter, a recent inventory of the specific preventive interventions performed within the scope of the Dutch preschool Child Health Care programme is presented, including vaccinations, screening and health education. The methodology for scientific evaluation of these preventive interventions is discussed. Activities of which the effectiveness has already been convincingly demonstrated are indicated and plans for an extensive research programme are presented. Effectiveness and efficiency should preferably be established in Randomised Controlled Trials (RCT). If this is not feasible, researchers should stay as close as possible to the theoretical points of departure of an RCT.

Generally, in comparing different interventions, unambiguous cost-effectiveness measures such as costs per gained quality adjusted life year (QALY) should be used. This method however does not include the intergenerational effects that are always present in Child Health Care and the necessity to discount for very long survival periods. Alternative cost-effectiveness measures should therefore be developed for this specific sector. From an effect-evaluation point of view, the difference between "screening" and "surveillance" is not very essential. Preschool Child Health Care in the Netherlands is a very popular preventive programme, which is generally cherished as a precious achievement. Its scientific foundation, however, is far from complete.

Chapter 3

In this chapter the characteristics of congenital heart malformations that determine the potential impact of screening for these disorders in child health care are described. Secondary prevention programmes like screening cannot prevent congenital heart malformations themselves. This requires primary prevention strategies, aimed at aetiologic factors. Since most of these factors are not well understood, such strategies are not feasible yet. Nevertheless, given the clinical qualities of congenital heart malformations, screening in child health care may potentially pay a substantial contribution to the optimal management of these disorders. Timely detection and subsequent intervention might prevent deterioration of these patients' condition and even death. The screening programme at the Dutch child health centres, however, has an important limitation in that a neonatal screening is lacking. As the first screening is scheduled at the age of 1 month, this programme will fail to cover those severe, fast-deteriorating conditions, which become symptomatic before that age.

Whether screening might have favourable consequences in the long run for a substantial number of patients is not easy to say. Current therapeutic interventions are so effective, that the final outcome in a majority of the patients, even in those in whom hemodynamic complications did occur, may be quite favourable.

Chapter 4

In this chapter the state of the art of evaluation of screening for congenital heart malformations in child health care during the neonatal period and the first years of life is clarified, based on the available international literature. Using Medline, a complete search of papers published from 1968 until November 1998, was performed. One hundred and eight publications matched with the searching criteria, of which only 2 were specifically concerned with the screening activities under discussion.

Although screening for congenital heart malformations is broadly advocated and actually applied on a large scale, effect evaluation of these activities has to be considered as a virtually unexplored research field.

Chapter 5

This chapter is concerned with the clarification of the place of patient follow-up studies in the armoury of observational study designs that have to be considered, when Randomised Controlled Trials are not feasible because of established practice and circumstantial evidence pointing to at least some effectiveness of early intervention.

For assessing the favourable effects of screening for many conditions, especially for cancer, the use of the patient follow-up study design is very problematic, or even unacceptable. However, for the evaluation of screening for some conditions with specific characteristics, this design may, under a number of strict conditions, be useful. This may particularly be the case for screening evaluation within the framework of

child health care, in particular for congenital heart disease and congenital hip dislocation.

In the case of these conditions, a patient follow-up study can offer an efficient alternative to more customary designs for screening evaluation. Although in principle bias, especially selection bias, may be avoided more successfully in a case-control evaluation, the patient patient-follow-up study is the more feasible design, may provide more supplementary information, and may still provide useful information on screening effectiveness.

The results of two pilot studies, in which patient follow-up studies were actually applied for both conditions mentioned above suggest that more elaborate studies following this design are feasible for these conditions and that both screening protocols probably yield considerable benefits.

Chapter 6

In this chapter, the test-properties and the proportions of false-positive and false-negative test results are estimated for the current programme as well as for an imaginary programme in which all children are adequately screened. The potency of the current screening programme in preventing congenital heart malformations from being diagnosed "too late", i.e. after haemodynamic complications have already occurred, is investigated. The same potency is estimated for the situation in which all children were to be adequately screened according to established guidelines.

All consecutive patients, aged between 32 days and 4 years, presented at the Sophia Children's Hospital Rotterdam during a period of two years with a congenital heart malformation were included in this study. Paediatric cardiologists established whether or not these patients were diagnosed after hemodynamic complications had already developed (diagnosed "too late"). Parents and CHC-physicians were interviewed in order to establish the screening and detection history. Test properties were established for all patients with a congenital heart malformation (n=290), intended effects of screening were established in patients with clinically significant malformations (n=82).

The sensitivity of the actual screening programme was 0.57(95%CI: 0.51-0.62), the specificity 0.985(95%CI: 0.981-0.990) and the predictive value of a positive test result 0.13(95%CI:0.10-0.19). Sensitivity in a sub-population of adequately screened patients was 0.89(95%CI: 0.74-0.96).

Adequately screened patients were less likely to be diagnosed "too late" than inadequately screened patients (OR=0.20 95%CI: 004-1.05). The actual risk of being diagnosed "too late" in the study-population (48 %) was only slightly less than the estimated risk for patients not exposed to CHC-screening (58% 95%CI: 43%-72%). Adequately screened patients, however, were at considerably less risk (17% 95%CI: 4%-48%)

Chapter 7

In this chapter, factors that determine the effectiveness of screening for congenital heart malformations at child health centres are identified and recommendations for the optimisation of the screening programme are formulated.

Incomplete performance of the screening examination by child health centre physicians has a more significant impact on the occurrence of delayed diagnoses than failure of parents to adhere to the complete visit schedule. Adequate screening advances detection of congenital heart malformations. In 25% of the patients diagnosed "too late" the occurrence of complications was preceded by a prolonged interval between detection and diagnosis, which was predominantly caused by delay on the part of general practitioners and general paediatricians. Screening is probably effective in neither swiftly deteriorating nor slowly progressive diseases, but may be quite successful in a relatively large group of patients with disorders progressing at a medium pace. In only 7 out of 39 patients diagnosed "too late", no avoidable cause for an adverse outcome could be indicated at all. This suggests that a considerable improvement of the prevention of complications of congenital heart malformations can be acquired. An improvement of the performance of the child health centre physicians and co-operation of all other physicians involved in reducing the time between referral and diagnosis are required to optimise the yield of the screening programme.

Chapter 8

Conclusions drawn in Chapters 6 and 7 are based on the presupposition that haemodynamic complications can yet be prevented in patients, who are diagnosed "in time". In this chapter it is investigated whether this is true for a follow-up period of two years. As an ultimate test for the effectiveness of the screening, the question of whether adequately screened patients are less likely to develop complications than inadequately screened patients during these two years, is investigated as well.

The patient-follow-up study, presented in chapter 5 was extended by 2 years. Data on complications were gathered by investigation of hospital files. General and functional health status were assessed by the Dutch versions of the "RAND general health rating index for children" and the 'Functional Status II(R) questionnaire'.

Patients diagnosed "in time" are significantly less likely to develop serious forms of heart failure (OR: 0.23 95%CI: 0.07 - 0.79) and hypoxemia (OR: 0.05 95%CI: 0.006 - 0.38) than patients diagnosed "too late". No preventive effect of adequate compared to inadequate screening can be demonstrated for heart failure For hypoxemia, however, such an effect is very likely (OR: 0.00 95%CI: 0.00 –0.78) There are no significant differences in general nor functional health status between patients diagnosed "in time" and "too late" and between patients "adequately" and "inadequately" screened. Timely diagnosis of congenital heart disease generally leads to fewer haemodynamic complications during the 2 years following the diagnosis. Adequate screening is

effective in preventing hypoxemia. Screening has no influence on the ultimate health status 2 years after diagnosis. Death may be occasionally prevented by screening.

Chapter 9

In this chapter an economic evaluation has been carried out of the management of congenital heart malformations that can be detected by screening at child health centres and estimations of costs per child benefiting from screening are estimated

Economic evaluations for the south-west of the Netherlands within a window two years, for a population in which 75441 children were born, are based on the extension of the patient follow-up study presented in chapter 6, population statistics, and registration of referrals by Rotterdam CHC-physicians. Costs of medical procedures, hospital expenditures and screening procedures are based on Dutch health care fees, hospital administration data and child health care administration data. Costs of medication are based on the Dutch Pharmacotherapeutic Manual.

The total costs of relevant disorders amount to over 5 million Dutch guilders, of which 79 % are to be attributed to diagnosis and therapy, 13 % to the screening and 8 % to referrals resulting from screening. Costs for patients diagnosed "too late" exceed by far those for patients diagnosed "in time", which is mainly attributable to hospitalisation in intensive care units. On average a saving of Dfl 5649,- may be expected from preventing a disorder for being diagnosed "too late". Costs of screening as actually performed per child benefiting from it are estimated at Dfl 121100,-. Were all children to be screened adequately, this estimate would drop to Dfl 25265,-. These results provide an extra motivation for complying with recommendations aimed at the improvement of this screening programme as formulated in chapter 7. The considerable expenditures on prevention of complications of congenital heart malformations, amounting to over 20% of all costs made on relevant disorders, are presently not being optimally spent. Improvement of the programme will, apart from better effectiveness, also upgrade the balance between costs and yield.

There is no straightforward answer to the question of whether spending over 25 thousand guilders to prevent potential episodes of haemodynamic complications is worthwhile, compared to the results of other child health care activities, as unambiguous outcome measures are lacking.

Chapter 10.

The main study questions of this thesis can be answered as follows

Question 1:
Does screening for congenital heart malformations, as actually performed at Dutch child health centres, prevent adverse outcomes of these disorders in the short and long run? What would be the answer to this question, if all children were optimally screened?
Answer
By screening at child health centres, the number of patients diagnosed "too late", i.e. after haemodynamic complications have already occurred, and the incidence of episodes of hypoxaemia during two years following diagnosis, can be reduced. Screening as actually performed at child health centres in the south-west of the Netherlands, however, will only lead to a small reduction of patients diagnosed "too late", i.e. from 58 % in an unscreened population to 48 %. Adequate screening, on the other hand, may reduce this percentage to 17%. Long-term effects of screening on the general and functional health status of these patients are unlikely. Death may be prevented occasionally by screening.

Question 2:
Will screening for congenital heart malformations as actually performed at Dutch child health centres, considering the test properties and proportions of false positive and false negative test results, lead to unfavourable effects? What would be the answer on this question, were all children optimally screened?
Answer:
Converted for the Netherlands as a whole, the proportion of children with false positive test results would amount to over 2.5 thousand children each year. Although unnecessary anxiety, particularly for the parents of these children, is inevitable, reassurance by means of simple non-invasive diagnostic procedures is relative straightforward. Considering the present state of paediatric care, over-treatment of children with false positive test results is unlikely.
The present low sensitivity leads to a substantial proportion of false negatives. Whether delayed diagnoses and consequently delayed treatment are also to be attributed to false reassurance of the parents of these children is not certain. However, reduction of the number of children with false negative test results, by improvement of the sensitivity, will in any case also reduce unfavourable side effects resulting from such test results. This will certainly be the case if all children are adequately screened. If the relation between the harm caused by false-negative and false-positive test results is expressed as a ratio of 10:1, the number of false-positives would almost have to be doubled to neutralise the effect of the reduction of false-negatives.

Question 3:
What costs and savings are involved in the management, including screening at child health centres, of relevant congenital heart malformations?
Answer:
The total costs within the framework of this study amount to over 5 million Dutch guilders, of which 79 % are to be attributed to diagnosis and therapy, 13 % to the screening and 8 % to referrals resulting from screening. Costs for patients diagnosed "too late" exceed those on patients diagnosed "in time", which is mainly attributable to hospitalisation in intensive care units. On average a saving of Dfl 5649,- may be expected from preventing a disorder from being diagnosed "too late".

Question 4:
What costs are made per child benefiting from the screening programme as actually performed? What would be these costs if all children were optimally screened?
Answer:
Costs of screening as actually performed per child benefiting from it are estimated at Dfl 121100,-. Were all children to be screened adequately, this estimate would drop to Dfl 25265,-.

Question 5
What measures will have to be taken to optimise the effect of screening for congenital heart malformations at Dutch child health centres?
Answer:
Optimising the training of child health centre physicians is probably the most important condition for improvement of the yield of the screening programme for congenital heart malformations. Avoiding delay on the part of general practitioners and paediatricians will also contribute to the improvement of the prevention programme. Parents should be stimulated to visit the consulting hours in time. Such measures, however, should not be expected to boost the yield of the programme to any major extent

General conclusion
This thesis has substantially helped to clarify the effectiveness and the efficiency of screening for congenital heart malformations at Dutch child health centres and the possibilities to optimise this prevention programme. The main conclusion is that adequate screening is an effective prevention strategy for complications of congenital heart malformations, particularly hypoxemia. Since the size of the study group was rather small the effect size is difficult to estimate. As to acquire a more precise estimation, larger studies with the same objective may be justified. .
Since actually only a minority of the children is adequately screened, the efficiency of the current prevention programme is limited. Optimisation of the programme is

feasible by a better screening performance of child health centre physicians and by more alert referral practices by general practitioners and specialists. This will also lead to a better balance between costs and yield.

SAMENVATTING

Samenvatting

Inleiding

Algemene achtergrond

In Nederland is het consultatiebureau een voorziening, die als vanzelfsprekend beschikbaar is voor alle zuigelingen, kleuters en hun ouders. Al sinds het begin van de twintigste eeuw worden op deze bureaus jonge kinderen periodiek medisch onderzocht en gevaccineerd. Daarnaast krijgen de ouders adviezen over voeding, verzorging en opvoeding. De bureaus zijn geworteld in de oer-Nederlandse traditie van het particulier initiatief van aanvankelijk verzuilde organisaties, die zich verantwoordelijk voelden voor het welzijn van hun achterban (voorheen "Kruiswerk", tegenwoordig "Thuiszorg"). Zij vormen een typisch voorbeeld van preventieve maatschappelijke gezondheidszorg. De belangrijkste doelstelling was oorspronkelijk het terugdringen van de kindersterfte, wat inderdaad in de eerste decennia van de twintigste eeuw voor een groot deel werd volbracht. In hoeverre dit een direct gevolg was van het werk van de consultatiebureaus is achteraf moeilijk vast te stellen. Ongetwijfeld vormden zij niet de enige bepalende factor in dat proces. Hoe het ook zij, vanaf het begin beschouwde men de consultatiebureaus als een doorslaggevend succes en een belangrijke sociale verworvenheid. Dit inzicht was mede gebaseerd op de groeiende overtuiging, dat het niveau van de volksgezondheid niet een autonoom gegeven is, maar gunstig kan worden beïnvloed door populatie gerichte preventieve maatregelen.

Ook aan het einde van de twintigste eeuw is preventie nog steeds de belangrijkste doelstelling van het consultatiebureau. De maatschappelijke houding tegenover preventie is thans echter enigszins genuanceerder. Tegenwoordig wordt er steeds meer belang gehecht aan de vraag of specifieke preventieve maatregelen ook werkelijk werkzaam zijn en in hoeverre zij gepaard gaan met ongunstige neveneffecten. Dit geldt in principe voor al het medisch handelen, maar sommige deskundigen zijn van mening, dat bewezen werkzaamheid voor de preventieve zorg een nog belangrijker eis is dan voor de curatieve geneeskunde.

De beroemde Britse epidemioloog Archibald Cochrane lichtte dit ooit als volgt toe. Curatieve interventies worden door dokters toegepast op verzoek van patienten, die uit eigener beweging om hulp komen vragen. Zolang deze dokters handelen in overeenstemming met de beste beschikbare medische kennis, kunnen onvoldoende werkzaamheid en vervelende bijwerkingen hun moeilijk worden aangerekend. Artsen die naar beste weten al het mogelijke doen, kunnen niet verantwoordelijk worden gesteld voor de onvolkomenheden van de medische wetenschap. Preventieve activiteiten daarentegen, zoals bijvoorbeeld bevolkingsonderzoek, worden ongevraagd aangeboden aan tot dan toe gezonde mensen. Deze mensen worden uitgenodigd zich te onderwerpen

aan een medisch onderzoek en mogelijk aan uitgebreid vervolgonderzoek en behandeling voor afwijkingen, waarvan zij het bestaan tot voor kort vaak zelfs niet vermoedden. Indien zo'n preventie programma niet tenminste op populatie niveau aantoonbaar gunstige effecten heeft, die opwegen tegen ongunstige neveneffecten, is het volstrekt redelijk dat degenen die het programma aanbieden hiervoor verantwoordelijk worden gesteld. Aldus Cochrane.
Verder wordt er, naast het afwegen van gunstige en ongunstige effecten van medisch handelen, toenemend aandacht gevraagd voor de financiële kosten en baten van de zorg. De overheid, verantwoordelijk voor het beheersbaar houden van de kosten van de gezondheidszorg, en zorgverzekeraars dringen aan op het uitsluitend toepassen van interventies met een zo gunstig mogelijke relatie tussen kosten en effecten.
Stammend uit een tijd, waarin dergelijke inzichten en navenante eisen nog niet aan de orde waren, zijn de consultatiebureaus tot voor kort, nauwelijks onderworpen geweest aan dergelijke evaluaties. De externe aandrang om dit wel te doen neemt echter toe. Het staat immers geenszins vast, dat soms honderd jaar geleden ontwikkelde preventie maatregelen ook nu zonder meer heilzaam zijn. Kosten-effectiviteits analyses kunnen aantonen in hoeverre dit nog wel het geval is, waar thans de zwakke plekken van het systeem zitten en tenslotte hoe de jeugdgezondheidszorg op basis van deze kennis geoptimaliseerd kan worden.

Doelstelling en specifieke achtergrond
In het kader van deze ontwikkelingen, richt dit proefschrift zich op de evaluatie van de gunstige en ongunstige effecten en de kosten en baten van het bevolkingsonderzoek naar aangeboren hartafwijkingen op het consultatiebureau.
De stethoscoop maakt de dokter. Voor veel mensen is het gebruik van de stethoscoop onverbrekelijk verbonden met een goed medisch onderzoek. Ouders die met hun kind het consultatiebureau bezoeken, zouden zich waarschijnlijk bedrogen voelen, indien de dokter deze handeling zou nalaten, wat daarom dan ook vrijwel nooit gebeurt. Vrijwel het enige logische doel van het routinematig beluisteren met de stethoscoop van alle jonge kinderen, is het door vroege interventie voorkomen van complicaties (met name hartfalen en zuurstofgebrek) bij tot dan toe onopgemerkt gebleven aangeboren hartafwijkingen. Of dit doel ook werkelijk wordt bereikt is tot voorkort nauwelijks onderzocht, zoals uit de in hoofdstuk 4 van dit proefschrift beschreven literatuurstudie blijkt. Evenmin staat vast hoeveel onbedoelde bijeffecten zich voordoen, zoals ernstige maar achteraf overbodige ongerustheid over kinderen, die worden verwezen, maar uiteindelijk geen afwijking blijken te hebben en ongerechtvaardigde geruststelling en zelfs te late behandeling, indien consultatiebureau artsen wel aanwezige afwijkingen over

het hoofd zien. Onderzoek naar de kosten en baten, tenslotte, ontbreekt eveneens.
Verder is het zo dat, hoewel de meeste consultatiebureau artsen ongetwijfeld stelselmatig de stethoscoop hanteren, dit niet zonder meer betekent dat het bevolkingsonderzoek goed wordt uitgevoerd. Naast het luisteren met de stethoscoop kunnen consultatiebureau artsen ook met ander routine onderzoek en door het stellen van routine vragen aangeboren hartafwijkingen op het spoor komen. Of dat wel of niet gebeurt kan van beslissend belang zijn voor het succes van het bevolkingsonderzoek. Bovendien is het belangrijk dat ouders op de juiste leeftijd van hun kind het bureau bezoeken. Tenslotte kan de loop en de duur van het verwijsproces via de huisarts en de perifere kinderarts naar de kindercardioloog van essentiële invloed zijn op het eindresultaat. Al deze factoren komen mogelijk in aanmerking voor optimalisering.

Vraagstelling
Dit proefschrift richt zich op beantwoording van de volgende vragen:
1. Leidt bevolkingsonderzoek naar aangeboren hartafwijkingen zoals thans uitgevoerd op het consultatiebureau op korte en lange termijn tot minder complicaties ten gevolge van dergelijke afwijkingen? Wat zou het antwoord op deze vraag zijn, indien alle kinderen optimaal zouden worden onderzocht?
2. Leidt bevolkingsonderzoek naar aangeboren hartafwijkingen zoals thans uitgevoerd op het consultatiebureau tot ongewenste effecten? Wat zou het antwoord op deze vraag zijn, indien alle kinderen optimaal zouden worden onderzocht?
3. Welke kosten en baten komen voort uit de bestrijding van aangeboren hartafwijkingen, inclusief het bevolkingsonderzoek op het consultatiebureau?
4. Wat zijn de kosten per kind dat feitelijk baat heeft bij het bevolkingsonderzoek naar aangeboren hartafwijkingen zoals thans uitgevoerd op het consultatiebureau? Wat zou het antwoord op deze vraag zijn, indien alle kinderen optimaal zouden worden onderzocht?
5. Welke maatregelen moeten er worden genomen om de werkzaamheid van bevolkingsonderzoek naar aangeboren hartafwijkingen op het consultatiebureau te optimaliseren?

Methode.
Zuiver wetenschappelijk gezien is een zogeheten "Gerandomiseerde Trial" de beste onderzoeksopzet voor het evalueren van een bevolkingsonderzoek. Indien een dergelijke opzet zou worden toegepast voor ons onderzoek zouden alle kinderen door het toeval worden ingedeeld in twee groepen. Kinderen uit de eerste groep zouden worden onderworpen aan het bevolkingsonderzoek,

kinderen uit de tweede groep niet. Beide groepen zouden worden vervolgd in de tijd. Indien uiteindelijk in de eerste groep zich evident minder complicaties zouden voordoen dan in de tweede, zou dat een bewijs zijn voor de werkzaamheid van het bevolkingsonderzoek, omdat beide groepen in principe verder uitsluitend verschillen wat betreft de toepassing van het bevolkingsonderzoek.
Indien een bevolkingsonderzoek al op grote schaal wordt uitgevoerd, zoals in het geval van onderzoek op het consultatiebureau, is het toepassen van een "Gerandomiseerde Trial" wegens ethische en praktische redenen onmogelijk. In deze gevallen moeten onderzoekers gebruik maken van een observationele studie. Dit is een studie waarin gebeurtenissen worden waargenomen in de door de onderzoekers niet beïnvloede werkelijkheid. Voor de huidige studie zou dat een vergelijking betekenen tussen kinderen, die om welke reden dan ook, wel en niet (goed) worden onderworpen aan het bevolkingsonderzoek. Een vergelijking tussen aldus samengestelde groepen is nooit zuiver, omdat beide groepen mogelijk ook verschillen ten aanzien van andere factoren die van invloed zijn op het voorkomen van complicaties. Daarom moeten onderzoekers bij een observationele studie veelal de vergelijkbaarheid van beide groepen zo goed mogelijk achteraf vaststellen en zo nodig voor verschillen corrigeren.
De in dit proefschrift beschreven observationele studie is een zogeheten "patienten follow-up studie". Alle patienten met een aangeboren hartafwijking in de leeftijdsklasse van 1 maand tot 4 jaar (de periode dat kinderen het consultatiebureau bezoeken), wonend in zuidwest Nederland, die gedurende twee jaar voor het eerst gezien werden door de kindercardiologen van het Sophia Kinderziekenhuis in Rotterdam, werden in het onderzoek opgenomen. De kindercardiolgen stelden vast of de patientjes "te laat" of "op tijd" waren verschenen om complicaties te voorkomen. Bovendien werden alle patienten nog twee jaar vervolgd, om na te gaan of bij de "op tijd" verschenen patiënten zich inderdaad als gevolg van tijdige behandeling geen problemen meer voordeden en om de gezondheidstoestand op de langere termijn vast te stellen. Bovendien werden de afwijkingen door de kindercardiologen onderscheiden in "zeer ernstig", "ernstig", "matig" en "triviaal".
De ouders werden geïnterviewd om na te gaan hoe de aangeboren hartafwijking aan het licht was gekomen. De betreffende CB-arts werd geïnterviewd om na te gaan of de ouders en het kind het bureau hadden bezocht volgens een standaard oproep schema en of aldaar het onderzoek had plaats gevonden volgens vastgestelde richtlijnen. Op basis van die criteria werden de kinderen ingedeeld in twee onderzoeksgroepen: "correct" en "niet correct" onderzochte kinderen.
Om de vergelijkbaarheid van deze twee groepen te verbeteren werden bij de effect analyses patiëntjes die uiteindelijk geen behandeling nodig bleken te hebben buiten beschouwing gelaten. Bovendien werden de uitkomsten zodanig

bewerkt, dat in feite steeds afwijkingen van gelijke ernst met elkaar werden vergeleken.
Voor de evaluatie van bevolkingsonderzoek naar een groot aantal afwijkingen, met name verschillende soorten kanker, is een patienten follow-up studie zeer problematisch, of zelfs onacceptabel. In hoofdstuk 5 van dit proefschrift wordt uitvoerig ingegaan op de redenen, waarom voor de evaluatie van bevolkingsonderzoek naar aangeboren hartafwijkingen, en ook aangeboren heupafwijkingen, deze opzet wel bruikbaar is.

Resultaten

Vraag 1:
Leidt bevolkingsonderzoek naar aangeboren hartafwijkingen zoals thans uitgevoerd op het consultatiebureau op korte en lange termijn tot minder complicaties ten gevolge van dergelijke afwijkingen? Wat zou het antwoord op deze vraag zijn, indien alle kinderen optimaal zouden worden onderzocht?
Antwoord:
Door bevolkingsonderzoek op het consultatiebureau kan het aantal patiënten dat "te laat" wordt gediagnostiseerd om complicaties te voorkomen en episodes van zuurstofgebrek in de twee jaar na de diagnose, aanzienlijk worden teruggebracht. Aangezien het bevolkingsonderzoek nu naar schatting slechts in 15 % van de gevallen op de juiste leeftijd en volgens het juiste onderzoeksprotocol wordt uitgevoerd, is de afname van het aantal "te laat" gediagnostiseerde patiënten beperkt: Van 58 % indien er geen bevolkingsonderzoek zou zijn tot 48 % in de huidige situatie. Indien het bevolkingsonderzoek evenwel bij alle kinderen correct zou plaats vinden, zou dit percentage dalen tot 17 %. Er zijn waarschijnlijk geen lange termijneffecten van bevolkingsonderzoek op de gezondheidstoestand van deze patiënten. Het is niet uitgesloten, dat door middel van het bevolkingsonderzoek soms sterfgevallen kunnen worden voorkomen.

Vraag 2:
Leidt bevolkingsonderzoek naar aangeboren hartafwijkingen zoals thans uitgevoerd op het consultatiebureau tot ongewenste effecten? Wat zou het antwoord op deze vraag zijn, indien alle kinderen optimaal zouden worden onderzocht?
Antwoord:
Het aantal kinderen in Nederland dat als gevolg van het bevolkingsonderzoek wordt verwezen, maar bij wie achteraf geen afwijking kan worden vastgesteld, bedraagt naar schatting jaarlijks bijna 3 duizend kinderen. (ter vergelijking: in Nederland worden jaarlijks ongeveer 200 duizend kinderen geboren). Hoewel onnodige ongerustheid bij de ouders van achteraf ten onterechte verwezen

kinderen onvermijdelijk is, kunnen zij in principe snel en met behulp van voor het kind relatief weinig bedreigende methoden (Elektrocardiogram en een Echo-onderzoek) worden gerustgesteld. Gezien de huidige stand van de kindercardiologische zorg is overbehandeling van deze kinderen zeer onwaarschijnlijk.
De huidige manier van werken leidt tot een relatief groot aantal kinderen met min of meer ernstige aangeboren hartafwijkingen, die niet door het consultatiebureau worden ontdekt (43 % van de in aanmerking komende kinderen). Mogelijk leidt dit tot valse geruststelling bij ouders en dientengevolge verlate diagnoses en behandeling.
Indien alle kinderen correct zouden worden onderzocht zou het aantal niet via het consultatiebureau opgespoorde patiënten aanzienlijk kunnen afnemen (tot 11 %). Het is echter niet uitgesloten dat daardoor het aantal achteraf ten onrechte verwezen kinderen zou stijgen. Over het algemeen wordt het niet opsporen van een afwijking als een veel ernstiger probleem gezien dan een achteraf onterechte verwijzing. Als we er van uitgaan dat het eerste 10 keer zo erg is als het tweede, dan moet door een beter uitgevoerd bevolkingsonderzoek het aantal achteraf onterechte verwijzingen verdubbelen, om het gunstige effect van de afname van niet opgespoorde patiënten te niet te doen.

Vraag 3:
Welke kosten en baten komen voort uit de bestrijding van aangeboren hartafwijkingen, inclusief het bevolkingsonderzoek op het consultatiebureau?
Antwoord:
De totale kosten besteed aan deze afwijkingen gedurende twee jaar in zuidwest Nederland, (in een bevolking waarbinnen in die periode ruim 75 duizend kinderen werden geboren), worden geschat op ruim 5 miljoen gulden. Van deze kosten werd 79 % besteed aan diagnose en therapie, 13 % aan het feitelijke bevolkingsonderzoek en 8 % aan verwijzingen ten gevolge van het bevolkingsonderzoek. Kosten voor "te laat" gediagnostiseerde patiënten zijn hoger dan die voor "op tijd" gediagnostiseerde, wat voornamelijk toe te schrijven is aan opnames op de intensive care afdeling. Gemiddeld kan preventie van een "te late" diagnose een besparing van ruim 5,5 duizend gulden opleveren.

Vraag 4:
Wat zijn de kosten per kind dat feitelijk baat heeft bij het bevolkingsonderzoek naar aangeboren hartafwijkingen zoals thans uitgevoerd op het consultatiebureau? Wat zou het antwoord op deze vraag zijn, indien alle kinderen optimaal zouden worden onderzocht?

Antwoord:
De kosten per kind dat feitelijk baat heeft bij het bevolkingsonderzoek naar aangeboren hartafwijkingen bedragen ruim 121 duizend gulden. Indien alle kinderen optimaal zouden worden onderzocht zouden deze kosten worden teruggebracht tot ruim 25 duizend gulden .

Vraag 5:
Welke maatregelen moeten er worden genomen om de werkzaamheid van bevolkingsonderzoek naar aangeboren hartafwijkingen op het consultatiebureau te optimaliseren?
Antwoord:
Het optimaliseren van de uitvoering door consultatiebureau artsen is waarschijnlijk de belangrijkste voorwaarde voor een verbetering van de opbrengst van het bevolkingsonderzoek naar aangeboren hartafwijkingen op het consultatiebureau. Slechts in 22 % van alle gevallen voerden consultatiebureau artsen een volledig onderzoeksprotocol uit.
Het voorkomen van vertraging in het verwijsproces kan ook bijdragen aan een betere opbrengst van het bevolkingsonderzoek. Bij 10 van de 39 "te laat" gediagnostiseerde patiënten, was er sprake van een te lang interval tussen de eerste verwijzing en de uiteindelijke diagnose (meer dan 4 weken). Dit was meestal het gevolg van vertraagde verwijzingen door de huisarts of het te lang onder controle houden van perifere kinderartsen.
Verbetering van de opkomst van ouders en kinderen zou in principe ook kunnen helpen bij het bewerkstelligen van een betere opbrengst van het bevolkingsonderzoek.

Discussie.
Goed uitgevoerd bevolkingsonderzoek naar aangeboren hartafwijkingen op het consultatiebureau is doeltreffend. Bij de meeste kinderen wordt dit bevolkingsonderzoek echter niet goed uitgevoerd.
Een aanzienlijke verbetering van de opbrengst zou kunnen worden bewerkstelligd indien alle consultatiebureau artsen het bevolkingsonderzoek volgens een vast protocol zouden uitvoeren. Goed uitgevoerd bevolkingsonderzoek is vooral een kwestie van alertheid en voldoende ervaring met de op te sporen symptomen. Vanwege de beperkte prevalentie moet de uitvoerende arts enige honderden nieuwe zuigelingen per jaar onderzoeken, om voldoende routine op te bouwen. In Nederland zijn consultatiebureau artsen, in tegenstelling tot schoolartsen, niet allemaal gespecialiseerde jeugdartsen. De aanstellingseis voor consultatiebureau artsen is het volgen van een 10 daagse cursus, waarin slechts één les wordt besteed aan aangeboren hartafwijkingen. Dit is niet voldoende om de vereiste vaardigheid te ontwikkelen en te onderhouden. Een goede basistraining, gevolgd door periodieke

herhalingstrainingen, met behulp van moderne simulatie technieken kan waarschijnlijk een aanzienlijke verbetering van de onderzoekskwaliteit opleveren.
Ouders moeten natuurlijk ook gestimuleerd worden het consultatiebureau volgens afspraak te bezoeken, maar dat speelt een minder belangrijke rol.
Bevolkingsonderzoek is zinloos en in veel gevallen schadelijk, indien afwijkende bevindingen niet vlot worden gevolgd door definitieve diagnostiek. Aangezien verwijzingen vanuit het consultatiebureau volgens de mores van de Nederlandse gezondheidszorg altijd via de huisarts lopen, is diens positie in dit proces weinig benijdenswaardig. Huisartsen zijn niet beter toegerust noch meer ervaren in het onderkennen van aangeboren hartafwijkingen dan consultatiebureau artsen. Aangezien hierdoor de rol van de huisarts uitsluitend die van doorverwijsinstantie kan zijn, met inherent het risico van vertraging van het verwijsproces, zou overwogen moeten worden de consultatiebureau artsen de bevoegdheid te geven direct te verwijzen naar een centrum voor gespecialiseerde diagnostiek.
Optimalisering van het bevolkingsonderzoek kan ook de huidige wanverhouding tussen de relatief hoge kosten en de relatief lage opbrengst van dit preventieprogramma aanzienlijk verbeteren. De kosten per kind dat feitelijk baat heeft bij het bevolkingsonderzoek kunnen worden teruggebracht van ruim 121 tot ruim 25 duizend gulden. De vraag of dit laatste bedrag veel of weinig is, in vergelijking met andere consultatiebureau activiteiten, is niet eenvoudig te beantwoorden, omdat het moeilijk is de ongelijksoortige gezondheidswinst van verschillende interventies in de jeugdgezondheidszorg te vergelijken. Voor de curatieve zorg voor volwassenen zijn wel technieken ontwikkeld om ongelijksoortige gezondheidsuitkomsten met elkaar te vergelijken, maar voor gebruik in de preventieve jeugdgezondheidszorg zijn deze methodieken niet zonder meer geschikt en zullen ze nog moeten worden aangepast.

Conclusie
Bevolkingsonderzoek naar aangeboren hartafwijkingen op het consultatiebureau werkt, maar kan veel beter.

APPENDICES

Appendix 1

RAND – questionaire

1. In general, would you say your child's health is excellent, good, fair or poor?
- ☐ excellent
- ☐ good
- ☐ fair
- ☐ poor

2. During the last 3 months, how much have you worried about your child's health?
- ☐ a great deal
- ☐ somewhat
- ☐ a little
- ☐ not at all

3. During the last 3 month, how much pain or distress has your child's health caused him/her?
- ☐ a great deal
- ☐ some
- ☐ a little
- ☐ not at all

I am going to make 4 statements. After each please indicate whether this statement is true or false for your child. You may each time choose for one of 5 options.

4. My child's health is excellent.
- ☐ definitely true
- ☐ mostly true
- ☐ don't know
- ☐ mostly false
- ☐ definitely false

My child seems to resist illness very well
- ☐ definitely true
- ☐ mostly true
- ☐ don't know
- ☐ mostly false
- ☐ definitely false

My child seems to be less healthy than other children I know.
- ☐ definitely true
- ☐ mostly true
- ☐ don't know
- ☐ mostly false
- ☐ definitely false

When there is something going around, my child usually catches it.
- ☐ definitely true
- ☐ mostly true
- ☐ don't know
- ☐ mostly false
- ☐ definitely false

Appendix 2

FSII-R items

The second question is exclusively asked when a asterisked answer is chosen by the respondent parent

	1. During the last 2 weeks, how often did your child:				*2. was this due to the heart malformation?*		
1	eat well	*never or rarely	*some of the time	almost always	yes	sometimes	no
2	sleep well	*never or rarely	*some of the time	almost always	yes	sometimes	no
3	see contented and cheerful	*never or rarely	*some of the time	almost always	yes	sometimes	no
4	act moody	*never or rarely	*some of the time	almost always	yes	sometimes	no
5	communicate what he/she wanted	*never or rarely	*some of the time	almost always	yes	sometimes	no
6	seem to feel sick and tired	never or rarely	*some of the time	*almost always	yes	sometimes	no
7	occupy him/herself	*never or rarely	*some of the time	almost always	yes	sometimes	no
8	seem lively and energetic	*never or rarely	*some of the time	almost always	yes	sometimes	no
9	seem unusually irritable	never or rarely	*some of the time	*almost always	yes	sometimes	no
10	sleep through the night	*never or rarely	*some of the time	almost always	yes	sometimes	no
11	respond to your attention	*never or rarely	*some of the time	almost always	yes	sometimes	no
12	seem unusually difficult	never or rarely	*some of the time	*almost always	yes	sometimes	no
13	seem interested in what was going on around him/her	*never or rarely	*some of the time	almost always	yes	sometimes	no
14	react to things by crying	never or rarely	*some of the time	*almost always	yes	sometimes	no

DANKWOORD

Dankwoord

Promotores
In de deftige proefschriften van vroeger was het steevast de gewoonte dat dankwoorden werden begonnen met enige plechtige woorden van beleefde hulde aan de hooggeleerde promotor. De jongelui van tegenwoordig trekken zich niets aan van zulke conventies en beginnen gewoon met wie volgens hen het meest heeft bijgedragen aan de feestvreugde. Een keuze tussen het volgen van generatiegebonden mores en pogingen tot aanpassing aan de tijdgeest hoef ik gelukkig niet te maken. Ik kom hoe dan ook uit op dezelfde persoon: mijn eerste promotor Paul van der Maas.
Ik zal niet in detail ingaan op alle bijdragen die Paul aan de totstandkoming van dit proefschrift heeft geleverd. Laat ik volstaan met de mededeling dat er veel van zijn werk in zit. Zijn allerbelangrijkste bijdrage was evenwel het zelfvertrouwen, dat hij mij heeft gegeven. Je kunt je afvragen wat deze gerenommeerde professor ooit in mij heeft gezien: een al wat oudere jeugdarts, zonder enige onderzoeksexpertise, die plotseling is bekeerd tot een wetenschappelijke roeping. Vanaf het eerste begin gaf hij mij echter de illusie, dat mijn ideeën uiterst relevant waren voor de voortgang van de wetenschap en dat hij eigenlijk al jaren zat te wachten op iemand zoals ik. Later heb ik begrepen, dat dit niet berustte op de verpletterende indruk die ik op hem maakte, maar dat het een soort grondhouding van hem is. Mensen met wat voor ideeën dan ook neemt hij in principe volstrekt serieus, er van uitgaand dat je nooit kan weten of het nog iets nuttigs oplevert. Voor mij heeft die houding heel veel betekend.
Hoewel mijn beide promotores in vele opzichten van elkaar verschillen, is mijn dankbetuiging aan mijn tweede promotor, John Hess, van dezelfde orde. Ook John heeft mij vanaf het eerste begin altijd het gevoel gegeven, dat mijn wankele schreden op het wetenschappelijke pad van het grootste belang waren. Bovendien heeft hij steeds zijn eigen inspanningen en die van zijn afdeling ruimhartig ter beschikking gesteld van mijn onderzoek. Ik ben er trots op dat hij de reis uit het verre München wil ondernemen om mijn promotie luister bij te zetten.

Het instituut MGZ
Mijn eerste maanden bij het instituut MGZ heb ik beleefd als Sjakie in de Chocoladefabriek (Dahl 1964), met Paul van der Maas in de rol van Willy Wonka. Welk een uitgelezen gezelschap van erudiete geleerden trof ik hier aan. En ze waren nog aardig ook en deden net alsof ik net zo clever was als zij zelf. Geleerde vrienden ik dank u allen zeer! Een aantal wil ik met name bedanken.
De manier waarop Gerrit van Oortmarssen concept manuscripten van kleur pleegt te doen verschieten is al door vele MGZ promovendi gememoreerd.

Maar laten we eerlijk zijn dames en heren. Deze zachtaardige Achterhoeker is ons aller absolute leermeester in het gedisciplineerd denken. De allermooiste momenten - maar oh wat zijn ze schaars! – zijn die wanneer je bij wijze van uitzondering op een "minor point" een keer je gelijk krijgt. (Wat je eigenlijk alleen maar lukt als je je daarbij laat helpen door Rob Boer).
Het zou de moeite waard zijn een meta-analyse te wijden aan alle dankbetuigingen in MGZ-proefschriften aan het adres van Caspar Looman. Ik wed dat het uiteindelijk resultaat zou overeenkomen met de haarscherpe analyse van Jan en Luc, namelijk dat hij "GLIMt van bekwame behulpzaamheid" en overigens "de aardigste biostatisticus is van het westelijk halfrond (en omstreken)"(Barendregt & Bonneux 1998). Ik sluit mij daar gaarne bij aan. Hoewel ik er nog steeds van overtuigd ben, dat statistiek iets is, waarvan ik begrijp dat het valt te begrijpen, slaagt Caspar er bij vlagen in mij te laten geloven, dat ik het echt begrijp.
Harry de Koning was de eerste die van de inhoud van het eerste concept van mijn eerste NTVG artikel beweerde dat het volgens hem wel klopte. Daarom treedt hij nu op als mijn paranimf, waarvoor ik hem dank.
Behalve hierboven genoemde personen hebben ook Jan Barendregt, Marie-Louise Essink-Bot , Willem-Jan Meerdink en van buiten ons instituut Remy Hirasing, Frank van Leerdam, Pauline Verloove-Vanhorick en Maarten Witsenburg als coauteur een bijdrage aan dit proefschrift geleverd, waarvoor ik hen allen dank.
Veel dank ben ik verschuldigd aan Aty Slikkerveer-Verhey voor de voortreffelijke manier waarop zij zorg heeft gedragen voor de dataverwerking in het begin van het project. Het is mij wel een zeer speciaal genoegen Iet Juttmann-Punt (zij was trouwens ook coauteur!) te bedanken voor de manier waarop zij de data verzameling en verwerking voor hoofdstuk 8 en 9 heeft verzorgd. Op haar kom ik nog wel even terug.
Speciale dank gaat voorts uit naar de collega's werkzaam binnen mijn andere projecten: Ilse Oonk in RAMSES, Bianca Das en Ida Korfage (die trouwens ook een essentiële bijdrage heeft geleverd aan hoofdstuk 9) in SOHO en Hein Raat in de JGZ Programmeringstudie. Ook als mijn hoofd meer dan gevuld was met proefschriftgedachten, bleven zij net doen of deze projecten ook nog steeds *mijn* projecten waren. Uitsluitend aan hun inspanningen is te danken, dat dit ook werkelijk zo is.
Heel veel dank gaat uit naar het secretariaat en de automatisering groep van MGZ. Het is al vaak gezegd maar het kan niet genoeg herhaald worden: deze ondersteunde diensten zijn van uitzonderlijk hoge kwaliteit en zij vormen één van de belangrijkste redenen waarom het werken bij MGZ zo'n genoegen is.
En dan tenslotte mijn kamergenoten. MGZ leidt aan een chronisch tekort aan vierkante meters. Dit heeft voornamelijk nadelen, maar ook een aantal didactische voordelen. Als je met vier geleerden op een relatief kleine kamer

moet werken, leef je in een soort sociale en wetenschappelijke hogedrukpan, hetgeen, zolang je je goede humeur bewaart, allerlei onvermoede revenuen oplevert. Feikje Groenhof en Henriëtte Treurniet hebben mij in het begin ingewijd in alle diepere geheimen van het MGZ-leven. Henriëtte heeft mij daarna nog jarenlang, ik mag wel zeggen tot beiderzijds genoegen, van mijn werk gehouden (Treurniet 1999). Ondertussen leerde ik wat over kwaliteitsbewaking en zij wat over jeugdgezondheidszorg, wat ons beide om weer geheel verschillende redenen goed uit kwam. Korte tijd was Gonda Neddermijer mijn kamergenoot, een verbazingwekkende ervaring, die mijn bewondering voor de wiskunde in het algemeen verdiepte en waardoor ik bovendien weer wat opstak over computers. Daarna begon voor mij het Aids/Soa-tijdperk. Ik heb het genoegen mijn kamer te mogen delen met Eline Koorenromp en Hélène Voeten, twee uiterst getalenteerde jongedames, die samen met hun andere "tropenhoek"-collega's, onze werkruimte zo nu en dan laten gonzen van ingenieuze simulaties van doortastende Aids bestrijding in Afrika. Ik ben er zeker van dat, als dit continent nog te redden is, hieraan bij mij op de kamer een beslissende bijdrage wordt geleverd. Voor de rest verheug ik me zeer op hun promotie. Het laatste half jaar werd ik tenslotte nog verrast met een heuse mede Jeugdgezondheidszorg wetenschapper, Hein Raat, met wie ik samen nog mooie dingen hoop te bewerkstelligen.

Thuiszorg Rotterdam

De Stichting Thuiszorg Rotterdam is mijn echte werkgever. Het is bij al het bovenstaande universitaire trompetgeschal goed te beseffen dat Thuiszorg de organisatie is, die waarschijnlijk het meest in dit proefschrift heeft geïnvesteerd, door de ruimhartige manier waarop het mij werd toegestaan meer tijd aan het onderzoek te besteden, dan strikt in de detacheringafspraken was voorzien. Ik ben het management daarvoor zeer erkentelijk.

Daarnaast blijft Thuiszorg gewoon een inspirerende werkomgeving, waarbinnen van alles aan de hand is. Met het vormen van een aparte afdeling Ouder- en Kindzorg enige jaren geleden (destijds onder leiding van Erik Scheppink) werd een lang door mij gekoesterd ideaal verwezenlijkt. De nieuwe ontwikkelingen, die nu worden ingezet (onderleiding van Flip Paas) en die mogelijk gaan leiden tot de verwezenlijking van stelling 10 bij dit proefschrift, vormen een nieuwe uitdaging. Ik ben blij dat ik als stafarts bij beide ontwikkelingen betrokken ben geweest en zal zijn.

Zeer persoonlijke dank wil ik uitspreken aan het adres van mijn directe baas, Peter de Loof. Zijn immer loyale steun, warme belangstelling en altijd nuchtere raadgevingen hebben de afgelopen jaren veel voor mij betekend. Ik hoop dat ik, als hij me in de komende tijd weer eens vraagt hoe het met mij gaat, niet weer begin te vertellen hoe het met mijn onderzoek gaat. (Alsof dat hetzelfde is!).

Verder wil ik al mijn mede ZIO-medewerkers bedanken voor hun hartelijke collegialiteit. Twee van hen dienen apart genoemd te worden, namelijk mijn beide kamergenoten Mayke Wala en Robert Haartsen.
Mayke heeft ongetwijfeld tijdens mijn veelvuldige afwezigheid voor mij de meeste kastanjes uit het stafartsen-vuur gehaald. Tenslotte heeft zij zelfs deels één van mijn universitaire taken overgenomen, namelijk met betrekking tot het "cryptorchisme-project". Voor deze inzet dank ik haar zeer. Het meest heb ik echter genoten van onze soms heftige inhoudelijke discussies. Het was vooral leuk als we het niet met elkaar eens waren en ongeruste collega's voorzichtig hun hoofd om de deur staken om te kijken of we elkaar niet naar het leven stonden. Quod non, natuurlijk. Zo scherpen intellectuelen aan elkaar de geest.
Robert is de meest aimabele kamergenoot die je je maar kan wensen. Zijn pragmatisme is een verademing naast al het getheoretiseer van de twee inhoudelijke diehards, met wie hij zijn werkdagen moet doorbrengen. Ik dank hem voor zijn vriendschappelijke collegialiteit.

Het Sophia Kinderziekenhuis
Mijn banden met het "Sophie" zijn oud en hecht. Het was mij een genoegen daar weer eens regelmatig rond te kunnen lopen en oude en nieuwe vrienden te ontmoeten. Het is en blijft een bewonderenswaardig instituut.
Zeer veel dank ben ik verschuldigd aan alle kindercardiologen en functie-assistenten van de Afdeling Kindercardiologie voor de voortreffelijke wijze waarop zij de data voor ons onderzoek hebben verzameld en voor hun gastvrijheid. Twee personen wil ik met name noemen. Laura Verhagen, die vanaf het eerste begin op voorbeeldige wijze de logistiek van de dataverzameling heeft bewaakt en Maarten Witsenburg, die na het vertrek van John Hess voor mij het aanspreekpunt werd, hetgeen nog geleid heeft tot aanzienlijke verbeteringen van sommige onderdelen van het proefschrift. Ik ben er trots op dat Maarten bereid is gevonden deel uit te maken van mijn promotiecommissie.
Tenslotte een speciaal woord van dank aan Emiel Ronda en zijn medewerkers van het medisch archief voor hun ongeëvenaarde klantvriendelijkheid.

En verder
Paul Poustochkine dank ik voor zijn bereidheid op te treden als mijn paranimf. Hij vertegenwoordigt een groep van oude vrienden. De rest zal het wel mooi vinden, dat wij onze gewichtige persoonlijkheden weer eens in het aloude zwart-wit moeten hijsen. Blijft de vraag wie ons strikje moet strikken.
Karen Gribling-Laird heeft verwoede pogingen gedaan de taal van dit proefschrift enigszins op Engels te laten lijken. (PJvdM: Is dit wel een Laird-zin? REJ: Nee, die heb ik zelf verzonnen. PJvdM: Dat dacht ik al)

Een speciaal woord van dank aan Karien Stronks, erudiet wetenschapper en ex-MGZ-er, maar vooral ook uiterst gezellige buurvrouw. Het was in de eerst genoemde capaciteit, dat zij tijdens een treinreis heen en weer naar Groningen het hele manuscript heeft voorzien van talloze ontbrekende leestekens en er bovendien nog enkele zeer nuttige wenken en vragen bijplaatste. Het was voor mij een hele opluchting dat zij er bij vermeldde, dat ze het een mooi en zelfs spannend boek vond, hoewel ik vermoed dat zij dat vanuit haar tweede capaciteit deed.

Mijn broer Rein, de enige echte artiest in de familie, heeft het kaftje ontworpen. Leuk heh?

Mijn zwager Maarten en schoonzusje Gillie hebben gedurende twee weken in maart hun gastvrijheid en hun computer ter beschikking gesteld, wat een "Grote Sprong Voorwaarts" betekende. Mijn dank is groot.

Het laatste stukje van het proefschrift, het dankwoord voor de "inner circle" is het ingewikkeldste. Je kunt wel beweren dat je het allemaal voor hen hebt gedaan, maar is dat wel waar? Ach nee, je weet dat zij niet dankzij maar ondanks het proefschrift trots op je zijn en dat is zeker een belangrijke drijfveer om het af te maken. Zo'n promotie is in zekere zin een familiefeest en ik hoop dat ze er allemaal van zullen genieten: mijn lieve vader en moeder, die het in feite natuurlijk allemaal mogelijk hebben gemaakt, mijn twee zeergeleerde broers en die ene artiest, en moeder Iet, die het op deze dag zonder vader Arie moet stellen. Hij zou zeker beretrots zijn geweest en ik mis, ondanks de prima vervanging, mijn beoogde paranimf zeer.

Dan lopen er bij ons thuis nog twee van die lange enden rond (nu nog wel).

- Wat deed jouw vader vroeger? O, die promoveerde. Zolang als ik me kan herinneren.
- Jongens, je vader is thuis, dus alsjeblieft, ik wil het p-woord niet horen!
- De promotie is voorbij. Ik word wakker als uit een roes. Waar zijn de jongens? Ja, die zijn geslaagd voor hun eindexamen en studeren nu in Amsterdam, is je dat ontgaan?

Kunnen we toch nog niet eens met z'n drietjes naar de film in het Venster?

En dan Ita, er is dit jaar heel wat volbracht, en nu gaan we weer verder, met z'n tweetjes. Mooi toch?

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Curriculum Vitae van Rikard Edgard Juttmann

21-11-1950	Geboren te Rotterdam.
1963-1970	Rotterdams Motessori Lyceum Eindexamen Gymnasium B
1970-1978	Opleiding Geneeskunde, Erasmus Universiteit Rotterdam doctoraal: 1977, artsexamen: 1978.
1978-1980	Arts assistent Kindergeneeskunde, Sophia KinderZiekenhuis Rotterdam.
1980-heden	Stafarts Stichting Samenwerkende Rotterdamse Kruisverenigingen, sinds 1994: Stichting Thuiszorg Rotterdam.
1981-1983	Opleiding tot Sociaal Geneeskundige tak Jeugdgezondheidszorg Katholieke Universiteit Nijmegen.
1991-heden	Op parttime basis gedetacheerd bij het instituut Maatschappelijke GezondheidsZorg (iMGZ) Erasmus Universiteit Rotterdam voor diverse projecten:
	1991: Evaluatie screening op heupluxaties
	1992: Kosten-effectiviteits analyse in de Jeugdgezondheidszorg voor 0-4 jarigen: Methode en Mogelijkheden (financier: Ziekenfondsraad)
	1994-1997: Screening naar aangeboren Hartafwijkingen (financier: Hartstichting)
	1996-heden: Rotterdam Amblyopia Screening Evaluation Study (RAMSES)(financier:Preventiefonds)
	1997-heden: Voorbereidingen GRAND-studie met betrekking tot Ouder en Kindzorg binnen Thuiszorg
	1998-heden: Onderzoek naar de invloed van millieufactoren op de vruchtbaarheid en ontwikkeling van de mens. (financier: Endocrine Modulator Steering Group)
	1999-heden: Programmering studie effectiviteit Jeugdgezondheidszorg (financier: ZorgOnderzoek Nederland)
	1999-heden: Pilotstudie voor een kosteneffectiviteitsanalyse voor houdingsafwijkingen in de jeugdgezondheidszorg (financier: ZorgOnderzoek Nederland)
	1999-heden: Medewerker Onderwijs Cluster iMGZ.