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DIARRHOEAL DISEASES CONTROL PROGRAMME

Case-Control Studies of Childhood Diarrhoea:

IV. Choice of Control Group

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PREFACE

This document is the fourth in a series prepared for the Diarrhoeal Diseases Control Programme of the World Health Organization. The series is a response to an upsurge of interest in the application of the case-control method to the study of childhood diarrhoea. That interest has been stimulated by the realization that, under certain circumstances, the case-control method can be a relatively quick, inexpensive, and reliable method for measuring the impact of diarrhoea control measures or for identifying and quantifying risk factors for diarrhoea.

Case-control studies can be complex in their design and analysis, and it is not possible to prepare a manual that details methods that are appropriate in all circumstances. A considerable amount of epidemiological judgement and skill must be exercised. The aim of this series is to provide the investigator with a clear view of the most important problems in the design, analysis, and interpretation of case-control studies of childhood diarrhoea, and to provide practical suggestions for the resolution of those problems. For the trained and experienced epidemiologist, these documents provide specialized guidance on the application of case-control methods. For others, the series provides an awareness of the methodological issues involved, and a familiarity with the language and concepts of case-control studies. While it is hoped that the entire series will be of interest to and available to readers, each document has been prepared as an independent piece. For this reason the documents overlap in some areas.

Diarrhoeal diseases remain one of the leading causes of morbidity and mortality among children in poor communities in all parts of the world. Epidemiological studies have already contributed to an understanding of the risk factors involved and to the design and evaluation of appropriate interventions. Continued study of the epidemiology of diarrhoea is essential to refine these interventions further and to maximize their impact in reducing the number of severe illnesses and deaths. The Diarrhoeal Diseases Control (CDD) Programme of WHO supports a range of research projects in this field in many countries. Those seeking financial or technical support for their research, or wishing to contact others undertaking similar investigations, are invited to contact the CDD Programme.

ABSTRACT

In this paper we discuss the advantages and disadvantages of different choices of control group in case-control studies conducted to quantify the effects of risk factors for, and interventions against, childhood diarrhoea. A number of studies are reviewed to examine, in particular, whether bias may have occurred through the use of an inappropriate control group. While no direct evidence concerning the presence or absence of such bias is generally available, it is possible to draw some broad conclusions and make some recommendations on the basis of indirect evidence. It appears that an appropriate choice of control group in studies of the association between diarrhoea morbidity and water supply and sanitation interventions consists of children attending clinics with acute respiratory or other infections, such as malaria. The use of controls selected at random from the community may be appropriate in situations where the investigator is able to identify and include in the study <u>all</u> cases arising in a defined area. The choice of controls from the same neighbourhoods as the cases offers the advantage over controls selected at random from the community of matching controls to cases with regard to access to health facilities and a range of socioeconomic and environmental variables. In many situations neighbourhood controls will be more appropriate than controls selected at random from the community.

RESUME

Ce document expose les avantages et les inconvénients de différentes méthodes de sélection de groupes témoins pour des études cas-témoins destinées à quantifier les effets de différents facteurs de risque pour la diarrhée de l'enfant et d'interventions visant à la combattre. Plusieurs études ont été passées en revue pour déterminer en particulier si le choix d'un groupe témoin inapproprié ne risquait pas d'introduire un biais. Bien que l'on n'ait généralement pas de preuve directe de la présence ou de l'absence d'un tel biais, il est possible de formuler des conclusions générales et certaines recommandations sur la base de preuves indirectes. Il apparait que dans les études sur la relation entre la morbidité par diarrhée et l'approvisionnement en eau et l'assainissement, il est bon de choisir comme groupe témoin des enfants soignés dans des dispensaires pour des maladies respiratoires aiguës ou d'autres affections tel le paludisme. Il peut être indiqué de choisir des témoins au hasard au sein de la communauté dans les situations où l'enquêteur est capable de repérer et d'inclure dans l'étude <u>tous</u> les cas survenant dans une région donnée. Le choix de sujets témoins appartenant au même voisinage que les cas présente, par rapport au choix aléatoire de témoins dans la communauté, l'avantage d'apparier les témoins aux cas des points de vue de l'accès aux services de santé et de toute une gamme de variables socio-économiques et environnementales. Ainsi, dans bien des situations, il sera préférable de choisir des témoins dans le voisinage plutôt que de les sélectionner au hasard dans la communauté.

1. INTRODUCTION

In 1985 the World Health Organization issued a document entitled "Measuring the impact of water supply and sanitation facilities on diarrhoea morbidity: prospects for case-control methods" (Briscoe et al., 1985). This document was one of the products of two scientific meetings held in Cox's Bazaar, Bangladesh, and Geneva, Switzerland, at which methodologies for measuring the impact of water supply and sanitation projects on health were discussed. In the document, case-control studies were put forward as an alternative to longitudinal studies, whose use in this field had been discouraged by a report of an expert panel to the World Bank (International Bank for Reconstruction and Development, 1976).

The present series of papers considers the wider application of the case-control method to the study of the epidemiology of diarrhoeal diseases and of interventions for their control. The previous papers in the series dealt with the minimization of bias (number I), the choice of sample size (number II), and matching (number III). This paper, the fourth of the series, focuses on the choice of control group. In the first paper of this series (Cousens et al., 1988), we described the problem of selection bias and discussed strategies for minimizing such bias when controls are selected from children reporting to health facilities with diseases other than diarrhoea. In this paper we consider alternative choices of control group and review the evidence currently available from completed studies concerning the choice of controls.

We avoid the use of complex algebraic expressions and present instead simple numerical examples wherever possible. The statistical formulae used in the presentation of these examples are cited in the Annex. We begin by considering a hypothetical case-control study.

2. AN EXAMPLE OF A CASE-CONTROL STUDY

A case-control study is conducted to assess the association between the presence of domestic animals in the home and the risk of diarrhoea morbidity in children aged less than 5 years. The study is based on patients attending a single health facility. "Cases" are children reporting to the clinic in whom diarrhoea caused by an enteric infection is diagnosed; "controls" are randomly selected from children reporting to the clinic with conditions not thought to be related to the presence of domestic animals in the home and who are not suffering from diarrhoea. Information is collected concerning the presence of animals in the households of both cases and controls.

In their simplest form, the results of the study may be presented in the form of a 2 x 2 table:

	Cases	Controls	
Animals present	10	4	14
Animals not present	30	36	66
Total	40	40	80

The measure of association used in the analysis of case-control studies is the odds ratio (OR). For the above table this is calculated as follows:

$$OR = \frac{10 \times 36}{4 \times 30} = 3.0$$

This result suggests that children who live in houses where domestic animals are present are approximately three times more likely to suffer an attack of diarrhoea leading to attendance at a clinic than children in houses without animals.

To assist in interpreting the results, it is necessary to test the statistical significance of the association observed in our sample. Is there really an underlying association between the presence of animals and risk of diarrhoea or could our result have been obtained by chance? Even when we are studying a factor that is not associated with diarrhoea (i.e., true odds ratio = 1.0), we are unlikely to obtain an estimate exactly equal to 1.0, owing to sampling variations. How likely is it that our estimate of 3.0 has arisen in this way? One method of testing the significance of an association in a 2 x 2 table is to perform a chi-squared (X^2) test with one degree of freedom (Annex). From the table,

$$X^2 = \frac{80\,(\,|10 \times 36 - 4 \times 30| - 0.5 \times 80)^2}{40 \times 40 \times 66 \times 14}$$

$$= 2.16$$

Comparing this value against a table of values for a chi-squared distribution with one degree of freedom, it may be seen that the probability of obtaining a similar or more extreme result <u>purely by chance</u>, in a situation in which the true odds ratio equals 1, is greater than 0.1. Thus, our result is not statistically significant at the 10% level of significance. In this particular example we have not found strong evidence of an association. There are two possible reasons for this:

(1) no association exists between the presence of animals and the risk of diarrhoea,

(2) an association <u>does</u> exist, but our study was too small to detect it (i.e., to find a statistically significant association).

In our analysis and discussion of the example above, we assume implicitly that the cases and controls included in the study constitute unbiased samples of the children with and without diarrhoea severe enough to be taken to a clinic. Our assessment of the statistical significance of the observed association is based on this assumption and may be invalid if bias has occurred. One way in which bias may occur in case-control studies is through the choice of inappropriate controls. Bias arising in this way is known as selection bias (Schlesselman, 1982; Cousens <u>et al</u>., 1988).

3. AN EXAMPLE OF SELECTION BIAS

To illustrate the effects of selection bias we consider a hypothetical situation. Suppose an investigator wishes to determine the impact of an existing vitamin A supplementation programme on diarrhoea morbidity. The table below describes the incidence of diarrhoea in the population under study over a short period of time.

	Cases of diarrhoea	Total population	Rate/1000
Not receiving vitamin A	360	6000	60
Receiving vitamin A	120	4000	30

Among the children receiving vitamin A supplements the rate of diarrhoea is 30 per thousand, while among those not receiving supplements it is 60 per thousand; i.e., those not receiving supplements are at twice the risk of diarrhoea. Suppose, in addition, that vitamin A supplements are effective in reducing the incidence of acute respiratory infections (ARI) and that the incidence of these infections in the population is as shown below.

	Cases of ARI	Total population	Rate/1000
Not receiving vitamin A	540	6000	90
Receiving vitamin A	120	4000	30

Among the children receiving supplements the rate of ARI is 30 per thousand, while among those not receiving supplements it is 90 per thousand; i.e., those not receiving supplements are at three times the risk of ARI.

A case-control study is conducted to investigate the impact of vitamin A supplementation on diarrhoea morbidity. "Cases" are recruited from among children presenting at a health facility with diarrhoea. Note that to become a "case" in this study a child must fulfill two conditions: s/he must have diarrhoea <u>and</u> must also present at a health facility participating in the study. Having diarrhoea does not alone, make a child a "case" of diarrhoea as far as the study is concerned. Controls are selected from children reporting to the same facility with an ARI. Suppose now that there are differences in the clinic attendance habits of mothers of children receiving vitamin A supplementation and of those not. All mothers involved in the supplementation programme take their children to the facility if they fall ill with diarrhoea or an ARI. Among mothers not participating in the programme, 40% take their children to the facility when they suffer an episode of diarrhoea or an acute ARI, but the remaining 60% of mothers do not use the clinics at all. In this situation the investigator can expect to obtain the following results:

	Cases	Controls (ARI cases)
Not receiving vitamin A	144*	216+
Receiving vitamin A	120	120
	264	336
	Odds ratio = 0.67	

*40% of 360; +40% of 540

This result suggests that children not receiving vitamin A supplements are at <u>less</u> risk of diarrhoea than children receiving supplements; i.e., that the programme is increasing the incidence of (reported) diarrhoea. This is incorrect since we specified at the beginning of the example that vitamin A supplementation <u>reduces</u> the risk of diarrhoea morbidity. The bias in this estimate has occurred because of the way in which the controls were selected (children with an ARI, which is itself associated with vitamin A supplementation), and is therefore known as <u>selection bias</u>.

Suppose now that the investigator is aware that there may be an association between vitamin A supplementation and ARI, and realizes that the choice of children with ARI as controls may lead to selection bias. It is decided, therefore, to recruit controls at random from the community and the following results are obtained:

	Cases	Controls
Not receiving vitamin A	144	158*
Receiving vitamin A	120	106
	264	264
	Odds ratio = 0.8	

*60% of 264, as 60% of the population do not receive vitamin A supplementation.

Once again the result obtained is incorrect, suggesting that vitamin A supplementation increases diarrhoea morbidity. This time the bias has occurred because the control group has been selected in such a way as to include children who would not have been taken to the health facility even if they had been ill and could not, therefore, have become "cases" in the study.

4. PRINCIPLES UNDERLYING THE SELECTION OF CONTROLS

Two basic principles should be adhered to when choosing controls:

(1) Controls should be drawn from among children who would have become "cases" had they suffered from an episode of diarrhoea of appropriate severity during the period of the study (i.e., they would have been taken to a participating clinic).

(2) The exposure of controls to the factor of interest should be representative of the exposure of the population from which the cases are drawn.

We may use the study of vitamin A supplementation to illustrate each of these principles. The first principle may be reformulated in the following way: children who are not at risk of becoming cases in the study - for example, because their mother would not take them to the health facility if they had diarrhoea - should be excluded from the control group. In choosing the controls at random from the community (second control group) the investigator violated this principle. In order to see this, we divide the community into four groups, according to exposure and health facility usage.

	Health facility	
	User	Non-user
Not receiving vitamin A	2400 (40%)	3600 (60%)
Receiving vitamin A	4000 (100%)	0 (0%)

The selection of 264 controls from the whole community resulted in 106 controls who were receiving supplements (264 x 4000/10 000) and 158 controls who were not. If, however, the investigator had excluded the children who were not facility users (assuming that such children could be identified) and, therefore, would not have become "cases" even if they had suffered an episode of diarrhoea, the following results would be expected:

	Cases	Controls
Not receiving vitamin A	144	99
Receiving vitamin A	120	165
	264	264

Odds ratio = 2.0

This time the controls have been drawn from the 6400 children who use the health facilities. Of these, 4000 (62%) were receiving supplements.

Thus, among 264 controls, 165 (after rounding) were receiving supplements. The estimate of the odds ratio is now 2.0, suggesting that children who do not receive vitamin A supplements are at twice the risk of diarrhoea, as stated at the beginning of the example. Thus, this choice of control group has not led to any bias in the estimate of the odds ratio. We should note here that if reporting behaviour is unrelated to the exposure of interest (participation in the supplementation programme), the inclusion of non-clinic users in the control group will <u>not</u> cause selection bias to occur. In studies of diarrhoea, however, in the absence of randomization of exposure, it seems likely that many exposures of interest may be associated with health facility usage. For example, mothers with good personal and domestic hygiene practices may be more likely to take their child to a health facility in the event of illness than mothers with poor practices. Similarly, families who own latrines and use improved water supplies may be more likely to use clinics than families who do not own a latrine or do not use an improved water source.

The second principle underlying the selection of controls states that their exposure should be representative of the exposure of the population from which the cases are drawn. As we have just seen, the cases in the study were drawn from a population of 6400 clinic-using children, of whom 4000 (62%) were receiving supplements. In this example, by choosing as controls children presenting with ARI (the first control group), the investigator satisfied the first principle of control selection, since all those children recruited as controls would have been brought to the clinic had they suffered from an episode of diarrhoea. The exposure history of this group of children is not, however, representative of the population from which the cases were drawn since only 120 out of 336 ARI controls (36%) were receiving supplements. Thus, choosing as controls children with ARI, a condition associated, in this hypothetical example, with vitamin A supplementation, has led us to underestimate the proportion of the population that was receiving supplements. In this example, the investigator has violated the second principle of control selection. We should also note here that we have assumed for the purposes of this example that mothers behave in the same way when their child has an ARI as when s/he has diarrhoea. If this is not true, then the first principle given above may be violated and this could result in selection bias.

5. CHOICE OF CONTROL GROUP

In section 3 we illustrated the problem of selection bias with two examples of control groups that result in bias. In this section we consider a wider range of possible control groups and review the experience accumulated so far with each of the different groups in actual field studies.

Some of the ways in which controls have been selected in recent case-control studies of diarrhoea are summarized in Table 1. This list is not intended to be comprehensive: other choices are possible, and their omission from the list does not imply that the use of such groups would necessarily be wrong.

Table 1. Some possible choices of control group for studies of diarrhoea morbidity and mortality

<u>Clinic controls</u>:

(1) diseased children attending the same health facility as the cases,

(2) healthy children attending immunization or well-baby clinics.

<u>Community controls</u>:

(3) neighbours of children recruited as cases,

(4) children selected at random from the community served by the clinic(s) at which cases are recruited.

We now discuss the theoretical advantages and disadvantages of each of the groups listed in Table 1, and review the present experience with each.

5.1 <u>Diseased controls</u>

Briscoe <u>et al</u>. (1985), in advancing the use of the case-control method for the study of the impact of water and sanitation interventions on diarrhoea morbidity, proposed that controls be selected from among children attending health facilities for complaints other than diarrhoea. More specifically, it was recommended that controls should be selected from children presenting with diseases of a "similar severity" to diarrhoea but which were not related to water or sanitation. The rationale behind this proposal is discussed below.

By choosing diseases of "similar severity" to diarrhoea, it is hoped to ensure that children brought to the facility with a control disease would also have been brought had they suffered an episode of diarrhoea and vice versa. In order to achieve this, control diseases must be chosen such that episodes of these diseases will lead the mother to take the child to a health facility with the same probability as for an episode of diarrhoea. If the control diseases chosen satisfy this criterion, then the first principle in selecting controls, namely, that they should be drawn from the same population as the cases, will be fulfilled.

Identifying complaints of a "similar severity" to diarrhoea may not be simple. We are <u>not</u> dealing with severity as measured by a clinician and, in many settings, a mother's propensity to take her child to a health facility will depend not only upon <u>her</u> perception of the severity of the particular complaint from which her child is suffering, but also upon her perception of the usefulness of medical care for that complaint. In the absence of any direct measure of a mother's propensity to report, it is very difficult to determine whether the choice of control disease(s) has achieved the desired effect. A crude assessment of the mother's perception of the severity of the complaint and the utility of reporting may be obtained by comparing cases and controls with regard to such variables as the duration of the episode prior to reporting and the distance travelled and time taken to reach the clinic.

The second requirement specified by Briscoe <u>et al</u>. (1985) is that children reporting with water- and sanitation- (exposure-) related diseases as the primary complaint should be excluded from the control series. This is necessary to meet the second principle underlying the selection of controls, namely, that the exposure of controls should be representative of the exposure of the population from which the cases are drawn. The recruitment of controls presenting with exposure-related complaints will lead to an overestimate of the exposure of the population and will tend to mask any impact of the intervention (as we saw in the example of vitamin A supplementation). Recruiting controls from children presenting with one of several diseases will dilute the bias that will occur if one of the diseases is related to the exposure of interest. Instead of recruiting all controls from one diagnostic category, it is preferable to select them from among children in at least two or three diagnostic categories. If possible, each category should contain a sufficient number of children to allow a separate comparison with the cases.

Two disadvantages of using diseased children as controls may be identified. First, for some risk factors/interventions (e.g., breast-feeding, vitamin A deficiency/supplementation) it may be difficult to identify enough children with complaints known to be unrelated to exposure. Both breast-feeding and vitamin A supplementation may offer children some protection against a wide range of infections. Thus, recruitment as controls of children with infectious diseases may lead to an underestimate of the impact of breast-feeding or vitamin A supplementation. Second, if only a small proportion of children are clinic users, the use of clinic cases and clinic controls will mean that, strictly speaking, the results from the study apply only to a relatively small section of the community (clinic users) rather than to the community as a whole. In theory, this will be a problem only in situations in which the exposure of interest has different effects on clinic users and non-users. In practice, we do not usually know whether this kind of effect occurs or is important.

Table 2 summarizes a number of clinic-based case-control studies of diarrhoea morbidity. All of these studies recruited as cases children presenting at selected health facilities with diarrhoea. Controls were selected from among children presenting at the same facilities with complaints other than diarrhoea. All the studies listed in Table 2 examined the impact of water and/or sanitation interventions on diarrhoea morbidity and were a direct outcome of the meetings held in Cox's Bazaar, Bangladesh, and Geneva, Switzerland, and the subsequent document advancing the case-control method (Briscoe <u>et al</u>., 1985).

Table 2. A summary of some clinic-based case-control studies of diarrhoea morbidity which recruited as controls diseased children presenting at health facilities

Country of study	Risk factor	Control diseases	Reference
Malawi	Water supply/ sanitation	malaria/ARI/pertussis/ measles	Young and Briscoe (1988)
Philippines	Water supply/ sanitation	ARI	Baltazar <u>et al</u>.(1988)
Sri Lanka	Water supply/ stool disposal	malaria/ARI/tonsillitis/ otitis/PUO/chickenpox	Mertens <u>et al</u>.(1990a)
Nicaragua*	Water supply	malaria/ARI/measles/otitis/ mumps/PUO/skin/disorders/ conjunctivitis/urinary tract/ disorders/oral candidiasis/ chickenpox/allergy	Sandiford (1988)
Lesotho	Sanitation	ARI/trauma	Daniels <u>et al</u>. (in press)

*Controls with conjunctivitis and skin disorders (which may be related to water quantity) were excluded from analyses of the association between water availability and diarrhoea.

Briscoe et al. (1988) have reviewed the findings of the first two studies in Malawi and the Philippines. Both studies reported reductions in diarrhoea morbidity of about 20% associated with improvements in both water supply and sanitation facilities. In neither study was the reduction statistically significant. Of particular methodological interest was the observation, in both studies, that the crude estimate of the odds ratio was very similar to the estimate obtained after taking account of a range of potential confounders, including socioeconomic and demographic characteristics of cases and controls (0.80 vs 0.77 in Malawi, 0.79 vs 0.80 in the Philippines). Similar findings have since been reported from Sri Lanka, Nicaragua, and Lesotho. In Lesotho, the similarity of the crude and adjusted estimates is particularly striking, both being equal to 0.76 (suggesting a 24% reduction in reported diarrhoea morbidity associated with latrine ownership).

In some circumstances selection bias may be controlled in the analysis by stratification. For example, suppose that the probability that the child will be taken to the clinic is related to the distance from the child's home to the clinic, and that this relationship differs between diarrhoea and the control diseases. Then, if exposure varies with the distance of the child's home from the clinic, selection bias will occur. This bias may be controlled at the stage of analysis by stratifying on distance from home to clinic (Cousens et al., 1988). The absence of evidence of confounding in the studies listed in Table 2 does not prove that no selection bias occurred in these studies. It does suggest, however, that either the cases and controls were drawn from the same underlying population of children (i.e., cases were at risk of becoming controls and vice versa) or the appropriate confounders were not measured or were measured inaccurately. Given the large number and wide range of potential confounding variables considered in these studies, it seems unlikely that any important confounding variables were missed altogether. We believe, therefore, that in these studies the first principle in selecting controls (namely, that they should come from the same population as the cases) probably was satisfied. Thus, provided that the controls were selected from among children with diseases unrelated to water and sanitation facilities, it seems probable that any selection bias that did occur in these studies was small.

5.2 Healthy children attending immunization or well-baby clinics

The selection of diseased controls may be inappropriate to the study of certain risk factors and interventions. In particular, the use of such controls in studies of breast-feeding and weaning practices and vitamin A deficiency or supplementation may lead to substantial selection bias and/or recruitment problems. Both of these risk factors may be associated with other infectious diseases. In particular, they may be strongly associated with ARI. This group of infections provided all the controls in the Philippines study, almost 98% of the controls in Lesotho, 65% of controls in Nicaragua, almost 50% of controls in Sri Lanka, and 48% of controls in Malawi. Exclusion from the control series of children with respiratory infections would have made it difficult to recruit sufficient controls in some of these studies, particularly in Lesotho where malaria is not prevalent.

An alternative to recruiting as controls children who come to health facilities because they are ill is to recruit children attending well-baby or immunization clinics. Such a choice needs to be carefully thought through. In many settings immunization coverage may be low, and the proportion of children attending well-baby clinics may be smaller still. In such situations it is probable that children who do attend for immunization, growth monitoring, etc. are not representative of the population as a whole. Their mothers may come from different backgrounds and have different attitudes and beliefs concerning health than the remainder of the population. In these circumstances, their children's history of exposure to, for example, breast-feeding may be very different to that of the population as a whole and their selection as controls could result in substantial selection bias. One approach to this problem would be to exclude from the case series any child who has not attended, for example, an immunization clinic. This would ensure that all cases are potential controls. Since it seems likely that mothers bringing children for immunization will also bring their child to a clinic when the child falls ill, such a strategy should substantially reduce any selection bias that might occur. In areas with low immunization coverage, this would, however, lead to the exclusion of a substantial proportion of potential cases and might make it difficult to obtain sufficient eligible cases. In addition, the results of a study conducted in such a way would, strictly speaking, be applicable to only a relatively small subset of the population.

An additional problem may arise with the choice of children attending immunization or well-baby clinics. A substantial majority of such children are likely to be under 1 year of age. This will not present a problem for studies of infantile diarrhoea. However, studies of diarrhoea across a wider age range will include a substantial number of cases aged 12-23 months. Selecting controls from children attending immunization clinics may provide insufficient controls in this age range, and the controls who are recruited in this age range may differ from the rest of the control group.

In a study of breast-feeding and diarrhoea conducted in Basrah, Iraq, cases were recruited from infants with diarrhoea admitted to Basrah Paediatric Hospital. Controls were selected from among healthy children attending Maternal and Child Health Clinics (MCHCs) for immunization and/or routine check-up (Mahmood, 1988). Immunization with BCG, DPT, and oral polio vaccines is compulsory in Iraq, and children cannot be issued with an identity card until they have completed immunization with these vaccines. In this setting, therefore, the breast-feeding status of such children should be representative of the population as a whole. In addition, to ensure that all cases were "at risk" of being selected as controls, those over 3 months of age with no record of immunization at an MCHC were excluded. These strategies will have substantially reduced, but not eliminated, the possibility of selection bias. This could have occurred if:

(i) within the population there was a group of children who attended MCHCs for vaccination but would not have been taken to hospital had they suffered an episode of diarrhoea, <u>and</u>

(ii) the breast-feeding practices of the mothers of these children differed from those of the rest of the population.

Mahmood (1988), in drawing attention to this potential problem, suggests that the fact that cases were hospitalized children (and therefore representative of more severe episodes) is likely to have reduced the variation in reporting practices among the different subsections of the population. Put another way, it is argued that it is unlikely that children who suffered an episode of diarrhoea of sufficient severity to warrant hospitalization would not have been brought to the hospital and therefore become "cases". This is less likely to be true when a study recruits more mild cases of diarrhoea. While this is an appealing argument, its strength depends upon there being a close correlation between the clinical assessment of the severity of the episode and the decision to hospitalize, and upon the assumption that almost all severe cases are seen at the hospital. In many situations the decision to hospitalize may be a poor surrogate for severity since that decision may be made on the basis of many other considerations, including anticipated compliance and remoteness of residence (J.D. Clemens, personal communication). Furthermore, the assumption that almost all severe cases are seen at the hospital may not hold in many settings.

The observation that in studies of water and sanitation little confounding appears to occur has led to the suggestion that it might be possible in future to conduct very simple case-control studies of the association between diarrhoea and water and sanitation interventions in which data on confounders would not be collected (Briscoe <u>et al</u>., 1988). It is interesting, therefore, to examine whether evidence of confounding was observed in the study of Mahmood (1988) (Table 3).

Table 3. Selected results from a study of breast-feeding and risk of diarrhoea, Basrah, Iraq (Mahmood, 1988)

Age in months	Breast-feeding status	Crude estimate of the odds ratio	Adjusted estimate* of the odds ratio
2-3	Exclusive	1.0	1.0
	Partial	4.1	6.2
	None	13.2	36.8
4-5	Exclusive	1.0	1.0
	Partial	1.9	2.9
	None	13.7	23.8
6-11	Exclusive	1.0	1.0
	Partial	2.3	1.4
	None	4.0	3.4

*Adjusted for month of recruitment, maternal education, place of residence, sex, home ownership, car ownership, type of housing, and boiling of drinking water.

In contrast to the studies of water supply and sanitation described above, some evidence of confounding was observed in this study. Among children aged less than 6 months, the estimates of the protective effect of breast-feeding after adjusting for confounding were substantially larger than those obtained from a crude analysis. Among children aged 6 months or more, adjustment for potential confounding variables led to some reduction in the apparent protective effect of breast-feeding. This suggests that the breast-feeding behaviour of the mother was related to her level of education and socioeconomic status, and that these factors were also independently associated with the risk of severe diarrhoea. It is worth noting here that any confounding effect of socioeconomic status in studies of breast-feeding is likely to be different to that in studies of water and sanitation interventions. Breast-feeding is frequently more common among the poor, so that adjustment for socioeconomic status is likely to lead to estimates of the odds ratio <u>further</u> from unity than the crude estimate. On the other hand, since water and sanitation tend to be less adequate among the poor, adjusting for socioeconomic status is likely to lead to estimates of the odds ratio <u>closer</u> to unity than the crude estimate.

5.3 <u>Neighbourhood controls</u>

"Neighbourhood" controls are those selected from children living as neighbours of cases. The choice of such controls offers the investigator two potential advantages.

First, in many settings neighbours tend to belong to similar socioeconomic groups, to share a common environment, and to have similar access to health facilities. Thus, by choosing neighbourhood controls and performing a matched analysis, the investigator may be able to control a range of potentially confounding variables which might otherwise be difficult to quantify (see Cousens <u>et al</u>., 1989). Second, if the choice of neighbourhood controls is appropriate, the results of a study that recruits such controls will apply to the community as a whole, rather than to just that section of the population which uses health facilities. Whether or not the choice of neighbourhood controls is appropriate will depend largely upon the way in which cases are recruited into the study. We have already presented an example of how, by selecting controls from the whole community, we may include children who could never be included in the study as cases, and how this may lead to substantial bias in the estimate of the odds ratio. It is important, therefore, that before selecting neighbourhood controls the investigator is satisfied that:

(i) all diarrhoea cases of appropriate severity will come to his/her attention and be included in the study, <u>or</u>

(ii) diarrhoea cases recruited into the study are representative of all episodes that occur in the community and meet the study's case definition, <u>or</u>

(iii) it is possible to identify among the neighbourhood controls those who could not have been included in the study as cases, and exclude them from the analysis.

The choice of neighbourhood controls may carry with it other disadvantages. First, it may be very inefficient for the study of some exposures. For example, in many settings neighbours tend to use the same water supply, so that the use of neighbourhood controls would lead to a high proportion of case-control pairs having identical exposure. These pairs would not contribute any information to a matched analysis and would therefore be "wasted". Second, the recruitment of neighbourhood controls will require fieldworkers to visit the place of residence of each case and identify a neighbouring child who fulfills the eligibility criteria for inclusion in the study. This may substantially increase the cost and logistic complexity of the study, particularly in comparison with a clinic-based study in which it may be possible to collect the required information at the clinic, it being necessary to visit only a subsample of cases and controls at home for validation purposes.

Neighbourhood controls have been used in a population-based case-control study of diarrhoea <u>mortality</u> conducted in Brazil (Victora <u>et al</u>., 1988a, 1988b, 1989). Infant deaths were identified by weekly visits to all hospitals, coroners' offices, and health authorities and registries in the study area. Cases were those infant deaths considered to be due to diarrhoea. For each case two neighbours were recruited as controls. The level of ascertainment of infant deaths was believed to be very high in this study, and thus the use of neighbourhood controls here probably did not introduce into the control series many, if any, children who would not have been detected as cases had they died from diarrhoea. This study therefore satisfied condition (i) above and so the recruitment of neighbourhood controls was appropriate and probably did not introduce any substantial selection bias.

The investigators have reported a strong protective effect of breast-feeding against death due to diarrhoea (Victora <u>et al</u>., 1989). Similar trends were apparent in both the crude analyses of the data and in the analyses adjusting for potential confounding variables. Some evidence of confounding of the association between breast-feeding and diarrhoea mortality is observed when the crude estimates obtained are compared with the adjusted estimates. Broadly speaking, the magnitude of the association between failure to breast-feed and risk of diarrhoea mortality appeared to <u>increase</u> when confounders were controlled.

The relationship between water supply, sanitation, and diarrhoea mortality was also examined in this study (Victora <u>et al</u>., 1988b). Statistically significant crude associations were observed between diarrhoea mortality and availability of water and type of toilet. When confounding variables were controlled in the analysis, the association between type of latrine and diarrhoea mortality disappeared. The association between availability of water and diarrhoea mortality remained statistically significant, but was somewhat reduced in magnitude. These observations are in contrast to those from the studies of diarrhoea morbidity and water supply/sanitation discussed above, in which little evidence of confounding was observed.

The Brazilian study also found some evidence of an association between low birthweight and diarrhoea mortality (Victora <u>et al</u>., 1988a). Adjusting for confounders tended to reduce the magnitude of this association.

5.4 Children selected at random from the community

As with the choice of neighbourhood controls, the choice as controls of children selected at random from the community will only be appropriate if:

(i) all diarrhoea cases of appropriate severity come to the investigator's attention and are included in the study, or

(ii) diarrhoea cases recruited into the study are representative of all episodes that occur in the community and meet the study's case definition, or

(iii) it is possible to identify among the community controls those who could not have been included in the study as cases, and exclude them from the analysis.

As with neighbourhood controls, if condition (i) or (ii) is met, the use of randomly selected community controls will provide results that apply to the whole community rather than a subgroup of clinic users. Compared with neighbourhood controls, this group does not carry the potential benefit of matching controls to cases with regard to a range of socioeconomic and environmental variables. Nor, in situations in which condition (i) is not met, will controls be matched to cases with regard to their access to the health facilities. On the other hand, if a cluster sampling technique is used to select the community controls, the resources required to recruit this group may be considerably fewer than those required by neighbourhood controls, especially in rural populations scattered over a large area.

In the foregoing discussions, we have considered some of the ways in which selection bias may arise and, in the light of these considerations, we have examined the likelihood that selection bias occurred in a number of studies. In these discussions we have taken account of theory, common sense, and some indirect evidence relating to selection bias. More direct evidence concerning the presence or absence of selection bias may be obtained by recruiting two or more groups of controls, each selected in a different way, and comparing the results obtained with each group. If both (all) the control groups yield similar results when compared with the cases then either both (all) control groups induced similar degrees of selection bias or no substantial selection bias occurred. If the control groups are chosen in quite different ways, it is unlikely that any selection bias arising in the different groups will be similar. Thus, such findings are often regarded as evidence that selection bias did not occur. (They do not, however, constitute proof that selection bias did not occur.) If, on the other hand, the groups produce different results, then selection bias is probably responsible. The problem that then arises is to determine which, if any, of the control groups provide unbiased results.

Two previously discussed studies in Sri Lanka (Mertens, 1989) and Lesotho (Daniels and Cousens, 1988), in addition to recruiting diseased, clinic-based controls, recruited second control groups at random from the community.

In Sri Lanka, community controls were selected using a multi-stage sampling scheme. Half of the administrative units within the catchment areas of three of the hospitals participating in the study were selected at random, and a census of households was performed. From the census list, households with children aged less than 5 years were selected at random. In each of the households selected the youngest child was recruited as a community control.

The comparison of cases with clinic controls led to a crude estimated odds ratio of the association between water supply and diarrhoea morbidity of 0.65 (95% confidence interval 0.58 to 0.74) (Mertens et al., 1990a). This result suggests that children living in households that draw water from an improved source (tap, handpump, or improved shallow well) suffer 35% fewer episodes of (reported) diarrhoea than children living in households that use unimproved sources. This association varied, however, among the five hospitals. In one hospital the reduction in diarrhoea morbidity associated with the use of improved water sources was of the order of 90%. In the other four hospitals a much smaller reduction of 18% was observed (odds ratio = 0.82, 95% confidence interval 0.69 to 0.98). When stratified analyses of the data from these four hospitals were performed, the estimate of the odds ratio remained remarkably stable, ranging between 0.80 (a 20% reduction) and 0.84 (a 16% reduction).

When clinic cases were compared with community controls, rather different results emerged (Mertens, 1989). In the catchment area of the hospital that showed such a large reduction in diarrhoea associated with improved water supplies when clinic cases were compared with clinic controls, some evidence of a reduction, albeit of smaller magnitude, was also observed when cases were compared with community controls. Of the other two areas in which community controls were recruited, one showed no evidence of an association between diarrhoea morbidity and type of water supply, while in the other the incidence of reported diarrhoea morbidity appeared to be higher among children in households that used improved supplies.

In Lesotho, community controls were selected using a cluster sampling scheme. Cases were recruited in four health facilities in one district of Lesotho. In order to select the community controls, villages in the district were randomly selected using a village register prepared for the 1986 census. The probability of selecting a village was weighted according to its population at the time of the census. From each village selected, 32 children were recruited as community controls.

The comparison of cases with clinic controls led to a crude estimated odds ratio of the association between latrine ownership and diarrhoea morbidity of 0.76 (95% confidence interval 0.62 to 0.93) (Daniels et al., in press). This result suggests that children living in households with latrines suffer 24% fewer episodes of reported diarrhoea than children living in households without a latrine. When stratified analyses accounting for potential confounding variables were performed, the estimate of the odds ratio remained relatively stable, ranging between 0.70 and 0.82. Logistic regression analyses of the data to control several confounders simultaneously resulted in an estimated odds ratio of 0.76 (95% confidence interval 0.58 to 1.01), the same point estimate as that obtained from the crude analysis. A crude comparison of cases with community controls, on the other hand, yielded an estimate of the odds ratio of 1.89 (95% confidence interval 1.52 to 2.34), suggesting that children in latrine-owning households suffer 89% more episodes of (reported) diarrhoea (Daniels and Cousens, 1988). When stratified analyses were performed, the estimate of the odds ratio varied considerably - between 1.40 (controlling area of residence) and 2.05 (controlling the number of rooms in the family home). Logistic regression analyses produced a wide range of estimates of the odds ratio, the lowest being 1.02.

In both Sri Lanka and Lesotho, comparisons of cases with community controls produced results that differed from those obtained in comparisons of cases with clinic controls. These ranged from differences in the estimated magnitude of an association to more fundamental differences in the apparent direction of the association. These findings strongly suggest that selection bias arose in the recruitment of one or both groups of controls. Such a situation leaves the investigator with a serious problem of interpretation: which set of results, if either, should be believed? Daniels and Cousens (1988), in discussing the results of the Lesotho study, argue in favour of the clinic-based control group on several grounds.

On the one hand, cases and clinic controls were all children who had been taken to one of four clinics because they were ill. On the other hand, the community control group will have included some children who would never have been taken to a clinic for an episode of diarrhoea. As we have seen, this may introduce substantial selection bias. At the time of recruitment mothers of community controls were questioned about what they did when their child fell ill. Exclusion from the analysis of children whose mothers did not report the use of health facilities did not, however, produce any great change in the results. In this study this strategy may have been unsuccessful in reducing selection bias if some mothers falsely reported using health facilities to an interviewer who was asking questions on behalf of the Ministry of Health. In addition, community controls were selected at random from the whole of the district and some children who would have been taken to clinics had they fallen ill would have been taken to facilities that were not participating in the study. Since the distribution of latrine ownership was not uniform throughout the district, but was highest in the areas around the clinics that participated in the study, this could also have introduced substantial bias. This hypothesis is supported by the results of the analysis of cases and community controls, which revealed a substantial degree of confounding. Constituency (an administrative subdivision of the district) of residence strongly confounded the association between latrine ownership and diarrhoea morbidity, altering the estimated odds ratio from 1.89 to 1.40. Unfortunately, information on constituency provides only a very crude categorization of a child's place of residence. It is likely, therefore, that some residual confounding of the association remained even after attempts to control it. The comparison of cases with clinic controls, on the other hand, revealed little evidence that confounding of the association between latrine ownership and diarrhoea morbidity had occurred. Finally, during the recruitment of community controls, mothers were asked if the child had diarrhoea at the time of the interview. Of 843 community controls recruited, 37 had diarrhoea at the time of the interview. A comparison of these 37 children with the remaining 806 community controls produced a crude odds ratio of 0.50; i.e., within the community control group itself, latrine ownership was associated with a 50% reduction in the odds of diarrhoea. This result is consistent with those obtained from the comparison of cases with clinic controls rather than with those from the comparison with community controls.

Similar arguments apply to the Sri Lankan study. There was little evidence of confounding of the association between diarrhoea morbidity and water supply when cases were compared with clinic controls. A greater degree of confounding was observed in the comparison of cases with community controls. There was some evidence that community controls came from wealthier households than either clinic cases or clinic controls, suggesting that it is the poorest sections of the population that use government facilities, better-off families preferring private practitioners (Mertens *et al.*, 1990b). That is, community controls and cases were drawn from different populations.

6. SUMMARY

In this paper we discuss the problem of selection bias in the context of case-control studies of risk factors for, and interventions for the control of, childhood diarrhoea. The theoretical advantages and disadvantages of each of four possible choices of control group are considered. In addition, a number of studies that used the different types of control group are reviewed to assess the likelihood that any substantial degree of selection bias occurred. Direct evidence concerning the presence or absence of selection bias can be obtained only by conducting a prospective study in the same setting as the case-control study and comparing the results obtained from each. This has been done in the Philippines, but the results are not yet available. In the absence of any truly direct evidence, the best evidence we have concerning selection bias comes from studies in which multiple control groups, selected in different ways, were recruited. From the indirect evidence currently available, it is possible to draw a number of tentative conclusions and make some general recommendations:

(1) When diseased clinic controls are recruited they should be recruited from children with diseases that are of similar severity to diarrhoea and are unrelated to the exposure of interest. The recruitment of children who present with one of several complaints will dilute any bias that may arise if one of the control diseases does not meet the above criteria. In studies of the impact of water supply and sanitation interventions on diarrhoea morbidity, an appropriate choice of control group appears to be children attending clinics with acute respiratory or other infections such as malaria.

(2) The use of neighbourhood or community controls will be appropriate in situations in which the investigator is able to identify and include in the study *all* cases of diarrhoea that occur in the community and meet the study's case definition. This condition is, perhaps, most likely to be met in studies of severe episodes of diarrhoea, i.e., those leading to hospitalization or death. Investigators should not assume, however, that neighbourhood or community controls will always be suitable in

studies of, for example, diarrhoea mortality. In some settings the level of ascertainment of deaths due to diarrhoea may be very poor indeed. In such situations it may be difficult to define any satisfactory control group. In theory, neighbourhood or community controls will also be appropriate if the investigator can identify and exclude children who could not have been included in the study as cases, for example, children in families that do not use health facilities. The investigator may attempt to do this by asking the mother what she does when her child is ill. Results from Lesotho suggest, however, that such a strategy may not always be successful in eliminating selection bias arising in this way and should, therefore, be used with caution. In general, it is recommended that neighbourhood or community controls be used only in situations in which the investigator can identify and recruit as cases nearly all the children in the community who meet the study's case definition, or in conjunction with another control group. The second control group may enable some assessment to be made of the appropriateness of the neighbourhood or community controls.

(3) The use of controls selected at random from the community does not have the advantage offered by neighbourhood controls of matching controls to cases with regard to access to health facilities and a range of socioeconomic and environmental variables. Results from Lesotho and Sri Lanka indicate that such controls should be used only with extreme caution. In most situations neighbourhood controls will be more appropriate than randomly selected community controls.

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ANNEX

STATISTICAL FORMULAE

1. Analysis of a single 2 x 2 table

	Case	Control	
Exposed	a	b	r1
Unexposed	c	d	r2
	m1	m2	n

$$\text{Odds ratio} = \frac{a \times d}{b \times c}$$

$$X^2 = \frac{n \times [\,|axd - bxc| - 0.5xn\,]^2}{m1 \times m2 \times r1 \times r2}$$

The statistical significance of the observed association is found by comparing the value of X^2 with the percentage points of the chi-squared distribution with one degree of freedom. If X^2 is greater than 3.84, then the association is significant at the 5% level; if X^2 is greater than 6.63, then the association is significant at the 1% level.

2. Stratified analysis

The data have been divided into several strata each of which may be represented in the form of a 2 x 2 table. The (i) indicates that this table represents the ith strata.

	Case	Control	
Exposed	a(i)	b(i)	r1(i)
Unexposed	c(i)	d(i)	r2(i)
	m1(i)	m2(i)	n(i)

$$\text{Mantel-Haenszel OR} = \frac{\dfrac{a(1)xd(1)}{n(1)} + \dfrac{a(2)xd(2)}{n(2)} + \ldots\ldots}{\dfrac{b(1)xc(1)}{n(1)} + \dfrac{b(2)xc(2)}{n(2)} + \ldots\ldots}$$

$$\text{Mantel-Haenszel } X^2 = \frac{N}{D}$$

where

$$N = \left[\left|\frac{a(1)xd(1) - b(1)xc(1)}{n(1)} + \frac{a(2)xd(2) - b(2)xc(2)}{n(2)} + \ldots\ldots\right| - 0.5\right]^2$$

and

$$D = \frac{m1(1) \times m2(1) \times r1(1) \times r2(1)}{n(1) \times n(1) \times [n(1)-1]} + \frac{m1(2) \times m2(2) \times r1(2) \times r2(2)}{n(2) \times n(2) \times [n(2)-1]} + \ldots\ldots$$

Annex

The statistical significance of the observed overall association, as estimated by the Mantel-Haenszel odds ratio, is found by comparing the value of the Mantel-Haenszel X^2 statistic with the percentage points of the chi-squared distribution with one degree of freedom. If X^2 is greater than 3.84, then the association is significant at the 5% level; if X^2 is greater than 6.63, then the association is significant at the 1% level.

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