Influence of cross-sex transmission on measles mortality in rural Senegal

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Previous studies of measles mortality in West Africa have shown a significantly higher case-fatality rate (CFR) among girls than among boys. This study aimed to find out whether the male/female difference in CFR is related to different risks for boys and girls of being infected as secondary rather than index cases and of transmission from someone of the same or the opposite sex.

The study was conducted in Niakhar, a rural area of Senegal (population 24 000). All cases of measles reported between March, 1983, and December, 1986, were investigated to determine source of infection and pattern of transmission. For each case, the closest source of infection was judged the most likely. Death was attributed to measles if it occurred within 6 weeks of the onset of rash. Girls had a higher measles CFR than boys (53 deaths/722 cases [7·3%] *vs* 45/778 [5·8%]); the relative risk of death was 1·30 (95% confidence interval [CI] 0·89–1·90). Secondary cases infected by a child of the opposite sex had a 2·44 (1·48–4·02) times higher risk of death than did secondary cases infected by a child of the same sex. The risk of cross-sex transmission of infection was significantly greater for female than for male secondary cases (1·26 [1·09–1·47]). When this difference in risk of exposure to infection from the opposite sex was taken into account, the difference in risk of death between girls and boys disappeared (1·06 [0·66–1·69]). Within families, the CFR was higher in huts with 1 boy and 1 girl affected than in huts of either 2 boys or 2 girls affected (relative risk 2·16 [0·99–4·70]).

Measles infection contracted from a person of the opposite sex is more severe. Variation in exposure may be an important determinant of sex differences in case fatality.

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Introduction

Studies of measles infection in Guinea-Bissau and elsewhere have shown that the case-fatality rate (CFR) is much higher among secondary cases (infection contracted from someone living in the same house) than in index cases (infection contracted from someone outside the house).[1,2] This finding suggests that intensive exposure is an important risk factor for severity of acute measles infection. More surprising, however, is the observation in several epidemics of a higher CFR among secondary cases infected by a person of the opposite sex rather than one of the same sex.[3] These observations suggest that cross-sex transmission is an important risk factor for mortality in infectious diseases, which may help to explain variation in mortality by sex. A longitudinal study of measles infection in rural Senegal[4] has found a significantly higher CFR for girls than for boys. The aim of the study reported here was to find out whether the male/female difference in CFR could be related to different risks for boys and girls of being infected as secondary cases and of being infected by a child of the opposite sex.

Subjects and methods

The Senegal study was conducted in thirty villages near Niakhar, region of Fatick.[2] This area (population 24 000) has been under demographic surveillance since March, 1983.[2,4] A third of the population has been under continuous surveillance since 1963.[4] The area is populated almost exclusively by the Sereer, who live in compounds with an average of 14 people. Larger compounds are usually divided into several households—ie, the group of people who eat together. Within a household, people may sleep in different huts; on average, there are 8·0 people per household and 2·5 per hut.

In the study area, there are only three large villages with a concentrated settlement pattern and most of the population is scattered in small hamlets. As a result, there may be long intervals between epidemics of measles in any particular village. The mean age at infection is high, around 4 years. Vaccine coverage against measles was poor during the study period. There were major vaccination campaigns in 1978–82, and again in 1987–89 during the acceleration phase of the Expanded Programme on Immunisation (EPI). During the study period, less than 33% of susceptible children under 14 years were protected by vaccination.

The study of measles epidemiology, which started in March, 1983, and ended in December, 1986, has been described in detail elsewhere.[2] Every year after the annual census, all reported cases of measles were investigated to determine the source of infection and the pattern of transmission within the compound. In every compound, the list of reported cases was checked. The first case (index case) was identified and the mother was asked about the probable source of infection. Other children were classified as secondary cases if rash appeared 6 or more days after that of the index case or cases. If mothers did not remember the interval specifically, they were asked whether the next child's rash had appeared before or after the previous child had been washed. Generations of cases could be easily distinguished because mothers usually do not wash sick children before the end of the rash (about 6–8 days after onset).[2] In many larger compounds, there were several distinct generations of cases.

This study is based primarily on parental reports. All cases reported by parents in the acute phase and examined by a physician were confirmed.[2] There are several other indications that parental diagnoses are reliable. Of the 1500 cases reported in 1983–86, 62 children were subsequently (1987–90) exposed at home and only 1 child developed clinical measles (unpublished).

As in other studies of measles transmission, the closest source of infection was judged the most likely. Thus, a child who had developed measles more than 6 days after another case in the same compound was classified as a secondary case, even though the child could have been infected by other children in the village. If there had been several sources of infection in the compound simultaneously, the closest was judged most likely; for example, if there had been two possible index cases, one in the same hut and one in a different hut, the source of infection was judged to be the child from the same hut.

Cases were classified into categories according to intensity of exposure: (a) index case in a compound having contracted infection after contact with someone from a different compound; (b) secondary case in the compound (ie, living in the same compound but not in the same household); (c) secondary case in the household (ie, living in the same household but not in the same hut); and (d) secondary in a hut. These categories reflect increasing frequency and intensity of contacts between children. Previous analysis of data from Niakhar has shown that there are often several generations of cases in a compound and that the CFR increases in subsequent

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TABLE I—CFR BY AGE AND SEX

Age (yr)	Males		Females	
	CFR (%)	No of deaths/cases	CFR (%)	No of deaths/cases
<0·5	6	1/16	10	2/20
0·5–1·0	11	8/73	14	8/56
1	10	13/136	12	16/131
2	12	14/114	15	15/99
3	5	4/80	10	8/83
4	3	3/87	1	1/71
5–9	1	2/210	2	3/197
⩾10	0	0/62	0	0/65
Total	5·8	45/778	7·3	53/722

TABLE II—CFR IN RELATION TO TYPE OF EXPOSURE

Sex and age (mo)	Index cases		Secondary cases	
	CFR	No of deaths/cases	CFR	No of deaths/cases
Males				
4–5	25	1/4	0	0/11
6–41	9	8/92	13	30/231
42–65	0	0/56	4	4/97
⩾66	0	0/74	1	1/148
Total	4·0	9/226	7·2	35/487
Females				
4–5	0	0/3	15	2/13
6–41	10	7/72	16	31/191
42–65	0	0/35	5	5/97
⩾66	0	0/68	1	1/131
Total	3·9	7/178	9·0	39/432

generations.[2] Generation was therefore also taken into account. Intensity of exposure was classified for 1310 of the 1500 documented cases (87·3%).[2] Another 13 cases were included in the analysis of index cases and secondary cases in the compound although information on generation was missing. The remaining 177 children (112 girls, 65 boys), most of whom had measles outside the area, could not be classified by intensity of exposure.

Death was attributed to measles if it occurred within 6 weeks of the onset of measles rash.[2] Children were classified in four age groups according to the previously reported CFR: at 4–5 months, maternal antibodies usually protect children; at 6–41 months, most deaths occur (CFR 12%); at 42–65 months the CFR is lower (4%); and above 66 months there are very few acute measles deaths (0·4%).[2]

On the principle that the closest source of infection was the most likely, we classified secondary cases by whether they had been infected by a boy or a girl. Secondary cases with equally close exposure to both sexes were excluded from the comparison of cross-sex and same-sex transmission. To ensure that recall data on exposure did not bias the analysis of cross-sex transmission, a separate analysis was made of huts with only 2 concurrent cases of measles. We noted whether the infected children from the huts were 2 boys, 2 girls, or 1 boy and 1 girl. In this analysis, information on who infected whom was disregarded.

The Mantel-Haenszel χ^2 test and relative risk were used to combine results from individual 2×2 tables corresponding to various subgroups.[5] Approximate confidence intervals (CI) were calculated by the test-based method.[5]

Results

In 1983–86, girls continued to have higher CFR than boys (table I), although the difference was not significant; the relative risk of death from measles (girls *vs* boys) was 1·30 (95% CI 0·89–1·90), indicating the same tendency as in 1963–81 (1·52 [1·07–2·16]).[4] Analysis of the data by type of exposure (table II) showed that secondary cases had a much higher CFR than index cases. There was no significant difference between girls and boys in risk of being a secondary rather than an index case (girls *vs* boys, relative risk 1·04 [0·97–1·11]) (table II). Female secondary cases had a slightly higher CFR than male secondary cases (relative risk 1·30 [0·85–1·98]), but there was no difference in CFR between female and male index cases (relative risk 1·00 [0·39–2·56]).

Among the 1500 cases, significantly more girls than boys contracted measles outside the study area (123 girls, 85 boys; relative risk 1·58 [1·22–2·05]). This tendency applied mainly to older girls (>5 years), many of whom serve as maids in the urban areas, especially Dakar.

Since there were more boys than girls infected inside the study area, there were more male than female index cases within the study area (table II). Therefore, girls had a higher risk than boys of being infected, as secondary cases, by a child of the opposite sex (relative risk 1·26 [1·09–1·47], table III). When this difference in risk of being infected by the opposite sex was taken into account, there was no longer any significant difference in CFR beween female and male cases (relative risk 1·06 [0·66–1·69]). However, the outlook was clearly worse for secondary cases infected by a child of the opposite sex than for those infected by someone of the same sex (relative risk 2·44 [1·48–4·02]). This tendency remained even if children who had contact with both sexes were judged to have been infected by their own sex (2·02 [1·31–3·16]). When intensity of exposure was taken into account (data not shown), the relative risk was 2·34 (1·43–3·83). There was very little difference between cross-sex and same-sex transmission among children who were secondary cases within a compound but did not belong to the same household (relative risk 1·44 [0·49–4·25]). Most of the effect of cross-sex/same-sex transmission was found among children who were secondary cases within a household (4·82 [1·43–16·22]) or within a hut (2·07 [1·05–4·09]). The risk hardly changed when generation within the compound was taken into account (2·26 [1·39–3·79]). The tendency to higher mortality after cross-sex transmission applied to both children under 3·5 years (2·01

TABLE III—CFR AMONG SECONDARY CASES OF MEASLES ACCORDING TO SEX OF INFECTING CHILD

Age (mo)	Same-sex transmission				Cross-sex transmission			
	Male to male		Female to female		Male to female		Female to male	
	CFR	No of deaths/cases	CFR	No of deaths/cases	CFR	No of deaths/cases	CFR	No of deaths/cases
4–5	0	0/6	0	0/2	33	2/6	0	0/4
6–41	9	9/99	12	8/69	17	14/81	21	18/85
42–65	0	0/45	3	1/39	10	4/41	9	3/34
⩾66	0	0/74	0	0/44	2	1/56	2	1/47
Total	4·0	9/224	5·8	9/154	11·4	21/184	12·9	22/170
Relative risk (95% CI)	1·0		1·4 (0·6–3·4)		2·8 (1·4–5·7)		2·9 (1·4–6·0)	

TABLE IV—CFR IN HUTS WITH ONLY 2 CONCURRENT CASES OF MEASLES

—	Male		Female	
	CFR	No of deaths/cases	CFR	No of deaths/cases
2 cases of same sex				
4–5 mo	0	0/3	50	1/2
6–41 mo	8	4/49	7	2/30
42–65 mo	0	0/34	0	0/20
⩾66 mo	3	1/36	0	0/35
Total	4	5/122	4	3/87
1 case of each sex				
4–5 mo	0	0/2	100	1/1
6–41 mo	12	5/43	20	10/49
42–65 mo	4	1/25	5	1/20
⩾66 mo	0	0/22	0	0/24
Total	7	6/92	13	12/94

[1·18–3·42]) and older children (10·1 [1·96–52·2], table III). The effect of cross-sex transmission was stronger for male secondary cases (relative risk of death in comparison with same-sex transmission 2·89 [1·40–5·95]) than for female secondary cases (1·93 [0·94–3·98]). By contrast, when all secondary cases were taken together, there was no significant difference in CFR between those infected by female and those infected by male index cases (1·24 [0·77–1·99]).

In huts with only 2 cases of measles (table IV), the CFR was higher in families with 1 boy and 1 girl affected than in families with 2 boys or 2 girls affected (relative risk 2·16 [0·99–4·70]). The difference was especially pronounced for girls; the CFR was 3·15 (1·02–9·69) times higher in huts with a boy and a girl affected than in huts with 2 girls affected. For boys the relative risk was only 1·47 (0·44–4·93).

Discussion

This study suggests that measles infection contracted from a person of the opposite sex is more severe than that contracted from someone of the same sex. Even if classifications of source of infection were biased, the higher CFR in families with 1 boy and 1 girl affected than in families with 2 girls or 2 boys affected shows that contact with an infected child of the opposite sex somehow increases the severity of measles infection. In the study from Guinea-Bissau,[3] the tendency was most pronounced for girls. In this study, the tendency was strong for both sexes but significant only for boys. Whereas the Guinea-Bissau study found the effect mainly in children under 3 years old, because there were very few deaths among older children, this study found a significant tendency for both younger and older children. There seems to be no form of confounding that can explain the findings.

In developed countries, it is usually assumed that higher mortality in infectious diseases is "natural" for boys.[6] Higher mortality among girls in areas such as Bangladesh[7] is interpreted as being a result of preferential treatment of boys. Such variations, however, could also be explained by differences in the transmission pattern. There is some evidence that girls in developed countries tend to be index cases.[8,9] Thus, boys should be more likely to be secondary cases.[8] By contrast, societies with higher reported female measles mortality[7,10-12] are Muslim, and it is possible that girls stay at home while their brothers contract infection elsewhere. If individuals of one sex are more likely to be index cases owing to specific behaviour patterns, those of the other sex are at a dual disadvantage; they would be more likely to be intensively exposed as secondary cases[1] and more likely to be infected by someone of the opposite sex.

These hypotheses could be tested in Niakhar in rural Senegal, where it was known from the previous surveillance of measles infection that girls had a higher CFR than boys.[4] There was little difference in the frequency of secondary cases between the sexes. However, because of the larger number of infected boys within the area and the higher risk of girls contracting infection outside the area, there were fewer female index cases among the children infected within Niakhar. Thus, girls had a significantly higher risk than boys of contracting infection from someone of the opposite sex. This difference in exposure pattern accounted for most of the difference in CFR between girls and boys. Thus, most of the higher measles mortality among girls may be related to the pattern of transmission. Girls do not have higher mortality from all causes in the Niakhar area. The same proportions of boys and girls are taken to health centres (unpublished). Thus, differential treatment is unlikely to explain the observed pattern of measles mortality.

The phenomenon of greater severity after cross-sex than same-sex transmission has been found in several studies of measles.[3,13-16] This unexpected tendency may not be limited to measles infection; we have found in Guinea-Bissau that male/female twins have a higher risk of postneonatal mortality than same-sex twins.[17] Furthermore, my examination of case-reports of severe and fatal chickenpox infection suggests that cross-sex transmission increases severity. However, preliminary observations of a severe whooping-cough epidemic in Guinea-Bissau with a high CFR suggested that cross-sex transmission was less important in pertussis infection (unpublished). Hence, the phenomenon may be associated mainly with viral infections.

Why is infection contracted from someone of the opposite sex more severe? The simplest explanation would be that close contact (eg, kissing), which increased the dose of virus or the risk of complicating infections, was more common between a boy and a girl than between 2 children of the same sex. No such difference in contact patterns has been documented in studies of child behaviour.[3] However, it may be necessary to look more specifically at interaction patterns during times of illness. Since the same tendency has been found in widely differing societies,[3,13-17] it seems unlikely that culturally determined behaviour patterns are the cause, but biologically based behaviour patterns could mean that transmission of a high dose is more common from someone of the opposite sex.

Basic mechanisms at cellular level should also be considered. The simplest possibility is that passage through cells of the opposite sex enhances infectivity and increases viral load or interferes with the immune system.[3] The plausibility of sex-specific interaction is supported by findings that different measles vaccines are related to sex-specific mortality patterns;[18-20] high-titre measles vaccine was associated with higher female mortality, whereas Schwarz standard measles vaccine was especially beneficial for girls.[19] Although the underlying process is not understood, an expert panel convened by the World Health Organisation has recommended that routine use of high-titre measles vaccine be stopped.[20] Further studies of the biological basis for such interaction between (vaccine) virus and sex are clearly warranted.

Sex-specific patterns of exposure and cross-sex transmission should be examined further for two reasons. First, they offer another explanation for variation in mortality by sex in different societies. This information could affect the general cultural understanding of the relative biological strength of the sexes and might ultimately

have consequences for research on sex and infections. Second, observations on cross-sex transmission point to an important and hitherto unnoticed mechanism for aggravating infections. Whether the cause is behavioural or biological, it is likely that a better understanding of the underlying mechanism will lead to improved control of severe and potentially fatal infections.

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Chromosome status of untransferred (spare) embryos and probability of pregnancy after in-vitro fertilisation

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Many spontaneous abortions are associated with chromosomal abnormality of the fetus. In in-vitro fertilisation (IVF) the chromosome status of untransferred ("spare") embryos and subsequent fate (pregnancy or not) of the transferred sibling embryos might be related. Since the spare and transferred embryos of a patient's cycle genetically are full siblings, the inherited chromosomal abnormalities in spare embryos have a 50% probability of also appearing in transferred embryos. We have tested whether chromosome analysis of spare embryos has predictive power for transferred embryos.

48 couples with a total of 437 embryos were selected because their spare embryos (1–4 per couple; 76 total) were successfully analysed for chromosome status. 16 patients became pregnant. These women produced a higher proportion of chromosomally normal spare embryos (9/24; 37·5%) than those who did not achieve pregnancy (1/52; 1·9%). The proportion of patients who had only normal embryos was significantly higher ($p=0·012$) in the pregnant group than in the non-pregnant group, and the proportion of patients who had only abnormal embryos was significantly higher ($p=0·001$) in the non-pregnant group. Patients with preclinical and clinical pregnancy losses had only chromosomally abnormal spare embryos; by contrast, 50% of spare embryos from patients with ectopic pregnancies were normal. The proportion of spare embryos that were normal (13%, 10/76), was similar to the livebirth rate of 11% per transferred embryo (19 infants from 171 transferred embryos).

These results suggest that chromosome analysis of spare embryos may have predictive value for their transferred sibling embryos. We conclude that improving detection of chromosomally normal embryos for transfer should improve the success rate in IVF.

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Introduction

Reproductive failure is closely associated with chromosomal abnormalities. A major cause of spontaneous abortion among clinically recognised pregnancies is a grossly abnormal chromosome complement (chromosome numbers departing from the normal 46—ie, aneuploidy).[1] Estimates of overall rates of chromosome abnormalities in spontaneous abortions and fetal deaths, adjusted for gestational age, are around 32%.[2] The frequency of chromosomal abnormality before week 8 of gestation (as measured from the onset of

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