Increased Childhood Morbidity After Measles Is Short-term in Urban Bangladesh

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In a 1995–1996 cohort study in the city of Dhaka, Bangladesh, morbidity in 117 hospitalized and 137 acute measles cases compared with age-matched children without measles (unexposed) was determined by weekly interview for 6 months. Compared with unexposed children, there were higher incidences of hospitalization (adjusted rate ratio (RR) = 3.1, 95% confidence interval (CI): 1.3, 7.6) and bloody diarrhea (adjusted RR = 2.7, 95% CI: 1.4, 5.1) in hospital measles cases during the 6 weeks after recruitment. Among community cohorts, there were higher incidences of bloody diarrhea (adjusted RR = 4.1, 95% CI: 1.1, 14.6), watery diarrhea (adjusted RR = 1.6, 95% CI: 0.9, 2.7), fast breathing (adjusted RR = 3.8, 95% CI: 2.1, 6.9), and the weekly point prevalence of pneumonia (adjusted prevalence ratio = 3.1, 95% CI: 1.0, 9.8) in measles cases during the same period. All measles cases regained lost weight within about 6 weeks. The prevalence of anergy to seven recall antigens 6 weeks after recruitment was higher in both hospital (adjusted odds ratio = 2.8, 95% CI: 1.2, 6.4) and community (adjusted odds ratio = 3.1, 95% CI: 1.1, 8.9) measles cases. Morbidity increased during the first 6–8 weeks after measles, but the authors found no consistent evidence of longer-term morbidity or wasting. The results support recent findings that measles is not associated with increased delayed mortality. Am J Epidemiol 2000;151:723–35.

The effect of measles on subsequent morbidity and mortality has long been debated. Some authors suggest that prevention of measles will not reduce overall mortality because children who are most likely to die of measles are also at high risk of death from other causes (1). On the other hand, measles worsens nutritional status (2, 3) and is associated with immune disruption (4–6); therefore, it could increase morbidity and mortality after an acute episode is over (3, 7). Studies in west Africa suggested an increase in mortality for several months after measles (7–11), particularly among children exposed during the first year of life (7) and in secondary cases (12). These studies had methodological problems, however, including potential selection bias, recall bias, and potential confounding by socioeconomic status (10). Two cohort studies in India found increased morbidity from diarrhea and respiratory illness in the 6 months after measles (2, 3). One study did not stratify by time since measles (3), while the other did not mention selection criteria and had a high rate of loss to follow-up (2). Thus, the magnitude and duration of any increase in morbidity after measles have not been demonstrated clearly.

We conducted a cohort study of childhood morbidity after measles in urban Bangladesh to investigate the hypothesis that measles leads to increased morbidity from other illnesses and to determine the duration of any increased morbidity. The study was approved by the ethics committees of both the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) and the London School of Hygiene and Tropical Medicine, London, United Kingdom.

MATERIALS AND METHODS

Study sites

The study was conducted in 1995–1996 at the ICDDR,B hospital and in Nandipara community, Dhaka, Bangladesh. ICDDR,B is a large, busy referral hospital for diarrhoeal illness, and Nandipara is a peri-urban, poor community where the ICDDR,B medical staff runs a weekly curative clinic. Preventive health care is available at a nongovernmental agency clinic 1 km away. Measles vaccine is offered through the
national Expanded Programme on Immunization to children aged 9–23 months; coverage is estimated at 58 percent in the city of Dhaka (1997) (13) and 50 percent in Nandipara community.

Recruitment

At ICDDR,B hospital, measles cases were recruited by active surveillance of each ward. Study health workers asked all mothers if their children had had measles in the last 6 weeks. Study physicians confirmed eligibility and obtained written informed consent. A case was eligible if he or she was aged 6 months or more; had a history of rash and fever with cough, coryza, or conjunctivitis (14); and lived within 25 km of the hospital. For each case, a child with other illness was identified on the same ward, who was matched by age band (6–8, 9–11, 12–17, 18–23, 24–35, 36–59, and 60–143 months) and had no history of measles during the last year. Exclusion criteria for measles cases and unexposed children were edema, any known congenital or metabolic disorder or chronic disease, or moribund status on admission.

In Nandipara community, a household census that had been conducted by ICDDR,B was updated in early 1995 to generate a database of the sex and birth date of each resident. Female health workers, recruited from the community, visited each household twice weekly to detect acute measles cases. Eligibility was confirmed, and an unexposed child in the same age bracket as the case was recruited randomly from the census list. The case and matched pair were referred to ICDDR,B for enrollment by study physicians.

Baseline Information

Trained health assistants completed standard questionnaires on the clinical, social, and demographic characteristics of the children. Information on socioeconomic characteristics such as household construction, water and electricity supply, and household assets was obtained by observation and interview during the first home visit.

For measles cases, information on morbidity for the period between rash onset and recruitment was collected retrospectively at recruitment by study physicians, who recorded clinical signs and results of laboratory investigations on standard forms. Radiograph readings were recorded on the World Health Organization (WHO)/Acute Respiratory Infection Programme Radiology Working Group data collection instrument (15), and the radiologist was blind to the clinical diagnosis. All children received oily vitamin A (age <1 year, 100,000 IU; age ≥1 year, 200,000 IU), as recommended by WHO (16), on recruitment; those who had signs of xerophthalmia received a second dose the following day. According to ICDDR,B treatment regimens, antibiotics were administered for clinical pneumonia, invasive diarrhea, cholera, or sepsis.

Follow-up

After the children were recruited into the study, health assistants followed them up weekly and interviewed their mothers by using standard questionnaires to ascertain daily morbidity. For each symptom that had occurred since a child was last seen, the assistants determined the number of days of illness by asking the mother about 1 day at a time, working forward from the last visit date. These weekly interviews commenced on the first day of the second week after recruitment. Symptoms present on the day of recruitment were included in the morbidity information for the first week. All illnesses reported by the mothers, and illnesses that occurred during referral or hospitalization, were also recorded during weekly interviews. At every weekly visit, a child’s respiratory rate was counted over 1 minute by using a timer (ARI-TIMER, stock no. 08-450-10; United Nations Children’s Fund, New York, New York), irrespective of the presence of respiratory symptoms. If the child was absent on a visit date, visits were continued daily until the child was located or information was obtained from neighbors that the child had left the city of Dhaka. If a measles case was lost to follow-up, the matched unexposed child was also dropped from the study; however, the reverse did not occur, as the data on measles cases were used in a subsequent nested case-control study of risk factors for measles severity.

Children who met WHO criteria for referral (17) because of suspected acute lower respiratory infection (ALRI), bloody diarrhea, or signs of severe illness were referred to study physicians. Children were admitted to the hospital if they had one or more of the following: chest in-drawing, lobar consolidation on radiographic examination, failure to improve after administration of amoxicillin, persistent dehydration or repeated vomiting after 2 hours of observation and oral rehydration, convulsion, lethargy and refusal of fluids, or edema. The number of clinic consultations and hospitalizations during follow-up was recorded.

At recruitment and at 6, 10, 14, 18, and 24 weeks, anthropometry was conducted at ICDDR,B. Stature (accurate to the nearest 0.1 cm) was measured by using stadiometers for children more than 2 years of age and length boards for younger children. Weight (accurate to within 5 g) was measured by using electronic weighing scales (Digital Baby Scale, model 727; Seca, Hamburg, Germany) following standard methods (18).
During the 6-week visit, we assessed delayed-type hypersensitivity by using the Multitest CMI skin test (lot K0092; Institut Merieux, Lyon, France). The applicator has eight heads, with nine tines on each, loaded with seven different antigens (tetanus, diphtheria, Streptococcus, tuberculin, Proteus, Trichophyton, and Candida) and a glycerin-negative control. Following manufacturer's instructions, we applied four heads on the volar surface of each forearm. At 48 hours, one study physician (for hospital cohorts) or an experienced health assistant (for Nandipara children) measured the responses by using a medium ballpoint pen to demarcate the area of induration (19). A reaction was considered positive if the average of the maximum horizontal and vertical induration was at least 2 mm. We repeated the multitest examination at week 24 on a subsample of children.

Unvaccinated children without measles were given measles vaccine during the recruitment visit; younger children were referred for vaccination during the first clinic visit after they reached 9 months of age. Children were vaccinated through routine immunization services at ICDDR,B with vaccines supplied to the national Expanded Programme on Immunization via the United Nations Children’s Fund.

We obtained 2 ml of blood by venipuncture at recruitment and at 6 and 24 weeks after recruitment. Blood was allowed to clot at room temperature and then was centrifuged, sera separated, labeled, and stored at -70°C (aliquots for serum retinol were covered with aluminum foil).

Quality assurance

Quality assurance included a 3-month period of questionnaire development and pilot studies; intensive staff training; standardization of study procedures, which were written in detailed manuals; regular staff meetings; and supervision by study physicians. To select appropriate terms for the questionnaires, we consulted previous ethnographic studies of childhood illness in Dhaka (Health Care Use Patterns in Dhaka City, Maarten Desment, ICDDR,B, unpublished manuscript, 1993) and Matlab subdistrict (20). Local names for different types of diarrhea have been well documented (20, 21). For respiratory illnesses, we conducted a rapid ethnographic survey following unpublished guidelines from the WHO/Acute Respiratory Infection Programme. The terms defined were similar to those reported from Matlab (22).

Exposed and unexposed children were assigned in pairs to health assistants. We assessed the repeatability of responses to interviews for 123 study children by comparing interviewer responses with those by physicians either during random spot checks or when a child was referred to physicians the same day. Kappa values of more than 0.7 were obtained for all respiratory symptoms except “cough on chest” (kappa = 0.42); values were 0.95 for bloody diarrhea and approximately 0.6 for watery or mucoid diarrhea.

Laboratory procedures

Measles immunoglobulin (Ig)M and IgG antibody levels were measured by using Behring Enzygnost enzyme immunoassay kits (Behring Diagnostics, Frankfort, Germany). Each run of IgM assays included a positive and a negative control. Serum retinol was measured by high performance liquid chromatography (23) at baseline.

Data management

Data were double-entered concurrently by using Epi Info version 6 software (Centers for Disease Control and Prevention, Atlanta, Georgia). Follow-up data were scanned visually on receipt and were entered within the week of the interview; consistency errors were reviewed by the principal investigator or were returned to the interviewers to verify with the parents during repeat visits if necessary.

Data analysis

Measles was confirmed by demonstrating specific IgM or a fourfold acute-convalescent increase in specific IgG levels. Unexposed children were confirmed not to have had recent measles by an absence of measles-specific IgM levels and no significant increase or decrease in IgG levels during the study period.

A mother’s statement of a child’s abnormal loose stool was accepted as a definition of diarrhea; separate local terms were used for bloody or mucoid diarrhea. It was predicted that 2 intervening diarrhea-free days would be required to define a new episode (24, 25). A sensitivity analysis showed that varying the number of intervening diarrhea-free days in the definition of an episode did not alter the final rate ratios. Pneumonia could be assessed only on visit days, when its point prevalence was defined as “cough on chest” or “fast breathing,” with a resting respiratory rate of ≥50 per minute in children aged less than 1 year and ≥40 in those aged 1 year or more or with chest in-drawing on inspection (17). Rates of reported fast breathing were also estimated, a minimum of 7 days free of symptoms being required between the end of one episode and the beginning of the next (26, 27).

We calculated weight-for-height and height-for-age scores by using the EPINUT module of Epi Info soft-
ware. Wasting was defined as a weight-for-height z score and stunting as a height-for-age z score of less than 2 standard deviations below the National Center for Health Statistics-WHO reference (28).

In all analyses, we separately compared exposed (measles cases) and unexposed children in hospital cohorts and exposed and unexposed children in community cohorts to respect the matching within cohorts. For baseline comparisons of categorical variables, we used the chi-square or Fisher’s exact test. To compare incidence rates following recruitment, we excluded the episodes present at recruitment; only new episodes that developed during follow-up were included in the analysis. Incidence rates were compared by using Poisson regression models. Interactions with age and sex were assessed by using the likelihood ratio test. These models were extended by using quasi-likelihood estimation with a random effects term to model clustering of episodes within children. We decided a priori to compare rates by 6-week follow-up periods as a convenient way to divide the total 24-week period.

Potential confounders were identified from the literature, and we assessed their influence on the crude rate ratios before including them in a final adjusted model. We included age as a potential confounding variable to account for any imbalance caused by losses to follow-up. Vaccination status varied with exposure and may have been a proxy for use of health care facilities, health care practices, and socioeconomic status. We were not able to control for measles vaccination status because unvaccinated, unexposed children received vaccines after recruitment.

RESULTS

Recruitment and follow-up

In the hospital, 143 suspected measles cases and age-matched children with diarreal illness (unexposed) were recruited over 1.5 years. Unconfirmed cases and their matched pairs were dropped from the study after their serology was known. Of 117 confirmed measles cases (exposed), 14 left the study area and could not be traced, 3 died, and the parents of 2 did not allow further blood drawing. Of 117 matched children (unexposed), 10 left the area, 7 died, the parents of 2 refused further blood drawing, and an additional 17 were dropped from follow-up when their matched case stopped follow-up. A total of 107 exposed and 93 unexposed children completed 6 weeks of follow-up, and 98 and 81, respectively, completed 24 weeks of follow-up.

In the community, 188 suspected measles cases and unexposed age-matched children were recruited. Of the suspect cases, 137 were confirmed to have measles. Losses to follow-up included 9 migrations, 10 refusals, and 2 deaths among the exposed and 2 migrations, 2 refusals, 20 whose matched cases were lost, and 6 who developed measles among the unexposed. A total of 129 exposed and 126 unexposed children completed 6 weeks of follow-up, and 116 and 107, respectively, completed 24 weeks of follow-up.

Baseline characteristics

Hospital cohorts were younger than community cohorts (table 1). Vaccine coverage was significantly lower in exposed versus unexposed groups. In the hospital cohorts, exposed children were less likely to live in houses with electricity or in-house piped water, and their mothers had less education, but many other indicators of socioeconomic status and household composition were similar (table 1). In the community exposed cohorts, the mothers were less educated, and a higher proportion of household heads were unskilled laborers, with significantly lower incomes, fewer assets, and less house ownership. Breastfeeding was almost universal, although fewer than one-third of the hospitalized children and fewer than half of the community children were exclusively breastfed up to 5 months of age.

Hospital and community measles cases were recruited a median of 12 (interquartile range, 7–18) and 5 (4–7) days, respectively, after rash onset. Fourteen percent of hospital and 13 percent of community cases were secondary. A large proportion of hospitalized children and exposed community children were wasted or stunted (table 2). In the hospital cohorts, all children had diarrhea, but mucoid diarrhea was more common in exposed children (p < 0.05) (table 2). Exposed children were significantly more likely to have ALRI (p < 0.01). Only 2 exposed and 2 unexposed children had xerophthalmia at recruitment, but 77 and 76 percent, respectively, had low (≤20 μg/dl) serum retinol levels. Of 13 exposed and 15 unexposed children for whom information was available, 10 and 9, respectively, received antibiotics before recruitment. During hospitalization, 52 percent of exposed and 31 percent of unexposed children received parenteral antibiotics (p = 0.001). During initial hospitalization, no exposed and 2 unexposed children died.

In the community, the unexposed cohort was generally healthy. Although 26 and 13 percent of exposed children had watery and mucoid diarrhea, respectively, and 36 percent had ALRI, only 2 children required hospitalization, 1 of whom died of severe pneumonia. Among exposed children, 84 percent had low serum retinol levels compared with 30 percent of unexposed children. Of 99 exposed and 20 unexposed children for
TABLE 1. Baseline demographic and socioeconomic characteristics of children exposed versus unexposed to measles, Cohort Study of Childhood Morbidity After Measles In Urban Bangladesh, 1995–1996†

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hospital cohorts</th>
<th>Community cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exposed</td>
<td>Unexposed</td>
</tr>
<tr>
<td></td>
<td>(n = 117)</td>
<td>(n = 117)</td>
</tr>
<tr>
<td>Sex: male</td>
<td>60</td>
<td>72</td>
</tr>
<tr>
<td>Age (months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–11</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>12–23</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>24–35</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>36–59</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>60–143</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Ever vaccinated</td>
<td>77</td>
<td>93**</td>
</tr>
<tr>
<td>Received BCG† vaccine (card or scar)</td>
<td>74</td>
<td>85*</td>
</tr>
<tr>
<td>BCG scar evident</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Received 3 doses of DTP‡ and OPV‡ (card)</td>
<td>26</td>
<td>41*</td>
</tr>
<tr>
<td>Received measles vaccine (card + history) if aged &gt;9 months (no. (%))</td>
<td>91 (23)</td>
<td>87 (70)**</td>
</tr>
<tr>
<td>Exclusively breastfed up to age 5 months</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>Mother's mean age (years) (SD‡)</td>
<td>26 (6)</td>
<td>25 (5)</td>
</tr>
<tr>
<td>Median birth order (no. (range))</td>
<td>3 (1–9)</td>
<td>2 (1–9)</td>
</tr>
<tr>
<td>Median family size (no. (range))</td>
<td>5 (2–18)</td>
<td>5 (3–13)</td>
</tr>
<tr>
<td>Children sleeping with study child: median (no. (range))</td>
<td>1 (0–5)</td>
<td>1 (0–4)</td>
</tr>
<tr>
<td>Median monthly family income (US$ (range))</td>
<td>62 (7–537)</td>
<td>75 (6–765)*</td>
</tr>
<tr>
<td>Occupation of head of household</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unskilled labor</td>
<td>39</td>
<td>44</td>
</tr>
<tr>
<td>Skilled</td>
<td>61</td>
<td>56</td>
</tr>
<tr>
<td>Mother's occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>78</td>
<td>77</td>
</tr>
<tr>
<td>Unskilled labor</td>
<td>17</td>
<td>21</td>
</tr>
<tr>
<td>Service/business</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Head of household: any schooling</td>
<td>54</td>
<td>66</td>
</tr>
<tr>
<td>Mother: any schooling</td>
<td>23</td>
<td>43**</td>
</tr>
<tr>
<td>Family-owned house</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Electricity supply present</td>
<td>70</td>
<td>83*</td>
</tr>
<tr>
<td>Piped water supply present in house</td>
<td>21</td>
<td>40**</td>
</tr>
<tr>
<td>Cooking place located in child's room</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Soap used to wash child's hands</td>
<td>30</td>
<td>21</td>
</tr>
<tr>
<td>Family assets (bicycle, furniture, radio/television)</td>
<td>78</td>
<td>81</td>
</tr>
<tr>
<td>Smoker in house</td>
<td>65</td>
<td>66</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01; *** p < 0.001.
† All values are percentages unless otherwise noted; all comparisons are between exposed and unexposed hospital cohorts or exposed and unexposed community cohorts.
‡ BCG, bacille billé de Calmette-Guérin vaccine; DTP, diphtheria-tetanus-pertussis vaccine; OPV, oral poliovirus vaccine; SD, standard deviation.

Morbidity after recruitment

Comparisons between hospital groups were adjusted for age, sex, stunting, vaccination status, mother's education, number of children in the household, electricity supply, and source of drinking water. To analyze hospital readmission rates, we also added duration of prior hospitalization to these variables. For community cohorts, we adjusted for age, sex, stunting, vaccination status, mother's education, number of children in the household, household income, head of household and mother's occupation, and whether the child lived in a family-owned house. To compare respiratory symptoms and signs, we also adjusted for whether the cooking place was located in the child's room, overcrowding, and the presence of smokers in the house. In hospital cohorts, repeat hospitalization rates were higher for exposed than for unexposed children during the 6 weeks after recruitment (2.7 vs. 0.9 per child-year, respectively; adjusted rate ratio (RR) = 3.1; p = 0.009) (table 3). About 70 percent of repeat hospitalizations were due to diarrhea and the rest to pneumonia. Of the repeat hospitalizations, oral candidiasis was present in 37 percent of exposed children but in no unexposed children. In both groups, more than 60 per-
There were seven hospitalized children. Hospitalization rates were much lower during the subsequent 18 weeks, and there was no difference between hospital cohorts or exposed and unexposed community cohorts.

Table 2. Incidence rates and crude and adjusted rate ratios for characteristics of children exposed versus unexposed to measles 6 weeks after recruitment, Cohort Study of Childhood Morbidity After Measles In Urban Bangladesh, 1995–1996

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hospital cohorts</th>
<th>Community cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exposed (n=117)</td>
<td>Unexposed (n=117)</td>
</tr>
<tr>
<td></td>
<td>Exposed (n=137)</td>
<td>Unexposed (n=137)</td>
</tr>
<tr>
<td>Watery diarrhea</td>
<td>91</td>
<td>93</td>
</tr>
<tr>
<td>Mucoid diarrhea‡</td>
<td>43</td>
<td>29‡</td>
</tr>
<tr>
<td>Bloody diarrhea§</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>ALRI§–WHO§ criteria</td>
<td>23</td>
<td>10‡</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>14</td>
<td>4**</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Wasted#</td>
<td>57</td>
<td>47</td>
</tr>
<tr>
<td>Vitamin A deficient††</td>
<td>61</td>
<td>63</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01; *** p < 0.001.
† All comparisons are between exposed and unexposed hospital cohorts or exposed and unexposed community cohorts.
‡ Illnesses present between rash onset and recruitment or at recruitment.
§ ALRI, acute lower respiratory infection; WHO, World Health Organization.
† Stunted, below –2 height-for-age z score based on the National Center for Health Statistics (NCHS) reference.
# Wasted, below –2 weight-for-height z score based on the NCHS reference.
†† Serum retinol ≤20 µg/dl.

cent of hospitalized children were infants. Hospitalization rates were much lower during the subsequent 18 weeks, and there was no difference between groups (data not shown). There were only seven hospital admissions in exposed and three in unexposed community cohorts throughout the whole follow-up period.

There were no significant differences in overall clinic referral rates between exposed and unexposed children in hospital or community cohorts during any period of follow-up. In hospital cohorts, referral rates for bloody diarrhea were significantly higher for exposed than for unexposed children during the first 6 weeks (RR = 3.1, p = 0.04). In the subsequent 18 weeks, the difference was not significant (0.4 vs. 0.2 per child-year, p = 0.1). In community cohorts, referral rates were low at all times, and there was no difference.

Figure 1 shows the incidence rates of different types of diarrhea and of fast breathing by 6-week periods. In both hospital and community cohorts, there were higher incidences of bloody diarrhea in exposed children during the 6 weeks after recruitment (adjusted RR = 2.7, p = 0.003 and adjusted RR = 4.1, p = 0.013, respectively) (table 3). The higher incidence of bloody diarrhea persisted in weeks 7–12 in the community exposed cohort (0.87 vs. 0.14 per child-year, p = 0.007). Community exposed children also had higher incidences of watery diarrhea (adjusted RR = 1.6, p = 0.103) and mucoid diarrhea (adjusted RR = 2.4, p = 0.003) during weeks 1–6; in the hospital cohorts, there was no increase in the incidence of watery or mucoid diarrhea.

In community cohorts, the rates of ALRI symptoms were significantly higher after measles during the first 6 weeks (adjusted RR for fast breathing = 3.8,
Increased Morbidity After Measles Is Short-Term

Watery diarrhea

1st 6 weeks 2nd 6 weeks 3rd 6 weeks 4th 6 weeks

Mucoid diarrhea

1st 6 weeks 2nd 6 weeks 3rd 6 weeks 4th 6 weeks

Bloody diarrhea

1st 6 weeks 2nd 6 weeks 3rd 6 weeks 4th 6 weeks

Fast breathing

1st 6 weeks 2nd 6 weeks 3rd 6 weeks 4th 6 weeks

FIGURE 1. Incidence rates of watery, mucoid, and bloody diarrhea and of fast breathing for exposed (measles cases) and unexposed children in hospital and community cohorts by 6-week periods of observation, Cohort Study of Childhood Morbidity After Measles in Urban Bangladesh, 1995-1996.

$p < 0.001$; adjusted prevalence ratio of ALRI = 3.1, $p = 0.049$). In hospital cohorts, there was no significant increase in any indicator of ALRI during the first 6 weeks. In weeks 7–12, the proportion of observed days with fast breathing was significantly higher in exposed children (4 vs. 2 percent, $p = 0.045$).

Exposed children initially were more wasted, although this finding was significant in only the community group. Children in all ill groups gained weight rapidly (figure 2). In both hospital and community settings, the differences in weight-for-height were non-significant after 6 weeks (figure 2). However, the prevalence of stunting increased over time in both hospital groups. Height-for-age was significantly lower in the exposed community cohort from week 6 ($p = 0.009$) onward (figure 2).

There were significant differences in the delayed-type hypersensitivity responses 6 weeks after recruitment (table 4), some of which persisted in the subsample of children tested at 24 weeks of follow-up. At 6 weeks, the prevalence of anergy (lack of response to all antigens) was higher in both hospital (adjusted odds

![Hospital cohorts](chart)

![Community cohorts](chart)

**FIGURE 2.** Mean weight-for-height and height-for-age $z$ scores based on the National Center for Health Statistics reference of exposed (measles cases) and unexposed children in hospital and community cohorts at 0, 6, 10, 14, 18, and 24 weeks of follow-up, Cohort Study of Childhood Morbidity After Measles in Urban Bangladesh, 1995–1996.

TABLE 4. Prevalence of anergy to recall antigens and odds ratios for anergy among children exposed versus unexposed to measles 6 weeks after recruitment, Cohort Study of Childhood Morbidity After Measles in Urban Bangladesh, 1995–1996

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Hospital cohorts</th>
<th>Community cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence of anergy (%)</td>
<td>OR* (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Exposed (n = 103)</td>
<td>Unexposed (n = 91)</td>
</tr>
<tr>
<td>Proteus</td>
<td>81</td>
<td>80</td>
</tr>
<tr>
<td>Tetanus</td>
<td>64</td>
<td>58</td>
</tr>
<tr>
<td>Trichophyton</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>88</td>
<td>77</td>
</tr>
<tr>
<td>Candida</td>
<td>59</td>
<td>47</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>97</td>
<td>91</td>
</tr>
<tr>
<td>Tuberculin</td>
<td>77</td>
<td>52</td>
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<tr>
<td>All antigens</td>
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* OR, odds ratio; CI, confidence interval.
† Not adjusted.
‡ Adjusted for the third dose of diphtheria-pertussis-tetanus (DPT) vaccine.
§ Adjusted for bacille bilié de Calmette-Guérin (BCG) vaccine.
¶ Adjusted for age, sex, BCG and three doses of DPT vaccines, illness at the time of the test, starching, and wasting.

ratio = 2.8, p = 0.01) and community (adjusted odds ratio = 3.1, p = 0.03) exposed children. After adjustment for vaccination status, the proportion that responded was significantly lower in hospital exposed children for tuberculin and diphtheria antigens and in community groups for tuberculin, diphtheria, tetanus, and Proteus antigens. In the subgroups also tested at 24 weeks, the response to tuberculin but not to the other antigens remained significantly reduced in the hospital exposed cohort (74 percent of 35 exposed children vs. 53 percent of 30 unexposed children, p = 0.02); in community cohorts, the prevalence of anergy remained lower (38 percent of 86 exposed children vs. 25 percent of 81 unexposed children, p = 0.06).

In hospital cohorts, there was no significant interaction with age for any outcome (table 5). In community cohorts, there was a significant interaction with age for watery diarrhea; the highest rate ratios were found for older children (p < 0.01) (table 5). Similarly, for fast breathing, the effect of measles was greatest in older children as rates remained high for exposed children while decreasing with age for those who were unexposed (p = 0.01).

In hospital groups, a significant interaction with sex was found for fast breathing (p = 0.03) (table 5). A sex difference was observed for bloody diarrhea but was not significant. In both instances, unexposed females had lower rates, while exposed males and females had similar rates. Thus, the rate ratios were higher for females. In community cohorts, the rate ratios between the sexes were similar.

**DISCUSSION**

To our knowledge, this is the first well-controlled study to assess the duration of an increased risk of diarrhea and ALRI after measles. We found that measles was associated with increased morbidity during the first 6 weeks after recruitment, that is, in the first 6–8 weeks after rash onset, but there was no evidence of a more prolonged risk.

When we compared children hospitalized with measles with those hospitalized without measles, the only significant differences were in the incidence of clinic referral for bloody diarrhea and of repeat hospitalization (due mainly to bloody diarrhea). The effect of measles on bloody diarrhea occurred mainly in females, for whom the rate ratio approached significance (p = 0.1). Although exposed children were more likely to have ALRI at recruitment, there were no significant differences regarding subsequent respiratory illness. Rates of fast breathing were almost identical for exposed and unexposed males; for females, the rate was lower in the unexposed group. The unexposed hospital cohort had relatively severe diarrhea, wasting, and low serum retinol at recruitment. These factors may have increased susceptibility to infections in unexposed children, reducing the difference between the groups. The rates of all events other than fast breathing were substantially higher in both hospital cohorts than in either of the community cohorts.

In the community cohorts, the higher incidence of mucoid and bloody diarrhea in exposed children during the first 6 weeks is consistent with results from a community-based retrospective cohort study in rural Bangladesh (29). The consistency of significantly increased rates of all ALRI symptoms and a higher point prevalence of ALRI in the community exposed children indicates that measles increases morbidity due to respiratory illness during the first 6–8 weeks. This conclusion is also supported by Shahid et al.'s
findings of a higher frequency of difficult breathing in measles cases compared with age-matched healthy controls during the 1 month after measles (29). The increase in morbidity after measles in our community cohorts was most evident in children more than 2 years of age, reflecting the sharp decrease in background incidence and severity of illness, which might have influenced subsequent comparisons. We therefore repeated our analyses, adjusting for mucoid diarrhea, ALRI, and antibiotic use at recruitment. For hospital readmissions, referral, bloody diarrhea, and fast breathing in the first 6 weeks, the rate ratios and significance levels did not change in either hospital or community cohorts. For example, after we adjusted for these additional variables, the rate ratio for hospital readmissions in hospital cohorts was 3.1 (95 percent confidence interval (CI): 1.4, 6.7) compared with 3.1 (95 percent CI: 1.3, 7.6) without adjustment for these variables. The only difference we found was an increase in the prevalence ratio for ALRI in the community cohorts after we adjusted for the additional variables (prevalence ratio = 5.5, 95 percent CI: 1.3, 24.3). Therefore, the increased morbidity during the first 6 weeks after recruitment could not be accounted for by the difference in the prevalence of symptoms and antibiotic use at recruitment.

Previous studies have reported increased morbidity from diarrhea and respiratory illness in the 3–6 months after measles but have not stratified by time after measles (2, 3). When we analyzed the entire 24-week period, we also found higher incidences of bloody diarrhea (adjusted RR = 1.66, 95 percent CI: 0.93, 2.97) and fast breathing (adjusted RR = 2.29, 95 percent CI: 1.58, 3.3) in community exposed children; in hospital exposed children, we found higher incidences of bloody diarrhea (adjusted RR = 1.70, 95 percent CI: 1.05, 2.72) and hospital readmissions (adjusted RR = 1.7, 95 percent CI: 0.90, 3.4). However, these increased incidences were confined to the first 6 weeks.

At no time was there a significant difference in nutritional status between hospitalized children with measles and those with nonmeasles diarrhea. In our

community cohorts, in contrast to the findings of other studies (2, 3), children gained weight rapidly after measles, and from 6 weeks after measles these children were not more wasted than unexposed children. Wasting might have been reduced by timely treatment, which could have lessened the severity of infections. Nonetheless, measles and severe diarrheal illness led to a persistent increase in stunting.

The short-term increase in morbidity was associated with depressed cell-mediated immune responses 6 weeks after recruitment (7–8 weeks after rash onset). The immune response to tuberculin but not the other antigens was depressed significantly in the exposed hospital cohort 24 weeks after recruitment but was not associated with a significant increase in morbidity 6 weeks after recruitment.

In our study, we avoided misclassification of exposure because measles was confirmed to be present or absent serologically. Standardized questionnaires, rigorous training, supervision, and quality assurance reduced intra- and interobserver variation in the measurement of outcomes. It was not possible to blind interviewers to exposure status, as mothers would mention measles spontaneously. However, interviewers were unaware of the study hypotheses. Had they been influenced by exposure status, we would have expected similar results in hospital and community exposed cohorts, whereas most of the differences were detected in only the community cohort. Biased recording also would be expected to lead to increased morbidity in exposed cohorts throughout the 24 weeks of follow-up, as interviewers were unaware of the strategy of analyzing by 6-week periods. Lastly, we analyzed morbidity among 77 suspect measles cases who were subsequently shown not to have measles. The prevalence of watery and bloody diarrhea and of ALRI symptoms was similar in serologically negative suspect cases and unexposed children (data not shown). Therefore, the differences in morbidity during the first 6 weeks of follow-up were unlikely to be due to observer bias.

Approximately 15 percent of the exposed children in our study were lost to follow-up, and additional unexposed children were dropped from follow-up when their matched pairs were lost. The reasons for migration of 35 children from the study area included the following: work not available for one or both parents (23 percent), separation of the mother from the family (11 percent), illness of the parents or grandparents (17 percent), flooding (9 percent), employment of the father in another city (6 percent), accidental burning of the homestead (3 percent), child visiting a native village and not willing to come back (3 percent), and unknown (28 percent). There is no reason to believe that these factors were associated with either exposure or morbidity. No significant difference in age, sex, or nutritional or socioeconomic status existed between the children who remained in the study and those who were lost to follow-up (data not shown).

As this was a prospective study from a tertiary-care hospital, children received better treatment than would have been available routinely in many low-income countries. Of 254 cases, only one death occurred. All children received at least one dose of oily vitamin A. In a double-blind, placebo-controlled, randomized clinical trial of children who received a single oral dose of 200,000 IU of vitamin A during the exanthematous stage of measles versus those who did not, supplementation did not significantly affect delayed-type hypersensitivity responses after 2 weeks (30) or morbidity during 4 weeks of follow-up (31). A dose of >200,000 IU of vitamin A reduces the severity of measles-associated diarrhea and pneumonia during hospitalization (32) but not the incidence of diarrhea and pneumonia episodes during hospitalization (33) or the 6-week postsupplementation period (32). Similarly, prophylactic administration of vitamin A does not affect the incidence of diarrhea or pneumonia (26, 34, 35), although it reduces the severity of diarrhea (34, 35). Therefore, it was difficult to determine whether administration of vitamin A affected our results. Since WHO recommends a single high dose of vitamin A for measles cases, and since most developing countries are now implementing this policy (36), our objective of assessing the effect of measles with vitamin A supplementation was more pragmatic.

Aaby et al. have hypothesized that measles vaccination is associated with nonspecific, long-term beneficial effects that reduce mortality (37). In that case, we would have expected increased morbidity in measles cases throughout the 24 weeks of follow-up, particularly in the hospital cohorts who had severe measles. The absence of an association of measles with increased long-term morbidity should not obscure the substantial health services burden from measles 6–8 weeks after rash onset. Mortality was low in our study, but higher case-fatality ratios would be expected in populations without access to high-quality case management. Measles vaccination is one of the most cost-effective health interventions available, and efforts to improve measles control in low-income countries must be intensified.

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REFERENCES

30. Rosales FJ, Kjolhede C. A single 210-μmol oral dose of retinol