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BRIEF REPORT

Changing Contact Patterns Over Disease Progression: Nipah Virus as a Case Study

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Contact patterns play a key role in disease transmission, and variation in contacts during the course of illness can influence transmission, particularly when accompanied by changes in host infectiousness. We used surveys among 1642 contacts of 94 Nipah virus case patients in Bangladesh to determine how contact patterns (physical and with bodily fluids) changed as disease progressed in severity. The number of contacts increased with severity and, for case patients who died, peaked on the day of death. Given transmission has only been observed among fatal cases of Nipah virus infection, our findings suggest that changes in contact patterns during illness contribute to risk of infection.

Keywords. Nipah virus; infectious disease transmission; social behavior.

Contact patterns play a key role in disease transmission. Understanding the determinants of contact patterns can be important in identifying targets for interventions. For example, during the 2009 H1N1 influenza pandemic, residents of Hong Kong with greater anxiety of infection were more likely to practice social distancing [1], a strategy associated with reduced risk [2]. Cultural and social norms can also affect contact patterns. In Bangladesh, female relatives are often responsible for providing hands-on care during illness [3], and this may contribute to the higher risk of Nipah virus infection observed among female spouses, compared with other family members [4].

Few studies have explored whether contact patterns change during the illness period. In a study conducted among university students in the United States, onset of influenza symptoms was associated with reduced contact durations, but not with contact frequency [5]. For more lethal diseases, the changing needs of the patient or social norms toward the end of life may alter the type and frequency of contacts as disease becomes more severe [3]. For certain pathogens such as Nipah virus, influenza virus and Ebola virus, more severe symptoms are also accompanied by changes in host infectiousness, as indicated by greater secretion of body fluids or higher viral loads [3, 6, 7].

Outbreaks of Nipah virus occur almost every year in Bangladesh, and person-to-person transmission has been reported in Bangladesh, India and the Philippines [4, 8, 9]. Person-to-person transmission can occur through exposure to bodily fluids [4], even after death [10]. Infection control practices in Bangladeshi healthcare facilities are generally poor [11] and most hands-on care is provided by family members rather than healthcare staff [3]. Cases are rarely diagnosed before death or recovery, limiting opportunities to prevent transmission. Clinical symptoms begin with fever, headache, and/or cough, progressing to altered mental status, respiratory difficulty, convulsions, and/or coma [12]. Approximately 70% of cases result in death [13]. In the current study, we used previously collected data to examine how contact patterns changed as disease progressed in severity for Nipah virus case patients.

METHODS

Patients

Full details regarding case and contact investigations were previously published [4]. In short, systematic investigations of Nipah virus cases in Bangladesh between December 2010 and April 2014 identified 96 Nipah virus case patients, including 19 secondary cases; these cases and their contacts or proxies were interviewed to quantify daily exposures (38 types) between the illness onset and up to 15 days thereafter, including exposures during burial. A physical contact was defined as an individual who had ≥1 exposure type involving a physical interaction with a case patient. A fluid contact was defined as an individual who had ≥1 exposure type involving bodily fluids. Two case patients were excluded from this analysis owing to missing dates of illness.

Measures of Disease Severity

We approached disease severity using 2 separate strategies. The first was by illness stage. We defined illness onset as the

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day on which case patients first had a fever. The febrile stage began on the day of illness onset and lasted until the case patient developed ≥1 sign of severe illness, including difficulty breathing, altered mental status, and/or convulsions; 9 patients did not have any signs of severe illness and only developed febrile illness. The severe stage was defined as the onset of ≥1 severe sign and ended on the day of death, hospital discharge, or when signs were resolved. Seventy-seven case patients (82%) had contact data covering their entire illness period, including 697 of 747 total person-days of illness (93%): 365 during febrile illness, 261 during severe illness, and 71 on the day of death (Supplementary Figure 1).

Our second approach involved describing contacts on the day of death and by each day preceding death for the 80 case patients who died. Time was considered a proxy of severity, where days closer to death represented more severe illness.

Statistical Analysis

In our first approach, we explored the relationship between illness stage and contacts using generalized linear mixed effects models with Poisson distributions and log link functions. We included stage, case patient sex, continuous case patient age, daily hospitalization status, and continuous year as fixed effects and case patient as a random effect. We also estimated the mean number of contacts by day of febrile illness to explore whether contact patterns might vary for pathogens that cause milder forms of disease.

In our second approach, we examined the relationship between time to death and contacts using generalized additive models with a thin plate regression spline to fit a nonlinear function to days until death and included the same additional fixed and random effects as the illness stage model. We also estimated the number of daily contacts, stratified by sex of case patients and contacts, to explore whether the sex of case patients was related to the sex of contacts.

To examine the relative contributions of healthcare staff, we estimated the proportion of contacts contributed by healthcare staff by illness stage. We reran our models after excluding all healthcare staff to explore whether associations with disease severity were influenced by healthcare services. We excluded data from the first year for these analyses because questions about profession were not included until December 2011.

Ethical Considerations

Written informed consent was obtained from Nipah virus case patients, contacts, or proxy respondents and/or guardians. Protocols were approved by the government of Bangladesh and the icddr,b human subjects review committee.

RESULTS

Among 94 case patients included in this analysis, 85 (90%) became severely ill, and 87 (93%) were hospitalized, including 84 of the 85 (99%) with severe illness (Table 1). Eighty case patients (85%) died. The median durations (interquartile range)

Table 1. Characteristics of Nipah Virus Case Patients and Person-Days of Illness, Bangladesh, 2010–2014

	Case Patients or Person-Days of Illness, No. (%)		
Case Characteristics	Case patients (N = 94)	Daily Physical Contacts (95% CI)	Daily Fluid Contacts (95% CI)
All case patients		7.2 (7.0–7.4)	2.0 (1.9–2.1)
Age group			
≤14 y	38 (40)	7.2 (6.9–7.5)	2.3 (2.1–2.5)
15–29 y	21 (22)	6.8 (6.4–7.2)	1.4 (1.3–1.6)
30–44 y	23 (24)	7.9 (7.5–8.4)	2.2 (1.9–2.4)
≥45 y	12 (13)	7.1 (6.5–7.7)	1.9 (1.6–2.2)
Sex			
Male	65 (69)	8.0 (7.7–8.2)	2.2 (2.1–2.4)
Female	29 (31)	5.8 (5.4–6.1)	1.6 (1.4–1.8)
Year (December to April)			
2010–2011	38 (40)	7.8 (7.5–8.2)	2.4 (2.2–2.6)
2011–2012	15 (16)	7.3 (6.8–7.8)	1.4 (1.2–1.7)
2012–2013	25 (27)	7.0 (6.6–7.4)	2.3 (2.1–2.5)
2013–2014	16 (17)	6.4 (6.0–6.9)	1.3 (1.1–1.5)
Person-day characteristics	Person-days of illness (N = 697)		
Stage			
Febrile	365 (52)	5.6 (5.3–5.8)	0.9 (.8–1.0)
Severe	261 (37)	8.5 (8.2–8.9)	3.1 (2.9–3.3)
Day of death	71 (10)	10.9 (10.2–11.7)	3.5 (3.0–4.0)
Hospitalized			
Yes	260 (37)	9.2 (8.8–9.6)	3.4 (3.2–3.6)
No	437 (63)	6.1 (5.8–6.3)	1.2 (1.1–1.3)

Abbreviations: CI, exact Poisson 95% confidence interval.

of febrile and severe illness were 3 (2–5) and 2 (1–4) days, respectively. A total of 1642 individuals reported ≥1 physical or fluid interaction with case patients.

Contact Rates by Illness Stage

There were no significant changes in physical or fluid contacts during the first 7 days of febrile illness (Supplementary Figure 2). Compared with febrile illness, the adjusted number of daily physical contacts was significantly higher during severe illness (rate ratio (RR), 1.25; 95% confidence interval [CI], 1.14–1.38) and on the day of death (1.38; 1.21–1.57) (Figure 1A and Supplementary Table 1). Differences were more pronounced for fluid contacts during severe illness (RR, 2.23; 95% CI, 1.84–2.70) and on the day of death (2.31; 1.80–2.96). Hospitalization was associated with significantly more physical contacts (RR, 1.26; 95% CI, 1.14–1.39) and fluid contacts (1.36; 1.13–1.63). Female case patients had fewer physical contacts (RR, 0.73; 95% CI, .58–.93) and fluid contacts (0.70; .53–.94) than male case patients.

Contact Rates by Day Relative to Death

Among case patients who died, the number of daily physical and fluid contacts increased during the week before death (Figure 1B). We estimated that, on average, a male case patient in 2010–2011 of mean age (23 years), who was not hospitalized, had 6.8 physical contacts (95% CI, 6.4–7.3) 6 days before death, 7.8 contacts (7.5–8.1) 3 days before death, and 9.6 contacts (8.7–10.5) on the day of death.

We estimated an average of 1.5 fluid contacts (95% CI, 1.3–1.7) 6 days before death, 2.3 contacts (2.1–2.5) 3 days before death, and 3.3 contacts (2.8–3.9) on the day of death. Similar to results from our illness stage models, the number of daily contacts was significantly higher on days when case patients were hospitalized for both physical contacts (RR, 1.27; 95% CI, 1.14–1.41) and fluid contacts (1.53; 1.26–1.86) (Supplementary Table 2). Female case patients had more female than male contacts at the end of life, and male case patients had more male than female contacts on the day of death (Supplementary Figure 3).

Contacts With Healthcare Staff

Healthcare staff accounted for 24% of all physical and 21% of all fluid contacts. During severe illness, healthcare staff accounted for 39% of all physical contacts, compared with 5% during febrile illness and 18% on the day of death (χ^2; $P < .01$). We also observed significant differences between fluid contacts with healthcare staff by stages (febrile, 2%; severe, 29%; death, 8%; χ^2; $P < .01$). Contacts remained positively associated with severe illness and days before death even after exclusion of healthcare staff (Supplementary Tables 3 and 4 and Figure 4).

DISCUSSION

Both physical and fluid contacts with Nipah virus case patients increased during severe illness, peaking on the day of death. This pattern was likely mediated by social practices. Family members and close friends of Nipah virus case patients often visited them when they were severely ill to make direct contact to signify the patient's importance [3]; sex selectivity among contacts provides further evidence of these patterns being driven by the social context. Furthermore, individuals involved in cleaning the body of the deceased in preparation for burial also increased the number of contacts on the day of death [3]; the sex of these contacts also matched the sex of the case patient, per common Muslim burial practices [14]. Given that transmission

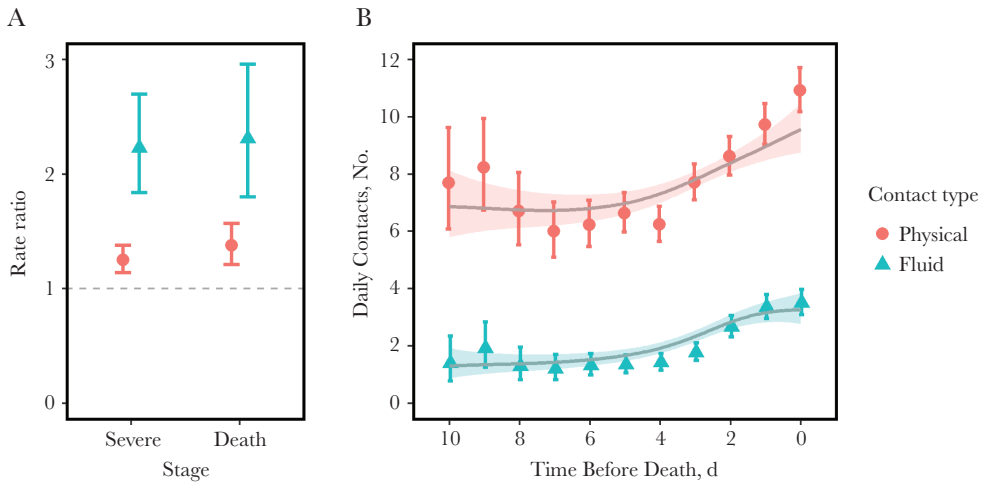

Figure 1. Relationship between contacts and disease severity among Nipah virus case patients identified in Bangladesh, 2010–2014. *A,* Rate ratios and 95% confidence intervals (CIs) by illness stage, relative to febrile illness, among all 94 Nipah virus case patients regardless of outcome, after adjustment for age, sex, year, and daily hospitalization status. *B,* Mean number of daily contacts by days before death among all 80 Nipah virus case patients that died. Points and error bars represent unadjusted values and 95% CIs. Shaded areas represent adjusted values with 95% CIs for a male case patient in 2010–2011 of mean age, who was not hospitalized.

has been observed only among fatal Nipah virus cases [13], our findings suggest this variation in contact patterns during illness may contribute to transmission risk, with synergistic effects from increased secretion of body fluids during severe illness [3]. Previously published analyses from this data set showed increased risk of infection after exposure to bodily fluids and found that exposure windows were often 4–6 days after illness onset [4], when severe signs of disease manifested.

The increase in contacts with disease severity has important implications for controlling onward spread of infection. Although we used Nipah virus infection in Bangladesh as a case study, it is likely that this relationship would hold true for other diseases in which increasing severity necessitates increasing contact for caregiving or desire to provide emotional support. Healthcare-seeking behavior played a smaller role in Nipah virus contact patterns compared with disease severity in the current study; however, owing to differences in healthcare seeking and hospital contact, healthcare seeking could be a more important factor in other contexts. A considerable portion of contacts during severe illness are due to healthcare staff (39%). Historically, healthcare staff have rarely been infected during Nipah virus outbreaks [4]; however, risk of infection may increase as healthcare systems in Bangladesh develop away from family-oriented caregiving and toward healthcare staff providing more direct patient care [4]. Healthcare facilities remain a key target for public health interventions, to prevent infections for staff and family caregivers.

The high number of contacts observed on the day of death is particularly worrisome for pathogens with the potential for postmortem transmission, such as Nipah virus [10] and Ebola virus [15]. During the 2013 Ebola outbreak, traditional burial practices, which involved touching and washing of the deceased played a major role in transmission [15]. We did not find any significant changes in contact frequency over time during the febrile illness stage, before the development of severe signs.

Our study had several limitations. First, contact surveys were conducted weeks after illness (median, 87 days; interquartile range, 59–117 days), because contacts were also screened for seroconversion at the same time. This could contribute to recall bias if contacts are more likely to remember events toward the end of the illness period, which could explain more contacts reported at the end of illness. However, given that contacts changed even within just the last 72 hours of illness, it seems unlikely that these small differences in recall periods would be responsible for the patterns we observed. Second, 7% of all illness days had missing contact data and, as contacts were collected only for the first 15 days of illness, most missing data were from case patients with longer illness periods. Surveys that place emphasis toward the end of illness may be valuable for diseases that cause severe illness, especially if host infectiousness is greatest during this period.

In conclusion, our findings show that contact patterns can vary as disease progresses in severity and should be taken into account in transmission models for diseases where severe presentations are common. Given the increasing contacts occurring during severe illness, effective interventions to prevent Nipah virus transmission should be targeted at this illness stage, particularly in hospital settings.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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