Research

Influenza-associated mortality in 2009 in four sentinel sites in Bangladesh

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Objective To estimate influenza-associated mortality in Bangladesh in 2009.

Methods In four hospitals in Bangladesh, respiratory samples were collected twice a month throughout 2009 from inpatients aged <5 years with severe pneumonia and from older inpatients with severe acute respiratory infection. The samples were tested for influenza virus ribonucleic acid (RNA) using polymerase chain reaction. The deaths in 2009 in five randomly selected unions (the smallest administrative units in Bangladesh) in each hospital’s catchment area were then investigated using formal records and informal group discussions. The deaths of those who had reportedly died within 14 days of suddenly developing fever with cough and/or a sore throat were assumed to be influenza-associated. The rate of such deaths in 2009 in each of the catchment areas was then estimated from the number of apparently influenza-associated deaths in the sampled unions, the proportion of the sampled inpatients in the local hospital who tested positive for influenza virus RNA, and the estimated number of residents of the sampled unions.

Findings Of the 2500 people known to have died in 2009 in all 20 study unions, 346 (14%) reportedly had fever with cough and/or sore throat within 14 days of their deaths. The estimated mean annual influenza-associated mortality in these unions was 11 per 100 000 population: 1.5, 4.0 and 125 deaths per 100 000 among those aged <5, 5–59 and >59 years, respectively.

Conclusion The highest burden of influenza-associated mortality in Bangladesh in 2009 was among the elderly.

Abstracts in العربية, 中文, Français, Русский and Español at the end of each article.

Introduction

Data on influenza-associated mortality can help estimate the burden posed by influenza, identify any high-risk age groups, and guide policy-makers in their allocation of scarce resources for related public health interventions. Estimation of influenza-related mortality is difficult,1 however, as only a small proportion of those with influenza-like illness (ILI) are tested for influenza viruses. In addition, as influenza-associated deaths often occur 1 to 2 weeks after infection with an influenza virus following secondary bacterial infection or the exacerbation of pre-existing chronic illness,2–4 few such deaths are attributed to influenza on death certificates.1,7,8

The information available on the impact of influenza virus infection on mortality in low-income countries such as Bangladesh is particularly limited. The high population densities, chronic malnutrition and inadequate access to health services commonly found in low-income settings may amplify the impact of influenza on morbidity and mortality.9,10 Bangladesh has not only one of the highest population densities in the world (about 1000 people per square kilometre) but also a modest health infrastructure, with, on average, only one hospital bed available for every 1860 residents.11 Furthermore, formal records of births and deaths are limited, with most deaths occurring at home.12 Together, these limitations hamper the use of standard modelling approaches to estimate influenza-attributable mortality.13,14 In this study we used a combination of hospital-based influenza surveillance and community surveys to estimate influenza-associated mortality in Bangladesh in 2009.

Methods

Hospital-based influenza surveillance

In 2009, the Institute of Epidemiology, Disease Control and Research (IEDCR) of the Government of Bangladesh and the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) conducted influenza surveillance in four sentinel hospitals (one private and three government-run) in four geographically diverse locations in Bangladesh: Kishoreganj, Bogra, Comilla and Barisal. The subdistricts that appeared most frequently in the log books of a study hospital as the places of residence of the patients and that represented at least 75% of the patients seeking care at the hospital were considered to be the catchment area of that hospital. Beginning in January 2009, on 2 days a month, surveillance physicians at each study hospital enrolled inpatients who presented within 7 days of symptom onset, resided in the hospital’s catchment area and were either younger than 5 years and had severe pneumonia or were 5 years or older and had severe acute respiratory illness (SARI). Severe pneumonia was defined as cough or difficulty breathing and at least one of the following: chest indrawing, history of convulsion, inability to drink, lethargy and intractable vomiting. SARI was defined as a history of fever with cough and/or sore throat.

Laboratory analysis

Surveillance physicians collected nasal and oropharyngeal swabs from each enrolled patient, placed them in viral transport medium and then stored them at −70 °C or lower.
until testing. At the icddr,b, the thawed samples were tested for influenza A and B virus ribonucleic acid (RNA) in assays based on real-time reverse-transcription polymerase chain reaction (RT–PCR).15 Any influenza A viruses detected were subtyped for seasonal H1N1, 2009 pandemic H1N1, H3N2 and H5N1, using primers and probes provided by the Influenza Division at the United States Centers for Disease Control and Prevention (CDC).16

Community survey

The influenza-associated annual mortality rates in Singapore and the United States of America have been reported to be between 9.0 and 16.7 deaths per 100 000.17,18 For the present study, we assumed that the corresponding rate in Bangladesh would be about the same, at 10 deaths per 100 000. Based on this assumption, we estimated that a sample size of 420 385 people would be sufficient to estimate the influenza-associated mortality in Bangladesh with a power of 80% and a precision of 5%.

We first listed all the unions – which are the lowest administrative units in Bangladesh – that lay within the catchment area of each study hospital. As each union in Bangladesh has a mean population of about 28 000,19 we estimated that we would need to investigate deaths in 15 average-sized unions to reach the desired sample size. To allow for unions with smaller-than-average populations, however, we decided to select 20 unions for study (i.e. five randomly selected unions from each of the four catchment areas investigated). Data collected in the catchment area of each study hospital were used to estimate the influenza-associated mortality rate for 2009 in Bangladesh.

Between February and May of 2010, the local administrative officer in each union selected for study was asked for a list of deaths from any cause that occurred in the union in 2009. In Bangladesh, such formal lists of deaths are incomplete and the causes of death that they record are assigned by lay individuals.20 The field teams therefore used informal group discussions in 2010 to collect additional information on the deaths that had occurred in 2009 in each study union. Such discussions, which had already proven to be a relatively low-cost method of estimating the incidence of Japanese encephalitis in Bangladesh,21 took place among small groups of community residents in different key gathering points such as tea stalls, local markets, mosques and schools. The household of any person who had died in a study union in 2009 from causes other than injury, homicide or suicide was then visited by a field team. In each visited household, a field team collected information from “proxy respondents” – the household member or members who had been involved in caring for the person who had died in 2009 and who had been present throughout that person’s last episode of illness. The proxy respondents were asked if the person who had died in 2009 had shown the symptoms of ILI (defined as the sudden onset of fever with cough and/or sore throat) within 14 days of his or her death. Further information on any person who had reportedly died with ILI in 2009 (demographics, medical history and care-seeking behaviour before death) was also collected from the proxy respondents.

Ethical issues

Swabs were only collected from an inpatient after written informed consent had been obtained from the patient (if aged at least 18 years) or his or her parents or guardians (if aged <18 years). Field teams obtained written informed consent from each proxy respondent. The study protocol was approved by the ethical review committees at both the icddr,b and the CDC.

Data analysis

Influenza-associated mortality in various age groups in Bangladesh was estimated, for the year 2009, using the following equation:

\[
I = \frac{df}{ps}
\]

where \(I\) is the age-specific influenza-associated mortality (in deaths per 100 000 population), \(df\) is the age-specific number of ILI-associated deaths in 2009 (as identified in the formal lists and informal group discussions in the surveyed unions), \(f\) is the age-specific number of inpatients found positive for influenza virus in any study hospital, \(p\) is the age-specific projected population of the surveyed unions in 2009, and \(s\) is the age-specific number of inpatients who were tested for influenza virus in any study hospital.

The values for \(p\) were estimated using data from the 2001 national census.21 The annual growth rate between the census and 2009 was estimated at 1.5% by using crude birth rates, assuming minimal net migration and estimating a national crude death rate.22 Three broad age groups were considered in estimating \(I\): < 5, 5–59 and > 59 years. Non-parametric bootstrapping22 was used to calculate 95% confidence intervals (CIs) for each estimated incidence.

We used similar methods to estimate the deaths occurring in Bangladesh in 2009 that were associated with H1N1 2009 pandemic influenza. Since 2009 pandemic influenza was first identified in Bangladesh in June 2009,23 we included in our analysis only those ILI-associated deaths that occurred during July–December 2009, the number of respiratory samples collected from the study hospitals during the same period, and the number of those samples found positive for A(H1N1)pdm09 RNA.

Population mortality estimates

Together, the data collected in the four study hospitals and their catchment areas were assumed to be representative of Bangladesh as a whole. Our estimates of the age-specific influenza-associated mortality rates in 2009 in the study unions were therefore extrapolated, using data on the total population of Bangladesh in 2009,21 to give estimates of the age-specific influenza-associated mortality rates throughout Bangladesh in that year.

Results

Hospital-based influenza surveillance

In 2009, surveillance physicians collected 340 respiratory samples from inpatients and 60 (18%) of them were found positive for influenza virus. Twenty-nine (48%) of the positive samples contained RNA from A(H1N1)pdm09, 26 (43%) from the influenza A/H3 virus and four (7%) from the influenza B virus. Five (5%) of the 104 samples from children aged < 5 years with severe pneumonia, 45 (25%) of the 177 samples from patients aged 5–59 years with SARI and 10 (17%) of the 59 samples from the older patients with SARI were found positive for influenza virus.

Between 1 July 2009 and 31 December 2009, A(H1N1)pdm09 was detected in one (2%) of the 50 samples collected
from children aged <5 years and in 28 (23%) of the 122 samples from patients aged 5–59 years, but in none of the 30 samples from inpatients aged >5 years.

**Patients with influenza-like illness**

In 2009, the 20 unions surveyed had a combined estimated population of 555,118 (about 23,000 per union on average), equivalent to 23% of the total estimated population of the four catchment areas investigated. The field teams identified 2,646 deaths as having occurred in the 20 unions in 2009, which amounts to a crude annual rate of about five deaths per 1,000 population. Of these deaths, 146 (5.5%) were attributed to injury, homicide or suicide. The proxy respondents reported that 346 (14%) of the 2,500 people who died in the study unions in 2009 of causes other than injury, homicide or suicide had experienced a sudden onset of fever with cough and/or sore throat (i.e. ILI) within 14 days of their death (Table 1). Of the 346 people who appeared to have had influenza when they died, 21 (6%), 78 (22.5%) and 247 (71%) were aged <5, 5–59 and >59 years, respectively. Of these people, 212 (61%) were male, 183 (53%) were smokers and 272 (79%) had co-morbidities identified before death: 162 (47%) had asthma, 43 (12%) had pulmonary tuberculosis, 69 (12%) had cancer, 38 (11%) had heart disease and 26 (7.5%) had diabetes. More than 70% (196) of the decedents with known co-morbidities were aged >59 years.

**Health-seeking practices**

Of the 346 people who died in the study unions in 2009 within 14 days of developing ILI, 273 (78.9%) had reportedly sought treatment from a health-care provider and had done so within a median of 1 day (interquartile range, IQR: 1–2) of the onset of their final illness. Nine (47%) of the 19 patients aged <5 years, 46 (61%) of the 57 patients aged 5–59 years and 88 (45%) of the 196 patients aged >59 years had first sought treatment from a registered medical practitioner or a hospital. The rest (51%) had initially sought treatment from a local informal health practitioner, a pharmacy or a traditional healer.

Of the patients who died within 14 days of developing ILI, only 76 (28%) were hospitalized for their last illness and only 38 (11%) died while hospitalized. The cause of death of 20 (53%) of the 38 who died in hospital was identified as pneumonia or respiratory illness by the attending physician. The other 18 in-hospital deaths among patients with ILI were attributed to cardiac failure, cerebrovascular disease or cancer. The median age of the 308 people with ILI who died at home was 70 years (IQR: 56–80). According to the proxy respondents, the most common causes of death among those dying at home within 14 days of developing ILI were respiratory failure (36%), fever (19%), cancer (12%) and pneumonia (7%).

Of the ILI-associated deaths that reportedly occurred in the study unions at some time in 2009, 178 (51%) occurred after 1 July in that year (i.e. after the emergence of the A(H1N1) 2009 pandemic in Bangladesh).23 According to the proxy respondents, of those dying with ILI after 1 July 2009, five (50%) of the 10 who were aged <5 years at death, 22 (41.5%) of the 53 aged 5–59 years and 38 (33%) of the 115 aged >59 years had sought treatment from a licensed physician but none of these people had received oseltamivir as part of their treatment.

**Influenza-associated mortality**

The estimated influenza-associated mortality rates during 2009 in the 20 study unions combined were 1.5 (95% CI: 0.9–2.4; 4.0 (95% CI: 3.5–5) and 125 (95% CI: 110–126) per 100,000 population. The age-specific influenza-associated mortality rates for the study unions in each of the four catchment areas investigated are presented in Table 1. The monthly data on identified deaths, ILI-associated deaths and the proportion of tested swabs found positive for influenza virus RNA are summarized in Fig. 1. Extrapolation of the results from the study unions to the whole of Bangladesh indicated that about 34,300 influenza-associated deaths occurred throughout the country in 2009: 300 among children aged <5 years, 4,000 among people aged 5–59 years and 30,000 among those aged >59 years. The corresponding estimated mortality rates associated with A(H1N1) pdm09 are 0.3 (95% CI: 0.1–0.4), 3.0 (95% CI: 1.6–3) and zero per 100,000, respectively. These values indicate that the deaths of about 6,000 people in Bangladesh in 2009 were associated with A(H1N1) pandemic influenza. The all-age mortality with pandemic influenza was about 4.0 per 100,000.

**Discussion**

Our findings indicate that, in 2009, influenza-associated deaths were frequent among the elderly living in Bangladesh, although >60% of the people...
In some previous studies, influenza-associated mortality has been estimated using cyclic regression models or the Serfling method. In low-income countries such as Bangladesh, where death registers may be very incomplete and many deaths occur at home and are never recorded by any administrative body, it is easy to underestimate the true influenza-associated mortality from formal reports. Unfortunately, few alternative methods to improve estimates of influenza-associated mortality in low-income countries have been tested.

In the present study, data from four sentinel hospitals participating in a pre-existing system for influenza surveillance were combined with data collected, mostly in group discussions at the community level, on deaths in the hospitals’ catchment areas. The collection and analysis of these data had several limitations. First, the data collected refer to a single year; it should be possible to determine the general burden posed by influenza in Bangladesh more accurately when more years of surveillance and vital statistics data become available. Second, most of the data on the number of deaths and final illnesses, including the identification of ILI (which can be caused by a wide range of respiratory viruses), came from proxy respondents – generally relatives of the deceased having no clinical expertise – who were interviewed months after the deaths. Third, fever (as identified by the proxy respondents) was used as a compulsory criterion in identifying ILI, even though children and elderly people with influenza do not always present with this symptom.

Fourth, some deaths may have gone undetected by the field teams. No attempt was made to perform a house-to-house survey, which might have revealed some more relevant deaths. The tightly knit social networks that are common in rural Bangladesh, however, make it unlikely that community members were unaware of any deaths within their communities.

Fifth, our study was conducted in only four sentinel sites and, although these sites were chosen to represent the different geographical regions of the country, the data collected may not be truly representative of the whole of Bangladesh. Encouragingly, despite these limitations, the present estimate of the crude annual death rate in the study unions was close to the estimate of six deaths per 1000 population made by the United Nations Children’s Fund for the whole of Bangladesh. The present estimate of the fraction of patients with ILI who die in Bangladesh (13%) is also similar to the World Health Organization’s estimated fraction of patients who die with lower respiratory infection in the country across all age-groups (11%).

Our data indicate that seasonal influenza viruses contributed more to mortality among the elderly people of Bangladesh in 2009 than A(H1N1)pdm09. Cost-effective public health interventions that can interrupt the transmission of diverse respiratory pathogens across all age groups may help lower the overall burden of deaths from respiratory ailments. Our method of combining community surveys and influenza surveillance data could be adopted in similar resource-poor settings to provide estimates of influenza-associated mortality where vital registries are not reliable and deaths frequently occur at home.

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Competing interests: None declared.
Objectif Estimer la mortalité liée à la grippe au Bangladesh en 2009.

Méthodes Des prélèvements respiratoires ont été collectés deux fois par mois tout au long de l'année 2009 sur quatre hôpitaux du Bangladesh, chez des patients âgés de 5 ans souffrant de pneumonie grave et chez des patients plus âgés souffrant d'infection respiratoire aiguë. Ces prélèvements ont été testés pour le virus de la grippe à acide ribonucléique (ARN) au moyen d'une réaction en chaîne par polymérase. Les décès en 2009 dans cinq régions sélectionnées (les plus petites unités administratives au Bangladesh) ont été analysés en moyenne et à partir de déclarations dans les hôpitaux et de centres de recherche informels de groupes. Les analyses ont été conduites sur les 14 jours précédant le décès de ces décès en 2009 dans chaque des zones couvertes une fois et après pour le virus de la grippe ARN et du nombre estimé de résidents des zones concernées.

Résultats Des 2500 personnes décédées en 2009 dans les 20 unions de l'hôpital local tests positifs pour le virus de la grippe ARN et du nombre estimé de résidents des zones concernées. L'âge moyen des décédés était de 11 ans parmi 10 000 habitants; 1,5, 4 et 125 décès par 100 000 habitants parmi les personnes âgées de respectivement <5, 5-59 et >59 ans.

Conclusion La plus grande charge de mortalité liée à la grippe au Bangladesh figurait parmi la population âgée.
Mortality associated to the gripe in 2009 in four sites centinela in Bangladesh

Objective Calculate the mortality associated to the gripe in Bangladesh in 2009.

Methods Se recogieron muestras respiratorias de pacientes con edades menores de 5 años con neumonía grave así como de otros pacientes de mayor edad con infecciones respiratorias agudas dos veces al mes en cuatro hospitales de Bangladesh durante el año 2009. Las muestras se sometieron a las pruebas del ácido ribonucleico (ARN) del virus gripal por medio de una reacción en cadena de la polimerasa. A través de métodos polimerazas de cadena de reacción las pruebas fueron realizadas en cuatro hospitales de Bangladesh cuatro veces al mes. Las muestras se sometieron a pruebas de polimerasa en 2009.

Results Finalmente, 2560 personas con edades menores de 5 años y 699 personas con edades mayores de 5 años murieron del gripe en Bangladesh en 2009. Las pruebas del ARN del virus gripal se realizaron en 2009.

Conclusions Se concluye que el número de defunciones asociadas a la gripe en Bangladesh en 2009 fue de 2560 personas menores de 5 años y 699 personas mayores de 5 años. La mortalidad asociada a la gripe en Bangladesh en 2009 fue de 2560 personas menores de 5 años y 699 personas mayores de 5 años.


