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


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.

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, 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, few such deaths are attributed to influenza on death certificates.

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. 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. Furthermore, formal records of births and deaths are limited, with most deaths occurring at home. Together, these limitations hamper the use of standard modelling approaches to estimate influenza-attributable mortality.

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, resident 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.

References

1 International Centre for Diarrhoeal Disease Research, Bangladesh, Saheed Tajuddin Ahmed Sarani, Mohakhalai, Dhaka-1212, Bangladesh.
2 Institute of Epidemiology Disease Control and Research, Dhaka, Bangladesh.
3 Centers for Disease Control and Prevention, Atlanta, United States of America.
Correspondence to Nusrat Homaira (e-mail: nhomaira@icddrb.org).
(Submitted: 4 September 2011 – Revised version received: 30 November 2011 – Accepted: 19 January 2012)
In June 2009, A(H1N1)pdm09 was detected in one (2%) of the 50 samples collected 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). 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).

**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. 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, 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. 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, 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 in-patient 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), \(d\) 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. 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. Three broad age groups were considered in estimating \(I\): < 5, 5–59 and > 59 years. Non-parametric bootstrapping 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, 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, 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...
Influenza-associated mortality in Bangladesh

Table 1. Total mortality and mortality associated with influenza-like-illness (ILI) and influenza in four study sites, by age group, Bangladesh, 2009

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study site (five unions per site)</th>
<th>Kishoreganj</th>
<th>Bogra</th>
<th>Comilla</th>
<th>Barisal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children aged &lt; 5 years</strong></td>
<td>No. of ILI-associated deaths</td>
<td>7</td>
<td>5</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Total no. of deaths</td>
<td>11</td>
<td>22</td>
<td>32</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>10 040</td>
<td>17 150</td>
<td>25 000</td>
<td>19 298</td>
<td></td>
</tr>
<tr>
<td>Influenza-associated mortalitya</td>
<td>3.5</td>
<td>1.5</td>
<td>1.0</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td><strong>People aged 5–59 years</strong></td>
<td>No. of ILI-associated deaths</td>
<td>22</td>
<td>25</td>
<td>26</td>
<td>34</td>
</tr>
<tr>
<td>Total no. of deaths</td>
<td>254</td>
<td>197</td>
<td>362</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>62 533</td>
<td>108 481</td>
<td>156 861</td>
<td>120 233</td>
<td></td>
</tr>
<tr>
<td>Influenza-associated mortalitya</td>
<td>8.0</td>
<td>5.5</td>
<td>4.0</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td><strong>People aged &gt; 59 years</strong></td>
<td>No. of ILI-associated deaths</td>
<td>38</td>
<td>42</td>
<td>60</td>
<td>78</td>
</tr>
<tr>
<td>Total no. of deaths</td>
<td>289</td>
<td>285</td>
<td>477</td>
<td>358</td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>5 409</td>
<td>7 721</td>
<td>12 432</td>
<td>9 960</td>
<td></td>
</tr>
<tr>
<td>Influenza-associated mortalitya</td>
<td>126</td>
<td>98</td>
<td>87</td>
<td>141</td>
<td></td>
</tr>
</tbody>
</table>

a Estimated, in deaths per 100,000, from the proportion of inpatients with ILI who were tested and confirmed to be infected with influenza virus at the hospital whose catchment area included the given study site.

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 >59 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 2646 deaths as having occurred in the 20 unions in 2009, which amounts to a crude annual rate of about five deaths per 1000 population. Of these deaths, 146 (5.5%) were attributed to injury, homicide or suicide. The proxy respondents reported that 346 (14%) of the 2500 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).21 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), 4.0 (95% CI: 3.5–5) and 125 (95% CI: 110–126) per 100 000 among those aged <5, 5–59 and >59 years, respectively. The corresponding all-age mortality was 11 (95% CI: 10–12) deaths per 100 000 population. The age-specific influenza-associated mortalities 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, 4000 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 6000 people in Bangladesh in 2009 were associated with A(H1N1)pdm09 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...
Influenza-associated mortality in Bangladesh

Nusrat Homaira et al.

In the present study, data from four sentinel hospitals participating in a pre-existing system for influenza surveillance were combined with data collected, mostly from proxy respondents – generally relatives of the deceased having no clinical expertise – who were interviewed from proxy respondents. This work was funded by the CDC’s Influenza Division, under a cooperative agreement (1U01CI000628-01).

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, 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 from proxy respondents – generally relatives of the deceased having no clinical expertise – who were interviewed from proxy respondents. This work was funded by the CDC’s Influenza Division, under a cooperative agreement (1U01CI000628-01).

None declared.

Acknowledgements

We thank inpatients, respondents, surveillance staff, field teams and the staff of the study hospitals for their contribution to the study. The icddr,b acknowledges with gratitude the commitment of the CDC to its research efforts.

Funding: This work was funded by the CDC’s Influenza Division, under a cooperative agreement (1U01CI000628-01).

Competing interests: None declared.
Influenza-associated mortality in Bangladesh

Nusrat Homaira et al.

Melخص

الوفيات المرتبطة بالأنفلونزا في 2009 في أربع مواقع خارفة في بنغلاديش

الغرض: تقدير معدل الوفيات المرتبطة بالأنفلونزا في بنغلاديش في 2009.

الطريقة: تم جمع عينات من الجهاز التنفسي، من المرضى الذين أصيبوا بالأنفلونزا، في أربع مراكز صحية في بنغلاديش، مرتين شهريًا على مدار عام 2009. تم استخدام聚链反应 (PCR) لتحديد كائن فيروس الأنفلونزا (H1N1) في العينات. قُدرت الوفيات المرتبطة بالأنفلونزا تحت تأثير أنفلونزا في بنغلاديش، من خلال استعلام المحلية السكانية والمستشفيات، خلال عام 2009.

النتائج: قُدر متوسط عدد الوفيات المرتبطة بالأنفلونزا في بنغلاديش لعام 2009 بين 1.5 و125 حالة لكل 100,000 شخص.

الاستنتاج: أعلى عبء للوفيات المرتبطة بالأنفلونزا في بنغلاديش كان في الفئة العمرية فوق 59 عامًا.

Résumé

Mortalité liée à la grippe en 2009 dans quatre sites sentinelles au Bangladesh

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 dans quatre hôpitaux du Bangladesh, chez des patients âgés de 5 ans souffrant de pneumonie grave ou 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 les régions sélectionnées ont été répertoriés par le local testé positif pour le virus de la grippe et du nombre estimé de résidents des unions prélevées.

Résultats Des 2500 personnes décédées en 2009 dans les 20 unions de l'année, 346 (14%) vivaient dans les 100,000 habitants: 1,5 et 125 décès par 100,000 habitants parmi les personnes âgées de respectivement <5, 5–19, et >59 ans.

Conclusion La plus grande charge de mortalité liée à la grippe au Bangladesh figurait parmi la population âgée.
Резюме

Смертность от гриппа в Бангладеш в 2009 г. по результатам наблюдений на четырех контрольных участках

Цель. Произвести оценку уровня смертности от гриппа в Бангладеш в 2009 г.

Методы. На протяжении 2009 г. в четырех больницах республики Бангладеш два раза в месяц брались дыхательные пробы у стационарных больных в возрасте до 5 лет с острой формой пневмонии, а также у стационарных больных старай возрастной категории с острой формой респираторной инфекции. Методом полимеразной цепной реакции данные пробы были исследованы на предмет наличия рибонуклеиновой кислоты (РНК) вируса гриппа. В 2009 г. путем изучения официальных документов и неформальных обсуждений в группах была исследована смертность в обслуживающих больницах районах в пяти случайными образом выбранных округах (наименьшие административные единицы в Бангладеше). Предполагалось, что смерть пациентов, которые согласной поступившей информации умерли в течение 14 дней после стремительного развития лихорадки, сопровождающейся кашлем и/или болями в горле, наступила в результате заболевания гриппом. Доля смертей по этой причине в 2009 г. для каждого района, обслуживающего медицинскими учреждениями, была рассчитана на основании количества смертей, предположительно наступивших в результате заболевания гриппом в исследуемых округах, пропорционально количеству стационарных больных в местных больницах, в пробах которых была обнаружена РНК вируса гриппа, по отношению к расчетному количеству жителей исследуемых округов.

Результаты. Из 2500 человек, которые умерли в 2009 году во всех 20 исследуемых округах, 346 (14%), согласно поступившей информации, за 14 дней до наступления их смерти были больны лихорадкой, сопровождающейся кашлем и/или болями в горле. Расчетные значения указывают, что ежегодная смертность из-за гриппа в этих округах была 11 человек на 100 000 населения: 1,5, 4,0 и 125 смертей на 100 000 человек населения в возрастных категориях < 5,5–59 и > 59 лет, соответственно.

Вывод. Наибольшее количество смертей в республике Бангладеш в 2009 году по причине заболевания гриппом наступило среди людей старшей возрастной категории.

References
Research

Influenza-associated mortality in Bangladesh

Nusrat Homaira et al.


