Hospital based surveillance revealed high prevalence of influenza in Bangladesh

We conducted influenza surveillance in 12 hospitals across Bangladesh to identify clusters of people with life threatening influenza virus infections and to characterize the diversity of circulating influenza strains. We looked for clusters of patients presenting with severe acute respiratory illness and once per month collected specimens from persons seeking care at outpatient departments with influenza like illness. Between May and December 2007, we collected 1,045 specimens; 117 (11%) were influenza positive. Among the positive samples, 46 (39%) were influenza A and 71 (61%) were influenza B. Hemagglutinin subtyping of influenza A positive specimens detected H1 and H3 but no H5 subtypes.

The influenza pandemic of 1918-1919 caused acute illness in 25-30% of the world's population resulting in an estimated 40 million deaths (1,2). Recent studies have suggested that the

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virus was an entirely avian-like virus directly adapted to humans (3). A new strain of highly pathogenic influenza A (H5N1) virus has been circulating among birds in Asia since 1996 (4). By December 2007, 61 countries, including Bangladesh, reported outbreaks among poultry (5). By 5 March 2008, 47 out of Bangladesh's 64 districts have reported outbreaks of H5N1 in poultry or non-migratory wild birds (6). In other countries, the H5N1 virus has crossed the species barrier and infected humans with high mortality. As of 22 February 2008, a total of 366 confirmed H5N1 human cases and 232 deaths (63%) were reported to the World Health Organization (WHO). Most human cases were reported from Asia, including some countries neighbouring Bangladesh (7). Scientists predict that the next influenza pandemic will evolve from Asia (8), and genetic changes in recently circulating H5N1 viruses indicate that this virus could mutate to become more easily transmissible between humans (3). However it is impossible to predict how, when, and from which influenza virus the next pandemic will evolve (9).

Bangladesh is the eighth most populous country in the world and, after only a few microstates and small island nations, has the highest population density (10). It also ranks second of any country for highest intrinsic risk for emergence of an avian influenza pandemic based on an index that considers risk of emergence, risk of spread, and capacity to contain an outbreak (11). Bangladesh is located near several countries that have reported human cases of avian influenza, and domestic poultry is raised widely throughout the country, ranging from backyard to large-scale commercial poultry firms.

There are some existing data on human influenza in Bangladesh. ICDDR,B's population based surveillance for influenza in the Kamalapur neighbourhood of Dhaka city identified influenza in 14% of children aged <5 years with acute respiratory illness. The incidence of influenza virus infection was 84.5 episodes/1000 children-years. Among positive samples, 58% were influenza A (H3N2, H1N1) and 42% were influenza B (12). However, the data are limited to children <5 years of age in one small geographic area in a single city of Bangladesh.

ICDDR,B in collaboration with Institute of Epidemiology, Disease Control and Research (IEDCR) launched hospital-based human influenza surveillance in 6 private and 6 public hospitals around Bangladesh (Figure 1). The aims of the surveillance are to identify individuals and clusters of people with life threatening infections with influenza virus and to characterize the diversity of strains of influenza in circulation in Bangladesh.

The surveillance commenced in April 2007 with Rajshahi Medical College

Figure 1: Map of Bangladesh showing the hospitals participating in hospital based influenza surveillance

01 Dhaka National Medical College Hospital
02 Community Based Medical College Hospital
03 Jahurul Islam Medical College Hospital
04 Rajshahi Medical College Hospital
05 Shaheed Ziaur Rahman Medical College Hospital
06 LAMB Hospital
07 Bangabandhu Memorial Hospital
08 Comilla Medical College Hospital
09 Khulna Medical College Hospital
10 Jessore General Hospital
11 Jalalabad Ragib-Rabeya Medical College Hospital
12 Sher-e-Bangla Medical College Hospital

Hospital and gradually involved all 12 hospitals by September 2007. Surveillance physicians, recruited from existing hospital staff, visited medicine and paediatric wards daily to identify patients suffering from severe acute respiratory illness (defined as fever over 38ºC and cough or sore throat and shortness of breath or difficulty breathing). They regularly reviewed the linelist to identify clusters, which was defined as 3 or more patients presenting with severe disease who lived within a 30 minute walk of each other and developed symptoms within 7 days of each other. In addition, on 2 consecutive days each month, surveillance physicians collected throat and nasal swab specimens from up to 20 patients presenting to outpatient departments with influenza like illness (defined as fever and cough or sore throat). Swabs were then transported to the ICDDR,B virology laboratory for analysis by real time reverse transcriptase polymerase chain reaction (rRT-PCR).

Between May and December 2007, we collected and analyzed specimens from 1,045 patients and 117 (11%) were influenza positive. The study identified 195 cases of severe acute respiratory illness but no clusters were found. Fourteen patients with severe acute respiratory illness had specimens collected and 3 (21%) were influenza positive. The remaining 1,031 (99%) specimens were obtained from patients with influenza like illnesses who sought treatment at the outpatient departments. Among all patients enrolled, 558 (53%) were male. Among the 12 poultry workers and 20 health care providers enrolled in the surveillance, 1 (8%) poultry worker and 5 (25%) health care workers had influenza. Forty-three percent (446/1045) of patients reported raising poultry at their households; 36 (8%) of them had influenza infection.

Among the influenza positive samples, 46 (39%) were influenza A and 71

(61%) were influenza B. Hemagglutinin subtyping was performed on 44 influenza A positive samples; 29 (66%) were H1 and 15 (34%) were H3 subtypes. No H5 virus infection was detected. Influenza was found in all age groups with highest prevalence among young adults and least among persons aged 26-40 (Table 1).

Table 1: Age distribution of influenza infection

Age group	Samples analyzed	Influenza positives	Percent positive
Below 5 years	488	53	11%
6-15 years	121	14	12%
16-25 years	166	26	16%
26-40 years	163	12	7%
Over 40 years	107	12	11%
Total	1,045	117	11%

Influenza virus infections were geographically distributed throughout the country. Cases were more commonly identified between May and September compared to the last 3 months of the year (Figure 2).

Figure 2: Percent of influenza positive specimens by month
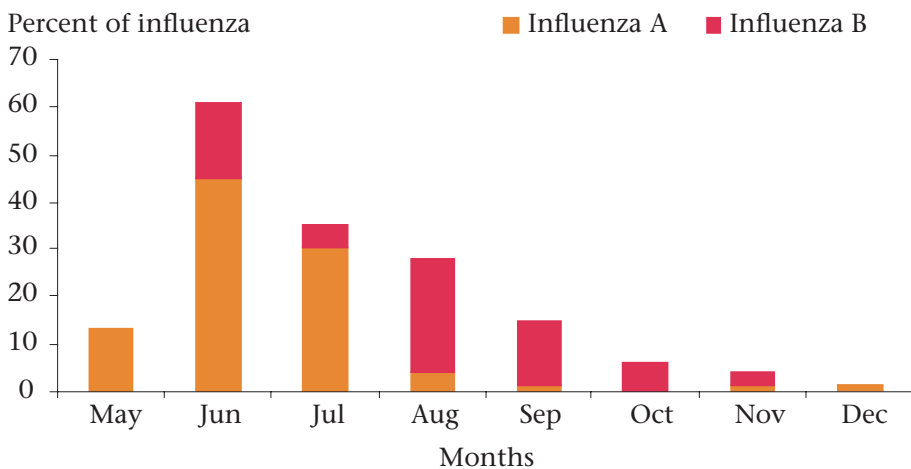
Comment

Patients presenting to outpatient departments at our hospitals commonly suffered from influenza infection, especially from May to September. Influenza infection was found throughout the country and, although children were more likely to present to outpatient departments with influenza like illness, the prevalence of influenza was similar between children and adults with this syndrome. This might be caused by greater health care seeking among children than adults; nonetheless, our data suggest that seasonal influenza is common throughout Bangladesh. The threat of an influenza pandemic is certainly concerning, however, seasonal influenza caused more deaths than pandemic influenza in the past century (13).

The high rate of human influenza coupled with the high rate of poultry exposure and the ongoing, widespread epidemic of H5N1 in poultry increases the opportunity for reassortment of avian viruses with human viruses in this country. Emergence of a new influenza strain with the capacity to be transmitted easily between humans could cause pandemic disease.

Our preliminary findings are consistent with reported seasonality of influenza infection from the population based surveillance in the Kamalapur neighbourhood of Dhaka city, where the peak season was April to September (12). This seasonality is in contrast to temperate zones, where peak transmission occurs between September and March (14).

Despite the wide distribution of our surveillance hospitals, it is possible that H5N1 infections in humans have gone undetected, especially isolated cases. In Bangladesh, many patients do not seek care at hospitals, even during life threatening illness. Moreover, we have not included all tertiary care facilities in our network. However, we believe that clusters of severe acute respiratory illness, which are of greatest public health interest, were less likely to escape detection given recent intensive efforts to increase outbreak reporting among physicians and the media attention that H5N1 infection has received in Bangladesh. The absence of identified clusters of severe disease suggests that highly pathogenic influenza virus is not being efficiently transmitted from person to person in Bangladesh.

Ongoing surveillance is important, especially for identifying clusters of severe acute respiratory illness. Clinicians throughout the country play an important role in identifying highly pathogenic influenza infections. They should be aware of any patients with severe respiratory illness in their health care facilities, as well as their communities, and immediately report to IEDCR any clusters of disease or isolated cases with a history of contact with sick or dead poultry.

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Invasive pneumococcal disease burden and implications for vaccine policy in urban Bangladesh

We conducted active population-based surveillance among children <5 years of age living in a low-income community in Dhaka to determine the incidence of invasive pneumococcal disease, serotype distribution, and clinical presentation. From April 2004 through March 2006, 5,903 blood cultures were collected from 6,167 eligible children. *Streptococcus pneumoniae* was isolated from 34 patients. Invasive pneumococcal disease was associated with pneumonia (24%), upper respiratory infection (62%) and febrile syndromes (14%). Overall and 13-valent vaccine related disease incidences were 447 episodes/100,000 child-years and 276 episodes/100,000 child-years, respectively. Penicillin resistance was 2.9%. Pneumococcal conjugate vaccines would be effective in Bangladesh.

Pneumonia is the primary cause of child mortality globally, causing 19% of 10.6 million deaths among children <5 years, or 2 million deaths per year in 2000-2003 (1); *Streptococcus pneumoniae* (pneumococcus) contributes to this burden (2). Pneumonia is also the primary cause of childhood death in Bangladesh (3). Early reports suggested that current protein-conjugate vaccines might offer poor protection against disease-causing pneumococcal serotypes in Bangladesh (4). We undertook this study to determine invasive pneumococcal disease incidence, clinical presentation, serotype distribution, seasonality and antimicrobial resistance patterns in an urban community. Detailed results of this study have been presented to the international scientific community (5).

The study was conducted in Kamalapur, an urban community in southeast Dhaka, where ICDDR,B operates an onsite field clinic and has collected health and demographic data since 1998. Five thousand households with children <5 years old were selected for surveillance using stratified cluster

sampling. Field workers visited enrolled households and screened children <5 years for specific illness signs using standardized questionnaires. Field workers referred children with signs of illness to the ICDDR,B clinic. Clinic physicians collected blood cultures from children who met standardized diagnoses of pneumonia, severe and very severe pneumonia, meningitis, otitis media and upper respiratory infection.

Invasive pneumococcal disease was confirmed by blood culture. Serotyping was performed at Dhaka Shishu Hospital Microbiology Laboratory by the capsular swelling procedure.

Vaccine serotypes were categorized based on vaccines that are likely candidates for introduction into Bangladesh; 10 valent – [GlaxoSmithKline] (1,4,5,6b,7f,9v,14,18c,19f & 23f) and 13 valent – [Wyeth] (1,3,4,5,6a,6b,7f,9v,14,18c,19a,19f,23f).

Drug susceptibility testing was assessed by disk diffusion (5). Results were interpreted as susceptible, intermediate, or resistant according to National Committee for Clinical Laboratory Standards defined break points.

Children diagnosed with pneumonia or otitis media were placed on antibiotics. Those with very severe pneumonia, meningitis or sepsis were referred to hospital after an initial antibiotic dose in clinic. CSF for meningitis was collected in hospital.

Research assistants visited all patients daily at home until illness resolved. End of illness was defined by a 7 consecutive day disease-free interval, after which the research assistants referred children to the clinic for an exit interview with the project physician to document clinical course and final disposition.

Between 01 April 2004 and 31 March 2006, 6,167 children met criteria for blood culture collection. 5,949 submitted blood cultures, of which 5,946 blood cultures were successfully tested (96.4%). There were 315 bacterial blood isolates during the period (5%), of which 34 (11%) were *S. pneumoniae*. Other isolates included 144 *Salmonella* Typhi (46%), 24 *Moraxella catarrhalis* (8%), and 13 *Salmonella* Paratyphi (4%). *Haemophilus influenzae* was not isolated. No additional organisms were identified from pneumococcal-positive specimens.

The mean age of children with invasive pneumococcal disease was 14.8 months (SD 9.5); 14 were male (41%) and 20 female (59%). Of 34 patients with invasive pneumococcal disease, 13 (38%) reported prior exposure to medications; including antibiotics 1 (3%) antihistamine 2 (6%), homeopathic remedy 1 (3%), and paracetamol 9 (27%).

During 7,600 child observation-years, we observed 3,840 clinical pneumo-

nia cases, of which 315 (8.2%) were severe and 65 (1.7%) very severe pneumonia. The overall pneumonia incidence was 50,526 episodes/ 100,000 child-years (0.51 episodes/child-year). There were 8 confirmed meningitis cases, for a meningitis incidence of 105 episodes/100,000 child-years.

Overall invasive pneumococcal disease incidence was 447 episodes/ 100,000 child-years; 10-valent specific incidence was 263 episodes/ 100,000 child-years and 13-valent incidence was 276 episodes/100,000.

Invasive pneumococcal disease incidence ranged from 0 in August-September to 1,150 episodes/100,000 child-years in February (Figure 1), peaking during the drier, cooler months.

Figure 1: Seasonality of invasive pneumococcal infection: Kamalapur, April 2004-December 2006

Number of isolates
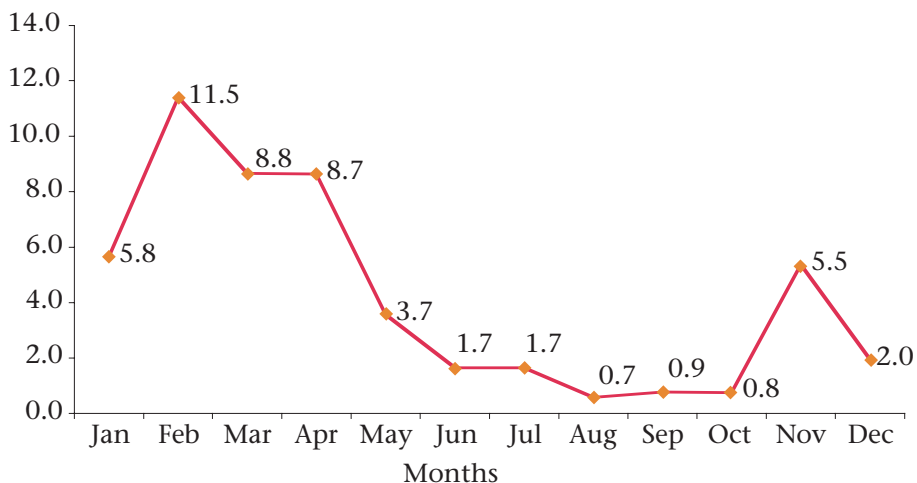
Of 8 pneumonia cases with confirmed invasive pneumococcal disease, 4 were severe or very severe. Four of 5 'other' final diagnoses were febrile bacteraemia, and the fifth otitis media, another respiratory tract disease. Thus 29/34 cases (85.3%) of pneumococcal disease had respiratory tract infections.

To compare these findings with other published reports, outcomes were re-categorized using WHO/IMCI criteria (6). These criteria increased the pneumonia proportion of invasive pneumococcal disease to 27 (79%). No meningitis cases had pneumococci isolated from their blood or CSF. There

were no deaths, although 5 patients recovered with disability (recurrent wheezing/night-time cough).

Antimicrobial resistance revealed modest intermediate penicillin resistance (Figure 2), due to serotype 14. Cotrimoxazole resistance was high; present in 7 of 8 (including all severe/very severe) pneumonia cases. Chloramphenicol resistance was low. Fluoroquinolone resistance was present, involving vaccine serotypes 1, 14, and 9V.

Figure 2: Antimicrobial resistance of pneumococcal isolates from Kamalapur: April 2004-March 2006
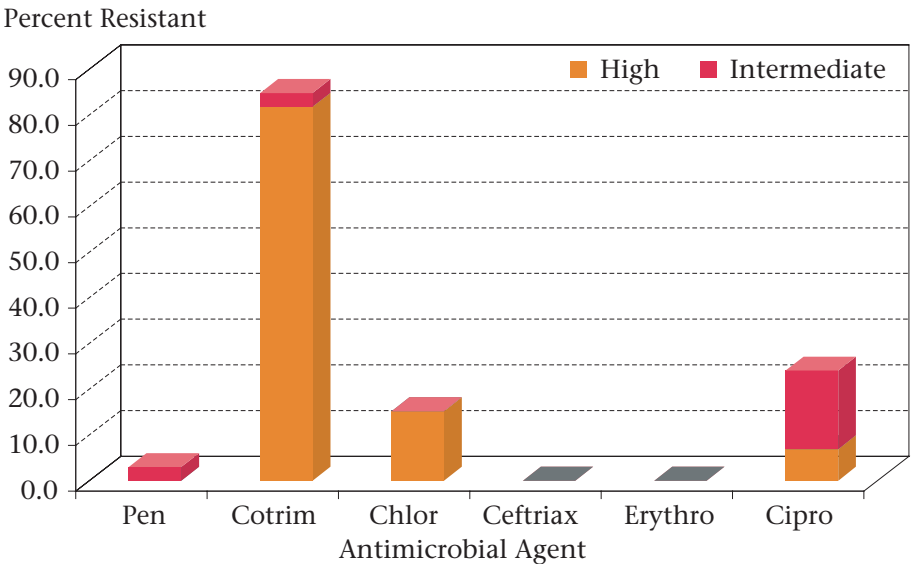
Percent Resistant

Comments

This population-based study used active surveillance and consistent collection of blood cultures among ill febrile children and found high rates of invasive pneumococcal disease among Bangladeshi children at high risk

for pneumonia. Indeed, the total and vaccine serotype-specific invasive pneumococcal disease incidence in Kamalapur is nearly identical to the incidence in the Gambia where children who received pnemococcal conjugate vaccine experienced 16% less mortality than children who received a placebo (7).

This study illustrates how surveillance methodology affects clinical syndrome estimates. Using a strict set of criteria, 24% of the cases were categorized as pneumonia. Using WHO definitions (6), nearly 80% of cases were classified as pneumonia, and 29% as severe or very severe pneumonia. The rationale for using the strict pneumonia definition is that the broad WHO definition may over-estimate potential vaccine impact and under-estimate true vaccine efficacy.

Many children in Bangladesh with serious respiratory illness, especially those from low-income households never visit a hospital (3). Therefore, Population based surveillance captures a more representative range of pneumococcal clinical presentations, serotypes and antimicrobial resistance.

Antimicrobial resistance to penicillin was low and seen only in a single vaccine serotype, serotype 14, similar to findings from hospital-based studies in Bangladesh (4,). Of note, high fluoroquinolone resistance has risen from 3.9% in 2005 to 6.9% in 2006; intermediate resistance rose from 0% to 17.2%. This may be due to frequent ciprofloxacin use in young children for febrile and respiratory illnesses. An efficacious pneumococcal vaccine should lower the overall prevalence of antimicrobial resistant invasive pneumococcal disease (8).

Limitations to this study include that it was conducted in a single area of one city in Bangladesh, and so may not be representative of communities throughout the country. The limited number of isolates means that some less common serotypes that are likely circulating were not identified, and the two year time frame precludes comparison of changes in serotype over time. However, this study illustrates that when carefully and systematically sought, invasive pneumococcal disease was common.

Invasive pneumococcal disease in this urban community in Bangladesh is primarily respiratory illness-related, and contributes to the pneumonia disease burden. The high infection rate indicates that introduction of a protein conjugate pneumococcal vaccine would substantially reduce both childhood illness, including pneumonia, and related antimicrobial resistance.

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Outbreaks of Nipah virus in Rajbari and Manikgonj, February 2008

In February, two clusters of Nipah virus encephalitis were identified in Manikgonj and Rajbari Districts. All 9 cases presented with fever and altered mental status; 8 have died. A collaborative team from the Institute for Epidemiology, Disease Control and Research (IEDCR), Ministry of Health and Family Welfare, Government of Bangladesh and ICDDR,B are conducting epidemiological studies to determine risk factors for disease. Findings from these investigations will be reported in future editions of the *Health and Science Bulletin*.

These clusters constitute the 8th outbreak of Nipah virus in Bangladesh since 2001. Outbreaks have occurred almost yearly between January and April and are consistently located in the west and northwestern parts of

the country. Person-to-person transmission has occurred in 4 outbreaks and consuming fresh date palm sap, presumably contaminated with bat secretions, continues to be an important suspected route of transmission from bats to humans. Based on scientific findings from these investigations, Nipah prevention messages from the government advise that date palm sap should be boiled before consumption by humans or animals; no fruits bitten by bats should be consumed by humans or other animals; and that persons caring for patients with severe disease (of any kind) should attempt to limit close physical contact with the patient, should not share food with the patient, and should regularly wash their hands with soap, including after feeding or cleaning patients.

Clinicians should immediately report suspect Nipah patients or any clusters of severe disease (multiple patients occurring at the same time from the same locality) to local health authorities.

Surveillance update

With each issue of the HSB, updates of surveillance data described in earlier issues are provided. These updated tables and figures represent the most recent observation period available at the time of publication. We hope these updates will be helpful to health professionals who are interested in current patterns of disease and drug resistance.

Proportion of diarrhoeal pathogens susceptible to antimicrobial drugs: March 2007-February 2008

Antimicrobial agents	*Shigella* (n=212)	*V. cholerae* O1 (n=738)
Nalidixic acid	21.4	Not tested
Mecillinam	92.9	Not tested
Ampicillin	51.9	Not tested
TMP-SMX	33.5	0.0
Ciprofloxacin	94.8	100.0
Tetracycline	Not tested	46.6
Erythromycin	Not tested	11.1
Furazolidine	Not tested	0.0

Monthly isolation of V. cholerae O1, Shigella *and Rotavirus: March 2007-February 2008*
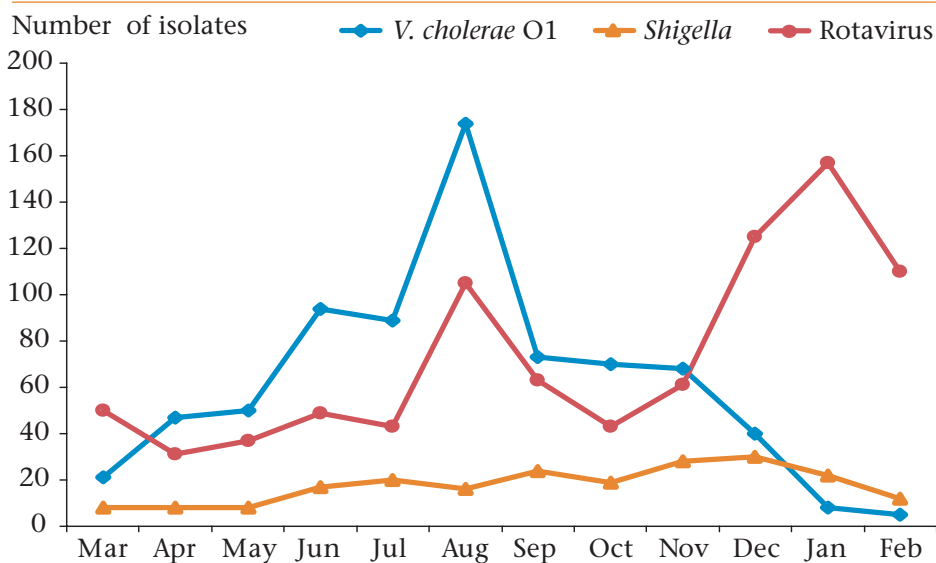
Antimicrobial resistance patterns of 119 M. tuberculosis *isolates: April 2007-November 2007*

Drugs	Resistance type		Total (n=119)
	Primary (n=107)	Acquired* (n=12)	
Streptomycin	26 (24.3)	0 (0.0)	26 (21.8)
Isoniazid (INH)	11 (10.3)	0 (0.0)	11 (9.2)
Ethambutal	2 (1.9)	0 (0.0)	2 (1.7)
Rifampicin	3 (2.8)	1 (8.3)	4 (3.4)
MDR (INH+Rifampicin)	2 (1.9)	0 (0.0)	2 (1.7)
Any drugs	27 (25.2)	1 (8.3)	28 (23.5)

() column percentage　　　* Antituberculous drugs received for one month or more

Antimicrobial susceptibility pattern of S. pneumoniae *among children <5 years during October-December 2007*

Antimicrobial agents	Total tested (n)	Susceptible n (%)	Reduced susceptibility n (%)	Resistant n (%)
Ampicillin	11	11 (100.0)	0 (0.0)	0 (0.0)
Cotrimoxazole	11	2 (18.0)	1 (9.0)	8 (73.0)
Chloramphenicol	11	11 (100.0)	0 (0.0)	0 (0.0)
Ceftriaxone	11	11 (100.0)	0 (0.0)	0 (0.0)
Ciprofloxacin	11	10 (91.0)	1 (9.0)	0 (0.0)
Gentamicin	11	0 (0.0)	0 (0.0)	11 (100.0)
Oxacillin	11	11 (100.0)	0 (0.0)	0 (0.0)

Source: Children participating in PneumoADIP surveillance in Dhaka Medical College Hospital, Chittagong Medical College Hospital, Sir Salimullah Medical College and Mitfort Hospital, ICH-Shishu Sasthya Foundation, Chittagong Maa Shishu O General Hospital, Dhaka Shishu Hospital, Kumudini Hospital-Mirzapur (Tangail), and ICDDR,B's urban surveillance in Kamalapur (Dhaka) and rural surveillance in Mirzapur (Tangail).

Antimicrobial susceptibility pattern of S. typhi *among children <5 years during October-December 2007*

Antimicrobial agents	Total tested (n)	Susceptible n (%)	Reduced susceptibility n (%)	Resistant n (%)
Ampicillin	98	46 (47.0)	0 (0.0)	52 (53.0)
Cotrimoxazole	98	48 (49.0)	0 (0.0)	50 (51.0)
Chloramphenicol	98	48 (49.0)	0 (0.0)	50 (51.0)
Ceftriaxone	98	98 (100.0)	0 (0.0)	0 (0.0)
Ciprofloxacin	98	44 (45.0)	53 (54.0)	1 (1.0)
Nalidixic acid	98	8 (8.0)	0 (0.0)	90 (92.0)

Source: Children participating in PneumoADIP surveillance in Dhaka Medical College Hospital, Chittagong Medical College Hospital, Sir Salimullah Medical College and Mitfort Hospital. ICH- Shishu Sasthya Foundation, Chittagong Maa Shishu O General Hospital, Dhaka Shishu Hospital and Kumudini Hospital, Mirzapur (Tangail). ICDDR,B's urban surveillance in Kamalapur (Dhaka) and rural surveillance in Mirzapur (Tangail).

Surveillance physician collecting data from a patient at Rajshahi Medical College Hospital

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