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Inside

New strategies for treating falciparum malaria in Bangladesh

Thirteen out of 64 districts in Bangladesh are seriously affected by malaria. The emergence and spread of antimalarial drug resistance and the resulting increase in treatment failures and case fatality rates due to falciparum malaria have seriously aggravated the malaria problem in Bangladesh. Two regimens for treatment of malaria were evaluated in two separate studies. Among 63 patients with confirmed falciparum malaria who received quinine, three times daily for three days followed by a single dose of sulfadoxine/pyrimethamine, 87% were cured at 42 days. Among 67 patients who received a combination of artemether and lumefantrine, 94% were cured at 42 days. Both combination regimens were effective in Bangladesh. Efforts to make effective antimalarial drugs widely available is vital for malaria control in Bangladesh.

Malaria is a substantial public health problem in Bangladesh. Up to 400,000 clinical cases and more than 57,000 laboratory confirmed malar-

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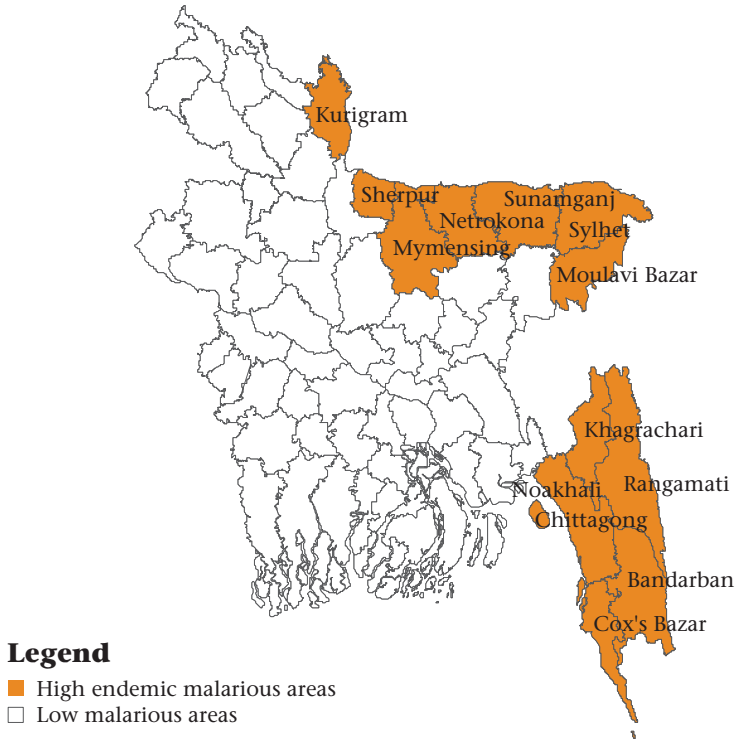
KNOWLEDGE FOR GLOBAL LIFESAVING SOLUTIONS

ia cases with more than 500 deaths per year have been reported from Bangladesh (1). Thirteen out of the 64 districts in the country are seriously affected by malaria, accounting for about 99% of the country's disease burden (Figure 1). About two-thirds of the laboratory confirmed cases occur in the Chittagong Hill Tracts. However, due to the lack of financial resources and the resulting shortcomings in malaria research, surveillance, and control, the disease burden may be far greater than reported. The most affected of these districts are home to populations and minorities living in the remote hill tract areas and the adjoining districts of the southeast, east, and northeast border of the country. Despite past successes in malaria control, a significant increase in malaria cases and *Plasmodium falciparum* infections has been seen over the years. Particularly the emergence and spread of antimalarial drug resistance and the resulting increase in treatment failures and case fatality rates have turned into a serious problem. Indeed, the vast majority of parasite populations may be resistant to chloroquine (2,3). However, chloroquine remains the most com-

Figure 1: Thirteen high endemic districts of Bangladesh 2004.

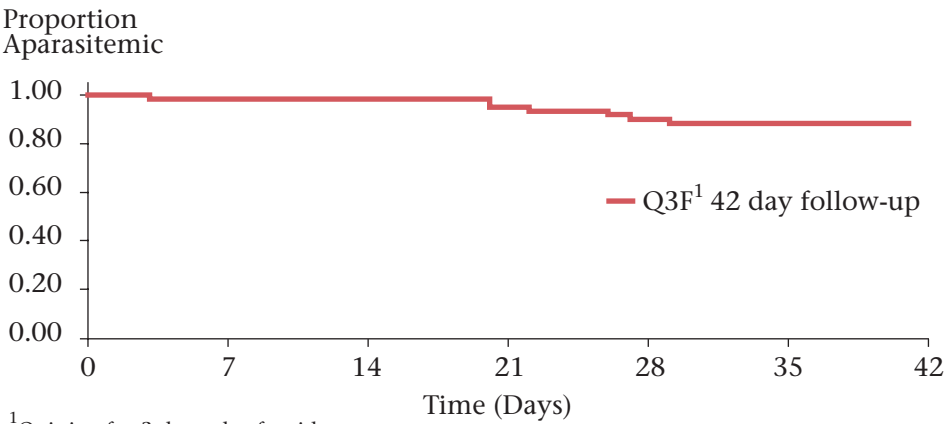


mon treatment for malaria throughout the country due to inadequate financial means for malaria control and the lack of data on the current drug resistance patterns, as well as the lack of research into affordable alternative treatments.

We evaluated two alternative regimens for treating malaria in Bangladesh. First, we investigated the therapeutic efficacy of the combination of sulfadoxine/pyrimethamine with three days of quinine for the treatment of uncomplicated falciparum malaria at the ICDDR,B field site in Chakaria, Cox's Bazaar District, Chittagong Division. In parallel, laboratory-based technologies (HRP2 drug susceptibility assay) were used to characterize the intrinsic drug sensitivity of individual patient isolates.

Sixty-three patients were enrolled in the study in 2004 (4). The study design essentially followed the WHO guidelines for the assessment and monitoring of antimalarial drug efficacy with an extension of follow-up until day 42. All patients received the second line treatment with quinine three times a day (10 mg/kg per dose) for three days, followed by a single dose of sulfadoxine (25 mg/kg) coformulated with 1.25 mg/kg of pyrimethamine on the fourth day. The overall cure rate with quinine followed by sulfadoxine/pyrimethamine in uncomplicated falciparum malaria in a 42-day follow-up after PCR adjustment was 87.3% (Figure 2). One patient was classified as early treatment failure, six patients had late treatment failures within a median time of 27 days. Significantly higher (P =

Figure 2: Kaplan-Meier curve for the PCR-adjusted cure rate for the combination of quinine with S/P in 63 uncomplicated falciparum malaria patients in southeastern Bangladesh.



[1]Quinine for 3 days plus fansider

0.008) *in vitro* inhibitory concentrations for pyrimethamine in treatment failures reflect the compromised drug sensitivity to this drug.

Parallel *in vitro* studies were performed to provide background data on intrinsic drug sensitivity for these parasite populations. The *in vitro* data suggest levels of chloroquine resistance (50% inhibitory concentration: 93.1 nM) comparable to those in Thailand, a country known for its particularly high levels of drug resistance. In contrast, the isolates were relatively sensitive to quinine (73.2 nM) and mefloquine (11.3 nM). The dihydroartemisinin (1.3 nM) inhibitory concentrations were equally low suggesting high sensitivity of the parasites to that drug. Interestingly, close correlations were found between *in vitro* drug sensitivity of pyrimethamine (1.7 µM) and clinical treatment response parameters, suggesting a significant impact of intrinsic pyrimethamine drug sensitivity on treatment outcome.

The cure rate with quinine plus sulfadoxine/pyrimethamine in the 42-day follow up is comparable to cure rates found in a previous study with a 28-day follow-up from a nearby area (5). These data suggest that the combination of 3 days of quinine with a single dose of S/P is a promising and affordable alternative as long as or whenever artemisinin-based combination therapy is not available.

In 2004/2005 the government of Bangladesh changed its first-line therapy for laboratory-confirmed falciparum malaria to the combination of artemether with lumefantrine (1). We aimed at determining the baseline therapeutic efficacy of artemether-lumefantrine used as a six-dose regimen for the treatment of uncomplicated falciparum malaria (6). Sixty-seven patients were enrolled in the study. The cure rate in a 42-day follow-up after PCR adjustment was 94.3%. The treatment led to rapid fever (25.82 ± 12.14 hrs) and parasite clearance (30.36 ± 19.43 hrs). These data suggest that this combination is a highly efficacious therapy. However, currently its use in Bangladesh is still constrained by relatively high cost and difficulties with supply.

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Comment

Quinine followed by sulfadoxine/pyrimethamine is an effective alternative

for the treatment of uncomplicated falciparum malaria whenever artemisinin-based combination therapy is not available. Both quinine and sulfadoxine/pyrimethamine are available from local producers and are relatively inexpensive. Compared to similar regimens (e.g. seven days of quinine plus tetracycline) it is cheaper and due to the shorter duration of treatment leads to better compliance. However, the *in vitro* drug sensitivity data demonstrate that some degree of sulfadoxine/pyrimethamine resistance exists among *P. falciparum* parasites in Bangladesh. Sulfadoxine/pyrimethamine should therefore only be used in combination with faster acting antimalarials that have a different mechanism of action to prevent a rapid progression of drug resistance.

The combination of artemether with lumefantrine, currently the first line therapy for laboratory-confirmed uncomplicated falciparum malaria in Bangladesh, results in cure rates considerably above 90%. With its rapid fever and parasite clearance this combination also leads to quick clinical and parasitological improvement. However, little is known regarding its safety in pregnancy and its use in Bangladesh is still constrained by the relatively high cost and difficulties with supply. Moreover the first reports of failures with artemisinin-based combination therapies in Southeast Asia urgently call for research into new alternatives (7).

Consequently, in 2006 we are planning to expand our research efforts to Bandarban District in the Chittagong Hill Tracts to evaluate new, safe, and affordable combination treatments for falciparum malaria in Bangladesh.

Following the example of malaria research and control in other South- and Southeast Asian countries, new cost effective intervention strategies that meet local needs and that are sustainable are urgently needed in Bangladesh. The future development and clinical testing of new, affordable, preferably locally produced combination treatments for falciparum malaria will therefore be essential.

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Nutritional status, knowledge and practices of unmarried adolescent girls in rural Bangladesh

The 2004 baseline survey of the Bangladesh National Nutrition Programme examined nutritional status, knowledge and practices of never married adolescent girls (aged 13-19) living in rural Bangladesh. Adolescents were of poor nutritional status; 9% were severely thin and 16% were moderately thin. More than half did not know the names of energy-dense and protein-rich foods. Most (65%) reported understanding of the need to take extra nutrients during adolescence to attain potential growth. On average adolescent girls ate 4.7 servings of protein rich and 3.3 servings of fat rich foods in the preceding week. Adolescents in the highest asset quintile (a proxy for economic condition) were 54% more likely to have had fish or meat and 91% more likely to have had egg or milk in the preceding week than those in the lowest asset quintile. Strong community-based nutrition counselling backed by basic services may improve adolescent nutrition knowledge and practices and address under nutrition 'carried-over' from childhood.

Adolescence is a period of rapid physical growth and additional nutrition is needed during this period to attain potential growth. Improved adolescent nutrition knowledge and practices offer an opportunity to address the nutritional problems 'carried over' from childhood, and set the stage for healthy adulthood. Available evidence suggests that adolescent girls in Bangladesh are of poor nutritional status. One survey reported that 27%

of female students aged 11-16 years in peri-urban Bangladesh had anaemia (Hb<12g/l), and 17% had depleted iron stores (SF<12 microg/l) (1). One way to improve female adolescent nutrition would be to improve their nutrition knowledge and practices. Today's female adolescents are tomorrow's mothers who will play important roles in maintaining family health and nutrition. As a first step, we attempted to understand nutritional knowledge and practices of female adolescents living in rural Bangladesh.

Data from the 2004 baseline survey of the National Nutrition Programme (NNP) of the government of Bangladesh (2) were analyzed to describe the nutrition knowledge and practices of adolescent girls. The baseline survey included a random sample of 5,106 never married adolescent girls aged 13-19 from 708 clusters in 113 upazilas (about one quarter of the sub-districts of Bangladesh) for interview. Upazilas were grouped into NNP (where nutrition intervention activities were yet to start) and Bangladesh Integrated Nutrition Project (BINP) areas (where a community-based nutrition intervention had been functioning from 1995 up to 2002). The BINP imparted health and nutrition education and supplied iron and folic acid supplements to adolescent girls (3). Trained female interviewers visited adolescents at their homes to obtain data on nutrition knowledge and practices. Seven-day food-frequency was recorded to capture eating patterns.

Adolescents were mostly young: 43% aged 13-14, 37% aged 15-16 and 19% aged 17-19 (Table 1). The study population included fewer older adolescents because many of them were married and so no longer fit the inclusion criteria. Education levels varied; 69% had completed grade 6 or above, but only 6% had passed grade 10. Very few (4%) had never attended school. By occupation, 66% were students and the rest were doing household chores (29%) and earning some income (4%).

Adolescent girls were of poor nutritional status; 9% were severely thin (BMI-for-age below the 5th percentile), another 16% were moderately thin (below the 15th percentile) and none were obese (above the 95th percentile). Prevalence of severe and moderate thinness did not vary by education or household asset quintile (a proxy for household economic condition).

Adolescent knowledge regarding the nutritional value of different types of food items was limited. When asked to name major energy-dense foods, 31% mentioned rice and 12% mentioned wheat and these are correct responses. Less than half correctly identified high protein foods: dal (20%), meat (32%) and fish (42%). Their knowledge about vitamin- and mineral-rich foods was better; 75% mentioned vegetables and 51% mentioned fruits as vitamin and mineral-rich foods.

Most of the adolescent girls (65%) reported understanding the need to take extra nutrients during adolescence to attain potential growth and this was positively associated with both education and household asset quintile (Table 1).

Table 1: Percent of adolescent girls who knew to take extra nutrients and who ever used iron supplements during adolescence by demographic characteristics and survey area (N=5106)

Characteristics	% of adolescent girls	% knew to take extra nutrients	% ever used iron supplements
Age (in year)			
13-14 (ref)	43	55	9
15-16	37	68**	14*
17-19	19	78**	19*
Education level			
Up to primary (ref)	31	45	8
Secondary +	69	74**	15*
Household asset quintile			
Lowest (ref)	20	47	9
Second	20	60**	11
Middle	20	65**	13
Fourth	20	70**	15
Highest	20	81**	15
Survey area			
NNP project (ref)	62	63	8
BINP project	38	67	21*
All	100	65	13

*p<0.05, **p<0.01 (compared with reference category)

Ever use of iron supplements was 8% in NNP project area and 21% in BINP project area. Higher education was associated with higher iron intake in both areas. Iron intake was also higher among adolescents who understood the need to take more food during adolescence in both the areas. Intake was not related to household asset quintile.

Participants were asked to recall the number of days in the past week that they ate specific foods. The mean days of eating protein (fish/meat) and fat (egg/milk) enriched foods in the past week were 4.7 and 3.3 respectively (Table 2). Household asset quintile strongly influenced adolescent intakes of protein and fat. Adolescents in the highest asset quintile were 54% more likely to have had fish or meat and 91% more likely to have had egg or milk than those in the lowest asset quintile.

Table 2: Mean days (and 95% confidence interval) of eating protein and fat food items by female adolescents in the last week, according to household asset quintile

Household asset quintiles	Protein and fat food items		No. of adolescents in each category
	Fish/meat Mean days (and 95% CI)	Egg/milk Mean days (and 95% CI)	
Lowest	3.8 (3.7 - 4.0)	2.2 (2.0 - 2.3)	1011
Second	4.1 (4.0 - 4.3)	2.9 (2.7 - 3.0)	1031
Middle	4.6 (4.5 - 4.8)	3.5 (3.3 - 3.6)	1022
Fourth	5.2 (5.1 - 5.3)	3.8 (3.7 - 4.0)	1021
Highest	5.9 (5.8 - 6.0)	4.2 (4.0 - 4.4)	1011
Overall	4.7 (4.7 - 4.8)	3.3 (3.2 - 3.4)	5106

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Comment

Female adolescent nutrition is a particularly important tool in combating the vicious cycle of intergenerational undernutrition. If not addressed properly, adolescent undernutrition perpetuates this cycle (undernourished mothers produce low birth weight babies, who grow into undernourished children and adolescents). The high incidence of teenage marriage and pregnancy in rural Bangladesh (4) puts adolescent females at risk of undernutrition. In rural areas, 25% of the adolescents were found to be thin (severely and moderately).

The majority of rural adolescents lacked knowledge of the nutritional value of different food items. Many (35%) did not know that adolescents need to take extra nutrients to achieve potential growth. Considering their future roles in maintaining the health and nutrition of their family members, especially their children, female adolescents should be the focus of nutrition interventions aimed at promoting nutrition knowledge and practices.

Adolescent intake of nutrients is limited by lack of knowledge and household resources. Despite the high prevalence (17%) of depleted iron stores (SF<12microg/l), intake of iron supplement was only 8% in areas without intervention. However, community-based nutrition counselling and distribution of iron pills free of cost had brought about a change in use of iron

supplements (21% in BINP area). Adolescents need to take healthy foods to attain potential growth. In rural areas, the main sources of animal protein in regular diets are fish and meat and sources of animal fat are egg and milk. Household asset quintile strongly influenced daily intakes of protein and fat foods needed for healthy growth and development. This reiterates the importance of reducing poverty and hunger to improve nutritional status.

Adolescent undernutrition may be addressed in a number of ways. One feasible way may be community-based health and nutrition counseling backed by basic services to bring about changes in their nutrition knowledge and practices. Because adolescents are not the sole decision makers and parents often make decisions on their behalf, parents, particularly mothers need to be provided information on the importance of adolescent nutrition for healthy growth and survival.

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Re-emergence of Inaba serotype of *V. cholerae* O1 El Tor and increased susceptibility to tetracycline

In June 2005 we reported the appearance of *V. cholerae* O1 El Tor serotype Ogawa, which had almost replaced the previously dominant Inaba serotype (1). We noted that both serotypes had developed resistance to tetracycline (doxycycline), routinely used in the management of severe cholera in adults, and erythromycin, used in treating cholera in children and pregnant women. Although the multiply resistant strains remained

susceptible to ciprofloxacin, as determined by the conventional Kirby Bauer test, they exhibited higher minimum inhibitory concentrations (MIC) by the E-Test method, indicating its decreased efficacy. We noted a much worse clinical response to ciprofloxacin in a recent study (2) conducted at ICDDR,B's Dhaka Hospital than we had observed in earlier randomised, controlled clinical trials (3,4). The change in predominant serotypes and the appearance of a new clone with resistance to commonly used drugs are known phenomena that have been observed previously (5-7); however, unlike previous observations, this resistance pattern has persisted for nearly two years.

We have noted two changes in the *V. cholerae* strains at the Dhaka Hospital of ICDDR,B since the last report. First, there has been a re-emergence of the Inaba serotype and a dramatic reduction in the isolation of the Ogawa serotype (Figure 1). Second, the proportion of *V. cholerae* strains with tetracycline resistance has decreased substantially (Figure 2). Importantly, tetracycline resistance of all *V. cholerae* O1 strains (both serotypes) decreased from 75% in January 2006 to 10% in August 2006. The near displacement of the Ogawa serotype and reversal to susceptibility to tetracyline is welcome news. A single dose treatment of 300 mg of doxycycline (a tetracycline derivative) is inexpensive and effective in treating cholera in adults. However, doxycycline is contra-indicated for use in young children, and pregnant and lactating women. Single dose ciprofloxacin is effective in the treatment of cholera in children, but the increase in the minimum inhibitory concentration of *V. cholerae* against this drug prevents its use as a single-dose therapy. In a pilot study we have observed that ciprofloxacin in multiple doses (twice a day for three days) yields better clinical and bacteriological response in cholera than single-dose therapy (personal communication, Saha *et al*.). In a study conducted at ICDDR, B ciprofloxacin in multiple doses (individual dose 15mg/kg) every 12 hours for 3 days was safe for treatment of children with acute shigellosis due to *S. dysenterie* type 1 (8). Thus, we recommend ciprofloxacin (15 mg/Kg) every 12 hours for 3 days for treatment of children and lactating women with cholera. However, for the management of pregnant women, we recommend only rehydration therapy and continued feeding.

Figure 1: Distribution of V. cholerae *O1 serotypes, Dhaka Hospital surveillance 2006*

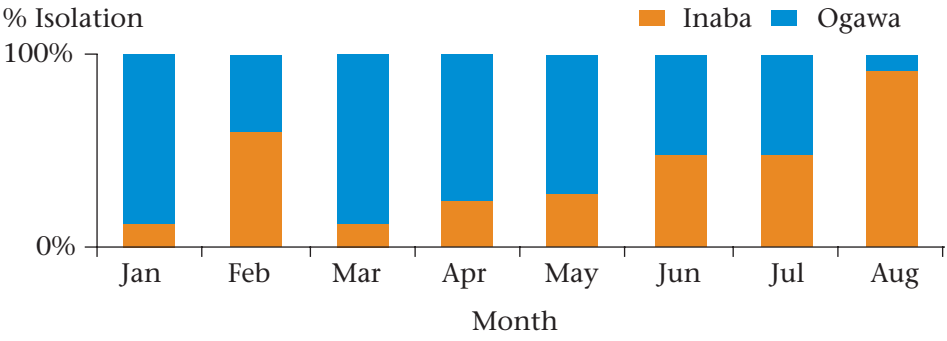
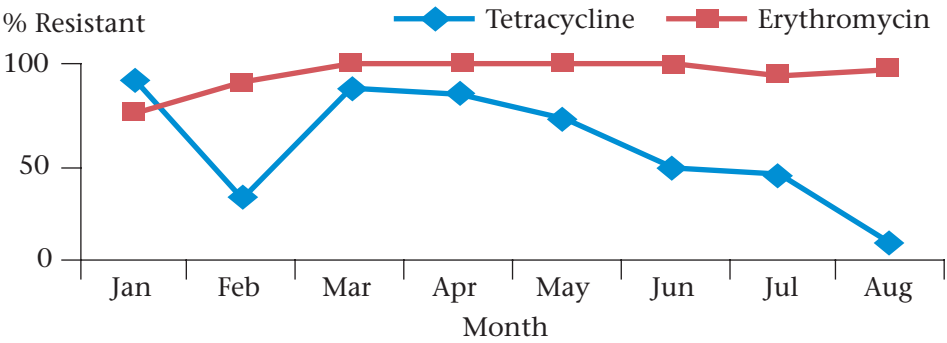


Figure 2: Resistance of V. cholerae *O1 (combined serotypes) to tetracycline and erythromycin, Dhaka Hospital surveillance 2006*



Reported by: Clinical Sciences Division, ICDDR,B

Supported by: ICDDR,B

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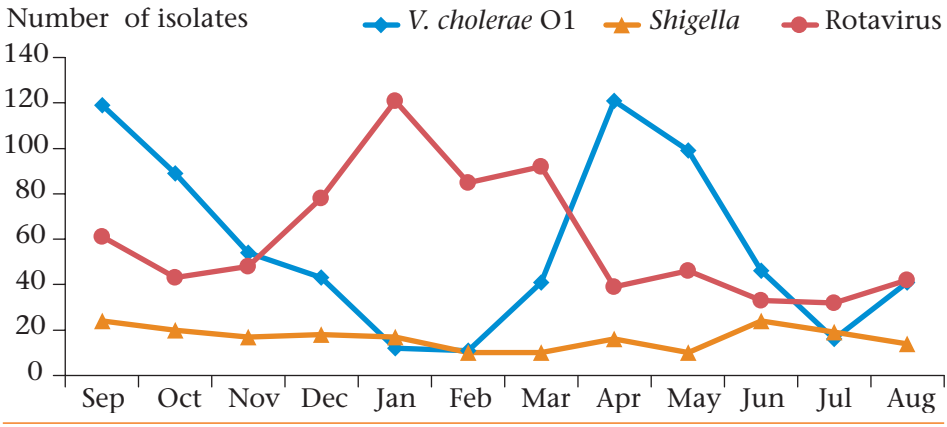
Surveillance update

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: September 2005-August 2006

Antimicrobial agent	*Shigella* (n=199)	*V. cholerae* O1 (n=692)
Nalidisic acid	29.1	Not tested
Mecillinam	97.0	Not tested
Ampicillin	54.8	Not tested
TMP-SMX	35.7	3.2
Ciprofloxacin	99.5	100.0
Tetracycline	Not tested	31.8
Erythromycin	Not tested	22.5
Furazolidine	Not tested	0.0

Monthly isolation of V. cholerae *O1,* Shigella *and Rotavirus: September 2005-August 2006*



Antimicrobial resistance patterns of 106 M. tuberculosis *isolates: July 2005-June 2006*

Drugs	Resistance type		Total (n=106)
	Primary (n=90)	Acquired* (n=16)	
Streptomycin	27 (30.0)	6 (37.5)	33 (31.1)
Isoniazid (INH)	12 (13.3)	5 (31.3)	17 (16.0)
Ethambutal	11 (12.2)	3 (18.8)	14 (13.2)
Rifampicin	12 (13.3)	7 (43.8)	19 (17.9)
MDR (INH+Rifampicin)	5 (5.6)	4 (25.0)	9 (8.5)
Any drugs	37 (41.1)	10 (62.5)	47 (44.3)

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

Antimicrobial susceptibility of N. gonorrhoeae *isolated during April-June 2006 (n=29)*

Antimicrobial agents	Susceptible (%)	Reduced susceptibility (%)	Resistant (%)
Azithromycin	96.6	3.4	0.0
Ceftriaxone	100.0	0.0	0.0
Ciprofloxacin	10.3	0.0	89.7
Penicillin	17.2	27.6	55.2
Spectimnomycin	96.6	3.4	0.0
Tetracycline	6.9	0.0	93.1
Cefixime	100.0	0.0	0.0

Antimicrobial susceptibility pattern of S. pneumoniae *among children <5 years during May-July 2006*

Antimicrobial agents	Total tested (n)	Susceptible n (%)	Reduced susceptibility n (%)	Resistant n (%)
Ampicillin	8	8 (100.0)	0	0 (0.0)
Cotrimoxazole	8	5 (62.0)	0	3 (38.0)
Chloramphenicol	8	8 (100.0)	0	0 (0.0)
Ceftriaxone	8	8 (100.0)	0	0 (0.0)
Ciprofloxacin	8	8 (100.0)	0	0 (0.0)
Gentamicin	8	2 (25.0)	0	6 (75.0)
Oxacillin	8	8 (100.0)	0	0 (0.0)

Source: Data obtained from children participating in PneumoADIP surveillance - a joint collaboration of ICDDR,B and Dhaka Shisu Hospital which has been conducted in Dhaka Medical College Hospital, Chittagong Medical College Hospital, Sir Salimullah Medical College Hospital, ICH- Shishu Sasthya Foundation, Chittagong Maa Shishu O General Hospital, Dhaka Shishu Hospital, Kumudini Hospital-Mirzapur, and ICDDR,B's rural surveillance in Mirzapur.

Antimicrobial susceptibility pattern of S. Typhi *among children <5 years during May-July 2006*

Antimicrobial agents	Total tested (n)	Susceptible n (%)	Reduced susceptibility n (%)	Resistant n (%)
Ampicillin	26	7 (27.0)	0	19 (73.0)
Cotrimoxazole	26	7 (27.0)	0	19 (73.0)
Chloramphenicol	25	7 (28.0)	0	18 (72.0)
Ceftriaxone	26	26 (100.0)	0	0 (0.0)
Ciprofloxacin	25	24 (92.0)	1 (4.0)	1 (4.0)

Source: Data obtained from children participating in PneumoADIP surveillance - a joint collaboration of ICDDR,B and Dhaka Shisu Hospital which has been conducted in Dhaka Medical College Hospital, Sir Salimullah Medical College Hospital, ICH- Shishu Sasthya Foundation, Chittagong Maa Shishu O General Hospital, Dhaka Shishu Hospital and Kumudini Hospital-Mirzapur

Study team in front of Bandarban District Hospital

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ICDDR,B
GPO Box 128, Dhaka 1000, Bangladesh
www.icddrb.org/hsb