

Burden and outcome of acute otitis media in rural Bangladesh

E Roy, K Z Hasan, J L Richards, A K M F Haque, A K Siddique, R B Sack

International Centre for Diarrheal Diseases and Research (icddr,b), Bangladesh

E Roy, MB BS, DCH, MSc Epidemiology

K Z Hasan, MB BS, MPH, DrPH

A K M F Haque, MSc Statistics

A K Siddique, MPH

Rollins School of Public Health, Emory University, Atlanta, GA, USA

J L Richards, MPH

Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA

R B Sack, MD, ScD

Corresponding author: E Roy (eliza@icddr.org)

Objectives. To report on the burden and outcome of episodes of acute otitis media (AOM) based on awareness of AOM and compliance to referral by community health workers (CHWs) in rural children aged under 2 in Bangladesh.

Study design. Retrospective population-based cohort study.

Method. Secondary data analysis on episodes of AOM, care-seeking pattern, compliance with referral, antibiotic use and duration of episodes from morbidity data collected by CHWs on 252 children aged under 2 who completed biweekly household surveillance starting from birth.

Results. A total of 375 episodes of AOM were observed in 45.6% (115/252) of the study subjects; 19.4% (49/252) experienced single and 26.2% (66/252) recurrent episodes. Just over 34% (129/375) of episodes were recognised by caregivers and reported to CHWs, and the remaining 246 episodes, unrecognised by caregivers, were detected by CHWs during home visits. CHWs referred all subjects with AOM to the study doctor. The caregivers complied with referral in all episodes they had recognised, but in only 21.5% (53/246) of episodes they had not recognised ($p < 0.0001$). Compliance was best among caregivers of babies in the first 3 months of life. Resolution occurred in 95.0% (356/375) of acute episodes of AOM in ≤ 6 weeks, comprising 176/182 of antibiotic-treated and 180/193 of untreated episodes ($p < 0.13$). Five per cent of episodes (19/375) progressed to chronic suppurative otitis media (CSOM). Doctor visits resulting in antibiotic use resulted in a 51% lower progression to CSOM (relative risk 0.49, 95% confidence interval 0.19 - 1.26).

Conclusion. AOM is a disease of public health importance in rural children aged under 2 in Bangladesh. Early assessment, community awareness of AOM intensified by motivational activities, and increased compliance with referral to the doctor in caregiver-unreported cases may help to decrease morbidity and burden from the disease.

SAfr J CH 2012;6(4):118-122. DOI:10.7196/SAJCH.486

Acute otitis media (AOM) is a common childhood condition that contributes significantly to the medical, social and economic burden of disease in children worldwide.¹⁻³ In developed countries, AOM is the most frequent reason for doctor visits for illness.⁴⁻⁶ Survey data show that approximately 10% of children in the USA have an episode of AOM by 3 months of age, 70% have at least one episode by age 2 years, and 20% have four or more episodes during their childhood.³ A significant problem in developing countries is inadequate awareness of AOM and lack of specialist care, leading to a substantial burden of acute, recurrent or chronic otitis media (OM) and death in children aged under 5.⁷⁻⁹

Management strategies for OM depend on disease severity and causation, and include local antibiotic drops, oral or injectable antibiotics, wicking and surgical interventions.¹⁰⁻¹² The American Academy of Physicians and the American Academy of Family

Physicians have adopted the option of observation with watchful waiting while withholding antibiotics for 48 - 72 hours after AOM diagnosis, initial pain management with analgesics, and changes in the doses of various antibiotic regimens as strategies for AOM management.¹³

There is a paucity of community-based longitudinal data on the burden of AOM in rural children in developing countries, but in order to establish relevant AOM management guidelines there is a need to understand awareness and care-seeking patterns, referral patterns and compliance with referral, morbidity patterns, and outcomes of antibiotic use for the disease.

The findings presented here are based on a secondary analysis of morbidity data on AOM collected in a birth cohort in rural Bangladesh,¹⁴ and could be of use in the setting up of management guidelines.

Material and methods

Study site and population

The study subjects were part of a larger study on causes of acute lower respiratory tract infections and diarrhoea in rural Mirzapur, Bangladesh.¹⁴ At the time the study was conducted, there were 16 510 people living in 2 962 households in the study area. Children aged under 5 constituted 10.8% ($n=1\ 551$) of the total population. In this study we recruited 288 babies at birth and completed follow-up of 252 for 2 years (the reasons for drop out of 36 subjects have been described earlier¹⁵). For recruitment of the newborns, community health workers (CHWs) noted all births in the study area.¹⁵ After a delivery was reported by a CHW or family member, the study doctor and nurse visited the family. Informed consent was obtained from the parent/guardian of each subject at the time of enrolment. Detailed baseline information on socio-demographic and household characteristics was collected from the subjects' families.

Study definitions and measurement of outcomes

Study diagnoses have been described previously; they were AOM with no perforation, acute suppurative OM with perforation and discharge, AOM with recurrent episodes, and chronic suppurative OM (CSOM).¹⁵ OM was defined as: (i) a single episode if only one episode occurred during the 2-year study period; (ii) recurrent otitis when two or more episodes of AOM occurred in the same child within 6 months or four episodes occurred within 12 months;¹⁶ (iii) acute otitis with perforation if discharge was present in the ear on swabbing; (iv) AOM without perforation if the tympanic membranes were intact on otoscopic examination; and (v) CSOM if discharge continued beyond 2 weeks with no resolution on follow-up.¹⁰

Methods

A study doctor trained a nurse and 12 CHWs to assess signs and symptoms of acute and chronic OM, with special emphasis on teaching CHWs to wick ears when perforation and discharge were present. CHWs underwent monthly refresher training on data collection procedures. Diagnosis and management of AOM cases was done according to a study algorithm that involved both CHWs and the study doctor. During biweekly household surveillance CHWs documented clinical suspicion of AOM when the caregiver reported that the child suffered from one or more of the following: earache, fever, irritability/lethargy, vomiting or diarrhoea. The ears of every child suspected to have AOM were examined by the CHWs, who recorded a clinical case diagnosis of OM if pus/discharge was present and confirmed the diagnosis by taking an ear swab. All cases were referred to the study doctor for management. If pus/discharge was not present but the subject had suggestive symptoms, CHWs motivated caregivers to take their child to the study doctor for confirmation of the diagnosis. The doctor examined all the children brought for their referral visit, and diagnosed AOM on the basis of clinical and otoscopic examination.

Details of each episode of AOM, recognition of signs/symptoms of AOM by caregivers, care-seeking pattern, antibiotic use, CHW referrals to the study doctor, caregiver non-compliance with referrals and outcome were documented in study forms by the CHWs during biweekly household surveillance.¹⁵

Children with a diagnosis of AOM were monitored until resolution of the episode, defined as subsidence of symptoms in a child without perforation or absence of any pus/discharge from the ear(s) in a child with perforation. Duration of each episode was determined using dates of onset of symptoms reported by the mother, and of resolution recorded by study staff. AOM episodes were recorded as new episodes if they occurred 21 disease-free days after the last episode.¹⁶

The study was approved by the Ethical Review Committee of the International Centre for Diarrhoeal Diseases and Research, Bangladesh.

Treatment algorithm

Subjects diagnosed by the study doctor as having AOM with discharge from the ears were treated with amoxicillin syrup for 10 days (50 mg/kg body weight). Subjects with acute symptoms and otoscopic findings of a bulging, tense tympanic membrane were treated with amoxicillin syrup for 5 days. Caregivers whose children were referred to the study doctor by CHWs but did not take them there despite referral and motivation were taught by the CHW to wick the child's ears with sterile cotton buds 2 - 3 times a day until the ears became dry. During home visits, CHWs also motivated caregivers to complete the full course of antibiotics prescribed by the doctor.

Analysis

The study data form part of a larger study on causes of acute lower respiratory tract infections and diarrhoea in rural Mirzapur, Bangladesh.¹⁴ Statistical analysis was done using STATA version 10. We calculated descriptive statistics for number of episodes, duration of episodes, type of ear disease, and visits made to the doctor. Statistical comparisons were made using the chi-square test or Student's *t*-test as appropriate. Results were considered significant at the alpha = 0.05 level.

Results

A total of 288 babies were born in the study area and enrolled in the birth cohort study. Of these, 252 (87.5%) completed surveillance for 2 years; 36 babies were excluded from analysis.¹⁵ Subjects were followed up with surveillance home visits for a total of 151 597 child days. Of the subjects 56.7% (143/252) were males and 43.2% (109/252) females, and 34.1% (86/252) had a birth weight <2 500 g.

Burden of otitis media

During household surveillance, CHWs documented 375 episodes of AOM in 115/252 (45.6%) of the children followed up until 2 years of age. A single episode was observed in 49 children (19.4%), and recurrent episodes were observed in 66 (26.2%).¹⁵ Of the 375 episodes of AOM documented, 14.1% ($n=53$) were not associated with perforation, and 85.9% (322/375) with perforation and discharge from the ear; of the latter, 218 episodes were unilateral and 104 bilateral.

Compliance with referral in caregiver-recognised and CHW-recognised episodes of AOM

Of the 375 episodes of AOM documented, 129 episodes with perforation and discharge were first recognised by caregivers and reported to the CHWs. The remaining 246 episodes, 53 with acute symptoms and 193 with perforation and discharge, were first recognised by CHWs (Fig. 1). All the children were referred to the study doctor by the CHWs, and all the caregivers who had recognised an episode complied with the referral; however, in only 21.5% (53/246) of unrecognised episodes of AOM was the caregiver compliant ($p<0.0001$). Fig. 2 shows that a higher proportion of subjects visited a doctor for ear problems during the first 3 months of life than at older ages.

Compliance with referral in first and recurrent episodes of AOM

Of the 115 children who experienced the 375 episodes of AOM, 49 had 1 episode and 66 had recurrent episodes. Although all episodes were referred to the doctor for assessment and management, 47 children (40.9%) were not taken to the doctor during their first episode. In the total of 260 recurrent episodes, caregivers were compliant with referral in 114 episodes and the children were given antibiotics, but in 146 episodes the caregivers were not compliant and the children were not treated with antibiotics. The difference in compliance with referral during first and recurrent episodes was not significant ($p<0.6$).

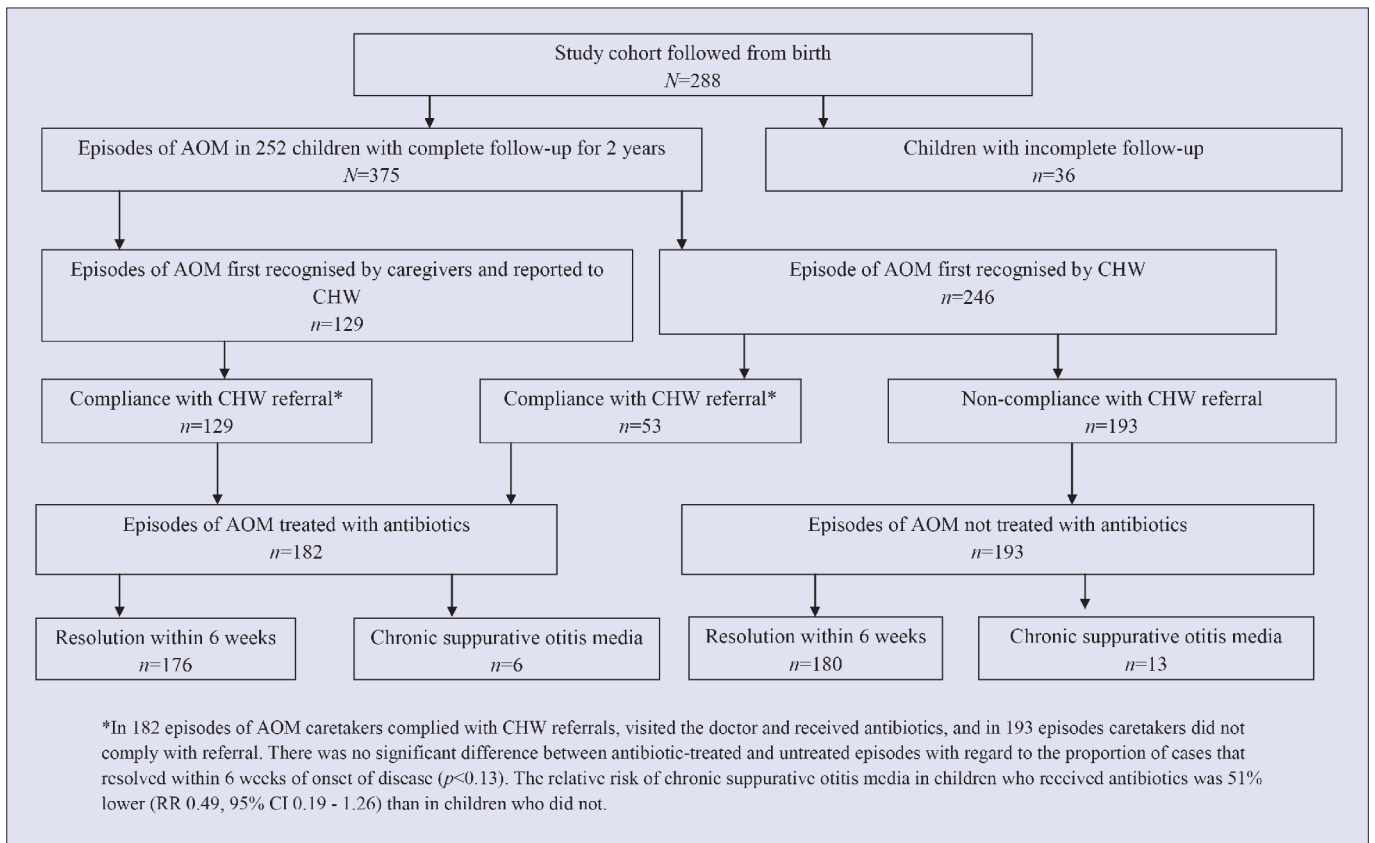


Fig. 1. Compliance with referrals and outcome of episodes of acute otitis media in children aged under 2 years in rural Bangladesh.

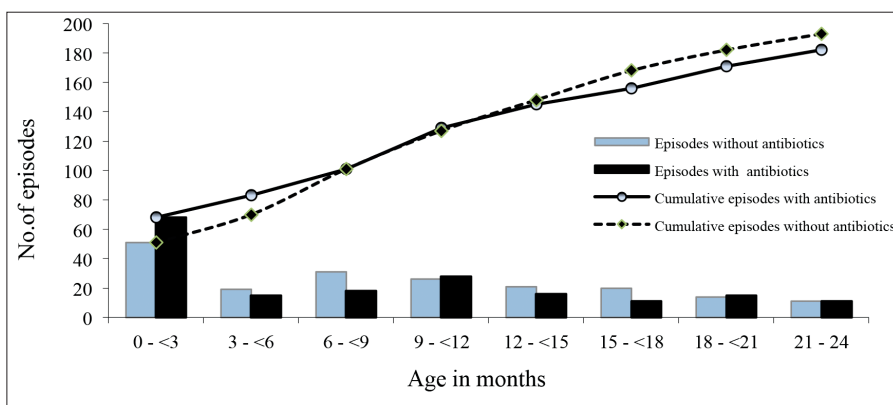


Fig. 2. Antibiotic use in episodes of acute otitis media according to age of subjects. Compliance with referral and antibiotic use was highest during the first 3 months of life. In 182 episodes of AOM caretakers complied with referrals by CHWs and received antibiotics from the doctor, and in 193 episodes the caregivers were non-compliant and no antibiotics were used.

Duration of episodes according to antibiotic use

Fig. 3 shows the duration of episodes of OM observed in the study children. There was complete resolution within 6 weeks in 96.7% (176/182) of antibiotic-treated episodes, and in 93.3% (180/193) of untreated episodes ($p < 0.13$). Early resolution (within 1 week) occurred in 52.2% (95/182) antibiotic-treated episodes and in 45.1% (87/193) of untreated episodes ($p < 0.16$). No significant difference was seen in resolution of antibiotic-treated and untreated episodes within 6 weeks. Overall, 5.1% of episodes progressed to CSOM. Although all 19 patients with CSOM were

referred, only 6 caregivers were compliant with referral and took the child to the doctor. Use of antibiotics resulted in a lower rate of progression to CSOM (relative risk (RR) 0.49, 95% confidence interval (CI) 0.19 - 1.26) compared with patients not treated with antibiotics.

Discussion

This study highlights the burden of AOM in children aged under 2 based on compliance with referrals made by CHWs in a rural setting, and demonstrates outcomes of treated and untreated episodes. The burden of AOM observed was high, but is likely to be even higher in this community

than the figures presented because our findings cover only children under 2 years of age. We also demonstrated significant deficiencies in recognition of symptoms of AOM by caregivers and failure to visit the doctor despite motivation and referral by CHWs.

AOM developed in 46.6% (115/252) of the children studied, and 26.2% (66/252) had recurrent episodes. Of the 375 episodes, 85.9% were associated with suppuration, 95.0% showed resolution by 6 weeks, and 5.1% progressed to CSOM. A high prevalence of AOM, especially of cases with suppurative complications and progression to chronicity, indicates a substantial public health problem and emphasises the crucial need for increasing awareness of the disease in rural Bangladesh. The findings are similar to a study of children in Greenland with high rates of CSOM early in life.¹⁷ In our cohort, only 34.4% (129/375) of episodes of AOM were reported to the CHWs before referral to the study doctor (Fig. 1). The remaining 65.6% (246/375) episodes were first recognised by CHWs during home visits and referred, but in only 21.5% (53/246) of these referred episodes associated with acute symptoms was the child taken to the doctor (Fig 1).

The findings carry the important message that care-seeking pattern and compliance with CHW referral differed according to presence or absence of acute symptoms

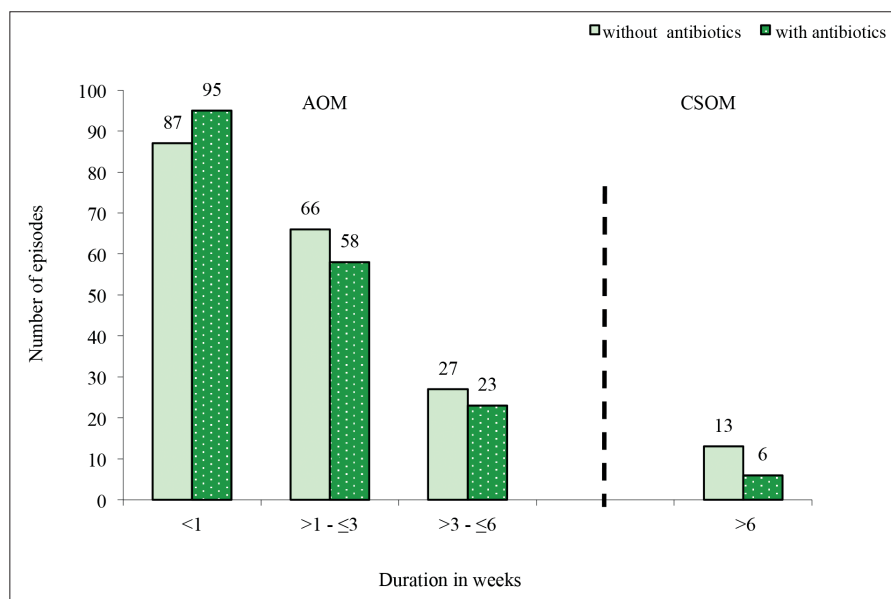


Fig. 3. Duration of episodes of otitis media in compliant (with antibiotics) and non-compliant (without antibiotics) physician-referred episodes in children aged under 2 years in rural Bangladesh. There was no significant difference between compliant and non-compliant doctor-referred episodes with regard to the proportion of cases that resolved within 6 weeks ($p < 0.13$). The relative risk of chronic suppurative otitis media in children who received antibiotics was 51% lower (RR 0.49, 95% CI 0.19 - 1.26) than in children who did not.

in caregiver-unrecognised cases. We also found that in 60.0% (193/322) of all episodes associated with perforation and discharge the caregiver did not comply with referral (Fig. 1). Studies show that delayed treatment for AOM can lead to recurrence, chronic suppuration, complications such as meningitis and septicaemia, and even death.^{2,5,18} In addition, severe and recurrent OM and persistent middle ear effusion in children can lead to delays in language acquisition and cognitive development and a risk of hearing impairment.² Recognition of the signs and symptoms of AOM, timely referral, and activities to increase awareness of the importance of follow-up by doctors are crucial to prevent recurrence and long-term complications.^{5,19,20}

Unawareness of AOM is likely to increase the disease burden. In developing countries there is a high prevalence of suppurative AOM,²¹ but awareness and hence healthcare-seeking behaviour are low compared with caregivers in developed countries.²² In our cohort, in 60.0% of AOM episodes with perforation and discharge from the ears the child was not taken to the study doctor for assessment, despite referrals by CHWs (Fig. 1). Furthermore, in 40.8% (47/115) of first episodes and 43.8% (114/260) of recurrent episodes the child received no antibiotics ($p < 0.6$). This shows that awareness of the disease did not improve in caregivers of children with recurrence of AOM. However, parental concern resulting in a doctor visit was high if the child developed AOM in the first 2 months of life (Fig. 2).

It is hypothesised that spontaneous resolution occurs in most cases of OM of viral origin and in a substantial proportion of cases with a bacterial cause.²³ Our findings support previous studies showing high rates of spontaneous resolution of AOM. A Cochrane review of reports between 1966 and 1992 showed spontaneous resolution in 81% of episodes.²² The high rate of acute upper respiratory tract infections in our cohort (7.5 episodes per child-year) may indicate that a high proportion of AOM episodes were of viral origin.¹⁵ In general, the duration of AOM is influenced by aetiological factors, host defence mechanisms, and changes in nasopharyngeal bacterial flora due to emergence of resistant organisms caused by misuse and overuse of antibiotics.^{19,24} The cost of management of AOM is high – as much as \$5 billion annually in the USA.²⁵ Consequences of antibiotic treatment for AOM include not only high cost, but the risk of development of antimicrobial resistance among AOM pathogens.¹³ Judicious use of antibiotics in AOM has reduced antimicrobial resistance in some countries, such as the Netherlands and Iceland,⁴ and in certain areas management strategies are now changing to watchful waiting. Although historical data support the effectiveness of antibiotic therapy in reducing the frequencies of complications such as mastoiditis and CSOM, judicious

use of antibiotics for AOM is an important policy topic. While some current AOM management strategies recommend watchful waiting and delay in starting antibiotic treatment, doctors in developing countries may be prompted to prescribe antibiotics immediately because they fear that caregivers will not seek follow-up care for their children after a waiting period (as we showed in this study), resulting in delayed resolution of episodes, suppurative complications and recurrent infection.^{4,21,22,26} Although we saw no cases of mastoiditis and there was no statistical difference in resolution of treated and untreated episodes of AOM within 6 weeks of the start of the disease process ($p = 0.16$), the findings need to be interpreted with caution. We observed that 3.3% (6/182) of episodes treated with antibiotics and 6.7% (13/193) of episodes not so treated proceeded to CSOM (Fig. 1). Use of antibiotics resulted in lower rate of progression to CSOM (RR 0.49, 95% CI 0.19 - 1.26) compared with cases not treated with antibiotics. The progression of disease to CSOM in 13 children whose caregivers failed to take them to the doctor suggests that assessment by a doctor could have altered the outcome in some cases. Failure to use antibiotics in developing countries may therefore increase the burden of acute and chronic complications, including long-term disability from hearing impairment in those who cannot access medical care.

The study has both strengths and limitations. We believe that the household surveillance was meticulous. However, we did not use laboratory diagnosis and were unable to determine the bacterial and viral aetiology of AOM; we relied on clinical diagnoses by the doctor, aided by otoscopic examination of the ears. Also, the longer-term burden and outcomes of AOM were not assessed, as the follow-up period was 2 years. Further studies are important to add evidence to our limited results.

In South-East Asian countries, including Bangladesh, the management of AOM is being addressed as part of the Integrated Management of Childhood Illnesses (IMCI) strategy introduced in 2001. The strategy advocates treatment of all episodes of acute or chronic OM with complications

**A significant problem
in developing countries
is inadequate awareness
of AOM and lack of
specialist care.**



with antibiotics in order to prevent further complications.²⁷ AOM management is only one of many components of the IMCI strategy. We expect that IMCI along with training programmes targeting CHWs will help to reduce the burden of AOM and its complications among children in developing countries such as Bangladesh. However, IMCI does not include focus on building of awareness and re-assessment of the AOM burden at the community level. Our study points to the necessity for increasing awareness at community level of the need for medical evaluation of and care for AOM, and attention to compliance with referrals to medical care by CHWs. This study also provides important comparison information describing the AOM burden and care-seeking practices in a rural birth cohort in a developing country with a high disease burden.

Funding. This research study was funded by the US Agency for International Development (USAID), grant number HRN-A-00-96-90005-02. The International Centre for Diarrhoeal Diseases and Research (icddr), Bangladesh, acknowledges with gratitude USAID's commitment to the Centre's research efforts.

Ethical approval. The study was approved by the Ethical Research Review Committee, icddr, Bangladesh.

Acknowledgements. We thank Kumudini Hospital, Mirzapur, for providing medical services to the study population, and the hospital staff, the field staff and the people of Mirzapur for their co-operation in the study. The icddr, and the Department of Epidemiology and International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, are acknowledged with gratitude.

References

- Leskinen K, Jero J. Complications of acute otitis media in children in southern Finland. *Int J Pediatr Otorhinol* 2004;68(3):317-324. [http://dx.doi.org/10.1016/j.ijporl.2003.10.018]
- Klein JO. The burden of otitis media. *Vaccine* 2000;19(Suppl 1):S2-8. [http://dx.doi.org/10.1016/S0264-410X(00)00271-1]
- Giles M, Asher I. Prevalence and natural history of otitis media with perforation in Maori school children. *J Laryngol Otol* 1991;105(4):257-260. [http://dx.doi.org/10.1017/S0022215100115555]
- Rutka J, Lekagul S. No therapy: use, abuse, efficacy, and morbidity – the European versus the Third-World experience. *J Otolaryngol* 1998;27(Suppl 2):43-48.
- Leach AJ. Otitis media in Australian Aboriginal children: an overview. *Int J Pediatr Otorhinol* 1999;49(Suppl 1):S173-178. [http://dx.doi.org/10.1016/S0165-5876(99)00156-1]
- Rovers MM. The burden of otitis media. *Vaccine* 2008;26(Suppl 7):G2-4. [http://dx.doi.org/10.1016/j.vaccine.2008.11.005]
- Gunasekera H, Morris PS, Daniels J, Couzos S, Craig JC. Otitis media in Aboriginal children: the discordance between burden of illness and access to services in rural/remote and urban Australia. *J Paediatr Child Health* 2009;45(7-8):425-430. [http://dx.doi.org/10.1111/j.1440-1754.2009.01532.x]
- Morris PS, Leach AJ. Acute and chronic otitis media. *Pediatr Clin North Am* 2009;56(6):1383-1399. [http://dx.doi.org/10.1016/j.pcl.2009.09.007]
- Berman S. Otitis media in developing countries. *Pediatrics* 1995;96(1 Pt 1):126-131.
- Pappas S, Nikolopoulos TP, Korres S, Papacharalampous G, Tzangaroulakis A, Ferekidis E. Topical antibiotic ear drops: are they safe? *Int J Clin Pract* 2006;60(9):1115-1119. [http://dx.doi.org/10.1111/j.1742-1241.2006.01005.x]
- Pichichero ME, Brixner DI. A review of recommended antibiotic therapies with impact on outcomes in acute otitis media and acute bacterial sinusitis. *Am J Manag Care* 2006;12(10 Suppl):S292-302.
- Mui S, Rasgon BM, Hilsinger RL Jr, Lewis B, Lactao G. Tympanostomy tubes for otitis media: quality-of-life improvement for children and parents. *Ear Nose Throat J* 2005;84(7):418, 420-422, 424.
- Coher MP, Johnson CE. Otitis media: review of the 2004 treatment guidelines. *Ann Pharmacother* 2005;39(11):1879-1887. [http://dx.doi.org/10.1345/aph.1G190]
- Hasan KZ, Pathela P, Alam K, et al. Aetiology of diarrhoea in a birth cohort of children aged 0-2 year(s) in rural Mirzapur, Bangladesh. *J Health Popul Nutr* 2006;24(1):25-35.
- Roy E, Hasan Kh Z, Haque F, Siddique AK, Sack RB. Acute otitis media during the first two years of life in a rural community in Bangladesh: a prospective cohort study. *J Health Popul Nutr* 2007;25(4):414-421.
- Teele DW, Klein JO, Rosner B. Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study. *J Infect Dis* 1989;160(1):83-94. [http://dx.doi.org/10.1093/infdis/160.1.83]
- Koch A, Homoe P, Pipper C, Hjuler T, Melbye M. Chronic suppurative otitis media in a birth cohort of children in Greenland: population-based study of incidence and risk factors. *Pediatr Infect Dis J* 2011;30(1):25-29. [http://dx.doi.org/10.1097/INF.0b013e3181efaa11]
- Sagai S, Suetake M, Yano H, et al. Relationship between respiratory syncytial virus infection and acute otitis media in children. *Auris Nasus Larynx* 2004;31(4):341-345. [http://dx.doi.org/10.1016/j.anl.2004.07.005]
- Tarlow M. Otitis media: pathogenesis and medical sequelae. *Ear Nose Throat J* 1998;77(6 Suppl):3-6.
- Jacob A, Rupa V, Job A, Joseph A. Hearing impairment and otitis media in a rural primary school in south India. *Int J Pediatr Otorhinolaryngol* 1997;39(2):133-138. [http://dx.doi.org/10.1016/S0165-5876(96)01479-6]
- Melaku A, Lulseged S. Chronic suppurative otitis media in a children's hospital in Addis Ababa, Ethiopia. *Ethiop Med J* 1999;37(4):237-246.
- Glasziou PP, Del Mar CB, Hayem M, Sanders SL. Antibiotics for acute otitis media in children. *Cochrane database of systematic reviews (Online)* 2000(4):CD000219.
- Rosenfeld RM, Kay D. Natural history of untreated otitis media. *Laryngoscope* 2003;113(10):1645-1657. [http://dx.doi.org/10.1097/00005537-200310000-00004]
- Rovers MM, Schilder AG, Zielhuis GA, Rosenfeld RM. Otitis media. *Lancet* 2004;363:465-473. [http://dx.doi.org/10.1016/S0140-6736(04)15495-0]
- Schuerman L, Borys D, Hoet B, Forsgren A, Prymula R. Prevention of otitis media: now a reality? *Vaccine* 2009;27(42):5748-5754. [http://dx.doi.org/10.1016/j.vaccine.2009.07.070]
- Kuzujanakis M, Kleinman K, Rifas-Shiman S, Finkelstein JA. Correlates of parental antibiotic knowledge, demand, and reported use. *Ambulatory Pediatrics* 2003;3(4):203-210. [http://dx.doi.org/10.1367/1539-4409(2003)]
- World Health Organization. 2007. http://www.who.int/child_adolescent_health/documents/IMCI_chartbooklet/en/indexhtml 2007 (accessed June 2012).