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The Epidemiology of Respiratory Infections in Children

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Respiratory infections produce diseases with global impact in children. These infections are important causes of morbidity and mortality in the developed and developing world.[1-5] A proper understanding of the impact of respiratory infection requires attention to the similarities and differences posed by challenges in these different environments, a working knowledge of common pathogens, and an appreciation of risk factors. This knowledge can guide sound approaches for prevention and therapy of respiratory disease in children.

Scope of the Problem in the Developed World

Pediatric respiratory infections in industrialized countries vary from the modest annoyance of rhinovirus coryza to life-threatening viral or bacterial pneumonia. Respiratory illness rates in boys and girls are highest in children 2 years of age and younger.[4,6-9] Because estimates of attack rates vary to some degree according to the type of surveillance for a given population, comparisons between studies are somewhat difficult. However, in a recent community study in which enrollees were surveyed weekly and cultured for each respiratory illness, infants younger than 2 years of age had a mean number of 5.7 respiratory illnesses per year.[4] The respiratory illness rate did not drop below 3 illnesses per year until subjects reached 15 years of age, and mean number of illnesses then averaged 2 per year. In circumstances for which diagnoses have been obtained, rhinoviruses accounted for 11% to 25% of all physician visits.[4,10,11]

Clearly, many respiratory infections go unrecognized in tallies of their impact, because affected children are never evaluated by a physician and are treated at home. Therefore, another estimate of the frequency of respiratory infection may be obtained from the prevalence of over-the-counter (OTC) drug use for treatment of "cold" symptoms. According to a recent analysis of a nationally representative sample, 35% of all 3-year-old children in the United States were given an OTC cold or cough medication in the preceding 30 days.[12] This likely represents an underestimate of the total number of respiratory illnesses; children who sought a physician's advice were less likely to receive OTC medications, and use of prescription medications was not captured in this study.

Even relatively benign upper respiratory infections have significant economic and health consequences. Nearly $2 billion are spent yearly in the United States by consumers for cough and cold remedies.[13] The direct cost of community-acquired respiratory infections treated in ambulatory settings has been estimated to be $10 billion.[14] Approximately $6 billion of this annual expense is encompassed by costs for diagnosis and treatment of otitis media and upper respiratory infection, with the remaining $4 billion attributable to lower respiratory tract infections. Children can be expected to account for a sizable portion of this expense.

A 5-year study in a suburban middle-class pediatric practice indicates that a cohort of 100 children might be expected to have nearly 50 lower respiratory tract illnesses in the first 2 years of life.[15] Moreover, the cost of lower respiratory tract infection diagnosed and treated in the first 2 years of life was estimated to be at least $35 for every child followed. More than 50% of the estimated cost was attributable to hospitalization. The majority of episodes correlated with the presence of four viruses in the community—respiratory syncytial virus (RSV), influenza, parainfluenza 1, and parainfluenza 3. In our 20-year experience (1973 to 1993) with cohorts of children followed from birth in the Vanderbilt Vaccine Evaluation Unit (VVEU), we have observed a total of 8,454 respiratory infections in 4,093 child-years of observation. The total rate of medically attended respiratory illness was 310.3 episodes per 100 child-years, for children younger than 2 years of age and 102.7 per 100 child-years for children age 2 to 5 years. We have observed a lower respiratory infection rate of 25.7 per 100 child-years during the first 2 years of life and 7.3 per 100 child-years for age 2 to 5 years. Although respiratory infections peak in winter months, otitis media and lower respiratory infections occur throughout the year and average nearly 50% of rates in peak months (Fig 1). It is clear that what may be seen by the anxious parent as a respiratory infection that "never goes away" often is really a series of sequential infections with no intervening asymptomatic period.[16]

Scope of the Problem in the Developing World

Respiratory infections are one of the most important causes of preventable deaths in the developing world. More than 98% of over 3.5 million pediatric respiratory disease deaths each year occur in developing countries.[17] Mortality rates from respiratory infections in some Latin American, Asian, and African countries are 10- to 30-fold higher than the death rate observed in North America.[3,18-23] In developing countries, the proportion of chil-

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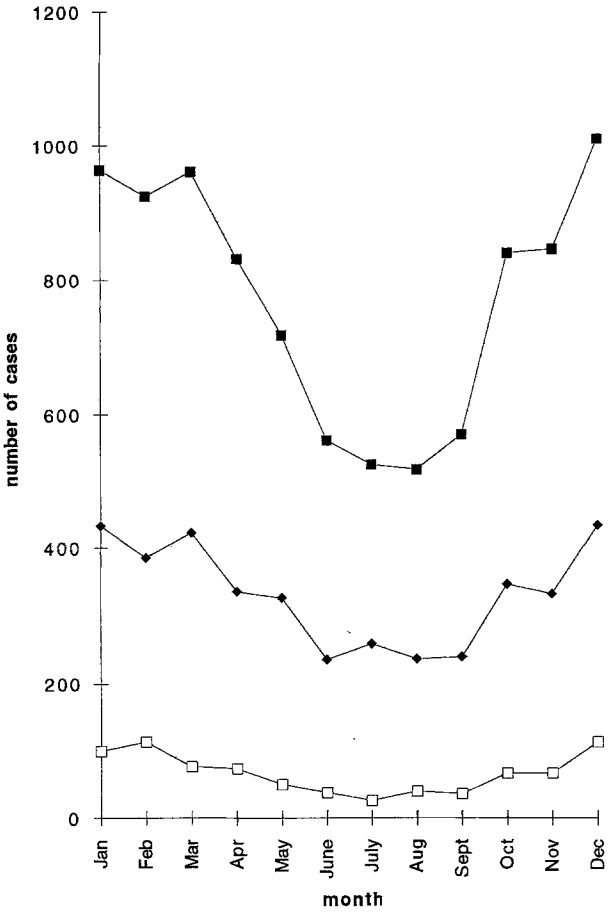

Figure 1. Respiratory disease in the Vanderbilt Vaccine Clinic, 1973 to 1993. -■-, upper respiratory infection; -□-, lower respiratory infection; -◆-, otitis.

dren dying from respiratory diseases is exceedingly large when compared with other causes of death (Fig 2); the death rate from respiratory disease often exceeds the proportion of the population dying from cardiovascular disease or cancer after a "normal" life span.[3]

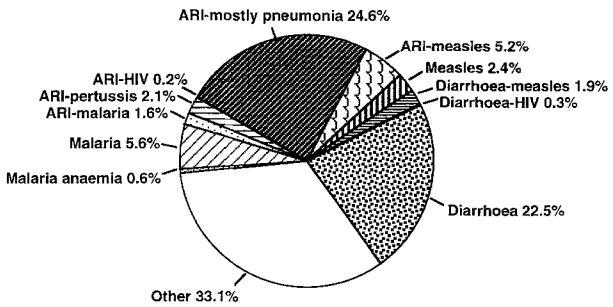

Figure 2. Distribution of 12.2 million deaths among children younger than 5 years old in all developing countries, 1993. Total associated with: ARI, 33.7%; malnutrition, 29.0%; diarrhea, 24.7%; measles, 9.5%; malaria, 7.7%; one or more of these five conditions, 71%. (Courtesy of World Health Organization, 1994.)

In 1982, in response to the formidable challenge posed by respiratory infections, a National Academy of Sciences/Institute of Medicine (IOM) committee assigned a high priority to international research of acute respiratory tract infection (ARI). The National Academy of Sciences Board on Science and Technology for International Development (BOSTID) determined much of what is known today about risk factors, pathogens, symptoms, and disease severity of ARI in the developing world.[18]

Incidence rates from the BOSTID studies ranged from 12.7 to 27.5 respiratory illnesses per 100 child-weeks at risk; the highest rate was observed when mild upper respiratory infections were included.[18] More lower respiratory tract infections were identified by auscultation in the home than were identified by examination of ill subjects in a clinic setting. Hence, the overall impact of LRI in a developing setting may be underestimated, and comparisons between different studies necessarily should pay strict attention to methods of surveillance. Children 5 years old or younger were observed to spend up to 40% and 14% of observed weeks with signs of respiratory infection and LRI, respectively.[18]

Microbiology of Respiratory Tract Infection

Upper respiratory infections are caused most often by viral pathogens, notably rhinoviruses, RSV, parainfluenza viruses, adenoviruses, influenza, enteroviruses, and coronaviruses. These agents, particularly rhinoviruses, may produce mild coryza that is self-limited. However, influenza, adenoviruses, RSV, and parainfluenza commonly are associated with the complication of otitis media.[24] During 20 years of active surveillance in the VVEU, nearly 50% of subjects evaluated for respiratory illness have been diagnosed with otitis at the time of influenza, parainfluenza, adenovirus, or RSV isolation from a respiratory specimen.

Most pharyngitis is caused by viral pathogens (primarily adenoviruses), mycoplasma or *Chlamydia pneumoniae* (TWAR) in adults and children. Epstein-Barr virus (EBV) is a common cause of purulent pharyngitis with massively enlarged tonsils in adolescents; pharyngitis caused by EBV in young children is often milder and not distinguishable from that caused by other pathogens. Pharyngitis caused by coxsackieviruses or echoviruses may herald aseptic meningitis or myocarditis.

Group A *Streptococcus* leads the list of bacterial causes of pharyngitis but other bacteria have been implicated including group B, C, and G streptococci, *Arcanobacterium* (formerly *Corynebacterium*) *hemolyticum*, gonococci or *Treponema pallidum* in sexually-exposed children or adolescents, anaerobes, and *N meningitidis*. *Corynebacterium diptheriae* as a cause of membranous pharyngitis is now a rarity in highly immunized populations.[25]

Viral upper respiratory infection also serves as a watershed for bacterial superinfection and lower respiratory tract disease. Viral upper respiratory infection has been associated for some time with increased nasopharyngeal colonization with bacterial pathogens such as pneumococcus, *Hemophilus influenzae*, and *Staphylococcus aureus*.[26] Viral infections, particularly influenza and RSV, interfere with ciliary function and augment the adherence

of both bacterial pathogens and inflammatory cells to respiratory epithelium.[27-30] Cases of otitis media, two thirds of which have a defined bacterial cause, apparently bear a closer relationship to circulation of respiratory viruses than to climate. Pneumococcal and *S aureus* bacterial tracheitis and pneumonia are well recognized complications of preceding influenza infection; wintertime morbidity and mortality have been tied inextricably to influenza and these subsequent bacterial complications.[8,31]

Lower respiratory infections in the first 5 years of life principally are caused by RSV, parainfluenza viruses 1, 2, and 3, influenza viruses A and B, adenoviruses, and enteroviruses. Although RSV is the most common isolate associated with significant illness, adenoviruses have been isolated next most frequently in the context of serious respiratory disease in some series.[6,32-36] However, these observations must be interpreted with caution. Unlike other respiratory viruses, adenoviruses may be shed for prolonged periods after acute infection, which may lead to difficulty in attributing a particular illness to adenovirus isolated from the nasopharynx. Nonetheless, adenovirus was implicated in 6 of 31 fatal cases of community-acquired pneumonia in Argentina[37]; in 4 of these cases, adenovirus was isolated from lung specimens obtained at autopsy.

Although measles is regarded generally as an exanthematous illness, it often causes severe lower respiratory tract disease in the developing world.[38-40] Other respiratory and enteric pathogens, both viruses and bacteria, have been isolated in up to 35% of children hospitalized with measles, and compound the associated morbidity.[41] Novel viral agents occasionally emerge as a cause of sometimes devastating respiratory illnesses. Notable among these is the hantavirus isolated from the southwestern United States.[42] As yet, young children have not been a target of this aggressive pathogen, but at least one case has been identified in a child 12 years of age.

Streptococcus pneumoniae, H influenzae, and *S aureus* are the most common isolates from lung aspirates obtained in children hospitalized for pneumonia.[43-47] *S pneumoniae* has been isolated from more than 30% of patients in the majority of such studies. Prior administration of antibiotics seems to reduce recovery of bacterial pathogens from the lung by approximately 50%.[44] Identification of bacterial pathogens from lung aspirates often is impractical, and blood cultures often are relied on to aid diagnosis of bacterial disease. Up to 40% of blood cultures have been positive for bacterial pathogens identified by lung aspiration.[48] Bacterial isolates account for the minority of diagnosed LRI.[48-51]

In recent years, the emergence of pneumococcal strains resistant to penicillin has raised the stakes for potential morbidity in both developed and developing countries.[52-54] Pneumococcus strains demonstrated increasing frequencies of resistance in Europe in the 1990s[55] but were uncommon in the United States through 1987. However, in 1993, nearly 30% of *S pneumonia* isolates obtained from middle ear effusions or nasopharyngeal swabs demonstrated intermediate resistance to penicillin (minimum inhibitory concentration [MIC] ≥ 0.1 μg/mL) in communities in Kentucky and Tennessee. One half to one fifth of resistant isolates from these populations, respectively, were characterized by high-level (MIC ≥ 2 μg/mL) penicillin resistance. Resistant pneumococcus has been noted to be prevalent in day care centers,[53] and use of antibiotics in the preceding month seems to increase the risk of systemic penicillin-resistant pneumococcal infection.[54] Multiply antibiotic–resistant pneumococcal strains have been identified in Europe and Africa.[55-57] The "global village" fostered by intercontinental travel has increased opportunities for rapid worldwide spread of multiply antibiotic–resistant pneumococci.[58]

Whooping cough caused by *Bordetella pertussis* is a vaccine-preventable disease. Yet in developed countries, local reactions and public concern about serious reactions have dampened enthusiasm for its use and prompted development of a less reactogenic acellular pertussis vaccine. Where immunization rates have declined (eg, Japan, Sweden, and the United Kingdom) pertussis has reemerged as a major problem.[59] In developing countries, where preventive measures remain limited, the mortality from pertussis approaches or exceeds that seen at the turn of the century in the industrialized world.[60]

Fungal respiratory disease is endemic to certain areas of developed and developing countries. Histoplasmosis was described originally as a prominent cause of pediatric respiratory illness in the southeastern part of the United States and remains so today, although previously described disseminated disease now seems rare in immunocompetent children.[61] Blastomycosis and coccidiomycosis are important causes of endemic disease in children in the United States. Outbreaks of these mycoses have occurred in school-age children. Paracoccidomycosis is a pathogen in South America; children and teenagers account for approximately 3% of cases.[62] Bronchopulmonary aspergillosis is an important cause of wheezing in children.

Tuberculosis (TB) has remained a significant cause of respiratory disease in the developing world and has recently reemerged as an important contributor to respiratory disease in the United States. From 1985 to 1990, increases in TB cases were the second largest (41.1%) and the largest (102.6%) among non-Hispanic blacks and Hispanics, respectively, between the ages of 5 and 15 years old. Recent urban epidemiological studies have demonstrated that 33% to 40% of new TB cases were the result of recent infection,[64,65] indicating a high rate of transmission to susceptibles. Transmission of TB from a single patient accounted for as much as 6% of newly diagnosed cases in San Francisco.[64] A single infected adult patient can have a devastating impact on attempts to control TB in an inner city. Although the consequence of pediatric TB was not included in these evaluations, it would be anticipated that the potential for childhood disease is high; children are themselves inefficient transmitters of TB, but young infants exposed to adult inner-city populations at risk are particularly vulnerable to severe disease.[66] The effect of the human immunodeficiency virus (HIV) epidemic on children seems to be largely conferred by an increase in the number of adults with active TB serving as potential sources of TB infection for children.[67]

Host and Environmental Risk Factors

The risk of significant respiratory disease is linked closely to characteristics of the host and environmental exposures. In many circumstances, these risk factors are interdependent and combine to increase susceptibility to respiratory illness (Table 1).

Table 1. Host and Environmental Risk Factors That Contribute to Respiratory Illness

Host factors
Young age
Prematurity/low birth weight
Malnutrition
Bottle feeding (?)
Vitamin A deficiency (?)
Environmental factors
Socioeconomic status
Crowding, birth order
Day care
Smoke pollution

Young age is a risk factor for viral respiratory illness. Numerous studies have shown that peak rates of ARI occur in the first 2 years of life (approximately 5 episodes per year) and decrease thereafter.[4,15,68-70] RSV and influenza are perhaps the most notable examples for which young age poses a risk. Over 20 years of observation in the Vanderbilt VEU, 23.7% of doctor visits for culture-confirmed RSV have been in infants younger than 6 months old, despite a mean age of 15.7 months for culture-confirmed RSV infection. Over 50% of hospitalizations for RSV infection in this population were in healthy infants younger than 3 months old.[71] During influenza epidemics in Harris County, Texas, the highest rates for ARI hospitalizations were observed in people 65 years of age or older, but the rates for children younger than 5 years old were nearly as high.[72] In World Health Organization–sponsored intervention studies in the developing world 20% to 40% of deaths from ARI occurred in infants younger than 3 months old.[2]

Prematurity and low birth weight are risk factors for severe ARI. Prematurity is associated with increased risk of hyaline membrane lung disease and bacterial pneumonia in the newborn period and subsequent development of bronchopulmonary dysplasia (BPD). The risk for severe RSV infection is clearly greater in such patients.[73,74] Although the incidence of upper or lower respiratory infection is similar in low birthweight and normal infants in developing countries, case fatality rates have been observed to be four to eight times greater than that documented for normal infants.[75-77] Confounding variables such as crowding, poverty, poor nutrition, and poor maternal education in developing countries make it difficult to determine whether the low birth weight independently leads to the greater risk.

Malnutrition does not seem to significantly affect the incidence of ARI but does seem to increase the severity.[78,79] However, in one study from Costa Rica, malnourished children experienced nearly 3 times more bronchitis and 19 times more pneumonia, and were nearly 4 times as likely to be hospitalized.[80] An association between lower percentiles for age measures and higher rates of upper and lower respiratory infections has been observed in older children.[18] Fatality rates have been 7 to 27 times greater in cohorts of malnourished children.[47,78]

Breast-fed infants have been observed to experience fewer episodes of otitis and LRI,[81,82] but demonstration of these effects requires correction for confounding socioeconomic factors.[83,84] A recently completed study in Denmark was unable to identify a protective effect of breast-feeding against infectious illness including respiratory disease.[85] In Rwanda and Brazil, LRI mortality rates were two to four times greater in hospitalized children who received formula or cows' milk than in those infants who received breast milk.[83,86] In contrast to its possible beneficial effects in some circumstances, breast-feeding is contraindicated in infants or mothers who are sputum-positive for *Mycobacterium tuberculosis*.

Only limited information is available that may tag increased ARI to specific micronutrient or vitamin deficiency. In Indonesia, Vitamin A deficiency was associated with increased ARI-associated morbidity and mortality[87]; vitamin A supplementation resulted in a 34% reduction in the population under study, but reductions attributable to respiratory disease were not differentiated.[88]

Vitamin A deficiency and therapeutic response to supplementation has been observed in patients with measles[89]; reductions in morbidity and mortality have been attributed in part to reduced respiratory complications after vitamin A administration. Recently, reductions in vitamin A levels that mirror RSV LRI severity have been reported,[90] but it remains to be determined whether supplementation will be of value in reducing morbidity or mortality. Vitamin A prophylaxis and treatment studies for ARI in developing countries have yielded mixed results, as summarized in a recent review.[91] A flurry of interest about the role that vitamin C might play in treating or preventing ARI has abated because no study has confirmed specific benefit from this nutrient.[92,93] Vitamin E is a antioxidant and may heighten humoral immune response, but a specific role in ARI is not known. Low vitamin B_6 and B_{12} levels are more likely a consequence of chronic disease such as TB and not a contributory factor. Although iron, zinc, selenium, copper, and chromium all play roles in supporting an adequate immune response, and judicious oral iron supplementation may reduce enteric infections, no clear role for these micronutrients as adjunctive therapy for ARI has been identified.

Crowding might be expected to increase the risk of exposure to respiratory disease pathogens and the attendant risk of disease. This appears to be the case. Whether from the presence of more siblings, abject circumstances, or the day care environment, the incidence of respiratory diseases is higher when there is close, sustained contact among many children.[83,94,95] Multiple toddlers in the family increase the risk of respiratory illness for all family members.[83] Influenza attack rates are highest in those families with school-age children.[96,97] Older children increase the risk of respiratory disease for younger children. Despite the important role that HIV infection plays in the resurgence of TB, poverty and household crowding continue to remain important factors for spread to children.[98]

Developed countries, particularly the United States, have seen a demographic shift in childcare as married and single parents enter the workplace. It now is estimated that nearly 75% of children are cared for in out-of-home care settings. ARI clearly is increased for children in out-of-home care, particularly for the young infant newly exposed to this environment. Grouping of older children with younger children and increased numbers of enrollees in any one environment are associated with increased vulnerability to ARI.[95,99,100] Respiratory disease rates tend to equalize with those of children cared for at home

within 2 years.[95,99] This information may be a source of some comfort to working parents who worry that they are jeopardizing their families and careers with young infants who seem to have more illness than had been expected. Problems are not limited to mild upper respiratory infection but include otitis media and LRI. Young infants in out-of-home care who are between 1 and 2 years old may be expected to experience nearly twice as many episodes of otitis as matched children in home care.[101]

Smoke and air pollutants are linked to ARI in children, particularly in the first 2 years of life.[102,103] Maternal smoking doubles the risk of ARI in the first 2 years of the child's life. Among infants exposed to cigarette smoke, saliva levels of cotinine (a nicotine metabolite that correlates with smoke exposure) were detected in significantly more wheezing children younger than 2 years of age than in older wheezing children.[104] Viruses were isolated in 70% of wheezing children younger than 2 years old, and the young infants enrolled in this study were nearly five times more likely to be wheezing if they had elevated cotinine levels. New episodes of otitis media with effusion occurred more frequently and lasted longer in children exposed to tobacco smoke.[105]

Although passive exposure to tobacco smoke grabs attention as a contributor to respiratory disease morbidity, it is less well appreciated that smoke from biomass fuels predicts increased respiratory disease burden. Particulates from indoor cooking with biomass fuels in developing countries exceed nearly 20-fold those produced by 2-pack per day smokers in homes of developed countries.[106] Increased exposure to cooking fires predicted increased respiratory illness in several studies.[107,108] In a recent case-control study in The Gambia, 129 children who were thought to have died from LRI were compared with 129 children who died from other causes. In comparison of multiple social and demographic factors, exposure to smoke during cooking was the strongest risk factor associated with death from LRI.[109] In the United States, woodburning stoves have been shown to pose a risk for both upper and lower respiratory illness.[110]

Epidemiology of Prevention and Treatment

Biomedical advances offer some prospect of reducing the impact of respiratory infections at home and abroad. However, although extensive research efforts should continue to develop vaccines against respiratory viruses and *S pneumoniae*, it is unlikely that a successful approach to either will be available before the next century.[111,112] It also is clear that favorable experience with vaccines in developed countries may not predict responses in the developing world. Poliovirus and measles vaccines are notable examples. What then can be done in the short term to reduce morbidity and mortality of respiratory infections in the developed and developing world? Minimizing risk factors that predispose people to respiratory infection and "low tech" approaches should be encouraged.

Attention must be paid to improving the socioeconomic status of families. Empowerment of women is believed by many to be a linchpin to achieving this goal in the developing world.[113,114] Improved status of the family reduces crowding, promotes better access to health care, reduces risks of low birth weight and malnutrition—all risk factors for more severe respiratory tract disease. Emphasis on environmental controls, improved compliance with therapy, and novel approaches to contact identification have all been recommended to reduce the impact of tuberculosis.[65] Controlled inquiries into interventions that improve the nutritional status of children also are needed. Inexpensive vitamin or micronutrient supplementation may reduce the morbidity and mortality of respiratory disease, as has occurred with vitamin A supplementation for measles. Hypoxemia may be a common pathway to death; perhaps the availability of oxygen concentrators in remote areas would improve the potential for saving young lives.[115]

Even simple measures to prevent or treat respiratory infection can be subverted by a sense of hopelessness in the inner cities of industrialized countries or geopolitical strife in developing countries. To assure success, responses to these challenges must not go unmet.

References

1. Bale JR: Creation of a research program to determine the etiology and epidemiology of acute respiratory tract infection among children in developing countries. Rev Infect Dis 12:S861-S866, 1990 (suppl 8)
2. Berman S: Epidemiology of acute respiratory infections in children of developing countries. Rev Infect Dis 13:S454-S462, 1991 (suppl)
3. Chretien J, Holland W, Maclem P, et al: Acute Respiratory Infections in Children. N Engl J Med 310:982-984, 1984
4. Monto AS, Sullivan KM: Acute respiratory illness in the community. Frequency of illness and the agents involved. Epidemiol Infect 110:145-160, 1993
5. Selwyn BJ: The epidemiology of acute respiratory tract infection in young children: Comparison of findings from several developing countries. Coordinated Data Group of BOSTID Researchers. Rev Infect Dis 12:S870-S888, 1990 (suppl 8)
6. Denny FW, Clyde WAJ: Acute lower respiratory tract infections in nonhospitalized children. J Pediatr 108:635-646, 1986
7. Glezen WP, Wulff H, Lamb GA, et al: Patterns of virus infections in families with acute respiratory illnesses. Am J Epidemiol 86:350-361, 1967
8. Glezen WP, Decker M, Joseph SW, et al: Acute respiratory disease associated with influenza epidemics in Houston, 1981-1983. J Infect Dis 155:1119-1126, 1987
9. Henderson FW, Collier AM, Clyde WAJ, et al: Respiratory-syncytial-virus infections, reinfections and immunity. A prospective, longitudinal study in young children. N Engl J Med 300:530-534, 1979
10. Kellner G, Popow-Kraupp T, Kundi M, et al: Contribution of rhinoviruses to respiratory viral infections in childhood: A prospective study in a mainly hospitalized infant population. J Med Virol 25:455-469, 1988
11. Monto AS, Cavallaro JJ: The Tecumseh study of respiratory illness. II. Patterns of occurrence of infection with respiratory pathogens, 1965-1969. Am J Epidemiol 94:280-289, 1971
12. Kogan MD, Pappas G, Yu SM, et al: Over-the-counter medication use among US preschool-age children. JAMA 272:1025-1030, 1994
13. Rosendahl I: Expense of physician care spurs OTC, self-care market. Drug Topics 132:62-63, 1988
14. Dixon RE: Economic costs of respiratory infections in the United States. Am J Med 78:45-51, 1985
15. McConnochie KM, Hall CB, Barker WH: Lower respiratory tract illness in the first two years of life: Epidemiologic patterns and

costs in a suburban pediatric practice. Am J Public Health 78:34-39, 1988
16. Glezen P, Denny FW: Epidemiology of acute lower respiratory disease in children. N Engl J Med 288:498-505, 1973
17. Leowski J: Mortality from acute respiratory infections in children under 5 years of age: Global estimates. World Health Stat Q 39:138-144, 1986
18. Selwyn BJ: The epidemiology of acute respiratory tract infection in young children: Comparison of findings from several developing countries. Rev Infect Dis 12:S870-S888, 1990 (suppl)
19. Brewster DR, Greenwood BM: Seasonal variation of paediatric diseases in The Gambia, west Africa. Ann Trop Paediatr 13:133-146, 1993
20. Douglas RM: Acute respiratory infections in children in the developing world (Review). Semin Respir Infect 6:217-224, 1991
21. Graham NM: The epidemiology of acute respiratory infections in children and adults: A global perspective (Review). Epidemiol Rev 12:149-178, 1990
22. Spika JS, Munshi MH, Wojtyniak B, et al: Acute lower respiratory infections: A major cause of death in children in Bangladesh. Ann Trop Paediatr 9:33-39, 1989
23. Wafula EM, Onyango FE, Mirza WM, et al: Epidemiology of acute respiratory tract infections among young children in Kenya. Rev Infect Dis 12:S1035-S1038, 1990 (suppl 8)
24. Henderson FW, Collier AM, Sanyal MA, et al: A longitudinal study of respiratory viruses and bacteria in the etiology of acute otitis media with effusion. N Engl J Med 306:1377-1383, 1982
25. Cherry JD: Pharyngitis (pharyngitis, tonsillitis, tonsillopharyngitis, and nasopharyngitis), in Feigin RD, Cherry JD (eds): Textbook of Pediatric Infectious Diseases, ed 3. Philadelphia, Saunders, 1992, pp 159-166
26. Box QT, Cleveland RT, Willard CY: Bacterial flora of the upper respiratory tract. I. Comparative evaluation by anterior nasal, oropharyngeal, and nasopharyngeal swabs. Am J Dis Child 102:293-301, 1961
27. Fainstein V, Musher DM, Cate TR: Bacterial adherence to pharyngeal cells during viral infection. J Infect Dis 141:172-176, 1980
28. Davison VE, Sanford BA: Adherence of staphylococcus aureus to influenza A virus-infected Madin-Darby canine kidney cell cultures. Infect Immun 32:118-126, 1981
29. Faden H, Hong JJ, Ogra PJ: Interaction of polymorphonuclear leukocytes and viruses in humans: Adherence of polymorphonuclear leukocytes to respiratory syncytial virus–infected cells. J Virol 52:16-23, 1984
30. Tosi MF, Stark JM, Hamedani A, et al: Intercellular adhesion molecule-1 (ICAM-1)–dependent and ICAM-1–independent adhesive interactions between polymorphonuclear leukocytes and human airway epithelial cells infected with parainfluenza virus type 2. J Immunol 149:3345-3349, 1992
31. Glezen WP, Keitel WA, Taber LH, et al: Age distribution of patients with medically-attended illnesses caused by sequential variants of influenza A/H1N1: comparison to age-specific infection rates, 1978-1989. Am J Epidemiol 133:296-304, 1991
32. Carlsen KH, Orstavik I, Halvorsen K: Viral infections of the respiratory tract in hospitalized children. A study from Oslo during a 90 months' period. Acta Paediatr Scand 72:53-58, 1983
33. de Arruda E, Hayden FG, McAuliffe JF, et al: Acute respiratory viral infections in ambulatory children of urban northeast Brazil. J Infect Dis 164:252-258, 1991
34. Edwards KM, Thompson J, Paolini J, et al: Adenovirus infections in young children. Pediatrics 76:420-424, 1985
35. Loda FA, Clyde WAJ, Glezen WP, et al: Studies on the role of viruses, bacteria, and *M pneumoniae* as causes of lower respiratory tract infections in children. J Pediatr 72:161-176, 1968
36. Pacini DL, Collier AM, Henderson FW: Adenovirus infections and respiratory illnesses in children in group day care. J Infect Dis 156:920-927, 1987
37. Carballal G, Siminovich M, Murtagh P, et al: Etiologic, clinical, and pathologic analysis of 31 fatal cases of acute respiratory tract infection in Argentinian children under 5 years of age. Rev Infect Dis 12:S1074-S1081, 1990
38. Oyejide CO, Osinusi K: Acute respiratory tract infection in children in Idikan Community, Ibadan, Nigeria: Severity, risk factors, and frequency of occurrence. Rev Infect Dis 12:S1042-S1046, 1990 (suppl 8)
39. Markowitz LE, Nieburg P: The burden of acute respiratory infection due to measles in developing countries and the potential impact of measles vaccine. Rev Infect Dis 13:S555-S561, 1991
40. Berman S, Duenas A, Bedoya A, et al: Acute lower respiratory tract illnesses in Cali, Colombia: a two-year ambulatory study. Pediatrics 71:210-218, 1983
41. Tupasi TE, de Leon LE, Lupisan S, et al: Patterns of acute respiratory tract infection in children: a longitudinal study in a depressed community in Metro Manila. Rev Infect Dis 12:S940-S949, 1990 (suppl 8)
42. Butler JC, Peters CJ: Hantavirus and hantavirus pulmonary syndrome. Rev Infect Dis 19:387-395, 1994
43. Hughes JR, Sinha DP, Cooper MR, et al: Lung tap in childhood: Bacteria, viruses, and mycoplasmas in acute lower respiratory tract infections. Pediatrics 44:477-485, 1969
44. Mimica I, Donoso E, Howard JE, et al: Lung puncture in the etiological diagnosis of pneumonia: a study of 543 infants and children. Am J Dis Child 122:278-282, 1971
45. Shann F, Graaten M, Germer S, et al: Aetiology of pneumonia in children in Goroka Hospital, Papua New Guinea. Lancet 2:537-541, 1984
46. Shann F: Etiology of severe pneumonia in children in developing countries. Pediatr Infect Dis 5:247-252, 1986
47. Escobar JA, Dover AS, Duenas A, et al: Etiology of respiratory tract infections in children in Cali, Colombia. Pediatrics 57:123-130, 1976
48. Wall RA, Corrah PT, Mabey DCW, et al: The etiology of lobar pneumonia in the Gambia. Bull World Health Organ 64:553-558, 1986
49. Borrero I, Fajardo L, Bedoya A, et al: Acute respiratory tract infections among a birth cohort of children from Cali, Colombia, who were studied through 17 months of age. Rev Infect Dis 12:S950-S956, 1990 (suppl 8)
50. Vathanophas K, Sangchai R, Raktham S, et al: A community-based study of acute respiratory tract infection in Thai children. Rev Infect Dis 12:S957-S965, 1990 (suppl 8)
51. John TJ, Cherian T, Steinhoff MC, et al: Etiology of acute respiratory infections in children in tropical southern India. Rev Infect Dis 13:S463-S469, 1991 (suppl 6)
52. Anonymous: Drug-resistant *Streptococcus pneumoniae*—Kentucky and Tennessee, 1993. MMWR Morb Mortal Wkly Rep 43:23-31, 1994
53. Doyle MG, Morrow AL, Van R, et al: Intermediate resistance of Streptococcus pneumoniae to penicillin in children in day-care centers. Pediatr Infect Dis 11:831-835, 1992
54. Tan TQ, Mason EOJ, Kaplan SL: Penicillin resistant systemic pneumococcal infections in children: a retrospective case-control study. Pediatrics 92:761-767, 1993
55. Klugman KP: Pneumococcal resistance to antibiotics. Clin Micro Rev 3:171-196, 1990
56. Friedland IR, Klugman KP: Antibiotic-resistant pneumococcal disease in South African children. Am J Dis Child 146:920-923, 1992
57. Marton A, Gulyas M, Munoz R, et al: Extremely high incidence of

antibiotic resistance in clinical isolates of *Streptococcus pneumoniae* in Hungary. J Infect Dis 163:542-548, 1991
58. Munoz R, Coffey TJ, Daniels M, et al: Intercontinental spread of a multiresistant clone of serotype 23F *Streptococcus pneumoniae*. J Infect Dis 164:302-306, 1991
59. Noble GR, Bernier RH, Esber EC, et al: Acellular and whole-cell pertussis vaccines in Japan. JAMA 257:1351-1356, 1987
60. Morley DC, Martin WJ, Woodland M: Whooping cough in Nigerian children. Trop Geogr Med 18:169-182, 1966
61. Butler JC, Heller R, Wright PF: Histoplasmosis during childhood. South Med J 87:476-480, 1994
62. Rios-Fabra A, Moreno AR, Isturiz RE: Fungal infections in Latin American Countries. Infect Dis Clin North Am 8:129-154, 1994
63. Anonymous: Prevention and control of tuberculosis in U.S. communities with at-risk minority populations. Recommendations of the Advisory Council for the Elimination of Tuberculosis. MMWR Morb Mortal Wkly Rep 41:1-11, 1992
64. Small PM, Hopewell PC, Singh SP, et al: The epidemiology of tuberculosis in San Francisco. A population-based study using conventional and molecular methods. N Engl J Med 330:1703-1709, 1994
65. Alland D, Kalkut GE, Moss AR, et al: Transmission of tuberculosis in New York city. An analysis by DNA fingerprinting and conventional epidemiologic methods. N Engl J Med 330:1710-1716, 1994
66. Starke JR, Jacobs RF, Jereb J: Resurgence of tuberculosis in children. J Pediatr 120:839-855, 1992
67. Jones DS, Malecki JM, Bigler WJ, et al: Pediatric tuberculosis and human immunodeficiency virus infection in Palm Beach County, Florida. Am J Dis Child 146:1166-1170, 1992
68. Cooney MK, Fox JP, Hall CE: The Seattle Virus Watch. VI. Observations of infections with and illness due to parainfluenza, mumps and respiratory syncytial viruses and Mycoplasma pneumoniae. Am J Epidemiol 101:532-551, 1975
69. Fox JP, Hall CE, Cooney MK, et al: The Seattle virus watch. II. Objectives, study population and its observation, data processing and summary of illnesses. Am J Epidemiol 96:270-285, 1972
70. Monto AS, Ullman BM: Acute respiratory illness in an American community. The Tecumseh study. JAMA 227:164-169, 1974
71. Gruber WC, Edwards K, Reed G, et al: Respiratory syncytial virus infection in outpatient and inpatient populations: Implications for effective intervention. Program and Abstracts of the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, Am Soc Microbiol 1993 (abstr 449A)
72. Glezen WP: Anatomy of an urban influenza epidemic. Options for the control of influenza II:11-14, 1993
73. Tammela OK: First-year infections after initial hospitalization in low birth weight infants with and without bronchopulmonary dysplasia. Scand J Infect Dis 24:515-524, 1992
74. Groothuis JR, Guttierrez KM, Lauer BA: Respiratory syncytial virus infection in children with bronchopulmonary dysplasia. J Pediatr 82:199-203, 1988
75. Datta N, Kumar V, Kumar L, et al: Application of case management to the control of acute respiratory infections in low-birthweight infants: A feasibility study. Bull World Health Organ 65:77-82, 1987
76. Lehmann D, Howard P, Heywood P: Nutrition and morbidity: acute lower respiratory tract infections, diarrhoea and malaria (Review). Papua New Guinea Med J 31:109-116, 1988
77. Lehmann D: Epidemiology of acute respiratory tract infections, especially those due to *Haemophilus influenzae,* in Papua New Guinean children (Review). J Infect Dis 165:S20-S25, 1992 (suppl 1)
78. Tupasi TE, Velmonte MA, Sanvictores ME, et al: Determinants of morbidity and mortality due to acute respiratory infections: implications for intervention. J Infect Dis 157:615-623, 1988
79. Tupasi TE, Mangubat NV, Sunico ME, et al: Malnutrition and acute respiratory tract infections in Filipino children. Rev Infect Dis 12:S1047-S1054, 1990 (suppl 8)
80. James JW: Longitudinal study of the morbidity of diarrheal and respiratory infections in malnourished children. Am J Clin Nutr 25:690-694, 1972
81. Aniansson G, Alm B, Andersson B, et al: A prospective cohort study on breast-feeding and otitis media in Swedish infants. Pediatr Infect Dis 13:183-188, 1994
82. Chen Y, Yu SZ, Li WX: Artificial feeding and hospitalization in the first 18 months of life. Pediatrics 81:58-62, 1988
83. Victora CG, Smith PG, Barros FC, et al: Risk factors for deaths due to respiratory infections among Brazilian infants. Int J Epidemiol 18:918-925, 1989
84. Cunningham AS, Jelliffe DB, Jelliffe EF: Breast-feeding and health in the 1980s: A global epidemiologic review (Review). J Pediatr 118:659-666, 1991
85. Rubin DH, Leventhal JM, Krasilnikoff PA, et al: Relationship between infant feeding and infectious illness: A prospective study of infants during the first year of life. Pediatrics 85:464-471, 1990
86. Lepage P, Munyakaze C, Hennart P: Breast feeding and hospital mortality in children in Rwanda. Lancet 2:409-411, 1981
87. Sommer A, Katz J, Tarwotjo I: Increased risk of respiratory disease and diarrhea in children with preexisting mild vitamin A deficiency. Am J Clin Nutr 40:1090-1095, 1984
88. Sommer A, Tarwotjo J, Djunaedi E, et al: Impact of vitamin A supplementation on childhood morbidity and mortality: A randomized controlled community trial. Lancet 1:1169-1173, 1986
89. Hussey GD, Klein M: A randomized, controlled trial of vitamin A in children with severe measles. N Engl J Med 323:160-164, 1990
90. Neuzil KM, Gruber WC, Chytil F, et al: Serum vitamin A levels in respiratory syncytial virus infection. J Pediatr 124:433-436, 1994
91. Semba RD: Vitamin A, Immunity, and Infection. Rev Infect Dis 19:489-499, 1994
92. Miller JZ, Nance WE, Norton JA, et al: Therapeutic effect of vitamin C. A co-twin control study. JAMA 237:248-251, 1977
93. Pitt HA, Costrini AM: Vitamin C prophylaxis in marine recruits. JAMA 241:908-911, 1979
94. Hurwitz ES, Gunn WJ, Pinsky PF, et al: Risk of respiratory illness associated with day-care attendance: a nationwide study. Pediatrics 87:62-69, 1991
95. Wald ER, Guerra N, Byers C: Frequency and severity of infections in day care: three-year follow-up. J Pediatr 118:509-514, 1991
96. Taber LH, Paredes A, Glezen WP, et al: Infection with influenza A/Victoria virus in Houston families, 1976. J Hyg 81:67-75, 1981
97. Frank AL, Taber LH, Glezen WP: Influenza B virus infections in the community and the family: the epidemics of 1976-1977 and 1979-1980 in Houston, Texas. Am J Epidemiol 118:313-325, 1983
98. Drucker E, Alcabes P, Bosworth W, et al: Childhood tuberculosis in the Bronx, New York. Lancet 343:1482-1485, 1994
99. Harsten G, Prellner K, Heldrup J, et al: Acute respiratory tract infections in children. A three-year follow-up from birth. Acta Paediatr Scand 79:402-409, 1990
100. Rasmussen F, Sundelin C: Use of medical care and antibiotics among preschool children in different day care settings. Acta Paediatr Scand 79:838-846, 1990
101. Wald ER, Guerra N, Byers C: Upper respiratory tract infection in young children: duration of and frequency of complications. Pediatrics 87:129-133, 1991
102. Fergusson DM, Horwood LJ: Parental smoking and respiratory illness during early childhood: A six year longitudinal study. Pediatr Pulmonol 1:99-106, 1985
103. Holberg CJ, Wright AL, Martinez FD, et al: Child day care, smoking by caregivers, and lower respiratory tract illness in the

first 3 years of life. Group Health Medical Associates. Pediatrics 91:885-892, 1993
104. Duff AL, Pomeranz ES, Gelber LE, et al: Risk factors for acute wheezing in infants and children: viruses, passive smoke, and IgE antibodies to inhalant allergens. Pediatrics 92:535-540, 1993
105. Etzel RA, Pattishall EN, Haley NJ, et al: Passive smoking and middle ear effusion among children in day care. Pediatrics 90:228-232, 1992
106. Frampton MW, Samet JM, Utell MJ: Environmental factors and atmospheric pollutants (Review). Semin Respir Infect 6:185-193, 1991
107. Armstrong JR, Campbell H: Indoor air pollution exposure and lower respiratory infections in young Gambian children. Int J Epidemiol 20:424-429, 1991
108. Johnson AW, Aderele WI: The association of household pollutants and socio-economic risk factors with the short-term outcome of acute lower respiratory infections in hospitalized pre-school Nigerian children. Ann Trop Paediatr 12:421-432, 1992
109. de Francisco A, Morris J, Hall AJ, et al: Risk factor for mortality from acute lower respiratory tract infections in young Gambian children. Int J Epidemiol 22:1174-1182, 1993
110. Honicky RE, Osborne JS, Akpom CA: Symptoms of respiratory illness in young children and the use of wood-burning stoves for indoor heating. Pediatrics 75:587-593, 1985
111. Sieber GR: Pneumococcal disease: Prospects for a new generation of vaccines. Science 265:1385-1387, 1994
112. Hall CB: Prospects for a respiratory syncytial virus vaccine. Science 265:1393-1394, 1994
113. Odebiyi AI, Ondolo O: Female involvement in intervention programmes: the EPI experience in Saradid, Kenya. East Afr Med J 70:25-33, 1993
114. Elliott M, Dickey C, Woodward KL: Body politics: Population wars. Newsweek 124:22-26, 1994
115. Steinhoff MC: Bellagio conference on the pathogenesis and prevention of pneumonia in children in developing regions. Introduction. Rev Infect Dis 13:S452-S453, 1991