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Acute Respiratory Infections

John R. T. Colley, M.D.; and David L. Miller, M.D.

The role of acute respiratory infections (ARI) in the natural history of chronic airways disease (CAD) is not clear. It seems probable that severe acute lower respiratory infections can cause irreparable damage to the delicate epithelium of the bronchi and bronchioles in infants and young children. They may thereby also render the small airways more susceptible to other harmful agents or to repeated infections in later life, thus initiating a process of progressive damage and deterioration of respiratory function. It is also possible that acute infections, at any stage of life, may accelerate declining respiratory function by their effects on airways already damaged by other pathologic conditions.

ARIs are usually regarded as a trivial problem except in countries where mortality rates are high. But if, by whatever mechanism, they also contribute to the development of CAD, their prevention is worthwhile even where they are rarely fatal.

We describe the magnitude of the problem of ARI and examine the evidence that ARIs in early life cause permanent...
Table 1—Mortality Rates Due to Acute Respiratory Infections* (per 100,000)

<table>
<thead>
<tr>
<th>Region</th>
<th>Infants</th>
<th>1-4</th>
<th>5-14</th>
<th>55-64</th>
<th>65-74</th>
<th>75+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>1,454</td>
<td>467</td>
<td>22</td>
<td>42</td>
<td>116</td>
<td>294</td>
</tr>
<tr>
<td>America</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North</td>
<td>145</td>
<td>8</td>
<td>2</td>
<td>33</td>
<td>88</td>
<td>415</td>
</tr>
<tr>
<td>Middle</td>
<td>1,495</td>
<td>149</td>
<td>16</td>
<td>100</td>
<td>279</td>
<td>986</td>
</tr>
<tr>
<td>South</td>
<td>1,110</td>
<td>113</td>
<td>11</td>
<td>61</td>
<td>183</td>
<td>746</td>
</tr>
<tr>
<td>Asia</td>
<td>112</td>
<td>132</td>
<td>16</td>
<td>42</td>
<td>129</td>
<td>552</td>
</tr>
<tr>
<td>Europe</td>
<td>390</td>
<td>15</td>
<td>2</td>
<td>31</td>
<td>108</td>
<td>380</td>
</tr>
</tbody>
</table>

We review the epidemiologic evidence identifying high-risk groups and associated factors that may be amenable to preventive intervention and discuss possible control strategies. We conclude with a brief account of currently available methods of prevention.

SIZE OF THE PROBLEM

Mortality and Morbidity Rates

Acute respiratory infections are extremely common at all ages, and incidence rates are similar in all countries, regardless of differences in environmental and social conditions. Most respiratory infections are mild, self-limiting conditions and are very rarely fatal, except in vulnerable groups such as low birth weight infants, malnourished children, and persons of all ages who have another severe acute condition or underlying chronic disease.

Mortality rates from ARIs (Table 1) are generally highest in children under 5 years of age in developing countries and in the elderly in developed countries. Mortality in older children and young adults is relatively low in all countries, but after the age of 55 years, rates increase steeply. Mortality rates in children are up to 40 times greater in some developing countries than in developed countries, but in older age groups they differ less between countries.

There are few reliable published statistics on ARI morbidity, and they depend mainly on small sample recording schemes and surveys of special groups. In a survey of consultations with a sample of family doctors carried out in the United Kingdom in 1981-82, morbidity for lower respiratory tract infections varied greatly by age and diagnosis (Table 2). The highest rates in children under 5 years of age were for acute bronchitis and bronchiolitis, whereas in those over 65 years pneumonia and chronic bronchitis were relatively much more common. Rates for mild ARIs are greater in females than in males, but those for the more severe infections and CAD are consistently greater in males than in females.

Interpretation of Statistics

The paucity and poor quality of most available statistics on ARI mortality and morbidity means that the problem of ARI is probably universally underestimated, in some countries more than in others. This is partly because of the fundamental problems with all such statistics, such as incompleteness of reporting of cases and difficulty in determining relevant population denominators. Other common problems include the following:

Confused classification of ARI. An attempt has been made in proposals for the tenth revision of the ICD to move toward a more coherent classification structure, but terminologic variation will likely to continue to be a source of confusion.

Lack of standardized and discriminating clinical diagnostic criteria and the complexity and cost of reliable microbiologic investigations lead to wide variation in the use and interpretation of diagnostic labels.

Inadequate evidence of cause of death. The role of ARIs as "immediate" and "underlying" causes of death without autopsy is uncertain. In developing countries the assessment of cause of death often depends on untrained recorders.

Classification rules determine that where there are multiple diagnoses the "underlying" condition is used for statistical purposes. ARI is frequently the "immediate" rather than "underlying" cause of illness, and thus will not feature in the statistics unless multiple-cause analysis is carried out.

These problems are emphasized because of their consequences both for the reliability of the published statistics used to measure the size of the problem of ARIs and for longitudinal studies of the relevance of such infections in early life to the later development of CAD.

ARD IN CHILDREN

Childhood Antecedents of Adult CAD

As long ago as 1958, Reid and Fairbairn* noted that postmen with chronic bronchitis often had a history of

Table 2—Morbidity Rates Due to Acute Lower Respiratory Tract Infections**

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>All Ages</th>
<th>0-4</th>
<th>5-14</th>
<th>15-24</th>
<th>25-44</th>
<th>45-64</th>
<th>65-74</th>
<th>75+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchitis and bronchiolitis</td>
<td>97</td>
<td>247</td>
<td>71</td>
<td>43</td>
<td>58</td>
<td>102</td>
<td>168</td>
<td>200</td>
</tr>
<tr>
<td>Influenza</td>
<td>20</td>
<td>15</td>
<td>15</td>
<td>18</td>
<td>27</td>
<td>23</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10</td>
<td>11</td>
<td>6</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>17</td>
<td>50</td>
</tr>
<tr>
<td>Chronic bronchitis + chronic obstructive lung disease</td>
<td>27</td>
<td>1</td>
<td>(0)</td>
<td>(0)</td>
<td>3</td>
<td>41</td>
<td>118</td>
<td>118</td>
</tr>
</tbody>
</table>

*Consultation rates per 1,000 persons at risk

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Chronic Airways Disease
respiratory illness going back into early adult life, and Oswald and colleagues in 1953 often found a history of childhood chest illness among patients with chronic bronchitis admitted to hospital. This and other evidence suggested that adverse childhood respiratory experience might lead to chronic bronchitis in later life. Recall bias could, in part, explain these associations, which throws some doubt on their significance. In 1983 Samet et al reviewed the evidence for an association between childhood respiratory illness and chronic airflow obstruction in adult life. Their general view was that the evidence for such an association was too incomplete to allow a firm conclusion. Since that review two separate lines of inquiry have provided further evidence on the subject.

The first involves the continued follow-up of the 1946 British Birth Cohort to age 36 years. Previous studies at ages 20 and 25 had suggested an association between childhood chest illness and respiratory symptoms in adult life. At 36, when peak expiratory flow rate (PEFR) was measured as well as respiratory symptoms (MRC Bronchitis Questionnaire), after allowing for smoking habit, an independent association was found between low PEFR, respiratory symptoms, and lower respiratory tract infection before age 10 (Table 3). Thus, in this cohort, there is evidence of a persisting association between childhood respiratory experience and adult respiratory symptoms and low PEFR. Various social and environmental factors in childhood were also investigated for associations with adult respiratory experience. Of these, crowding at age 2 years was significantly associated with mean PEFR and respiratory symptoms at 36 years.

If, on subsequent follow-up, this association between childhood respiratory experience and adult CAD is confirmed, the question arises as to whether this represents a causal or noncausal association. Is it simply the expression of a genetic susceptibility to respiratory diseases, or is it the long-term effect of lung damage suffered in childhood? This question cannot yet be answered. However, the strong associations between environmental factors and chest dis-

Table 3—Risk Factors for Chronic Cough and Respiratory Function at 36 years of age

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Prevalence of Chronic Cough (%)</th>
<th>Mean PEFR (L/Min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted for Other Factors</td>
<td>Adjusted for Height and Other Factors</td>
</tr>
<tr>
<td>Crowding at age 2 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to 1 person per room</td>
<td>6.7*</td>
<td>456.8†</td>
</tr>
<tr>
<td>Over 1 person per room</td>
<td>10.0</td>
<td>476.7</td>
</tr>
<tr>
<td>Respiratory illness up to age 10 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No illness</td>
<td>7.4‡</td>
<td>455.0‡</td>
</tr>
<tr>
<td>Cigarette smoking at age 36 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>15.9</td>
<td>478.8*</td>
</tr>
<tr>
<td>Ex</td>
<td>5.3</td>
<td>486.6</td>
</tr>
<tr>
<td>Non</td>
<td>3.3</td>
<td>490.9</td>
</tr>
</tbody>
</table>

*p<0.05. †p<0.001. ‡p<0.02.

ease in childhood are highly suggestive of a cause-and-effect relationship. Further, in another study, children who developed a chest illness during the first five years of life had ventilatory function in the neonatal period similar to those who were spared such illnesses.

The second recent line of enquiry explored the hypothesis that birth cohorts who suffered heavy respiratory mortality in infancy would also show high chronic bronchitis mortality in adult life. A strong association was found between infant mortality rates from bronchitis or pneumonia during 1921–25 and mortality rates from bronchitis in adults during 1968–79 in 212 geographic areas of England and Wales. The authors concluded that these findings support the hypothesis of a causal link between lower respiratory infection in childhood and adult chronic bronchitis.

Agents of ARI

A large number of microbial agents can cause ARI (Table 4). The most common primary agents are viruses and the most lethal are bacteria, often as secondary invaders. Agents that affect the bronchi and bronchioles tend to be associated with long-term abnormalities more than those that cause pneumonia. It is difficult, however, to obtain quantitative information about the relative frequency of different pathogens by diagnostic categories or pathology.

The laboratory diagnosis of viral infections by traditional means, such as culture and serum antibody detection, is cumbersome, time-consuming, and expensive. Because the result has little influence on case management, it is not usually carried out routinely, except in special surveys. Recent advances in developing simple, rapid diagnostic tests, such as immunofluorescence and enzyme immunoassay techniques, may assist epidemiologic studies in future.

Bacterial respiratory pathogens are frequently found as harmless commensals in the upper respiratory tract, so that when they are recovered in persons with ARI, their etiologic significance is uncertain. Carrier rates for the most common causes of bacterial pneumonia, *Streptococcus pneumoniae* and *Haemophilus influenzae*, vary with age and geographic location, but rates up to 100% have been reported in young children. It is impractical to obtain specimens from the lower respiratory tract routinely, and blood culture alone is too insensitive to be reliable. Newer techniques for antigen detection in body fluids and assays of serologic responses are promising but not yet available for routine use.

These problems in identifying microbial etiologies are important, because it means that the relative significance of
different agents as causes of ARIs and possible damage to the respiratory tract cannot easily be defined. Therefore, the most appropriate focus and value of specific prophylaxis cannot be determined.

**Risk Factors for ARI**

There is considerable evidence that social and environmental factors have a major influence on the incidence and severity of childhood respiratory infections. Most of the evidence comes from studies on populations of children in developed countries. What evidence there is from studies in developing countries suggests that the same factors operate. Low birth weight and malnutrition are of great importance in influencing the incidence and mortality from ARI. Other factors include overcrowding, number and age of other siblings, sharing a bedroom, parental cigarette smoking, and outdoor and domestic air pollution. These factors appear to have a greater influence in infants than in older children. Breast feeding may reduce the risk of respiratory infections. Passive smoking by infants of their parents’ tobacco smoke has been found in a number of studies to be associated with increased risk of lower respiratory tract illness. The evidence for this being a cause and effect relationship has been reviewed by Tager, who concluded that the evidence supports such a relationship.

The above factors may act by: (1) increasing the opportunity for cross infection, eg, crowding, sharing a bedroom; or (2) influencing the susceptibility of the respiratory tract to microbial agents, eg, malnutrition, exposure to air pollutants.

**Effects of ARI on the Respiratory Tract**

Children who survive an acute lower respiratory tract infection may be left with evidence of damage to the respiratory tract of which the most readily available indicator is impairment of ventilatory function. There is now reliable evidence that respiratory syncytial virus infections in infants may be followed by changes in several indices of lung function that last for up to 2 years. Whether these persist into later childhood and early adult life is as yet unknown. Evidence from the follow-up of the 1946 British Birth Cohort can be interpreted as indicating some permanent lung damage following childhood ARI. In contrast, childhood pertussis infection was not associated with respiratory impairment in adult life.

**ARI in Adults**

There are 3 ways in which ARI might influence the development of chronic airways disease in adults: (1) By initiating the onset. There is no reliable evidence to support this suggestion. (2) By speeding progression of established disease. Fletcher and Petro argued on the basis of a follow-up of 30-59-year-old men in West London that ARI has no permanent effect on mucous hypersecretion or lung function. However, the length of follow-up may have been too short for permanent changes to have become apparent. There are few other studies that enable any firmer conclusions. (3) By causing or contributing to mortality in those with CAD. Influenza epidemics have been associated with excess respiratory mortality, and it is possible that other respiratory viral infections may similarly affect mortality rates.

**Prevention of ARI**

Three approaches to prevention need to be considered. (1) Reduction of opportunities for exposure to microbial agents of ARI. The factors that facilitate cross-infection, such as poor housing standards leading to crowding and sharing of bedrooms, are linked to social and economic conditions that are essentially outside the scope of a practical preventive strategy in many countries. (2) Control of factors that increase susceptibility to ARI. The main factors are exposure to air pollution in the home, in particular cigarette smoke and the products of combustion of cooking fuels. The former could be influenced by general efforts to reduce tobacco consumption and the latter by improved ventilation, but this may conflict with efforts to conserve energy. (3) Increase resistance to the agents of ARI by immunization. This is the principal currently available means of primary prevention of respiratory infections. Vaccines protect against ARI both by stimulating specific immunity in the vaccinated person and by enhancing population immunity, which partially protects unimmunized individuals by impeding transmission. At present the only available vaccines against respiratory agents are pertussis, diphtheria, measles, and BCG vaccines, which are recommended for routine use in infancy and early childhood, and influenza and pneumococcal vaccines, which are used selectively in adults. Diphtheria is not usually associated with invasion of the lower respiratory tract, and tuberculosis is outside the scope of this symposium. These two vaccines will not, therefore, be considered further.

**Pertussis Vaccine**

Current whole cell vaccine is generally highly effective in protecting susceptible children against whooping cough after household exposure. However, concern about the safety of the vaccine has led to poor rates of administration in many countries. Acellar pertussis vaccines that include only those purified and toxoided antigens thought to be necessary to stimulate protective antibodies, have recently been developed. Trials have shown these to evoke as good antibody responses and fewer local and mild systemic reactions than whole cell vaccines, but efficacy trials have proved disappointing. Further work is needed to evaluate different component vaccines before they can be recommended routinely.

**Measles Vaccine**

This is a highly effective vaccine when given to young children in the second year of life. Since measles has no reservoir other than man, its elimination is theoretically possible, but to achieve this, a very high proportion (over 95%) of the child population must be immunized. Several countries have come close to reaching this goal, and in the United States, for example, most cases are now related to occasional vaccine failure or importations of the infection from countries where it is still endemic.

**Influenza Vaccine**

Killed influenza virus vaccines have been in routine use for the protection of vulnerable persons, such as the elderly and those with chronic disease, for many years. In the short
term they are moderately effective. However, the composition of the vaccine has to be revised annually to ensure that it contains contemporary A and B antigenic variants. When a major antigenic shift occurs, no protection can be expected from vaccines prepared from earlier variants, and pandemics occur. Fortunately, this has not happened for 2 decades, but it is a constant and unpredictable threat. Live-attenuated virus vaccines have considerable theoretical advantages over conventional killed virus vaccines, especially their relative ease of mass administration, but it is difficult to achieve adequate attenuation of virus virulence without impairing its immunogenicity. A live virus vaccine with few reactions and good protective efficacy that could be produced rapidly on a large scale would be extremely valuable, especially in pandemics when influenza and secondary bacterial pneumonia cause many deaths. Trials with cold-adapted influenza A and B recombinant viruses have been encouraging.

Respiratory Syncytial (RS) Virus and Other Respiratory Virus Vaccines

The RS virus is the most common cause of bronchiolitis in infants worldwide. It is associated with significant mortality and possible damage to bronchioles, with residual abnormalities of function. An effective vaccine could be expected to have a significant impact on incidence and mortality from ARI in infants and prevent associated long-term damage. Attempts to prepare vaccine against RSV by traditional methods were not successful—indeed, inactivated RSV vaccine had the effect of exacerbating subsequent natural disease, rather than conferring protection. Recent molecular research has shown that the viral envelope proteins are immunologically the most important components, and vaccines prepared from them may be available for trial in the next few years. Prospects for vaccines for other respiratory viruses still seem to be remote.

Pneumococcal Vaccine

Current pneumococcal vaccines are polyvalent capsular polysaccharide vaccines, containing the 23 serotypes that most commonly cause pneumococcal disease. However, since the protection from vaccines is serotype specific, local variations in the prevalence of particular serotypes will influence their efficacy. These vaccines have been shown to be moderately effective in reducing mortality in adults and are commonly recommended in high-risk groups, but capsular polysaccharides are poorly immunogenic, and antibody levels are poorly sustained in children under the age of 2 years. Despite this, a recent report on a double-blind, placebo-controlled trial of a multivalent pneumococcal vaccine in Papua New Guinea suggested that the vaccine can offer worthwhile protection against death in children younger than 2 years of age.

Haemophilus influenzae Vaccine

Haemophilus influenzae is the second most common cause of bacterial pneumonia in children. Vaccine against H influenzae type b is widely used and effective against invasive infection in children over 2 years of age. However, a high proportion of H influenzae infections, especially in developing countries, are due to other serotypes and nonencapsulated strains for which no vaccine currently exists. Moreover, like the pneumococcal vaccine, the Haemophilus capsular polysaccharide vaccine is not effective in very young children.

Capsular polysaccharide pneumococcal and H influenzae vaccines conjugated to a protein carrier appear to elicit higher antibody responses in young children than nonconjugated vaccines, and trials of the efficacy of such vaccines are in progress. However, the cost of conjugate vaccines may prohibit their widespread use, at least until evidence of their value generates demand for their large-scale production.

Conclusions

1. In many parts of the world, data on the morbidity and mortality from ARI are sparse and unreliable. This emphasizes the need to improve the quality and validity of available statistics.

2. There is increasing evidence to support the link between childhood ARI and adult CAD. However, the importance of the link and how it operates is not yet known. Studies to determine the relative importance of different agents and their long-term consequences in the respiratory tract are needed.

3. Social and environmental factors probably influence the incidence of childhood ARI. Of these, indoor pollution from domestic fuels and cigarette smoke appear to be the only factors that could be altered.

4. In adults the major effect of ARI is to increase mortality in those already afflicted by CAD.

5. The main possibilities for prevention of ARI lie in reducing susceptibility to the agents of ARI with vaccines, but relatively few suitable vaccines are available.

6. Other effective interventions include improved nutrition and better prenatal care to reduce the number of low birth weight infants.

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