Public health classics

This section looks back on a ground-breaking contribution to public health, reproduces an extract of the original and adds a commentary on its significance from a modern perspective. To complement the theme of this month's issue, Anthony Scott reviews a paper by BJ Selwyn that was published in 1990 in a supplement to *Reviews of infectious diseases*.[1] Pages S870, S886 and S887 are reproduced with kind permission of Chicago University Press at: http://www.who.int/bulletin/volumes/86/6/08-052753/en/index.html

The global epidemiology of childhood pneumonia 20 years on

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Any reflection on history, even as recent as the past 20 years, invites a humble re-evaluation of the myth of human progress. In public health, progress has been made; certainly the number of children who die each year has declined progressively. However, rereading the work of scientists who investigated the major cause of death in childhood, acute respiratory tract infection (ARI), in the 1980s evokes an uncanny resonance with present-day concerns.

At that time, the attention of the global public health community was on oral rehydration therapy, universal immunization, promotion of breastfeeding and the use of growth monitoring charts.[2] Lower respiratory tract infections (LRTIs) attracted relatively little attention. With considerable perspicacity, the Board of Science and Technology for International Development (BOSTID) at the National Academy of Sciences, United States of America, defined ARI as one of six priority areas for research funding in 1983 and convened an international ARI meeting. The participants identified three prerequisites for relevant research:

1. Studies should be undertaken in a wide variety of countries to give full geographical representation to the children of the developing world and they should be standardized to facilitate international comparisons.
2. The etiology of ARI should be investigated first because it would be essential for later research on prevention and case management.
3. The international research group should be coordinated by a centre that could provide technical assistance and quality control, and could foster active collaboration between investigators.[3]

Over the next 5 years, BOSTID undertook such a project, involving investigators from 12 sites who met on an annual basis to agree on clinical definitions, laboratory methods, study designs and analysis plans. The results of the programme were published in 1990 in a supplement of the *Reviews of Infectious Diseases*. The supplement illustrates the wide diversity of research activities in the programme from community-based epidemiology to laboratory comparisons of antigen detection methods, evaluations of recent antibiotic exposure and pathological studies of postmortem specimens. The anchor of the supplement is the paper "*The epidemiology of acute respiratory tract infection in young children: comparison of findings from several developing countries*" by Beatrice Selwyn on behalf of the BOSTID investigator group, reporting a standardized analysis of the epidemiology of ARI in young children from 10 sites.[1]

It is a paper of truly astonishing ambition, combining 16 studies of upper and lower respiratory tract infections in both community- and hospital-based settings. It examines incidence, prevalence, duration, case-fatality and the effects of age, sex and season on the patterns of disease. It describes bacterial and viral etiology and interrogates the clinical signs of respiratory tract infections to define these diseases more accurately. It evaluates risk factors for respiratory tract infections across several sites, including mother's age and education, weight-for-age percentiles, and crowding and smoking in the household. The hospital-based studies alone reported nearly 4000 episodes of ARI and the eight community-based cohort studies each included reports of between 8000 to 93 000 home visits.

The key findings of the analysis were:

1. The incidence of LRTIs varied forty-fold across the sites but the incidence of all respiratory tract infections (upper and lower combined) was remarkably consistent.
2. The incidence and case-fatality of LRTIs were consistently higher among younger children aged < 18 months.
3. The prevalence of ARI symptoms, at any one time, was 22–40%.
4. Viruses caused more episodes of ARI than did bacteria.

Respiratory syncytial virus was the commonest viral cause of LRTIs and *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae* were the commonest bacterial causes. A significant fraction (one-third in one hospital) of all *H. influenzae* infections were nontypeable.

Not all of the insights of the BOSTID research group could be sum-

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marized in a single paper or even a supplement. The programme provided an intellectual forum in which many lines of enquiry were distilled.[2] The complete lack of understanding of how or why children die from pneumonia was identified as a critical future research question. The pathogenesis of ARI, including the complex synergism between viral and bacterial pathogens, was a second significant area. The investigators believed that understanding the mechanisms that controlled the magnitude and selectivity of the human inflammatory response would offer practical opportunities to influence disease outcome. This insight would need to be augmented by knowledge of the modulating effects of nutritional status and immune deficiency. The role of access to health care, and the quality of that care, in the outcome of disease was a third significant area of research that was likely to be fruitful.[2] The list is strikingly similar to an evaluation of the research required to tackle pneumonia today.[4] With the exception of oxygen therapy for severe pneumonia and zinc supplementation to prevent disease, there has been little clinical amelioration of pneumonia through developments in clinical science in 20 years.

The reasons for this apparent neglect probably lie with subsequent advances in public health policy and vaccine development. In 1991, WHO formulated its case-management strategy for pneumonia. The strategy was driven by bacteriological studies, particularly those incorporating lung aspirates, which identified pneumococcus and *H. influenzae* type b (Hib) as the dominant causes of severe and fatal pneumonia. These infections were treatable with cheap and widely available antibiotics. The policy was designed to identify patients with the syndrome of pneumonia at an early stage, often without a doctor's examination, and to initiate treatment with life-saving antibiotics. Studies undertaken around this time indicated that the case-management approach was capable of reducing all-cause mortality in children aged < 5 years by 20–24%.[5] Access to antibiotics has improved generally over the past 15 years but the fact that two million children still die of pneumonia each year suggests that the potential of this policy was never fully realized.

Focus on case management was followed, in the second half of the 1990s, by enthusiasm for new vaccines. A protein-conjugated Hib vaccine was shown to prevent approximately 20% of radiologically confirmed pneumonia in a trial in children in the Gambia. This seeded the idea that Hib vaccine, and possibly the pneumococcal conjugate vaccines that were in development at that time, could be deployed in low-income countries to prevent a significant fraction of the burden of childhood pneumonia. The taxing questions were how to finance and distribute these relatively expensive products in countries with inadequate resources.

The task was taken up by the GAVI Alliance (formerly known as the Global Alliance of Vaccines and Immunization), which has funded Hib vaccine introduction since 2001 and will begin supporting the introduction of the pneumococcal vaccine in a few developing countries in 2008. Experience with Hib vaccine suggests that the introduction process is slow but the fact that it has started challenges us to consider the management of a spectrum of pneumonia pathogens that may no longer be dominated by the easy targets of pneumococcus and Hib.[6]

Over this period the epidemiology and etiology of pneumonia have also evolved, particularly as a consequence of HIV. Unusual pathogens such as *Pneumocystis jiroveci* and cytomegalovirus have a prominent place in the etiology of pneumonia among children with HIV. *Mycobacterium tuberculosis* is a common cause of presentation with pneumonia in areas of high HIV prevalence regardless of HIV status.[7] With advances in molecular diagnostic tools, we have also identified novel pathogens, such as human metapneumovirus and new human coronaviruses, in immunocompetent children with respiratory disease.

The process initiated by the BOSTID studies has therefore developed a new relevance two decades later: interest in pneumonia research is currently being rekindled by both scientists and funders.[8] In her introduction to the BOSTID supplement, Judith Bale reflects: "With all the complexities of ARI, it is unrealistic to search for a 'magic bullet'. Research must include a focus on basic understanding of ARI, particularly the factors leading to severe disease." Given the complexities of the problem, a comprehensive and accurate description of the epidemiology and etiology will once again become the foundation of pneumonia research. As we rebuild a global network of pneumonia research sites, we might ponder how we failed to sustain the investment of the BOSTID initiative. Childhood pneumonia has remained the dominant public health problem in the developing world but we have not cultivated local research capacity in pneumonia.

What can be gleaned from the BOSTID studies to optimize a new pneumonia research network? The paper by Selwyn et al.[1] was prescient, courageous and comprehensive but it also revealed some of the difficulties in creating an integrated global description of respiratory tract infections. The inclusion of upper respiratory tract infection (URTI) affirmed its biological connection with LRTI but also undermined the public health impact of the studies, given the generally benign perception of URTI. Site selection gave preference to underprivileged populations but, because the sites had to be close to competent laboratories (which are rare in low-income countries), the representation of the developing world was uneven. For example, five out of the 12 sites were located in Central and South America. A standardized case-definition is essential for international comparisons but most of the BOSTID investigators amended the standardized definitions, thus producing, in some cases, exceptional incidence results. The failure to obtain lung aspirate material reduced the sensitivity of the study to bacterial causes of pneumonia.

These factors do not detract from what was a Herculean task performed in an era when global networks were uncommon and international communications were challenging. However, the scientific community of today needs to regenerate pneumonia research in developing countries and the first step will be to learn from the difficulties encountered by this pioneering programme. As we take up the task, we are indebted to the BOSTID group for this far-sighted publication. ■

Competing interests: None declared.

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COMPARISONS AMONG COUNTRIES

The Epidemiology of Acute Respiratory Tract Infection in Young Children: Comparison of Findings from Several Developing Countries

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Investigators from 10 countries studied the epidemiology of acute respiratory tract infection (ARI) among children 0–59 months old. Data on incidence rates, by age, gender, and season; on pathogenic agents; on case-fatality rates; and on selected risk factor findings are presented. Incidence rates from six of the community-based studies ranged from 12.7 to 16.8 new episodes of ARI per 100 child-weeks at risk, and rates of lower respiratory tract infection (LRI) ranged from 0.2 to 3.4 new episodes per 100 child-weeks at risk. Children spend from 21.7% to 40.1% of observed weeks with ARI and from 1% to 14.4% of observed weeks with LRI. The incidence rates for ARI are highest in younger children. Viruses, especially respiratory syncytial virus, are isolated more frequently than bacteria from children with episodes of LRI. Risk factors exhibited different patterns of association with ARI in different studies. Interventions could have great impact on high-risk levels common in the study populations. These studies provide interesting and useful data on the epidemiologic dynamics of ARI.

Investigators from 10 countries studied the epidemiology of acute respiratory tract infection (ARI) among young children. The data provided the opportunity to compare the epidemiology of ARI in different developing countries, to explore the commonality of pathogenic agents and risk factors, and to assess differences in findings for clues about the epidemiology of this worldwide killer of young children.

These projects of the Board on Science and Technology for International Development (BOSTID) of the National Research Council used similar case definitions and methods of ascertainment (see Bale [1] for a complete description of the program). The investigators at various sites collected data from children hospitalized with ARI, from those seen in ambulatory care settings, and from those at home within defined populations.

Longitudinal studies of ARI are difficult to carry out. Previously published studies have used dissimilar methods and definitions, which makes comparison of findings difficult [2–5]. Estimates of worldwide incidence rates of ARI based on such data may represent an unclear reality, since the type of ARI measured differs from study to study.

The BOSTID studies overcame many of the most common methodologic problems that hinder comparability. The methods permit comparison of ...

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LRI and smoking, and the patterns differ in direction and strength of association.

When the presence of smokers in the household affects the incidence rate of ARI, the APe is 25.5%–34%. Incidence of LRI remains higher in households without smokers in Uruguay and among young children in Colombia.

Summary and Discussion

The BOSTID projects that studied the epidemiology of ARI in young children included 10 countries, which produced a coordinated set of selected data. Analysis of those data makes up this synthesis.

Summary of Findings

(1) Incidence rates from the BOSTID studies range from 12.7 to 16.8 new episodes of ARI per 100 child-weeks at risk, with one study reporting 27.5 episodes per 100 child-weeks at risk after the inclusion of mild URI, which other studies excluded. Rates of LRI range from 0.2 to 8.1 new episodes per 100 child-weeks at risk. The number of episodes of ARI (whether URI or LRI) depends on the methods used.

(2) Most episodes—whether ARI or LRI—last <2 weeks, although variation in the median duration occurs in some study populations.

(3) Children spent on average from 21.7% to 40.1% of their observed weeks with signs of respiratory tract infection and from <1% to as much as 14.4% of observed weeks with episodes of LRI.

(4) The incidence rates of respiratory tract infection, especially of LRI, are higher in younger than in older children in all studies. Risk factor analysis enhances this finding: in all studies the incidence rates of respiratory tract infection are higher in children <18 months of age no matter what the other characteristics are.

(5) The incidence rates of respiratory tract infection are slightly higher in boys than in girls in all studies.

(6) Study sites vary in the patterns of ARI and LRI over the months of the year. Patterns of LRI do not necessarily coincide with ARI patterns.

(7) Viral agents were recovered more frequently than bacterial agents.

(8) RSV is the virus most frequently identified.

(9) *S. pneumoniae* and *H. influenzae* are the predominant bacteria isolated from children with LRI in all studies.

(10) More cases of LRI are ascertained by auscultation in the home than by screening for symptoms of LRI and referring potentially infected children to a clinic for physical examination. This is important to note when interpreting other studies, and methodologic research needs to be done to verify the finding.

(11) Case-fatality ratios are somewhat higher for girls than for boys even though the incidence rates of disease are higher among boys and boys predominate among both inpatients and outpatients.

(12) The case-fatality ratios are highest among the youngest of children <1 year of age.

(13) The risk factors we examined exhibited dissimilar patterns of association with the incidence rates of respiratory tract infection among the different studies. Risk factors seem to perform differently in some societies and study populations. Generally, these factors are as follows.

Maternal age: the incidence rates of respiratory tract infection tend to be higher among younger children of younger mothers, but young maternal age is not consistently associated with higher incidence rates.

Maternal education: the rates of respiratory tract infection are not necessarily higher among children of less-educated mothers.

Weight-for-age measure: the impact of a low weight-for-age measure appears to be most important among children ⩾18 months of age.

Sharing of sleeping room: as a measure of crowding, this variable has mixed results, mostly showing a lack of positive association.

Smoking in the household: presence of a smoker in the child's household is not regularly associated with increased rates of ARI, although in some study groups there is a positive effect.

Discussion

For all the risk factors, the strength of association with incidence rates of ARI or LRI is modest (indicated by the RR_{adj}). Although the RR_{adj} values are often statistically significant, they usually are closer to 1.0 than to 2.0 (1.0 means there is no association between the risk factor and incidence rates; 2.0 means a doubling of rates between the high- and low-risk levels). Most of the analyzed risk factors relate to socioeconomic status, and in the BOSTID studies the general socioeconomic status of study subjects was more alike than different, which would decrease the RRs. Also, the socioeconomic factors were self-

reported and were remeasured once or twice a year. Since human communities change constantly, random misclassification could have occurred during the study, thereby resulting in a further reduction in the RR.

Even though the RRs are of modest magnitude, the effect that an intervention could have is often large precisely because some of the high-risk levels are common in the study populations (using the attributable proportion as an indicator). More work on risk factors is necessary to determine why they increase the risk of disease: currently, surrogates are being measured for the behaviors, habits, and conditions that enhance transmission of agents or the susceptibility of the child. Although the study populations appear similarly poverty-stricken, there are variations in the incidence rates within those studied, and the reasons for the differences need further elucidation. Furthermore, the duration of illness and percentage of time ill need analysis for associated risk factors. Risk factors for acquiring an ARI (incidence rates) may differ from those associated with large amounts of time spent ill with ARI.

Laboratory techniques need improvement, as outlined by McIntosh [8]. Studies that identify pathogenic agents are difficult to do, yet information about the distribution of agents and the characteristics of the accompanying illnesses would be very useful in attempts at proper treatment or prevention of ARI.

The BOSTID studies used similar and comparable methods so the conditions of ARI recorded in each study were similar. Other published studies, e.g., that by James [9] or the Tecumseh study in the United States [10], used different methods of ascertainment and case definitions, thus making the incidence rates found in those studies not strictly comparable to those in the BOSTID studies. Study methods differ in important ways from those in the BOSTID studies; e.g., two of the most cited studies from the United States [11, 12] used daily diaries reinforced with weekly or biweekly home visits from project staff to detect episodes of ARI. Freij and Wall [13] showed that more frequent notation of episodes produces more cases of ARI than do the once-a-week visits used in the BOSTID studies. Furthermore, both the Cleveland [11] and the Seattle [12] studies included illnesses of simple rhinitis or the sniffles, illnesses excluded by BOSTID. This inclusion results in a further increase in the number of cases identified in the United States studies.

In the study by Black et al. [14] in Bangladesh, children spent 60% of their observed days in the study with signs of ARI, a percentage higher than the maximum of 40% found in the BOSTID studies. Although the signs and symptoms ascertained in Bangladesh were similar to those in the case definition of BOSTID, the methods of ascertainment differ. In Bangladesh home visits occurred every 2 days for collection of data regarding daily signs of ARI. In the BOSTID studies home visits occurred once a week, so that an illness that occurred during the last week could be documented. These are important methodologic differences to keep in mind when comparisons of data on ARI are made.

Further analysis of the incidence and duration of ARI on an individual study basis would be interesting. As suggested by the work of Freij and Wall [13], the incidence rates of ARI might be lower in children with illnesses of long duration, but the time spent being ill may be greater. Another possibility is that, as in the United States, the illnesses of long duration may actually be sequential infections with no intervening asymptomatic period [15], but further investigation of this is needed in developing countries.

Each new episode of respiratory tract infection can be an invitation to more serious disease with potential progression to death, especially in children living in disadvantaged environments, who have lowered resistance to infection. Apparently small differences in incidence rates of ARI can be important, especially between developed and developing countries, since different incidence rates represent different population averages and, perhaps, a different mix of illness. Thus, knowledge of the dynamics of the epidemiology of respiratory tract infections is critical for intervention. Children not only die of respiratory tract infection but also are ill for long periods of time, a burden that affects growth and energy for learning. Prevention of respiratory tract infection is possible but only if we accept that as a desirable goal.

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