Respiratory syncytial virus mortality among young children

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Acute lower respiratory infection (ALRI) continues to be one of the leading causes of morbidity and mortality in children younger than 5 years across the globe.[1] However, significant challenges remain in determining the epidemiology and aetiology of, and risk factors for, ALRI, severe ALRI, and death. These challenges include addressing a number of biases in clinical diagnosis (with variable clinical and radiological definitions of ALRI), microbiological diagnosis (with known insensitivity of bacterial blood culture and nasopharyngeal viral immunofluorescence and culture, and increased sensitivity but reduced specificity by PCR analyses of nasopharyngeal specimens), and case and control ascertainment in the hospital and community.[1–3]

During the past 30 years, several complex multicentre studies have grappled with these challenges to better define the epidemiology and natural history of ALRI among young children in low-income, middle-income, and high-income countries.[1–7] Differing methods of patient ascertainment, changes in laboratory diagnostic methods, and the introduction of conjugate vaccines against *Haemophilus influenzae* type b and *Streptococcus pneumoniae* have made synthesis of the data into global estimates of ALRI mortality difficult. Nevertheless, it is estimated that the most commonly identified viral pathogen in children with ALRI—respiratory syncytial virus (RSV)—causes 33·1 million episodes, 3·2 million hospital admissions, and 59 600 in-hospital deaths annually among children younger than 5 years.[1]

In *The Lancet Global Health*, Nienke Scheltema and colleagues[8] present a novel retrospective case series analysis of RSV-ALRI mortality among hospitalised children younger than 5 years in 23 countries across six continents during 1995–2015. This analysis is notable for both its breadth and coverage across low-income, middle-income, and high-income countries, and for its attempts to recognise, if not counter, biases in variable case ascertainment and microbiological diagnostic methods. The study, termed RSV-GOLD, obtained patient data from both a comprehensive literature search and direct communication with ALRI, pneumonia, and RSV research networks, and then synthesised the data in a customised, online study questionnaire instrument to produce analyses of mortality by income level of country, paediatric comorbidity, and clinical characteristics.[8] The results contribute to the knowledge base of RSV-ALRI mortality among young children, 99% of which occurs in low-income and middle-income countries.

Scheltema and colleagues found that a substantial proportion (70%) of RSV-ALRI in-hospital deaths in high-income countries were in children with medical comorbidities; a smaller proportion of deaths in children in middle-income and low-income countries were also associated with medical comorbid conditions (28%). Children in low-income countries dying with in-hospital RSV-ALRI had a lower median age at death than did those in high-income countries (5·0 months [IQR 2·3–11·0] *vs* 7·0 months [3·6–16·8], respectively). As we move closer to the development of safe and effective RSV vaccines,[9,10] these data again suggest that to effectively prevent RSV-associated mortality in young children, maternal immunisation (with passive transfer of maternal antibodies) will likely be required, perhaps along with additional interventions for children suffering comorbidities.

Scheltema and colleagues note some limitations of their work, which will require further study to refine the characterisation of children dying with RSV-ALRI. First, although their RSV-GOLD study appears to be the largest case series of in-hospital RSV-ALRI young child deaths reported to date, only half or fewer of all paediatric RSV-ALRI deaths globally occur in hospital, and children dying in the community may have different characteristics.[1] The study drew data from 23 countries over a 20 year period, but a few countries contributed proportionally greater amounts of data than did their neighbours on the same continents, potentially leading to biases in the validity of the estimates. More importantly, the introduction of *H influenzae* and *S pneumoniae* conjugate vaccines over time, and the movement away from viral culture and immunofluorescence towards PCR diagnostic methods, likely add to both secular variation in ALRI aetiological attributable fraction and case ascertainment. An incomplete response rate among queried ALRI researchers may also have led to some decreased precision and accuracy of the data.

Despite such limitations, Scheltema and colleagues are to be commended for performing this important first-pass effort in the characterisation of global RSV-ALRI

mortality among hospitalised young children. The approach can be refined as microbiological methods are improved, and case and control ascertainment is stratified. This approach may be relevant for other potentially vaccine-preventable causes of paediatric ALRI as well, such as human parainfluenza viruses.[11,12]

From the initial BOSTID respiratory disease studies of the 1980s,[6,7] through the ongoing analyses by the PERCH,[2,3] GABRIEL,[4] EPIC,[5] and NVSN[13,14] study groups, and now the RSV-GOLD group,[8] a more accurate and precise estimate of the burden of global RSV infection is being formed. The world's children deserve no less.

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