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Elucidating the outpatient burden of RSV disease in children

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Respiratory syncytial virus (RSV) was first identified as a cause of human infection more than six decades ago, after the virus was isolated from respiratory swabs from two children with outpatient illnesses.¹ Studies of RSV in hospitalised children have predominated because RSV is a leading cause of severe lower respiratory tract infection in infants and young children.² In a 2009 landmark paper on RSV burden in children younger than 5 years, Hall and colleagues noted “the total burden of RSV infection during the first 5 years of life remains poorly defined, particularly in the outpatient setting”.³ In their study, Hall and colleagues prospectively surveilled medically attended acute respiratory tract infection via systematic RSV testing in children younger than 5 years in three US counties, and found that RSV was associated with 355 (16·3%) of 2175 and 173 (22·1%) of 784 annual outpatient visits for acute respiratory tract infection in children younger than 5 years and those younger than 1 year, respectively.

Since Hall and colleagues’ study, few prospective studies have further elucidated the outpatient burden of RSV in young children.^{4,5} Estimating this burden is challenging because outpatient clinical testing for RSV is infrequent and inconsistent, given that it is unlikely to change the management of RSV disease. Estimation of outpatient RSV disease burden based on clinical testing alone might be biased if testing occurs more frequently in specific patient subgroups, such as children with underlying medical conditions, or if testing is influenced by the pretest probability of RSV disease based on clinical presentation.

In *The Lancet Respiratory Medicine*, Sarah F Hak and colleagues, on behalf of the RSV ComNet Network, report findings from a large, multiseason, prospective network study of children younger than 5 years who presented with acute respiratory tract infection symptoms in the outpatient setting in five European countries (Belgium, Italy, Spain, the Netherlands, and the UK) during 2021–23.⁶ The Network group aimed to systematically test children presenting for outpatient care at participating sites, and enroll and follow-up the subset of children with RSV. During RSV circulation periods, the authors found that RSV was associated with 25·9% (24·0–27·9; n=513 of 1979) of visits for acute respiratory

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tract infection symptoms in children aged 1 to <5 years, and 38.9% (36.1–41.7; n=466 of 1198) of visits in those younger than 1 year (post-hoc $p<0.0001$). However, between countries, there was an almost 3-times difference in RSV detection rates (ranging from 16.4% [14.3–18.7; 187 of 1138 children] in the UK to 42.6% [39.6–45.6; 459 of 1078] in Italy). Children with RSV followed up after their index outpatient visit up to day 30 had a mean illness duration of 11.7 days (95% CI 11.2–12.2; N=794), and 459 of 810 children (56.7% [95% CI 53.2–60.1]) had at least one additional primary care visit. Strengths of this study include the prospective design, systematic RSV testing, follow-up at two timepoints (day 14 and day 30) after the index outpatient visit to mitigate recall bias about illness duration and resource utilisation, high cohort retention, and several sensitivity analyses to examine potential limitations. However, two key limitations should be considered. Despite describing testing methods as systematic, Hak and colleagues did not collect information about total visits for acute respiratory tract infection symptoms at participating sites, and acknowledge the possibility of selection bias with respect to children tested for RSV that could have affected estimates of the proportion of outpatient visits for acute respiratory tract infection symptoms that were associated with RSV. Additionally, the absence of year-round surveillance precludes estimation of the proportion of overall acute respiratory tract infection burden associated with RSV, which could provide important context for policy decisions.

In 2022–23, two new RSV prevention products became available to protect infants and young children against severe RSV disease: a monoclonal antibody (nirsevimab), and a maternal RSV vaccine (RSVpreF, commercially known as Pfizer's Abrysvo). Although data about severe RSV disease burden is likely to drive initial prevention product policy decisions in many countries, data on outpatient burden and associated resource utilisation and lost productivity can provide complementary information for decision making. Outpatient visits for acute respiratory tract infection can strain health-care systems during surges in respiratory virus circulation. Additionally, visits for acute respiratory tract infection can result in considerable direct and indirect costs; indeed, estimation of outpatient cost has been encouraged for other viral causes of acute respiratory tract infection.⁷ In many of the studied countries, Hak and colleagues documented high rates of additional medical visits, missed parental workdays and child daycare (including preschool and school), and medication use, including antibiotics, inhaled corticosteroids, and bronchodilators, which are not routinely indicated for outpatient RSV management;⁶ their findings related to medication prescribing warrant clinician outreach and education efforts to reduce overuse.

Data such as those presented by Hak and colleagues could inform models of the cost effectiveness of new RSV prevention products if these agents prove effective against mild outpatient RSV disease. To date, it remains unclear what proportion of outpatient RSV disease among infants might be prevented with the new RSV monoclonal antibody and maternal RSV vaccine. Preliminary trials of these products focused on the prevention of RSV-associated lower respiratory tract infection (ie, severe RSV disease),⁸ although emerging data suggest that nirsevimab might effectively prevent some fraction of outpatient RSV illness.^{9–10} Ongoing monitoring of outpatient RSV disease burden will remain important after the introduction of RSV prevention products to examine whether product uptake leads to age, care setting, or other shifts in overall RSV and acute respiratory tract infection burden and associated resource utilisation in young children.

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