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SUPPLEMENT ARTICLE

All Infants Are at Risk of Developing Medically Attended Respiratory Syncytial Virus Lower Respiratory Tract Infection and Deserve Protection

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In the United States, respiratory syncytial virus (RSV) infects two-thirds of infants by the age of 12 months [1] and has been identified as the leading cause of infant hospitalization [2]. RSV is historically seasonal, with cases accumulating rapidly over a few weeks at the start of the winter respiratory disease season [3] and with notable geographic variation in the timing of onset [4, 5]. RSV is not a reportable disease in the United States [6]. However, the US Centers for Disease Control and Prevention (CDC) National Respiratory and Enteric Virus Surveillance System monitors trends in RSV positivity using laboratory data [7, 8] and provided notification of interseasonal circulation during the summer of 2021 [9, 10] after the onset of coronavirus disease 2019 (COVID-19) in early 2020.

No RSV prevention strategy is currently available for all infants, but with several candidates scheduled to complete phase III clinical development in the coming years [11] universal immunization against infant RSV lower respiratory tract infection (LRTI) may soon be feasible. RSV prevention in infants first became possible in the 1990s with the licensure and availability of RSV intravenous immunoglobulin (RespiGam; MedImmune) and then the monoclonal antibody (mAb) palivizumab (Synagis; MedImmune), both administered monthly during the RSV season [12, 13]. Although the CDC Advisory Committee on Immunization Practices has not made a recommendation for the use of palivizumab, the American Academy of Pediatrics Committee on Infectious Diseases recommends a risk-based strategy for the prevention of RSV LRTI in a targeted population of high-risk infants [14]. The limited benefit of palivizumab for the prevention of severe disease in the general population of infants has prevented expansion to the entire infant cohort [14]. However, the substantial burden of RSV disease in infants makes it clear that the adoption of a broad public health aim of reducing RSV LRTI among all infants could have a significant impact on healthcare utilization. To support the upcoming policy discussion, this supplement demonstrates the burden of RSV-associated medically attended LRTIs (RSV MA-LRTIs) in all infants across all healthcare settings.

MORBIDITY: EPIDEMIOLOGY AND BURDEN OF RSV

RSV is recognized as the leading cause of infant hospitalization in the United States based on a study from >20 years ago [2]. In this supplement, Suh et al [15] update and expand on this work and show that acute bronchiolitis due to RSV continues to be the leading cause of infant hospitalization, despite being a seasonal disease. Notably, acute unspecified bronchiolitis ranks as the third leading cause of infant hospitalization and likely includes undiagnosed RSV episodes. Thus, the burden of hospitalized RSV bronchiolitis is underestimated, and the combined total of RSV bronchiolitis and unspecified bronchiolitis reflects an upper limit of the true burden. These results are consistent across chronological age at onset, birth month, race/ethnicity, and Medicaid and private insurance status.

RSV LRTI is widely understood as a seasonal disease that drives infant healthcare visits across all settings. Nevertheless, a systematic literature review of the burden and healthcare utilization associated with infant RSV infections revealed an absence of national emergency department (ED) or outpatient (OP) assessments [16]. When data were available from across settings, RSV testing frequency was higher in the hospital inpatient (IP) setting than in the ED or OP settings [17, 18] and higher among younger patients [19]. This suggests that those tested for RSV are not representative of the overall infant MA-LRTI population. These results support the hypothesis that RSV MA-LRTI burden is underestimated.

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Among the available subnational studies, Movva et al [20] show that the decision to test for RSV varies across and within settings, with only approximately 50% or less of infants seen in an OP setting being tested, except in urgent care clinics where testing is common (84%). Arriola et al [19] showed that viral testing varies by age. Changing trends in testing type have also led to variation in case ascertainment, with polymerase chain reaction (PCR) and, particularly, multiplex PCR becoming more common, although the speed of adoption varies by healthcare system and setting [17–19]. The American Academy of Pediatrics does not recommend routine RSV testing, mostly because pathogen identification generally would not affect clinical care [21].

Furthermore, even when RSV-positive laboratory results are available, they may not be captured in the coding for LRTI and bronchiolitis, thus contributing further to the underestimation of the burden [22]. Arriola et al [19] sought to address this by applying multipliers. Similarly to Suh et al [23], Gantenberg et al [24] and Movva et al [20] have addressed this limitation by reporting both the RSV-specific MA-LRTI and the combined total of RSV bronchiolitis and unspecified bronchiolitis as the lower and upper bounds of burden estimates, respectively.

Using national claims data from 2016 to 2020, Gantenberg et al [24] show that >75% of the RSV MA-LRTI burden during an infant's first RSV season occurred among otherwise healthy term infants, similar to the 72% reported previously for hospitalized infants [19]. Most cases present in the OP setting, consistent with previous reports of subnational data [25, 26]. Notably, a higher incidence of ED visits for RSV MA-LRTI was seen among healthy term infants insured by Medicaid, compared with commercially insured infants, contributing to a substantially higher burden of RSV MA-LRTI among Medicaid-insured infants overall.

Using the most recent nationally representative data from the National (Nationwide) Inpatient Sample and National Emergency Department Sample, Suh et al [23] show that, since a drop in 2014, RSV IP and ED visit rates and burden trended higher through 2019. Across peak months, RSV MA-LRTI can account for up to 27% of infant hospitalizations [15], and in specific age groups RSV LRTI can account for up to 45% of peak month hospitalizations [23]. Average annual hospitalizations for RSV from 2011 through 2019 were 1.7 times those used in the model of the impact of RSV immunization presented by Rainsich et al [27], consistent with the RSV IP burden among infants being underestimated.

Although these overall estimates are useful to understand the impact of RSV, they mask important variations within the infant population [23]. For example, Native American and Alaskan Native infants had the highest rates of RSV IP events but the lowest burden because of small population size. As another example, among infants insured by Medicaid the IP rate was >2 times and the ED rate was approximately 3 times that of commercially insured infants. These higher rates result in the overall burden of RSV IP and ED visits being approximately 2 and 2.5 times higher, respectively, in Medicaid-insured infants, reflecting how the higher rate affects the slightly smaller Medicaid population. Estimating rates and understanding the dynamic of how these rates affect burden in a population are important because they highlight groups that are disproportionately affected and those that drive healthcare utilization, which is key to achieving clinical and public health goals.

MORTALITY

In the United States, RSV-associated infant mortality is not a nationally notifiable outcome, although a case definition has recently been developed to facilitate improved reporting and monitoring [28, 29]. Prill et al [30] indicate that fundamental improvements, such as this, are needed to better define the magnitude of the problem, populations at risk, and impact of future interventions. In their systematic literature review, Bylsma et al [31] detail that most US studies of RSV infant mortality rates capture IP deaths only, lacking data for out-of-hospital deaths. These studies also report that limited data exist for mortality by subgroup such as chronological age, gestational age, comorbid conditions, race/ethnicity, and insurance payer type, all of which have been associated with high risk of disease.

Several recent studies address these issues. Hansen et al undertook an evaluation of excess mortality using 1999–2018 US death certificate data similar to the classic analysis by Thompson et al [32, 33]. They found that RSV accounted for an estimated 96 deaths in infants <12 months old each year, and infant mortality was 5-fold higher for RSV than for influenza over this period.

Additional analysis showed that infants were more likely to die outside the hospital from RSV, bronchiolitis, or influenza compared with all-cause mortality [34]. Out-of-hospital deaths were substantially more prevalent for unspecified bronchiolitis, a portion of which is likely caused by RSV, raising the possibility that out-of-hospital RSV infant mortality is underrecognized.

Reichert et al [35] used linked US birth and death certificates from 1999 to 2018 to assess the association between RSV infant mortality and infant characteristics at birth. They also compared mortality for RSV and influenza and found that the number of RSV deaths and rates of RSV mortality in infants were higher than those for influenza. Importantly, significant portions of RSV and bronchiolitis deaths, 21% and 54% respectively, occurred outside the IP setting. Furthermore, they also report that RSV mortality rates were exceptionally high for Native American and Alaska Native infants.

As expected, the RSV and bronchiolitis mortality rates were highest among the relatively small population of premature infants. However, the mortality burden was highest among full-

term infants, as even a low incidence in this large population would produce a substantial number of deaths. Both the rates and burden of RSV and bronchiolitis infant mortality were higher among Medicaid-insured infants than among infants with commercial insurance, reflecting high incidence in infants with Medicaid. These results highlight, again, the importance of RSV prevention for all infants.

HEALTH ECONOMICS

Systematic literature reviews by Bowser et al [36] and Glaser et al [37] originally focused on an assessment of the cost of RSV-related illness and the burden of this outcome on US infant quality of life, respectively. The small number of resulting citations led to an expansion of the objectives to include systematic analyses.

Using data from Rainisch et al [27], Bowser et al [36] generated nationally representative findings and found that full-term infants were the predominant source of US infant RSV costs and hospitalizations, despite extremely premature infants having the highest mean hospitalization costs per RSV episode. The annual aggregate cost of these hospitalizations for infants aged 0–11 months indicates the high economic burden of RSV MA-LRTI.

Publicly insured infants accounted for half of RSV IP costs, despite representing fewer births and lower costs per episode than commercially insured infants. Public payers (primarily Medicaid) paid less per hospitalization than private payers because of negotiated payment rates. Nevertheless, based on the cost per birth, public payers paid more than private payers, reflecting the higher incidence in this population despite the lower negotiated rates.

Glaser et al [37] found that published data on the quality of life of US children with RSV were scarce and considered only premature hospitalized infants. Their review identified a key observational study that included follow-up data on both infants and caregivers. To disentangle the impact of the RSV episode on quality of life from the impact of prematurity alone, they calculated net quality-adjusted life-years lost that were directly attributable to RSV. Remarkably, the quality-adjusted life-year burden to the child from a hospitalized RSV episode was 67% higher than that from prematurity alone. More work is needed to fill the gap in our knowledge of the impact of an RSV LRTI episode in healthy children who were born at term or in those who present in the ED or OP settings, who represent the vast majority of RSV MA-LRTI cases.

MODELING

Kieffer et al [38] use a static decision analysis model to estimate that, without immunization, 1 in 7 infants have RSV MA-LRTI each year; that is, 47 281 hospitalizations (IP), 129 070 ED visits, and 353 563 OP visits, for a total of 529 915 encounters at an estimated cost of $1.24 billion annually. The authors go on to show that although IP visits accounted for 9% of encounters (24% ED visits; 67% OP visits), these encounters represented 91% of the annual RSV MA-LRTI economic burden, with mechanical ventilation (24%) and intensive care unit admissions (46%) composing 70% of those IP costs. Hospitalizations accounted for <10% of annual infant RSV MA-LRTI healthcare utilization but represented >90% of the annual RSV MA-LRTI economic burden.

Importantly, term infants accounted for most of the burden of RSV MA-LRTI visits in all healthcare settings, with 90% of IP costs and 95% of ED and OP visit costs, annually. By contrast, palivizumab-eligible infants made up 6% of IP visits and 1% of ED and OP visits. Kieffer et al also show that 69% of all RSV MA-LRTI and 47% of IP RSV MA-LRTI occurred among infants born before the start of the season [38].

With 70% immunization coverage for all infants entering into or born during the RSV season, the model estimated a >50% reduction in RSV MA-LRTI healthcare utilization and costs annually. As expected, the vast majority of these averted medical encounters and costs occur among term infants because term infants make up >90% of all encounters. Importantly, infant deaths both in and outside the health system would also be reduced [38]. These results further support the importance of preventing RSV MA-LRTI among all infants.

REIMBURSEMENT PATHWAYS

Among eligible infants, palivizumab is not accessed through a vaccinelike pathway, despite being used for infectious disease prevention. Variability in access reflects the diversity of US insurance plans and coverage, as well as the impact of barriers to access such as prior authorization mandates. If universal immunization were recommended for RSV LRTI prevention among infants, reimbursement would be through an access pathway similar to that of a vaccine. The CDC recently changed the charter of the Advisory Committee on Immunization Practices to clarify the committee's scope, including their review of specific antibody products for prevention of infectious diseases, potentially allowing a mAb to be added to the routine childhood immunization schedule for the first time [39].

Gomez et al [40] assessed the distribution of benefits for a single-dose long-acting mAb for RSV LRTI prevention among infants, via reimbursement pathways similar to those for pharmaceuticals and vaccines. Using the previously published model of RSV immunization impact [27], the authors found that a vaccinelike pathway would improve access for all infants but would have more than twice the benefit for publicly insured compared with commercially insured infants. In particular, a vaccinelike reimbursement pathway that includes Vaccines for Children program support would expand access among infants who are Medicaid eligible, underinsured, uninsured,

American Indian, or Alaska Native [41], all of whom have been identified as associated with high risk and/or being major drivers of RSV LRTI mortality and RSV MA-LRTI morbidity.

CONCLUSIONS

The findings reported in this supplement contribute to our understanding of infant RSV disease in several ways. First, the systematic literature reviews consider currently available reports and highlight how much remains unknown about this important pediatric pathogen, especially for healthy term infants and healthcare visits outside the IP setting. Additional articles in the supplement seek to fill these evidence gaps by reporting the RSV and bronchiolitis burden in all infants across all settings, highlighting that most disease and healthcare costs from RSV are seen in healthy, full-term infants. Publicly insured infants are at higher risk of severe RSV disease and would benefit more than commercially insured infants as a group from new interventions for RSV prevention. Finally, two modeling articles included in this supplement demonstrate that a mAb administered to infants entering their first RSV season can prevent a substantial proportion of infant RSV MA-LRTI, especially for publicly insured infants with coverage through the Vaccines for Children program.

Given the impact of COVID-19 on RSV circulation and disease since 2020, more work is needed to monitor RSV epidemiology going forward. As the work in this supplement shows, the burden of RSV in infants has been historically underestimated. As new interventions are introduced for RSV prevention in infants, an accurate understanding of the burden of disease in this population is critical to measuring the impact of the new prevention strategies, as well as informing the administration timing of a preventative long-acting mAb.

It may soon be programmatically feasible to immunize all infants against RSV LRTI with a single dose of a long-acting mAb to cover the entire RSV season [11]. The administration of a long-acting mAb can be tailored to the start of the RSV season and be provided to infants, regardless of health status, gestational age at birth, or chronological age at the start of the season. With uptake similar to other pediatric vaccines, a mAb would have the greatest effect on burden of disease compared to other passive immunization strategies [27]. Coverage by the Vaccines for Children program would provide equitable access and ensure that the most vulnerable populations are also protected, consistent with the intention and past successes of this program [42].

Notes

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