

**Title: Born to soon and vulnerable: The disproportionate burden of Respiratory Syncytial Virus among Preterm babies in low- and middle-income countries**

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**Abbreviations:** ALRI: Acute Lower Respiratory Infection; HICs: High-income countries; LMICs: Low- and Middle-income countries; RSV: Respiratory Syncytial Virus; GA: gestational age.

## COMMENT

Respiratory Syncytial Virus (RSV)-associated Acute Lower Respiratory Infections (ALRI) are a leading global cause of severe respiratory illness and deaths in infants and children, with a disproportionate burden in low- and middle-income countries (LMICs)<sup>1,2</sup>. They cause overload and saturation of healthcare systems during seasonal outbreaks and extensive economic resource consumption<sup>3</sup>. Preterm infants are particularly at risk and encounter additional hindrances in LMICs due to reduced access to quality prenatal, maternal, and neonatal care, nutritional deficiencies, higher risk of concomitant infections, or a generalized difficulty to handle chronic conditions.

In this issue of *The Lancet*, Wang et al.<sup>4</sup> present a systematic analysis of aggregated data from published studies combined with individual participant data from an investigator network, estimating the global disease burden and risk factors for RSV-associated ALRI during the first two years of life of preterm born children. The literature systematic review covered data (47 published articles and 17 studies from individual participant data collaborators) spanning from January 1995 to December 2021. The analysis was stratified according to gestational age (GA), country income and development status.

Despite declining incidence and hospitalization rates over the past decades, authors estimated an unacceptably high global burden. Indeed, in 2019, the RSV incidence rate among preterm born babies was 1 in 65 million cases (CI 95%: 1 in 35-1 in 99), with 533,000 (385,000-730,000) hospital admissions, and 26,760 (11,190-46,240) deaths (of which only around an 11% were in-hospital). Importantly, such figures were inversely proportional to gestational age, increasing with the degree of prematurity. Preterm babies entailed a quarter of all hospital admissions, and early preterm children (<32 weeks GA) showed higher risk for hospitalisation that persisted until the second year of life, in contrast to other gestational ages. Children with cardiopulmonary underlying diseases presented higher risk for severe outcomes.

Of note, authors estimated that 94% of RSV-associated ALRI episodes, 92% hospitalisations, and 89% of in-hospital deaths disproportionately clustered in LMICs<sup>4</sup>, underscoring the tremendous burden disease gap existing between socioeconomic strata. Previous reports by the same group in this journal already hinted at such disparities, with 95% of RSV-associated ALRI episodes and 97% of deaths across all age bands occurring in LMICs, irrespective of gestational age.<sup>5</sup>

Large studies regarding RSV-attributable burden in LMICs are scarce<sup>6</sup>, and further epidemiological research providing local data is warranted. This is particularly challenging in LMICs because of the scarcity of RSV diagnostic tests, and the existing challenges to accurately determine GA among preterm births. In fact, though methodologically robust, the analyses presented by Wang et al.<sup>4</sup> include comparatively much fewer studies from LMICs and acknowledge the substantial difficulties assessing GA data. In this respect, landmark surveillance efforts such as the ongoing CHAMPS network, studying causes of death in children from seven African and Asian countries using advanced post-mortem methodologies, estimated RSV to account for up to 6 in 5% of all deaths in younger infants, a figure which should be considered as the minimum estimate of the true burden, particularly among community deaths<sup>7</sup>. Other reports showed that 82% of RSV-attributable deaths in LMICs may occur in the community and that the infant case fatality ratio may be as high as 6 in 6%<sup>3</sup>. Despite sparse data, RSV undoubtedly

associates a huge burden of severe disease and death, disproportionately affecting resource-constrained settings. The added challenges that preterm babies present to thrive and survive in the context of the fragile health systems of LMICs, magnify the risk already posed by any infection, but particularly so for RSV, which typically affects those younger and more vulnerable.

The World Health Organization (WHO) has identified RSV-associated ALRI prevention in LMICs as a global health priority<sup>3</sup>. We learned during the COVID-19 pandemic that non-pharmaceutical preventive interventions remain effective but on their own are insufficient to address the global picture<sup>8,9</sup>. In spite of the WHO's recommendations to focus on the development of products with single dose regimens, that can be shipped and stored in warm temperatures, and importantly, with a cost per dose under \$5<sup>10</sup>, the current Research and Development of pharmaceutical products against RSV is still severely biased to their use in HICs<sup>3</sup>. Indeed, several products on the pipeline, including long-acting monoclonal antibodies for neonates, and vaccines for infants and mothers<sup>3</sup>, have demonstrated efficacy and cost-effectiveness to reduce RSV-associated hospitalizations and improve quality of life, but only in HIC<sup>11</sup>. Their current prohibitive costs and associated production and distribution challenges, hinder their potential implementation in LMICs, where they could have more impact and benefit. It is perhaps the moment to explore, similarly to what has been done in the field of antimalarials and antiretrovirals<sup>12</sup>, a tiered pricing strategy that could foster affordability among those most in need but with less resources. Unless the multiple implicated international actors do not promote the integration of affordable products in the public health strategies, preventing RSV-associated morbidity and mortality will be a privilege of the wealthier.

Wang's<sup>4</sup> study provides valuable data in the highly vulnerable but neglected preterm infant population, highlighting the enormous geographical inequities in healthcare assistance. The intrinsic susceptibility conferred by prematurity is exacerbated in settings with restricted access to healthcare, diagnosis, treatment and preventive measures. Although more research providing accurate local data is welcomed, together with better diagnostic tests and economic analysis, the key elements to prevent and minimize the impact of RSV-associated ALRI are well known. Thus, our global efforts should prioritise the wider implementation of public health measures and preventive pharmaceutical programs in LMICs, while simultaneously striving to improve access to, and quality of, their healthcare systems.

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