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## Mucosal nirsevimab levels in respiratory syncytial virus breakthrough bronchiolitis

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mistrust, cultural differences, and misinformation. Involving community leaders, at-risk groups, and survivors is vital. As vaccine campaigns roll out, community engagement will be key to ensuring uptake and controlling the spread of mpox. Prioritising this approach can foster cooperation, reduce stigma, and ultimately improve health outcomes.

The recent upsurge of mpox in Africa was declared a PHEIC by WHO because of the risk of international spread and the need for a coordinated global effort. The recent detection of travel-associated clade I cases in Sweden and Thailand, the first reports outside Africa, is indicative of the potential for clade I mpox to spread from Africa to the rest of the world, reminiscent of the 2022 global clade II outbreak.<sup>15,16</sup> The time for global solidarity and partnership is now.

The views expressed here are those of the authors and do not represent official positions or statements that may be made by their respective organisations, national government agencies, or WHO. DO and ID are the current Chair and Vice Chair of the WHO International Health Regulations Emergency Committee for mpox, and JD is a member of the same committee. KK was previously a member of the WHO mpox technical team from May, 2022, to April, 2024. DM-B and PM declare no competing interests.

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## Mucosal nirsevimab levels in respiratory syncytial virus breakthrough bronchiolitis

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Respiratory syncytial virus (RSV) is responsible for substantial morbidity and mortality in young children (<6 months old), especially during the first infection.<sup>1</sup> Nirsevimab, a monoclonal antibody with Fc modifications and YTE mutations to triple its half-life

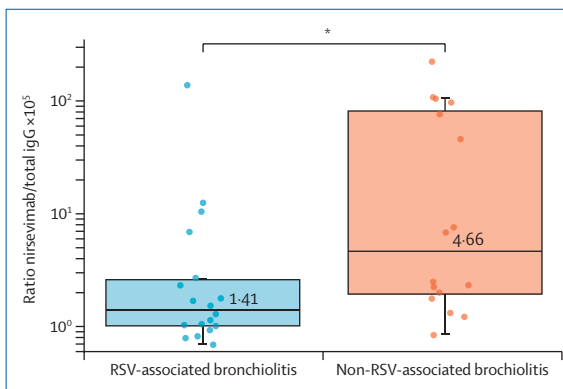
compared with unmodified IgG, targets the metastable prefusion form of the RSV glycoprotein F. Administered intramuscularly, this monoclonal antibody reduces hospitalisation and severe forms of RSV bronchiolitis in infants<sup>2</sup> for approximately 6 months after

administration. During the 2023–24 season, a large portion of newborns in France were immunised and over 200 000 doses were administered to protect the youngest children during their first RSV season. This policy led to a reduction of RSV infections in immunised children.<sup>3</sup> However, failures in protection (10–30%) were observed, with some immunised children still experiencing episodes of RSV bronchiolitis.<sup>2</sup> The reasons for these failures are not comprehensively explained. Pharmacokinetic data are available only in serum samples<sup>4</sup> and levels of nirsevimab are correlated to serum RSV-neutralising antibodies in animal models as well as in humans<sup>5</sup> and the mucosal concentration of the monoclonal antibody has not yet been measured.

We measured nirsevimab levels in respiratory secretions of children with bronchiolitis, associated with RSV or not, during the 2023–2024 season at the University Hospital of Saint-Etienne.<sup>3</sup> Nasopharyngeal aspirates were assessed by a Luminex-based multiplex PCR assay (NxTAG Respiratory Pathogens panel + SARS-CoV-2, Diasorin, Antony, France). 21 children with RSV-associated bronchiolitis and 16 children with bronchiolitis without RSV were included between Nov 21, 2023, and Jan 20, 2024. All children were born full-term and received nirsevimab after birth. Children receiving palivizumab were excluded. The study was approved by the local ethical committee (Terre d’Ethique, no. IRBN1212023/CHUSTE). An information notice was sent to families and validated by the ethics committee. Residual nasopharyngeal aspirate samples were stored at  $-80^{\circ}\text{C}$  and monoclonal antibody levels were analysed using an adapted nirsevimab immunoassay (ProteoGenix, Schiltigheim, France). Levels were normalised based on total IgG.<sup>6</sup> Outliers ( $n=3$ ), which likely occurred due to a technical error, were removed after validation by a local outlier factor.

Both groups were demographically similar, except for gestational week. Hospitalisation rate, time to intensive care unit admission, duration of ventilatory support, oxygen therapy, and time since injection were similar in both groups (appendix p 1). A higher severity (Wang score) was observed in children infected with RSV, as is typically the case.<sup>1</sup> Coinfection was common in the RSV group ( $n=12$ , 57.1%; appendix p 1).

The mucosal nirsevimab levels in the RSV group (median 78.6 ng/mL [IQR 53.6–376.6]) were statistically



**Figure:** Distribution of nirsevimab normalised levels (expressed as ratio against total IgG  $\times 100\,000$ ) in children who developed RSV-associated bronchiolitis versus children who experienced non-RSV-associated bronchiolitis after nirsevimab infusion

Median values are depicted on the box plot: 1.41 (IQR 1.02–2.61) for RSV-associated bronchiolitis group versus 4.66 (1.94–81.63) for non-RSV-associated group,  $p=0.0014$ . The mean value was 10.38 (SD 32.10) for RSV-associated bronchiolitis group versus 42.79 (63.72). As the IgG level was too low and after statistical validation (local outlier factor), three outlier samples were removed from the RSV-associated bronchiolitis group. RSV=respiratory syncytial virus. \* $p<0.05$ .

significantly lower than in the non-RSV group (169.5 ng/mL [125.2–3342.8],  $p=0.008$  [Mann-Whitney test]). Total IgG levels were similar between the groups (mean 23525.30 ng/mL [SD 9260.93] for the non-RSV group vs 20731.48 ng/mL [6378.92] for the RSV group,  $p=0.31$ ). The nirsevimab/total IgG ratio showed a statistically significant difference between both groups (figure, Mann-Whitney test,  $p=0.001$ ). There was no correlation between the mucosal ratio of nirsevimab and the time since immunisation (Pearson Coefficient= $-0.17$ ,  $p=0.32$ ). A multivariate analysis (appendix pp 1–2) including potential influencing factors (time since nirsevimab injection, age at injection, history of bronchiolitis, ratio of nirsevimab/IgG, breastfeeding, and gestational age at birth) identified only the mucosal ratio of nirsevimab/IgG as statistically significantly associated with RSV infection (coefficient  $-1.38$  [95% CI  $-2.663$  to  $-0.101$ ],  $p=0.034$ ).

Nirsevimab is administered intramuscularly and distributed through body fluids to the lower respiratory tract, where it blocks RSV entry through direct viral neutralisation.<sup>4,5</sup> Mucosal RSV-specific IgA is associated with protection in the upper respiratory tract in animal models,<sup>7</sup> low RSV-specific nasal IgA is a risk factor of RSV infection in adults with IgA memory deficiency,<sup>8</sup> and IgA mediates recovery during primary RSV infection in young children (<8 months old).<sup>9</sup> Although nirsevimab

See Online for appendix

is an IgG, the mechanisms of mucosal protection are likely to be similar.

Our results are preliminary and based on a small sample size. Furthermore, we could not measure concurrent serum nirsevimab levels. In a maternal vaccination trial, mucosal IgG levels were more relevant than systemic IgG levels for local protection against RSV,<sup>10</sup> although systemic and mucosal levels are probably related. Importantly, we only have mucosal antibody levels from children with established disease, who have already mounted an immune response. Measurements just before infection or at its start would be valuable, as our current measurement could be biased by the immune response.

In conclusion, this study highlights the crucial role of sufficient mucosal nirsevimab in protecting infants against RSV bronchiolitis. The mechanisms leading to breakthrough infections despite nirsevimab administration remain incompletely understood. Although impaired mucosal antibody transfer is one potential explanation, other factors such as inadvertent underdosing, increased nirsevimab loss due to underlying conditions, rapid degradation of the monoclonal antibody, production of inhibiting anti-drug antibodies, insufficient serum levels, or RSV strains harbouring resistance mutations cannot be excluded. Further research is necessary to elucidate these mechanisms and optimise the effectiveness of nirsevimab in preventing RSV bronchiolitis.

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