



Respiratory syncytial virus after the SARS-CoV-2 pandemic — what next?

Lucy G. Mosscrop¹, Thomas C. Williams² and John S. Tregoning¹  

Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract infection. It is a large contributor to infant hospitalization and also has a substantial burden in older adults (≥ 65 years). The non-pharmaceutical interventions that were introduced to limit the spread of SARS-CoV-2 have had a marked effect on the transmission of RSV, particularly its seasonality. Here, we consider the implications of these changes to RSV transmission for future prevention strategies.

Until 2019, respiratory syncytial virus (RSV) had predictable seasonality in temperate regions, with case numbers peaking in the winter months. However, the non-pharmaceutical interventions (NPIs; such as masking, ‘stay at home’ guidance and social distancing) that were introduced to control the spread of SARS-CoV-2 have had a marked effect on RSV circulation, with a significant reduction in RSV cases in the Northern Hemisphere during the winter of 2020–2021 and an unusual spring–summer wave of infection in 2021. Altered patterns of RSV circulation were also seen in the Southern Hemisphere¹, and the RSV season still seems to be aberrant in the Northern Hemisphere in the spring–summer of 2022. NPIs have affected RSV transmission by increasing the number of children that are naive for RSV and reducing community levels of immunity against RSV². The lack of RSV circulation in the population during the SARS-CoV-2 pandemic might also have resulted in reduced transfer of passive immunity from mothers to their infants.

The differential effect of NPIs on the spread of different respiratory infections can potentially inform us about their modes of transmission and therefore relevant prevention strategies. RSV is not the only pathogen to have reduced in circulation as a result of NPIs; for example, the B/Yamagata lineage of influenza B virus may have become extinct³, and human metapneumovirus and adenovirus have seen shifts in their seasonality. In the UK, RSV transmission was considerably lower than historical norms in the winter of 2020–2021, when nurseries and pre-schools were open but adult activities were more constrained by ‘stay at home’ orders, which suggests that adult-to-child transmission of RSV might have a previously under-looked role. It is not known from where RSV re-seeded populations in each country, but a study from Australia looking at the re-emergence of RSV concluded that cryptic human-to-human transmission of the virus may have had a role¹.

Against this background of changing RSV transmission, the prevention landscape for RSV has also

undergone marked changes in recent years. Two classes of immune-mediated intervention are close to licensure, involving improved prophylaxis by monoclonal antibodies and vaccination.

Passive immunization

The currently licensed prophylaxis for RSV is passive immunization with the humanized mouse monoclonal antibody palivizumab, directed against the RSV fusion (RSV-F) protein, which is administered monthly to high-risk infants throughout the RSV season. Palivizumab prevents approximately 50% of RSV-related hospitalizations in premature children⁴. But it is costly and has to be regularly administered, meaning that it is predominantly used in high-risk children in high-income countries. The recent changes to RSV circulation have important implications for prophylaxis schedules, as the normal season-based administration may no longer align with RSV surges, leaving infants vulnerable to infection. Indeed, in the UK from June 2021 to the end of January 2022, the number of doses of palivizumab was increased from five to seven, and those eligible for prophylaxis could start in July rather than the usual October. With the possibility of further unpredictable changes to RSV seasonality, prophylaxis by monoclonal antibodies will require continual monitoring. This will be particularly pertinent if the age profile of those developing severe RSV infections or who are at high risk of doing so changes.

Other monoclonal antibodies that target RSV-F that are in development include nirsevimab (also known as MEDI8897; developed by AstraZeneca and licensed to Sanofi) and MK-1654 (Merck), which both have a longer half-life than palivizumab. In a phase 3 clinical trial, nirsevimab had 74.5% efficacy against medically attended RSV in healthy and pre-term infants (ClinicaTrials.gov: [NCT03979313](https://clinicaltrials.gov/ct2/show/study/NCT03979313))⁵, and it is expected to undergo regulatory review in 2022. MK-1654 is currently being evaluated in a phase 3 study for infants at increased risk of severe RSV infection (ClinicalTrials.gov: [NCT04938830](https://clinicaltrials.gov/ct2/show/study/NCT04938830)).

¹Department of Infectious Disease, Imperial College London, London, UK.

²Child Life and Health, University of Edinburgh, Edinburgh, UK.

[✉]e-mail: john.tregoning@imperial.ac.uk

<https://doi.org/10.1038/s41577-022-00764-7>

Active immunization

The field of RSV vaccines has finally overcome the legacy of the failed formalin-inactivated vaccine in the 1960s, with much progress being made over the past decade and several vaccine candidates now in clinical trials. Much of this progress came after the determination of the structure of the pre-fusion conformation of RSV-F and the engineering of a stabilized pre-fusion form (pre-F)⁶; indeed, lessons from the engineering of pre-F were crucial for the development of SARS-CoV-2 vaccines.

Subunit vaccines that use recombinant RSV-F are currently in clinical trials. Whereas previous unsuccessful RSV vaccine trials have targeted infants, two target groups have been considered in the current trials — expectant mothers and older adults (≥60 years). The late-phase maternal vaccine trials have been unsuccessful. The phase 3 trial by GlaxoSmithKline of an un-adjuvanted pre-F protein antigen in pregnant women aged 18–49 was voluntarily halted in February 2022, and enrolment and vaccination since then have been stopped owing to safety concerns (ClinicalTrials.gov: [NCT04605159](#), [NCT04980391](#) and [NCT05229068](#)). Another maternal vaccine trial of ResVax (Novavax), an aluminium-adjuvanted, recombinant RSV-F nanoparticle vaccine, failed to meet the primary endpoint of reducing the incidence of medically significant RSV lower respiratory tract infection in infants in the first 90 days of life (ClinicalTrials.gov: [NCT02624947](#))⁷. These two trials were unsuccessful for different reasons, with a safety signal for one and a lack of efficacy for the other, demonstrating the complexity of developing a vaccine for pregnant women specifically to protect the infant.

However, vaccines that target older adults seem to be more promising. The phase 3 trial of a pre-F subunit vaccine, RSVpreF (Pfizer), is currently recruiting in adults ≥60 years (ClinicalTrials.gov: [NCT05035212](#)), with trial completion estimated for June 2024. A recent human challenge study in 18–50 year olds showed significant reduction of viral load and symptoms in those immunized with RSVpreF⁸. Furthermore, GlaxoSmithKline have recently announced significant efficacy for their over-60s vaccine, RSVpreF3 OA (RSV pre-F adjuvanted with AS03).

Surveillance for immune escape

Surveillance for sequence variations in RSV will be important after the introduction of new monoclonal antibodies or vaccines. Both approaches target RSV-F; although the gene that encodes F protein is more genetically stable than the gene that encodes the other surface protein G, RNA viruses can mutate, particularly when under immune selective pressure, as has been seen for SARS-CoV-2. A mutation in RSV-F (K272E) has been detected in children treated with palivizumab, conferring resistance to it and another monoclonal antibody, motavizumab. More worryingly, antibody-resistant mutations of RSV-F have already been documented after nirsevimab prophylaxis, and these affect the binding affinity of the antibody without significantly affecting viral replication⁹. A cautionary tale is that of suptavumab

(also known as REGN2222; Regeneron), which was predicted to have 10-fold more neutralization activity than palivizumab for RSV-A and 5-fold more for RSV-B in vitro. However, in the phase 3 trial, suptavumab was completely ineffective against RSV-B strains owing to a spontaneous mutation in the site to which the antibody binds¹⁰.

The future of RSV prevention

There is likely to be a new monoclonal antibody with a longer half-life available for RSV prophylaxis in the near future, which depending on pricing could enable much wider use. Whether this will reduce cases of RSV disease or delay them into the second year of life is an important question, and the effect on disease severity is unknown. Monitoring RSV sequences will be important to ensure antibodies remain effective against circulating strains, and also following the deployment of a vaccine. Although the failures of the phase 3 trials make further maternal vaccine trials unlikely, the possibility of an effective vaccine for older adults is an exciting prospect. The deployment of such a vaccine and how it impacts disease in infants will be of interest for other respiratory infections. One consideration from SARS-CoV-2 vaccines is the required end state; these vaccines have had a significant effect on disease without necessarily reducing infection. A disease-reducing RSV vaccine would be of considerable benefit. However, returning to the possibility that adult-to-child transmission is important in RSV, a potential strategy could be to immunize adults to protect children, which would require the vaccine to effectively block RSV transmission. The next decade will see considerable changes in RSV control; as we have seen with influenza virus and SARS-CoV-2, respiratory viruses seldom behave as we expect, so close monitoring will be required in parallel with the deployment of new prevention strategies.

1. Eden, J.-S. et al. Off-season RSV epidemics in Australia after easing of COVID-19 restrictions. *Nat. Commun.* **13**, 2884 (2022).
2. Li, Y. et al. Understanding the potential drivers for respiratory syncytial virus rebound during the coronavirus disease 2019 pandemic. *J. Infect. Dis.* **225**, 957–964 (2022).
3. Koutsakos, M., Wheatley, A. K., Laurie, K., Kent, S. J. & Rockman, S. Influenza lineage extinction during the COVID-19 pandemic? *Nat. Rev. Microbiol.* **19**, 741–742 (2021).
4. IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics* **102**, 531–537 (1998).
5. Hammitt, L. L. et al. Nirsevimab for prevention of RSV in healthy late-preterm and term infants. *N. Engl. J. Med.* **386**, 837–846 (2022).
6. McLellan, J. S. et al. Structure-based design of a fusion glycoprotein vaccine for respiratory syncytial virus. *Science* **342**, 592–598 (2013).
7. Madhi, S. A. et al. Respiratory syncytial virus vaccination during pregnancy and effects in infants. *N. Engl. J. Med.* **383**, 426–439 (2020).
8. Schmoele-Thoma, B. et al. Vaccine efficacy in adults in a respiratory syncytial virus challenge study. *N. Engl. J. Med.* **386**, 2377–2386 (2022).
9. Zhu, Q. et al. Prevalence and significance of substitutions in the fusion protein of respiratory syncytial virus resulting in neutralization escape from antibody MEDI8897. *J. Infect. Dis.* **218**, 572–580 (2018).
10. Simões, E. A. F. et al. Suptavumab for the prevention of medically attended respiratory syncytial virus infection in preterm infants. *Clin. Infect. Dis.* **73**, e4400–e4408 (2021).

Competing interests

The authors declare no competing interests.