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# Prevention of respiratory syncytial virus disease by immunisation

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## INTRODUCTION

Respiratory syncytial virus (RSV) is a common respiratory virus consisting of two subgroups: RSV-A and RSV-B. It causes a range of clinical symptoms from asymptomatic infection/mild upper respiratory tract infection through to severe bronchiolitis and pneumonia. RSV bronchiolitis in infants places significant pressure on healthcare services every winter and remains a leading cause of hospital admissions, with an average annual rate of 35.1 per 1000 infants.[1] Moreover, admission rates for viral bronchiolitis of any cause (the majority of which are due to RSV) have risen nearly sevenfold in the last three decades.[2] In infants, RSV accounts for almost double the number of primary care consultations and nearly five times the number of hospital admissions in comparison with influenza.[3] Standard treatment for infants with RSV bronchiolitis is supportive care. Until recently, the only prophylaxis against severe disease has been a short-acting, high-cost monoclonal antibody, palivizumab, limited in the UK to a very small cohort of high-risk infants. Recently, new immunisations have become available against RSV disease in both infants and adults.

There is increasing appreciation RSV is an important cause of respiratory disease in UK adults, estimated to account for half a million primary care episodes, nearly 18 000 hospitalisations and over 8000 deaths annually, with the majority of severe and fatal episodes in adults over 75 years old.[4] There is some suggestion that variation in diagnostic testing of RSV in adults contributes to an underestimation of disease burden, and the true RSV hospitalisation burden in older adults could be more than double what is reported in recent studies.[5]

While severe RSV disease in pregnant women is uncommon,[6] antenatal RSV vaccination can protect the newborn infant via transplacental transfer of mother's antibody, as well as removing mothers from the chain of infection.

This paper will outline the available RSV immunisations and plans for the roll-out of a national immunisation programme in the UK.

### Key messages

- The burden of respiratory syncytial virus (RSV) disease in young children is high and is a leading cause of hospital capacity pressures.
- There are currently five internationally licensed products offering protection against RSV. Two monoclonal antibodies are approved for infants. A maternal (antenatal) vaccine is licensed for infant passive protection, and vaccines are approved for older adults.
- Modelling has found that routine immunisation to prevent infant RSV disease could be cost-effective in the UK. A national immunisation programme has been offered from 12 August 2024 in Scotland and from 1 September 2024 in the rest of the UK in the form of maternal vaccination. There is also a national vaccine programme for older adults.

## RSV IMMUNISATIONS

There are currently five internationally approved products offering protection against severe RSV disease; these consist of both vaccines and monoclonal antibodies. Three of these offer protection to infants from severe RSV bronchiolitis. There are currently no licensed vaccines for administration to infants.

### Licensed products

Monoclonal antibody: palivizumab (Synagis, AstraZeneca)

Palivizumab is a monoclonal antibody providing passive immunity against RSV disease. It targets the RSV fusion (F) protein responsible for the virus fusing

with, and entering, the host cell.[7 8] The F protein exists in two forms, pre-fusion (pre-F) and post-fusion (post-F), with the more recently identified pre-F form being significantly more immunogenic. Palivizumab targets both the pre-F and post-F forms. Palivizumab was first licensed in the 1990s for prophylactic use in high-risk infants to prevent RSV-associated hospitalisations. Palivizumab is given as monthly injections during the RSV season due to its short half life of 18–21 days. It is very expensive but is safe and moderately effective in reducing RSV-associated hospitalisation in very high-risk infants.[9]

#### Monoclonal antibody: nirsevimab (Beyfortus, Sanofi/AstraZeneca)

Nirsevimab is a new long-acting monoclonal antibody providing passive immunity against RSV disease. It inhibits the membrane fusion required for viral entry, by targeting the pre-F protein, thus neutralising the virus. It has an extended half life (65–70 days), giving protection for at least 5 months based on both clinical and pharmacokinetic data. Nirsevimab was licensed in the UK in November 2022 to prevent RSV lower respiratory tract infection (LRTI) in infants during their first RSV season. It is safe and effective in reducing medically attended RSV LRTI and RSV hospitalisation in both term-born and preterm infants.[10 11] Nirsevimab's efficacy against hospitalisation for RSV-associated LRTI was 83.2% (95% CI 67.8% to 92.0%), and 75.7% (95% CI 32.8% to 92%) in very severe RSV-associated LRTI.[12] Nirsevimab is suitable for high-risk children born preterm and/or with serious heart or lung disease.[13] In Galicia, Spain, a universal nirsevimab immunisation programme was introduced to all infants born between September 2023 and March 2024. Early data have shown excellent uptake of nirsevimab with 91.7% coverage, and RSV-related LRTI hospitalisations were reduced by 89.8% (IQR 87.5–90.3) for infants given nirsevimab. The number needed to immunise to avoid one RSV-related LRTI hospitalisation was 25 (IQR 24–32).[14]

#### Maternal and older adult RSV vaccine: Abrysvo (Pfizer pre-F protein vaccine)

Abrysvo is a bivalent RSV vaccine containing two recombinant stabilised prefusion F antigens (presenting RSV-A and RSV-B). The prefusion F protein on the RSV cell membrane is the primary target of neutralising antibodies that block RSV infection. Abrysvo is licensed by the Medicines and Healthcare products Regulatory Agency, the regulatory body in the UK, for pregnant women between 28 and 36 weeks' gestation for passive protection of RSV LRTI in infants via passive transfer of maternal antibodies. It is licensed in Europe by the European Medicines Agency in women between 24 and 36 weeks' gestation and in the USA by the Food and Drug Administration (FDA) between 32 and 36 weeks' gestation. The variation in the gestational age of licensure was due to a small, non-significant difference in preterm births between the vaccinated and placebo groups in the phase III trial, which was only observed in upper middle-income countries, predominantly South Africa. This had no correlation with vaccination timing, and both groups had equal median gestational age at birth and birth weight. While this difference is consistent with a chance finding, different regulators have applied, on a precautionary basis, different gestations, while further evidence accrues from post implementation surveillance. The vaccine efficacy of Abrysvo against severe RSV LRTI in infants was 81.8% (99.5% CI 40.6% to 96.3%) at 90 days after birth and 69.4% (97.58% CI 44.3% to 84.1%) at 180 days after birth.[15] The same product is also licensed for use in adults over 60 years old to protect against RSV LRTI. Vaccine efficacy in the phase III trial was 66.7% (96.66% CI 28.8% to 85.8%) after a mean duration of surveillance of 7 months.[16]

#### Older adult vaccine: Arexvy (GSK adjuvanted pre-F protein vaccine)

Arexvy is licensed for use in adults 60 years of age and older to prevent RSV LRTI. Clinical trials have shown a vaccine efficacy of 82.6% (96.95% CI 57.9% to 94.1%) in preventing RSV-associated LRTI over a median follow-up of 6.7 months following vaccination.[17]

#### Older adult vaccine: mRESVIA (Moderna mRNA-based vaccine)

In May 2024, the US FDA approved an mRNA-based RSV vaccine, targeting the pre-F protein, developed by Moderna for older adults. In the pivotal phase III trial, vaccine efficacy was 83.7% (95.88% CI 66.0% to 92.2%) against RSV-associated LRTI over a median follow-up of 112 days following vaccination.[18]

#### Products in late-stage clinical trials

There is currently one product that is nearing completion of phase III clinical trials for RSV prevention. It is an extended half-life monoclonal antibody (clesrovimab) from Merck/MSD targeting the RSV F protein (both pre-F and post-F). Preliminary results from a phase Ib/IIa trial have shown efficacy of 80.6% against medically attended RSV LRTI (BM Maas, unpublished data). Other products in late-stage development include vaccines that could be used in older infants and toddlers, including a live-attenuated nasal spray (Sanofi), and a maternal indication for Moderna's mRNA vaccine.

## RECOMMENDATIONS

In June 2023, the UK Joint Committee on Vaccination and Immunisation (JCVI) advised there should be a universal programme of RSV infant protection through either immunisation of infants at birth with nirsevimab or vaccination of pregnant women for passive infant protection through transplacental antibody transfer, with no preference for one programme over another. Seasonal immunisation to

protect only those born at higher risk times of the year was also considered, but with a preference for a year-round programme.[19] Following a competitive tender process, a universal maternal year-round RSV vaccination programme with *Abrysvo* for infant protection was introduced in Scotland from 12 August 2024 and the rest of the UK from 1 September 2024. All pregnant women are eligible to receive the vaccine from 28 weeks' gestation until the time of delivery through commissioned services (https://www.gov.uk/government/publications/respiratory-syncytial-virus-rsv-vaccination-programmes-letter).

This population-based approach is likely to have a substantial impact in reducing infant RSV disease, with commensurate reduction in hospital admissions and use of other health services.[20] Population-level approaches in general and in RSV modelling have higher impact on disease than interventions focusing on risk groups and thus are the priority for implementation programmes.

There are considerations for targeted immunisation using a monoclonal antibody to protect high-risk infants and young children who may not be optimally protected or not protected at all by the universal programme. In February 2023, the JCVI recommended the current palivizumab programme be replaced with nirsevimab, if a suitably priced product is available, otherwise the high-risk programme should continue with palivizumab.[21]

An older adult RSV vaccine programme has also been approved which will commence at the same time with the same product (*Abrysvo*). All adults turning 75 years old on or after 1 September 2024 will be eligible for the routine programme, with a one-off catch-up campaign offered for those already 75–79 years old.

This paper has summarised recent advances in RSV immunisation, presenting opportunities for cost-effective prevention, with evidence supporting universal RSV protection programmes. A national immunisation programme in the UK is underway, which will hopefully significantly reduce RSV-related hospitalisations and healthcare utilisation.

## Test your knowledge

1. Which one of the following is an approved extended half-life monoclonal antibody for the protection of infants from RSV disease?
   a. Abrysvo
   b. Arexvy
   c. Nirsevimab
   d. Palivizumab
   e. Ribavirin
2. What is the approximate estimated efficacy of the currently approved maternal vaccine against infant RSV up to 180 days after birth?
   a. 50%
   b. 60%
   c. 70%
   d. 80%
   e. 90%
3. Which immunisation programme has been commissioned for the universal protection of infants from RSV disease in the UK?
   a. Infant seasonal monoclonal antibody programme
   b. Infant year-round monoclonal antibody programme
   c. Maternal seasonal vaccination programme
   d. Maternal year-round vaccination programme
   e. Older adult year-round immunisation programme

*Answers to the quiz are at the end of the references.*

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## Answers to the multiple choice questions

1. c
2. c
3. d