Seasonal immunisation against respiratory syncytial virus disease

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Respiratory syncytial virus (RSV) causes a major burden of disease in children, especially within the first year of life.[1] Although development of promising vaccines is progressing,[2] there is a need to plan the best public health approach for when these become available. The study by Deborah Cromer and colleagues[3] reported in the *Lancet Public Health* examined the cost-effectiveness of immunisation strategies against RSV disease. The investigators combined clinical and laboratory data in a regression analysis to estimate the burden of RSV in children younger than 5 years in England (UK). These estimates were used to compare the cost-effectiveness of different paediatric and maternal immunisation strategies. In line with previous studies,[1] the highest burden occurred in infants younger than 6 months, with a nine-fold higher risk of being admitted to hospital and a two-fold higher risk of needing to visit a general practitioner (GP), compared with children aged between 6 months and 5 years.

Cromer and colleagues' study[3] underscores the need for maternal and newborn immunisation. Their findings suggest that there are advantages to seasonal immunisation for RSV, since epidemics of the disease have a seasonal pattern in countries with temperate climates.[4] According to their modelling study,[3] the most cost-effective option for the UK was to selectively immunise neonates born before the start of the RSV season (peaks of incidence are in December and January), which resulted in a predicted maximum price of £220 (95% uncertainty interval 208–232) per fully protected person. Seasonal active vaccination in infants during the winter months was also suggested to be the most appropriate approach in a previous cost-effectiveness study.[5]

Nevertheless, the concept of seasonal immunisation strategies raises additional questions. Are patterns of RSV seasonality clearly defined worldwide? Which newborn infants are at increased risk of infection based on their birth month in relation to the RSV season? What are the advantages of seasonal active, passive, and maternal immunisation?

Although generally, mid-winter epidemics of RSV tend to occur in temperate zones, seasonality is less pronounced and occasionally absent in tropical and arctic climates.[4] A gap in knowledge of RSV seasonality and infant disease burden in low-income and middle-income countries exists because of the absence of systematic surveillance.[4] In Europe, the highest risk of hospital admissions due to RSV is in infants born between August and February.[6,7] This finding matches the observation that infants younger than 6 months during the RSV season are at an increased risk of being admitted to hospital with RSV.[1] Seasonal immunisation against RSV might therefore be an attractive strategy in these countries.

Palivizumab, administered through monthly intramuscular injections, provides passive immunisation as an effective strategy to prevent RSV-associated admissions to hospital for high-risk patients. Recently, two monoclonal antibodies with extended half-life were developed (REGN2222 and MEDI8897) to decrease the number of injections.[2] MEDI8897 provided a serum concentration of more than 90% of the effective concentration for at least 5 months, suggesting that immunisation with this therapy close to the start of the RSV season might be a viable strategy to prevent severe RSV infections in all infants.[8] With 70% of hospital admissions for RSV occurring between October and January, estimates by Cromer and colleagues[3] suggest that about 20 admissions to hospital per 1000 births in infants younger than 6 months can be averted under the assumption of complete vaccine efficacy of newborn passive immunisation. With an estimated rate of 44 admissions to hospital per 1000 births, simple passive immunisation of newborn infants is estimated to decrease the burden of RSV-related hospital admissions by almost half.

Cromer and colleagues[3] also suggest that a single dose seasonal maternal vaccination strategy against RSV would be cost-effective. However, the advantages of seasonal maternal vaccination versus year-round maternal vaccination are not immediately evident. Currently, available maternal vaccines, including influenza subunit vaccines, provide protection for approximately 2 months after birth.[9] Timing is less of an issue since maternal vaccination before

30–32 weeks gestation results in a good antibody response.[10] Additionally, maternal vaccination will need to protect women with an expected date of delivery from 2 months before the start of the RSV season until well after the end of the season to protect prematurely born children. Since this would imply maternal vaccination almost throughout the year, seasonal vaccination seems to offer little advantage over vaccination of all pregnant women.

Active infant immunisation is another approach to prevent RSV-related morbidity. A downfall of this strategy, however, is that infants younger than 2 months, who have the highest incidence of RSV-related admissions to hospital, generally respond poorly to active vaccination because of the presence of maternal antibodies and immaturity of the adaptive immune system.[11] When administered at 2 months with complete protection assumed until 5 years of age, immunisation prevented 110 GP consultations and five admissions to hospital per 1000 children annually in children aged between 6 months and 5 years according to Cromer and colleagues.[3] Combined maternal vaccination or passive immunisation at birth with subsequent active infant vaccination clearly averts more RSV-related morbidity than any single intervention and merits further attention by vaccine manufacturers.

With prophylactic interventions on the horizon, Cromer and colleagues[3] have made an excellent step in assessing the cost-effectiveness of future immunisation strategies against RSV. This study builds a case for seasonal immunisation, particularly in the case of passive immunisation of newborn infants. Robust country-specific surveillance data for RSV seasonality and incidence of RSV burden per birth month are required to optimise future RSV-immunisation strategies.

*Koos Korsten, *Louis Bont*
Department of Paediatrics, University Medical Center Utrecht, Utrecht, 3508AB, Netherlands (KK, LB)
l.bont@umcutrecht.nl

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