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REVIEW

Respiratory syncytial virus seasonality and its implications on prevention strategies

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ABSTRACT

With maternal and infant vaccines against respiratory syncytial virus (RSV) in development, it is timely to consider how the deployment of these vaccines might vary according to local RSV disease seasonality. In temperate regions RSV infection is predictably limited to a period of 3 to 5 months, while in tropical regions disease seasonality is often both more variable and more prolonged. Accordingly, in tropical regions a year-round immunisation schedule for both maternal and infant immunisation might be appropriate. In contrast, in temperate regions the benefit of year-round maternal immunisation would be heavily dependent on the duration of protection this provided, potentially necessitating a strategy directed at children due to be born in the months immediately prior to the RSV season. This review will consider the impact of seasonality on maternal and infant immunisation strategies against RSV, and the potential of an alternative approach of passive immunisation for all infants immediately prior to the RSV season.

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Introduction

Respiratory Syncytial Virus (RSV) has been recognised as the second most common cause of death in infants from 1 months to 1 year of age and each year is responsible for 34 million new episodes of lower respiratory tract infection (LRTI) worldwide.[1] An estimated 199,000 deaths were caused by RSV in 2005 in children younger than 5 years, 99% of which occurred in low-resource settings. In high income countries such as the UK, the average rate of hospital admissions due to RSV bronchiolitis has increased by an average of 1.8% per year since 2004[2] and RSV bronchiolitis accounts for 12% of PICU admissions.[2] These data highlight the significant health, financial and social impact of RSV in both high- and low-income countries.

Developing interventions to prevent RSV disease has been complex. Not only has the field been working in the shadow of the vaccine-enhanced disease following formalin inactivated vaccine in the 1960's,[3,4] but it is clear that the immune response of the target population (RSV-naïve infants under 6 months of age) differs greatly from older age groups who have had multiple prior RSV exposures, making it difficult to predict vaccine effectiveness from clinical trials in older children and adults.[5] There are 13 candidate RSV vaccines designed to prevent paediatric disease in phase 1 to 3 clinical trials. These have focussed on two, potentially complementary, strategies: maternal immunisation (to provide passive immunisation to infants) and active infant immunisation.[6] In addition, 2 new monoclonal antibodies for passive immunisation against RSV recently entered phase 2 and 3 clinical trials, one of which was stopped prematurely due to lack of efficacy.[7,8,9]

Of relevance to these prevention strategies is that in temperate regions the burden of RSV disease is concentrated in a predictable annual 3 to 5 month season,[10] while in tropical regions RSV season is less predictable and more prolonged,[11,12,13] potentially necessitating region or country specific immunisation strategies. In this paper we will discuss the implications of RSV seasonality on the different preventive strategies currently proposed.

RSV seasonality around the globe

RSV is one of the most contagious human pathogens, with over 80% of children experiencing RSV infections by 2 years of age.[14] Reinfection occurs throughout life and can occur more than once in the same season.[15] RSV seasonality is highly dependent on geographic location and climate. In northern and southern hemisphere temperate regions an annual seasonal pattern is predictably limited to 3–5 months during winter and autumn (Fig. 1).[12,16] Numerous explanations for this have been proposed, including the possibility that inclement climate modifies human behaviour, reducing outdoor activities and increasing indoor crowding enhancing exposure and transmission of RSV,[13,17,18] or that the low temperatures present during winter prolong the stability of RSV in fomites.[19] Other authors have found that low absolute humidity during this season increases the risk of RSV disease,[20] however none of these associations have been proven to be causal. In the tropics, humidity and temperature play a different role than the one observed in temperate regions, with studies in tropical regions suggesting that higher levels of humidity and stable temperatures allows

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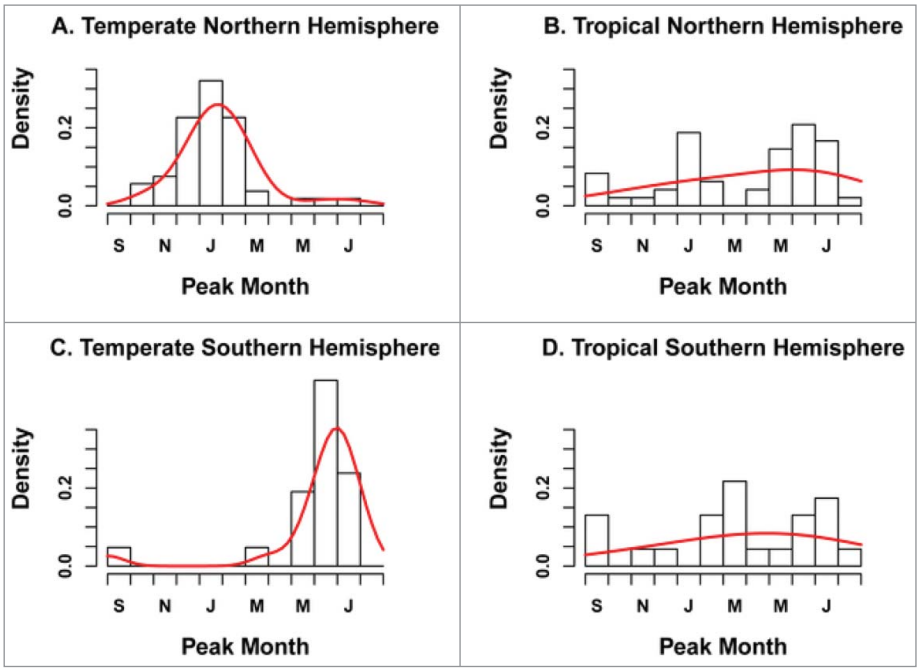

Figure 1. Distribution of RSV peak month by geographic zone (n = 96 locations). The black histogram represents observations while the red curve illustrates the fit of a Gaussian density kernel. Reproduced from: Bloom-Feshbach K, Alonso WJ, Charu V, Tamerius J, Simonsen L, Miller MA, Viboud C. Latitudinal Variations in Seasonal Activity of Influenza and Respiratory Syncytial Virus (RSV): A Global Comparative Review. PLOS ONE 2013;8:e54445.

large aerosol droplets to sustain RSV transmission all year around.[18,21] Nonetheless, the correlations between RSV incidence, temperature and relative humidity are particularly variable and inconsistent amongst the tropical regions[22]; for example one Colombian study demonstrated that RSV cases were distributed throughout the year with different epidemic trends amongst different cities around the country.[23] Interestingly, RSV has been found to be perennially present mostly in coastal areas, islands or along the equator.[24] Regardless of the cause, identifying seasonal patterns is important when planning strategies for prevention such as vaccination.

Maternal immunisation strategies

Inspired by the success of the maternal tetanus elimination program and the influenza and pertussis vaccination strategies,[25,27] manufacturers and policy makers are exploring the potential for maternal vaccination against RSV to significantly reduce the burden of RSV disease. While this approach potentially offers significant benefits over active infant immunisation in terms of protection in the first 2 to 4 months of life, it has a fundamental limitation in that any vaccine-induced protection will subsequently wane. Understanding the nature and duration of this protection will be critical in determining how such a strategy could be best employed, especially in light of the seasonality of RSV infections.

Support for a potentially protective role for trans-placental protection antibodies against RSV was provided by a US study of pregnant women previously experiencing natural RSV infection, demonstrating that higher titers of neutralising maternal antibodies near the onset of illness were correlated with partial protection against RSV severe infection in infants, and high titers at birth delayed the age of first RSV infection.[28] In a Danish cohort a clear temporal association was found between the incidence of RSV hospitalisations in infants younger than 6 months and the mean maternal RSV neutralising antibodies titers in cord blood.[29] In addition, the proven protective effect of passive immunisation via palivizumab,[30,31] a monoclonal antibody targeting a neutralising epitope at the antigenic site A of RSV F protein,[32] provides direct evidence of the protective effect of passively acquired neutralising antibodies; it is in light of this that vaccine-induced antibodies that compete with palivizumab to bind at this site (palivizumab competitive antibodies, PCA) have been adopted as a potential correlate of protection.

At present two phase II trials have evaluated maternal RSV immunisation in pregnant women. Munoz *ET AL*. randomised 35 US women in the third trimester of pregnancy to receive either a vaccine based on purified fusion protein (RSV-PFP-2 subunit) or placebo. The study raised no safety concerns, with no enhanced disease observed in either population.[33] In the second trial investigators randomised 50 pregnant women in their third trimester to receive one dose of an RSV F protein nanoparticle vaccine or placebo. There were no safety concerns in the vaccine group, and no enhanced disease was observed in the infants of vaccinated mothers.[34] Although some concerns have been raised by disappointing efficacy data for RSV prevention in the elderly for a non-adjuvanted version of this vaccine, an ongoing phase 3 efficacy trial will address the efficacy of this vaccine for prevention of infant RSV.[35]

With potentially effective maternal vaccines against RSV in the pipeline, the appropriate timing of any such immunisation campaign needs to be identified. While superficially there would be some similarities with seasonal maternal influenza vaccination campaigns,[36,37] the little data that are available does not suggest a significant burden of RSV disease in

pregnancy.[38,39] On that basis, the overriding objective of maternal RSV vaccination would be protection of the neonate, in contrast to influenza immunisation that aims to protect both mother and infant.

Maternal RSV immunisation in temperate climates

In temperate climates, babies due to be born during, or shortly before, the RSV season could potentially benefit from maternal RSV immunisation, while babies due to be born outside this period are unlikely to do so (Fig. 2). As one example, the United Kingdom has a RSV season which typically starts in late October and has mostly finished by the beginning of March. Accordingly, English children less than 1 year of age with respiratory infections who were born in September to November were more than twice as likely to have RSV detected than those born in December to May.[40] The 'expected due date' is therefore likely to be a key determinant of which babies born in a temperate climate could potentially benefit from maternal immunisation against RSV, but this will also be influenced by the duration of immune protection afforded. Furthermore, the optimal gestational timing for immunisation will influence the nature of any maternal RSV immunisation campaign.

Length of protection offered by naturally induced transplacental antibodies against RSV was explored by Brandenburg *ET AL*., who studied 45 Dutch children with detectable natural maternally derived neutralising antibodies at birth and found that these antibodies decline steadily over the first 3 months of life, with a mean half-life of 26 days; at 6 months of age these antibodies were detectable in only 4.5% of the infants.[41] Ochola ET AL. studied 635 Kenyan mother-child pairs and identified that 97% of infants had RSV specific maternal antibodies at birth, with 50% of the children remaining seropositive at 4–5 months of age, with a mean half-life of 2.5 months.[42] Chu ET AL. in Bangladesh found a strong correlation between the titers of naturally induced RSV neutralising antibodies in the third trimester and those of infant cord blood, with higher cord blood titers being associated with protection against infection. The half-life of neutralizing antibodies in this study was 38 days, and the median time to fall below a proposed correlate of protection of titers $\geq$1:256 was 17 weeks (95% CI: 14 to 20 weeks).[43]

While these studies provide important information about the duration of protection from natural maternal infection, they do not necessarily apply to antibodies induced by maternal immunisation, which aims to surpass naturally induced immunity. In the Munoz study, infants born to vaccine recipients had higher concentrations of anti-F IgG binding antibody to RSV at birth, 2 and 6 months of life than those born to placebo recipients. RSV A and B neutralising antibodies were reported as being higher in infants of vaccine recipients than placebo at 0 and 2 months, although no specific data were provided for this or the statement that the half-life of 'maternal antibodies' in infants was $\geq$3 weeks.[33] In the study of the nano-particle vaccine, the half-life of palivizumab competitive antibodies in the infant was 41 days, with a predicted persistence $\geq$30 μg/mL to 16 weeks; or 14 μg/mL up to 22 weeks.[34] Interpretation of these data remains difficult in the absence of an established correlate of protection and this will potentially be one of the most important outcomes of the ongoing efficacy study.[44] Of possible relevance to this is a recent study of maternal influenza immunisation in South Africa suggesting little infant protection against influenza infections beyond 2 months of age.[45] Regardless, protection from maternal immunisation is unlikely to be an 'all-or-none' phenomenon; whatever impact is achieved will be at its greatest immediately after birth, and waning of efficacy is likely to be a progressive decline from this peak over months, rather than a sudden cessation at a given time.

Accordingly Fig. 2 and 3 display, using a descriptive approach, the likely impact of maternal immunisation on different birth cohorts and in different settings, adjusting for different potential durations of protection. If, like antenatal influenza immunisation, antenatal RSV immunisation provided 2 months of protection, then only babies born in January and February would both receive protection throughout their first RSV season in the UK (Fig. 2A). Babies born earlier than this (e.g. in November), would receive protection during the peak of the RSV season, but become vulnerable at 3 months of age in February, when RSV is still circulating. Babies born in September may receive some benefit in their second month of life (October), but would still become vulnerable during the peak of the RSV season. Babies born in April to August in the UK would receive no benefit from maternal RSV immunisation.

If, however, the vaccine was to provide 4 months protection, then babies born in the UK between October and February would receive protection throughout the peak of their first RSV season (with the greatest potential reduction of disease compared to unimmunised children occurring in those born in October to November) (Fig. 2B). Babies born in June to November may be protected during the early stages of their first RSV season but become susceptible later, while those born in December to February would be protected against the latter stages of the RSV season but have less overall benefit in terms of RSV infections prevented. UK children born after the season from 13th March to June (i.e. approximately 33% of an annual birth cohort) would be unlikely to receive any benefit as they are less likely to have an RSV infection before 4 months of age.

It is worth emphasising that, even though this suggests that only 66% of infants would benefit from a maternal RSV vaccine providing 4 months protection, with sufficient uptake and a highly effective vaccine such an intervention could delay the first RSV infection to the age of 4 months for 41% of the birth cohort (born end of June to November) with babies born in December to February (25% of the birth cohort) having an 8 to 10-month delay to their first RSV infection. Given the age of hospitalisation for RSV infection is skewed towards the first 3 months of life (Fig. 4),[46] with a median age of hospital admission of 120 days[47] this could potentially dramatically reduce hospital admissions for this illness. By contrast, a vaccine providing only 2 months protection would have less of an impact, with the babies born August to January (50% of the birth cohort) still becoming susceptible to circulating RSV at 2 months of age.

Optimal gestational age for immunisation to induce trans-placental antibodies

The UK guidelines for maternal immunisation against pertussis were recently modified to reduce the minimum

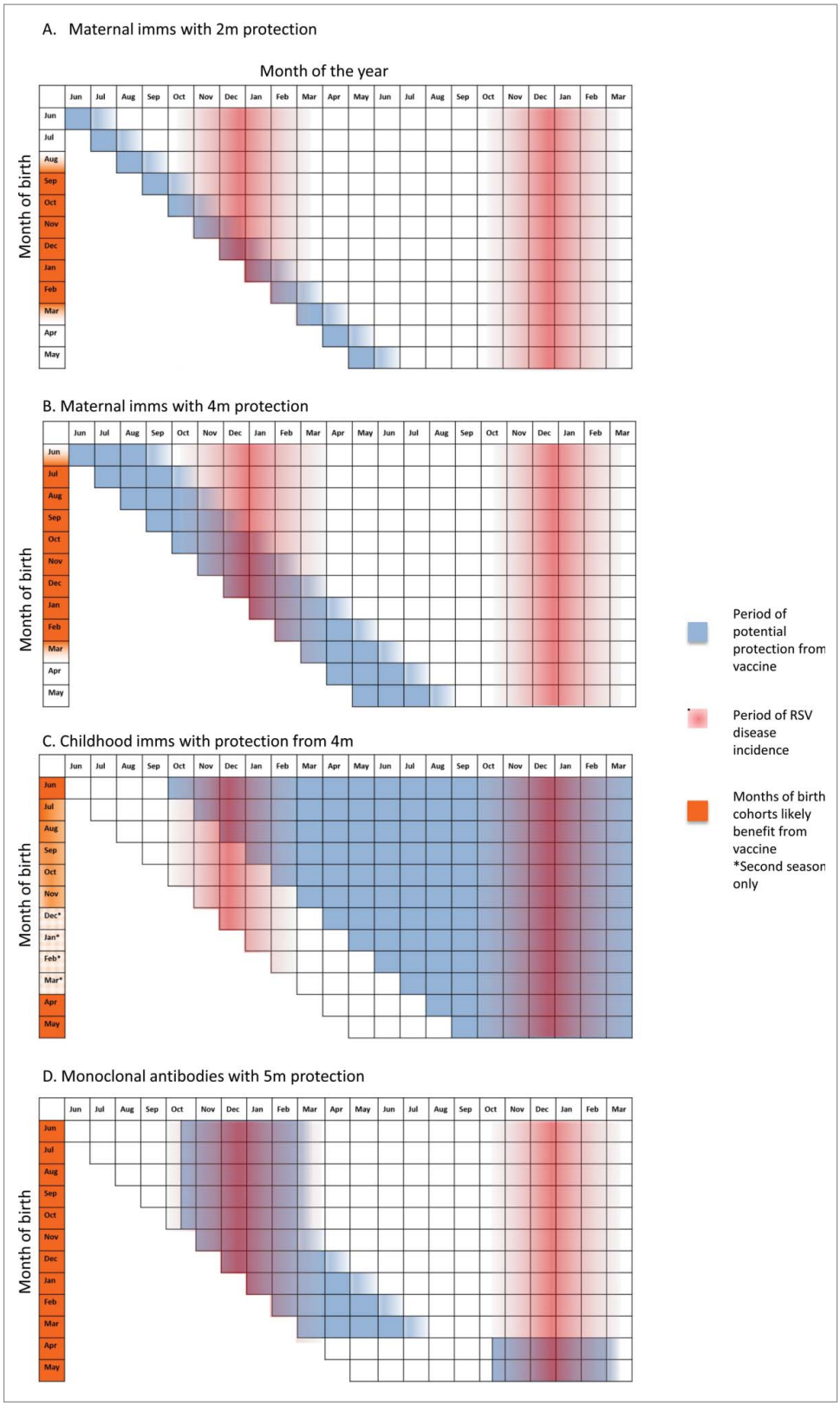

Figure 2. Period of potential protection from RSV infection using different vaccine strategies, using UK as an example of temperate countries assuming RSV season 16th October- 12th March.

gestational age from 26 to 16 weeks in light of observational data suggesting that early second trimester immunisation with tetanus-diphtheria-acellular pertussis vaccine resulted in significantly higher vaccine-induced neonatal antibodies than third trimester immunisations.[48,49] Potentially, an effective antenatal vaccine against RSV could also be given at this early gestational age, but regardless immunisation against RSV would ideally be administered well before 36 weeks gestation to allow sufficient time for the mother's immune system to respond prior to birth.

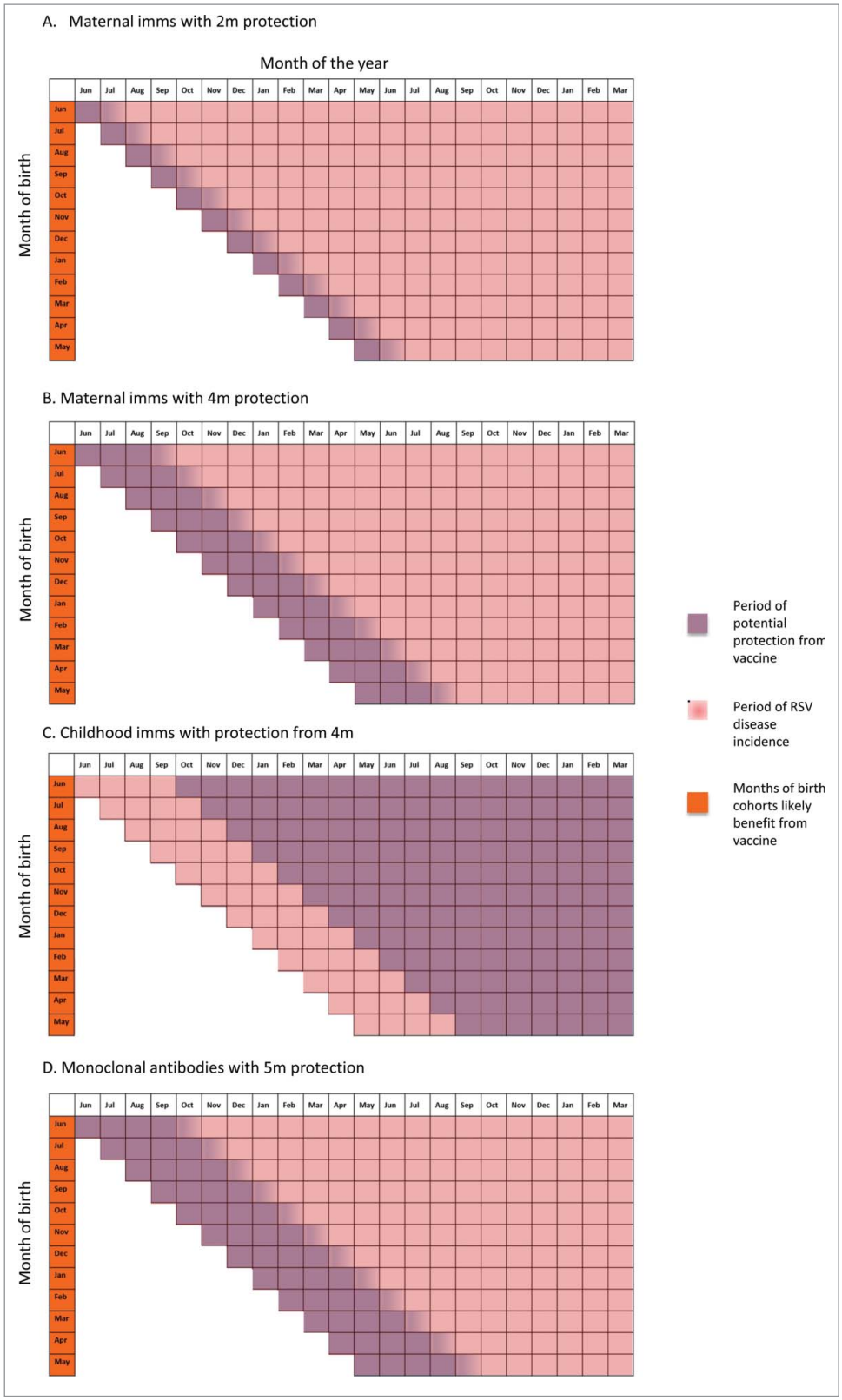

Figure 3. Period of potential protection from RSV infection using different vaccine strategies, tropical countries.

As shown in Fig. 5, a possible gestational window of 16 to 36 weeks suggests an RSV vaccine providing 4 months protection could be administered between January and June to women expecting to deliver in July, and between August and January to women expecting to deliver in February. Alternatively, the campaign could be focussed on the months of April to September, with all 'eligible' women being at an appropriate gestation within this period (i.e.

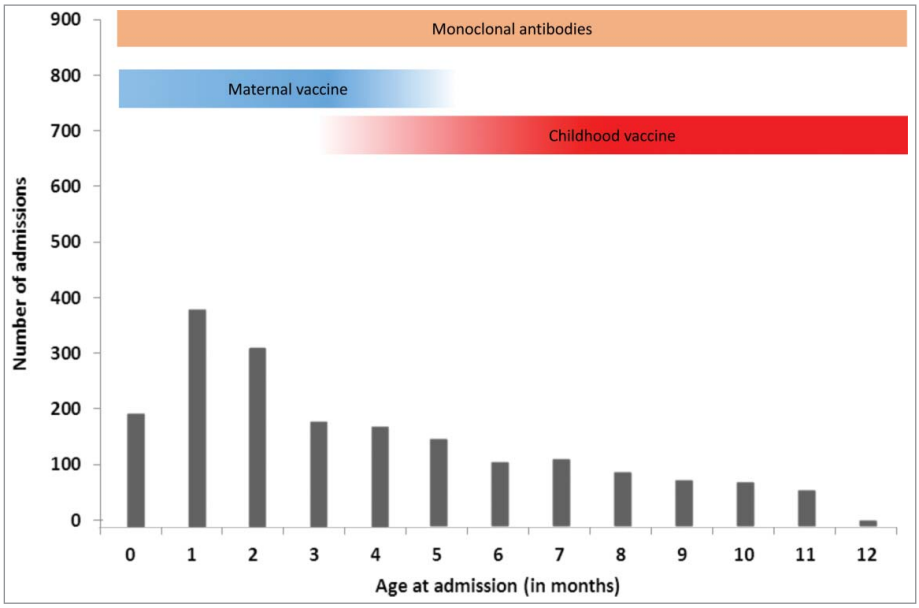

Figure 4. Period of benefit of vaccination strategies on hospital admissions for bronchiolitis in temperate countries (adapted from Parikh ET AL. 2017). Adapted from: Murray J, Bottle A, Sharland M, Modi N, Aylin P, Majeed A, Saxena S, Medicines for Neonates Investigator Group. Risk factors for hospital admission with RSV bronchiolitis in England: a population-based birth cohort study. PloS one. 2014 Feb 26;9(2):e89186.

women with expected due dates in August would be immunised from April, and those with expected due dates in March would be immunised in September).

Antenatal RSV immunisation in a tropical/sub-tropical region

In contrast to temperate climates, in many tropical and sub-tropical areas prolonged RSV seasons have been identified. Taiwan is reported as having a 10 month RSV season,[50] and similarly sustained RSV seasons are reported in Hawaii,[51] Hong Kong,[21] Lombok island, Indonesia,[52] Florida (USA),[53] Singapore,[54] and crowded urban cities such as Dhaka,[55] Bangkok,[56] Benin City,[57] and Kampala.[58] In such regions maximal reduction in the burden of RSV disease could only be achieved by a year-round maternal RSV vaccination program, and even with this all infants are likely to experience ongoing exposure to RSV as their transplacental immunity wanes. Therefore, while a maternal immunisation programme with an effective RSV vaccine is likely to provide protection during the period of greatest vulnerability to severe RSV disease (i.e. the first 2 to 4 months of life),[59,60] in countries with prolonged RSV seasons each monthly cohort will continue to experience RSV infections at the point their transplacental immunity wanes (Fig. 3).

Active immunisation in infants and children

Paediatric RSV vaccine development has been challenging, especially in light of the deaths and increased morbidity due to vaccine-enhanced-disease in seronegative infants receiving a formalin-inactivated RSV (FI-RSV) vaccine in the 1960s. Fortunately this is now an area of great activity, and there are currently seven vaccines being developed for use in infants in phase 1 to 2 clinical trials.[61] Two of these candidate vaccines use viral vectors with genetic inserts coding for RSV antigens.[62,63] Two candidate vaccines use particle-based technology, including an intranasal administration of RSV F protein carried on a bacterium-like-particle, and a folded RSV F nano-protein with aluminium adjuvant.[64,65] Three live- attenuated vaccines, currently being trialled in RSV sero-negative children, contain genetic deletions coding for viral replication and protein downregulation.[66,67] In January 2017, a phase II clinical trial was started of a gene-based vector vaccine against RSV to evaluate safety and immunogenicity in healthy RSV sero-positive children aged 12 to 17 months compared with placebo.[62]

Direct protection afforded by infant immunisation

The early peak of infant RSV disease burden creates an inherent challenge for direct prevention by infant immunisation, given most infant vaccine schedules commence at 6 to 8 weeks and require multiple doses to achieve full effectiveness. In this regard there are parallels with immunisation against pertussis disease, a disease that has also required a maternal immunisation campaign to maintain control in the absence of herd immunity.[25] It is highly likely that an active vaccine would be used year-round as part of a routine schedule. Despite this, some children would remain susceptible during their first RSV season, and during their most vulnerable months of age. For example, a child born in the UK in October and immunised in a 2, 3, 4-month infant schedule (i.e. December, January, February) would remain susceptible during their first RSV season (Fig. 2C) and any benefit would depend on immune protection extending to their second season (with or without a booster dose at 12 months of age). In comparison, a child born in March is likely to receive protection upon their first exposure to RSV from the age of 7 months. While children experiencing RSV disease at 9 to 12 months are less likely to experience severe disease or be hospitalised, preventing

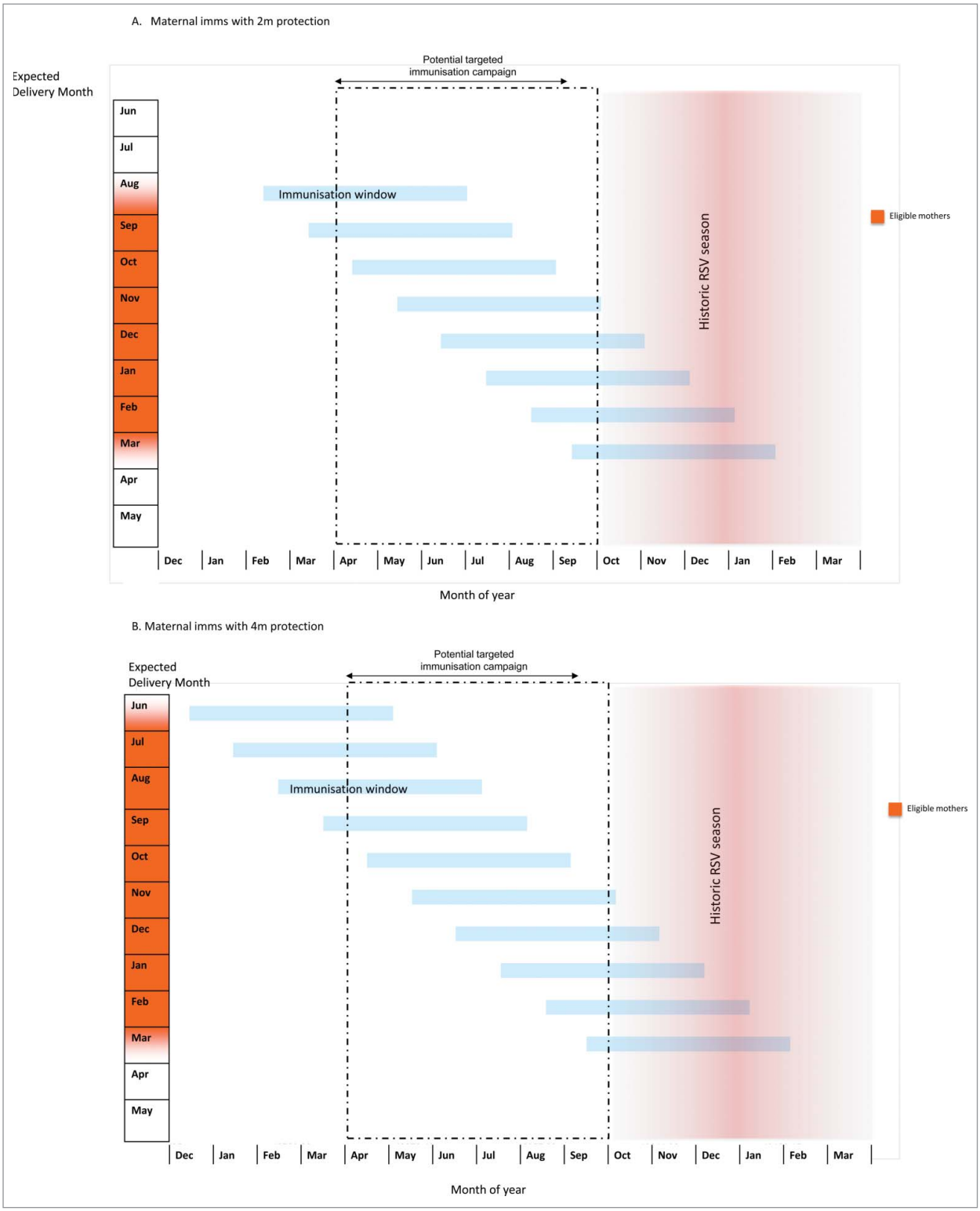

Figure 5. Suggested maternal RSV immunisation strategy by expected due date (EDD) in United Kingdom (Northern temperate climate), assuming (A) 2 and (B) 4-month period of protection from trans-placental antibodies. Assuming RSV season 16th October- 12th March. Dotted box represents potential targeted immunisation campaign for pregnant women between 16 weeks and 36 weeks gestation in the UK.

RSV infection would have other benefits including reduction of subsequent viral induced wheeze.[68]

An alternative approach for temperate countries would be to immunise all children under 1 year shortly before the RSV season (e.g. in August/September in the Northern Hemisphere), similar to influenza vaccines. However, this may be more challenging programmatically. By contrast, in countries with year-round RSV exposure, there would be a benefit to all birth cohorts, but all children born in these areas will still remain susceptible during their first few months of life while they develop protection from multiple dose active immunisation (Fig. 3C). Future data on immunogenicity of the paediatric

RSV vaccines, currently in early clinical trial phases, will better inform the right immunisation strategy to be implemented in each setting.

An important consideration with active infant immunisation is the potential for this to be combined with maternal immunisation. This could achieve the most comprehensive protection from RSV infection during the child's first RSV season, and may be of particular benefit in countries with perennial RSV exposure. One important aspect to consider with such a combined approach is the potential for maternally derived antibodies to interfere with the responses to infant immunisation. This has been observed for maternal immunisation with a combination diphtheria, tetanus, acellular pertussis, polio and *Haemophilus influenza* type B vaccine, which has inhibited infant responses to pertussis, diphtheria and some CRM-conjugated vaccine antigens in the routine infant schedule.[69] Should this be the case, this would further support the argument to limit maternal RSV immunisation to those children expected to be born in an 'at-risk' period.

Herd immunity

In addition to providing direct protection, active paediatric RSV immunisation could potentially provide benefits through reduced circulation of the RSV virus (herd immunity) if long-term immunity is induced. Children under 5 years of age are the group predominantly responsible for transmission,[70] suggesting that by vaccinating this age group it is likely that a reduction in disease in unvaccinated age groups would also be seen. Modelling work by Yamin ET AL. and Poletti *ET AL*. suggest that immunisation strategies to ensure immunity across this age range could reduce RSV burden in infants and adults.[70,71] Future studies using immunogenicity data from phase II and III trials, once available, should inform these models further.

Passive immunisation

Passive immunisation with monoclonal antibody (palivizumab) has been used widely in high risk populations as an effective method to protect such individuals from RSV infection, and this is the only approach to RSV prevention with proven efficacy. A seasonal course of monthly immunisations over five months is the preferred schedule given to high-risk preterms in most temperate climate countries. Two new monoclonal antibodies recently entered clinical trials. In 2015, a phase III clinical trial started comparing a one or two-dose schedule of a monoclonal antibody to placebo in healthy preterm children; unfortunately this has recently been stopped due to lack of efficacy and further development of this product has been halted.[8,9] In 2016, a phase IIb trial started comparing a one –dose monoclonal antibody to placebo in healthy preterm children using altered Fc binding to generate an extended half life.[7] If a single dose of the monoclonal antibody in development at the beginning of RSV season could provide 5 months protection,[72] this could potentially provide the most direct way of preventing the seasonal peak of RSV disease in temperate countries, during the age of highest vulnerability and (depending on cost effectiveness) could be expanded from high risk infants to all children entering their first RSV season.

An effective annual, universal campaign of this nature could render unnecessary maternal and active infant immunisation in temperate climates. However, unlike active infant immunisation it could not provide herd immunity, as children would acquire RSV infections in their second RSV season. In contrast, in tropical regions children would become susceptible from 5 months of age, although this could still protect infants during the age of highest vulnerability. The use of monthly immunisations with palivizumab over a 6 month period to at risk preterm newborns in Taiwan was shown to be effective in reducing RSV related hospitalisations across their prolonged (10 month) RSV season by 86% within 6 months after discharge independently of the time of the year.[50,73] Alternative schedules may need to be applied to cover the different patterns of RSV season. Other areas with perennial RSV season such as coastal areas in the sub/tropical regions face the same dilemma observed in Taiwan.[13] The use of monoclonal antibodies to provide optimal reduction in the burden of RSV disease would require administration to all children within the first few weeks of life. The feasibility of this would, of course be heavily dependent on the cost of this product; which would need to be significantly lower than the estimated average 2016–2017 seasonal cost of palivizumab treatment per child which ranges from $3221 to $12,568, (£2500-£9600; €2725-€ 10625) for this to be affordable.[74]

Conclusion

The benefits of an RSV immunisation programme that selectively immunises children born at the periods of greatest risk for RSV disease are supported by a recent UK cost-effectiveness analysis suggesting that 9 of the 10 most cost-effective strategies focussed disease prevention on babies born in 4 months of the year or fewer.[75] This analysis also emphasised the critical importance of prevention of disease in the first few months of life (whether by monoclonal antibodies or maternal immunisation) to a cost-effective RSV prevention programme, with an incremental direct benefit of active immunisation providing protection from 3 months onwards.

Nevertheless, RSV prevention policy needs to be adapted to the seasonal patterns of RSV, to protect the most vulnerable citizens from severe disease; in tropical regions with longer, more variable RSV seasons a year-round immunisation schedule for both maternal and infant immunisation might be appropriate. It is therefore critical that, in anticipation of the availability of effective maternal or paediatric RSV vaccines, each country obtain accurate epidemiological RSV surveillance data in order to inform future decisions about the most appropriate immunisation schedule for their local circumstances.

Abbreviations

FI-RSV	formalin-inactivated respiratory syncytial virus
LRTI	lower respiratory tract infection
PCA	Palivizumab competitive antibodies
RSV	Respiratory Syncytial Virus
UK	United Kingdom
US/USA	United States of America

Disclosure of potential conflicts of interest

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