

RSV vaccine use- the missing data

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Conflict of Interest statement

AJP has previously conducted clinical trials of RSV vaccines on behalf of Oxford University funded by vaccine manufacturers but he no longer does so and did not receive any personal reimbursement from them. AJP is chair of the Department of Health's (DH) Joint Committee on Vaccination and Immunisation (JCVI) but the reviews expressed herein do not necessarily represent those of DH or JCVI.

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Abstract

Respiratory syncytial virus (RSV) infection is the most important cause of hospitalisation in infants and one of the leading global causes of infant mortality and as such its prevention through vaccination is a public health priority. While essential for the successful implementation of vaccine programmes, there remains a paucity of data on the epidemiology of the virus in different settings and age groups and limited knowledge about virus transmission and the healthcare costs of the disease. Such data are now needed to populate health economic models and to inform optimal approaches to disease control through vaccination.

RSV vaccine use- the missing data

Respiratory syncytial virus (RSV) infection is the most important cause of hospitalisation in infants and one of the leading global causes of infant mortality and as such its prevention through vaccination is a public health priority. RSV results in disease ranging from mild upper respiratory tract infection to severe lower respiratory tract infection (LRTI). The aim of this review is to demonstrate the importance and potential of an RSV vaccine to improve child health and to discuss the data that are needed beyond vaccine development to accelerate the use of such vaccines.

RSV is the single most important vaccine preventable disease without a vaccine programme

RSV infection is the leading cause of hospitalisation of infants in developed countries and places a substantial strain on healthcare infrastructure. In the UK up to 3% of the entire birth cohort is hospitalised each year due to RSV bronchiolitis and up to 8% of all paediatric intensive care unit (PICU) admissions are due to RSV bronchiolitis [1]. Worldwide, RSV pneumonia is the second biggest cause of post-neonatal infant mortality, after malaria, causing an estimated 137,000 deaths/year (6.7% of all deaths in infants) [2]. Outside the hospital setting there are a lack of epidemiological data on the burden of RSV infection. Few studies have investigated the burden of RSV infection in infants and children discharged home from emergency departments or in primary care. No studies have investigated the healthcare burden on ambulance services. As well as affecting the infant, RSV bronchiolitis also impacts the rest of the family. Parents often require time off work to care for the infant and in the more severe cases there is a psychological burden. In addition, recent data from the USA shows that RSV disease burden in elderly adults is

comparable to influenza [3,4]. Clearly an effective RSV vaccine could result in a huge reduction in this burden of disease.

RSV bronchiolitis is also associated with the development of chronic respiratory morbidity with up to 50 percent of infants with severe disease subsequently developing wheezing episodes or asthma [5], though the potential for a vaccine to prevent this morbidity, and therefore to impact on healthcare costs, remains unclear. One recent Dutch study, 'the MAKI trial', has demonstrated that preventing RSV infection in moderately premature infants by using the RSV monoclonal antibody palivizumab, was associated with a 47% relative reduction (10% absolute reduction) in subsequent parental-reported recurrent wheeze [6] but did not investigate associated healthcare utilisation or costs. If an RSV vaccine were to induce a similar reduction in recurrent wheezing there would be a large impact on healthcare costs above the direct benefit of disease prevention.

There are also few data on the associated healthcare costs of RSV infection. Most of the economic analyses for RSV thus far have focussed on the very specific issue of the use of palivizumab, which is only relevant for a small proportion of the infants and children with chronic lung or cardiac disease who are eligible for this intervention due to its high cost. A small UK study prospectively followed a cohort of prematurely born infants, most of whom were ineligible for palivizumab as they did not fulfil the strict UK Department of Health Joint Committee on Vaccination and Immunisation (JCVI) criteria for receiving palivizumab (most infants were born moderately prematurely), and investigated the primary and secondary care costs after neonatal or maternity unit discharge. It was demonstrated that infants who developed RSV lower respiratory tract infections (LRTIs) had a significantly higher mean [SD] healthcare cost over the first year of life compared with those infants who did not develop LRTIs

(£4816 [9268] versus £1531 [3649]) [7]. Similar data for term born infants, the majority of infants with RSV bronchiolitis, are not available.

Treating and preventing RSV disease

There are currently no specific treatments for RSV bronchiolitis and the management of infants is purely supportive (oxygen supplementation and feeding support). There are, however, early clinical trials of several new antiviral medications underway including in infants [8]. RSV monoclonal antibodies including palivizumab and motavizumab are available as prophylaxis against severe RSV infection, however, they are currently only used in a tiny proportion of infants. RSV vaccine candidates have been in clinical evaluation for nearly 50 years without any reaching licensure. There are currently over 50 active vaccine development programmes at various stages of development. As of August 2015 twelve of these were in clinical evaluation and one Phase 3 clinical trial immunising pregnant women is due to start in 2016 [9,10]. Potential vaccine strategies for protecting infants against RSV infection include infant vaccination, maternal vaccination and vaccinating contacts of infants to block transmission. There are potential problems with each of these strategies. Although several different vaccine candidates have been developed since [11] clinical experience with the formalin-inactivated RSV (FI-RSV) vaccine candidate in the 1960s, which potentiated subsequent natural infection [12], continues to cast a shadow on the development of RSV vaccines for use in infants. Fears of a recurrence of the FI-RSV vaccine phenomenon in modern non-replicating paediatric vaccines, and the early age of disease onset, have favoured the exploration of maternal immunisation strategies, with the aim of providing indirect protection to the infant by boosting the levels of transplacental antibody [13]. How long the infant will remain protected after maternal immunisation, however, is unclear. The median age of hospitalisation for infants with RSV bronchiolitis is approximately three months old

[14] when maternal antibody has already significantly waned [15], but the peak of hospitalisation (modal age) occurs in infants at one month of age [14], despite higher levels of maternal antibody being present at this age than at any other time later in infancy [15]. In addition, geographical variation in factors that influence the efficiency of transplacental antibody transfer (e.g. maternal diseases such as placental malaria) may result in geographic differences in vaccine efficacy. Clearly more data are needed to quantify the effect of such factors on the success of maternal immunisation strategies. Despite these concerns, the results of a recent phase 2 clinical trial in women of childbearing age to whom an F protein subunit vaccine was administered provides some grounds for optimism. Vaccination resulted in the potent induction of both neutralising and palivizumab-competing antibody as well as a significant reduction in RSV infections [16]. Vaccinating siblings, parents and/or other contacts of infants requires detailed knowledge of the transmission dynamics of RSV infection which are not yet well understood (see below) as well as the ethical considerations that arise when vaccinating people who may receive minimal benefit themselves from the vaccine.

Transmission of RSV infection

The success of any vaccination strategy against RSV is inextricably linked to the transmission characteristics of the virus. Understanding the chains of virus transmission within epidemiological microenvironments, such as the family, is central to developing transmission blocking vaccines. Recent studies conducted in rural Africa have shown the critical role of household contacts such as parents and siblings in transmitting the virus to the infant [17,18]. These studies highlight the potential for providing indirect protection to the infant by vaccinating household contacts in order to interrupt the chain of virus transmission to the infant. Unfortunately, these results are yet to be confirmed in alternative geographical and

social contexts where differences in social structure and contact patterns may suggest alternative models of transmission. Further studies of household transmission in different geographical/social contexts are therefore urgently needed in order to identify the optimal strategies that both directly protect vulnerable infants and reduce transmission to maximise programme benefit. These data are also critical for inclusion into cost-effectiveness models.

Cost –effectiveness analysis

Prior to any vaccine being widely used, once safety and efficacy have been demonstrated, data on cost-effectiveness are needed. Most countries require a health economic model incorporating appropriate regional data to be developed so that cost-effectiveness can be formally considered in the deliberations about use of a potentially effective vaccine. An accurate assessment of the overall healthcare burden, associated costs, potential sequelae and transmission data are required for an accurate model. However, much of these data for RSV are unknown. Despite the importance of RSV infection and the likelihood of a vaccine becoming available for widespread use in the next few years, few countries have developed cost-effectiveness models for an RSV vaccine. One study from the USA and another from the Netherlands have demonstrated an infant RSV vaccine may be cost-effective but did not look at other vaccine strategies [19,20]. The recent progress in vaccine development for RSV must now be matched by research on the burden, transmission and cost of RSV infection, and the development of health economic models, to underpin policy decisions so that there is a future in which all vulnerable infants and older adults can be protected from RSV disease.

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