Seminars in Immunology 25 (2013) 160–171

Contents lists available at SciVerse ScienceDirect

Seminars in Immunology

journal homepage: www.elsevier.com/locate/ysmim

Review

Respiratory syncytial virus vaccine development

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ARTICLE INFO

Keywords:
Respiratory syncytial virus
Vaccines

ABSTRACT

The importance of RSV as a respiratory pathogen in young children made it a priority for vaccine development shortly after it was discovered. Unfortunately, after over 50 years of vaccine development no vaccine has yet been licensed and it is not certain which if any vaccines being developed will be successful. The first candidate vaccine, a formalin inactivated RSV vaccine (FI-RSV), was tested in children in the 1960s and predisposed young recipients to more serious disease with later natural infection. The ongoing challenges in developing RSV vaccines are balanced by advances in our understanding of the virus, the host immune response to vaccines and infection, and pathogenesis of disease. It seems likely that with efficient and appropriately focused effort a safe and effective vaccine is within reach. There are at least 4 different target populations for an RSV vaccine, i.e. the RSV naïve young infant, the RSV naïve infant >4–6 months of age, pregnant women, and elderly adults. Each target population has different issues related to vaccine development. Numerous vaccines from live attenuated RSV to virus like particle vaccines have been developed and evaluated in animals. Very few vaccines have been studied in humans and studies in humans are needed to determine which vaccines are worth moving toward licensure. Some changes in the approach may improve the efficiency of evaluating candidate vaccines. The complexity of the challenges for developing RSV vaccines suggests that collaboration among academic, government, and funding institutions and industry is needed to most efficiently achieve an RSV vaccine.

1. Introduction

In 1955, Morris et al. isolated a virus from Chimpanzees, chimpanzee coriza agent [1], and shortly thereafter a similar virus was isolated from young children and designated respiratory syncytial virus (RSV) [2,3]. The importance of this virus as a cause of acute respiratory illness in young children was quickly recognized and efforts to develop an RSV vaccine began. RSV infections are usually symptomatic and in the young child cause the full spectrum of acute respiratory illnesses including a common cold-like illness, croup, bronchitis, bronchiolitis, and pneumonia [4]. Bronchiolitis, i.e. a lower respiratory tract illness with wheezing, is the signature RSV illness in infants and young children. The virus spreads efficiently and is estimated that 50% of children become infected during their first year of life and nearly 100% by 2 years of age [5]. Since infection provides limited protective immunity, repeat infections and disease occur throughout life. Infants <6 months of age, persons of any age with compromised cardiac, pulmonary and immune systems, and the elderly are especially susceptible to more serious complications with infection [6,7]. RSV is considered the single most important cause of serious acute respiratory illness in infants and young children world-wide causing an estimated 66,000 to over 200,000 deaths and 3.4 million hospitalizations in children <5 years of age each year [8,9]. In the United States, it is estimated that between 57,000 and 175,000 children <5 years of age are hospitalized each year with RSV [10,11,12]. It is also estimated that RSV is associated with over 500,000 emergency room visits [10] but <500 deaths in children <5 years of age each year in the United States. It also causes substantial disease in elderly persons resulting in an estimated 177,000 hospitalizations and between 10,000 and 15,000 deaths each year in the United States [13–15]. In temperate climates, most illness occurs in yearly outbreaks in the late fall, winter, and early spring months, e.g. October to April in the northern hemisphere and April to September in the southern hemisphere [16–18]. Outbreaks often last from 4 to 5 months in a community.

Another potential outcome of RSV infection in the infant is later development of reactive airway disease. Multiple studies have shown that children hospitalized with RSV have a substantially increased risk of having reactive airway or asthma through adolescence [19–22]. What is still unclear, however, if this occurs because children likely to develop reactive airway disease are also more likely to be hospitalized with RSV and the RSV infection is not causally related to the later reactive airway disease or because

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http://dx.doi.org/10.1016/j.smim.2013.04.011

infection alters the architecture of the airways or patterns for future immune responses associated with reactive airway disease.

The importance of RSV as a respiratory pathogen in young children made it a priority for vaccine development shortly after it was discovered. Unfortunately, after over 50 years of vaccine development no vaccine has yet been licensed and it is not certain which if any vaccines being developed will be successful. The first candidate vaccine, a formalin inactivated RSV vaccine (FI-RSV), was tested in children in the 1960s and predisposed young recipients to more serious disease with later natural infection [23–26]. Older children who likely had been previously infected with RSV did not suffer this enhanced disease. It appears that prior infection patterned for a safe immune response to the vaccine and prevented development of enhanced disease. A study in mice showed prior live virus infection prevented enhanced disease in mice later vaccinated with FI-RSV vaccine and challenged with RSV [27]. The experience with FI-RSV continues to effect vaccine development. Because of the FI-RSV trial, only attenuated live RSV or RSV proteins expressed in a live virus vector have, so far, been considered safe for testing in RSV naïve children. Unfortunately, no live attenuated RSV or live virus vectored vaccine has yet been licensed. Since older, RSV primed children are not considered at risk for enhanced disease, a variety of other types of vaccines including purified proteins, virus-like particles (VLPs), nanoparticles, and DNA or vectors expressing RSV proteins are being developed for older children and adults. The efficacy of RSV immune prophylaxis first with polyclonal immune globulin [28] and then a neutralizing, anti-F protein monoclonal antibody shows [29] that an effective RSV vaccine should be achievable.

The ongoing challenges in developing RSV vaccines are balanced by advances in our understanding of the virus, the host immune response to vaccines and infection, and pathogenesis of disease. It seems likely that with efficient and appropriately focused effort a safe and effective vaccine is within reach. A number of recent reviews provide excellent discussions of many aspects of RSV and development of RSV vaccines [30–32]. In this chapter, I will highlight some less frequently considered strategies that, I believe, may facilitate the quest for an RSV vaccine.

2. Target populations

Our understanding of the epidemiology and burden of RSV disease now suggests that there are at least 4 potential target populations for a vaccine, the young infant, infants >4–6 months of age, pregnant women, and the elderly. Each of these target populations presents different challenges for vaccine development. The young infant is the target population with the greatest potential benefit from an RSV vaccine. However, the young infant has an immature immune system and residual maternal antibody that may prevent induction of a good immune response to a vaccine [33]. The young infant is also especially susceptible to disease with infection and may require a more attenuated live virus vaccine than an older child. Finally, the young, RSV naïve infant is at risk for enhanced disease and live RSV or live viruses as vectors for RSV proteins have been the only candidate vaccines tested in this age group. Vaccinating infants $\geq$4–6 months of age, will prevent less disease but still sufficient disease ($\sim$40% of hospitalizations in children <5 years of age occur after 6 months of age) to warrant vaccination [10,11]. These older children have a more mature immune system, less maternal antibody, and should respond better to vaccines. They also are less susceptible to severe complications with infection. A substantial portion of these children will be RSV naïve and at risk for vaccine induced enhanced disease and similar to the younger infant only live, attenuated RSV or live virus vectors for RSV proteins have been seriously considered for these children. Pregnant women are another potential target population. Since high titer maternal antibody provides some protection from RSV disease, it is likely that boosting levels of these antibodies through maternal immunization will provide protection to the infants during their first few months of life when they are greatest risk from RSV infection. The pregnant women has a mature immune system that should respond well to appropriately designed vaccines and is not at risk for vaccine induced enhanced disease but will require boosting immunity in the face of multiple earlier infections and raises real or perceived concerns of the risk of vaccination to the fetus. The potential benefits of delaying risk of infection until an older age when the infant is better able to handle infection or can be vaccinated has encouraged some groups to pursue this strategy. The elderly have substantial disease with RSV infection and would benefit from a safe and effective vaccine. Inducing an effective immune response in this multiply primed age group in the face of immune senescence may be difficult [34,35].

3. Strategies for developing RSV vaccines

Developing an RSV vaccine continues to challenge researchers. Some of these challenges are not surprising giving the clinical and epidemiologic features of the disease. As noted above, the need to vaccinate the very young infant to achieve maximal impact of a vaccine presents the challenge of inducing effective responses in infant's who have an immature immune system and residual maternal antibody and safety of a live virus vaccine in children especially vulnerable to RSV disease. The fact that people get infected repeatedly throughout life portends the challenge in inducing a durable protective immune response with a vaccine. It is also likely that virus induced host immune responses contribute to disease and these responses may need to be accounted for to achieve in a vaccine, e.g. be avoided during vaccination to improve safety. It is also possible that a vaccine will benefit from inducing responses that prevent later infection from inducing these responses. The enhanced disease after FI-RSV vaccine illustrated the risk that vaccine induced immunity could contribute to disease and the need to consider this risk especially for the RSV naïve child. An incomplete understanding of safe and protective immune responses and how to apply findings from animal models and in vitro studies to RSV infection in humans makes it difficult to determine which candidate vaccines are likely to be successful without expensive clinical trials. Finally, past difficulties in achieving an RSV vaccine may hinder investment in new candidate vaccines. There are many vaccines being developed or considered for development as illustrated by the PATH web site "RSV Vaccine Snapshot" (http://sites.path.org/vaccinedevelopment/files/2012/12/RSV_vaccine_landscape_snapshot.pdf).

Appropriately so, the primary goals for an RSV vaccine have been safety at the time of vaccination and induction of an immune response that is safe during later natural infection and highly effective at blocking viral replication. Other aspects of virus infection may also be worth including as goals for a vaccine including preventing virus associated immune suppression and virus induced host responses that contribute to disease. There have been two distinct approaches, one for the RSV naïve infant and one for RSV primed older children and adults. For the RSV naïve infant, live attenuated RSV and other viruses as vectors to express RSV genes are being actively developed. The challenge for development of live attenuated RSV vaccines has been achieving a level of attenuation that is both safe and immunogenic. The challenge for virus vector vaccines has been to induce highly effective protective immunity usually indicated by neutralizing antibodies. Most virus vector vaccines have expressed F to induce a protective immune response. Some have been developed that express G, N, and M2. For RSV