The status of RSV vaccines: an update

George Karatsais, Maria Exindari, Georgia Gioula, Maria Christoforidou, Angeliki Melidou
Microbiology Laboratory, Medical School, Aristotle University of Thessaloniki, 541 24 Thessaloniki, Greece

Summary

Respiratory syncytial virus (RSV) is one of the most important causes of viral lower respiratory tract illness in infants and children globally. It often causes severe and even fatal infections, particularly in children aged under 6 months, and RSV is considered responsible for one-third of deaths resulting from acute lower respiratory infection (ALRI) in the first year of life. There is no vaccine currently available to protect from RSV infection, especially the severely affected risk groups. Immunoprophylaxis with the neutralizing monoclonal antibody, palivizumab, is used to prevent RSV disease in very premature infants and high risk individuals. Live-attenuated vaccine approaches have been in development for the past decades, but to achieve immunogenicity, their safety was compromised in the past. In recent years, several RSV vaccine candidates using various technologies and targeting different populations and age-groups have emerged. In the present review, the current status of RSV vaccine development is presented. Sixty RSV vaccine candidates are in development, targeting the whole range of age-groups, of which 16 vaccine candidates are currently in clinical development, while most are at a preclinical stage.

Key words
Respiratory Syncytial Virus, RSV, palivizumab, vaccine, LAV

Corresponding author
George Karatsais,
Panepistimioupolis,
Microbiology Laboratory , Medical School,
Aristotle University of Thessaloniki,
54124, Thessaloniki, Greece
email: karatsais@gmail.com

1. Introduction

Respiratory syncytial virus (RSV) is one of the most important causes of viral lower respiratory tract illness in infants and children globally. It often causes severe and even fatal infections, particularly in children aged under 6 months, and RSV is considered responsible for one-third of deaths resulting from acute lower respiratory infection (ALRI) in the first year of life.[1] However, the overall burden of RSV disease is underestimated, especially in older age-groups. Recent studies have shown that the morbidity and mortality associated with RSV in the elderly and high-risk individuals is also substantial.[1]

1.1. RSV epidemiology and burden of disease

RSV, which is transmitted by direct and indirect contact with oral or nasal secretions, may cause repeating infections throughout life and significant disease in various age-groups, mostly in paediatric and elderly populations.[2,3] For most infants and young children, the infection is restricted to the upper respiratory tract. For a small percentage, infection with RSV can lead to bronchiolitis, inflammation of the small airways of the lungs, or pneumonia, severe conditions that may become fatal. During the early stages of the disease, occurs a peribronchiolar inflammation with lymphocytes. During the progression of the disease, the inflammation progresses to the characteristic necrosis of the bronchiolar epithelium, which blocks the bronchioles resulting to the obstruction of the air flow, the hallmark of bronchiolitis. This effect is maximized due to the small width of bronchioles in infants.[4] Tachypnea, wheezing and especially cough are important signs of RSV infection. However, almost half of RSV-infected children present without fever.[5] The absence of fever is the major distinction from Influenza-Like-Illness (ILI) symptoms. The presence of fever is often considered an indication of a lower respiratory tract infection in children. RSV infection can sometimes present only with apnea in infants <6 weeks of age.[5] The incubation period of the virus varies, but it is usually between 4-6 days.[5]

The virus seasonal circulation pattern has been identified and, in temperate regions, it usually coincides with influenza virus circulation, between the late fall and early spring, and lasts three to four months. However, the timing of circulation varies between years and different regions, as well as within communities. The annual global burden of RSV is estimated to be 33.8 million new cases of ALRI in children less than five years old, 3.4 million hospital admissions, and in 2010 253,000 deaths, with most of the fatalities occurring in developing countries.[6]

1.2. RSV virus characteristics

RSV virus is an enveloped RNA Pneumovirus with a non-segmented, single-stranded, negative-sense RNA genome and belongs to the family Paramyxoviridae. The viral genome consists of a total of 10 genes encoding 11 proteins. The RSV virion encodes three surface envelope proteins: the attachment protein G, the fusion protein F, and the small hydrophobic protein SH. The fusion (F) and attachment (G) surface glycoproteins are the most important for vaccine production because of their ability to induce neutralizing antibodies. There are two major subgroups: A and B.[7]

1.3. Viral F and G proteins

RSV F is a membrane anchored glycoprotein that mediates viral entry into host cells. The F glycoproteins undergo a conformational change that brings the viral and cellular membranes into proximity, ultimately leading to their fusion during cell entry. RSV F protein is present on the viral surface in two states: a metastable pre-F and α stable postfusion (post-F) form. The prefusion and postfusion forms of RSV F protein are important for the use as vaccine antigens. There are large structural differences between the lollipop-shaped prefusion F trimer and the crutch-shaped postfusion F trimer. To prevent viral entry, F-specific neutralizing antibodies must bind the pre-

fusion conformation of F on the virion, before the viral envelope fuses with a cellular membrane.[8]

The heavily glycosylated RSV G protein is responsible for viral attachment to cells. The majority of the differences between the two major RSV strains (A and B) are attributed to the antigenic variability in this protein. The G protein of the A and B strains can differ by up to 47%, whilst G proteins from the same strain can differ by as much as 20%.[8]

The success of passive immunization with an antibody that target the viral F protein (palivizumab) provided the rationale for developing a vaccine that elicits functional antibody responses. The efficacy of palivizumab, which bind to antigenic site II on the RSV F protein, has led many developers to focus on RSV F as a primary immunogen).[9] Antibodies targeting the F protein exhibit and increased cross-reaction across both RSV subtypes compared to antibodies to G protein.

2. RSV infection prevention and therapy

There is no vaccine currently available to protect from RSV infection, especially the severely affected risk groups and the current knowledge of RSV epidemiology and burden of RSV disease still has gaps that will need to be addressed by proper RSV surveillance at a national and international level. However, several target populations for RSV vaccines have been selected: 1) infants younger than six months of age, which as mentioned above is the age-group at highest risk of severe disease; 2) children six months of age and older, which will also indirectly help decrease transmission to other high-risk individuals; 3) pregnant women to decrease their own infection rates, and protect their newborns by placental antibody transfer and 4) the elderly, who are also at risk for severe disease, similar to that of influenza, though the burden of RSV disease to this age-group is underestimated.[10] RSV is also a significant concern for other high-risk individuals, such as pre-term infants, immunocompromised individuals, and those with pulmonary or congenital heart disease.

The fact that RSV infects early in life is one of the main challenges of RSV immunisation. Immune responses are limited in infancy compared to older age groups, and the safety of any vaccine is a major concern. The incidence of severe RSV disease is considered to be higher in infants younger than six months of age. Peak hospitalizations occur at about one month of age, while the RSV-related fatality rate is highest in infants younger than two months. A strategy of vaccinating pregnant women to prevent infant disease is under consideration. A single immunization in late pregnancy could be sufficient to boost infant RSV antibody concentrations to protective levels.[11] Several studies have demonstrated a reduced incidence of RSV disease during the first several months of life that coincides with higher concentrations of RSV-specific maternal antibody transplacentaly introduced to the infant.[11] Further, prevention of RSV in the mother resulting in reduced transmission to the infant due to their intimate contact is another potential benefit of vaccinating pregnant women. Most importantly, any vaccine administered to pregnant women will need to be in accordance with the highest safety standards.

2.1. Therapeutic options

Immunoprophylaxis with the neutralizing monoclonal antibody (mAb) palivizumab is used especially in some high and middle income countries to prevent RSV disease in very premature infants or those with other underlying medical conditions, such as congenital heart disease. Palivizumab is a humanized monoclonal antibody (IgG) directed against an epitope in the A antigenic site of the F protein of RSV. Palivizumab was shown to reduce the risk of hospitalization due to RSV infection by 55% and 45% during two Phase III clinical trials. Palivizumab is dosed once a month via intramuscular injection, and is administered prophylactically throughout the duration of the RSV season. The high cost and requirement of monthly administration, precludes its use in resource-constrained public health settings.[12]

Recently two major pharmaceutical companies announced to develop and commercialize a monoclonal antibody –called MEDI8897– for the prevention of Respiratory Syncytial Virus (RSV) associated illness in newborns and infants. MEDI8897 is a highly potent monoclonal antibody (mAb) that neutralizes RSV by binding the RSV fusion (F) protein expressed on virions and infected cells; it has been developed to have long half-life so that only one dose would be needed for the entire RSV season, which facilitates its administration to infants. MEDI8897 received fast-track designation from the U.S. FDA in 2015 and it is currently being investigated in a Phase IIb study in preterm infants with plans for a Phase III trial in healthy full-term infants.

Alternative symptomatic treatment for patients with severe ALRI consists of supportive care, supplemental oxygen and mechanical ventilation. Bronchodilators, corticosteroids, and ribavirin have failed to prove clearly beneficial in randomized controlled trials and are not currently recommended for use in many countries. Prophylaxis, either with palivizumab

administration or vaccination, is thus considered the optimal solution.

2.2. Vaccines under development

Live-attenuated vaccine approaches have been in development for the past decades, but to achieve immunogenicity, sometimes their safety was compromised. Several RSV vaccine candidates using various technologies and targeting different populations and age-groups have emerged in recent years.[13] There are now 60 RSV vaccine candidates in development, targeting the whole range of age-groups, of which 16 vaccine candidates are currently in clinical development, while most are at a preclinical stage.

In the past, RSV vaccine development in the 1960s was shaded by the vaccine-caused illness that occurred after a formalin-inactivated RSV vaccine was administered to seronegative infants. Proposed mechanisms for the cause of the disease included the production of high titers of non-neutralizing antibodies and Th2-biased cellular immune profile. These immunologic responses may have caused the deposition of immune complexes, the activation of the complement and allergic inflammation. The severe lung inflammation, the diminished health status, and fatalities that occurred in vaccinated infants raised concerns that other non-replicating RSV vaccines might also predispose infants and RSV-seronegative children to unpredictable immune responses.[14]

Presently, sixteen RSV candidates are currently advancing through Phase 1 to Phase 3 clinical trials (Table 1,2). The regulatory pathways for RSV vaccines are strict: 1) to establish evidence of protection against RSV disease affecting the youngest age group; 2) to provide enhanced respiratory disease safety assurances, especially for vaccines intended for pregnant women or infants; 3) to generate safety information about the technology that will be used.[15]

A WHO Consultation on Respiratory Syncytial Virus Vaccine Development held on 23-24 March 2015 concluded that safety, immunogenicity, and efficacy data in preclinical models should be reviewed when considering the advancement of a vaccine candidate into the clinic. In general, safety and immunogenicity studies should first be performed in healthy adults. Early trials that involve seronegative infants should occur in a setting with appropriate facilities for the management of adverse events.[15]

The RSV vaccine development is by nature a prolonged, risky, and increasingly expensive process. Multiple candidates are now in the human testing phase, targeting different age-groups and populations- young children, older adults, pregnant women and high-risk individuals. As previously described, among neonates and young infants the vaccine development has great potential benefit due to the increased disease burden on these age-groups.[16]

A growing number of RSV vaccine candidates, across multiple platforms, has emerged as of late.[2] The type of vaccine used will be dependent on the target population.

2.2.1 Live-attenuated vaccines

Live-attenuated vaccines (LAVs) are the most ad-

Table 1 List of LAIV vaccines in clinical trials[19]

VACCINE	CLINICAL TRIAL STATUS	MANUFACTURER	APPROACH	OUTCOME
Live attenuated MEDI 557	Phase 1/2a	MedImmune LLC	Live attenuated	Increased rate of LRTIs in vaccine recipients, further study on-going
LID ΔM2-2	Phase 1 Adults	NIAID	Recombinant live attenuated	Estimated completion May 2016
ΔNS2 Δ1313	Phase 1 Children 12- 59 RSV+ and 6-12 mo RSV	NIAID	Single Dose of Recombinant Live-Attenuated	Estimated completion May 2016
cps2	Phase 1	Medimmune, NIAID	Recombinant live attenuated	Completed

vanced vaccine candidates in RSV-naive infants.[17] LAVs to protect pediatric populations from RSV disease have been in development for decades and do not appear to cause enhanced disease in RSV naïve infants. Recent approaches include engineered viruses that use knowledge of RSV gene function to create 'knock-out' viruses that are attenuated but still immunogenic, such as the M2-2 deletion mutant that favors transcription over replication of the genome, leading to increased protein production, but limited virus am-

Table 2 List of recombinant viral vectors expressing RSV antigens

VACCINE	CLINICAL TRIAL STATUS	MANUFACTURER	APPROACH	OUTCOME
RSC 001	Phase 1	Kairos	Adenovirus vector and an MVA vector encoding RSV antigens	Commenced 2013, outcome awaited
MEDI-7510	Phase 1a	Medimmune LLC	RSV sF antigen + synthetic glucopyrasonyl lipid A adjuvant	Estimated completion 2015
Nanoparticle RSV F	Phase 2 Healthy 3rd semester pregnant	Novavax	Recombinant RSV F protein	Commenced October 2013, outcome awaited
RSV-F Vaccine with Adjuvant	60-75 yrs 75+	Novavax	RSV-F Protein Nanoparticle Vaccine, With or Without Aluminum Adjuvant	Commenced October 2013, outcome awaited
RSV F subunit	Phase 1	Novartis /GSK	F subunit/MF59	Estimated completion 2015
GGSK 3003891A. etc	Phase 1 Healthy males	GSK	Prefusion F subunit	Estimated completion 2016
GSK 3003895A, 3003898A, 3003899A	Phase 1 healthy women	GSK	Viral Proteins Encoded by Chimpanzee-derived adenovector (ChAd155- RSV)	Estimated completion 2016
GSK 3389245A	Phase 1 healthy adults	GSK	ChAd155-RSV	Estimated completion 2016
MVA BN RSV	Phase 1	Bavarian Nordic	Recombinant MVA BN® RSV Vaccine	Estimated completion 2016
DPX-RSV(A)	Phase 1	Dalhousie univ	SHe antigen and DepoVaxTM adjuvant	Estimated completion 2016
Ad26.RSV Ad35.RSV	Phase 1	Crucell Holland	Human adenovirus-vectored vaccine candidate	Estimated completion 2016

plification. Achieving a proper balance between attenuation (safety) and immunogenicity, as well as genetic stability, has been difficult. A live vaccine approach targeted to older infants and young children could ultimately complement a maternal/passive immunization approach by protecting these older populations and decreasing transmission of the virus.[9]

2.2.2. Protein-based vaccines

Protein-based vaccine approaches have been developed for protecting the elderly population from severe disease and are often formulated with adjuvant. Particles can display viral proteins, peptides, or neutralizing epitopes with increased density to enhance B cell receptor binding. Particle and protein-subunit vaccines are also being developed for immunization during pregnancy to boost pre-existing immunity to increase transplacental transfer of RSV-specific antibody to infants. Maternal RSV vaccines will likely be more acceptable either as unadjuvanted formulations or adjuvanted only with alum given their history of safe use in this population.[9]

2.2.3. Vaccines encoding RSV surface antigens

Replication competent and deficient alphavirus, adenovirus, and modified vaccinia virus Ankara (MVA) vectors encoding RSV surface antigens are being developed for use in infant and pediatric populations. These vectors are intended to express surface proteins in their authentic conformation and processed by MHC class I and class II pathways, thus eliciting robust humoral and cellular immunity.[9]

2.2.4. Nucleid acid vaccines

Nucleic acid vaccines using either plasmid DNA or messenger RNA encoding RSV antigens are being targeted to protect both pediatric and elderly populations. Combination approaches with DNA and protein are in early development as well and could induce both cellular and humoral immunity.[9]

Preclinical vaccine development is a target of pharmaceutical companies, government agencies, academic institutions, and biotechnology organizations focusing on infant, child, and elderly populations. An Innovative Medicines Initiative funded project (RESCEU) on RSV burden, surveillance and severity-associated biomarkers has recently commenced and will support the RSV surveillance and research needed for vaccination purposes in Europe.[18]

While vaccines are considered among the most cost-effective health interventions for infectious diseases, there are none yet available for RSV. RSV is considered to be the most important missing indication in the vaccination schedule of new-borns and the prediction is that the first vaccines will become available in the EU market within the next 5-10 years. A vaccine to protect infants and children from RSV disease is a high public health priority. The World Health Organisation (WHO) is also focusing on the development of a global RSV surveillance system prior to the entry of the RSV vaccine in the market.[18] Such a vaccine has unique challenges to overcome, including the young age at peak onset of severe disease and the history of vaccine-enhanced illness and death. A number of pivotal studies are under way that will ensure a licensed RSV vaccine will be a short-term reality.

Περίληψη

Νεότερα δεδομένα στην εξέλιξη του εμβολίου έναντι στον αναπνευστικό συγκυτιακό ιό (RSV)

Γιώργος Καρατσάης, Μαρία Εξηντάρη, Γεωργία Γκιούλα, Μαρία Χριστοφορίδου, Αγγελική Μελίδου
Μικροβιολογικό εργαστήριο, Ιατρική σχολή, Αριστοτέλειο πανεπιστήμιο Θεσσαλονίκης, 54 124 Θεσσαλονίκη, Ελλάδα

Ο αναπνευστικός συγκυτιακός ιός αποτελεί μια από τις σημαντικότερες αιτίες ιογενών λοιμώξεων κατώτερου αναπνευστικού σε βρέφη και παιδιά παγκοσμίως. Συχνά προκαλεί σοβαρές ακόμη και θανατηφόρες λοιμώξεις ειδικότερα σε παιδιά ηλικίας κάτω των έξι μηνών και συγκεκριμένα θεωρείται η αιτία για το ένα τρίτο των θανάτων που προκαλούνται από λοιμώξεις κατώτερου αναπνευστικού στον πρώτο χρόνο της ζωής. Σήμερα δεν υπάρχει διαθέσιμο εμβόλιο έναντι του αναπνευστικού συγκυτιακού ιού. Η ανοσοπροφύλαξη με το μονοκλωνικό αντίσωμα palivizumab χρησιμοποιείται για την πρόληψη της λοίμωξης σε πολύ πρόωρα νεογνά και σε άτομα υψηλού κινδύνου. Τις περασμένες δεκαετίες έγιναν προσπάθειες για τη δημιουργία εμβολίου από ζώντες εξαθενημένους ιούς, που όμως έχουν αμφισβητηθεί λόγω των πιθανών επιπλοκών τους. Τα τελευταία χρόνια έχουν προκύψει πολλά υποψήφια εμβόλια έναντι του ιού, τα οποία χρησιμοποιούν διάφορες τεχνολογίες και στοχεύουν σε διάφορούς υπερπληθυσμούς και ηλικίες. Στη συγκεκριμένη ανασκόπηση παρουσιάζεται η τρέχουσα κατάσταση στις προσπάθειες για τη δημιουργία εμβολίου έναντι του αναπνευστικού συγκυτιακού ιού. Εξήντα υποψήφια εμβόλια βρίσκονται υπό δημιουργία αυτή τη στιγμή εκ των οποίων τα 16 είναι υπό κλινικές δοκιμές.

Λέξεις κλειδιά
Αναπνευστικός συγκυτιακός ιός, RSV, εμβόλιο

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