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Vaccines for prevention of respiratory syncytial virus infection

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Abstract. Respiratory syncytial virus is a virus that causes infections in lower respiratory tract among infants aged under 5 years old, older adults aged above 65 years old and populations with other potential complications. Some susceptible populations to RSV may develop pneumonia and bronchiolitis. The mechanism of RSV virus transmission is through air droplets. The burden of hospitalization causes by the infection of RSV is severe and episodic, with the prevalence mainly concentrated in winter periods. The development of vaccines against RSV virus statutes in the early 1960s, but was paused and halted due to the failure of formalin inactivated vaccine. The current study first reviewed the prevalence, structure, mechanism and development history of RSV and its vaccines, following which the present work focus on a summary of the results of clinical trials of vaccines against RSV on different groups of populations, especially those with special condition, such as older adult and pregnant women.

Keywords: RSV, infants, older adults, pneumonia, bronchiolitis, mechanism, clinical trials, formalin inactivated vaccines.

1. Introduction

1.1. Respiratory syncytial virus and infection

Respiratory Syncytial Virus (RSV) is a pathogen which causes lower respiratory tract infection and associated respiratory illnesses, such as bronchiolitis. When infected with RSV, the majority of the susceptible population of RSV, including children who are aged under 5 years old, elderly aged above 65 years old and the population who possesses other potential diseases, develops clinical symptoms, such as sneezing, cough, fever and etc. On the other hand, the virulence of RSV is less severe for adults compared to the virulence for its susceptible population [1, 2]. Susceptible population of RSV may also develop complications like pneumonia, middle ear infection or asthma later. In addition to the previous complications, RSV is also to be found as a major cause of bronchiolitis in 1957. The prevalence of RSV focuses during winter and it varies among different populations [3]. For instance, the prevalence of RSV among adults is 3-10% in each winter. Similar to influenza, RSV infections among adults are usually more serious and elongated than the common cold. The trend shown by RSV infection indicates that it increases along with age of the adults and other risk factors. For instance, the proportion of hospitalized adults aged above 65 years old among the elderly who are infected with RSV is approximately 1 or 2 per 1000 people. These population develops pneumonia or aggravated potential cardiopulmonary complications, with a case facility rate of 1 to 2%.

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1.2. Mechanism of RSV infection

The structure of RSV mainly consists of two types of glycoproteins: attachment glycoprotein and fusion glycoprotein, which contribute to the initiation of infection. Attachment glycoprotein infects the ciliated cells in the airways, while fusion glycoprotein causes the surface membrane of the virus to combine with the target cell's membrane. In addition to ciliated epithelial cells, RSV virus also infects $CDT4^+$ and $CDT8^+$ T lymphocytes, which results in the reduction of interleukin 2 and interferon y production [3]. After the virus infection, both attachment and fusion glycoprotein will combine with the neutralizing antibodies and trigger an active immune response and the patients will develop clinical symptoms. RSV infects people with high exposure as a form of droplets produced by coughing and sneezing, which later contacts with the patients' eyes, nose and mouth. Also, the droplets are able to land on inorganic surfaces and the RSV can be transmitted by touching the surfaces, given that the patients do not clean their hands with soap afterwards.

1.3. History and development of RSV vaccines

The earliest development of RSV vaccine can be traced back to the 1960s [4]. Before the initiation of development of RSV vaccine, the whole-inactivated polio vaccine invented by Jonas Salk was proven to be a stable intervention against polio.

It was validated in 1955. Since the 1960s, the cases of paralytic polio in the United States decreased from thousands to a few of dozens each year. After the success of the polio vaccine, researchers started the development of whole-inactivated RSV vaccine. Furthermore, researchers conducted 4 studies with large scale in 1965 and 1966, in which the experiment participants were vaccinated before 6 months of age and before their first RSV infection. Nevertheless, the result of the experiment was disastrous. An RSV outbreak occurred within the youngest experiment participants during the winter of 1966 to 1967. Among the 31 immunized infants, 20 were infected, 16 were transported to hospitals, 2 died [2]. Subsequent investigation revealed the whole-inactivated vaccine developed in the early 1960's did not offer protection against RSV diseases to infants. Moreover, the vaccine aggravated the virulence of the diseases. As a result of the tragedy from 1966 to 1967, the development of RSV vaccine paused.

Despite the high prevalence of RSV infection in young children, there is lack of effective treatment against RSV and the routine management are supportive therapy [5]. Several newly-developed vaccines have been tested for the prevention. An example of protection against RSV is palivizumab, an artificial monoclonal antibody, which is validated for prevention of severe RSV illnesses to infants with potential risk factors [6]. Other monoclonal antibodies are also proven to effectively prevent against RSV fusion protein by clinical trials, such as nirsevimab and motavizumab. On the other hand, there are some improvements currently regarding on the allocation of multiple doses of palivizumab during epidemic, on the suggestion of the antibody use on a small population of infants who are susceptible to severe RSV illnesses, on the effectiveness of the antibodies, which is about 45 to 55% among susceptible infants, and on their prices. Despite these improvements that needed to be implemented in the future, researchers have proven these monoclonal antibodies are relatively reliable.

2. A summary of clinical trials in RSV vaccine

In the following section, we reviewed the clinical trial results regarding vaccines against RSV infection with a focus on infants, older adults and pregnant women.

2.1. The results of clinical trials in infants

Currently, there are some candidate RSV vaccines that can be injected into infants [7]. For example, a randomized, double-blind phase 1 trial was conducted among 114 children aged from 1 to 59 months old, in order to test the efficacy of candidate live-attenuated, intranasal RSV vaccine cpts-248/404 on children. cpts-248/404 was infective between 104 and 105 plague-forming units in RSV-naive children. Also, the vaccine was widely immunizing among children greater than 6 months old. Antibody responses among serum and nasal cavities only showed the activity of IgA antibody and they had prevailing response towards RSV attachment protein, with no increase signs of neutralizing activity.

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However, the release of viral load was limited on the second dose and initial evidence showed that second infection of RSV is able to prevent severe clinical symptoms. Overall, candidate vaccine cpts-248/404 did not lead to lower respiratory tract infection or other related clinical symptoms. Nevertheless, the vaccine has a potential harmful effect among the youngest infants, since upper respiratory tract obstruction may occur during viral recovery with the highest rate. The cpts-248/404 vaccine candidate did not cause fever or lower respiratory tract illness. In the youngest infants, however, cpts-248/404 was unacceptable because of upper respiratory tract congestion associated with peak virus recovery. Therefore, the live attenuated RSV vaccine designed for infants will have additional mutations compared to typical cpts-248/404 candidate vaccine.

Another example is B1 cp-52/2B5 (cp-52) candidate vaccine, which is a live-attenuated vaccine made in the combination with Vero cells [8]. However, the clinical trials on infants indicates that the vaccine was over-attenuated. Later analysis shows the vaccine has a large section of coding sequence of hydrophobic and attachment proteins deleted, which results in the absence of a complete attachment protein. Despite the incompleteness of the viral structure, the virus of the candidate vaccine remains replicable and infectious to stimulate immune response. Cp-52 candidate vaccine shows partial deletion of genes of RSV virus may provide a new approach of developing live attenuated vaccines.

2.2. The results of clinical trials in older adults

Currently, there are some probable approved candidate RSV vaccines that can be used for older adults [9]. For instance, a phase 3, placebo-controlled trial is being conducted among 17 countries in the globe in 2023. The researchers have assigned single doses of AS01-adjuvanted RSV pre-fusion F protein-based uncertified vaccine E or placebo to experiment participants, who are above 60 years of old, in a 1:1 ratio before RSV prevalence. Before the trial starts, all participants have known the agreement and potential risks from written or visual documents. The aim of the trial is investigating the effect of single dose of RSV pre-fusion F protein-based vaccine protecting against RSV-associated lower respiratory tract illnesses during single RSV prevalence. Researchers expect the efficacy of the vaccine that it should remain within 20 percent of correction of the confidence interval. During the clinical trial, researchers assess and analyze the efficacy of the invalidated pre-fusion F protein-based vaccine against serious RSV-associated lower respiratory tract illnesses in accordance to RSV subtypes. Meanwhile, safety measures are also conducted.

Among 24,966 participants of the trial, 12,467 of them is injected with single doses of RSV pre-fusion F3 OA vaccine, while other 12,499 participants are injected with placebo. In the following median of 6.7 months after the end of the study, the vaccine efficacy on protecting against RT-PCR-confirmed RSV-associated lower respiratory tract is 82.6% (the 96.95% confidence interval of the vaccine lies between 57.9% to 94.1%). Among the group which the participants are injected with the vaccine, 7 participants are infected with RSV (equivalent to 1 per 1000 people), while 40 are infected in the placebo group (equivalent to 5.8 per 1000 people). On the other hand, the efficacy of the pre-fusion F3 OA vaccine is 94.1% against serious RSV-associated lower respiratory tract illnesses, with a confidence interval of 95% (confidence lies between 62.4% and 99.9%). Finally, the efficacy of the pre-fusion F3 OA vaccine is 71.7% against RSV-associated acute respiratory tract infection, with a confidence interval of 95% (the confidence lies between 56.2% to 82.3%). Specifically for RSV subtype A, the vaccine has an efficacy of 84.6% for RSV-associated lower respiratory tract illnesses and 71.9% for scute RSV-associated infections. For RSV type B, the vaccine has an efficacy of 80.9 towards RSV-associated lower respiratory tract illnesses and 70.6% towards acute RSV-associated respiratory infections. Overall, the data collected from the trial indicates that the effect of RSV pre-fusion F3 OA vaccine is stronger on type A RSV than type B RSV. Nonetheless, the efficacy of the vaccine is significant among participants with different age groups and with various health risk-factors. The reactogenicity of RSV pre-fusion F3 OA vaccine is stronger than placebo. However, the side effects cases reported during the trial are relatively mild to moderate in the level of severity. The incidence of the difference of severe side effects of the vaccine is similar among the two trial groups [9].

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In conclusion, the RSV pre-fusion F3 OA vaccine is proven to be relatively reliable to elderly above 60 years of age. From this international phase 3, placebo-controlled trial, one dose of the RSV pre-fusion F3 OA vaccine is able to prevent acute RSV-associated lower respiratory infections and illnesses among elderly aged above 60 years old, without the factor of the RSV subtype and the underlying potential health risk factors of the infected patients [9].

However, there are also some unapproved candidate RSV vaccines for older adults [10]. For example, a randomized, double-blind phase 2b study was conducted between 2015 to 2016 to investigate the effectiveness of a pre-fusion RSV vaccine's prevention on acute RSV associated respiratory illnesses. The investigation assessed 120 μg of RSV post-fusion F protein in a combination with 5 μg of glucopyranosyl lipid assistance, in 2% of stable emulsion. Participants aged 60 years old or above were randomly allocated in a ratio of 1:1. One of the groups would receive the candidate vaccine, the other group would receive placebo (inactivated influenza vaccine). After observations, participants who developed clinical illnesses would be recorded and whose blood and nasal swab would be taken for testing.

Among 1894 participants, 1.7% of the vaccine recipients developed acute RSV-associated respiratory illnesses for more than 14 days. For placebo group, 1.6% of the participants developed acute RSV-associated respiratory diseases. The vaccine efficacy was indicated as 7.1%, with a 90% confidence interval between 44.3% to 106.9%. The effect of the vaccine was not observed in the following analysis, which ranges from seroresponse to non-vaccine RSV antigens. Efficacy of the vaccine is 8.9%, with a confidence interval between 28.5% to 35.4%. When clinical symptoms combined with seroresponse, the vaccine efficacy was 10.0%, with a 90% confidence interval between 44.4% to 45.4%. On the 29th day of the investigation, 92.9% of the vaccine recipients generated anti-F immunoglobulin G antibody and established seroresponse. Consequently, 48.5% of the participants receiving vaccines had local systematic solicit symptoms, while 30.9% of the participants receiving placebo had systematic solicit symptoms [10].

In conclusion, although the candidate RSV pre-fusion vaccine showed immunogenicity, its efficacy was below the expected data and did not protect older adults against acute RSV-associated respiratory diseases effectively [10].

2.3. The results of clinical trials in pregnant women

In 2022, some researchers conducted a phase 2b trial, who randomly allocate pregnant women to receive 120 μg or 240 μg of RSV pre-fusion vaccine in addition (or not) of catalyst aluminum hydroxide, or equivalent amount of placebo. When experimenting, the researchers include safety precaution and immunogenicity precaution, which ensures that 50% concentrated of RSV subtype A, B and a combination of both subtypes' neutralizing antibodies are delivered as forms in maternal serum, in umbilical-cord blood and in maternal-to-infant transplecental transfer. The concentration must remain in the required ratio [11].

The scheduled, phase 2b trial contains 406 women and 403 infants. Of all 406 women, 327 are injected with RSV pre-fusion vaccine. The majority of the reactions after vaccination are mild to moderate, while the local reactions are higher among the women who receive the vaccine and aluminum oxide, compare to the women who only receive the vaccine. The percentage of side effects occurring within women and infants is similar among the vaccine and placebo groups, which the events' type and frequency are accordant with the background incidences among the participants. The probability of the variety and frequency of these events were coincident with the background incidences among pregnant women and infants. The geometric mean proportion of 50% neutralizing concentration between the infant participants who receive the vaccine and the infants who receive placebo varies from 9.7 to 11.7 for recipients who receive RSV A neutralizing antibodies and the variation ranges from 13.6 to 16.8 for recipients who receive RSV B neutralizing antibodies. The ratio of transferring neutralizing antibodies which travel through placenta varies from 1.41 to 2.10, of which the data is higher for non-aluminum group than for the group with aluminum. Also, the infants whose mothers are immunized have alike

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concentration of antibodies in umbilical-cord blood and similar transmitting ratio which travels in the transplacental passage across analyzed gestational ages [11].

In conclusion, RSV pre-fusion vaccine causes antibody responses with resultful transplacental transport, in the absence of safety worries [11].

3. Conclusion

In conclusion, the risk for susceptible population infecting the RSV virus and develop clinical diseases is relatively high as usual. Despite the high risk of infection, many researchers have planned and conducted clinical trials on populations with different age groups. Among these clinical trials, the majority of the candidate RSV vaccines meet up with approximate expectation and are able to provide relatively effective immune response. The outcomes of success trials indicate that most candidate RSV vaccines may have the potential for administration and for domestic use. However, the exception of the candidate RSV pre-fusion vaccine trial on older adults between 2015 to 2016 did not protect partial participants against RSV-associated acute respiratory diseases, even though it was immunogenic. The failure of the candidate RSV pre-fusion vaccine on older adults indicates that the efficacy of different types of vaccines against RSV remains as a variable. Overall, the development of vaccine against RSV associated illnesses needs to continue and further tests under regulations are needed.

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