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Vaccination against RSV

Is maternal vaccination a good alternative to other approaches?

Patricia Kaaijk,* Willem Luytjes and Nynke Y. Rots

Centre for infectious Diseases Control; National Institute for Public Health and the Environment (RIVM); Bilthoven, the Netherlands

The respiratory syncytial virus (RSV) is the major cause of lower respiratory tract illness (LRI) in infants worldwide. Also persons with heart/lung disease or an immunodeficiency disorder, and the elderly are at increased risk for severe LRI upon RSV infection. Although there is at present no licensed RSV vaccine available, it is a priority target for several vaccine developers. For the implementation of a future RSV vaccination within national immunization schemes, various strategies can be considered even without the availability of extended clinical data on RSV vaccines. For this purpose, the extensive knowledge on RSV with respect to disease pathology, epidemiology and immunology can be used. This article discusses different aspects that should be considered to enable a successful implementation of a new RSV vaccine in national immunization programs. In addition, gaps in knowledge that needs further attention are identified. The maternal immunization strategy is highlighted, but also vaccination in the youngest infants and specific risk group immunization strategies are evaluated in this paper. Key factors such as the seasonality of RSV disease, interference of maternal antibodies and the immaturity of the infants' immune system are addressed.

Keywords: RSV, vaccination strategy, immunology, maternal immunization, infant immunization, risk groups, seasonality

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*Correspondence to: Patricia Kaaijk; Email: patricia.kaaijk@rivm.nl

Introduction

The RS virus infects more than 70% of all children in the first year of life and nearly 100% of all children by the age of 2 y.[1] The greatest morbidity and mortality from RSV occurs in infants. Hospitalization for severe lower respiratory tract illness (LRI) caused by RSV is most frequent in infants from 6 weeks to 6 mo, with a peak incidence at 2–3 mo of age.[2] Premature infants experience greater morbidity and mortality than term infants.[3] Later in life, RSV causes primarily upper respiratory tract disease. However, specific risk groups, i.e., persons with heart/lung disease or immunodeficiency disorder as well as the elderly, remain at risk for severe lower respiratory tract disease.[2,4-6] Based on annual RS surveillance data from 2003–2008 obtained from 13 states of the US, mean rates of RSV-associated hospitalizations were 55.3 (95% CI, 44.4–107) per 100 000 persons per year. Children ≤ 1 y had the highest hospitalization rate (2350/100,000; 95% CI, 2220–2520), followed by children aged 1–4 y (178/100,000; 95% CI, 155–230) and elderly aged ≥ 65 y (86/100 000; 95% CI, 37.3–326.2).[7] Results of this comprehensive study were comparable with other published study results on RSV hospitalization rates in the US.[8,9]

At present, an effective RSV vaccine reducing the high disease burden is not available. The clinical and scientific experience and knowledge on RSV disease taken together may encourage vaccination of certain age groups or persons at high risk. However, for a proper analysis and design of an optimized vaccination scheme for RSV, more clinical data regarding the safety and efficacy of new RSV vaccines tested in different schemes and various age groups is required. This article discusses different aspects that should be considered when implementing a new RSV vaccine

within national immunization schemes, regardless of the specific vaccine type that will become available.

Discussion

Immunity against RSV. The fusion protein (F) and surface glycoprotein (G) are the only viral antigens able to induce neutralizing antibodies as well as relatively long-lived protection in animal models.[10,11] Two major antigenic groups of RSV, A and B, have been identified.[12] Antibody responses to the F protein have been found to be cross-reactive between the two antigenic A and B groups, whereas responses to the G protein were largely group-specific.[13] Antibody responses after infections with group A viruses have shown to be more cross-reactive than were the responses which followed primary infection by group B viruses.[14,15] Reinfections may occur by repeated exposure to the same viral isolate, confirming that antigenic variation is not strictly required to cause reinfections.[2,15,16] Nevertheless, antigenic variation may play a role in the ability of RSV to escape the immune response and establish infections.[15]

RSV does not appear to induce an effective immunological memory, hence reinfections can occur repeatedly.[1,5,17] Especially, in young infants aged between 0 and 6 mo a primary RSV infection elicits a poor immune response, and has limited effect on subsequent reinfection.[5,17,18] Once a host is exposed to RSV, the innate mucosal immune response is activated. The mucosal immune response, including secretory antibodies (IgA), will help curtail the infection. If the virus spreads to the lower respiratory tract, sufficient levels of serum neutralizing antibodies can prevent LRI.[19,20] After primary infection in young infants, levels of virus-specific neutralizing antibody and antibodies directed to the two main viral surface proteins (F or G) are often low. More appropriate immune responses occur in older infants (> 9 mo) and young children after primary infection and reinfection, although the response is still less than that of an adult.[2] Neutralizing antibody response seems the best correlate of protection for RSV-associated illness.[16,21] However, even when high levels of virus-neutralizing antibodies are present, reinfection can occur.[16]

T cell immunity is probably also important in the protection against RSV associated illness, but its role has not been extensively studied.[1,20,22] The cellular immune response (including cytotoxic and helper T cells) promotes RS viral clearance.[17,20] Children with T cell deficiencies are unable to efficiently clear the RS virus, indicating that T cells indeed play a role in virus eradication.[17,23] On the other hand, T cells may be involved in disease enhancement by the induction of an inadequate allergic Th2-type immune response that can cause severe respiratory tract inflammation with infiltration of eosinophils and neutrophils, resulting in lung damage.[1,24,25] It is thought that effective RSV clearance requires the induction of balanced Th1-type immunity, involving the activation of IFN-γ-secreting cytotoxic T cells.[1] Use of a live RS virus has shown to stimulate a Th1-type response, whereas use of an inactivated virus or subunit F glycoprotein more selectively skews toward a disadvantageous Th2 cytokine expression pattern.[17,24,25]

RSV vaccine candidates. *Experience from clinical trials in mid-1960s.* Vaccine trials for RSV were first performed with an intramuscularly administered formalin-inactivated RSV formulation (FI-RSV; "lot 100") at the mid-1960s with a dramatic outcome.[26,27] In these clinical trials, vaccinated RSV naïve children experienced exacerbated pulmonary disease and the majority required hospitalization upon subsequent wild-type RSV infection. Two fatalities occurred in the group of vaccinated children that were attributed to the vaccine. Children from the control group that did not receive the RSV vaccine experienced significantly milder symptoms.[26,27] The failure of FI-RSV remained unexplained for at least 2 decades, primarily because of the poor understanding of the immune response triggered by RSV infection. However, at present accumulating evidence supports the hypothesis that the FI-RSV vaccine failed because of the induction of an allergic-like Th2 cellular immune response against the virus in the RS virus naïve vaccinated infants.[1,20,24,25] This particular Th2-type response seems responsible for the accelerated infiltration of eosinophils and neutrophils into the lung tissues as observed in the affected children.

Current RSV vaccine development. There are various experimental approaches for the development of a safe and effective vaccine against RSV. Over the last two decades, several RSV vaccine concepts have been tested in (early) clinical trials with published results. These include live attenuated vaccines for intranasal application, i.e., a cold-passaged, temperature sensitive (*cpts*) RSV vaccine concept[28] and a live recombinant viral (chimeric) vector vaccine against RSV (F-protein) and parainfluenza (MEDI-534).[29,30] In addition, the following subunit RSV vaccines (with and without aluminum containing adjuvant) intended for intramuscular administration have been developed and tested clinically with published data: purified F protein,[31,32] a purified fragment of the RSV G protein fused to the albumin-binding domain of streptococcal protein G (BBG2Na)[33] and a subunit RSV-A vaccine containing purified F, G, matrix protein (M) antigens.[34,35] Also other vaccine concepts have been designed that have not yet reached the clinical phase, including epitope-based approaches[36,37] and live vaccine virus candidates attenuated by deletion of genes, such as non-essential genes or the G-protein.[36,38-40] However, at present none of the vaccine concepts have entered advanced stages of clinical development.

Vaccination strategy. The aim of a RSV vaccine program should be to prevent severe RSV illness in young infants, the primary risk group. This paper focuses on the possibility of maternal immunization in the second or third trimester of pregnancy. Other vaccination strategies are discussed as well, including infant vaccination, high risk group immunization and/or the cocooning strategy.

Maternal immunization. The aim of maternal immunization is to boost the serum neutralizing antibody response in the mother during the second or third trimester of pregnancy, which results in an increased amount of serum neutralizing antibodies transferred from mother to infant via the placenta. Breastfeeding may have an additional beneficial effect on maternal vaccination. Maternally

derived antibodies have shown to be effective in protecting very young, RSV-naïve, infants against RSV disease.[5,17,41,42] This is in agreement with the finding that infants younger than 6 weeks are relatively spared from serious RSV illness, an age when maternal antibodies are at their peak.[20] RSV immunization during pregnancy may decrease the incidence of RSV hospitalization in infants. In a study in infants, maternal antibodies against RSV detected at birth appeared to decline steadily over the first 3 mo with a calculated mean half-life of 26 d. At the age of 6 mo, maternal antibodies were undetectable in the majority of the infants.[5,43] In contrast, in another study in young infants in a tropical country, the half-life of maternal RSV antibodies appeared to be as long as approximately 2.5 mo. In this study, at least 50% of the infants remained seropositive at 4–5 mo of age.[44] Because the majority of infants hospitalized for RSV are younger than 6 mo of age, maternal immunization could potentially prevent a significant proportion of serious LRI in early infancy. Furthermore, high-risk preterm infants may also be protected with this vaccination strategy. Nevertheless, it should be taken into account that the presence of maternal antibodies may suppress the induction of an immune response against RSV by the infants themselves.[45] Therefore, the question that remains is whether the infants, when maternal antibody levels have diminished, are able to induce a sufficient immune response or are they at that moment at risk for severe RSV illness. In the latter case, additional infant vaccination may be necessary. Further clinical studies are needed to explore this matter. A first clinical trial with a subunit RSV vaccine in pregnant women has been reported.[32] A RSV vaccine consisting of purified F protein with adjuvant was intramuscularly administered to 35 healthy women in the third trimester of pregnancy and appeared to be safe and well tolerated without any indication of enhanced T-cell or cytokine activity in infants of the vaccine recipients. In this study, the functional neutralizing antibody response was disappointing.[32] A certain degree of immunosuppression in late pregnancy has been suggested. It has been shown that upon natural winter RSV exposure, an increase in the serum antibody levels was observed for women in the second trimester, but not in the third trimester of pregnancy.[46] In addition, exposure to RS virus in the first two trimesters, but not in the third trimester, was associated with high colostral IgA antibody levels that were maintained after delivery.[46] Therefore, RSV vaccination in the second trimester of pregnancy instead of the third trimester may be more effective. Another aspect, that needs to be investigated for selecting the best time point of vaccination during pregnancy, is the seasonal-dependency of naturally acquired immunity against RSV. The concentration of maternal serum antibodies to the F protein of RSV in non-vaccinated pregnant women has been found to be significantly higher during the second and third quarters (respectively April–June and July–September) of the year compared with the first quarter (January–March).[47] The seasonal variation of maternally derived antibodies in cord blood was confirmed in another study.[42]

Live attenuated vaccines pose a theoretical risk to the fetus when administered to a pregnant woman. For this reason, in the absence of clinical data proving safety of the vaccine during pregnancy, live vaccines are generally contraindicated in pregnancy. However, in the course of the influenza pandemic in 2009, experts of the WHO judged that in this particular case the risks outweighs the benefits and therefore recommended that any licensed H1N1 influenza vaccine, thus including live vaccines, could be used in pregnant women despite lack of clinical data for this specific group. They came to this advice because of the substantially elevated risk for a severe outcome following H1N1 influenza infection in pregnant women. No concerning patterns of maternal or fetal outcomes were observed in the pregnant women that received the live attenuated influenza vaccine.[48] Through this experience, it seems inappropriate to exclude in advance maternal immunization with a live vaccine. Nevertheless, maternal immunization with a live RSV vaccine will only be feasible when the vaccine is proven safe in preclinical studies with pregnant animals from relevant species and subsequently in clinical studies among pregnant women in which infants are closely monitored.

Primary immunization with the first dose at/or shortly after birth. The highest hospitalization rate of RSV infection in children without underlying conditions is < 6 mo of age, with a peak incidence at 2–3 mo of age.[2] For the induction of an adequate protective immune response in young infants, it is generally presumed that a live-attenuated RSV vaccine is necessary. Live attenuated vaccines are usually more immunogenic and have a broader protective potential in comparison with inactivated or subunit vaccines. Furthermore, an inactivated vaccine may be less appropriate for RSV naïve young infants considering the dramatic clinical experience with the FI-RSV ("lot 100") vaccine leading to enhanced respiratory disease upon exposure to the wild-type virus. Development of a live-attenuated RSV vaccine that is well tolerated in young infants and still provides sufficient immunogenicity to prevent RSV infection is challenging. The live RSV vaccines that have been tested in clinical trials were administered intranasally. The advantage of the nasal route, the natural route of infection, is that it offers both mucosal and systemic immunity for the prophylaxis of respiratory diseases. Currently, the only licensed intranasal vaccine in the US and Europe is a live influenza vaccine. Clinical studies with this intranasal vaccine in children from 6 mo and older showed an increased risk of hospitalizations in recipients aged 6–11 mo compared with the placebo control group. In addition, prolonged wheezing was observed in young children 6–23 mo of age. Therefore, the indication was restricted to individuals above 2 y of age. This should be taken into account when a live attenuated RSV vaccine for intranasal application in infants is being developed. Another aspect that should be considered with respect to this vaccination strategy is that the presence of maternal antibodies may suppress the induction of an adequate immune response in the young infants. Furthermore, probably multiple vaccinations will be necessary to evoke an adequate immune response, because the immune system of these very young infants is not optimally operating (immature). As a consequence, the young infants

may be unprotected during the most vulnerable early months after birth.

High-risk immunization strategy. Apart from infants that are at high risk for RSV-associated LRI, other specific risk groups remain prone to severe LRI and complications later in life, i.e., persons with congenital heart disease, chronic lung disease, neuromuscular impairment, immunodeficiency or Down Syndrome, as well as the elderly.[2,4-6] Vaccination based on risk-stratification may be a good and cost-effective approach, provided that the vaccine is safe and effective enough for these high-risk groups. Ideally, if the same groups at risk for influenza, pneumococcal and RSV disease are identified, one visit for simultaneous administration of the influenza and/or pneumococcal vaccine and RSV vaccine prior to the winter season can be considered to save money.

Cocooning strategy. Cocooning is an immunization strategy that has been implemented in several countries to protect newborn infants from pertussis by immunization of any individuals who would come into regular contact with the infants. From these experiences, cocooning has proven to be a challenge due to practical and logistical barriers.[49] In addition, in a cost-effectiveness analysis of various pertussis vaccination strategies, cocooning was the more expensive compared with maternal immunization, whereas the latter strategy would offer better protection of infants, due to maternally acquired antibodies.[50] Furthermore, it is questionable whether transmission of the RS virus to the high-risk groups is preventable by the cocooning strategy considering the fact that the RS virus is very common and highly contagious. Therefore, cocooning does not seem a feasible strategy to protect infants or other persons at risk for severe RSV illness.

Summarizing, maternal immunization with a RSV vaccine seems a feasible approach that may be effective in protecting infants during the most vulnerable period against severe LRI. Therefore, this vaccination strategy deserves more attention. Although immunization of the young infants might also be promising, it needs to be determined whether the presence of maternal antibodies will interfere with the induction of an adequate immune response. Furthermore, the immature immune system may necessitate repeated vaccination, making it more difficult to reach protective immunity during the vulnerable early months after birth. Apart from infants, other groups at high-risk for severe RSV disease, have been identified. Since these risk groups largely seem to overlap with those at risk for severe influenza and pneumococcal disease, simultaneous vaccinations against these infectious diseases should be considered for these selected groups. Especially, since the seasonality of these diseases also largely overlap. Finally, additional data are needed to determine whether maternal immunization may be a successful approach to prevent severe RSV illness in young infants.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

P.K. drafted the outline and the text of the manuscript. W.L., expert of virology, has contributed to the intellectual content with respect to the virology and disease pathology of RSV. N.R., clinical vaccinologist, gave critical input regarding the clinical study data and different immunization strategies. All authors were actively involved in reviewing the content and editing the text of the manuscript. All authors read and approved the final version of the manuscript.

References

1. Bueno SM, González PA, Cautivo KM, Mora JE, Leiva ED, Tobar HE, et al. Protective T cell immunity against respiratory syncytial virus is efficiently induced by recombinant BCG. Proc Natl Acad Sci U S A 2008; 105:20822-7; PMID:19075247; http://dx.doi.org/10.1073/pnas.0806244105.
2. Collins PL, Melero JA. Progress in understanding and controlling respiratory syncytial virus: still crazy after all these years. Virus Res 2011; 162:80-99; PMID:21963675; http://dx.doi.org/10.1016/j.virusres.2011.09.020.
3. Resch B, Kurath S, Manzoni P. Epidemiology of respiratory syncytial virus infection in preterm infants. Open Microbiol J 2011; 5:135-43; PMID:22262986; http://dx.doi.org/10.2174/1874285801105010135.
4. Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003; 289:179-86; PMID:12517228; http://dx.doi.org/10.1001/jama.289.2.179.
5. Groothuis JR, Hoopes JM, Jessie VG. Prevention of serious respiratory syncytial virus-related illness. I: Disease pathogenesis and early attempts at prevention. Adv Ther 2011; 28:91-109; PMID:21318606; http://dx.doi.org/10.1007/s12325-010-0100-z.
6. Sommer C, Resch B, Simões EA. Risk factors for severe respiratory syncytial virus lower respiratory tract infection. Open Microbiol J 2011; 5:144-54; PMID:22262987; http://dx.doi.org/10.2174/1874285801105010144.
7. Zhou H, Thompson WW, Viboud CG, Ringholz CM, Cheng PY, Steiner C, et al. Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993-2008. Clin Infect Dis 2012; 54:1427-36; PMID:22495079; http://dx.doi.org/10.1093/cid/cis211.
8. Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med 2009; 360:588-98; PMID:19196675; http://dx.doi.org/10.1056/NEJMoa0804877.
9. Holman RC, Curns AT, Cheek JE, Bresee JS, Singleton RJ, Carver K, et al. Respiratory syncytial virus hospitalizations among American Indian and Alaska Native infants and the general United States infant population. Pediatrics 2004; 114:e437-44; PMID:15466069; http://dx.doi.org/10.1542/peds.2004-0049.
10. Connors M, Collins PL, Firestone CY, Murphy BR. Respiratory syncytial virus (RSV) F, G, M2 (22K), and N proteins each induce resistance to RSV challenge, but resistance induced by M2 and N proteins is relatively short-lived. J Virol 1991; 65:1634-7; PMID:1995956.
11. Stott EJ, Taylor G, Ball LA, Anderson K, Young KK, King AM, et al. Immune and histopathological responses in animals vaccinated with recombinant vaccinia viruses that express individual genes of human respiratory syncytial virus. J Virol 1987; 61:3855-61; PMID:3316707.
12. Mufson MA, Orvell C, Rafnar B, Norrby E. Two distinct subtypes of human respiratory syncytial virus. J Gen Virol 1985; 66:2111-24; PMID:2413163; http://dx.doi.org/10.1099/0022-1317-66-10-2111.
13. Hendry RM, Burns JC, Walsh EE, Graham BS, Wright PF, Hemming VG, et al. Strain-specific serum antibody responses in infants undergoing primary infection with respiratory syncytial virus. J Infect Dis 1988; 157:640-7; PMID:3346563; http://dx.doi.org/10.1093/infdis/157.4.640.
14. Muelenaer PM, Henderson FW, Hemming VG, Walsh EE, Anderson LJ, Prince GA, et al. Group-specific serum antibody responses in children with primary and recurrent respiratory syncytial virus infections. J Infect Dis 1991; 164:15-21; PMID:2056202; http://dx.doi.org/10.1093/infdis/164.1.15.
15. Sullender WM. Respiratory syncytial virus genetic and antigenic diversity. [table of contents.]. Clin Microbiol Rev 2000; 13:1-15; PMID:10627488; http://dx.doi.org/10.1128/CMR.13.1.1-15.2000.
16. Hall CB, Walsh EE, Long CE, Schnabel KC. Immunity to and frequency of reinfection with respiratory syncytial virus. J Infect Dis 1991; 163:693-8; PMID:2010624; http://dx.doi.org/10.1093/infdis/163.4.693.
17. Piedra PA. Clinical experience with respiratory syncytial virus vaccines. Pediatr Infect Dis J 2003; 22(Suppl):S94-9; PMID:12671459; http://dx.doi.org/10.1097/01.inf.0000053893.15894.ff.
18. Ohuma EO, Okiro EA, Ochola R, Sande CJ, Cane PA, Medley GF, et al. The natural history of respiratory syncytial virus in a birth cohort: the influence of age and previous infection on reinfection and disease. Am J Epidemiol 2012; 176:794-802; PMID:23059788; http://dx.doi.org/10.1093/aje/kws257.

19. Mejías A, Ramilo O. Review of palivizumab in the prophylaxis of respiratory syncytial virus (RSV) in high-risk infants. Biologics 2008; 2:433-9; PMID:19707374; http://dx.doi.org/10.2147/BTT.S3104.
20. Domachowske JB, Rosenberg HF. Respiratory syncytial virus infection: immune response, immunopathogenesis, and treatment. Clin Microbiol Rev 1999; 12:298-309; PMID:10194461.
21. Piedra PA, Jewell AM, Cron SG, Atmar RL, Glezen WP. Correlates of immunity to respiratory syncytial virus (RSV) associated-hospitalization: establishment of minimum protective threshold levels of serum neutralizing antibodies. Vaccine 2003; 21:3479-82; PMID:12850364; http://dx.doi.org/10.1016/S0264-410X(03)00355-4.
22. Kruijsen D, Bakkers MJ, van Uden NO, Viveen MC, van der Sluis TC, Kimpen JL, et al. Serum antibodies critically affect virus-specific CD4+/CD8+ T cell balance during respiratory syncytial virus infections. J Immunol 2010; 185:6489-98; PMID:20971927; http://dx.doi.org/10.4049/jimmunol.1002645.
23. Fishaut M, Tubergen D, McIntosh K. Cellular response to respiratory viruses with particular reference to children with disorders of cell-mediated immunity. J Pediatr 1980; 96:179-86; PMID:6243354; http://dx.doi.org/10.1016/S0022-3476(80)80799-2.
24. Waris ME, Tsou C, Erdman DD, Zaki SR, Anderson LJ. Respiratory synctial virus infection in BALB/c mice previously immunized with formalin-inactivated virus induces enhanced pulmonary inflammatory response with a predominant Th2-like cytokine pattern. J Virol 1996; 70:2852-60; PMID:8627759.
25. Graham BS, Henderson GS, Tang YW, Lu X, Neuzil KM, Colley DG. Priming immunization determines T helper cytokine mRNA expression patterns in lungs of mice challenged with respiratory syncytial virus. J Immunol 1993; 151:2032-40; PMID:8345194.
26. Kim HW, Canchola JG, Brandt CD, Pyles G, Chanock RM, Jensen K, et al. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. Am J Epidemiol 1969; 89:422-34; PMID:4305198.
27. Kapikian AZ, Mitchell RH, Chanock RM, Shvedoff RA, Stewart CE. An epidemiologic study of altered clinical reactivity to respiratory syncytial (RS) virus infection in children previously vaccinated with an inactivated RS virus vaccine. Am J Epidemiol 1969; 89:405-21; PMID:4305197.
28. Wright PF, Karron RA, Belshe RB, Shi JR, Randolph VB, Collins PL, et al. The absence of enhanced disease with wild type respiratory syncytial virus infection occurring after receipt of live, attenuated, respiratory syncytial virus vaccines. Vaccine 2007; 25:7372-8; PMID:17868959; http://dx.doi.org/10.1016/j.vaccine.2007.08.014.
29. Bernstein DI, Malkin E, Abughali N, Falloon J, Yi T, Dubovsky F; MI-CP149 Investigators. Phase 1 study of the safety and immunogenicity of a live, attenuated respiratory syncytial virus and parainfluenza virus type 3 vaccine in seronegative children. Pediatr Infect Dis J 2012; 31:109-14; PMID:21926667; http://dx.doi.org/10.1097/INF.0b013e31823386f1.
30. Gomez M, Mufson MA, Dubovsky F, Knightly C, Zeng W, Losonsky G. Phase-I study MEDI-534, of a live, attenuated intranasal vaccine against respiratory syncytial virus and parainfluenza-3 virus in seropositive children. Pediatr Infect Dis J 2009; 28:655-8; PMID:19483659; http://dx.doi.org/10.1097/INF.0b013e318199c3b1.
31. Piedra PA, Cron SG, Jewell A, Hamblett N, McBride R, Palacio MA, et al.; Purified Fusion Protein Vaccine Study Group. Immunogenicity of a new purified fusion protein vaccine to respiratory syncytial virus: a multi-center trial in children with cystic fibrosis. Vaccine 2003; 21:2448-60; PMID:12744878; http://dx.doi.org/10.1016/S0264-410X(03)00098-7.
32. Munoz FM, Piedra PA, Glezen WP. Safety and immunogenicity of respiratory syncytial virus purified fusion protein-2 vaccine in pregnant women. Vaccine 2003; 21:3465-7; PMID:12850361; http://dx.doi.org/10.1016/S0264-410X(03)00352-9.
33. Power UF, Nguyen TN, Rietveld E, de Swart RL, Groen J, Osterhaus AD, et al. Safety and immunogenicity of a novel recombinant subunit respiratory syncytial virus vaccine (BBG2Na) in healthy young adults. J Infect Dis 2001; 184:1456-60; PMID:11709789; http://dx.doi.org/10.1086/324426.
34. Falsey AR, Walsh EE, Capellan J, Gravenstein S, Zambon M, Yau E, et al. Comparison of the safety and immunogenicity of 2 respiratory syncytial virus (rsv) vaccines--nonadjuvanted vaccine or vaccine adjuvanted with alum--given concomitantly with influenza vaccine to high-risk elderly individuals. J Infect Dis 2008; 198:1317-26; PMID:18855558; http://dx.doi.org/10.1086/592168.
35. Langley JM, Sales V, McGeer A, Guasparini R, Predy G, Meekison W, et al. A dose-ranging study of a subunit Respiratory Syncytial Virus subtype A vaccine with and without aluminum phosphate adjuvantation in adults > or =65 years of age. Vaccine 2009; 27:5913-9; PMID:19651171; http://dx.doi.org/10.1016/j.vaccine.2009.07.038.
36. Hurwitz JL. Respiratory syncytial virus vaccine development. Expert Rev Vaccines 2011; 10:1415-33; PMID:21988307; http://dx.doi.org/10.1586/erv.11.120.
37. Anderson R, Huang Y, Langley JM. Prospects for defined epitope vaccines for respiratory syncytial virus. Future Microbiol 2010; 5:585-602; PMID:20353300; http://dx.doi.org/10.2217/fmb.10.22.
38. Widjojoatmodjo MN, Boes J, van Bers M, van Remmerden Y, Roholl PJ, Luytjes W. A highly attenuated recombinant human respiratory syncytial virus lacking the G protein induces long-lasting protection in cotton rats. Virol J 2010; 7:114; PMID:20525213; http://dx.doi.org/10.1186/1743-422X-7-114.
39. Jin H, Cheng X, Traina-Dorge VL, Park HJ, Zhou H, Soike K, et al. Evaluation of recombinant respiratory syncytial virus gene deletion mutants in African green monkeys for their potential as live attenuated vaccine candidates. Vaccine 2003; 21:3647-52; PMID:12922094; http://dx.doi.org/10.1016/S0264-410X(03)00426-2.
40. Teng MN, Whitehead SS, Bermingham A, St Claire M, Elkins WR, Murphy BR, et al. Recombinant respiratory syncytial virus that does not express the NS1 or M2-2 protein is highly attenuated and immunogenic in chimpanzees. J Virol 2000; 74:9317-21; PMID:10982380; http://dx.doi.org/10.1128/JVI.74.19.9317-9321.2000.
41. Ogilvie MM, Vathenen AS, Radford M, Codd J, Key S. Maternal antibody and respiratory syncytial virus infection in infancy. J Med Virol 1981; 7:263-71; PMID:7038043; http://dx.doi.org/10.1002/jmv.1890070403.
42. Stensballe LG, Ravn H, Kristensen K, Meakins T, Aaby P, Simoes EA. Seasonal variation of maternally derived respiratory syncytial virus antibodies and association with infant hospitalizations for respiratory syncytial virus. J Pediatr 2009; 154:296-8; PMID:19150677; http://dx.doi.org/10.1016/j.jpeds.2008.07.053.
43. Brandenburg AH, Groen J, van Steensel-Moll HA, Claas EC, Rothbarth PH, Neijens HJ, et al. Respiratory syncytial virus specific serum antibodies in infants under six months of age: limited serological response upon infection. J Med Virol 1997; 52:97-104; PMID:9131465; http://dx.doi.org/10.1002/(SICI)1096-9071(199705)52:1<97::AID-JMV16>3.0.CO;2-Y.
44. Ochola R, Sande C, Fegan G, Scott PD, Medley GF, Cane PA, et al. The level and duration of RSV-specific maternal IgG in infants in Kilifi Kenya. PLoS One 2009; 4:e8088; PMID:19956576; http://dx.doi.org/10.1371/journal.pone.0008088.
45. Shinoff JJ, O'Brien KL, Thumar B, Shaw JB, Reid R, Hua W, et al. Young infants can develop protective levels of neutralizing antibody after infection with respiratory syncytial virus. J Infect Dis 2008; 198:1007-15; PMID:18702606; http://dx.doi.org/10.1086/591460.
46. Nandapalan N, Taylor CE, Greenwell J, Scott M, Scott R, Hey EN, et al. Seasonal variations in maternal serum and mammary immunity to RS virus. J Med Virol 1986; 20:79-87; PMID:3760842; http://dx.doi.org/10.1002/jmv.1890200110.
47. Le Saux N, Gaboury I, MacDonald N. Maternal respiratory syncytial virus antibody titers: season and children matter. Pediatr Infect Dis J 2003; 22:563-4; PMID:12828155; http://dx.doi.org/10.1097/01.inf.0000069796.72540.0a.
48. Moro PL, Broder K, Zheteyeva Y, Walton K, Rohan P, Sutherland A, et al. Adverse events in pregnant women following administration of trivalent inactivated influenza vaccine and live attenuated influenza vaccine in the Vaccine Adverse Event Reporting System, 1990-2009. Am J Obstet Gynecol 2011; 204:146, e1-7; PMID:20965490; http://dx.doi.org/10.1016/j.ajog.2010.08.050.
49. Healy CM, Rench MA, Baker CJ. Implementation of cocooning against pertussis in a high-risk population. Clin Infect Dis 2011; 52:157-62; PMID:21288837; http://dx.doi.org/10.1093/cid/ciq001.
50. Westra TA, de Vries R, Tamminga JJ, Sauboin CJ, Postma MJ. Cost-effectiveness analysis of various pertussis vaccination strategies primarily aimed at protecting infants in the Netherlands. Clin Ther 2010; 32:1479-95; PMID:20728761; http://dx.doi.org/10.1016/j.clinthera.2010.07.017.