Published in final edited form as:
Vaccine. 2007 October 16; 25(42): 7372–7378. doi:10.1016/j.vaccine.2007.08.014.

The Absence of Enhanced Disease with Wild-Type Respiratory Syncytial Virus Infection Occurring After Receipt of Live, Attenuated, Respiratory Syncytial Virus Vaccines

Peter F. Wright[1], **Ruth A. Karron**[2], **Robert B. Belshe**[3], **Jian R. Shi**[1], **Valerie B. Randolph**[4], **Peter L. Collins**[5], **Alice F. O'Shea**[1], **William C. Gruber**[4], and **Brian R. Murphy**[5]

[1] Vanderbilt University, Nashville, TN

[2] Johns Hopkins School of Public Health, Baltimore, MD

[3] St. Louis University, St. Louis, MO

[4] Wyeth Vaccines Research, Pearl River, NY

[5] Laboratory of Infectious Diseases, NIAID, NIH, Bethesda, MD

Abstract

Early in the development of respiratory syncytial virus (RSV) vaccines severe disease occurred in children after receipt of formalin-inactivated RSV vaccine. Continuing efforts to develop an appropriately attenuated and immunogenic live RSV vaccine have given opportunities to assure that live vaccines are safe through surveillance of children after vaccination. In the present study, the rate of RSV-associated upper respiratory tract illness in 388 children was lower in RSV vaccinated children than in controls (14% versus 20% in a 6–24 month old group and 16% versus 25% in infants). Additionally, there was no evidence that vaccination predisposed to more severe lower respiratory tract illness. Thus infection with a series of live attenuated RSV vaccines did not result in enhanced disease upon infection with wild type RSV. The impact of RSV during this surveillance will inform the design of future efficacy studies with RSV vaccines.

Keywords

respiratory syncytial virus; vaccines; safety

1. Introduction

There is an urgent need for a respiratory syncytial virus (RSV) vaccine that will ameliorate or prevent illness on exposure to naturally circulating wild-type RSV. The primary approach taken in recent years has been to identify appropriately attenuated live, intranasally administered vaccines that can be given early in infancy[1–4]. However, there is residual concern that a live attenuated virus vaccine might create the same immunologic milieu in which disease of enhanced severity was seen in recipients of an inactivated RSV vaccine upon infection with

Corresponding author: Peter F. Wright, M.D., D-7219-MCN, Vanderbilt University, Nashville, TN, 37232, Tel 615-322-3017, Fax 615-343-9723, peter.wright@vanderbilt.edu.

wild type RSV[5–8]. Twentysix percent (37/140) of children participating in early trials of an inactivated RSV vaccine were hospitalized with severe RSV lower respiratory tract disease and there were 2 deaths[5–8]. This severe illness has profoundly influenced subsequent approaches to RSV vaccination and led to extensive animal trials to elucidate the nature of this immune-mediated injury. These animal models have both increased our immunologic understanding of enhanced disease [9] and are reassuring that such illness should not be seen with live vaccine[10]. However, it was essential to obtain direct confirmation in humans that infection with live attenuated RSV strains do not prime for enhanced disease.

In the course of development of a suitably attenuated and immunogenic live RSV vaccine there have been a substantial number of RSV seronegative children and young RSV naive infants with maternal antibody who have received vaccines or participated in trials as placebo recipients. All of the available children were followed through the subsequent winter season with clinical evaluation and viral detection in tissue culture with each clinically significant respiratory illness. Although limited data on vaccine safety was incorporated into some of the primary manuscripts, [1–4] the collation of this data in the current report provides the first comprehensive evidence of the safety of live RSV vaccines on subsequent exposure to wild-type virus.

2. Methods

2.1. Vaccines

The RSV vaccines studied are shown in Table 1. The derivation and characterization of these vaccines have been previously described [11–16]. Those vaccine candidates preceded with an rA2 in Table 1 were recombinant viruses derived by reverse genetics as described by Collins [17]. The vaccines had differing attenuating mutations and/or deletions, but all were live attenuated virus vaccines derived from RSV A2 and all had intact F and G surface glycoproteins, the two RSV neutralization antigens of RSV. Only the rA2cp 248/404/1030/ΔSH vaccine candidate was considered satisfactorily attenuated for young infants, and the others were considered slightly under attenuated (cpts 248/955, cpts 530/1009, cpts 248/404, and rA2cp 248/404 ΔSH) or over attenuated (rA2cp 530/1009 ΔNS2 and rA2cp 248/404 ΔNS2).

2.2. Populations under surveillance

In the winter season immediately following each child's vaccination surveillance was carried out at 3 sites in the United States and 1 site in South Africa. The vaccine trials and subsequent surveillance were done as part of an RSV vaccine development program conducted in part by Wyeth Vaccines, Pearl River, NY through two Cooperative Research and Development Agreements (AI-0087 and AI-0099) with the Laboratory of Infectious Diseases, NIAID, NIH.

Evaluation of these vaccines typically has proceeded in a step wise fashion from studies in adults, to older seropositive children, to seronegative children aged 6–24 months, and, with the appropriate safety and immunogenicity observations, to infants who received 2 doses of vaccine 1 month apart beginning at 1–2 months of age. Children in the vaccine trials were previously healthy with no underlying respiratory or cardiopulmonary disease that put them at special risk of more serious RSV disease. Surveillance was not done in adults or seropositive children. The seronegative and infant vaccinees, placebo recipients, and age-matched controls (included to amplify the number of unvaccinated subjects) make up the total of 388 study subjects followed through a subsequent winter respiratory viral season, Table 1. The surveillance was not blinded as parents of participants were informed of their child's vaccine assignment at the end of the acute phase of the vaccine trial nor were the trials designed to have the statistical power to show vaccine efficacy.

2.3. Surveillance

Surveillance was carried out from the first recognition of RSV in the community until 2 weeks after the last isolate. Samples were collected using nasal washes or aspirated nasal secretions as described for the acute phase of the vaccine trials [1–4]. Surveillance varied in intensity by trial and site with either active surveillance (phone calls at a biweekly intervals and culturing of all respiratory illness) to a more passive effort (culturing all respiratory illness that led to a physician visit). Only small differences in the frequency of illness sampled were seen between active and passive surveillance; and, therefore, the data has been combined in the analysis.

HEp-2 cells were used to isolate virus with confirmation of cytopathic effect with immunofluorescent staining. PCR was not performed and rapid antigen detection not routinely done. Serotyping of strains to distinguish between RSV A and B was done for most but not all isolates as described [18]. For a subset of children pre and post season serology were drawn to determine the incidence of RSV infection in the cohorts being followed using a neutralization assay previously described [1,2].

2.4. Data analysis

The primary aim was to determine if enhanced illness occurred on natural exposure to wild type RSV after receipt of a live attenuated RSV vaccine. For all analyses, children were divided into seronegative subjects 6–24 month old at the time of vaccination who received 1 dose of vaccine and RSV naïve subjects 1–3 months of age at vaccination who received 2 doses of vaccine. The data are presented in two ways. First, in an “intent to treat” analysis in which the data is combined for all the vaccinees regardless of their response to vaccine in comparison with age-matched placebo recipients and controls. Second, in an “efficacy in vaccine responders” analysis, the data originated from the study of only two vaccine candidates, cpts 248/404 and rA2cp 248/404/1030/ΔSH, which were administered to the largest number of subjects and which were evaluated in both RSV seronegative children and RSV naïve infants. For calculation of “efficacy”, vaccinees were counted only if they had a response to vaccine, which is defined as recovery of vaccine virus from the respiratory tract, a rise in serum neutralizing antibody, or response to 2 ELISA antibody assays detecting rises in antibody to the fusion, F, or attachment, G, proteins. Note that, for these two vaccine candidates, this involved between 63 and 100% of the recipients.

3. Results

3.1. Rate and severity of RSV infection in all vaccinees- “intent to treat”

An analysis based on all recipients of all vaccines compared to placebo and age matched controls is shown in Table 2. The purpose of this analysis is to determine if illness was more frequent or was skewed towards more serious LRI in vaccine recipients versus control subjects. Neither of these outcomes was observed. In the 62 subjects vaccinated at 1–3 months of age, 10 (16%) had an RSV-associated URI compared to 15 (25%) in 60 age matched controls. In the 113 children vaccinated at 6–24 months of age, 16 (14%) experienced an RSV-associated URI compared to 30 (20%) in 153 controls. In both age groups there were overlapping confidence intervals. Total and RSV associated LRI occurred with similar frequency in vaccinees and controls confirming the absence of disease enhancement in recipients of live attenuated RSV vaccine. A single hospitalization was seen that was not due to respiratory tract illness.

3.2. Comparison of severity and frequency of RSV infection in vaccine trials with cpts 248/404 and rA2cp 248/404/1030/ΔSH – "efficacy in vaccine responders"

The most specific way of identifying an adverse effect of vaccination was to compare only those vaccinees who had a response to vaccination (virus shedding or antibody response) with the matched control groups. This comparison was undertaken for two vaccines (cpts 248/404 and rA2cp 248/404/1030/ΔSH) that were given to the largest number of children and to both RSV seronegative children and RSV naïve infants (Table 2). The 47 1–3 month old vaccine responders had an incidence of RSV associated disease of 7 (15%) compared to 15 (25%) in 60 age-matched controls. In the 47 6–24 month old vaccine responders the incidence of RSV associated URI was 3 (6.4%) whereas the 85 controls had an incidence of 13 (15%). Again there was no evidence of an increase in severity or frequency of total or RSV associated LRI in either cohort (Table 2). Although it was not an aim of this analysis, the vaccines could be interpreted as offering some protection against RSV associated URI with a calculated vaccine efficacy of 54% in the infants and 40% in 6–24 month olds. Since the vaccines differed in their level of replication and attenuation and included vaccines that were insufficiently attenuated, the use of the word efficacy is meant to convey only that less illness was observed in the vaccine groups than in control groups following infection with wild type virus. The low rate of LRI did not allow any conclusions to be drawn about the induction of protection against more serious RSV disease by the live virus vaccine.

The RSV subgroup assignment for RSV isolates obtained in this study was determined, and 42 illnesses were caused by RSV subgroup A and 23 by subgroup B. The number of subgroup A isolates were less frequent in vaccinees than placebo recipients, 8.6/100 child years versus 12.7/100 child years. Type B isolates also occurred with a lower frequency in vaccinees (4.6/100 child years) than in placebo recipients (7/100 child years). The differences in both cases were not significant.

3.3. Overall rate of virologically proven RSV infection

Surveillance in placebo recipients and age matched controls offers an opportunity to describe the frequency and severity of RSV disease in a population of otherwise healthy children undergoing primary exposure to RSV (Table 3). The total incidence of URI was significantly higher in the 6–24 month age group than in the 1–3 month old infants. In contrast, the incidence of RSV-associated URI was greater in the 1–3 month old group. From this data one can expect to document RSV associated upper respiratory illness by culture in about 30% of infants and 21% of young children who have not previously experienced RSV. Culture-documented RSV accounted for 24% of the upper respiratory illness during the winter season in the youngest age group and 15% of the illness in 6–24 month olds. The incidence of lower respiratory illness (12% of the rate of upper respiratory infections in infants and 5.5% the rate in the older group) did not allow such precise calculations, but roughly 3.3 episodes of RSV associated LRI can be anticipated per 100 children in both age groups.

3.4. Serologic evidence of RSV infection

We also carried out surveillance for rises in RSV-specific serum antibodies during the winter/spring RSV season following the vaccine trials. Previous observations indicated that infection with RSV occurs frequently in this age group, and this was confirmed in vaccine and control groups (Table 4) in whom 13–42% seroresponse rates to infection with wild type RSV were documented. A seroresponse was defined as a 4-fold or greater increase in RSV-specific serum antibody titer using a plaque neutralization assay. The occurrence of frequent 4-fold seroresponses to wild type RSV infection in vaccinees, even in those with an initial seroresponse to vaccination (data not shown), indicates that infection with wild type RSV will occur with high frequency in both vaccinees and control subjects. Thus, a reduction in serologic

responses in vaccinees will not be a good indicator of vaccine efficacy. Rather, illness associated with RSV infection should be the measure of vaccine efficacy.

Vaccination in early infancy, while not often producing a detectable rise in neutralizing antibody titer following infection with vaccine virus, appeared to prime for such a serologic response after wild-type RSV infection. This conclusion was based on the observation that 20/54 1–3 month old vaccinees had a rise in neutralizing antibody titer during the subsequent RSV season versus only 6/46 controls (Table 4, p= 0.01). Since RSV was isolated with similar frequency from both groups, it is reasonable to assume that exposure to RSV was comparable in both groups and the enhanced seroresponse in the vaccinees was a reflection of immunological priming.

A comparison of illness and virus isolation in those with and without serum antibody rises was next undertaken (Table 4). There were 20 RSV illnesses in the 1–3 month old vaccinees and controls and only 7 of these (5 vaccinees and 2 controls) were accompanied by a seroconversion. Thus, only 35% (7 of 20) of this cohort had a seroresponse to infection with wild type RSV indicating that the incidence of infection with RSV would be significantly underestimated in this young age group if only a seroresponse was used as evidence of infection. The seroconversion rate is greater in those 1–3 month old subjects who received vaccine (5/9 infections accompanied by a serologic rise than in controls (only 2 of 11 infections with a rise in antibody supporting the suggestion offered above that prior receipt of vaccine primes for a RSV neutralizing antibody response to infection with wild type RSV. Almost all (11/13 or 85% of the 6–24 month old cohort with a documented infection with wild type RSV had an antibody response to that infection versus only 35% of the younger cohort.

The incidence of total illness (RSV plus non-RSV) experienced by vaccinees and control in the 6–24 month old cohort differed (Table 4). A higher percentage of symptomatic total respiratory infections were seen in controls with a seroresponse to RSV (23/27; 85%) than in vaccinees (9/18; 50%), p=0.02. The same trend was seen in the RSV-associated illnesses. This observation is consistent with the findings indicated above that are suggestive of vaccine efficacy.

4. Discussion

The primary goal of this study was determine if infection of recipients of a live RSV vaccine with wild type RSV resulted in enhanced RSV disease. Reassuring, but descriptive, data on severity of disease following wild-type RSV infection after receipt of some of these vaccines has been previously published [1–3]. The current, more comprehensive, analysis of surveillance presents very compelling data that the tested live attenuated, intranasal RSV vaccines do not potentiate disease on natural exposure to wild-type RSV. These vaccines varied with regard to their replicative capacity in humans, ranging from under-attenuated to over-attenuated, indicating that the lack of disease enhancement is likely to be a general property following infection with a live attenuated RSV vaccine and not a function of the replicative capacity of the vaccine candidate in humans. There was neither more frequent illness nor skewing towards more severe lower respiratory tract disease in the live virus vaccinees. The lower percentage of RSV-associated illness that was LRI in this study (12.3% of total RSV illness in controls) than in previous studies (37.8% of total RSV illness)[19] presumably reflects the intensity with which even minor illness was documented. Both subgroup A and B strains were isolated with high frequency from the vaccinees during the surveillance period indicating that the absence of disease enhancement was not a result of a lack of exposure to the diversity of RSV strains that circulate. The composite size of groups receiving a live attenuated RSV vaccine in these studies was larger (175) than in the historical groups receiving inactivated vaccine (140), indicating that there was a strong opportunity to have detected vaccine-

associated enhanced disease at any level comparable to that associated with the inactivated vaccine. The recipients of inactivated vaccine had a RSV associated hospitalization rate of 26%, compared to no hospitalizations for respiratory illness in current study. The observed rate of hospitalization in a comparable group of otherwise healthy unvaccinated children was 0.6 % [19] - similar to that in the controls and vaccinees in the current analysis. The above data indicate that surveillance for disease enhancement on exposure of vaccinees to wild type RSV should not be a required part of the vaccine evaluation when Phase I trials of similar live attenuated RSV vaccines are undertaken in the future, since this analysis has now been performed for 7 different vaccine candidates in the Phase I setting. Rather, this safety information will be more usefully obtained from larger Phase IIb trials designed to identify the correlates of immunity or to measure efficacy.

As noted in the papers describing the responses of infants to infection with cpts 248/404 and rA2cp 248/404/1030/ΔSH, the antibody responses, but not virus shedding, were diminished in young infants with residual maternal antibody when compared to older seronegative infants and children [1–3]. The young infants also exhibited a lower frequency of seroresponse to wild type infection compared to the 6–24 month-old children (35% versus 85%). This indicates that the reduced response observed in young infants in the vaccine trials might not be due to reduced immunogenicity of the vaccine resulting from attenuation, since the diminished response to wild type infection seems quantitatively similar. In spite of the near absence of a neutralizing antibody response of the young infants infected with the RSV vaccine, the vaccinees had diminished virus shedding after receipt of a second dose [1,3]. This indicated that an immune response capable of restricting RSV replication had occurred in the vaccinees. This short term surrogate for vaccine efficacy may also have been observed in the current study since total respiratory illness and RSV-associated upper respiratory illness were more frequently seen in controls than in RSV vaccinees suggesting that receipt of a RSV vaccine had decreased replication of wild type RSV sufficiently to modify illness. The trend of decreasing RSV-associated illness in vaccine recipients during the subsequent RSV season was suggestive of vaccine efficacy, but this conclusion would be premature since the studies involved multiple vaccines over multiple years and were not designed to evaluate efficacy.

The observations from the present study can be used to design an RSV efficacy trial for a live attenuated RSV vaccine that has achieved a satisfactory balance between attenuation and immunogenicity. A number of variables will be critical to the design of trials designed to measure efficacy of an RSV vaccine. The demographic features will include the risk profile of the population studied, the age of immunization, the intensity of RSV surveillance for disease after vaccination, and the endpoint chosen – all illness or hospitalizations, a graded severity score of illness, all RSV associated illness, or RSV associated LRI or hospitalization. The discrepancies between virologic and serologic evidence of infection in infants in this study suggests that additional techniques for virus detection at the time of illness, such as the polymerase chain reaction to quantitate viral RNA, should be incorporated into the trials. Specifically, the observations from the present study can be used to define the population size needed for an RSV efficacy trial. If RSV LRI is selected as one endpoint, the rate observed in the current study in controls was 3.3/100. The number of subjects experiencing RSV associated illness previously calculated from a different database on otherwise healthy children 0–24 months of age was very similar, specifically, 3.7/100 children [19]. Using data from these two sets of observations, assuming a vaccine efficacy of 50% and a power of 0.8, a study with 1500 per arm is estimated to be adequate to define efficacy against RSV associated LRI. Establishing an expanded safety profile of a live attenuated RSV vaccine in infants and/or using hospitalization as an endpoint will require numbers greater than 1500 subjects. However, the initial demonstration of efficacy against RSV LRI would be an important proof of concept of the live, intranasal vaccine approach to prevention of serious RSV disease. The design of such a trial could be modeled on the pediatric trials that showed the efficacy of live, attenuated,

intranasal influenza vaccines that used medically attended respiratory tract illness as an endpoint [20] or the prophylactic use of paluvizimab in which frequency and severity of illness in hospitalized, high risk patients was used as an endpoint [21].

Finally, the results of this paper provide assurance that it is safe to proceed with the development of live attenuated, intranasal RSV vaccines with minimal concern that enhanced disease will develop in the vaccinees upon natural infection with wild type RSV. Furthermore, the present study provides an experimental framework, i.e. a model, for the detection of disease enhancing potential of other RSV vaccines that are felt after preclinical testing to warrant evaluation in humans.

Acknowledgments

For surveillance done in South Africa. Shabir Madhi, M.D. Chris Hani-Baragwanath Hospital, Republic of South Africa and Nigel Blackburn, Ph.D., National Institute of Virology Loretta Moody provided a great deal of assistance in confirming primary clinical data. This work was supported in part by the Intramural Research Program of the NIAID through contract #NO1 AI15444.

References

1. Karron RA, Wright PF, Belshe RB, Thumar B, Casey R, Newman F, et al. Identification of a recombinant live attenuated respiratory syncytial virus vaccine candidate that is highly attenuated in infants. J Infect Dis 2005;191(7):1093–104. [PubMed: 15747245]
2. Karron RA, Wright PF, Crowe JE Jr, Clements-Mann ML, Thompson J, Makhene M, et al. Evaluation of two live, cold-passaged, temperature-sensitive respiratory syncytial virus vaccines in chimpanzees and in human adults, infants, and children. J Infect Dis 1997;176(6):1428–36. [PubMed: 9395351]
3. Wright PF, Karron RA, Belshe RB, Thompson J, Crowe JE Jr, Boyce TG, et al. Evaluation of a live, cold-passaged, temperature-sensitive, respiratory syncytial virus vaccine candidate in infancy. J Infect Dis 2000;182(5):1331–42. [PubMed: 11010838]
4. Wright PF, Karron RA, Madhi SA, Treanor JJ, King JC, O'Shea A, et al. The interferon antagonist NS2 protein of respiratory syncytial virus is an important virulence determinant for humans. J Infect Dis 2006;193(4):573–81. [PubMed: 16425137]
5. Chin J, Magoffin RL, Shearer LA, Schieble JH, Lennette EH. Field evaluation of a respiratory syncytial virus vaccine and a trivalent parainfluenza virus vaccine in a pediatric population. Am J Epidemiol 1969;89(4):449–63. [PubMed: 4305200]
6. Fulginiti VA, Eller JJ, Sieber OF, Joyner JW, Minamitani M, Meiklejohn G. Respiratory virus immunization. I. A field trial of two inactivated respiratory virus vaccines; an aqueous trivalent parainfluenza virus vaccine and an alum-precipitated respiratory syncytial virus vaccine. Am J Epidemiol 1969;89(4):435–48. [PubMed: 4305199]
7. 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(4):405–21. [PubMed: 4305197]
8. 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(4):422–34. [PubMed: 4305198]
9. Peebles RS Jr, Graham BS. Pathogenesis of respiratory syncytial virus infection in the murine model. Proc Am Thorac Soc 2005;2(2):110–5. [PubMed: 16113477]
10. Polack FP, Teng MN, Collins PL, Prince GA, Exner M, Regele H, et al. A role for immune complexes in enhanced respiratory syncytial virus disease. J Exp Med 2002;196(6):859–65. [PubMed: 12235218]
11. Connors M, Crowe JE Jr, Firestone CY, Murphy BR, Collins PL. A cold-passaged, attenuated strain of human respiratory syncytial virus contains mutations in the F and L genes. Virology 1995;208(2): 478–84. [PubMed: 7747420]
12. Crowe JE Jr, Firestone CY, Whitehead SS, Collins PL, Murphy BR. Acquisition of the ts phenotype by a chemically mutagenized cold-passaged human respiratory syncytial virus vaccine candidate

results from the acquisition of a single mutation in the polymerase (L) gene. Virus Genes 1996;13 (3):269–73. [PubMed: 9035372]

13. Firestone CY, Whitehead SS, Collins PL, Murphy BR, Crowe JE Jr. Nucleotide sequence analysis of the respiratory syncytial virus subgroup A cold-passaged (cp) temperature sensitive (ts) cpts-248/404 live attenuated virus vaccine candidate. Virology 1996;225(2):419–22. [PubMed: 8918930]
14. Prince GA, Curtis SJ, Yim KC, Porter DD. Vaccine-enhanced respiratory syncytial virus disease in cotton rats following immunization with Lot 100 or a newly prepared reference vaccine. J Gen Virol 2001;82(Pt 12):2881–8. [PubMed: 11714962]
15. Whitehead SS, Firestone CY, Karron RA, Crowe JE Jr, Elkins WR, Collins PL, et al. Addition of a missense mutation present in the L gene of respiratory syncytial virus (RSV) cpts530/1030 to RSV vaccine candidate cpts248/404 increases its attenuation and temperature sensitivity. J Virol 1999;73 (2):871–7. [PubMed: 9882287]
16. Whitehead SS, Bukreyev A, Teng MN, Firestone CY, St Claire M, Elkins WR, et al. Recombinant respiratory syncytial virus bearing a deletion of either the NS2 or SH gene is attenuated in chimpanzees. J Virol 1999;73(4):3438–42. [PubMed: 10074199]
17. Collins PL, Whitehead SS, Bukreyev A, Fearns R, Teng MN, Juhasz K, et al. Rational design of live-attenuated recombinant vaccine virus for human respiratory syncytial virus by reverse genetics. Adv Virus Res 1999;54:423–51. [PubMed: 10547682]
18. Wright PF, Gruber WC, Peters M, Reed G, Zhu Y, Robinson F, et al. Illness severity, viral shedding, and antibody responses in infants hospitalized with bronchiolitis caused by respiratory syncytial virus. J Infect Dis 2002;185(8):1011–8. [PubMed: 11930309]
19. Fisher RG, Gruber WC, Edwards KM, Reed GW, Tollefson SJ, Thompson JM, et al. Twenty years of outpatient respiratory syncytial virus infection: a framework for vaccine efficacy trials. Pediatrics 1997;99(2):E7. [PubMed: 9099764]
20. Belshe RB, Mendelman PM, Treanor J, King J, Gruber WC, Piedra P, et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine in children. N Engl J Med 1998;338(20):1405–12. [PubMed: 9580647]
21. The IMpact-RSV Study Group. Palivizumab a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 1998;102(3 Pt 1):531–7.

Table 1

Numbers of infants and seronegative children with surveillance in the winter after participation in RSV vaccine trials

Dates of Surveliance	Live RSV Vaccine	Number of Pediatric Subjects Studied			Ref.
		Total	Infant*	Seronegative Child**	
			(vac/cont)***	(vac/cont)***	
'94-'95	cpts 248/955****	10		6/4	[2]
'94-'96	cpts 530/1009****	66		16/50	[2]
'95-'98	cpts 248/404****	182	32/51	29/70	[3]
'99-'03	rA2cp 248/404/1030/SH	83	30/9	29/15	[1]
'98-'99	rA2cp 248/404/SH	12		9/3	[1]
'01-'03	rA2cp 530/1009 NS2	21		14/7	[4]
'00-'02	rA2cp 248/404/NS2	14		10/4	[4]

* Infants were 1–3 months of age at the time of vaccination.

** Children were 6–24 months old at the time of vaccination.

*** Vaccinees/ Controls with each vaccine in each age group

**** Biologically-derived viruses; the others are recombinant.

Table 2

Rate of total and RSV - associated respiratory illness in participants[†] in surveillance.

Age	Group	No. Studied	Total URI	RSV-URI	Total LRI	RSV-LRI
1–3 months (2 doses)**	All Vaccinees	62	32* *(52, 39–64)**	10 *(16, 9–25)*	5 *(8.1, CI 1.3–15)*	3 *(4.8, 0–10)*
	Controls	60	35 *(58, 46–71)*	15 *(25, 14–36)*	7 *(12, 3.6–20)*	2 *(3.3, 0–7.8)*
6–24 months (1 dose)***	All Vaccinees	113	59 *(52, 43–61)*	16 *(14, 7.7–20.6)*	5 *(4.4, 0.6–8.2)*	3 *(2.6, I 0–5.6)*
	Controls	153	109 *(71, 64–78)*	30 *(20, 13–26)*	11 *(7.2, 3–11.3)*	5 *(3.3, 0–6.1)*
1–3 months (2 doses)**	Vaccine Responders	47	23 *(49, 35–63)*	7 *(15, I 4.7–25)*	3 *(6.4, 0–13.4)*	1 *(2.1, 0–6.3)*
	Controls	60	35 *(58, 46–71)*	15 *(25, 14–36)*	7 *(12, 3.6–20)*	2 *(3.3, 0–7.8)*
6–24 months (1 dose)**	Vaccine Responders	47	25 *(53, 39–68)*	3 *(6.4, 0–13.4)*	2 *(4.3, 0–10)*	1 *(2.1, 0–6.3)*
	Controls	85	62*(73, 63–83)*	13*(15, 7.6–23)*	4*(4.7, 0–9.2)*	2*(2.4, 0–5.6)*

[†] URI, upper respiratory illness, and LRI, lower respiratory illness, were scored as mutually exclusive with the later coding being assigned with any lower respiratory component

* No of children.(%, 95% Confidence Intervals)

** In respiratory syncytial virus vaccine trials with cpts 248/404 and rA2cp 48/404/1030/SH.

*** This encompasses the experience with all 7 strains.

Table 3

The impact of RSV–associated illness as indicated by the number of episodes of RSV-associated respiratory illnesses in placebo recipients and age–matched controls

Vaccination Age (months)	No. of subjects	Illness			
		URI		LRI	
		Total	RSV-associated*	Total	RSV associated *
1–3	60	73 (122 +/− 111–132)**	18 (30 +/− 18–42)	9 (15 +/− 6–24)	2 (3.3 +/− 0–7.9)
6–24	153	220 (144 +/− 136–152)	32 (21 +/− 15–27)	12 (7.8 +/− 3.6–12)	5 (3.3 +/− 0.4–6.1)

* = Episodes of illness from which RSV was isolated

** (Episodes per 100 children +/− 95% CI)

Table 4

Seroresponses to RSV during the subsequent respiratory viral season in trials with vaccine candidates cpts 248/404 and rA2cp 248/404/1030/ΔSH.

Vaccination Age (months)	Group	Seroresponse**** (%)	Total illness in those with/without a seroresponse		RSV associated illness with/without a seroresponse	
			Response	No response	Response	No response
1–3	Vaccine	20/54 (37%) *	13/20 (65%)	19/34 (56%)	5/20 (25%)	4/34 (12%)
	Control	6/46 (13%)*	4/6 (66%)	27/40 (68%)	2/6 (33%)	9/40 (23%)
6–24	Vaccine	18/51 (35%)	9/18 (50%)***	21/33 (65%)	2/18 (11%)**	0/33 (0%) **
	Control	27/64 (42%)	23/27 (85%)***	29/37 (78%)	9/27 (33%)**	2/37 (5.4%)**

* Statistically greater seroconversion in vaccinees than controls, p=0.01.

** Statistically greater RSV isolation with illness in seroresponders(11/35) when compared with nonresponders (2/70), p= 0.001.

*** Statistically less total illness in vaccinees than controls, p=0.02.

**** 4-fold or greater rises in RSV-specific serum antibodies during the winter/spring RSV season following the vaccine study as measured by a 60% plaque reduction assay (1,2)