RSV Vaccines and the Elderly

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The Virus

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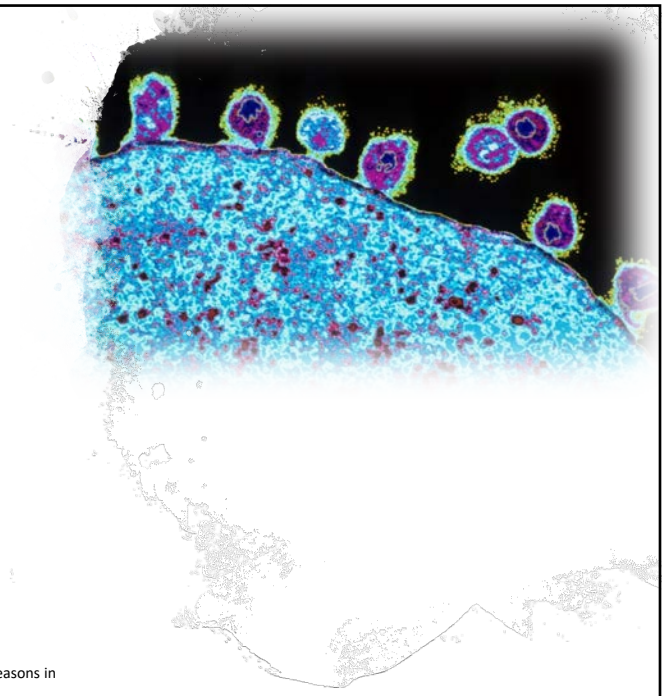
Respiratory Syncytial Virus

- RSV is a negative-sense single-stranded RNA virus (family Pneumoviridae) with a 15 kb genome that encodes 10 proteins.
- Two distinct antigenic subgroups have been identified, subtypes A and B (RSVA and RSVB, respectively) that show clear phylogenetic divergence.
- The glycoprotein (G), responsible for attachment to the host cell, exhibits the greatest genetic diversity within and between the subtypes. This is thought to reflect strong immune pressure and the subsequent generation of escape variants in a process analogous to antigenic drift in the hemagglutinin (HA) protein of the influenza A virus.
- Hence, reinfection with RSV is common.
- F – responsible for membrane fusion



Di Giallonardo et al.: Evolution of Human Respiratory Syncytial Virus (RSV) over Multiple Seasons in New South Wales, Australia. *Viruses* 2018;10:476; doi:10.3390/v10090476

3

RSV F-Protein Presents Multiple Conserved Sites

RSV Surface Proteins

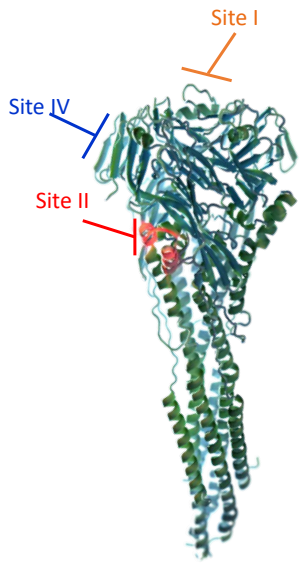
- G protein: Variable
- F protein: Conserved

Antigenic site II

- Targeted by palivizumab (Synagis®) and motavizumab
- Antibodies shown to prevent RSV disease in infants in 5 randomized clinical trials
- RSV F Vaccine induces antibodies with similar activity

Antigenic site I, Antigenic site IV

- Known broadly neutralizing antibodies
- Likely to contribute to protection[1]
- Also poorly elicited by natural infection



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[1]Beeler et al, *Neutralization Epitopes of the F Glycoprotein of Respiratory Syncytial Virus: Effect of Mutation upon Fusion Function.* J Virol, 1989

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The Disease

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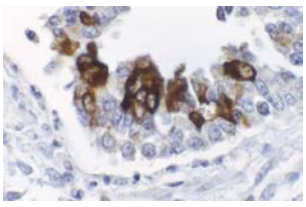
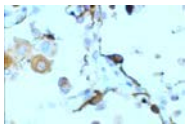
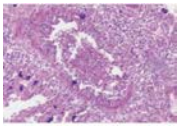
RSV Pathogenesis and Virology

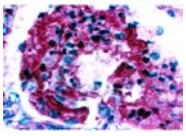
Ciliated epithelium and Type 1 Pneumocyte



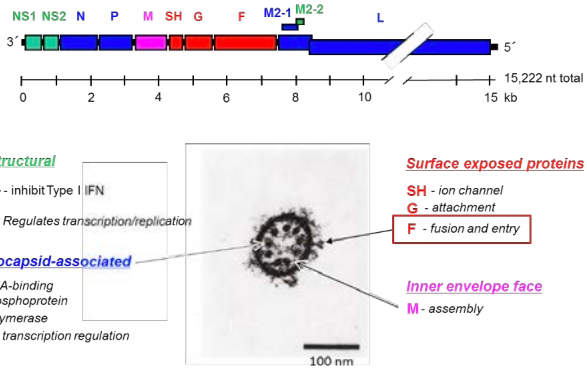




Obstructed airway



Mucus



Johnson JE, Graham BS, et al. Mod Pathol 2007; 20:108-19.

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Enhanced RSV disease with formalin-inactivated RSV vaccines

- In the late sixties, following initial encouraging results in small clinical trials, field evaluation trials of a formalin inactivated vaccine targeting RSV, called FI-RSV, were initiated in the United States. FI-RSV was cultured on monkey kidney cells, harvested, inactivated with formalin and aluminum-precipitated (FI-RSV lot 100).
- Four clinical studies in different age groups were conducted in in 1965-1967 [Chin, 1969; Fulginiti, 1969; Kapikian, 1969; Kim, 1969]. Results indicated that the FI-RSV vaccine did not protect against RSV infection.
- More importantly, children who had been vaccinated with the FI-RSV vaccine developed more severe clinical symptoms upon subsequent natural infection with RSV compared to the children who had not been vaccinated with the FI-RSV vaccine (resulting in 2 deaths in the study in which the youngest children were vaccinated [Kim, 1969]). In the study where the youngest subjects were vaccinated [Kim, 1969], 2 of the vaccinated children died, one at the age of 14 months, the other at the age of 16 months.

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Pathophysiology of FI-RSV enhanced RSV disease

Based on the clinical and pathological observations in the vaccinated children in combination with a large body of data from animal models, two (non-mutually exclusive) *hypotheses* on the immunological factors that contributed to FI-RSV enhanced RSV disease have been proposed:

- **Induction of low-quality, non-neutralising antibodies**. Murphy *et al* observed that upon natural RSV infection, the FI-RSV vaccinated subjects produced high amounts of poorly neutralising antibodies, indicating that natural infection boosted the low-quality antibody response induced by the FI-RSV vaccine [Murphy, 1986]. These antibodies did not neutralise RSV replication and contributed to the formation of immune complexes that may have contributed to the severe clinical symptoms and potentially immunopathology [Polack, 2002].
- **An unbalanced cellular immune response**. Another potential explanation is the induction of an unbalanced cellular immune response skewed towards Th2 (disturbed Th1/Th2 balance) [Connors, 1992; Connors, 1994; Waris, 1996]. This latter hypothesis is however mainly based on preclinical data in mouse models and is not consistently supported by data from other model animals [Antonis, 2003; Castilow, 2008; Phipps, 2007] and more likely a cytokine storm (irrespective of Th balance) has been contributing to FI-RSV enhanced RSV disease [Boukhvalova, 2006].

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Epidemiology

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RSV Epidemiology

- 35 million lower respiratory tract disease
- 3.5 million hospitalizations
- ~118,000 deaths
- Everyone infected by 2-3 years of age
- Recurrent infections every 3-10 years
- Severe disease associated with wheezing and asthma
- Major vaccine target populations: pediatric, maternal, older adults

Lancet 2010; 375: 1545–55

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Global burden of RTIs in elderly

- In 2015, there were 2.74 million deaths and 103 million DALYs (Disability Adjusted Life Years) attributable to RTI
- 1.27 million deaths in adults >70 years
- LRIs were the second-leading cause of DALYs globally after ischaemic heart disease
- Pneumococcal pneumonia caused 55% of LRI deaths in all ages; 693K in adults >70 years
- Between 2005 - 2015: number of deaths due to LRI decreased by 3.2% (from 2.83 to 2.74 million)
- 14% decrease in mortality rate in all ages, offset by population growth and ageing

Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory tract infections in 195 countries: a systematic analysis for the Global Burden of Disease Study 2015

GBD 2015 LRI Collaborators*

Summary

Background The Global Burden of Diseases, Injuries, and Risk Factors (GBD) Study 2015 provides an up-to-date analysis of the burden of lower respiratory tract infections (LRIs) in 195 countries. This study assesses cases, deaths, and aetiologies spanning the past 25 years and shows how the burden of LRI has changed in people of all ages.

Lancet Infect Dis 2017; 17: 1133–61
Published Online August 23, 2017

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RSV seasonality

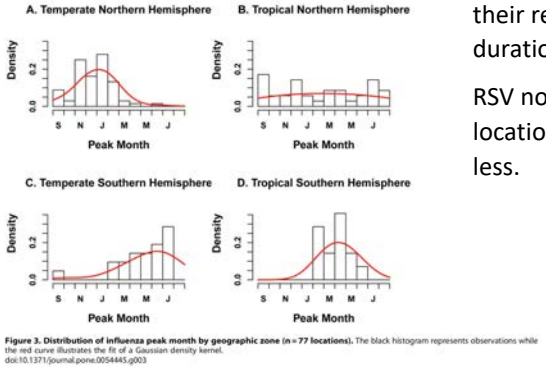

Figure 3. Distribution of influenza peak month by geographic zone (n = 77 locations). The black histogram represents observations while the red curve illustrates the fit of a Gaussian density kernel.
doi:10.1371/journal.pone.0054445.g003

Global seasonal patterns of influenza and RSV are broadly similar, with temperate locations of the Northern and Southern Hemisphere characterized by focused peaks of activity during their respective winters, and a wide range in the timing and duration of epidemics in the tropics.

RSV not prevalent year-round in the tropics – 80% of tropical locations experienced distinct RSV seasons lasting 6 months or less.

Bloom-Feshbach K, Alonso WJ, Charu V, Tamerius J, Simonsen L, et al. (2013) Latitudinal Variations in Seasonal Activity of Influenza and Respiratory Syncytial Virus (RSV): A Global Comparative Review. PLoS ONE 8(2): e54445. doi:10.1371/journal.pone.0054445

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Respiratory Syncytial Virus Infection in Elderly and High-Risk Adults

The NEW ENGLAND JOURNAL of MEDICINE

RESULTS

A total of 608 healthy elderly patients and 540 high-risk adults were enrolled in prospective surveillance, and 1388 hospitalized patients were enrolled. A total of 2514 illnesses were evaluated. RSV infection was identified in 102 patients in the prospective cohorts and 142 hospitalized patients, and influenza A was diagnosed in 44 patients in the prospective cohorts and 154 hospitalized patients. RSV infection developed annually in 3 to 7 percent of healthy elderly patients and in 4 to 10 percent of high-risk adults. Among healthy elderly patients, RSV infection generated fewer office visits than influenza; however, the use of health care services by high-risk adults was similar in the two groups. In the hospitalized cohort, RSV infection and influenza A resulted in similar lengths of stay, rates of use of intensive care (15 percent and 12 percent, respectively), and mortality (8 percent and 7 percent, respectively). On the basis of the diagnostic codes of the *International Classification of Diseases, 9th Revision, Clinical Modification* at discharge, RSV infection accounted for 10.6 percent of hospitalizations for pneumonia, 11.4 percent for chronic obstructive pulmonary disease, 5.4 percent for congestive heart failure, and 7.2 percent for asthma.

Table 3. Diagnostic Tests.

Test	RSV Infection	Influenza A	Influenza B
	no. of patients with positive test/total no. tested (%)		
Viral culture	64/2356 (3)	80/2356 (3)	18/2356 (<1)
RT-PCR*	163/2355 (7)	154/2354 (7)	Not done
Serologic test	183/2058 (9)	120/2051 (6)	29/2051 (1)
Total infections diagnosed by any method	244/2514 (10)	198/2514 (8)	35/2514 (1)

* RT-PCR denotes reverse-transcriptase polymerase chain reaction.

Table 4. Infections in Healthy Elderly Patients and High-Risk Patients.*

Variable	RSV Infection		Influenza A	
	Healthy Elderly Patients (N=46)	High-Risk Patients (N=56)	Healthy Elderly Patients (N=24)	High-Risk Patients (N=20)
Duration of illness — days	16±8	15±13	16±10	17±10
Contact with health care services — no. (%)				
Telephone call to doctor	7 (15)	13 (23)	4 (17)	9 (45)
Office visit	8 (17)	16 (29)	10 (42)	12 (60)
Emergency room visit	0	5 (9)	2 (8)	2 (10)
Hospitalization	0	9 (16)	0	4 (20)
Medications — no. (%)				
Antipyretic	21 (46)	18 (32)	15 (62)	7 (35)
Cough suppressant	19 (41)	25 (45)	11 (46)	8 (40)
Decongestant	15 (33)	7 (12)	4 (17)	4 (20)
Systemic corticosteroid	1 (2)	12 (21)	0	5 (25)
Bronchodilator	2 (4)	16 (29)	1 (4)	6 (30)
Antibiotic	4 (9)	24 (43)	8 (33)	12 (60)
Findings on chest radiography — no. (%)				
Performed	3 (7)	11 (20)	2 (8)	6 (30)
Infiltrate	1 (2)	4 (7)	0	2 (10)
Congestive heart failure	0	0	0	1 (5)
Other	1 (2)	1 (2)	0	3 (15)
Functional impairment ≥1 day — no. (%)				
Housebound	14 (30)	23 (41)	16 (67)	11 (55)
Confined to bed	3 (7)	14 (25)	6 (25)	5 (25)
Unable to perform activities of daily living	18 (39)	25 (45)	13 (54)	12 (60)
Death — no. (%)	0	2 (4)	0	0

* Plus–minus values are means ±SD. Patients with asymptomatic infections were included in the total number of infections, even though they did not seek medical services.

Falsey et al. NEJM 2005;352:1749-59

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Respiratory Syncytial Virus and Other Respiratory Viral Infections in Older Adults With Moderate to Severe Influenza-like Illness

Ann R. Falsey,[1,*] Janet E. McElhaney,[2,4,5] Jiri Beran,[3,4,5] Gerrit A. van Essen,[4,6,5] Xavier Duval,[5,6,c] Meral Esen,[7,5,c] Florence Galtier,[8,5,c] Pierre Gervais,[9,c] Shinn-Jang Hwang,[10,11,c] Peter Kremsner,[7,c] Odile Launay,[8,12,13,5,c] Geert Leroux-Roels,[14,5,c] Shelly A. McNeil,[15,c] Andrzej Nowakowski,[16,17,c] Jan Hendrik Richardus,[18,c] Guillermo Ruiz-Palacios,[19,5,c] Suzanne St Rose,[20,c] Jeanne-Marie Devaster,[21,4,5] Lidia Oostvogels,[21,4,5] Serge Durviaux,[20] and Sylvia Taylor[20,c]

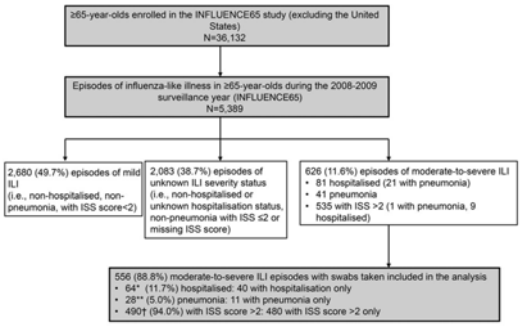
RSV and Respiratory Viruses in Older Adults • *JID* 2014;**209**:1873-81.

Background. Few studies have prospectively assessed viral etiologies of acute respiratory infections in community-based elderly individuals. We assessed viral respiratory pathogens in individuals ≥65 years with influenza-like illness (ILI).

Methods. Multiplex reverse-transcriptase polymerase chain reaction identified viral pathogens in nasal/throat swabs from 556 episodes of moderate-to-severe ILI, defined as ILI with pneumonia, hospitalization, or maximum daily influenza symptom severity score (ISS) >2. Cases were selected from a randomized trial of an adjuvanted vs non-adjuvanted influenza vaccine conducted in elderly adults from 15 countries.

Results. Respiratory syncytial virus (RSV) was detected in 7.4% (41/556) moderate-to-severe ILI episodes in elderly adults. Most (39/41) were single infections. There was a significant association between country and RSV detection ($P = .004$). RSV prevalence was 7.1% (2/28) in ILI with pneumonia, 12.5% (8/64) in ILI with hospitalization, and 6.7% (32/480) in ILI with maximum ISS > 2. Any virus was detected in 320/556 (57.6%) ILI episodes: influenza A (104/556, 18.7%), rhinovirus/enterovirus (82/556, 14.7%), coronavirus and human metapneumovirus (each 32/556, 5.6%).

Conclusions. This first global study providing data on RSV disease in ≥65 year-olds confirms that RSV is an important respiratory pathogen in the elderly. Preventative measures such as vaccination could decrease severe respiratory illnesses and complications in the elderly.



Take home message:
In a prospective study of relatively healthy community living or in retirement homes elderly, about 1 in 13 moderate to severe ILI episodes were associated with RSV. Bedridden elderly individuals were not eligible for enrolment in this study.

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RSV Hospitalisations in Australia, 2006-15

- In the UK, the estimated hospitalisation rate for adults aged 65 or more was 156 per 100,000 population (1995–2009). Australian estimates, based on RSV-specific codes, were lower, but there was a 20-fold increase in RSV-coded hospitalisations in this age group during 2006–2015, probably reflecting increased recognition of and testing for RSV disease in older adults; RSV-associated hospitalisations in this age group may still be under-recognised.
- Compared with other age groups, we found that adults over 65 had longer hospital stays, and the proportion of in-hospital deaths was greater. This is consistent with overseas findings of longer hospital stays and high mortality rates for older adults hospitalised with RSV infections. Older people are a recognised target group for preventing RSV disease, and further investigation of their disease burden is needed.
- the risk of RSV-associated Hospitalisation was 2.9–4.3 times as high for Indigenous adults aged 35–54 years as for non-Indigenous adults of corresponding age.

G. Saravanos et al. MJA 2019;210(10):447-53.

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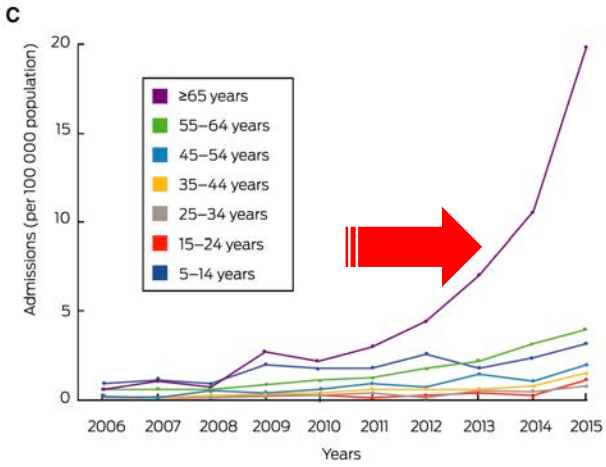
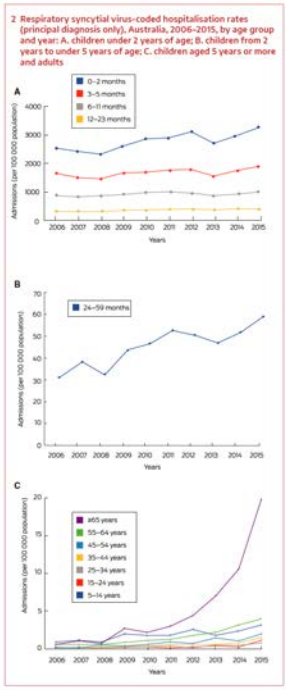
RSV hospitalisations 2006-15

Australia





G. Saravanos et al. MJA 2019;210(10):447-53.

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RSV Hospitalisations, 2006-15, Australia

4 Respiratory syncytial virus-coded hospitalisations (principal diagnosis only) of Indigenous and non-Indigenous Australians, 2011–2015, by age group

	Indigenous Australians		Non-Indigenous Australians		
Age group	Number	Rate* (per 100 000 population)	Number	Rate* (per 100 000 population)	Incidence rate ratio (95% CI)
Total number	3395	97	32 629	29	3.3 (3.2–3.5)
< 6 months	1851 (54.5%)	4310	16 155 (49.5%)	2253	1.9 (1.8–2.0)
< 5 years	3310 (97.5%)	789	30 063 (92.1%)	420	1.8 (1.8–2.0)
0–2 months	1003 (29.5%)	4671	10 364 (31.8%)	2890	1.6 (1.5–1.7)
3–5 months	848 (25.0%)	3949	5791 (17.7%)	1615	2.5 (2.3–2.6)
6–11 months	805 (23.7%)	1875	6386 (19.6%)	891	2.1 (2.0–2.3)
12–23 months	497 (14.6%)	589	5323 (16.3%)	371	1.6 (1.4–1.7)
24–59 months	157 (4.6%)	63	2199 (6.7%)	51	1.2 (1.1–1.5)
5–14 years	22 (0.6%)	3	311 (1.0%)	2	1.2 (0.7–1.8)
15–24 years	7 (0.2%)	1	58 (0.2%)	< 0.5	2.5 (1.0–5.6)
25–34 years	4 (0.1%)	1	70 (0.2%)	< 0.5	1.9 (0.5–5.1)
35–44 years	9 (0.3%)	2	120 (0.4%)	1	2.9 (1.3–5.6)
45–54 years	16 (0.5%)	5	170 (0.5%)	1	4.3 (2.4–7.1)
55–64 years	10 (0.3%)	5	317 (1.0%)	2	2.0 (1.0–3.7)
≥ 65 years	17 (0.5%)	8	1520 (4.7%)	9	0.9 (0.5–1.4)

CI = confidence interval. * Denominator based on Australian Bureau of Statistics census data.

G. Saravanos et al. MJA 2019;210(10):447-53.

17

A Vaccine

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Rationale for an RSV vaccine

- The humoral immune response is capable of neutralizing the virus and inhibiting viral replication, thereby playing a major role in protection against lower RSV infection and severe disease. Passive immunization with RSV-specific monoclonal antibodies (palivizumab – *Synagis*), when given prophylactically, has been shown to reduce RSV disease in premature infants and newborns with bronchopulmonary dysplasia or underlying cardiopulmonary disease.
- T-cells are also involved in the control of RSV disease. Lethal RSV infections have been described in patients with low CD8 T-cells counts as in the case of severe combined immunodeficiency, bone marrow and lung transplant recipients.
- A vaccine based on recombinant viral vectors carrying relevant RSV antigens, mobilizing both humoral and cellular arms of the immune response, offers a balanced and more effective immune response against the RSV virus in a naïve population. Adenoviral vector-based vaccines have been shown to be potent inducers of CD8 T-cells producing IFN-γ and antibodies against expressed antigens.

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The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates

Natalie I Mazur, Deborah Higgins, Marta C Nunes, José A Melero, Annefleur C Langedijk, Nicole Horsley, Ursula J Buchholz, Peter J Openshaw, Jason S McLellan, Janet A Englund, Asuncion Mejias, Ruth A Karron, Eric AF Simões, Ivana Knezevic, Octavio Ramilo, Pedro A Piedra, Helen Y Chu, Ann R Falsey, Harish Nair, Leyla Kragten-Tabatabaie, Anne Greenough, Eugenio Baraldi, Nikolaos G Papadopoulos, Johan Vekemans, Fernando P Polack, Mair Powell, Ashish Satav, Edward E Walsh, Renato T Stein, Barney S Graham, Louis J Bont; in collaboration with Respiratory Syncytial Virus Network (ReSViNET) Foundation

The global burden of disease caused by respiratory syncytial virus (RSV) is increasingly recognised, not only in infants, but also in older adults (aged ≥65 years). Advances in knowledge of the structural biology of the RSV surface fusion glycoprotein have revolutionised RSV vaccine development by providing a new target for preventive interventions. The RSV vaccine landscape has rapidly expanded to include 19 vaccine candidates and monoclonal antibodies (mAbs) in clinical trials, reflecting the urgency of reducing this global health problem and hence the prioritisation of RSV vaccine development. The candidates include mAbs and vaccines using four approaches: (1) particle-based, (2) live-attenuated or chimeric, (3) subunit, (4) vector-based. Late-phase RSV vaccine trial failures highlight gaps in knowledge regarding immunological protection and provide lessons for future development. In this Review, we highlight promising new approaches for RSV vaccine design and provide a comprehensive overview of RSV vaccine candidates and mAbs in clinical development to prevent one of the most common and severe infectious diseases in young children and older adults worldwide.

Lancet Infect Dis 2018; 18: e295–311
Published Online June 15, 2018
http://dx.doi.org/10.1016/S1473-3099(18)30171-6
This online publication has been corrected. The corrected version first appeared at thelancet.com/infection on July 25, 2018

Laboratory of Translational Immunology (N I Mazur MD)

	Vaccine type
Pregnant mothers	
RSV F nanoparticle (Novavax)	Particle-based
GSK RSV F (GSK)	Subunit
RSV F DS-Cav1 (NIH/NIAID/VRC)	Subunit
Paediatric	
RSV F nanoparticle (Novavax)	Particle-based
ChAd155-RSV (GSK)	Vector-based
SynGEM (Mucosis)	Particle-based
Ad26.RSV.preF (Janssen)	Vector-based
rBCG-N-hRSV (Pontificia Universidad Catolica de Chile)	Chimeric
RSV D46 cp ΔM2-2 (Sanofi Pasteur/LID/NIAID/NIH)	Live-attenuated
RSV LID ΔM2-2 1030s (Sanofi Pasteur/LID/NIAID/NIH)	Live-attenuated
RSV ΔNS2 Δ1313 I1314L (Sanofi Pasteur/LID/NIAID/NIH)	Live-attenuated
RSV D46/NS2/ N/ΔM2-2-HindIII (Sanofi Pasteur/LID/NIAID/NIH)	Live-attenuated
RSV LID cp ΔM2-2 (Sanofi Pasteur/LID/NIAID/NIH)	Live-attenuated
MEDI8897 (MedImmune)	Monoclonal antibody
Older adults	
RSV F nanoparticle (Novavax)	Particle-based
SynGEM (Mucosis)	Particle-based
MVA-BN RSV (Bavarian Nordic)	Vector-based
VXA-RSVf oral (Vaxart)	Vector-based
Ad26.RSV.preF (Janssen)	Vector-based
DPX-RSV-Protein (Immunovaccine, VIB and Dalhousie University)	Subunit
RSV F DS-Cav1 (NIH/NIAID/VRC)	Subunit

NIH=National Institutes of Health. NIAID=National Institutes of Allergy and Infectious Diseases. LID=Laboratory of Infectious Diseases. VIB=Flemish Institute of Biotechnology. VRC=Vaccine Research Center. RSV=respiratory syncytial virus.

Table 3: **Overview of vaccines and monoclonal antibodies by target population**

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RSV Vaccine Candidates

Live-attenuated		
rBCG-N-hRSV (Pontificia Universidad Catolica de Chile)	P	Pre-F and post-F
RSV D46 cp ΔM2-2 (Sanofi Pasteur/LID/NIAID/NIH)	P	Pre-F and post-F
RSV LID ΔM2-2 1030s (Sanofi Pasteur/LID/NIAID/NIH)	P	Pre-F and post-F
RSV ΔNS2 Δ1313/I1314L (Sanofi Pasteur/LID/NIAID/NIH)	P	Pre-F and post-F
RSV D46 ΔNS2 N ΔM2-2-HindIII (Sanofi Pasteur/LID/NIAID/NIH)	P	Pre-F and post-F
RSV LID cp ΔM2-2 (Sanofi Pasteur/LID/NIAID/NIH)	P	Pre-F and post-F

	Target Population	Pre-F Immunity[35]
Particle-based		
RSV F nanoparticle (Novavax)	M	Pre-F<post-F
RSV F nanoparticle (Novavax)	O	Pre-F<post-F
RSV F nanoparticle (Novavax)	P	Pre-F<post-F
SynGEM (Mucosis)	O and P	Unclear F conform
Vector-based		
MVA-BN RSV (Bavarian Nordic)	O	Pre-F<post-F
ChAd155-RSV (GSK)	O	Pre-F>post-F
VXA-RSVf oral (Vaxart)	O	Pre-F<post-F
Ad26.RSV.preF (Janssen)	P	Pre-F
Ad26.RSV.preF (Janssen)	O	Pre-F
Subunit		
GSK RSV F (GSK)	M	Pre-F
DPX-RSV (Dalhousie University, Immunovaccine, and VIB)	O	None
RSV F DS-Cav1 (NIH/NIAID/VRC)	O and M	Pre-F

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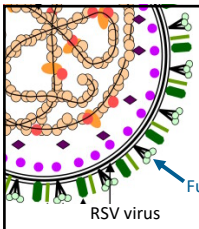


RSV vaccine candidates

Novavax: Purified, recombinant near-full-length RSV F fusion glycoprotein trimers. Trimers spontaneously assemble into 40-60 nm nanoparticle structures. Present neutralizing sites such as Site II, palivizumab binding site, in a multimeric format.

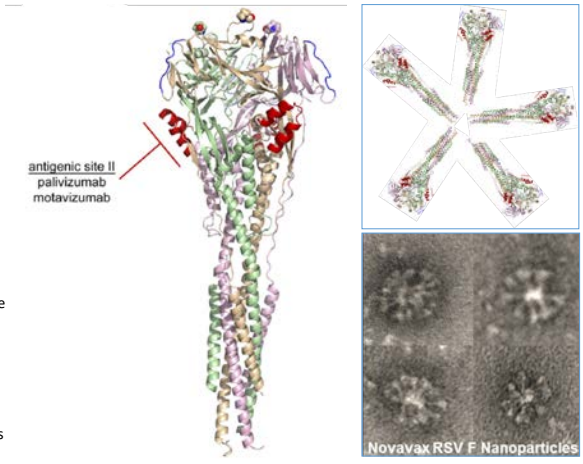
GSK: Based on the RSV viral proteins F, N and M2-1 encoded by a chimpanzee-derived adenovector (ChAd155-RSV).

Janssen: adenovirus-vectored vaccine candidate

Ad26.RSV.preF (JNJ-64400141-AAA), a replication-incompetent adenovirus serotype 26 (Ad26) containing a deoxyribonucleic acid (DNA) transgene that encodes for the pre-fusion conformation-stabilized F protein (pre-F) derived from the respiratory syncytial virus (RSV) A2 strain.

The F protein of RSV F undergoes a conformation transition from a metastable pre-fusion conformation to a stable post-fusion conformation. Neutralizing sensitive epitopes reside on both proteins, but recent evidence indicates that those epitopes specific to the pre-F protein seem to be more potent than those previously identified and present on the post-F protein.

NIH: pre-F target, DS-Cav1



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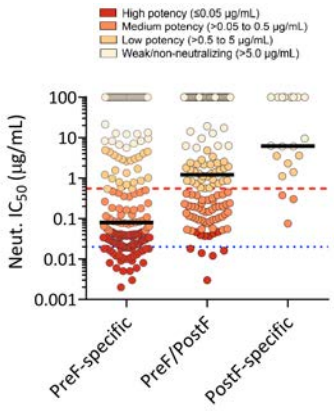
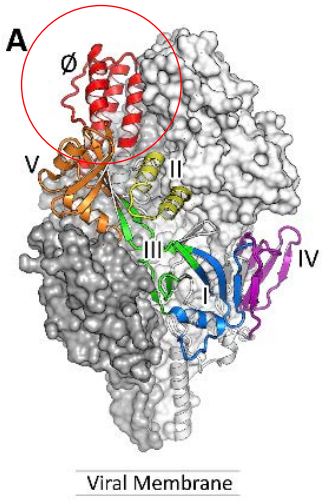
NIH candidate: pre-F target, DS-Cav1

Antibodies Targeting the Apex of Pre-F are the Most Potent





Gilman, McLellan, Walker et al. Science Immunology 2017

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NIH RSV vaccine candidate DS-Cav1

Clinical proof-of-concept for structure-based vaccine design

- Atomic-level resolution of the RSV pre-F structure enabled the stabilization and development of the DS-Cav1 subunit vaccine, which preserved the most neutralization-sensitive antigenic sites.
- DS-Cav1 boosted neutralization by >10-fold, with a robust increase at all doses with and without adjuvant.
- Serologic and cellular readouts demonstrated highly potent neutralizing antibodies, and stimulation of both dual-binding and pre-F exclusive IgG+ and IgA+ B cells.
- DS-Cav1 immunization stimulated CD4+ T cells with a Th1-type profile

A proof of concept for structure-based vaccine design targeting RSV in humans. Michelle C. Crank, … Barney S. Graham, the VRC 317 Study Team. Science 2019:365(6452):505-9.

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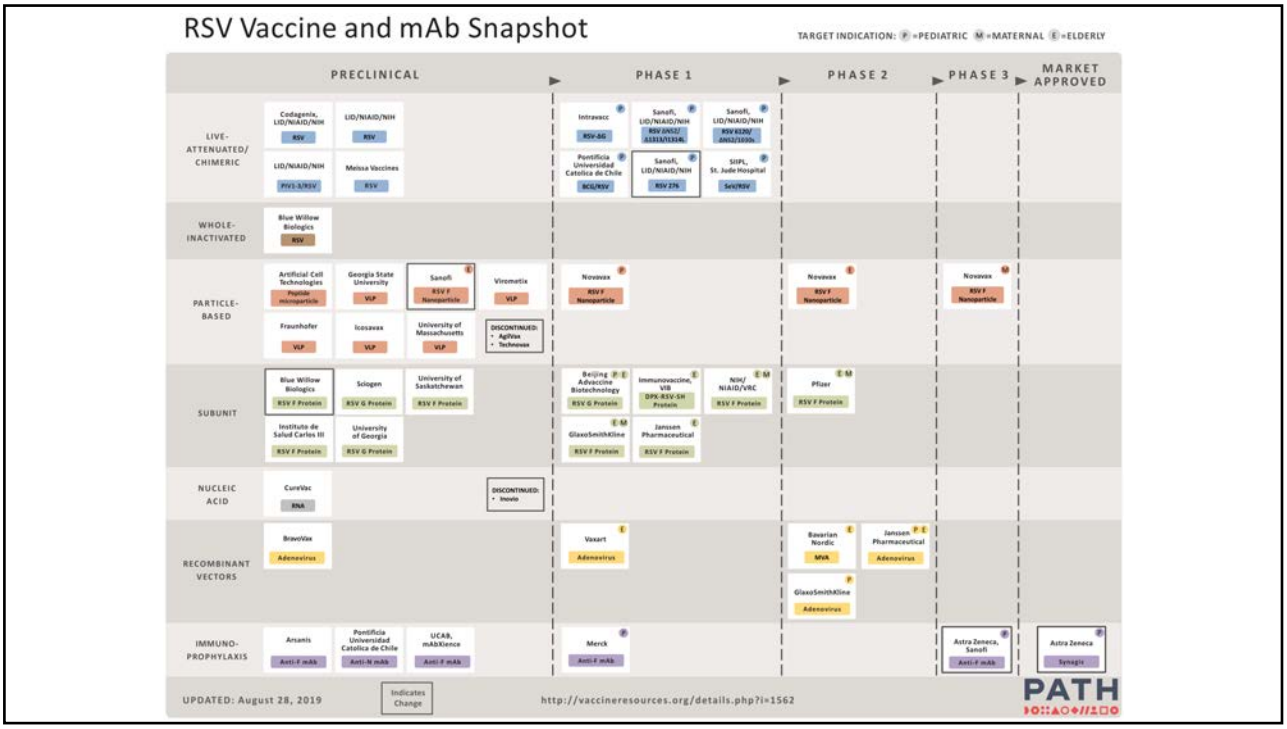

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Clinical Trials

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Novavax E-301 Results from elderly Phase 3 RCT:

RSV moderate to severe lower respiratory tract disease (RSV-msLRTD).

Efficacy Primary endpoint

	Placebo	RSV-F Vaccine	Efficacy % (95% CI)	P-value
Per protocol Efficacy N	5917	5892		
RSV msLRTD n (%)	26/5905 (0.44%)	28/5885 (0.48%)	-7.9% (-84, 37)	0.779
60-75 years	23/4517 (0.51%)	25/4519 (0.55%)	-8.6%	NS
>75 years	3/1392 (0.22%)	3/1379 (0.22%)	-0.9%	NS
With COPD or CHF	1/426 (0.23%)	4/456 (0.88%)	-273.7%	NS
No COPD or CHF	25/5484 (0.46%)	24/5497 (044%)	3.3%	NS
IIV administered Day 0	6/2142 (0.28%)	9/2115 (0.43%)	-52%	NS
IIV NOT administered Day 0	20/3768 (0.53%)	19/3782 (0.50%)	5.4%	NS
ITT efficacy N	5935	5921		
E-301 RSV-msLRTD n (%)	26 (0.44%)	28 (0.47%)	-7.9% (-84, 37)	0.778

Source: Novavax

NOTE: In a post-hoc subgroup analysis, the vaccine candidate showed efficacy against hospital admissions for all-cause chronic obstructive pulmonary disease (COPD) exacerbations.

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An Adjuvanted, Post-fusion F Protein–Based Vaccine Did Not Prevent Respiratory Syncytial Virus Illness in Older Adults

Phase 2b study evaluated MedImmune's (MEDI7510) RSV post-fusion F protein with glucopyranosyl lipid adjuvant (Toll-like receptor 4 agonist in a squalene-based oil-in-water emulsion). Subjects aged ≥60 years were randomly assigned 1:1 to vaccine or placebo. (N=1894)

Falloon J et al. J Infect Dis 2017

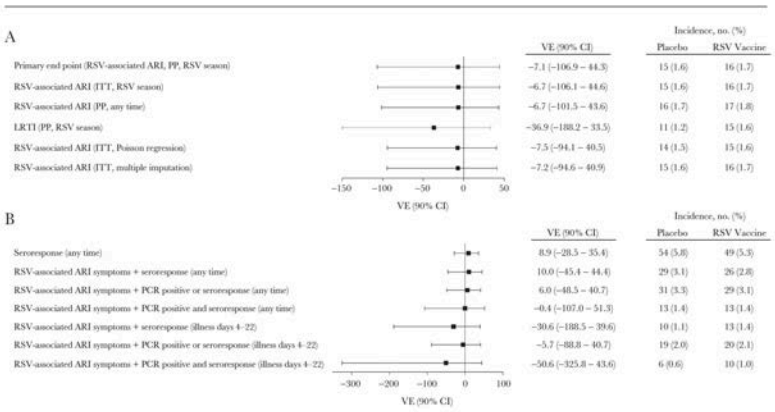

Figure 2. Forest plot of vaccine efficacy (VE) for the first episode of acute respiratory syncytial virus (RSV)–associated respiratory illness (ARI) or by seroresponse in the per protocol (PP) population. Assessment was during the surveillance period, starting 14 days after dosing, unless otherwise noted. *A*, Efficacy according to RSV-associated ARI definition (first episode of RSV-associated ARI symptoms plus RSV detection in respiratory specimen by polymerase chain reaction analysis). *B*, Efficacy according to seroresponse definition (ie, RSV-associated ARI symptoms plus seroresponse to nonvaccine antigens). CI, confidence interval; ITT, intention to treat; LRTI, lower respiratory tract illness.

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M-301 Novavax RSV-F vaccine Pregnancy

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Maternal Immunization to Address Infant LRTI

- Young age at infection is the most significant factor predicting severity of acute LRTI[1,] probably due to:
  - Small calibre airways
  - Immature immune system
- Achieving timely immunity via active immunization in the first few months of life is challenging, but
- Immunization of pregnant women could provide protection to their infants in the first months of life via transplacental transfer of maternal antibody
  - Influenza, pertussis, and tetanus vaccines in pregnancy are successful precedents

1. Prasad N. Epidemiol Infect 2018; 146:1861

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The RSV F Nanoparticle Vaccine Trial: Study Design

Primary objective

Determine the **efficacy** of maternal immunization with the RSV F vaccine against **medically significant RSV lower respiratory tract infection (LRTI)** through 90, 120, 150 and 180 days of life in infants.

Design	Randomized, Observer-Blind, Placebo-Controlled	
	Participants	• **4,636** third trimester pregnant women **randomized 2:1 (vaccine:placebo) at 87 sites in 11 countries**
	Length of Study Participation	• Mothers: up to 9 months • Infants: 1 year after delivery
	Dosing	• 1 intramuscular (IM) Injection of RSV F vaccine or placebo at **28-36 weeks** Estimated Gestational Age (EGA)
	Safety Assessment	• Through 6 months post-partum in mothers • Through 1 year in infants
	Efficacy Assessment	• **Active/passive surveillance in mothers and infants** • Confirmation of RSV infection by RT-PCR • Medically significant tachypnea or pulse oximetry (infants only) • Confirmation of LRTI (infants only)

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Summary of key efficacy findings:

Per protocol population

Efficacy (%) (97.52%CI and 95%CI for MS RSV LRTI primary endpoint, all others 95%CI) Placebo, Vaccine cases	MS LRTI	LRTI hospitalizations	LRTI w/ severe hypoxemia
Primary and secondary RSV⁺ w/ Site data through 90 days	**39.4** (-1, 63.7)[1] (5.3, 61.2)[2] 35/1430, 41/2765	**44.4** (19.6, 61.5) 53/1430, 57/2765	**48.3** (-8.2, 75.3) 14/1430, 14/2765
Pre-specified exploratory RSV⁺ w/expanded data through 90 days	**40.9** (15.9, 58.5) 56/1430, 64/2765	**41.7** (16.7, 59.2) 55/1430, 62/2765	**59.6** (32.1, 76.0) 32/1430, 25/2765
All-cause LRTI data through 90 days Expanded data (RSV⁺ not required)	**21.7** (1.0, 38.1) 116/1547, 175/2980	**36.4** (17.4, 51.0) 102/1547, 125/2980	**47.0** (21.8, 64.2) 50/1547, 51/2980

1. (97.5% CI); 2. (95.0% CI) Madhi SA/Munoz F et al ESPID; Ljubljana, Slovenia | May 6 – 11, 2019; Abstract 19-1046

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Effect Modification by Country: Primary and Secondary Endpoints

Vaccine Efficacy Estimates by Place (PP, Site Data)[1]

0 to 90 days	USA	S. Africa	ROW[3]
MS RSV LRTI (primary)	11.6% 6/346 (1.7%) vs 10/652 (1.5%)	42.5% 22/732 (3.0%) vs 25/1447 (1.7%)	54.7% 7/352 vs 6/666
LRTI w/ severe hypoxemia	46.9% 2/346 (0.6%) vs 2/652 (0.3%)	49.4% 9/732 (1.2%) vs 9/1447 (0.6%)	47.1% 3/352 vs 3/666
LRTI w/ hospitalization	-112.3% 2/346 (0.6%) vs 8/652 (1.2%)	58.5% 39/732 (5.3%) vs 32/1447 (2.2%)	25.1% 12/352 vs 17/666

Note the control group rates in US subjects much lower than South Africa. There was not enough RSV-related disease except in ZA to permit a reliable estimate of vaccine effect.

[1] Display format: VE
Placebo vs Vaccine, cases/N (rate%)

[3] ROW = rest of world

Source: Novavax

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Impact of Maternal RSV Immunization on Pneumonia over One Year of Life

		Counts (%)			
Endpoint	Time Interval	Placebo (N = 1562)	Vaccine (N = 3010)	Efficacy	95% CI
Clinical pneumonia reported (All Cause)	0 to 90 days	51 (3.27)	45 (1.50)	54.2%	32.0, 69.2
	0 to 180 days	66 (4.23)	65 (2.16)	48.9%	28.4, 63.5
	0 to 364 days	80 (5.12)	78 (2.59)	49.4%	31.3, 62.7
Clinical pneumonia with CXR positive (All Cause)	0 to 90 days	33 (2.11)	24 (0.80)	62.3%	36.4, 77.6
	0 to 180 days	42 (2.69)	34 (1.13)	58.0%	34.2, 73.2
	0 to 364 days	47 (3.01)	39 (1.30)	56.9%	34.5, 71.7
Clinical pneumonia with positive CXR and RSV+ by PCR	0 to 90 days	21 (1.34)	11 (0.37)	72.8%	43.8, 86.9
	0 to 180 days	23 (1.47)	12 (0.40)	72.9%	45.7, 86.5
	0 to 364 days*	23 (1.47)	12 (0.40)	72.9%	45.7, 86.5

Data on all SAEs coded as "pneumonia," excepting "congenital pneumonia" in first 24 hours. Based on safety database as of 09 Jul 19.
*No active surveillance for RSV post day 180
**Pneumococcal vaccine NNV calculated from Cutts FT. Lancet 2005; 365:1139 and Palmu A. Vaccine 2018; 36:1826

- Clear *post-hoc* observation of efficacy against infant pneumonia through one year.
- Number-needed-to-vaccinate (NNV) to prevent one hospitalized case of pneumonia ~40, (All Cause).
- NNV for pneumococcal conjugate vaccines to prevent one case of clinical or x-ray confirmed all-cause pneumonia 47 to 185**

Source: Novavax

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Monoclonal antibodies

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Medimmune – RSV preF mAb (Nirsevimab)

- Passive RSV vaccine strategy using RSV F mAb
- Fully human, high potency IgG1 mAb derived from human B-cells
- Targets site on RSV prefusion F site O
- Neutralizes RSV A and B clinical isolates
- Single fixed IM dose given; expected to protect up to 6 months
- Given at birth or at onset of RSV season

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Monoclonal antibody – *Nirsevimab*

Phase 2b Overview

- Single dose of 50 mg IM Nirsevimab: statistically significant 70% relative reduction in the incidence of RSV-confirmed LRTI (in and outpatients) through 150 days in healthy preterm infants
- Nirsevimab also demonstrated a statistically significant 78% relative reduction in the incidence of RSV LRTI hospitalization through 150 days post dose
- Nirsevimab was effective in preventing both RSV A and RSV B subtypes
- In healthy preterm infants, the safety profile of Nirsevimab was favorable with similar types and frequencies of adverse events reported in Nirsevimab and placebo recipients.

From Renato Stein (ESCMID Vaccines, Bilbao 2019); and Pam Griffin (Medimmune)

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Conclusions

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Conclusions

- Epidemiologic data for elderly still not good enough to evaluate cost effectiveness of an RSV vaccine. Urgent need for better studies with RSV-related disease identification.
- 3 clinical trial 'failures', need careful interpretation – evidence of VE is there in part. 'Failure' of the clinical trial as opposed to failure of the vaccine.
- Pipeline of several promising candidates based on very strong science (especially structural biology) means that a licensed vaccine is probably not far off.
- Safety is always a concern, but vaccine-responsible enhanced respiratory disease possibly of historical interest only, but in any case, should not be an issue for seropositive vaccinees.
- Long-acting monoclonal antibody may be an attractive option for elderly with significant risk factors, depending on cost.

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Thank you.

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