Global Vaccine and Immunization Research Forum

RSV vaccine development for Low and Middle Income Countries: Challenges and Progress

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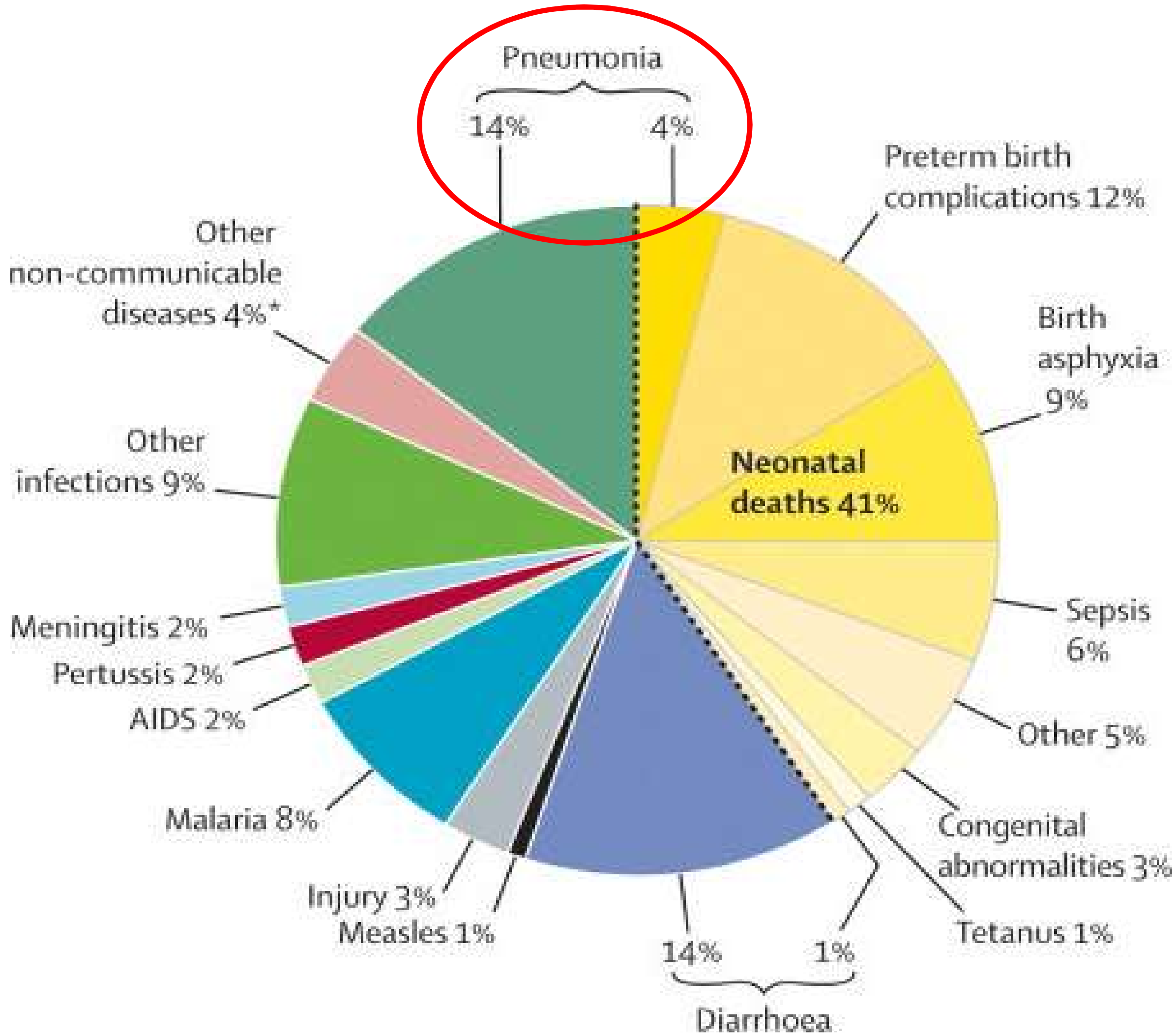
Global causes of child deaths



Burden of RSV in the world

- Systematic review of studies published 1995-2009
- For 2005:
  - 33.8 (95% CI 19.3-46.2) million RSV cases in children <5
  - 96% in developing countries
  - 3.4 million severe RSV cases, 91% in developing countries
- Case fatality in RSV severe ALRI
  - 0.3% in children <5 y in developed countries
  - 2.1% in children <5 in developing countries
- Global mortality estimates in children <5 global:
  - 65,590 deaths, 99% in developing countries by CFR method
  - 155,232 deaths in dev countries by hypoxaemia method
  - 199,260 deaths in dev countries extrapolating from Indonesia study

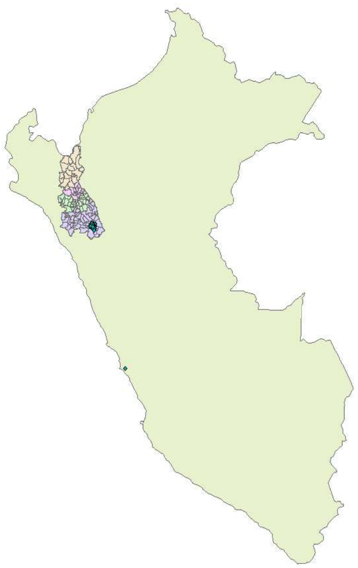
Ref: Nair H et al. Lancet 2010;375:1545-55.

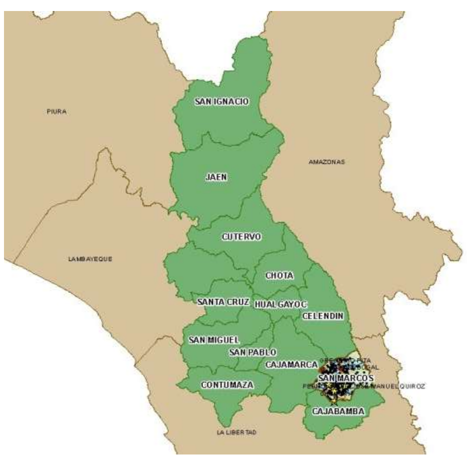
RSV as caused of Severe Acute Lower Respiratory Infections in the World

- Estimated burden of pneumonia and applied etiological fractions, adjusted for Hib and Strep pneumo vaccine use, with models applied for each country in the world.
- RSV burden:
  - 29% of all ALRI
  - 23% of all severe ALRI
- 3.2 million cases of RSV severe ALRI in children <5 y in the world in 2010 (95% CI: 1.7-6.1 million):
  - SEARO 38%
  - AFRO 17%
  - AMRO 13%
  - WPRO 13%
  - EMRO 11%
  - EURO 8%
- No mortality estimates

Ref: Rudan I et al. J Glob Health 2013;3:010401

Ubicacion geografica del estudio





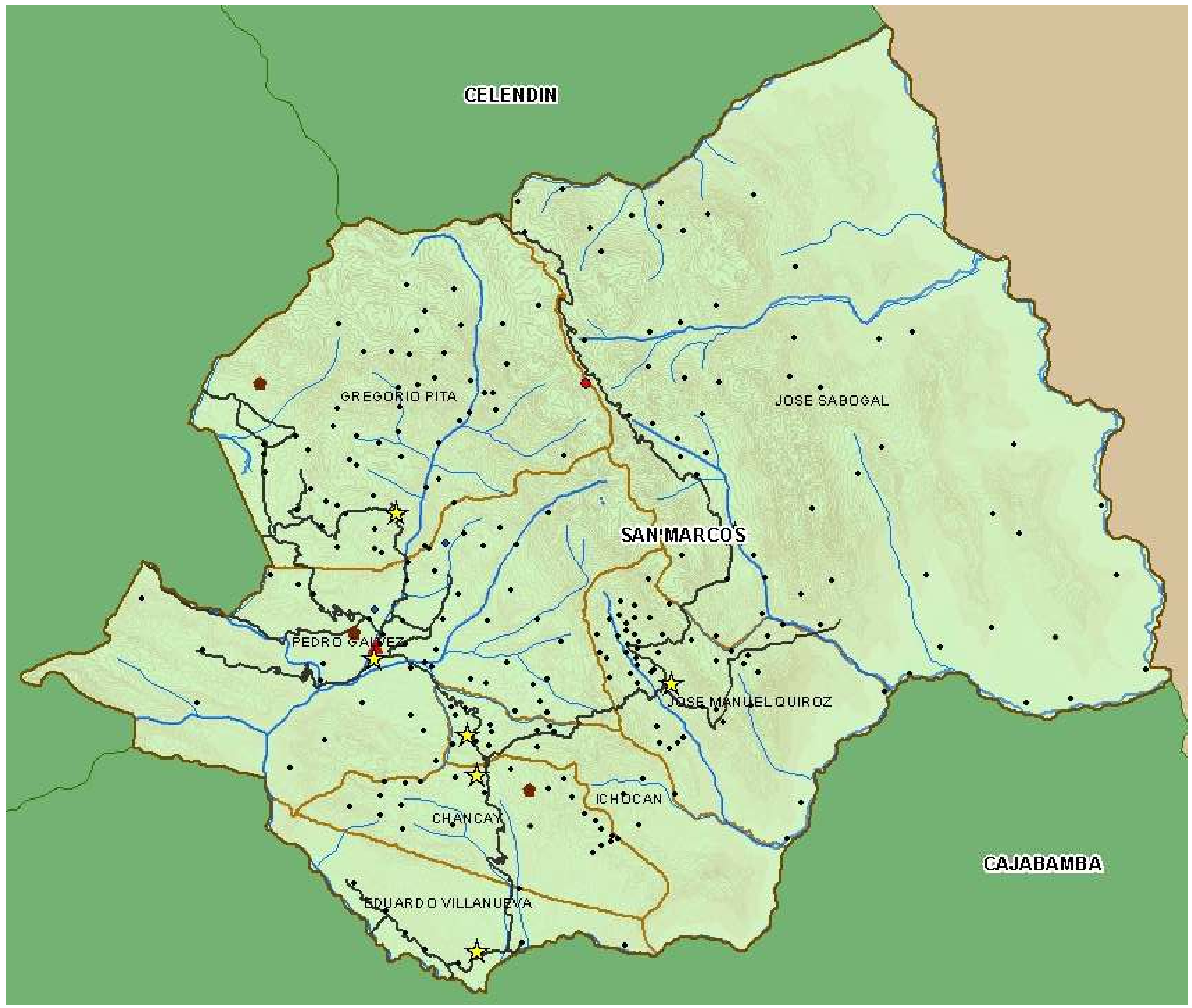
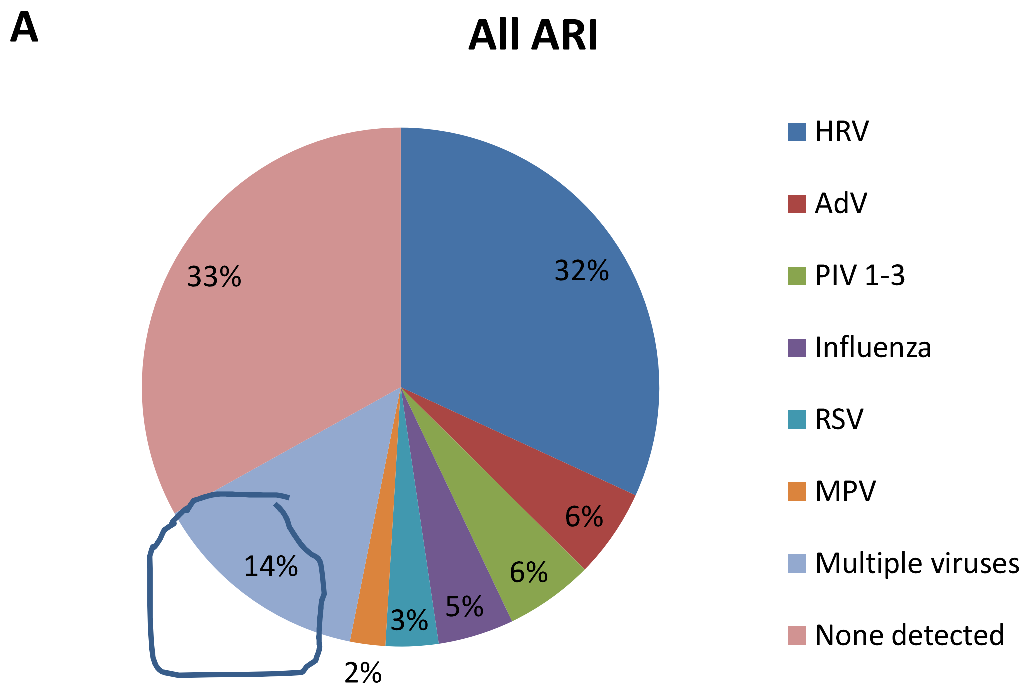


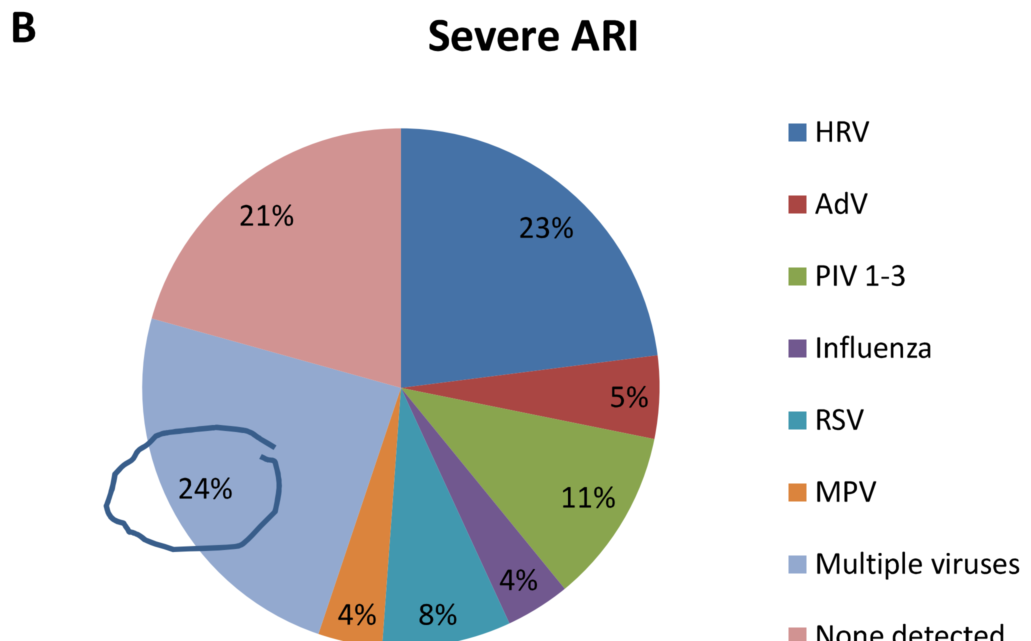
Table 1: Adjusted incidence per 100 person-years

Virus	Incidence (95% CI)			
	All ages	0 - 5 months	6 - 11 months	12 - 35 months
Human rhinovirus	236 (221 - 252)	266 (234 - 303)	313 (280 - 351)	206 (190 - 224)
Adenovirus	73 (65 - 82)	27 (19 - 38)	99 (78 - 125)	81 (71 - 93)
Parainfluenza 1-3	46 (41 - 51)	41 (31 - 53)	54 (43 - 68)	45 (39 - 51)
Influenza	37 (31 - 43)	35 (26 - 48)	44 (34 - 57)	31 (27 - 37)
Respiratory syncytial virus	30 (26 - 34)	34 (25 - 47)	34 (25 - 45)	28 (23 - 33)
Human metapneumovirus	17 (14 - 20)	12 (8 - 20)	27 (19 - 37)	16 (13 - 20)
Any one of the above viruses	360 (340 - 380)	365 (327 - 409)	472 (430 - 518)	328 (306 - 352)

Budge PJ et al. Pediatr Infect Dis J 2013 Dec 30. [Epub ahead of print]

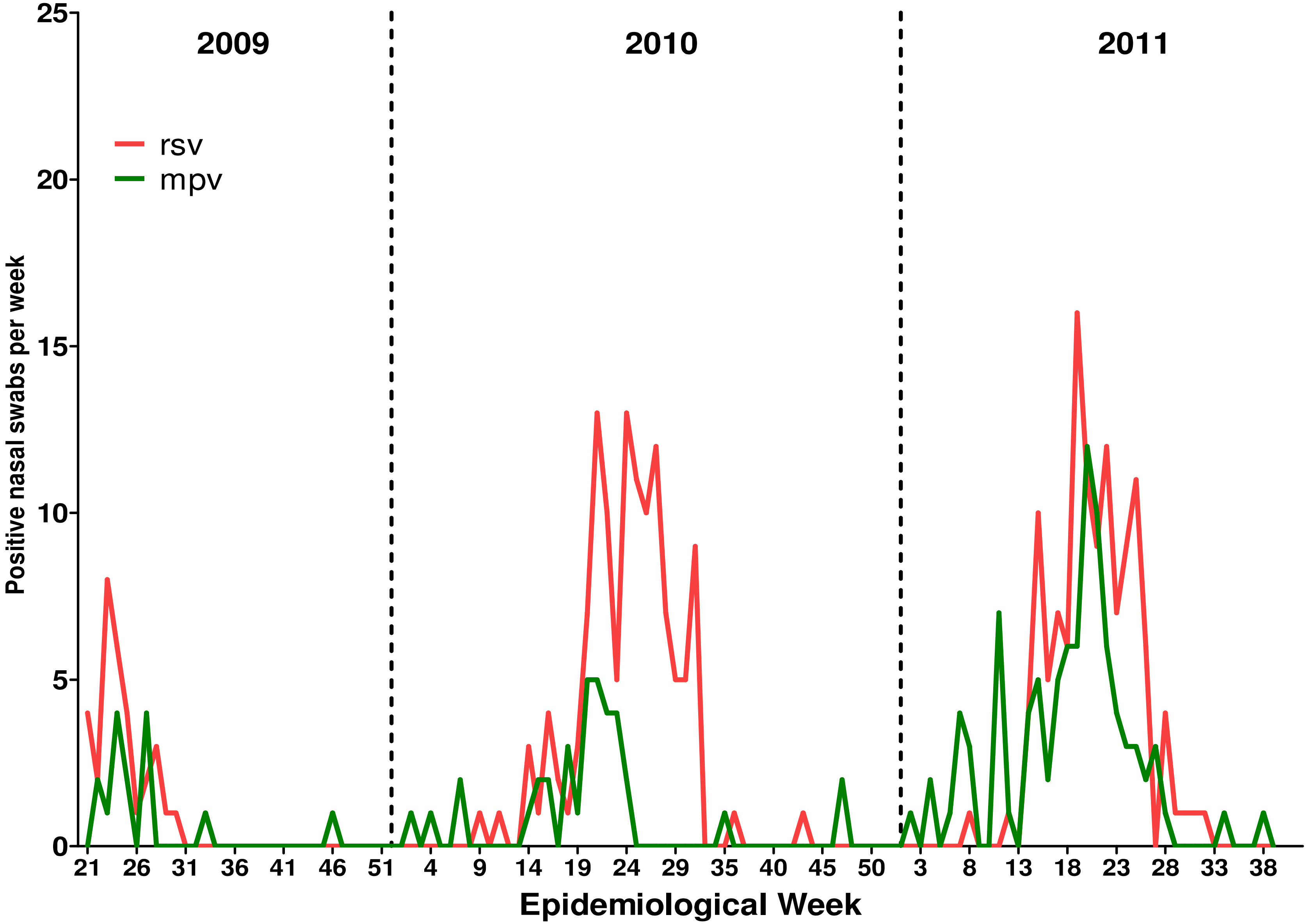
Causes of ARI and Severe ARI in children <3 in San Marcos, Cajamarca, Peru





Budge PJ et al. Pediatr Infect Dis J 2013 Dec 30. [Epub ahead of print]

RSV and metapneumovirus



Budge PJ et al. Pediatr Infect Dis J 2013 Dec 30. [Epub ahead of print]

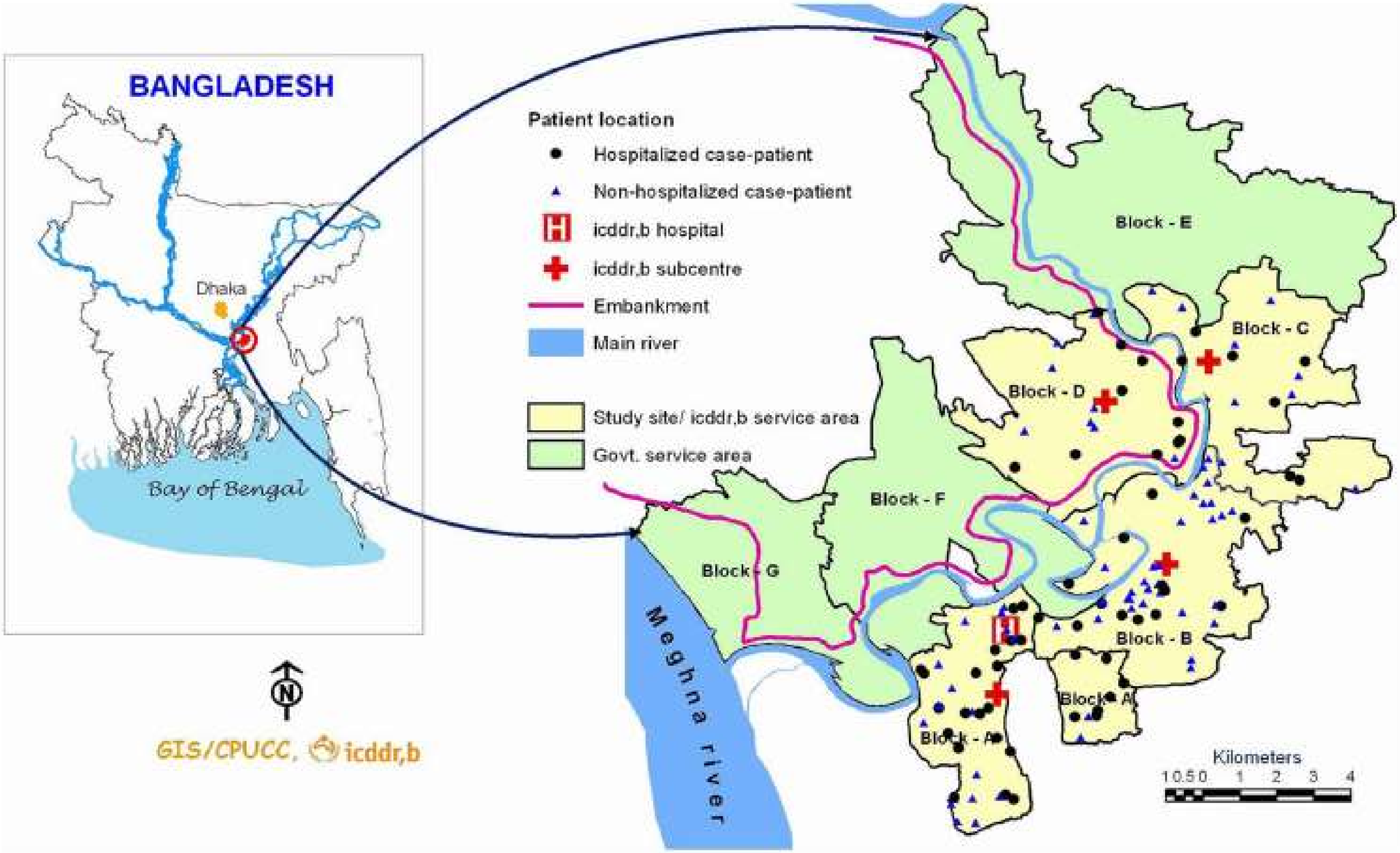


Figure 1. Study site and location of all severe acute respiratory infection cases, Matlab, Bangladesh–2010.

doi:10.1371/journal.pone.0089978.g001

Table 4. Incidences of severe acute respiratory virus infections among children aged <5 years in Matlab, Bangladesh, June–October 2010.

Respiratory virus	Incidence (95% CI)					
	<1 month	1–2 months	3–6 months	7–12 months	12–59 months	All ages
Total SARI	166.2 (66.8–342.3)	163.5 (84.5–285.6)	102.8 (61.9–160.6)	96.5 (61.9–143.6)	35.3 (27.9–43.9)	50.5 (42.5–59.6)
Hospitalized cases						
RSV per 100,000 person-weeks (pw)	47.5 (5.8–171.5)	68.1 (22.1–159.0)	32.5 (11.9–70.7)	16.1 (4.4–41.2)	2.2 (0.7–5.2)	7.9 (4.9–11.9)
HPIV3 per 100,000 pw	–	13.6 (0.3–75.9)	–	12.1 (2.5–35.3)	0.9 (0.1–3.2)	2.2 (0.8–4.7)
Influenza per 100,000 pw	–	–	–	4.0 (0.1–22.4)	0.9 (0.1–3.2)	1.1 (0.2–3.2)
Influenza per 1,000 person-years (py)	–	–	–	2.1 (0.1–11.7)	0.5 (0.1–1.7)	0.6 (0.1–1.6)
Multiple viruses per 100,000 pw	–	13.6 (0.3–75.9)	–	8.0 (1.0–29.1)	–	1.1 (0.2–3.1)
Non-hospitalized cases						
RSV per 100,000 pw	–	13.6 (0.3–75.9)	37.9 (15.2–78.1)	24.1 (8.9–52.5)	7.1 (4.1–11.6)	10.8 (7.3–15.4)
HPIV3 per 100,000 pw	–	–	–	12.1 (2.5–35.3)	0.9 (0.1–3.2)	1.8 (0.6–4.2)
Adenovirus per 100,000 pw	–	–	–	–	0.4 (0.0–2.5)	0.4 (0.0–2.0)
Influenza per 100,000 pw	–	–	–	4.0 (0.1–22.4)	1.3 (0.3–3.9)	1.4 (0.4–3.7)
Influenza per 1,000 py	–	–	–	2.1 (0.1–11.7)	0.7 (0.1–2.0)	0.7 (0.2–1.9)
Multiple viruses per 100,000 pw	–	–	–	–	0.9 (0.1–3.2)	0.7 (0.1–2.6)

doi:10.1371/journal.pone.0089978.t004

Respiratory Syncytial Virus and Recurrent Wheeze in Healthy Preterm Infants

Maarten O. Blanken, M.D., Maroeska M. Rovers, Ph.D., Jorine M. Molenaar, M.D., Pauline L. Winkler-Seinstra, M.Sc., Adam Meijer, Ph.D., Jan L.L. Kimpen, M.D., Ph.D., and Louis Bont, M.D., Ph.D., for the Dutch RSV Neonatal Network

Table 1. Proportion of Infants with Proven Respiratory Syncytial Virus (RSV) Infection.*

Variable	Palivizumab (N=214)	Placebo (N=215)	Absolute Risk Reduction†	Relative Risk Reduction (95% CI)†	P Value
	no. (%)		*percentage points*	%	
Total RSV infection	10 (4.7)	30 (14.0)	9.3	67 (27 to 107)	0.001
Hospitalization for RSV infection	2 (0.9)	11 (5.1)	4.2	82 (18 to 157)	0.01
Medically attended RSV infection without hospitalization	2 (0.9)	10 (4.7)	3.7	80 (11 to 161)	0.02
RSV infection without medical attention	6 (2.8)	9 (4.2)	1.4	33 (−56 to 126)	0.40

* Medical attention was registered during the home visits and reported by parents on the daily log.

† The absolute and relative values for risk reduction are for the palivizumab group as compared with the placebo group.

Blanken MO et al. NEJM 2013;368:1791-9

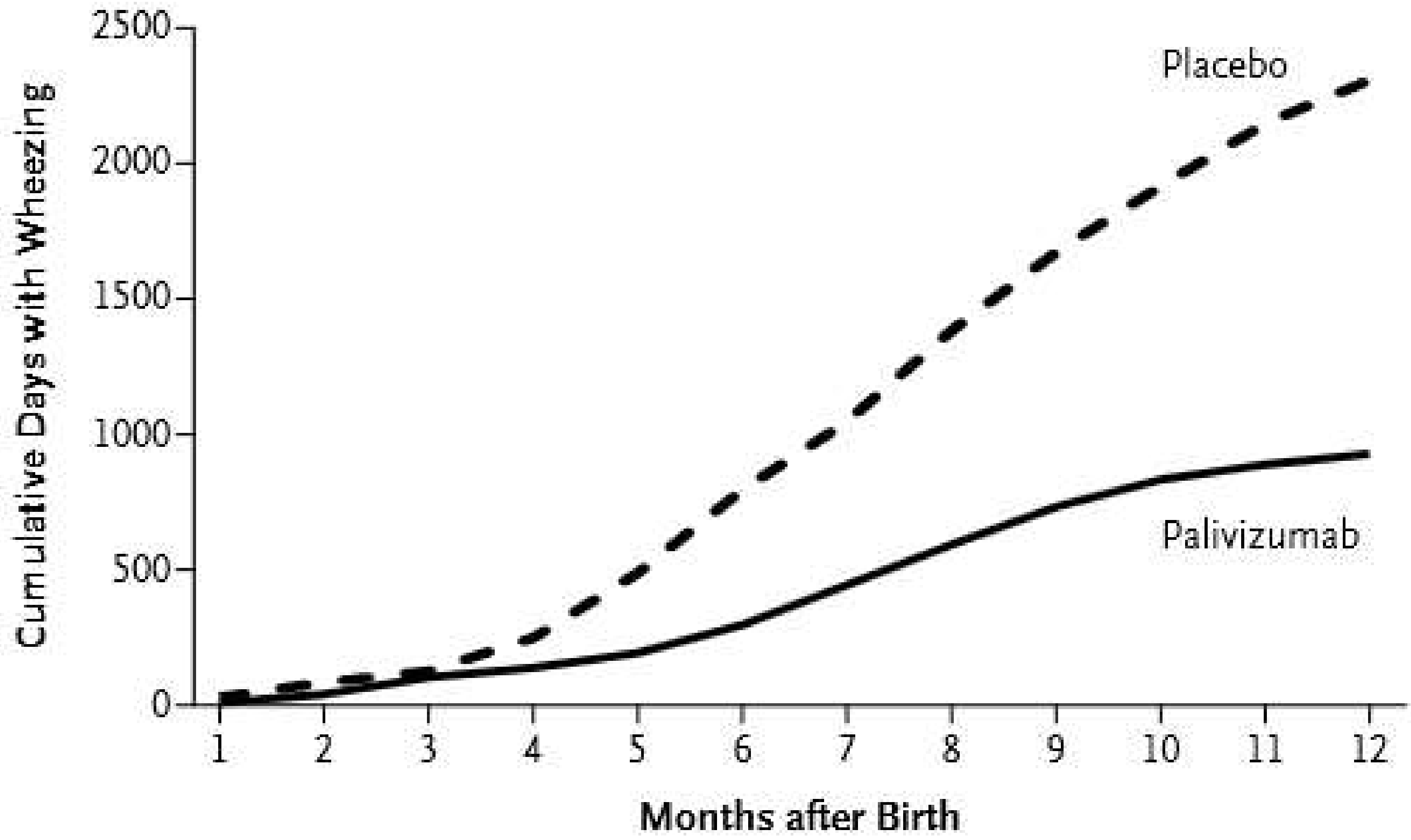
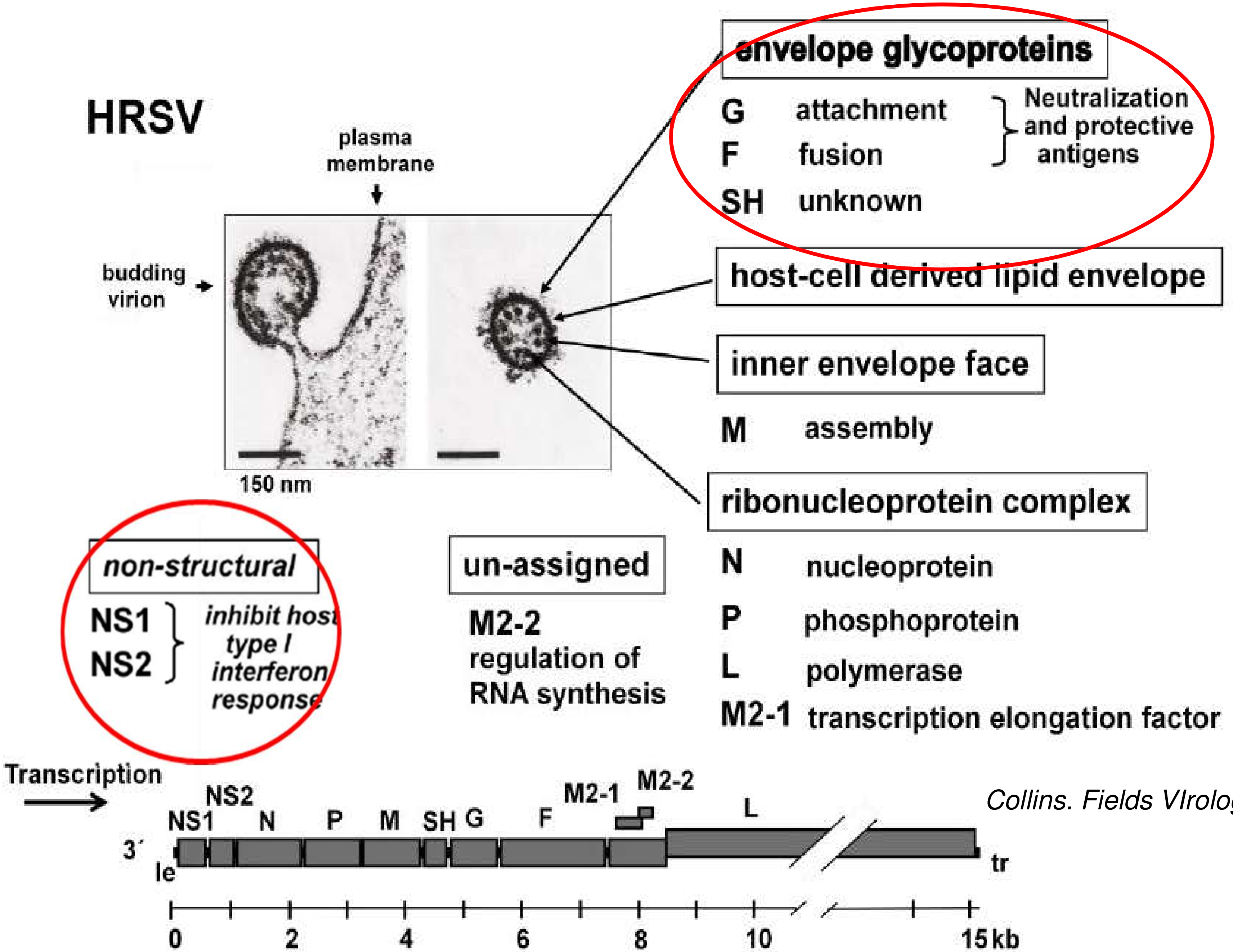


Figure 2. Cumulative Wheezing Days for 429 Preterm Infants during the First Year of Life.

P<0.001 for the comparison between palivizumab and placebo with the use of Poisson regression.



Collins. Fields VIrology

RSV Vaccine Snapshot

PATH

	Preclinical	Phase 1	Phase 2	Phase 3	Market Approved
Live-Attenuated	Codagenix – RSV intravacc – Delta-G RSV St. Jude Children's Research Hospital – SeV/RSV Emory University – RSV Pontificia Universidad Católica de Chile – BCG	MedImmune, NIH/NIAID/LID – Medi-RSV ΔM2-2 NIH/NIAID/LID – RSV ΔNS2 Δ1313 MedImmune, NIH/NIAID/LID – RSV cps2 MedImmune – Medi-534, RSV/PIV3	MedImmune, NIH/NIAID/LID – Medi-559, RSV		
Whole-Inactivated	NanoBio – RSV				
Particle-based	Agilvax – VLP Fraunhofer – VLP Georgia State University – VLP TechnoVax – VLP Artificial Cell Technologies, Inc. – Peptide microparticle Mucosis – VLP Ruhr-Universität Bochum (RUB) – VLP University of Massachusetts – VLP Emory University – VLP Mymetics – Virosome Takeda Vaccines – VLP vlp Biotech – VLP		Novavax – RSV F Nanoparticle		
Subunit	IMV Immunovaccine – DPX-RSV NIH/NIAID/VRC – RSV pre-F protein PeptiVir – RSV peptides Universiteit Gent, VIB – SH protein University of Illinois – RSV F protein Instituto de Salud Carlos III – RSV F protein Novartis Vaccines – RSV F protein Renaptys – RSV peptides University of Georgia – RSV G protein University of Saskatchewan – RSV F protein	GSK GlaxoSmithKline – RSV F protein			
Nucleic Acid	CureVac – RNA Inovio – DNA Novartis Vaccines – RNA Ruhr-Universität Bochum (RUB) – DNA				
Gene-based Vectors	AlphaVax – Alphavirus Bavarian Nordic – MVA RuenHuei Biopharma – Adenovirus University of Pittsburg – Adenovirus AmVac Innovative Vaccines – Sendai virus Janssen – Adenovirus Ruhr-Universität Bochum (RUB) – Adenovirus Vanderbilt University Medical Center – Alphavirus	okairos – Adenovirus/MVA (Acquired by GSK)			
Combination	BRM Biomedical Research Models, Inc. – DNA prime, Protein boost Fudan University – DNA+protein combo				

Updated: February 25, 2014

Source http://sites.path.org/vaccinedevelopment/respiratory-syncytial-virus-rsv/

Barriers to RSV Vaccine Development

- Legacy of enhanced RSV disease by a killed RSV vaccine.
- Early age of first RSV infection
- Capacity of RSV to evade innate immunity
- Failure of RSV-induced adaptive immunity to prevent reinfection
- Lack of an animal model fully permissive to human RSV infection

Generating Live Attenuated RSV Vaccine Candidates

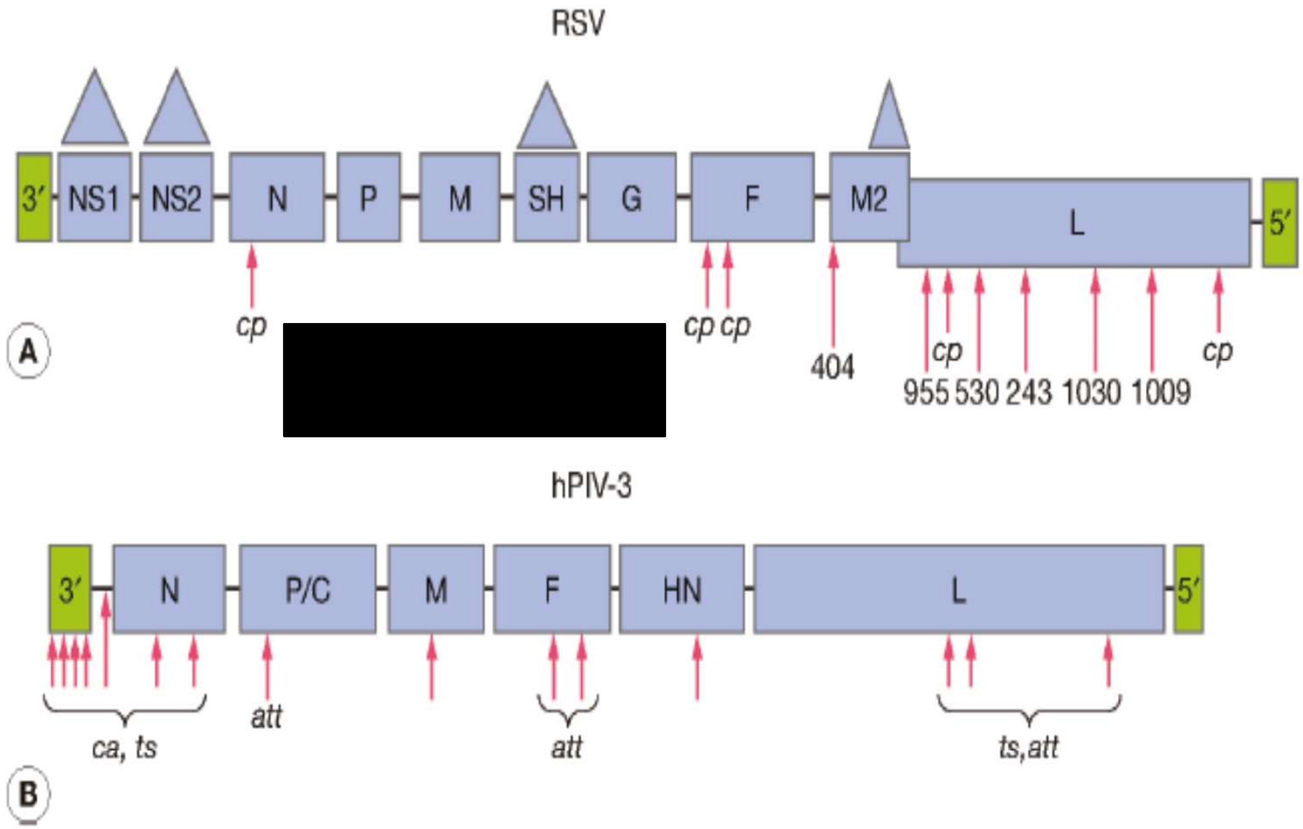


Figure 55-2 Schematic Representation (Not to scale) of the Mutations found in Live Attenuated Respiratory Syncytial Virus (RSV) Vaccine Candidate Viruses (A) and in the Human Parainfluenza Virus 3 (HPIV3) Candidate Vaccine Virus *cp45* (B). A, Mutations in the RSV genome are identified as point mutations (arrows) or as gene deletions (Δ). Point mutations are further identified as mutations induced by serial cold-passage (*cp*) or as temperature-sensitive (*ts*) mutations induced by chemical mutagenesis (identified numerically). The number assigned to the *ts* mutation indicates the clone number of the virus in which the mutation was first identified. B, The 15 mutations in *cp45* that are thought to be important for conferring attenuation are identified at the site of the mutation (arrows). Those mutations that are known to produce virus that is cold adapted (*ca*), temperature-sensitive (*ts*), or attenuated in nonhuman primates (*att*) are indicated by the corresponding abbreviation.

Kotloff In Plotkin Vaccines

Identification of a Recombinant Live Attenuated Respiratory Syncytial Virus Vaccine Candidate That Is Highly Attenuated in Infants

Ruth A. Karron,[1] Peter F. Wright,[5] Robert B. Belshe,[3] Bhagvanji Thumar,[1] Roberta Casey,[1] Frances Newman,[3] Fernando P. Polack,[1] Valerie B. Randolph,[4] Anne Deatly,[4] Jill Hackell,[4] William Gruber,[4] Brian R. Murphy,[2] and Peter L. Collins[2]

Participants, virus given	Dose, $\log_{10}$ pfu	No. of participants	Participants infected, %	Participants who shed virus, %
Infants				
rA2cp248/404/1030ΔSH				
First dose	4.3	16	63	63
Second dose	4.3	14	29	29
rA2cp248/404/1030ΔSH				
First dose	5.3	16	94	94
Second dose	5.3	16	44	44
Placebo				
First dose	...	12	0	0
Second dose	...	9	0	0

The Journal of Infectious Diseases 2005;191:1093–104

Chimeric Vaccines

Phase 1 Study of the Safety and Immunogenicity of a Live, Attenuated Respiratory Syncytial Virus and Parainfluenza Virus Type 3 Vaccine in Seronegative Children

David I. Bernstein, MD, MA, Elissa Malkin, DO, MPH,† Nazha Abughali, MD,‡ Judith Falloon, MD,† Tingting Yi, PhD,† and Filip Dubovsky, MD, MPH,† for the MI-CP149 Investigators*

TABLE 1. Seroresponse to RSV and PIV3 in Subjects Who Received the RSV/PIV3 Vaccine

	Seroresponse					
	Cohort 1 (10^4 $TCID_{50}$)		Cohort 2 (10^5 $TCID_{50}$)		Cohort 3 (10^6 $TCID_{50}$)	
	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
RSV						
Dose 1	2/11 (18.2)	2.3–51.8	3/7 (42.9)	9.9–81.6	4/9 (44.4)	13.7–78.8
Dose 2	1/10 (10)	0.3–44.5	1/5 (20.0)	0.5–71.6	5/9 (55.6)	21.2–86.3
Dose 3	3/8 (37.5)	8.5–75.5	1/5 (20.0)	0.5–71.6	4/8 (50.0)	15.7–84.3
PIV3						
Dose 1	6/11 (54.5)	23.4–83.3	5/7 (71.4)	29.0–96.3	8/10 (80.0)	44.4–97.5
Dose 2	6/10 (60.0)	26.2–87.8	4/5 (80.0)	28.4–99.5	7/9 (77.8)	40.0–97.2
Dose 3	8/10 (80.0)	44.4–97.5	3/5 (60.0)	14.7–94.7	8/8 (100)	63.1–100

Seroresponse was defined as a ≥4-fold rise from baseline. Microneutralization assay (RSV) and HAI assay (PIV3) results were excluded from analysis upon demonstration of wild-type RSV/PIV3 shedding. For microneutralization assay analysis, a value of 2.5 was assigned if the result was below the LOQ (<5); and for HAI analysis, a value of 2 was assigned if the result was below the LOQ (<4).

CI indicates confidence interval; RSV, respiratory syncytial virus; PIV3, parainfluenza virus type 3; HAI, hemagglutination inhibition; LOQ, limit of quantification.

(*Pediatr Infect Dis J* 2012;31: 109–114)

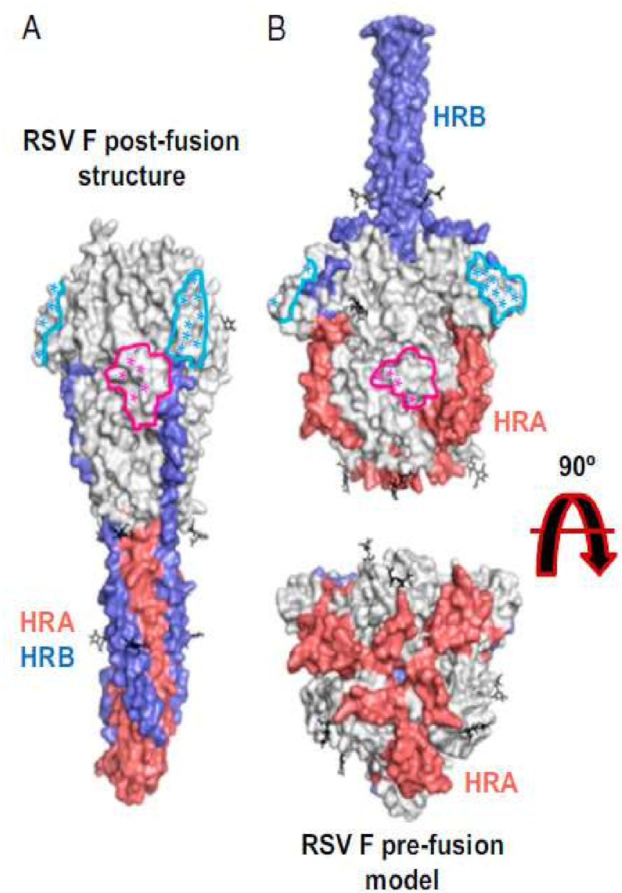
Absence of enhanced RSV disease after live, attenuated RSV vaccines

	Live attenuated RSV vaccine	Placebo
RSV –Upper Resp Infect: • Vaccinated 1-3 mo age	15%	25% (VE 54%)
• Vaccinated 6-24 mo age	6.4%	15% (VE 40%)
RSV Sub Group A rate	8.6 / 100 ch-y	12.7 / 100 ch-y
RSV Sub Group B rate	4.6 / 100 ch-y	7 /100 ch-y

Wright PF et al. Vaccine 2007;25:7372-8

Subunit Vaccines: Advances in Understanding RSV F Protein Structure and Function

- RSV F glycoprotein mediates viral entry into host cells
- During cell entry: F undergoes a conformational change that brings viral and cellular membranes together, ultimately leading to fusion (Lamb, 2007)
- Activation of RSV F from pre-fusion state requires cleavage by furin at 2 sites, and a vast structural change in F conformation. (Gonzales-Reyes, PNAS 2001)
    - The structure of RSV protein in circulating virus and virus attached to cell surface differs remarkably (Swanson PNAS 2011)
    - Antigenic targets for pre and post fusion also differ



PNAS | June 7, 2011 | vol. 108 | no. 23 | 9621

Structural basis for immunization with postfusion respiratory syncytial virus fusion F glycoprotein (RSV F) to elicit high neutralizing antibody titers

Kurt A. Swanson[1], Ethan C. Settembre[1], Christine A. Shaw, Antu K. Dey, Rino Rappuoli[2], Christian W. Mandl, Philip R. Dormitzer, and Andrea Carfi[2]

Novartis Vaccines and Diagnostics, Cambridge, MA 02139

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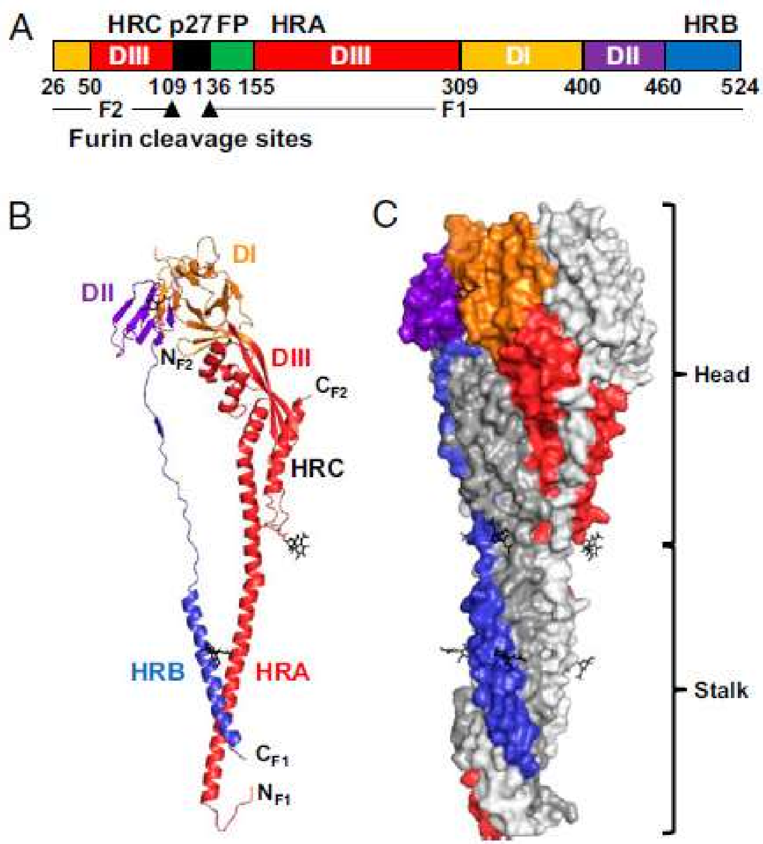


Fig. 1. RSV F ectodomain structure. (*A*) Linear diagram. Listed residue numbers correspond to the N terminus of each segment, the furin cleavage sites (arrowheads), and the C terminus. DI–III, domains I–III; p27, excised peptide; FP, fusion peptide; HRA, -B, and -C, heptad repeats A, B, and C. (*B*) Ribbon representation of one subunit. Domains colored as in *A*. Glycans are black. (*C*) Surface representation of the trimer. One subunit colored by domains as in *A*; the other two are white and gray.

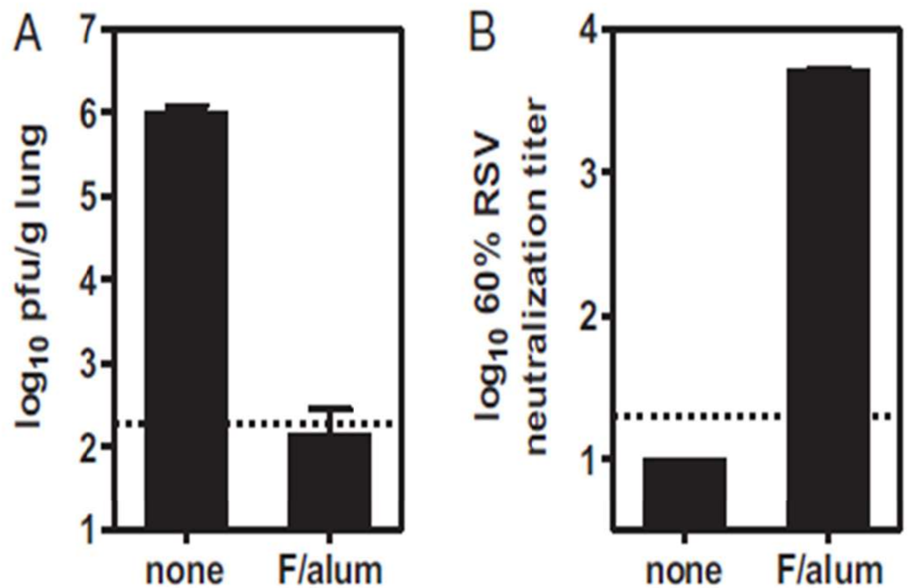
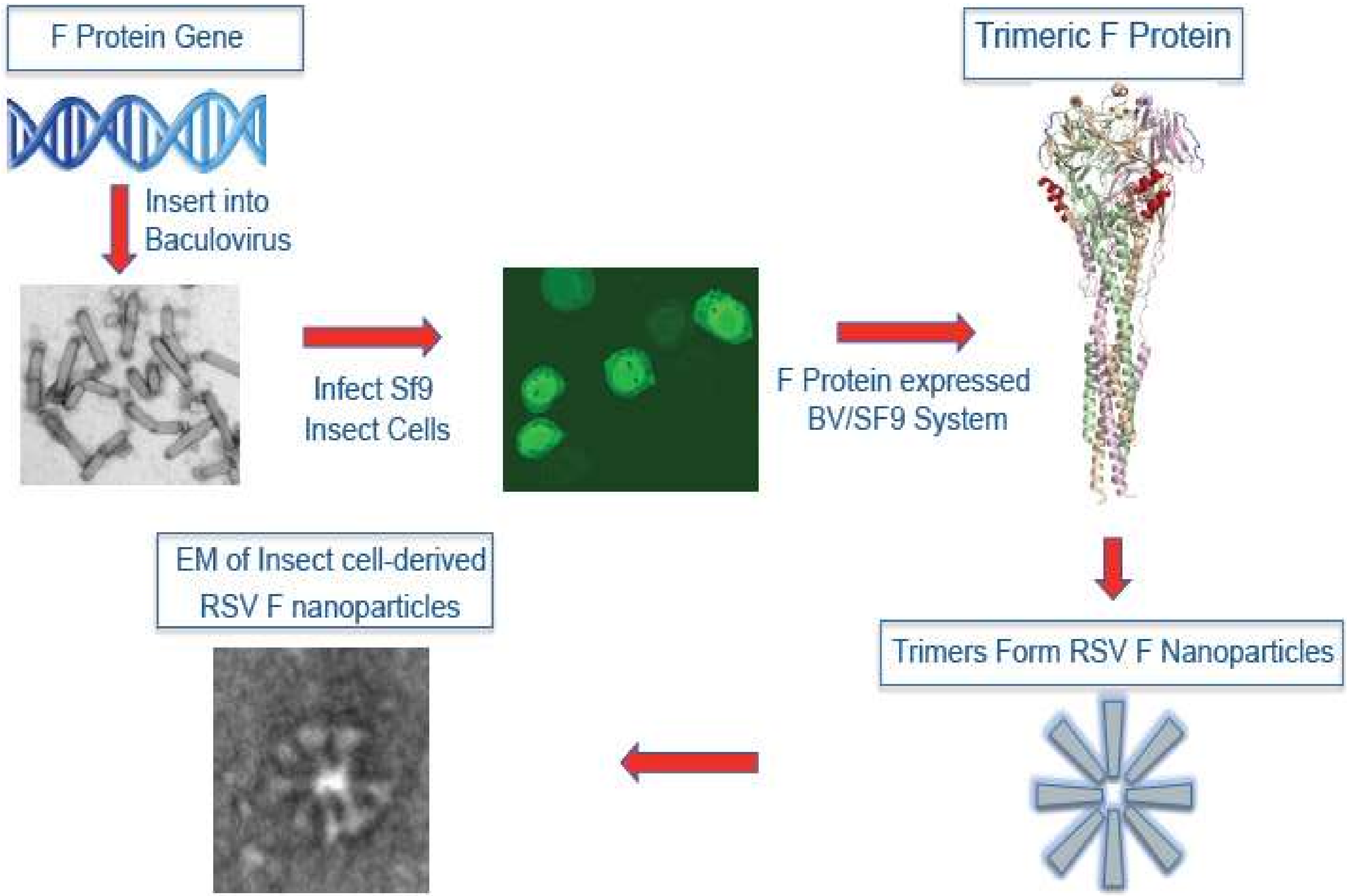


Fig. 2. Immunization of cotton rats with the postfusion RSV F trimer elicits neutralizing antibodies and protects from RSV challenge. Cotton rats were immunized intramuscularly with 5 μg of RSV F trimer adsorbed to alum on days 0 and 21 or were not immunized. Sera for neutralization assays were obtained on day 35. The cotton rats were challenged intranasally on day 49 with 1×10^5 pfu of RSV, strain Long. (*A*) Titers of RSV 5 d after challenge by plaque assay in the lungs of immunized (F/alum) or not immunized (none) cotton rats. Values shown are the means with SD of eight cotton rats per group. (*B*) Serum RSV neutralization titers. Values shown are the mean and range of two pools of four cotton rats per group.

Recombinant Nanoparticle Vaccine : Novavax



*www.novavax.com/go.cfm?do=Page.View&pid=147

Impact of Maternal RSV Antibody on Hospitalizations

TABLE I. Titer of maternally derived RSV neutralizing antibodies and the incidence rate ratio of RSV hospitalization among children below 6 months of age; RSV hospitalized infants were compared with randomly selected infants

Maternally derived RSV neutralizing antibodies titer	Birth to 5 mo	
	N (Nsub)	IRR (95% CI)*
0-6	48 (49)	Reference
6.5	25 (45)	0.40 (0.18-0.92)
7.0-7.5	57 (98)	0.57 (0.29-1.10)
8-8.5	35 (84)	0.41 (0.20-0.85)
9+	32 (118)	0.27 (0.13-0.57)
All	197 (394)	0.74 (0.62-0.87)†

N, Number of cases; *Nsub*, number of children in subcohort.

*The estimates are adjusted for sex, premature birth, nonatopic chronic disease, maternal atopic dermatitis, maternal asthma, season, children below 12 years of age in the home ("siblings"), maternal smoking and occupation, and RSV seasonality.

†Test for trend when titers were analyzed as a continuous variable—that is, per 1 unit increase in titer.

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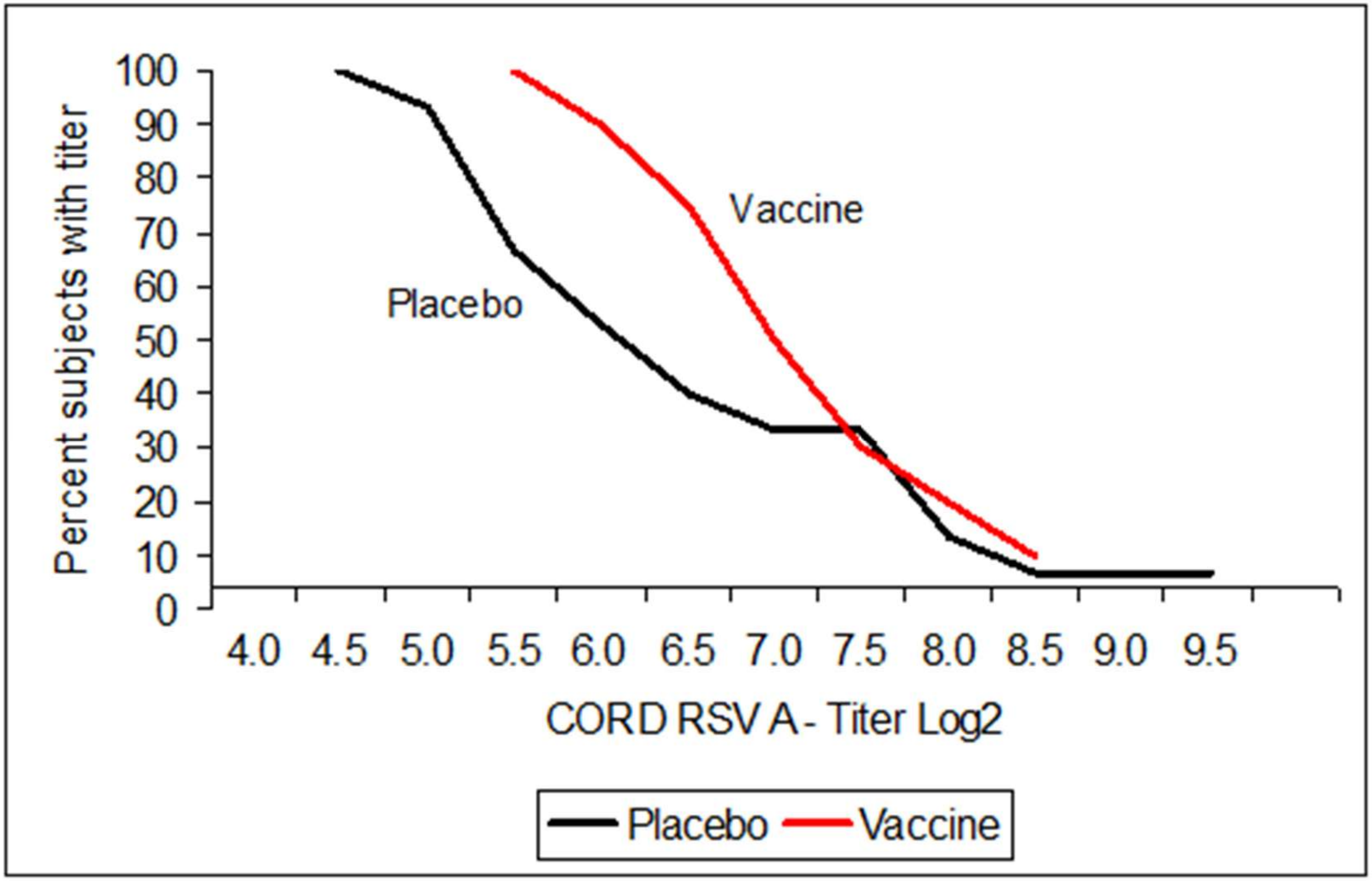
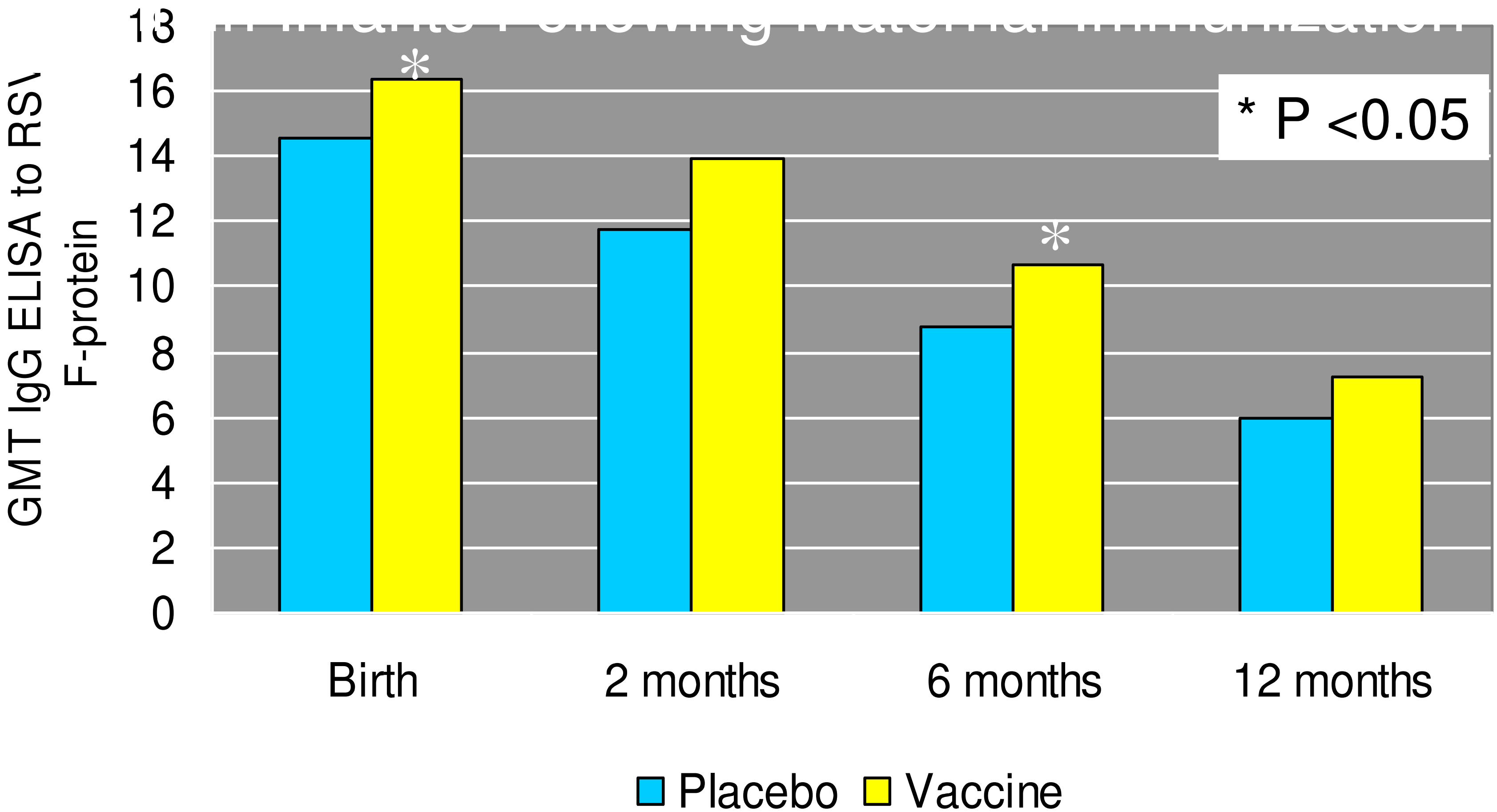
RSV-A Neutralization antibodies in Cord Blood of newborns from mothers vaccinated in 3rd trimester of pregnancy with RSV purified fusion protein-2 vaccine



Munoz, Piedra, Glezen. Vaccine 2003;21:3465

Increased RSV IgG antibodies in infants from women immunized with RSV purified fusion protein-2 vaccine



*Munoz, et al. Vaccine 2003

Conclusions

- A safe and effective RSV vaccine is needed for low and middle income countries in the world.
- Maternal immunization needs further exploration
- Infants need to receive 1st vaccine dose below or at 10w of age to receive maximum benefit.
- Vaccine study outcomes:
  - RSV-associated severe ALRI
  - Recurrent wheeze

Problems that need further research

- Fear of enhanced severity or RSV disease by RSV vaccines (not clear why inactivated RSV vaccines produced this effect).
- Is there mortality associated with severe wheeze in developing countries? Are all classified as pneumonia?
- How to deal with mixed infections detected by sensitive PCR diagnostic tools?
- How to separate symptomatic from asymptomatic RSV infected infants?
- Are infants with poor immune response to RSV vaccine protected? How to measure functional antibody response.
- Will maternal immunization interfere infant immunization?
- No new vaccines have been licensed for pregnant women: licensing pathway may be complicated!

Thanks!

PATH:
- Deborah Higgins
- Cheryl Keech

WHO:
- Vasseharan Sathiyamoorthy

Vanderbilt:
- Kathryn Edwards