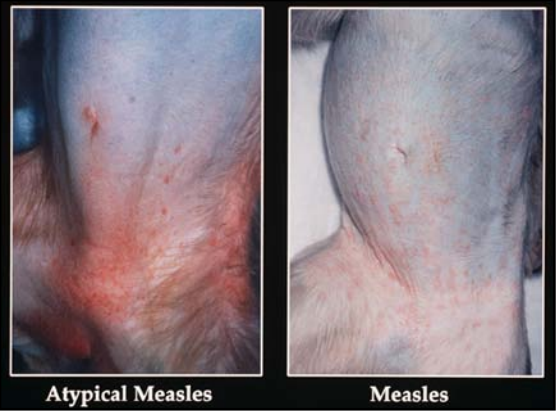
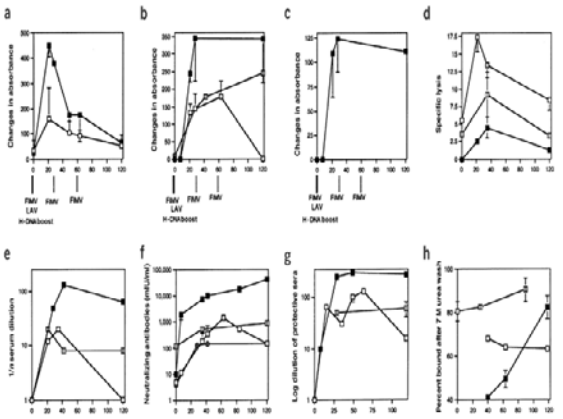
Prevention of RSV LRTI in healthy infants

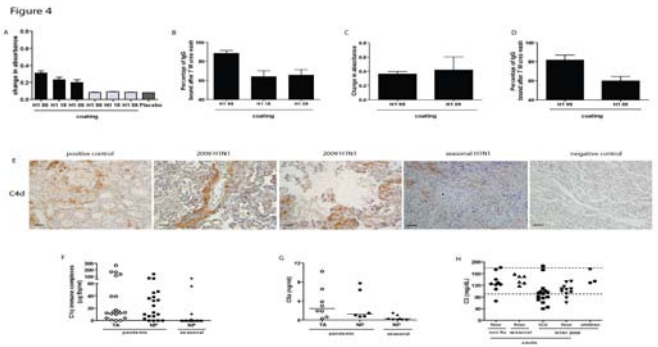
Fernando P. Polack, MD
Fundacion INFANT



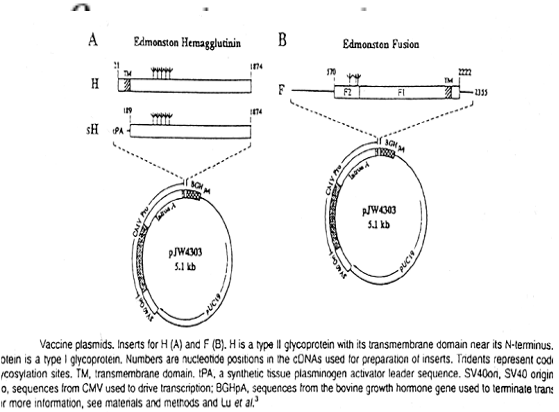
Atypical measles. **Nat Med 99**



Avidity & AM. **Nat Med 03**

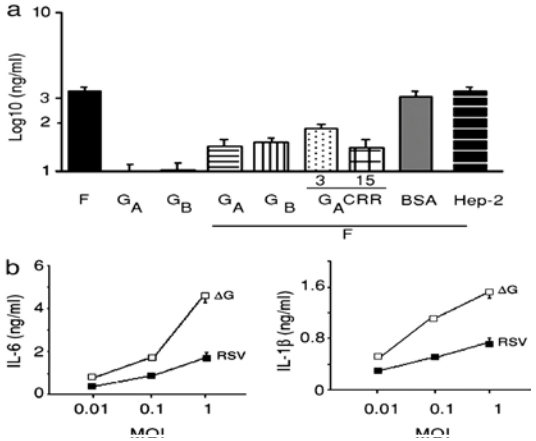


Pandemic influenza. **Nat Med 11**

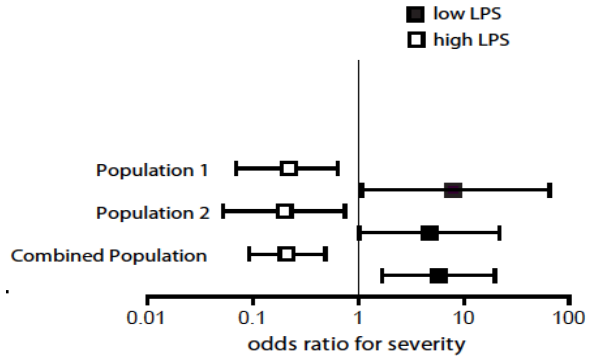


Vaccine plasmids. Inserts for H (A) and F (B). H is a type II glycoprotein with its transmembrane domain near its N-terminus. otein is a type I glycoprotein. Numbers are nucleotide positions in the cDNAs used for preparation of inserts. Tridents represent codi /cosylation sites. TM, transmembrane domain. tPA, a synthetic tissue plasminogen activator leader sequence. SV40on, SV40 origin o, sequences from CMV used to drive transcription; BGHpA, sequences from the bovine growth hormone gene used to terminate trans r more information, see materials and methods and Lu *et al.*[3]

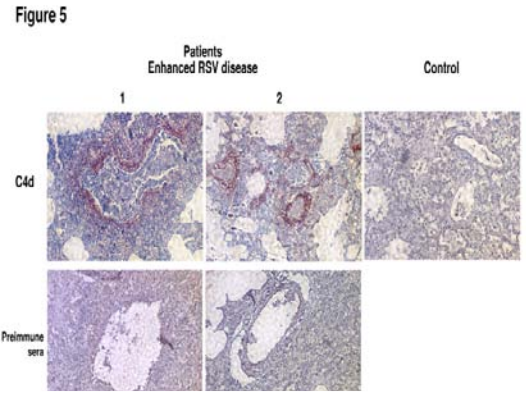
Abs and measles. **Nat Med 00**



RSV G and TLR4. **PNAS 05**



RSV hu and TLR4. **JCI 15**



RSV ERD. **J Exp Med 02**

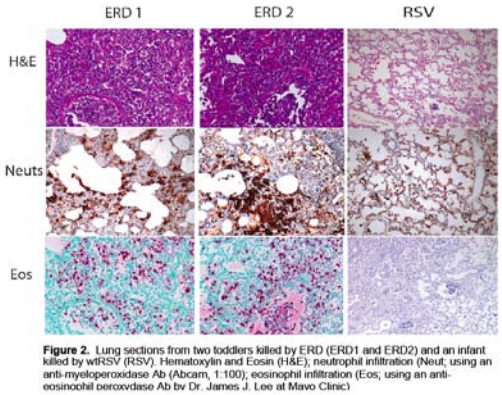
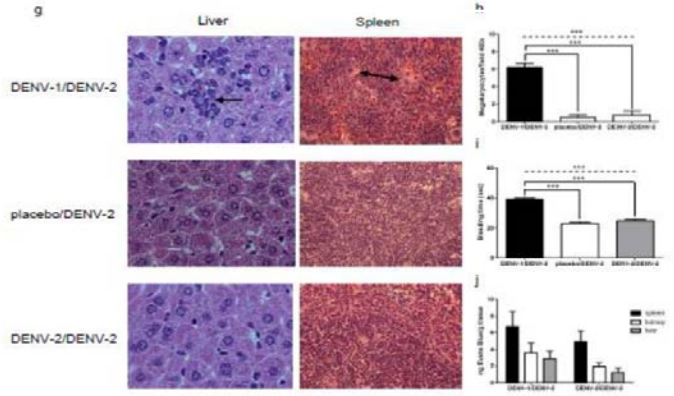
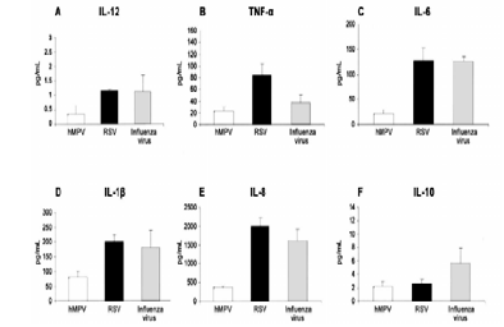


Figure 2. Lung sections from two toddlers killed by ERD (ERD1 and ERD2) and an infant killed by wtRSV (RSV). Hematoxylin and Eosin (H&E); neutrophil infiltration (Neut; using an anti-myeloperoxidase Ab (Abcam, 1:100); eosinophil infiltration (Eos; using an anti-eosinophil peroxydase Ab by Dr. James J. Lee at Mayo Clinic)

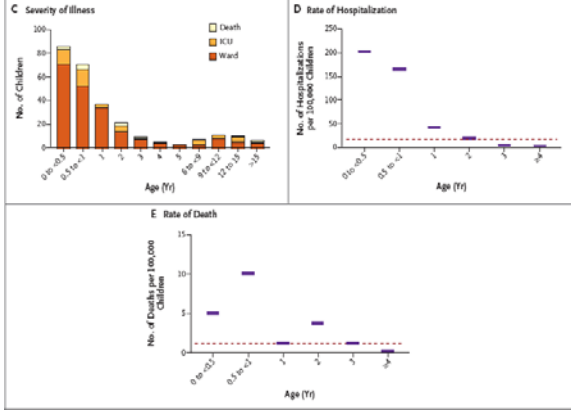
Avidity, TLR4, RSV. **Nat Med 09**



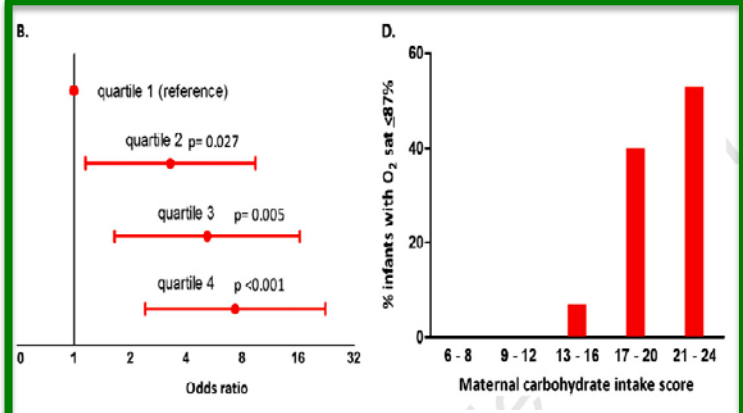
DHF and OAS. **EBiomedicine 17**



TLRs and RSV-hMPV. **JID 04**



Pandemic flu . **NEJM 10**



RSV and carbs. **AJRCCM 13**

Table 4. Comparison of clinical manifestations in infants infected with respiratory viruses.

Characteristic	Infants infected with hMPV	RSV	hPIV3	Influenza virus	All infants
Episodes of infection, no.	12	33	24	10	567
URI, no. (%)	2 (17)	7 (21)	4 (17)	5 (50)	193 (32)
LRI, no. (%)	10 (83)	26 (79)	20 (83)	5 (50)	407 (68)
Bronchiolitis, %	10	25	15	5	387
Pneumonia, %	0	0	2	0	10
Croup, %	0	1	3	0	10
Severity, no.	10	26	20	5	407
Mild, no. (%)	7 (70)	10 (38)	14 (70)	5 (100)	280 (69)
Moderate, no. (%)	2 (20)	4 (16)	4 (20)	0	77 (19)
Severe, no. (%)	1 (10)	12 (46)	2 (10)	0	50 (12)
Hospitalized, no. (%)	1 (10)	15 (58)	5 (25)	0	93 (23)
Received ventilation, no. (%)	0	5 (19)	0	0	10 (2)
Died, no. (%)	0	1 (4)	0	0	2 (1)

NOTE. Because the vast majority of children with lower-respiratory-tract infections (LRIs) have manifestations in the upper respiratory tract, a child presenting with signs and symptoms of both upper-respiratory-tract infection (URI) and LRI was analyzed only in the LRI group. hMPV, human metapneumovirus; hPIV, human parainfluenza virus; RSV, respiratory syncytial virus.

hMPV in VLBW. **JID 06**

The NEW ENGLAND JOURNAL of MEDICINE

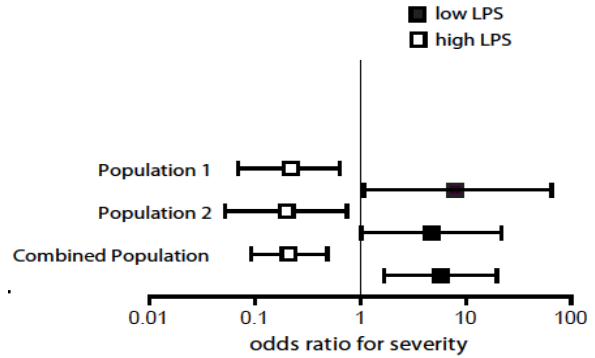
Pediatric Hospitalizations Due to Influenza in 2010 in Argentina

TO THE EDITOR: Much concern has been raised about the upcoming 2010–2011 flu season in the Northern Hemisphere. In preparation for this event, we investigated the burden of influenza during the 2010 season in the Southern Hemisphere in the same hospitals involved in our report in the *Journal* (Jan. 7 issue)[1] of serious disease in children in Argentina during the 2009 season.

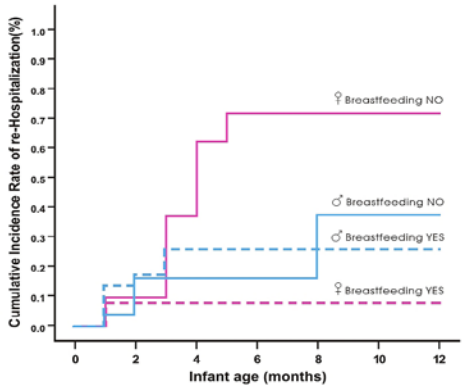
During 2009, Argentina had the third largest number of deaths due to pandemic influenza in the Americas.[2] As reported in the *Journal*,[1] our retrospective case series consisted of 251 hospitalizations and 13 deaths between May 1 and July 31, 2009, in a catchment population of 1.2 million children. The hospitalization and death rates were similar to those in the United States.[3] Vaccine in infants, children under 5 years of age, and children with high-risk medical conditions was 93% before this season.[3] In the previous season, this group accounted for 98% of admissions.[3,4] In addition, the availability and use of oseltamivir may have contributed to the lessening of severe presentations. Oseltamivir was not widely available in Argentina early in 2009.[1] Finally, an estimated one child in every three acquired the 2009 H1N1 virus during that year, leaving many protected during the subsequent season.[5]

Although additional surveillance data from other countries are needed, these data from Argentina suggest that the severity of the upcoming 2009 H1N1 season in the Northern Hemisphere may be diminished.

Post-pandemic flu. **NEJM 10**

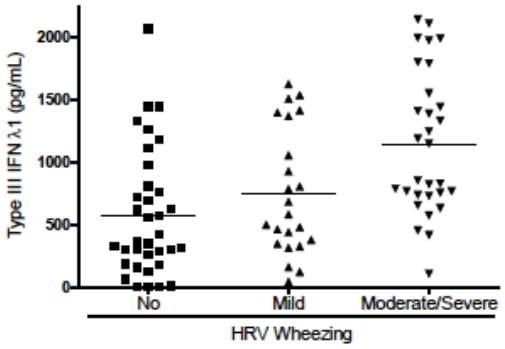


RSV hu and TLR4. **JCI 15**

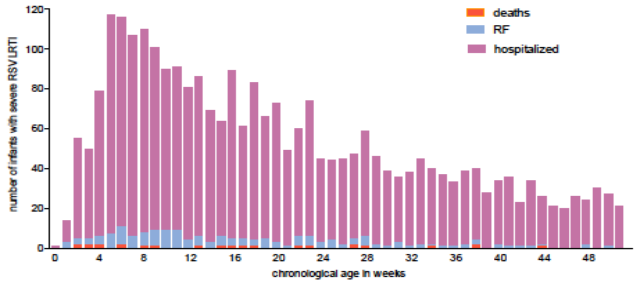


LRTI and milk. **Pediatr 08**

F



hRV and IFN . **AJRCCM 12**



RSV mortality. **AJRCCM 17**

Topics for review

- RSV burden in industrialized and developing countries. Who should we protect? What can we prevent?

- Different approaches to prevention of illness. Complementarity and competition.

RSV burden in industrialized and developing countries. Who should we protect?

Location of incidence and hospital mortality studies (n=157)

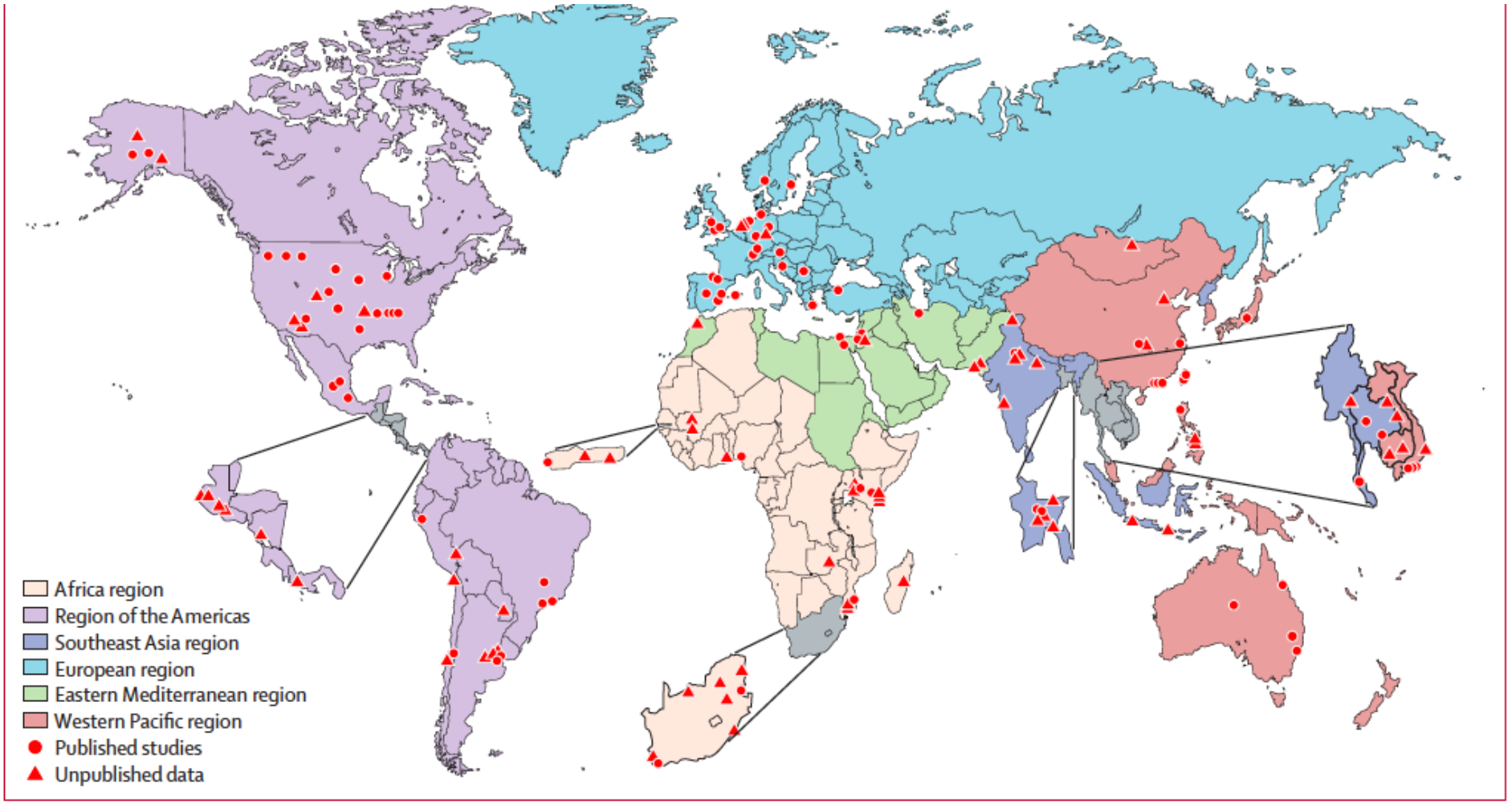


Figure 3: Location of studies reporting incidence, hospital admission, and in-hospital case fatality in children with RSV-ALRI

Funded by Bill & Melinda Gates Foundation

RSV Global Burden Estimates (2015)

- 30.5 (95% CI, 19.5-47.9) million episodes of RSV LRI annually in children < 5 years (22% of all ALRI episodes)
- 2.8 million episodes requiring hospitalization
- 95,000-149,000 deaths in 2005, 99% in developing countries
- Updated estimates for RSV ALRI, severe ALRI (community based and hospitalized) and deaths in press by the RSV Global Epidemiology Network (RSV-GEN) .

Lancet 2017

Hospitalizations in countries according to income

Hospital admission for RSV-associated ALRI				
0–5 months				
Studies‡	5 (2)	17 (8)	15 (9)	34 (25)
Hospital admission rate	7·4 (2·4–22·6)	22·9 (17·7–29·7)	23·0 (16·1–32·9)	26·3 (22·8–30·2)
Number of episodes (thousands)	79 (26–240)	737 (569–955)	407 (284–582)	205 (178–237)
6–11 months				
Studies	4	9	5	9
Hospital admission rate	3·4 (0·6–19·5)	11·3 (6·1–21·0)	18·5 (9·8–34·7)	11·3 (6·1–20·9)
Number of episodes (thousands)	36 (6–207)	362 (195–674)	327 (174–615)	88 (48–163)

Mortality in countries according to income

	Low income	Lower-middle income	Upper-middle income	High income	Developing countries	Industrialised countries	Global*†
Studies	9	16	12	6	41	2	43
0–5 months							
hCFR (%)‡	1·7 (0·4–6·8)	2·7 (2·0–3·6)	1·8 (1·2–2·6)	0·2 (0·0–12·8)	2·2 (1·8–2·7)	0·0 (0·0–0·1)	..
Number of deaths‡§	1300 (200–7900)	20 000 (13 500–29 500)	7200 (4200–12 300)	400 (1–228 200)	27 100 (20 700–35 500)	<50 (0–2000)	27 300 (20 700–36 200)
6–11 months							
hCFR (%)‡	9·3 (3·0–28·7)	2·8 (1·8–4·4)	2·4 (1·1–5·4)	0·9 (0·2–4·0)	2·4 (1·9–3·2)	0·1 (0·0–0·4)	..
Number of deaths§‡	3400 (400–26 600)	10 300 (4800–21 600)	8000 (2800–22 100)	900 (200–4600)	16 500 (10 400–25 800)	<50 (0–300)	16 500 (10 500–26 100)
12–59 months							
hCFR (%)‡	4·7 (0·7–33·7)	2·7 (1·7–4·3)	0·5 (0·1–3·5)	0·7 (0·1–5·2)	2·2 (1·6–3·0)	0·1 (0·0–0·3)	..
Number of deaths§‡	1400 (100–16 100)	12 300 (6500–23 100)	1500 (200–11 700)	700 (100–5600)	15 300 (9500–25 000)	100 (0–300)	15 400 (9500–24 900)
0–59 months							
Number of deaths‡§	8200 (2200–36 900)	43 600 (31 400–60 400)	17 900 (10 300–34 500)	3300 (700–231 100)	59 600 (47 800–74 300)	200 (100–2200)	59 600 (48 000–74 500)

RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection. hCFR=in-hospital CFR. hCFR and number of deaths are presented with 95% CI. *Global total for a given age band is sum of the deaths in developing and industrialised countries. We have taken this more conservative approach because there are only a small number of studies contributing to deaths by World Bank income region in narrow age bands leading to large uncertainties in some of these estimates. †Although the overall number of deaths was obtained by summing the age and region-specific numbers for each of the 10 000 samples in the Monte Carlo simulation, the point estimates and uncertainty interval limits for the overall deaths are not equal to the sum of the age and region-specific results. This reflects the fact that the overall estimates are determined by the full uncertainty distributions for each age and region-specific estimates, and not simply the point estimates. ‡Data in parentheses are 95% CI. §The number of deaths has been rounded to the nearest hundreds.

Table 2: CFR meta-estimates and number of in-hospital deaths in children with RSV-ALRI in children younger than 5 years in 2015, by World Bank Income regions

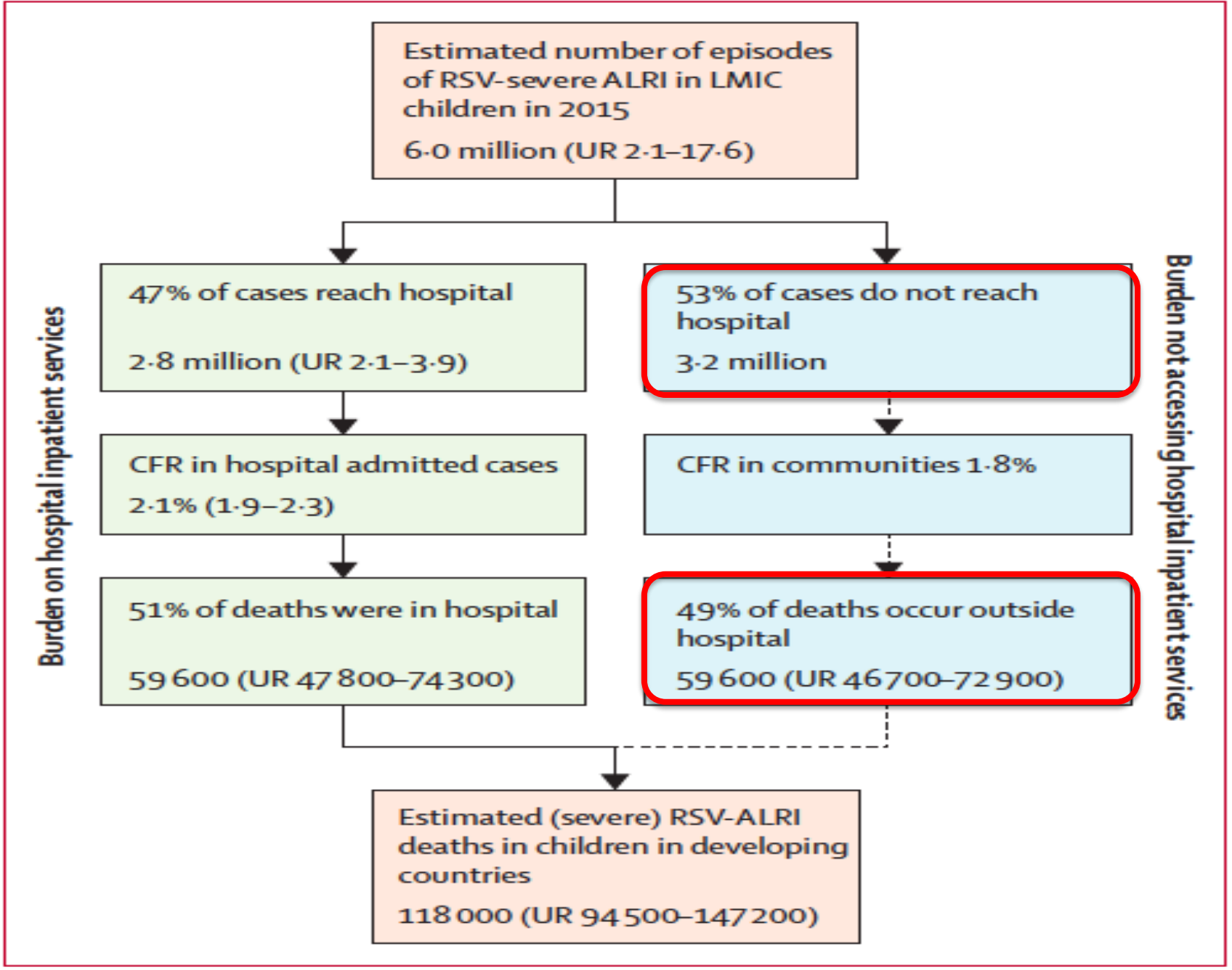


Figure 4: Global burden of RSV-associated severe ALRI including burden on hospital services

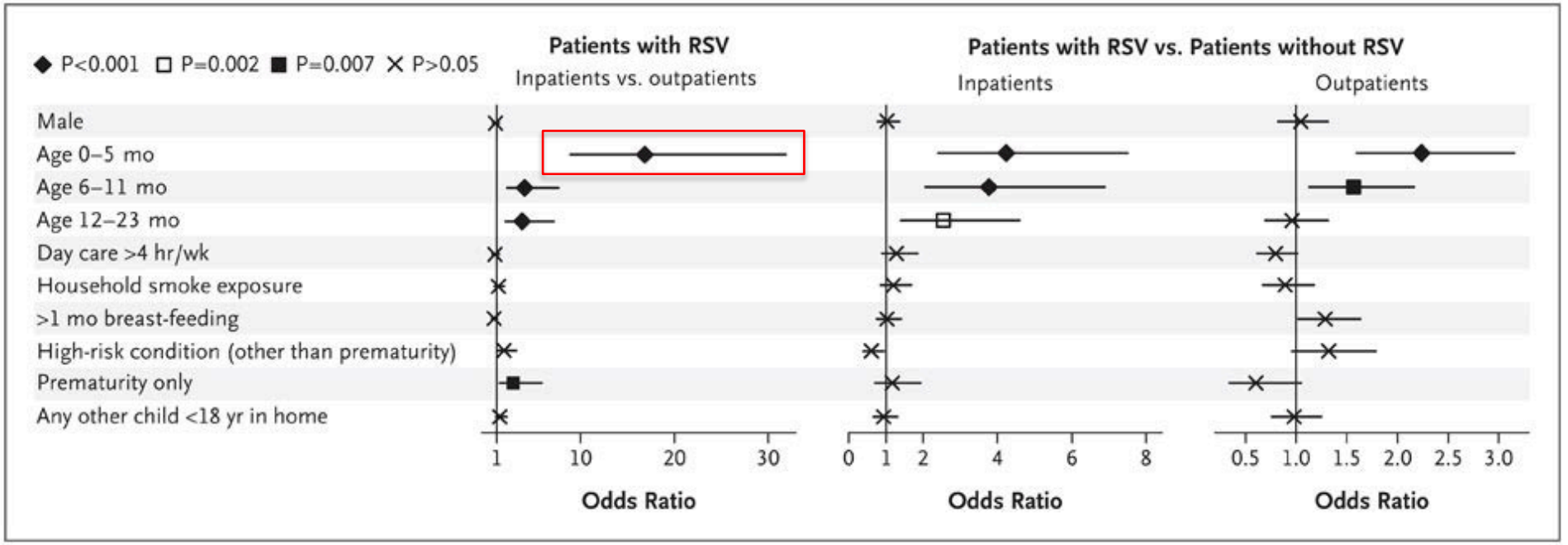
Rates in the United States

Table 2. Rates of Inpatient and Outpatient Treatment for Children under 5 Years of Age with Confirmed Respiratory Syncytial Virus (RSV) Infection per 1000 Children, According to Year.*

Treatment Site and Year	Age, in Months				
	0–5	6–11	12–23	24–59	0–59
	rate/1000 patients (95% CI)				
Inpatient					
Hospital					
2000–2001	18.5 (14.4–22.9)	7.4 (5.1–9.9)	3.2 (1.9–4.8)	0.4 (0.2–0.7)	3.5 (2.9–4.1)
2001–2002	11.7 (9.1–14.7)	4.1 (2.4–5.8)	2.5 (1.5–3.6)	0.2 (0.0–0.4)	2.2 (1.8–2.7)
2002–2003	12.4 (9.4–15.2)	3.4 (1.9–5.0)	1.9 (1.1–2.8)	0.2 (0.0–0.4)	2.1 (1.7–2.5)
2003–2004	21.7 (18.8–24.6)	5.4 (3.8–7.0)	3.1 (2.3–3.9)	0.5 (0.3–0.8)	3.7 (3.3– 4.1)
2000–2004	16.9 (15.3–18.5)	5.1 (4.6–5.5)	2.7 (2.3–2.7)	0.4 (0.3–0.4)	3.0 (2.8–3.4)
Outpatient†					
Emergency department					
2002–2003	39 (12–124)	45 (13–157)	24 (7–87)	15 (5–44)	22 (10–49)
2003–2004	69 (34–143)	68 (27–175)	38 (15–102)	11 (3–39)	32 (19–54)
2002–2004	55 (24–126)	57 (20–161)	32 (11–92)	13 (4–41)	28 (15–50)
Pediatric practice					
2002–2003	108 (33–346)	194 (77–492)	53 (13–222)	31 (9–100)	61 (24–154)
2003–2004	157 (54–462)	160 (45–576)	80 (22–282)	77 (26–230)	99 (44–219)
2002–2004	132 (46–383)	177 (61–511)	66 (18–245)	57 (19–167)	80 (36–179)

Hall CB et al. NEJM 2009

Risk factors in the industrialized world



Hall CB et al. NEJM 2009

TABLE 2 Characteristics of Infants and Children With RSV-Associated Hospital Mortality

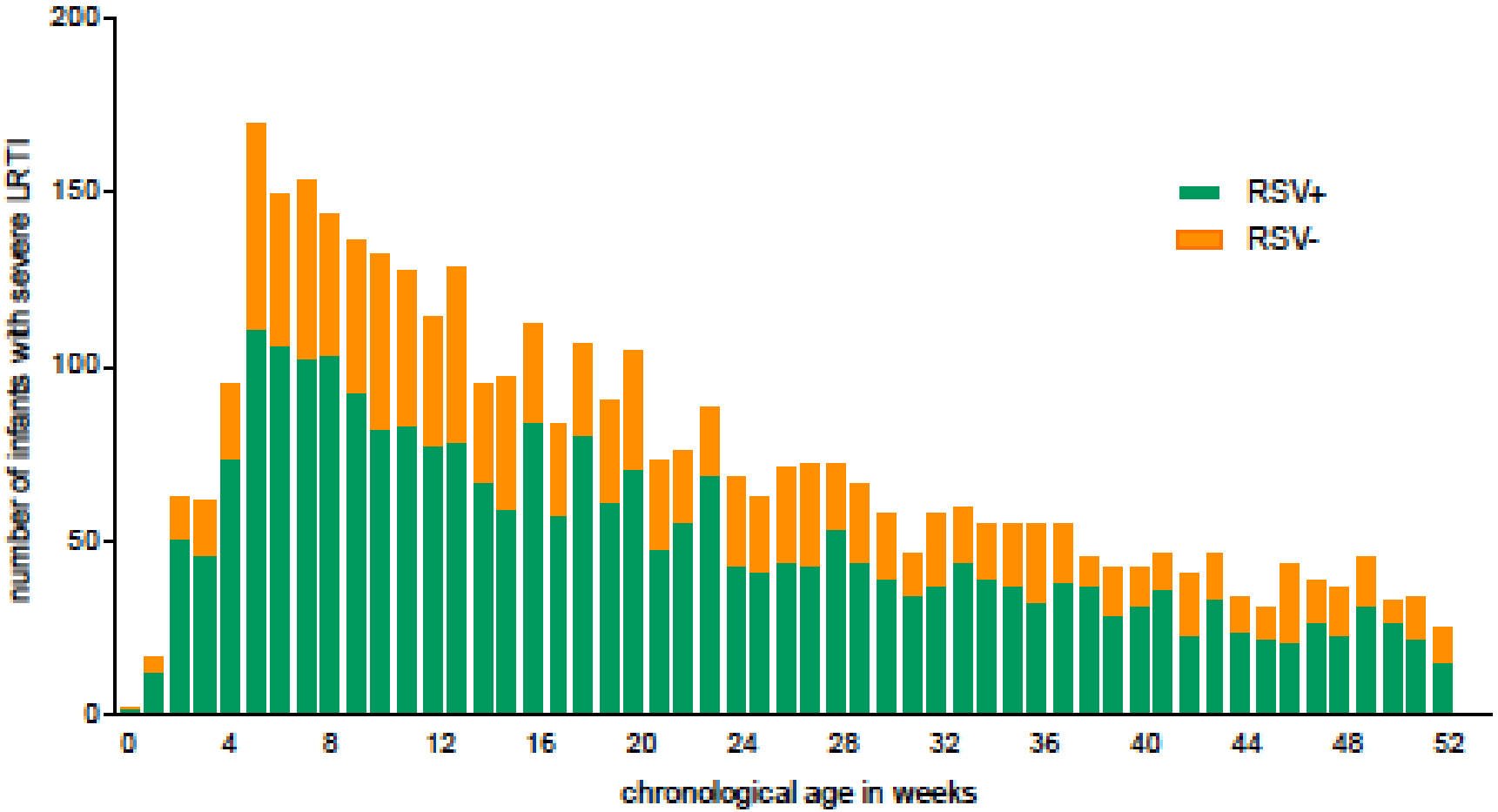
Variable	No. (%) of RSV-Associated Deaths	
	KID 2009	PHIS 2000–2011
Annual deaths	121 (100)	56[a]
Deaths occurring in a children's hospital	58 (48)	56 (100)
Deaths during RSV season, November–March	84 (70)	39 (70)
Deaths with a primary ICD-9-CM code for RSV	42 (34)	21 (38)
Death associated with CCC, any	92 (76)	44 (79)
Cardiovascular condition	45 (37)	25 (45)
Neuromuscular condition	32 (26)	11 (20)
Respiratory condition	26 (21)	10 (19)
Congenital or genetic condition	15 (13)	11 (19)
Multiple conditions, range: 2–5	47 (39)	21 (37)
Other conditions associated with death[b]	99 (82)	42 (74)
Sepsis	50 (41)	24 (42)
Cardiac arrest	41 (34)	18 (32)
Surgical complication	33 (28)	18 (32)
Hospital length of stay >30 days	45 (38)	21 (37)

[a] Mean number of annual deaths.

[b] Subjects may have had >1 condition.

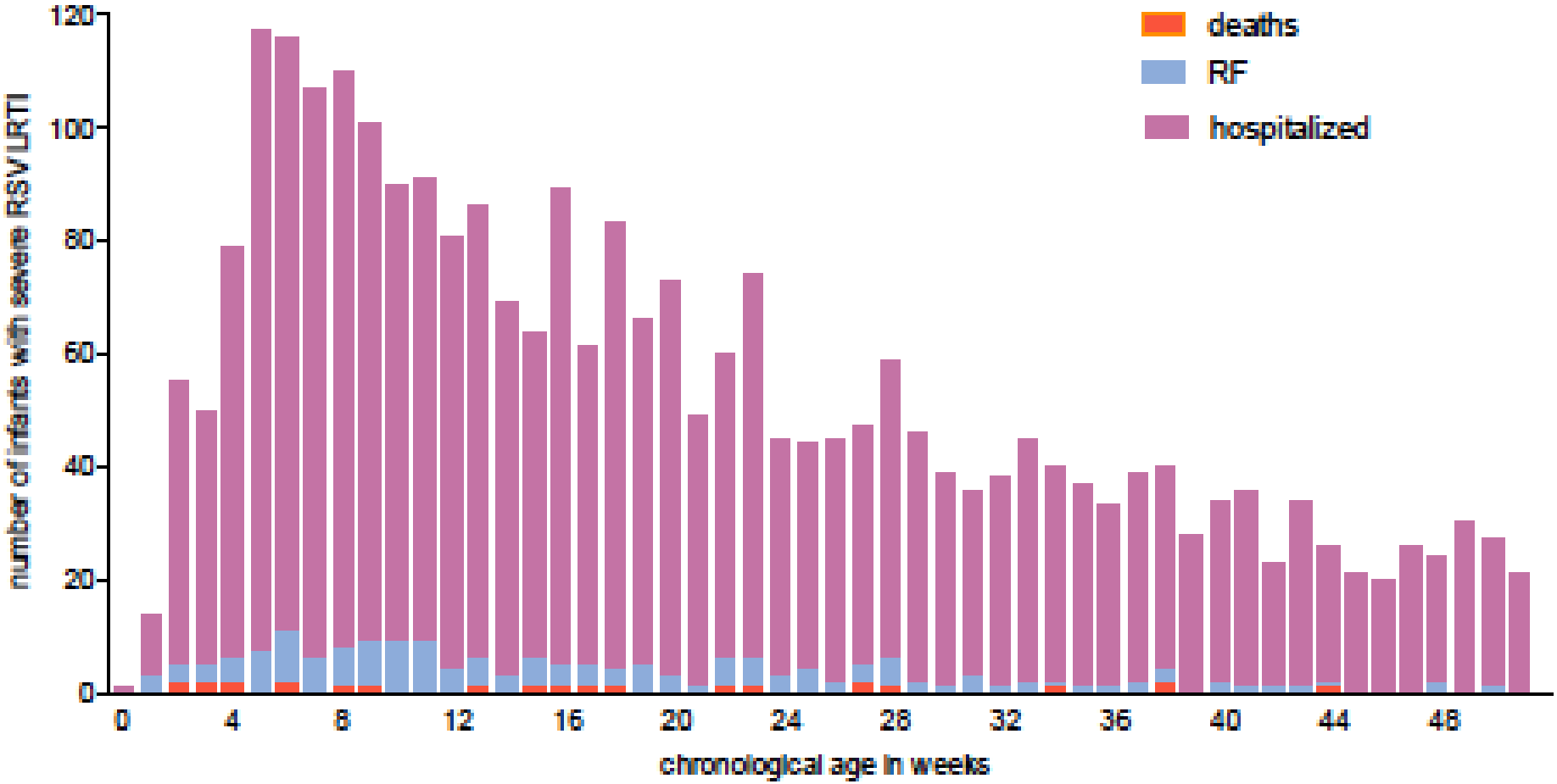
Byinghton CL et al. Pediatrics 15

RSV and non-RSV LRTI in the developing world (Argentina)



Geogeghan S et al, AJRCCM 17

Severe RSV LRTI in developing country hospitals



Hospital mortality in socially vulnerable populations

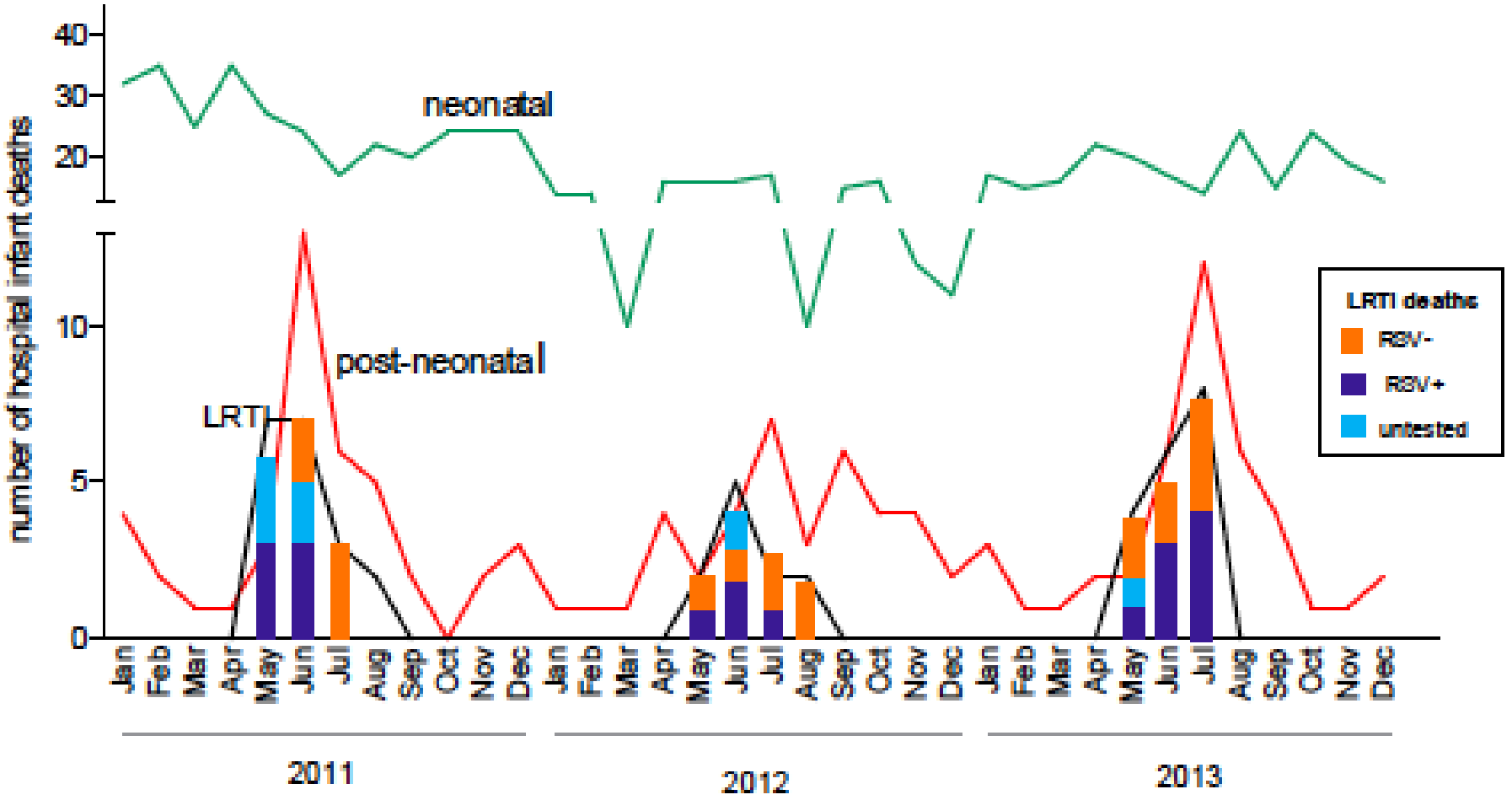


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Table 3. Multivariable analysis: Risk factors for death due to RSV

	OR (CI 95%)	*p*	OR (CI 95%)	*p*	OR (CI 95%)	*p*
Tin or mud house	1.92 (0.75 – 4.66)	0.156	1.51 (0.52 – 3.92)	0.412	2 (0.57 – 6.77)	0.263
Prematurity			2.01 (0.56 – 5.73)	0.227	0.27 (0.03 – 1.60)	0.205
Age ≤6m			2.25 (0.74 – 9.79)	0.202	1.19 (0.29 – 6.62)	0.82
Cardiac disease			4.27 (0.23 – 22.84)	0.171	8.26 (0.30 – 84.85)	0.127
Sepsis					151.9 (44.78 – 580.52)	**<.001**
Pneumothorax					77.4 (14.69 – 381.74)	**<.001**

Geogeghan S et al, AJRCCM 17

Mortality at the hospitals

- RSV is the most frequent viral pathogen associated with post-neonatal infant mortality.

- The virus was detected in 16% of all-cause hospital deaths; 57% of LRTI deaths where tests were performed.

- Its CFR was lower than that of non-RSV LRTI cases. Its importance relied on its dominating role as an agent of severe LRTI (65%), rather than on its specific lethality.

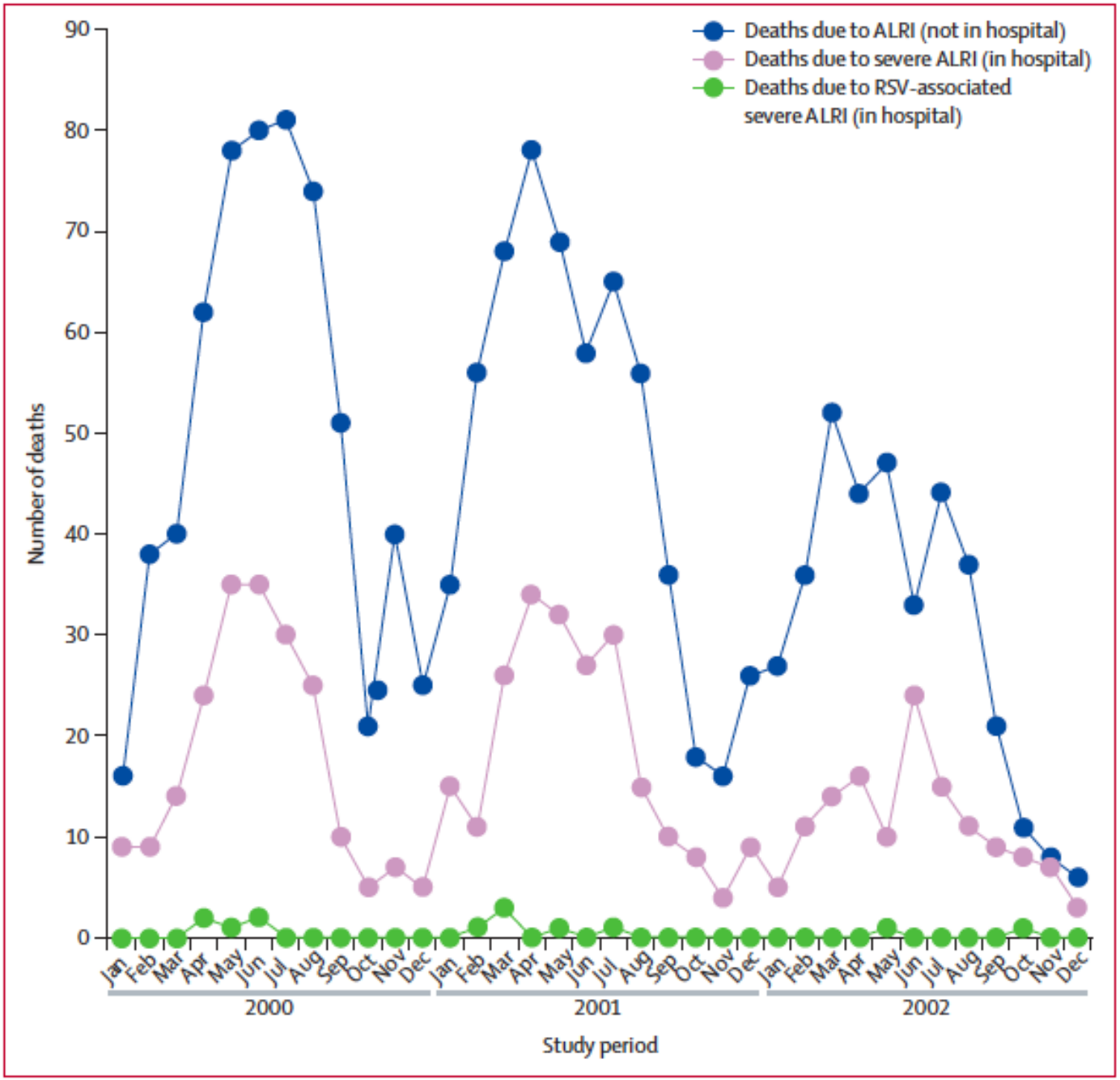
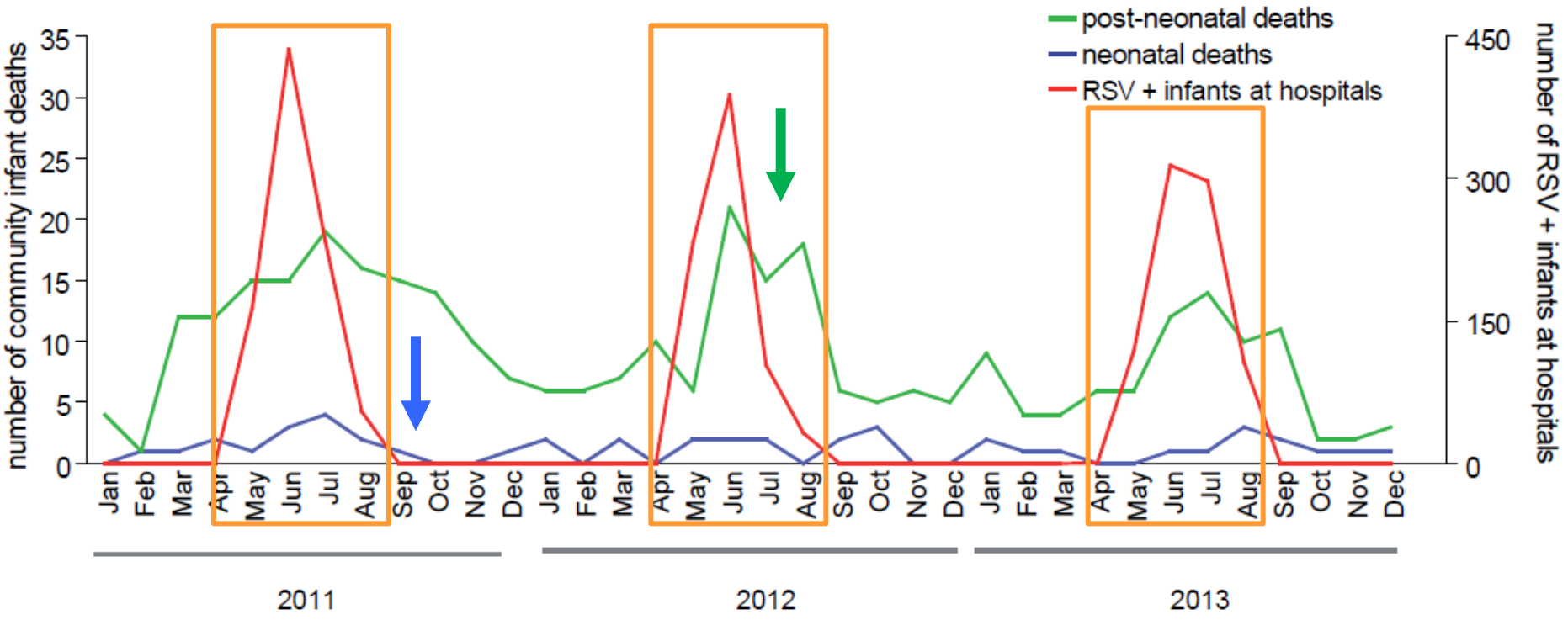


***Figure 4*: ALRI-associated mortality pattern in children younger than 2 years in Lombok, Indonesia**
RSV=respiratory syncytial virus. ALRI=acute lower respiratory infection.

Nair H. Lancet 2005

Community deaths in infants



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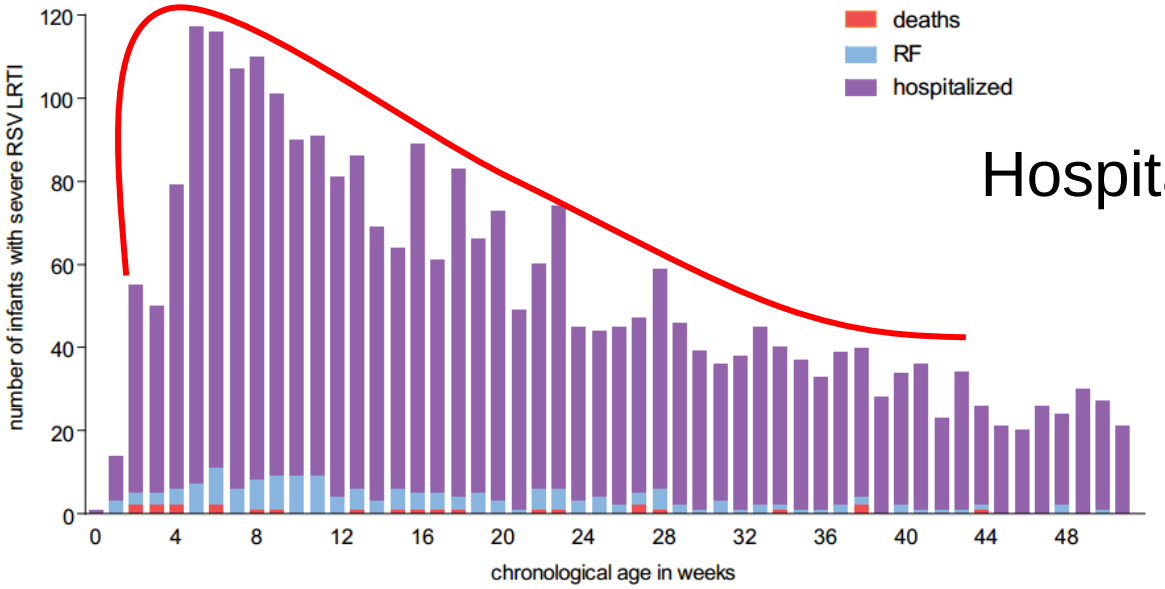
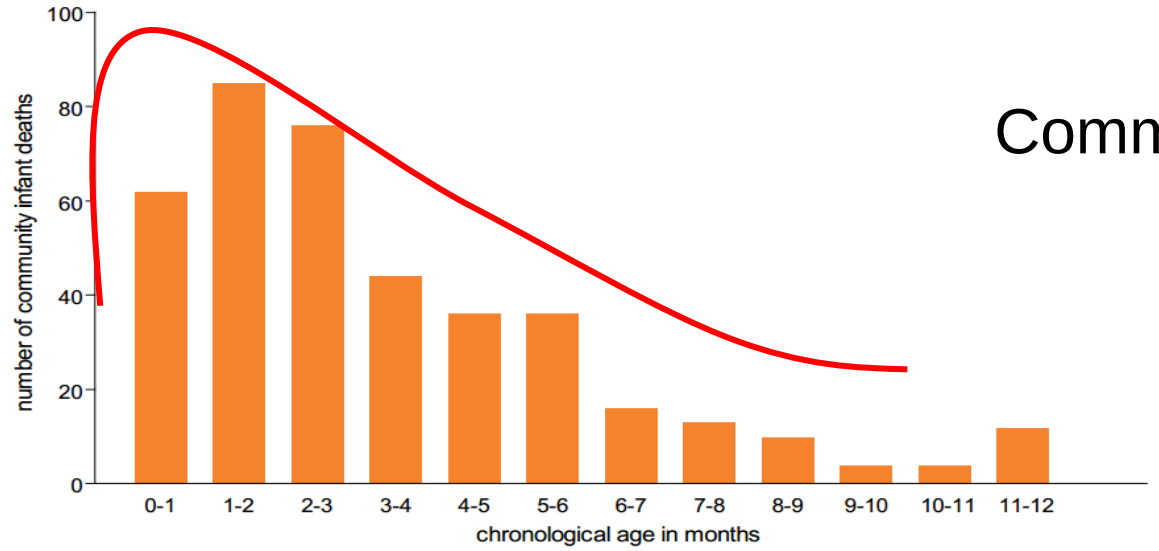
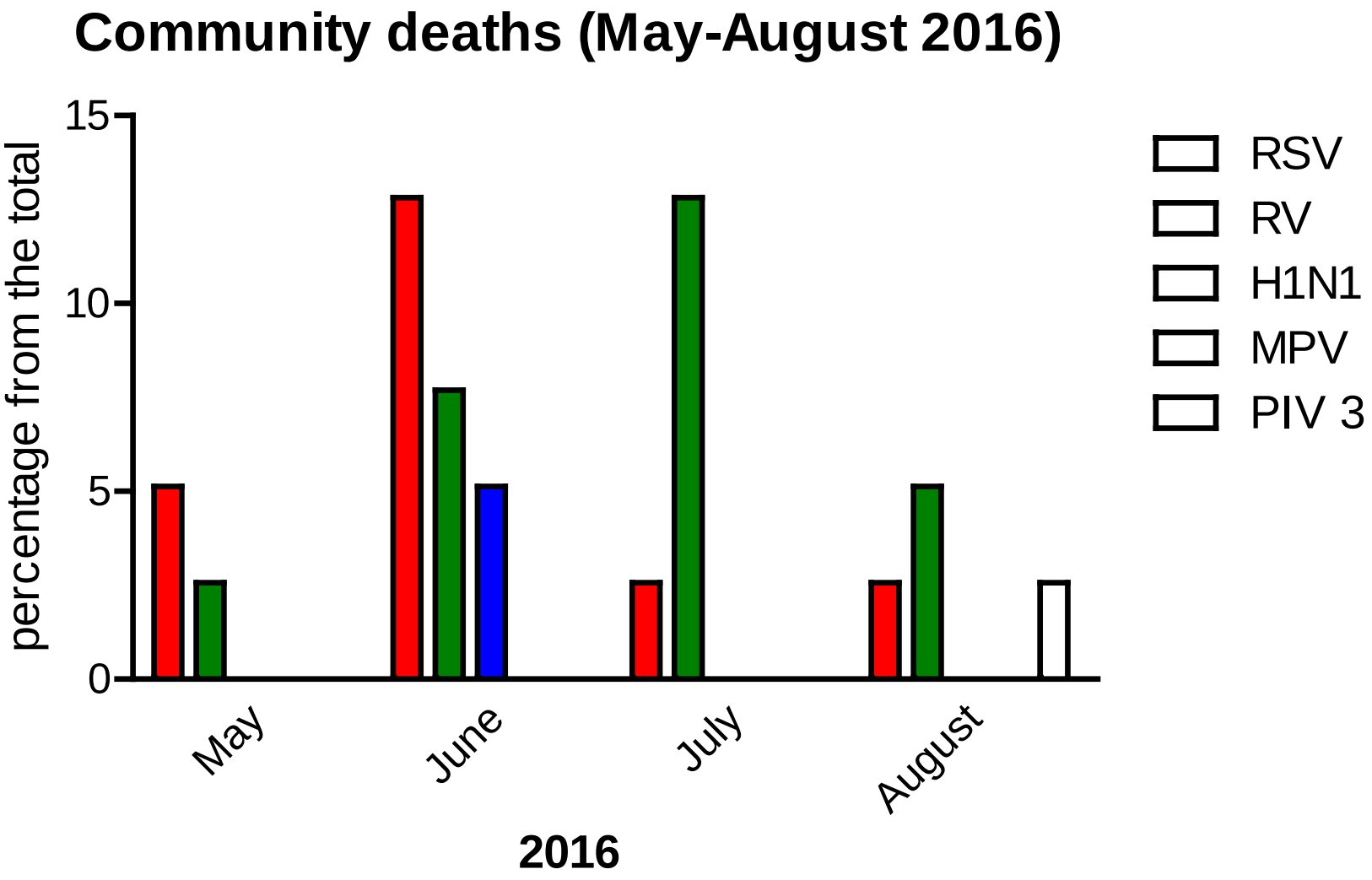
DOES THE AGE DISTRIUBTION OF DEATHS IN THE COMMUNITY RESEMBLE RSV DEATHS OR HOSPITALIZATIONS?

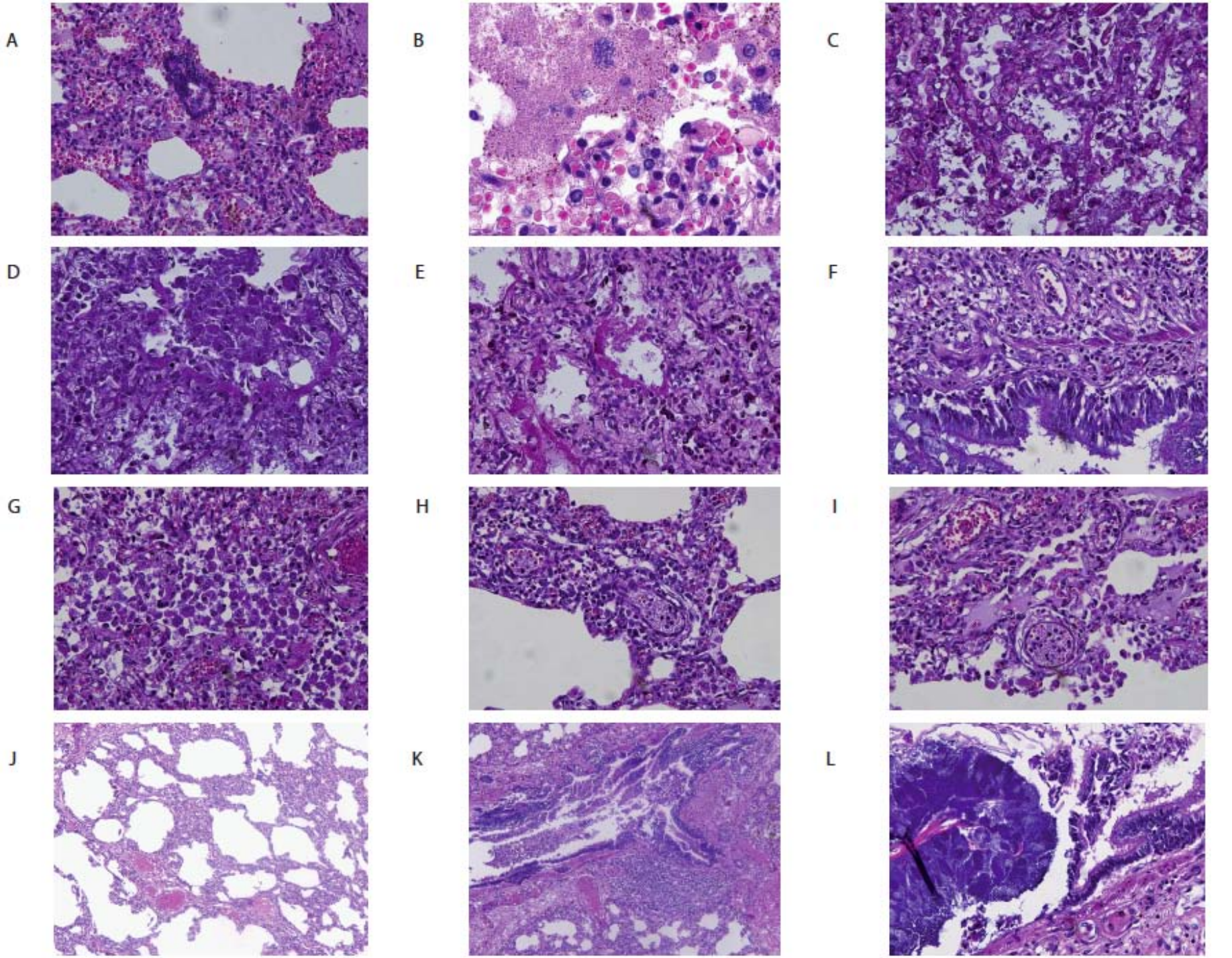


Hospitalizations



Community deaths


Community deaths (May-August 2016)
percentage from the total
15
10
5
0
May
June
July
August
2016
RSV
RV
H1N1
MPV
PIV 3


A
B
C
D
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G
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RSV LRTI in infants

- Almost never lethal (severe co-morbidity), frequent disease (up to 50%) in the industrialized world responsible for ~1% hospitalizations* in infants and 5-10 fold higher rates of physician-confirmed LRTI.

- Frequent disease in the developing world with hospitalization rates 2-3%*, uncertain rates of LRTI and several distinct characteristics:

  A significant number of severe cases do not reach the hospital.

  99% deaths occur in developing countries, most often in post-neonatal infants.

  Deaths at the hospital associate with poor medical practice, secondary bacterial infections and, less frequently, with comorbidities.

Special populations

- TLR4 heterozygosity in urban sites.
- Children of asthmatic mothers.
- Navajo and Apache, Alaska, Maori.

TLR4 heterozygosity and the environment

palivizumab protection

TABLE 2. Summary of Analysis of RSV Hospitalization

	Placebo	Palivizumab	% Reduction (95% CI)	*P* Value
Primary analysis (incidence of RSV hospitalizations)*	53/500 (10.6%)	48/1002 (4.8%)	55% (38, 72)	<.001
Alternative analysis (Kaplan-Meier†)	53/500 (10.6%)	48/1002 (4.8%)	55% (38, 72)	<.001
Sensitivity analyses				
Dropout before 150 days and no endpoint‡	53/500 (10.6%)	49/1002 (4.9%)	55% (38, 72)	<.001
Respiratory hospitalization but no RSV test done§	56/500 (11.2%)	54/1002 (5.4%)	52% (35, 69)	<.001
Primary inclusion populations				
Premature (no BPD)	19/234 (8.1%)	9/506 (1.8%)	78% (66, 90)	<.001
BPD	34/266 (12.8%)	39/496 (7.9%)	39% (20, 58)	.038

TLR4$^{+/-}$ in US premature babies failing palivizumab

Table II. *Analysis of carrier and allele frequencies of Asp299Gly TLR4 polymorphism in a case series[a] of high-risk infants with symptomatic RSV*

Asp299Gly	Literature Controls	RSV Subjects	χ^2 p value
Total subjects	7092	105	
AA (Asp/Asp)	6313 (89.0%)	11 (10.5%)	
AG (Asp/Gly)	742 (10.5%)	94 (89.5%)	
GG (Gly/Gly)	37 (0.5%)	0 (0.0%)	
Carrier frequency	0.11	0.90	<0.0001
(95% CI)	(0.10,10.12)	(0.82,0.95)	
Range	0.00–0.21	–	
Allele (G) Frequency	0.06	0.45	<0.0001
(95% CI)	(0.05,0.06)	(0.38,0.52)	
Range	0.00–0.11	–	

[a] The case series of 105 infants and children with symptomatic RSV comprises two separate study samples composed of 54 and 51 subjects (of 64 and 101 subjects in the original studies, respectively). Frequencies of the two polymorphisms were virtually identical in the two studies (Asp299Gly, 90.2% vs 88.9%, χ^2 p = 0.83, Fisher's exact p = 1.00).

RSV and TLR4 in Tel Aviv

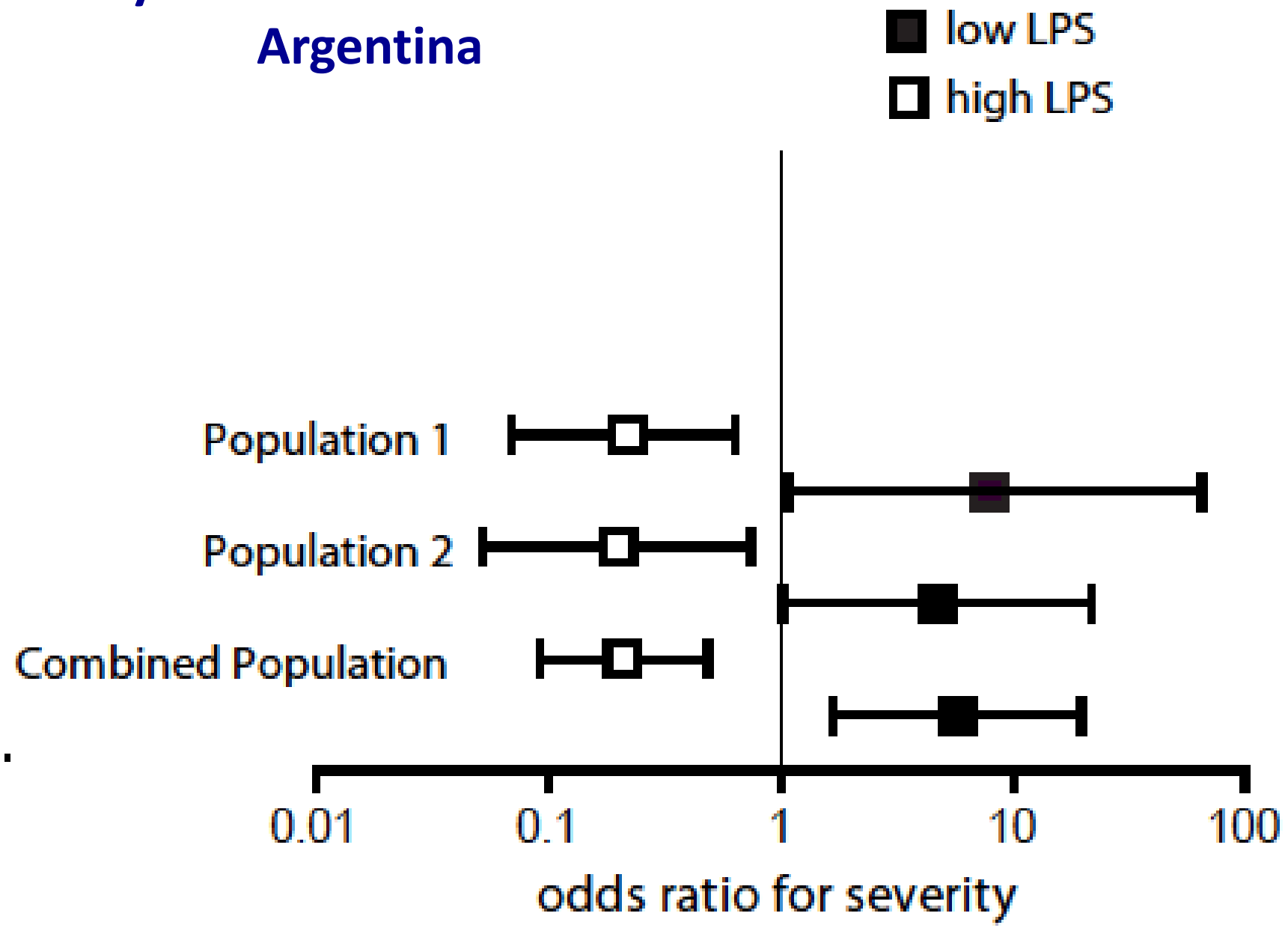
Table 2. Distribution of mutant Toll-like receptor 4 (TLR4) alleles among infants with severe and mild respiratory syncytial virus (RSV) bronchiolitis.

	RSV bronchiolitis			
TLR4 mutation(s)	Severe (n = 99)	Mild (n = 82)	OR (95% CI)	P
Pooled frequencies of Asp299Gly and Thr399Ile	20 (20.2)	4 (4.9)	4.9 (1.6–15.3)	.003
Asp299Gly	16 (16.2)	3 (3.7)	5.1 (1.4–18.1)	.014
Thr399Ile	17 (17.2)	4 (4.9)	4.0 (1.3–12.5)	.01
Cosegregation	13 (13.1)	3 (3.7)	4.0 (1.1–14.5)	.034

NOTE. Data are no. (%) of infants, unless otherwise noted. CI, confidence interval; OR, odds ratio.

Tal G et al. J Infect Dis 2004

Gene by environment interaction
Argentina



Caballero et al. J Clin Invest 15

Navajo, Apache & Alaska natives

Severe RSV LRTI in Alaska

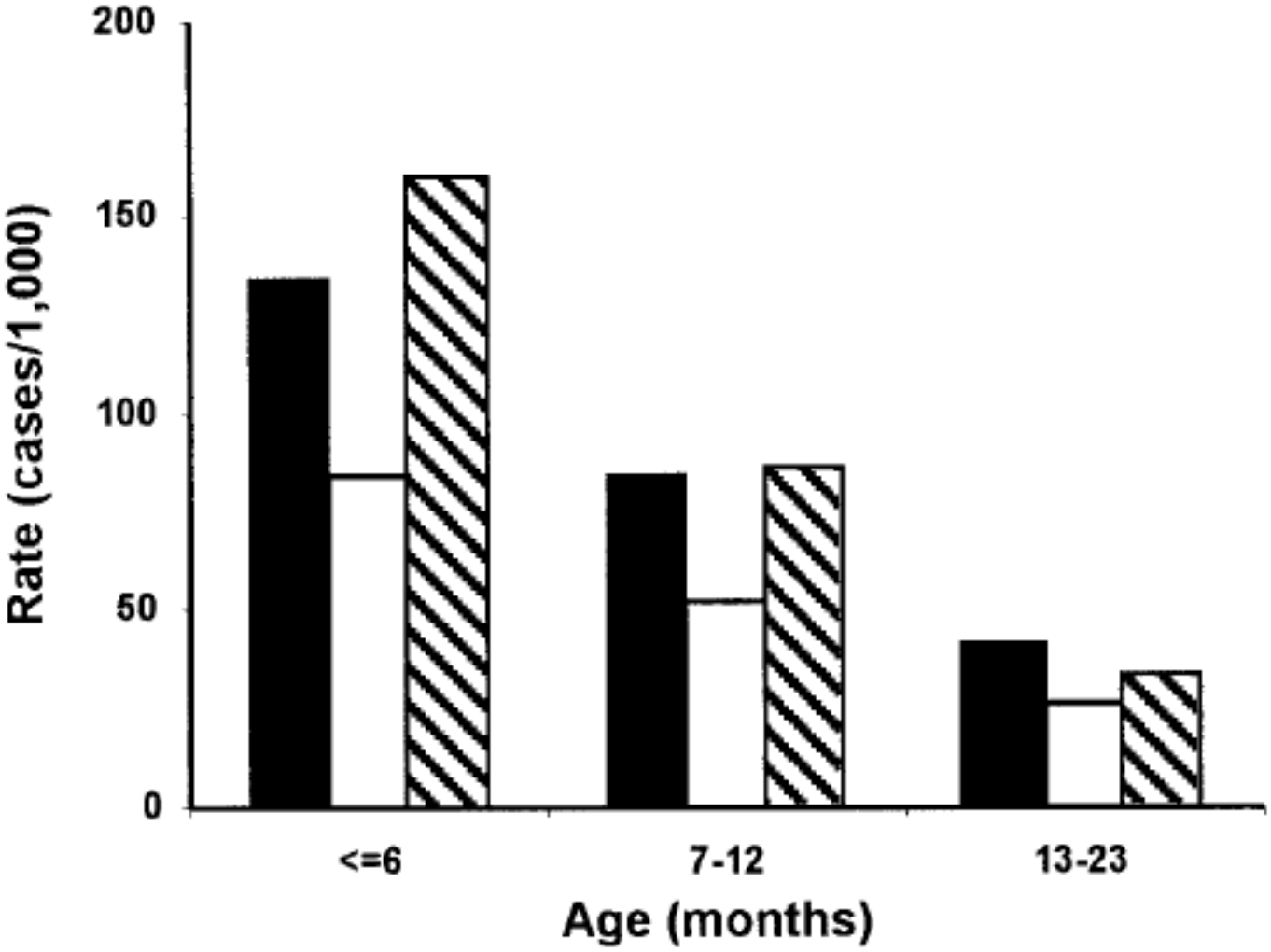
Table 1. Hospitalizations for respiratory syncytial virus (RSV) infection in the Yukon-Kuskokwim (YK) Delta, 1993–1996.

Category	Month/year of study 10/93–9/94	10/94–9/95	10/95–9/96	Total
All admissions	364	563	459	1386
Acute respiratory illness admissions	226	413	301	940
RSV admissions	41	246	144	431
RSV admissions, infants <1 year[a]	32	152	95	279
Births in YK Delta	609	611	581	1801
RSV admissions/1000 infants <1 year[a]	53	249	164	—

[a] Data do not include readmissions.

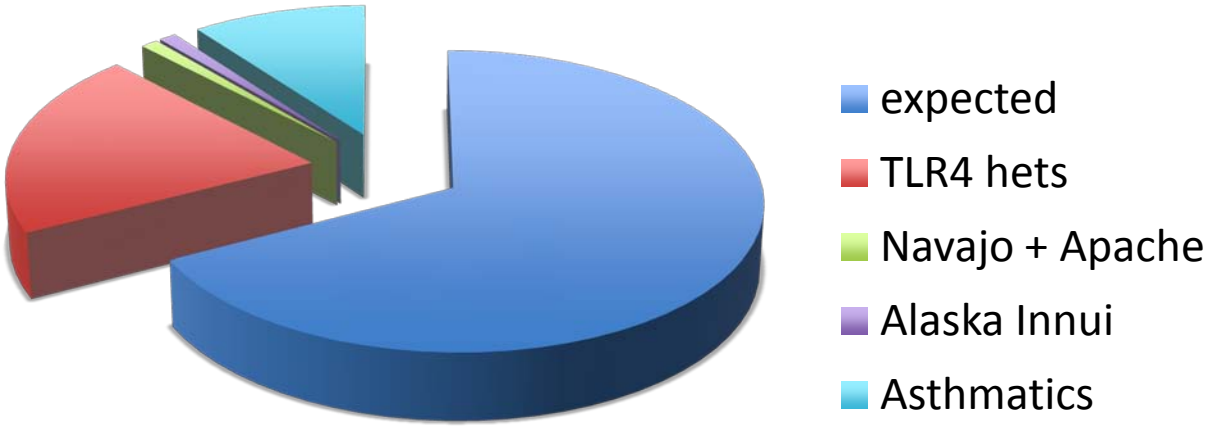
Karron RA et al. JID 1997

Severe RSV LRTI in Native Americans



Bokova J et al. Pediatr 2002

Severe RSV disease is a syndrome

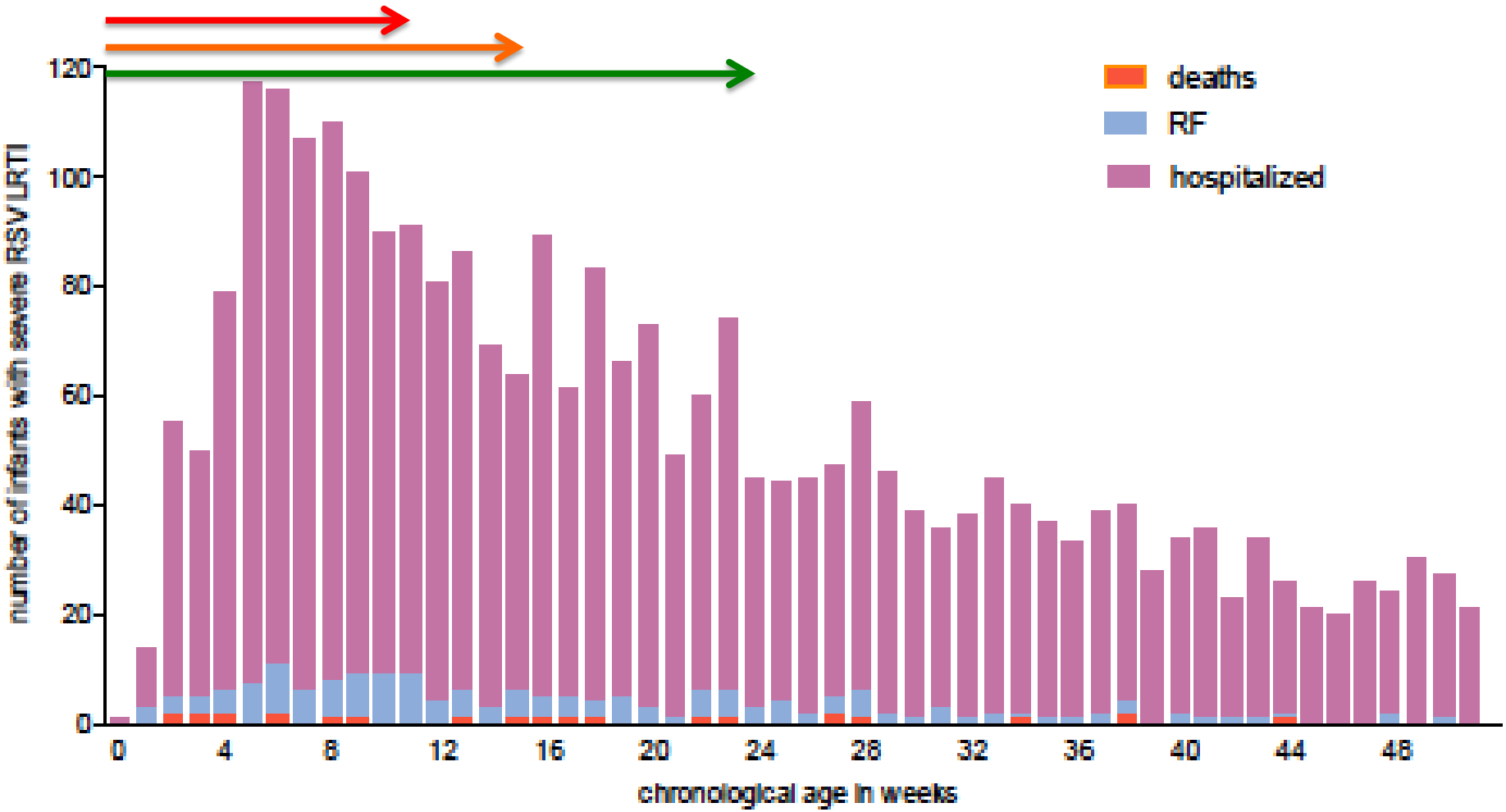


with numerous endotypes that may benefit from different approaches

RSV vaccines and monoclonal antibodies

Maternal immunization to protect infants

Severe RSV LRTI in developing country hospitals



RSV Vaccine and mAb Snapshot

TARGET INDICATION: (P) = PEDIATRIC (M) = MATERNAL (E) = ELDERLY (T) = TBD

	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	MARKET APPROVED
LIVE-ATTENUATED/ CHIMERIC	AmVac — Sendai virus Intravacc — Delta-G RSV Meissa Vaccines — RSV Sanofi Pasteur — RSV Codagenix — RSV LID/NIAID/NIH — PIV1-3/RSV Pontificia Universidad Catolica de Chile — BCG/RSV St. Jude Hospital — SeV/RSV	LID/NIAID/NIH (P) — RSV LID ΔM2-2 LID/NIAID/NIH (P) — RSV D46 cpΔM2-2 MedImmune, LID/NIAID/NIH (P) — RSV cps2 LID/NIAID/NIH (P) — RSV ΔNS2 Δ1313 MedImmune, LID/NIAID/NIH (P) — RSV Medi ΔM2-2			
WHOLE-INACTIVATED	NanoBio — RSV				
PARTICLE-BASED	AgilVax — VLP Fraunhofer — VLP Ruhr-Universität Bochum — VLP University of Massachussetts — VLP Artificial Cell Technologies — Peptide microparticle Georgia State University — VLP TechnoVax — VLP VBI Vaccines — RSV F eVLP DBV Technologies/ INRA — RSV N/F rings Mucosis — BLP RSV pre-F University of Massachussetts — VLP VLP Biotech — VLP	Novavax (P) — RSV F Nanoparticle		Novavax (M) — RSV F Nanoparticle Novavax (E) — RSV F Nanoparticle	
SUBUNIT	Advaccine Biotech — RSV G+CSA Instituto de Salud Carlos III — RSV F protein NIH/NIAID/VRC — RSV pre-F Protein University of Saskatchewan — RSV F protein University of Illinois — RSV F protein GlaxoSmithKline — RSV F protein Janssen Pharmaceutical — RSV pre-F Protein PeptiVir — RSV peptides University of Georgia — RSV G protein	GlaxoSmithKline (M) — RSV post-F Protein Immunovaccine/ VIB (E) — DPX-RSV-SH Protein	GlaxoSmithKline (M) — RSV F protein MedImmune (E) — RSV F protein		
NUCLEIC ACID	CureVac — RNA GlaxoSmithKline — RNA Inovio Pharmaceuticals — DNA Ruhr-Universität Bochum — DNA				
GENE-BASED VECTORS	AlphaVax — Alphavirus GenVec — Adenovirus University of Pittsburg — Adenovirus Emergent BioSolutions — MVA Ruhr-Universität Bochum — Adenovirus Vanderbilt University — Alphavirus	Bavarian Nordic (T) — MVA Janssen Pharmaceutical (P) — Adenovirus GlaxoSmithKline (P) — Adenovirus Vaxart (E) — Adenovirus			
COMBINATION/ IMMUNO-PROPHYLAXIS	Biomedical Research Models — DNA prime, particle boost Fudan University — DNA+protein combo UCAB/mAbXience — Anti-F mAb		MedImmune (P) — Anti-F mAb	Regeneron (P) — Anti-F mAb	MedImmune (P) — Synagis

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

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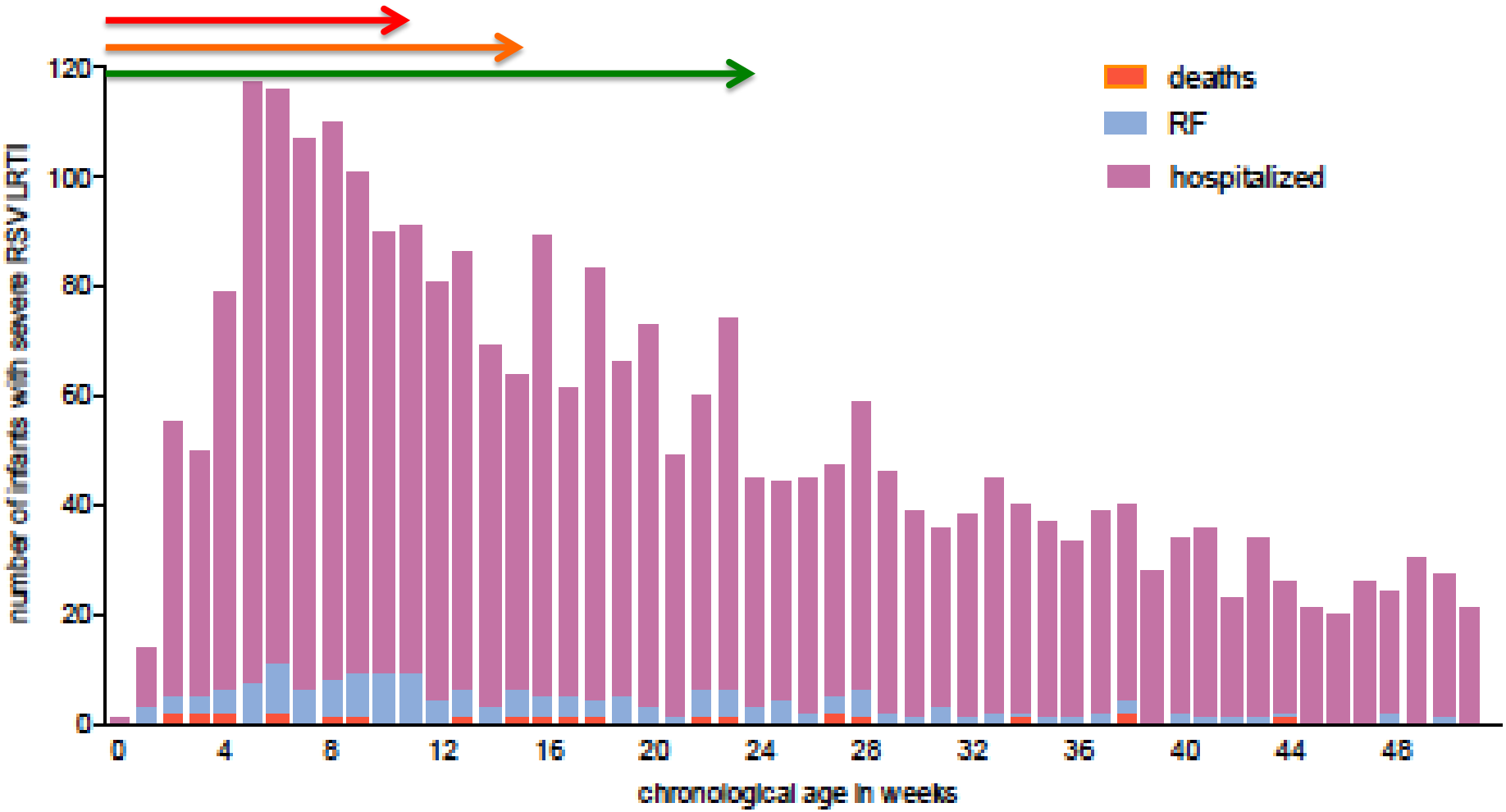
Novavax– fusion protein nanoparicles (alum)

- RCT, placebo-controlled, group sequential: pregnant women 28-36 weeks of pregnancy to prevent symptomatic RSV-associated LRTI with hypoxemia for 90 days in infants
- Follow up: mothers until 6 months post-delivery, infants follow up for 12 months.
- Entering Y3.
- US, Mexico, Argentina, Chile, New Zealand, Australia, South Africa, Spain, UK, Philippines.

RSV vaccines and monoclonal antibodies

Monoclonal antibodies

Severe RSV LRTI in developing country hospitals



RSV Vaccine and mAb Snapshot

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	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	MARKET APPROVED
LIVE-ATTENUATED/ CHIMERIC	AmVac — Sendai virus Intravacc — Delta-G RSV Meissa Vaccines — RSV Sanofi Pasteur — RSV Codagenix — RSV LID/NIAID/NIH — PIV1-3/RSV Pontificia Universidad Catolica de Chile — BCG/RSV St. Jude Hospital — SeV/RSV	LID/NIAID/NIH (P) — RSV LID ΔM2-2 LID/NIAID/NIH (P) — RSV D46 cpΔM2-2 MedImmune, LID/NIAID/NIH (P) — RSV cps2 LID/NIAID/NIH (P) — RSV ΔNS2 Δ1313 MedImmune, LID/NIAID/NIH (P) — RSV Medi ΔM2-2			
WHOLE-INACTIVATED	NanoBio — RSV				
PARTICLE-BASED	AgilVax — VLP Fraunhofer — VLP Ruhr-Universität Bochum — VLP University of Massachussetts — VLP Artificial Cell Technologies — Peptide microparticle Georgia State University — VLP TechnoVax — VLP VBI Vaccines — RSV F eVLP DBV Technologies/ INRA — RSV N/F rings Mucosis — BLP RSV pre-F University of Massachussetts — VLP VLP Biotech — VLP	Novavax (P) — RSV F Nanoparticle		Novavax (M) — RSV F Nanoparticle Novavax (E) — RSV F Nanoparticle	
SUBUNIT	Advaccine Biotech — RSV G+CSA Instituto de Salud Carlos III — RSV F protein NIH/NIAID/VRC — RSV pre-F Protein University of Saskatchewan — RSV F protein University of Illinois — RSV F protein GlaxoSmithKline — RSV F protein Janssen Pharmaceutical — RSV pre-F Protein PeptiVir — RSV peptides University of Georgia — RSV G protein	GlaxoSmithKline (M) — RSV post-F Protein Immunovaccine/ VIB (E) — DPX-RSV-SH Protein	GlaxoSmithKline (M) — RSV F protein MedImmune (E) — RSV F protein		
NUCLEIC ACID	CureVac — RNA GlaxoSmithKline — RNA Inovio Pharmaceuticals — DNA Ruhr-Universität Bochum — DNA				
GENE-BASED VECTORS	AlphaVax — Alphavirus GenVec — Adenovirus University of Pittsburg — Adenovirus Emergent BioSolutions — MVA Ruhr-Universität Bochum — Adenovirus Vanderbilt University — Alphavirus	Bavarian Nordic (T) — MVA Janssen Pharmaceutical (P) — Adenovirus GlaxoSmithKline (P) — Adenovirus Vaxart (E) — Adenovirus			
COMBINATION/ IMMUNO-PROPHYLAXIS	Biomedical Research Models — DNA prime, particle boost Fudan University — DNA+protein combo UCAB/mAbXience — Anti-F mAb		MedImmune (P) — Anti-F mAb	Regeneron (P) — Anti-F mAb	MedImmune (P) — Synagis

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

PATH

Medimmune – preF mAb

- **Passive RSV vaccine strategy using RSV F mAb**

- Fully human, high potency IgG1 mAb derived from human B-cells
  - YTE half-life extension technology

- Targets site on RSV **prefusion F**
  - 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

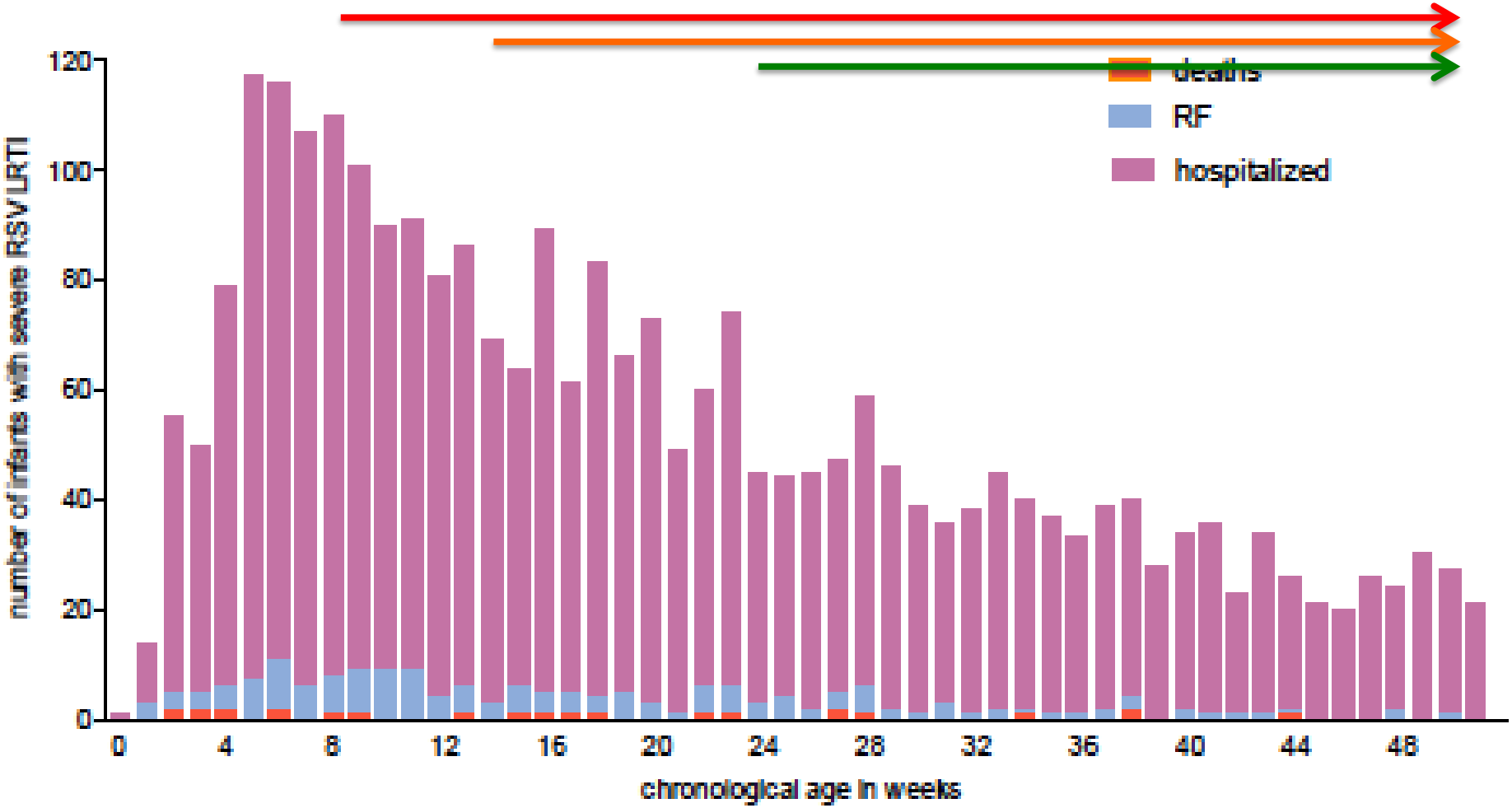
Biosimilar palivizumab– WHO and University of Utrecht

- Palivizumab off patent in 2015
- Plan to develop **a 'biosimilar' of palivizumab** and **reduce costs** through
  - Using high expression cell line.
  - Estimated lower price
  - Roll out the product in LMICs

RSV vaccines and monoclonal antibodies

Infant vaccines

Severe RSV LRTI in developing country hospitals



RSV Vaccine and mAb Snapshot

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	Codagenix — RSV	LID/NIAID/NIH — PIV1-3/RSV	Pontificia Universidad Catolica de Chile — BCG/RSV	St. Jude Hospital — SeV/RSV		LID/NIAID/NIH (P) — RSV ΔNS2 Δ1313	MedImmune, LID/NIAID/NIH (P) — RSV Medi ΔM2-2				
WHOLE-INACTIVATED	NanoBio — RSV										
PARTICLE-BASED	AgilVax — VLP	Fraunhofer — VLP	Ruhr-Universität Bochum — VLP	University of Massachussetts — VLP		Novavax (P) — RSV F Nanoparticle				Novavax (M) — RSV F Nanoparticle	
	Artificial Cell Technologies — Peptide microparticle	Georgia State University — VLP	TechnoVax — VLP	VBI Vaccines — RSV F eVLP						Novavax (E) — RSV F Nanoparticle	
	DBV Technologies/ INRA — RSV N/F rings	Mucosis — BLP RSV pre-F	University of Massachussetts — VLP	VLP Biotech — VLP							
SUBUNIT	Advaccine Biotech — RSV G+CSA	Instituto de Salud Carlos III — RSV F protein	NIH/NIAID/VRC — RSV pre-F Protein	University of Saskatchewan — RSV F protein	University of Illinois — RSV F protein	GlaxoSmithKline (M) — RSV post-F Protein			GlaxoSmithKline (M) — RSV F protein		
	GlaxoSmithKline — RSV F protein	Janssen Pharmaceutical — RSV pre-F Protein	PeptiVir — RSV peptides	University of Georgia — RSV G protein		Immunovaccine/ VIB (E) — DPX-RSV-SH Protein			MedImmune (E) — RSV F protein		
NUCLEIC ACID	CureVac — RNA	GlaxoSmithKline — RNA	Inovio Pharmaceuticals — DNA	Ruhr-Universität Bochum — DNA							
GENE-BASED VECTORS	AlphaVax — Alphavirus	GenVec — Adenovirus	University of Pittsburg — Adenovirus			Bavarian Nordic (T) — MVA	Janssen Pharmaceutical — Adenovirus				
	Emergent BioSolutions — MVA	Ruhr-Universität Bochum — Adenovirus	Vanderbilt University — Alphavirus			GlaxoSmithKline (P) — Adenovirus	Vaxart (E) — Adenovirus				
COMBINATION/ IMMUNO-PROPHYLAXIS	Biomedical Research Models — DNA prime, particle boost	Fudan University — DNA+protein combo	UCAB/mAbXience — Anti-F mAb						MedImmune (P) — Anti-F mAb	Regeneron (P) — Anti-F mAb	MedImmune (P) — Synagis

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

PATH

Vectored RSV vaccines for infants

- Janssen: Ad26.RSV.FA2
- GSK: ChAd155 RSV F, N and M2.1
- Bavarian Nordic: MVA F_A, G_A+G_B, N and M2

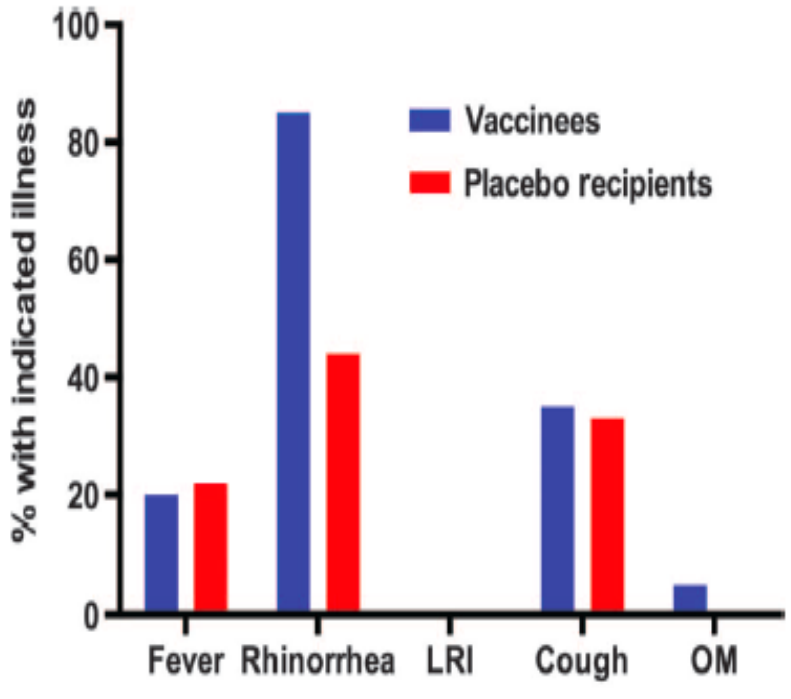

Fig. 2. Proportions of RSV-seronegative vaccinees and placebo recipients with indicated illnesses. Vaccinees are shown in blue; placebo recipients are shown in red. The placebo recipient (twin B) infected with vaccine virus is not included. Fever occurred in 4 of 20 vaccinees (1 of grade 0 severity, 1 of grade 2 severity, and 2 of grade 3 severity) and in 2 of 9 placebo recipients (both of grade 2 severity): grade 0, <38°C; grade 1, ≥38°C but ≤38.6°C; grade 2, ≥38.7°C but ≤39.1°C; grade 3, ≥39.2°C but ≤40.5°C. The two episodes of grade 3 fever in vaccinees occurred on days 24 to 26 after vaccination, when shedding of vaccine virus was not detected. URI (rhinorrhea) occurred in 17 of 20 vaccinees and 4 of 9 placebo recipients; cough occurred in 7 of 20 vaccinees and 3 of 9 placebo recipients; all of these illnesses were of grade 1 severity (that is, not requiring medical attention). An episode of OM (grade 2 severity) occurred in a single vaccinee.

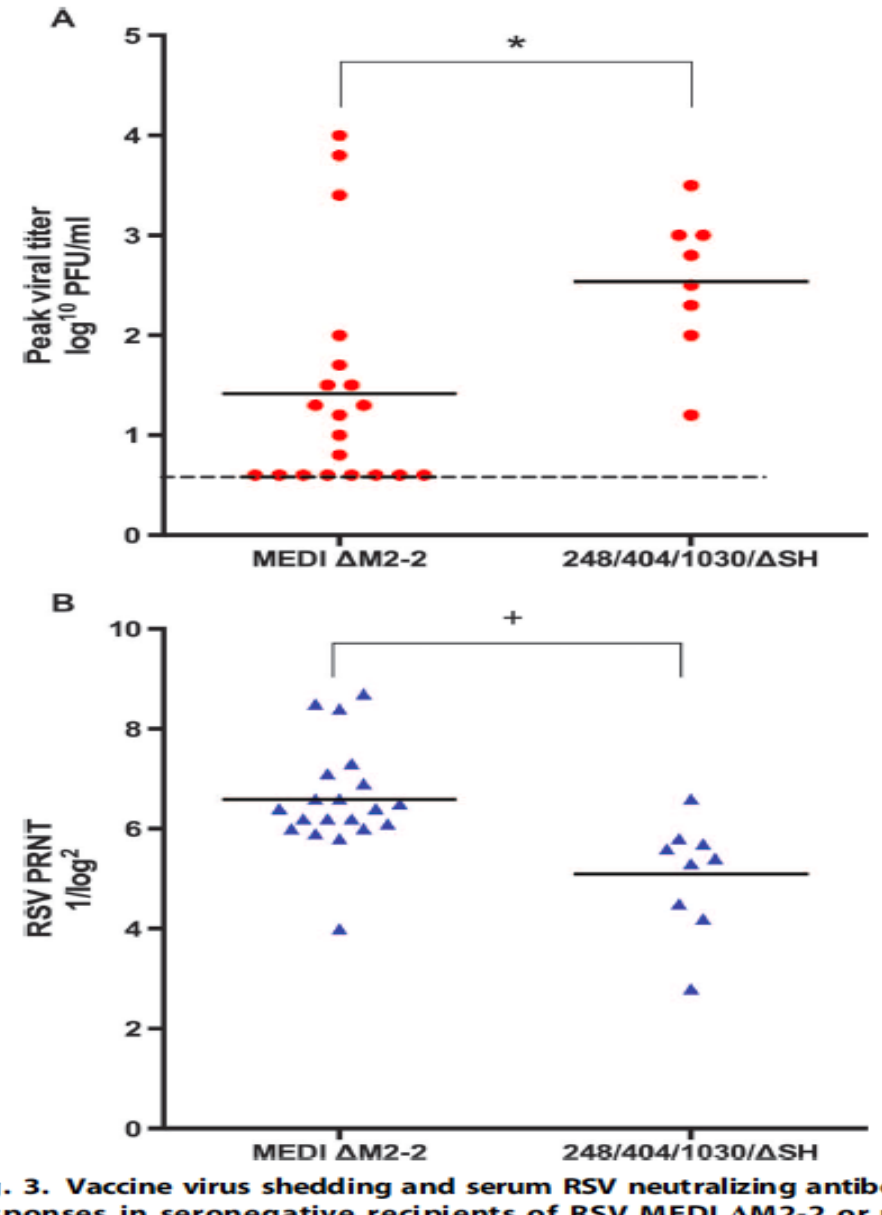

Fig. 3. Vaccine virus shedding and serum RSV neutralizing antibo responses in seronegative recipients of RSV MEDI ΔM2-2 or rA cp248/404/1030/ΔSH. NW and serum specimens from the present stu were evaluated for vaccine virus titer and serum neutralizing antibodies, r spectively. Antibody testing was performed in parallel with specimens fro the previous clinical evaluation of rA2 cp248/404/1030/ΔSH (*8*). (**A**) Peak vi titer (expressed as $\log_{10}$ PFU/ml). (**B**) RSV PRNTs, expressed as $1/\log_2$. *P 0.005; $^{+}P = 0.002$ (Student's t test).

In summary…

- Certain endotypes of RSV disease will probably continue to associate with severe disease, and will require personalized medicine approaches for prevention and treatment.

- Some episodes of RSV LRTI will probably be replaced by episodes of non-RSV LRTI.

- Mortality will decrease at hospitals and in the community, even though mortality is driven by underlying baseline deficits in living standards and public health in developing countries.

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