RSV vaccine: a changing landscape

Romina Libster
Vaccinology 2018
Panama

Disclosures

Travel/speaking grants, advisory boards and clinical trials participation: *MSD, Janssen and Novavax.*
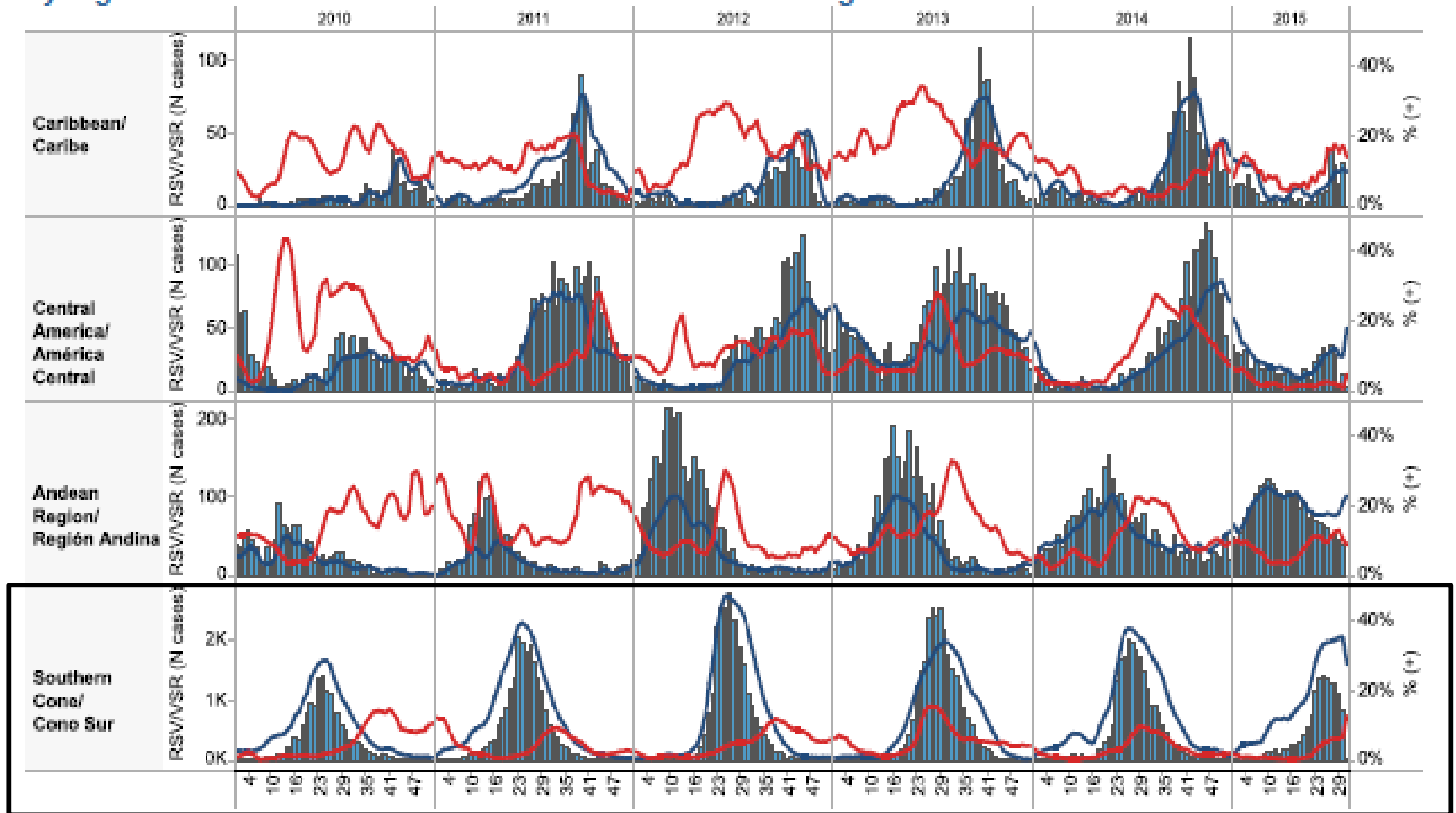
Respiratory syncytial virus (RSV) circulation by region. 2010-15

Circulación de virus sincitial respiratorio por región. 2010-15

Respiratory viruses/
Virus respiratorios

- ☐ RSV/VSR (n cases)
- ☐ % influenza(+)
- ☐ % RSV/VSR (+)

Paho 2015

USUAL RSV SEASONALITIES WORLDWIDE
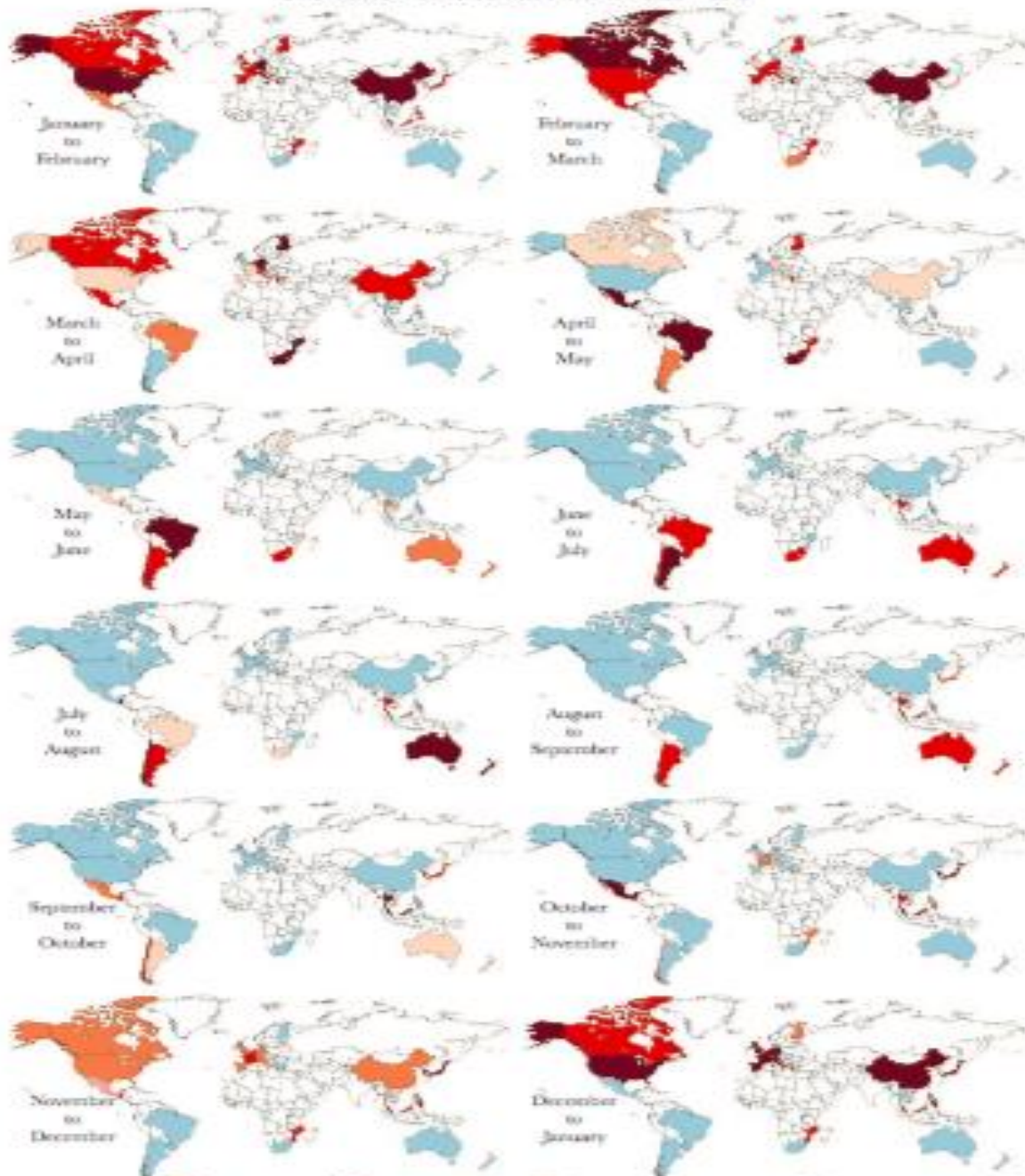
RSV is **seasonal** problem

Obando-Pacheco P, et al. JID 2018

Increasing RSV activity   RSV Epidemic   Peak RSV activity   Decreasing RSV activity   Low RSV activity   No data

RSV is **Global** problem

Legend:
- RSV (red)
- FLU (blue)
- RSV & FLU (yellow)

RSV Global Burden Estimates - 2005
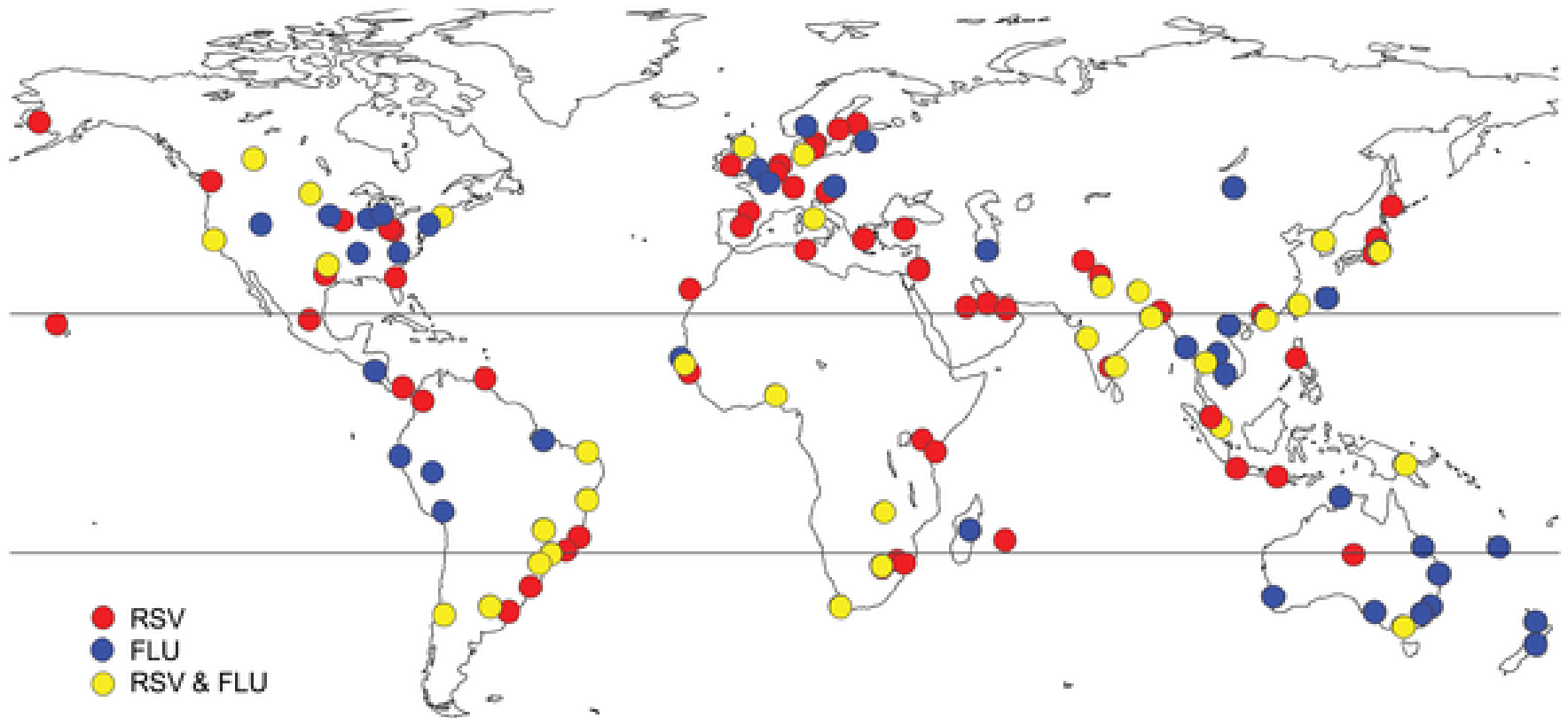
- 33.8 (95% CI 19.3–46.2) million new episodes of RSV-associated ALRI (22% of ALRI episodes)

- 3.4 (2.8–4.3) hospital admissions due to severe RSV-associated ALRI

- 66 000–199 000 deaths (99% in developing countries)

- RSV was the most common cause of childhood ALRI

- RSV was an important cause of death in childhood from ALRI, after pneumococcal pneumonia and Haemophilus influenzae type b

Nair H, et al. Lancet 2010

RSV Global Burden Estimates

2005

- 33.8 (95% CI 19.3–46.2) million new episodes of RSV-associated ALRI (22% of ALRI episodes)

- 3.4 million (2.8–4.3) hospital admissions due to severe RSV-associated ALRI

- 66 000–199 000 deaths (99% in developing countries)

2015

- 33.1 million (21.6–50.3) new episodes of RSV-associated ALRI

- 3.2 million (2.7–3.8) hospital admissions due to severe RSV-associated ALRI

- 59 600 (48 000–74 500) in-hospital deaths

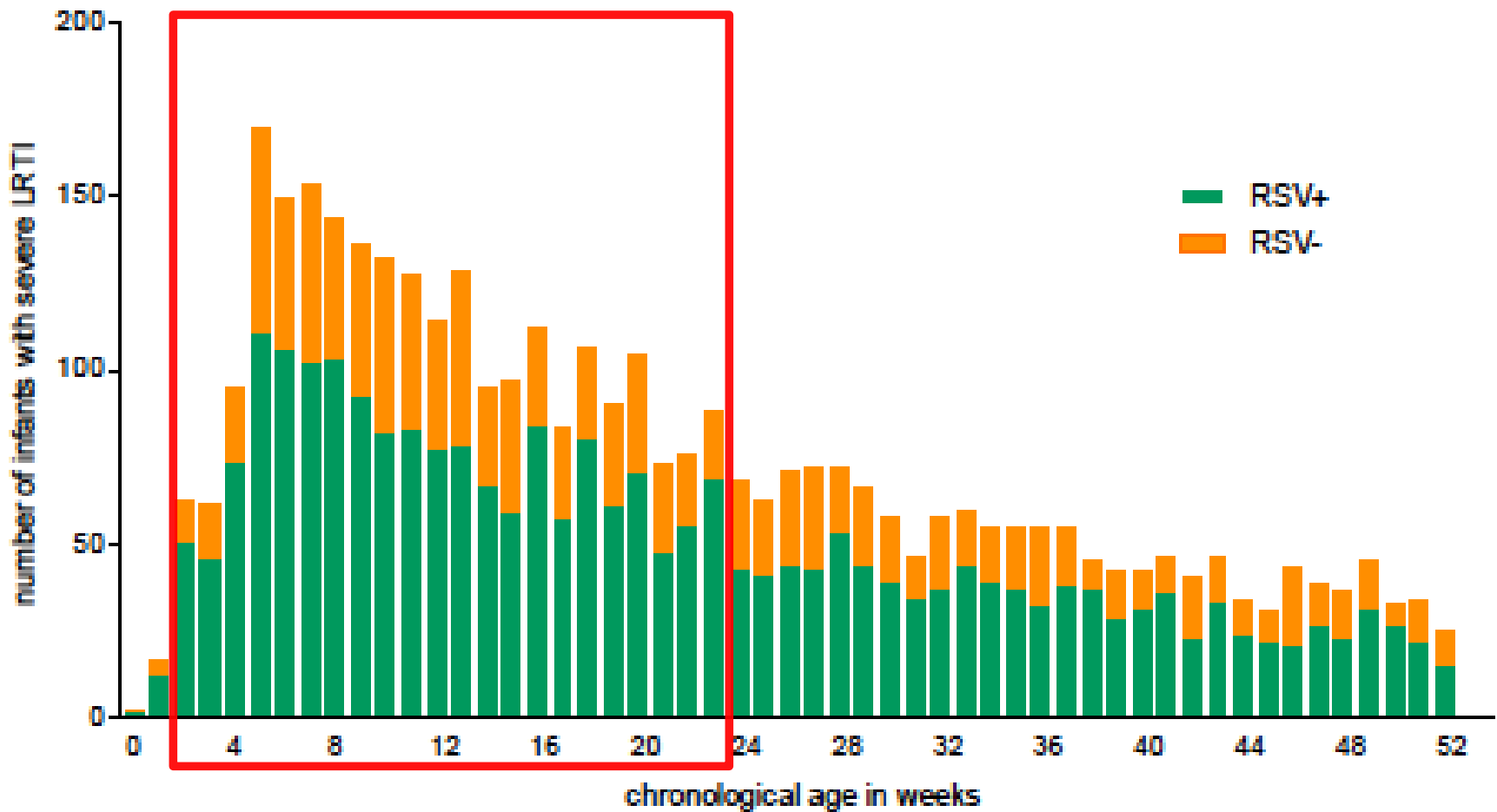- overall RSV-ALRI mortality could be as high as 118 200 (UR 94 600–149 400)

Nair H, et al. Lancet 2010 / Shi T, Lancet 2017

3.2 million hospital admissions due to severe RSV-associated ALRI

Severe RSV LRTI in developing country hospitals

Burden on hospital inpatient services (left side label)

Burden not accessing hospital inpatient services (right side label)

Estimated number of episodes of RSV-severe ALRI in LMIC children in 2015

6·0 million (UR 2·1–17·6)

47% of cases reach hospital

2·8 million (UR 2·1–3·9)

53% of cases do not reach hospital

3·2 million

CFR in hospital admitted cases 2·1% (1·9–2·3)

CFR in communities 1·8%

51% of deaths were in hospital

59 600 (UR 47 800–74 300)

49% of deaths occur outside hospital

59 600 (UR 46 700–72 900)

Estimated (severe) RSV-ALRI deaths in children in developing countries

118 000 (UR 94 500–147 200)

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

Mortality in countries according to income

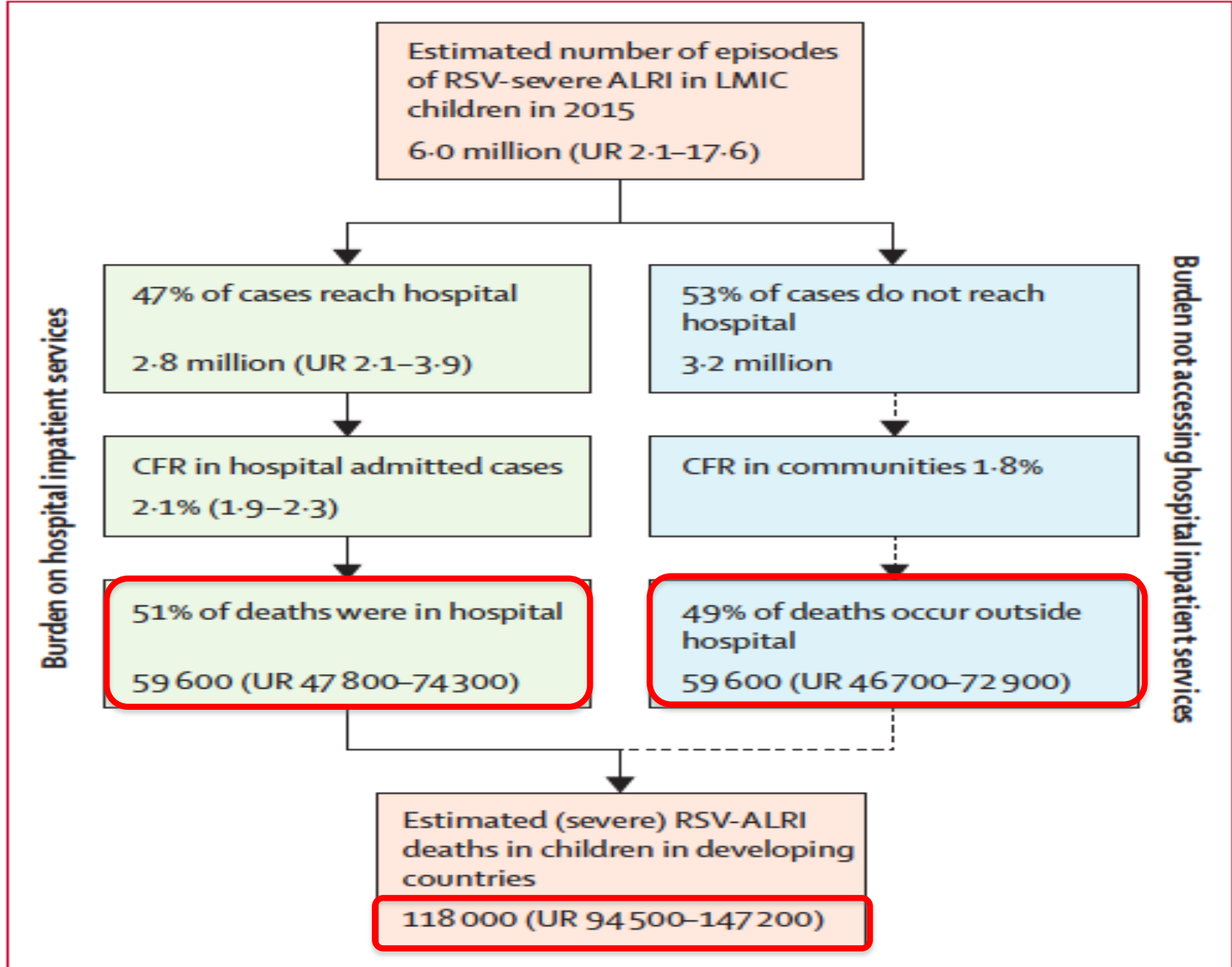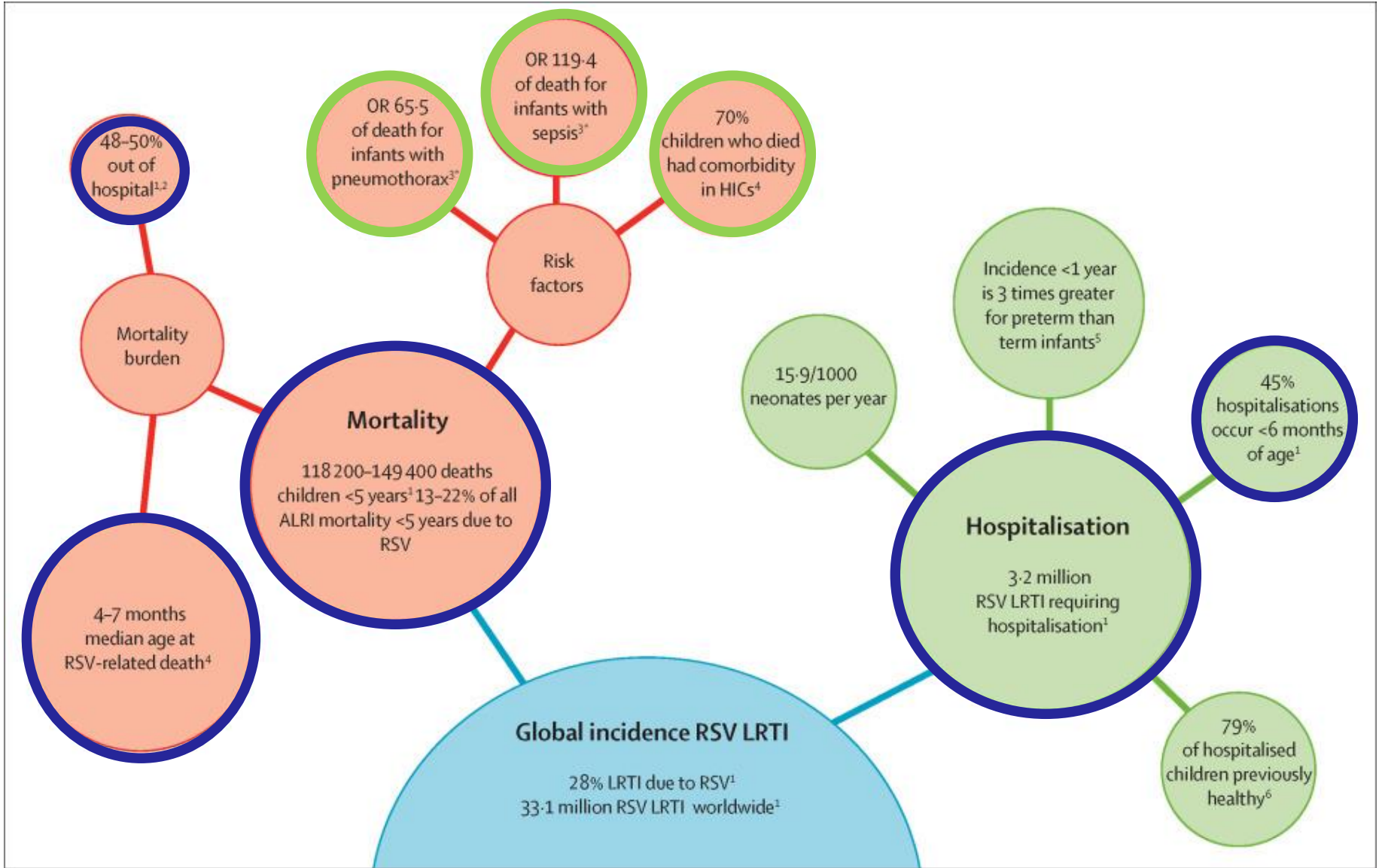|	Low income	Lower-middle income	Upper-middle income	High income	Developing countries	Industrialised countries	Global*†
Studies	9	16	12	6	41	2	43
0–5 months							
hCFR (%)‡	1·7 (0·4–6·8)	2·7 (2·0–3·6)	1·8 (1·2–2·6)	0·2 (0·0–12·8)	2·2 (1·8–2·7)	0·0 (0·0–0·1)	··
Number of deaths‡§	1300 (200–7900)	20 000 (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

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

Global burden of RSV in children under 5 years of age

Risk factors

OR 65·5 of death for infants with pneumothorax[3*]

OR 119·4 of death for infants with sepsis[3*]

70% children who died had comorbidity in HICs[4]

Mortality burden

48–50% out of hospital[1,2]

4–7 months median age at RSV-related death[4]

Mortality

118 200–149 400 deaths children <5 years[1] 13–22% of all ALRI mortality <5 years due to RSV

Hospitalisation

3·2 million RSV LRTI requiring hospitalisation[1]

15·9/1000 neonates per year

Incidence <1 year is 3 times greater for preterm than term infants[5]

45% hospitalisations occur <6 months of age[1]

79% of hospitalised children previously healthy[6]

Global incidence RSV LRTI

28% LRTI due to RSV[1]
33·1 million RSV LRTI worldwide[1]

- RSV infects 3%–9% of older adults yearly, and may be responsible for **6%–10% of seasonal hospital admissions**

- Mortality attributable to RSV in adults aged 65 years or older is estimated to be **7·2 per 100 000 person-years**

- Underlying cardiovascular disease is associated with hospitalization in 45% to 63% of adults with confirmed RSV

- **RSV is not being considered in the differential diagnosis at ED**

Mazur NI, et al, Lancet ID 2018; Binder W et al Am J Emerg Med 2017; Ivey KS, et al, J Am Coll Cardiol 2018

Young infants (0–6 months of age)

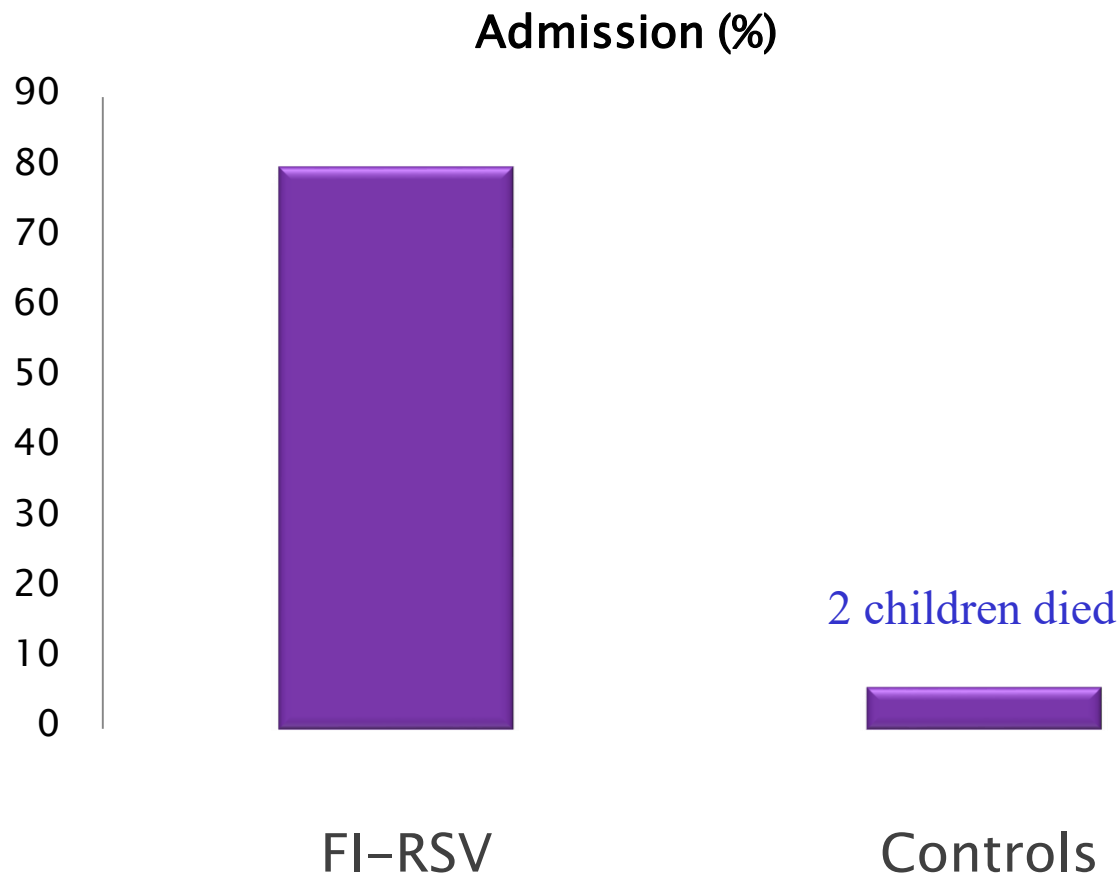Older infants and young children

Older adults and adults with cardiopulmonary disease

RSV vaccines and monoclonal antibodies

Different approaches to prevention of illness

Challenges for RSV vaccine development: ERD

Admission (%)

Kim HW et al, Am J Epidemiol 1969

RSV Vaccine Landscape: 2004

(n=3)
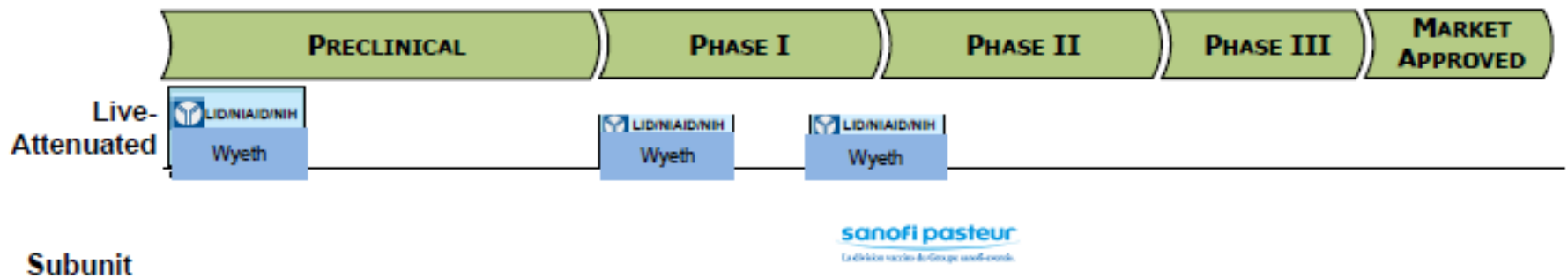
PRECLINICAL	PHASE I	PHASE II	PHASE III	MARKET APPROVED

Live-Attenuated

LID/NIAID/NIH Wyeth | | LID/NIAID/NIH Wyeth | LID/NIAID/NIH Wyeth | |

Subunit

sanofi pasteur

RSV Vaccine and mAb Snapshot

	PRECLINICAL				PHASE 1			PHASE 2	PHASE 3	MARKET APPROVED
LIVE-ATTENUATED/ CHIMERIC	Codagenix, LID/NIAID/NIH — RSV	LID/NIAID/NIH — RSV			Intravacc — Delta-G RSV (P)	Sanofi, LID/NIAID/NIH — RSV ΔNS2/Δ1313/I1314L (P)	Sanofi, LID/NIAID/NIH — RSV 6120/ΔNS2/1030s (P)			
	LID/NIAID/NIH — PIV1-3/RSV	Meissa Vaccines — RSV			Pontificia Universidad Catolica de Chile — BCG/RSV (P)	Sanofi, LID/NIAID/NIH — RSV D46/NS2/N/ΔM2-2-HindIII (P)	SIIPL, St. Jude Hospital — SeV/RSV			
WHOLE-INACTIVATED	Blue Willow Biologics — RSV									
PARTICLE-BASED	AgilVax — VLP	Fraunhofer — VLP	TechnoVax — VLP	VBI Vaccines — VLP	Novavax — RSV F Nanoparticle (P)			Novavax — RSV F Nanoparticle (E)	Novavax — RSV F Nanoparticle (M)	
	Artificial Cell Technologies — Peptide microparticle	Georgia State University — VLP	University of Massachussetts — VLP	Virometix — VLP						
SUBUNIT	Beijing Advaccine Biotechnology — RSV G Protein	University of Georgia — RSV G Protein	Sciogen — RSV G Protein		GlaxoSmithKline — RSV F Protein (E M)	Janssen Pharmaceutical — RSV F Protein (E)	Pfizer — RSV F Protein (E M)			
	Instituto de Salud Carlos III — RSV F Protein	University of Saskatchewan — RSV F Protein			Immunovaccine, VIB — DPX-RSV-SH Protein (E)	NIH/NIAID/VRC — RSV F Protein (E M)				
NUCLEIC ACID	CureVac — RNA	Inovio Pharmaceuticals — DNA								
RECOMBINANT VECTORS					Vaxart — Adenovirus (E)			Bavarian Nordic — MVA (E)	Janssen Pharmaceutical — Adenovirus (P E)	
								GlaxoSmithKline — Adenovirus (P)		
IMMUNO-PROPHYLAXIS/ COMBINATION	Arsanis — Anti-F mAb	Biomedical Research Models — DNA prime, Particle boost	Pontificia Universidad Catolica de Chile — Anti-N mAb	UCAB, mAbXience — Anti-F mAb				MedImmune, Sanofi — Anti-F mAb (P)		MedImmune — Synagis

UPDATED: September 12, 2018

Indicates Change

http://vaccineresources.org/details.php?i=1562

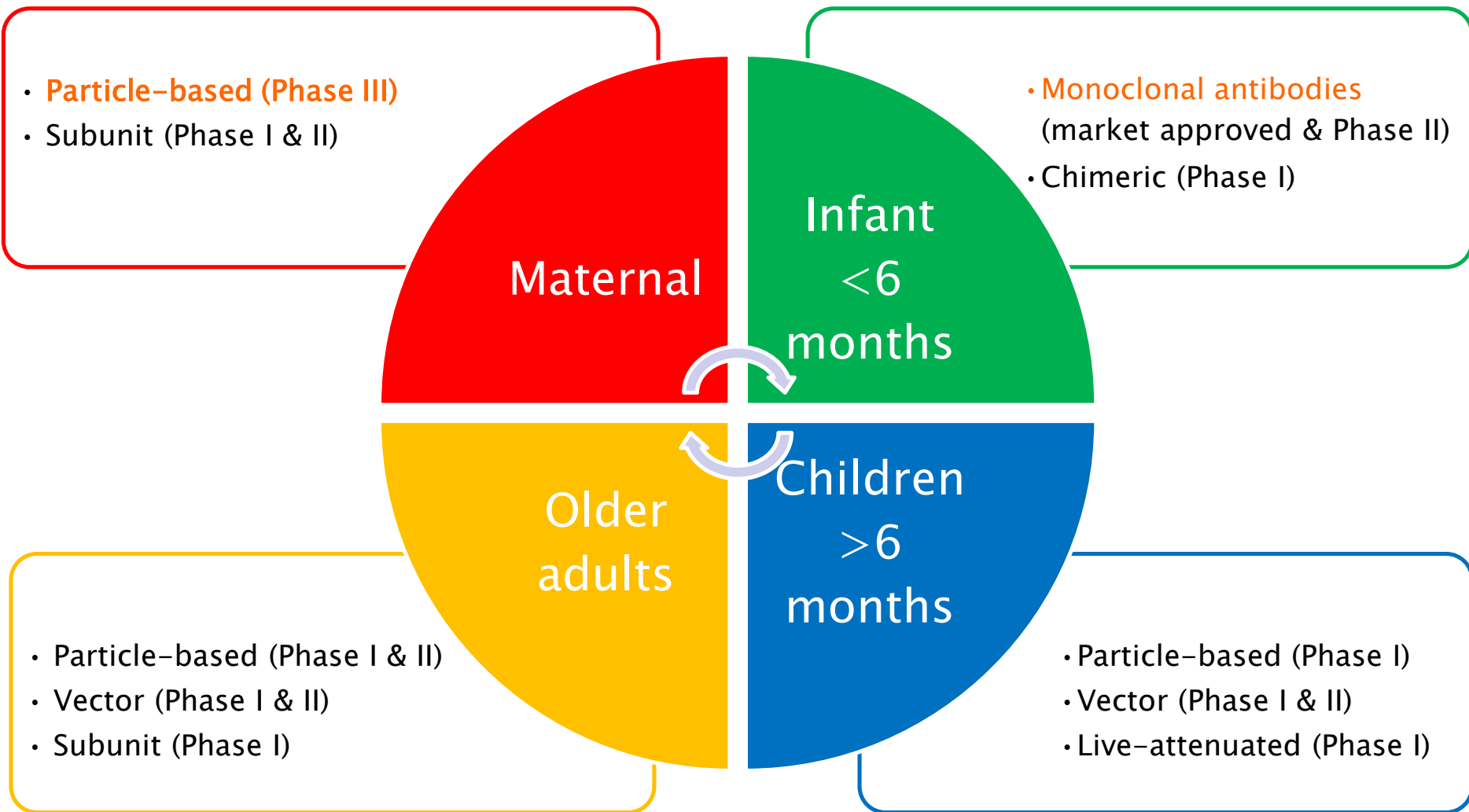**PATH**

- Increased attention, and efforts to determine RSV burden of disease

- Advances in protein F biologic structure: discovery and stabilization of prefusion conformation (new targets)
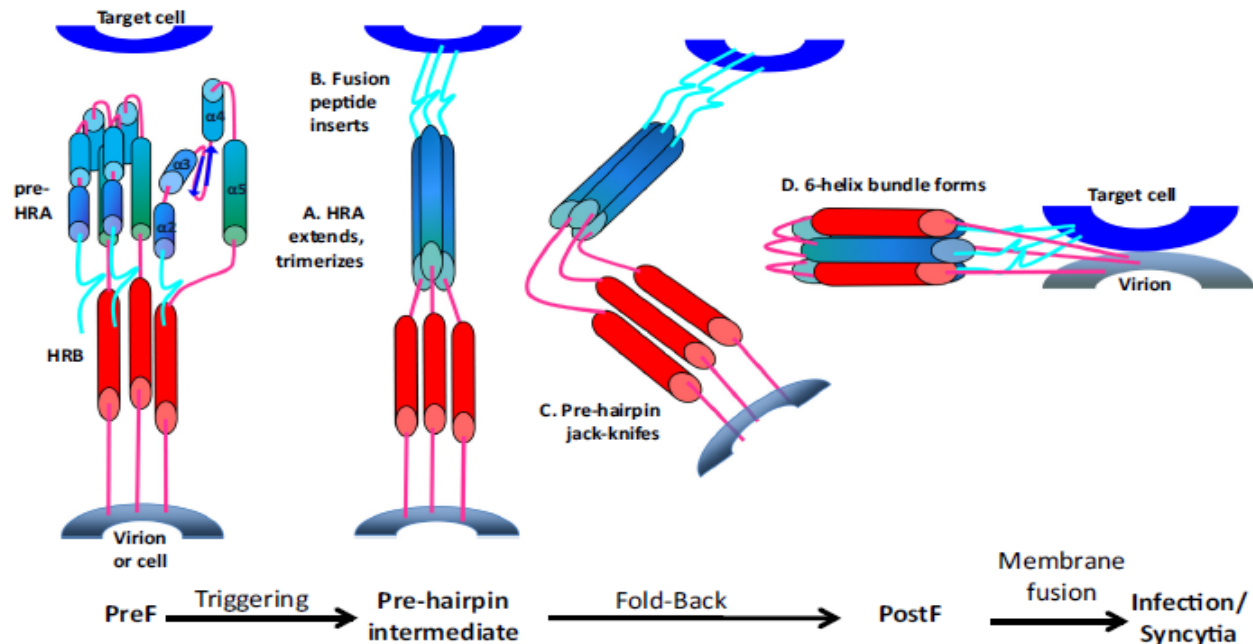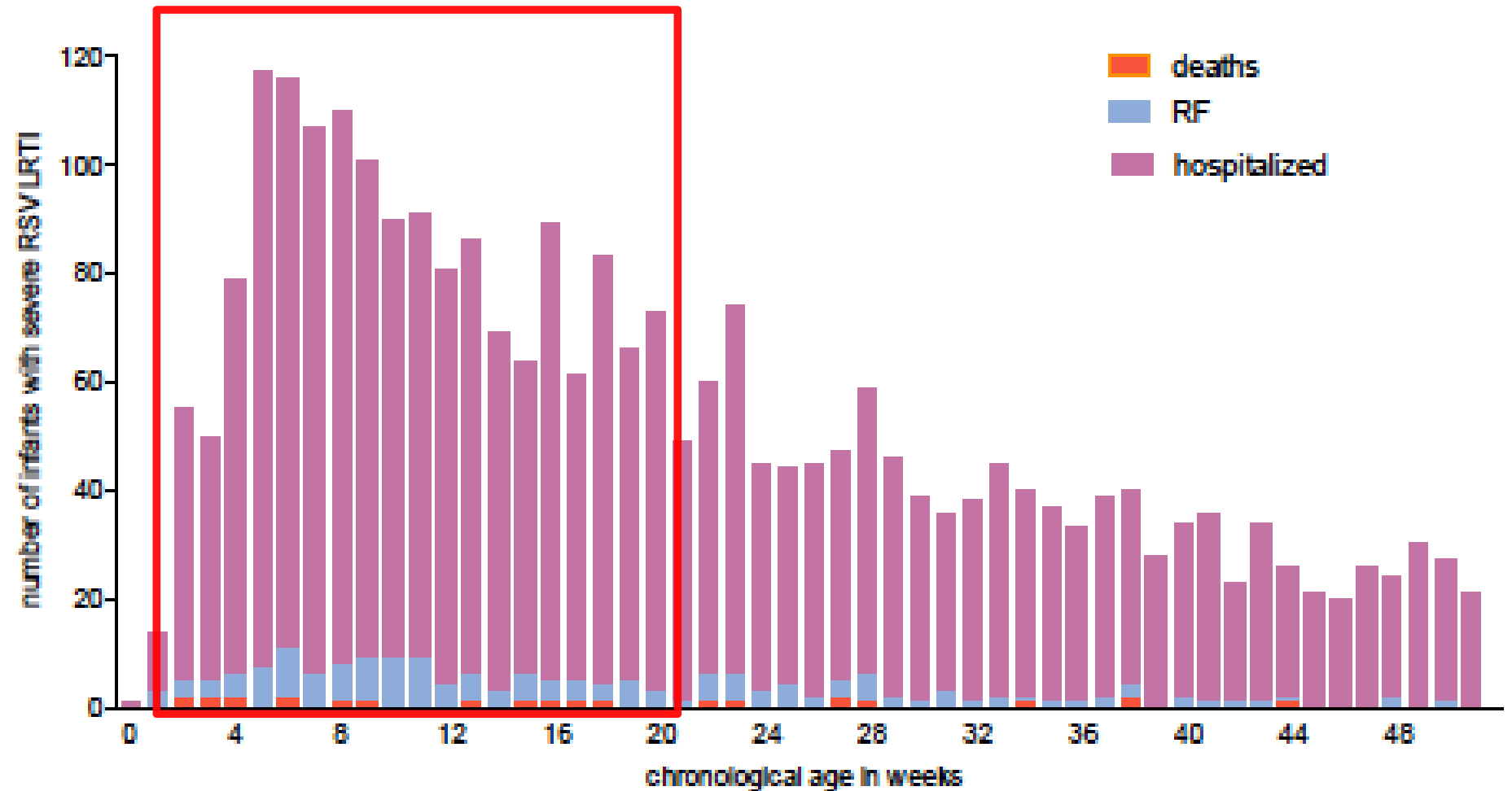
Types of vaccines in clinical phase

Maternal
- **Particle−based (Phase III)**
- Subunit (Phase I & II)

Infant <6 months
- Monoclonal antibodies (market approved & Phase II)
- Chimeric (Phase I)

Older adults
- Particle−based (Phase I & II)
- Vector (Phase I & II)
- Subunit (Phase I)

Children >6 months
- Particle−based (Phase I)
- Vector (Phase I & II)
- Live-attenuated (Phase I)

Maternal immunization to protect infants

Severe RSV LRTI in developing country hospitals

ELSEVIER

Vaccine

CrossMark

A Phase 2 randomized, observer-blind, placebo-controlled, dose-ranging trial of aluminum-adjuvanted respiratory syncytial virus F particle vaccine formulations in healthy women of childbearing age

Allison August [a], Gregory M. Glenn [a], Eloi Kpamegan [a], Somia P. Hickman [a], Dewal Jani [a], Hanxin Lu [a], D. Nigel Thomas [a], Judy Wen [a], Pedro A. Piedra [b], Louis F. Fries [a,*]

[a] Novavax, Inc., 20 Firstfield Road, Gaithersburg, MD 20878, USA
[b] Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA

- 1 or 2 vaccine doses/ 60 or 120 mcg RSV F protein
- 0.2, 0.4 o 0.8 mg alum
- 720 women of childbearing age
- Randomized in 8 groups
- Well tolerated.
- Serologic evidence of disease reduction
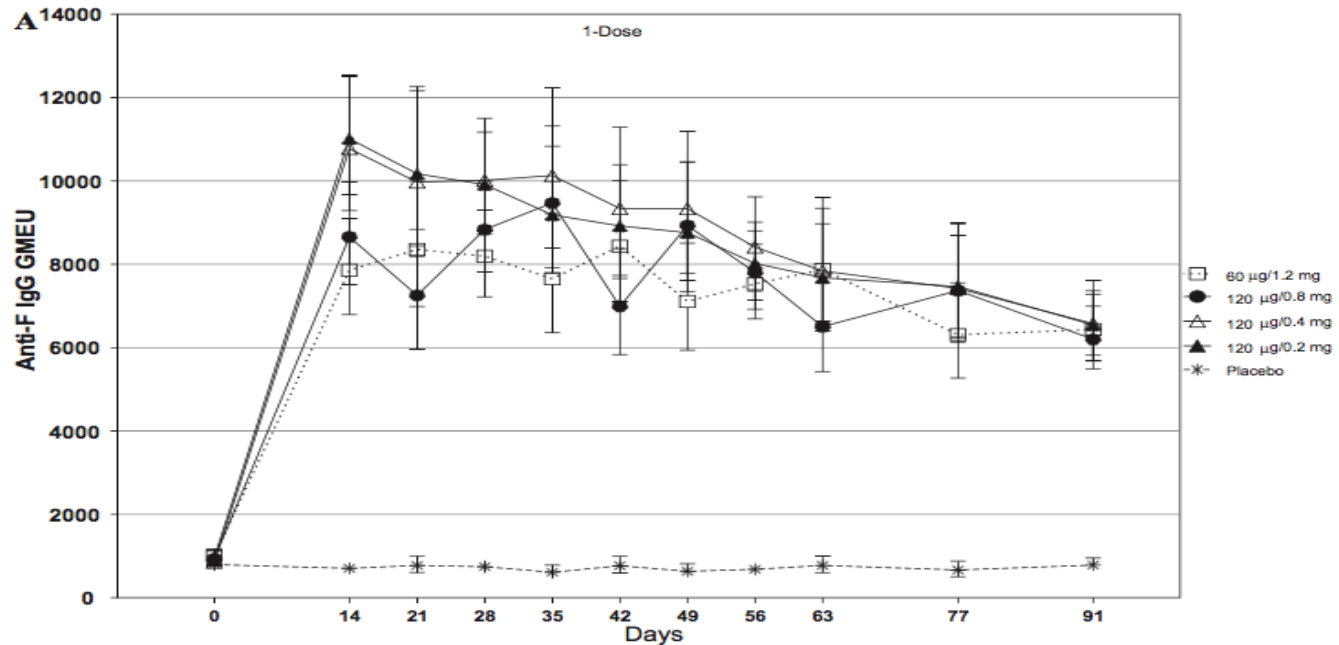
- Phase III study started in 2015
- Results will be available 1st quarter of 2019
- Informational analysis related to the prevention of medically significant RSV-positive LRTI in a subset of 1,300 infants from the Prepare trial: vaccine's potential observed efficacy in this subset group is in the range of 45% and 100%

# Monoclonal antibodies

Extended half-life antibody

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

- Fully human, high potency IgG1 mAb
- YTE half-life extension technology (triple amino acid substitutions (YTE) into the Fc domain

- Targets site on RSV **prefusion**
- Neutralizes RSV A and B clinical isolates

- Single IM dose given; expected to protect up to 6 months
- Given at birth or at onset of RSV season

Next generation mAb
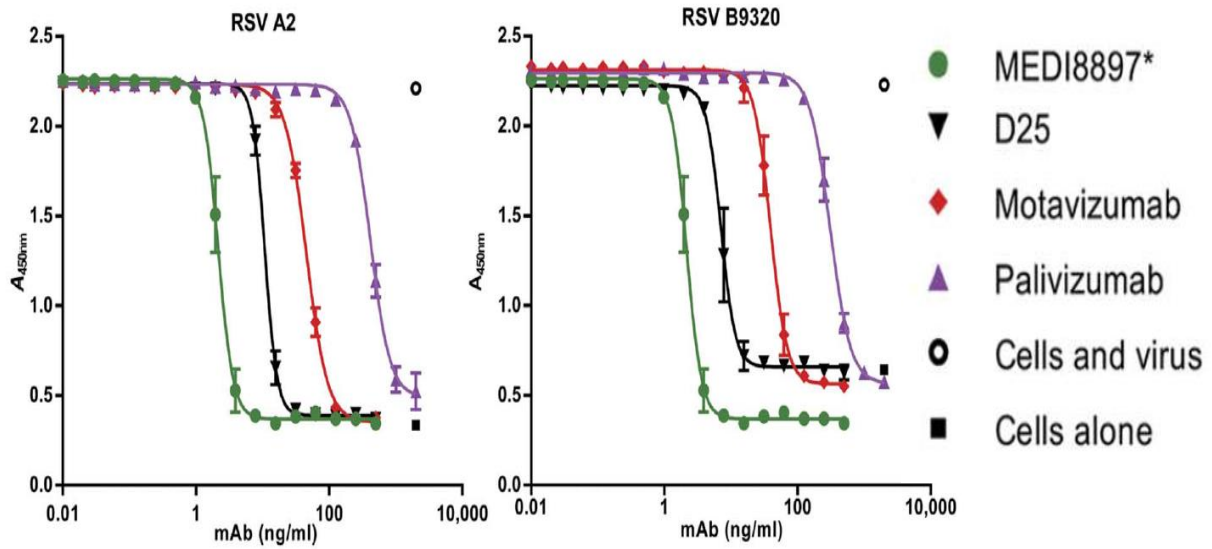
Neutralization activity curves of mAbs against RSV A and B laboratory strains
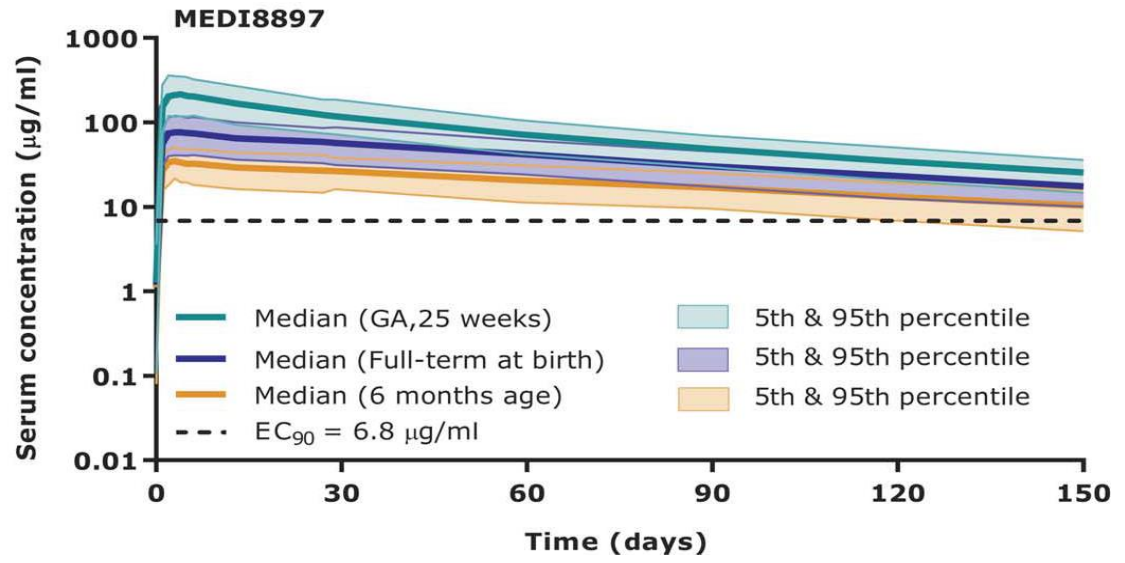
Predicted MEDI8897 serum PK profile in infants after a single fixed intramuscular dose (50 mg)

Zhu Q, et al. Sci Transl Med 2017

Infant Vaccines

RSV vaccines for infants

- **Particle-based**: RSV F nanoparticle (Novavax) and SynGEM (Mucosis)

- **Vector-based**: ChAd155-RSV (GSK), Ad26.RSV.preF (Janssen)

- **Live-attenuated**: RSV D46 cp AM2-2 (Sanofi Pasteur/LID/NIAID/NIH)

- **Chimeric**: rBCG-N-hRSV (Pontificia Universidad Catolica de Chile)

In summary

- RSV is a main cause of hospitalization and mortality worldwide, mainly in the developing world

- Identification of high risk groups guided the development of different approaches to prevent severe RSV disease

- Several vaccines and monoclonal antibodies are now being evaluated

- Many challenges still need to be addressed but we are much closer to have an intervention that can reduce RSV disease

Long term secondary endpoints

Can additional benefits emerge from vaccination?

RSV and asthma

RSV LRTI <u>causes</u> recurrent wheezing and asthma → **Prevention of RSV LRTI <u>decreases rates</u> of recurrent wheezing and asthma**

**RSV LRTI does <u>not cause</u> asthma, but asthmatic children experience severe wheezing with RSV** → **Prevention of RSV LRTI <u>identifies</u> those infants who will develop asthma (marker of susceptible children)**

Palivizumab reduces the number of wheezing **episodes** in the first year of life in preterm babies

Table 3. Infants with Wheezing.*	Palivizumab (N=214)	Placebo (N=215)	Absolute Reduction†	Relative Risk Reduction (95% CI)†
Variable				
Any wheezing — no. of infants (%)	66 (30.8)	101 (47.0)	16.2	34 (14–53)
Wheezing episodes — no.	137	266	129	48 (32–62)
Recurrent wheezing — no. of infants (%)	24 (11.2)	45 (20.9)	9.7	47 (14–80)

Palivizumab reduces the number of wheezing days in the first year of life
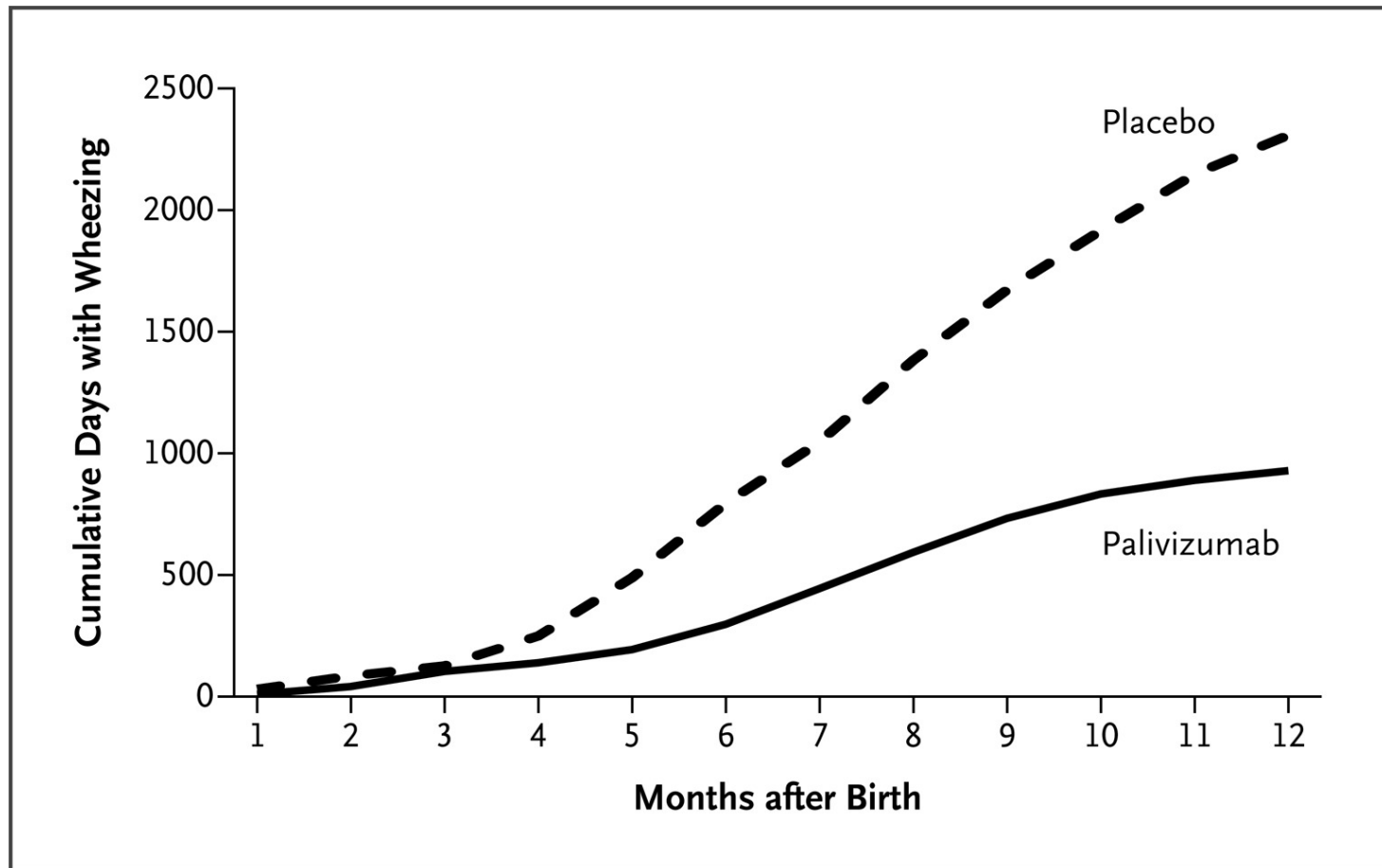
RSV associates with recurrent wheezing at age 24 months

	RSV LRTI n=144	Non–RSV LRTI n=102
Recurrent wheezing at 24 mo (any)*	84 (58%)	38 (36%)
Recurrent wheezing at 24 mo (≥3)**	42 (29%)	16 (15%)

* P value is 0.001
**P value is 0.014

Passaro C, Erviti A

Thanks !!