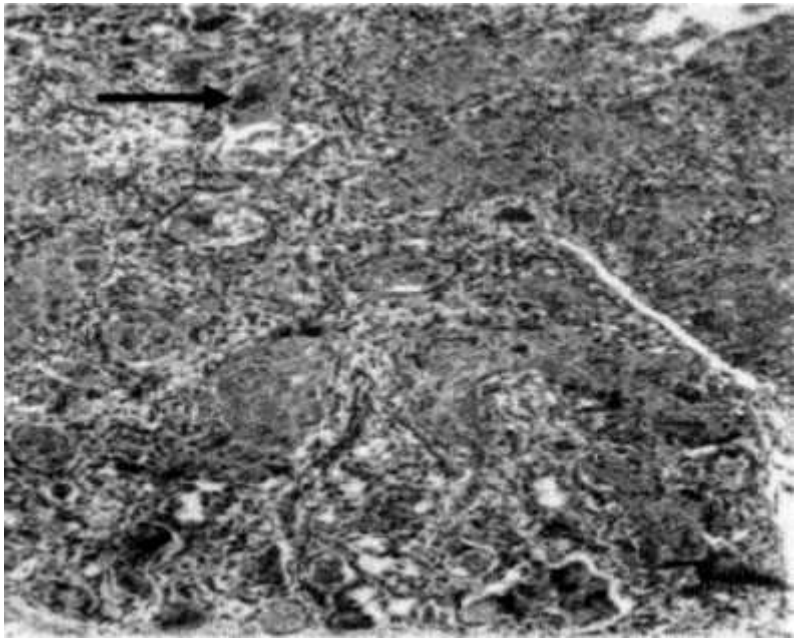


RSV

Respiratory Syncytial Virus

It has been a long journey

Populations at risk of severe RSV disease

very young infants

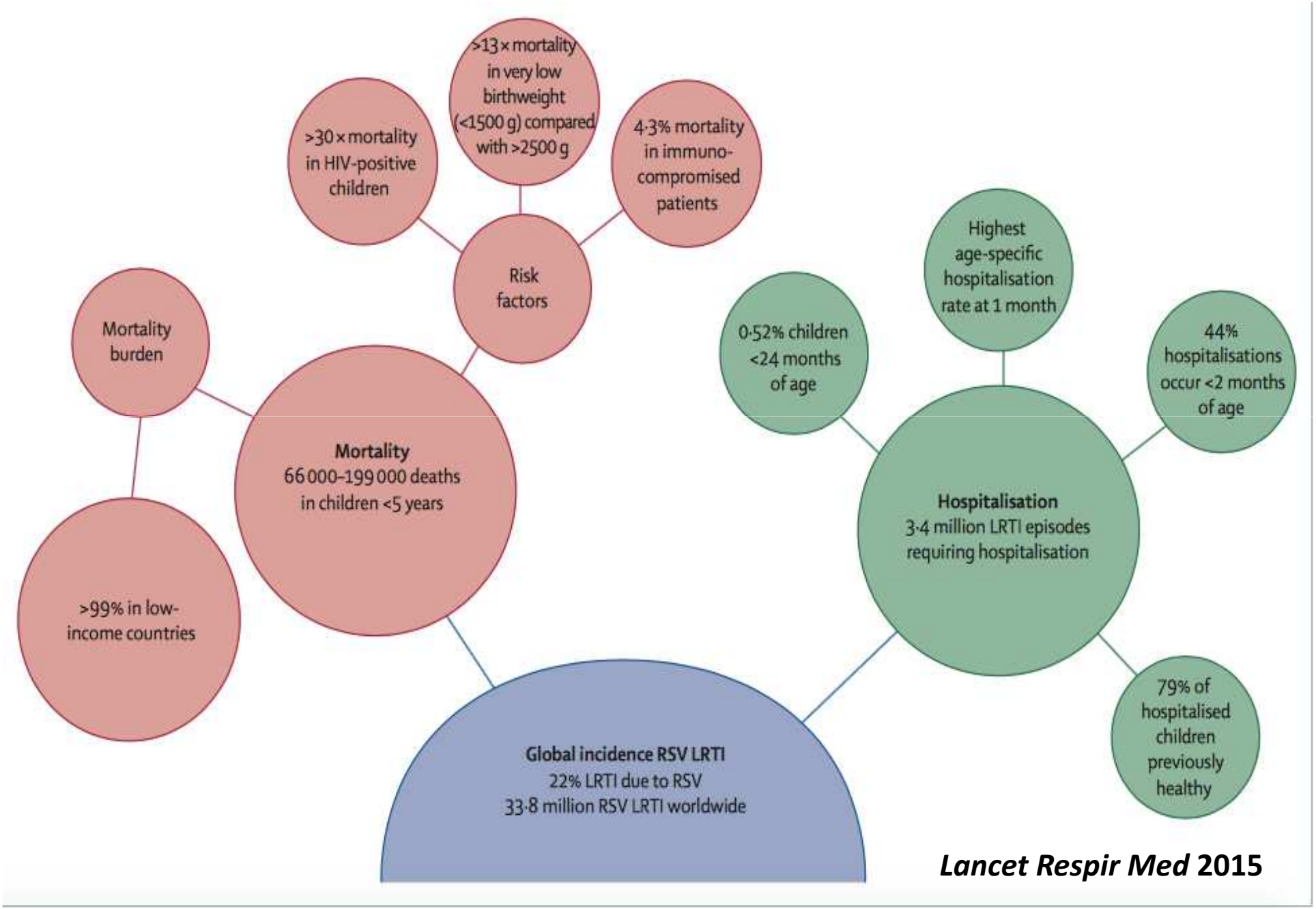
older infants and toddlers

elderly

RSV

The Disease

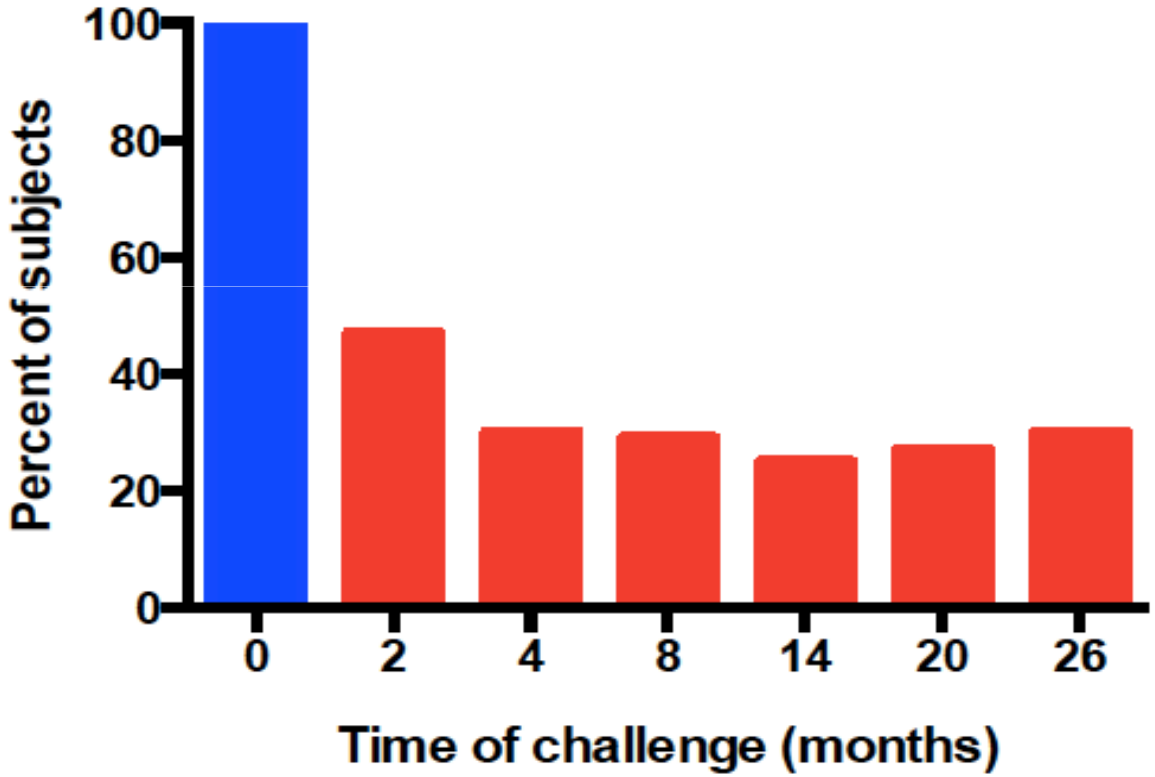
RSV Overview



***Lancet Respir Med* 2015**

Problem:

Repeated RSV infections do not induce sterilizing immunity



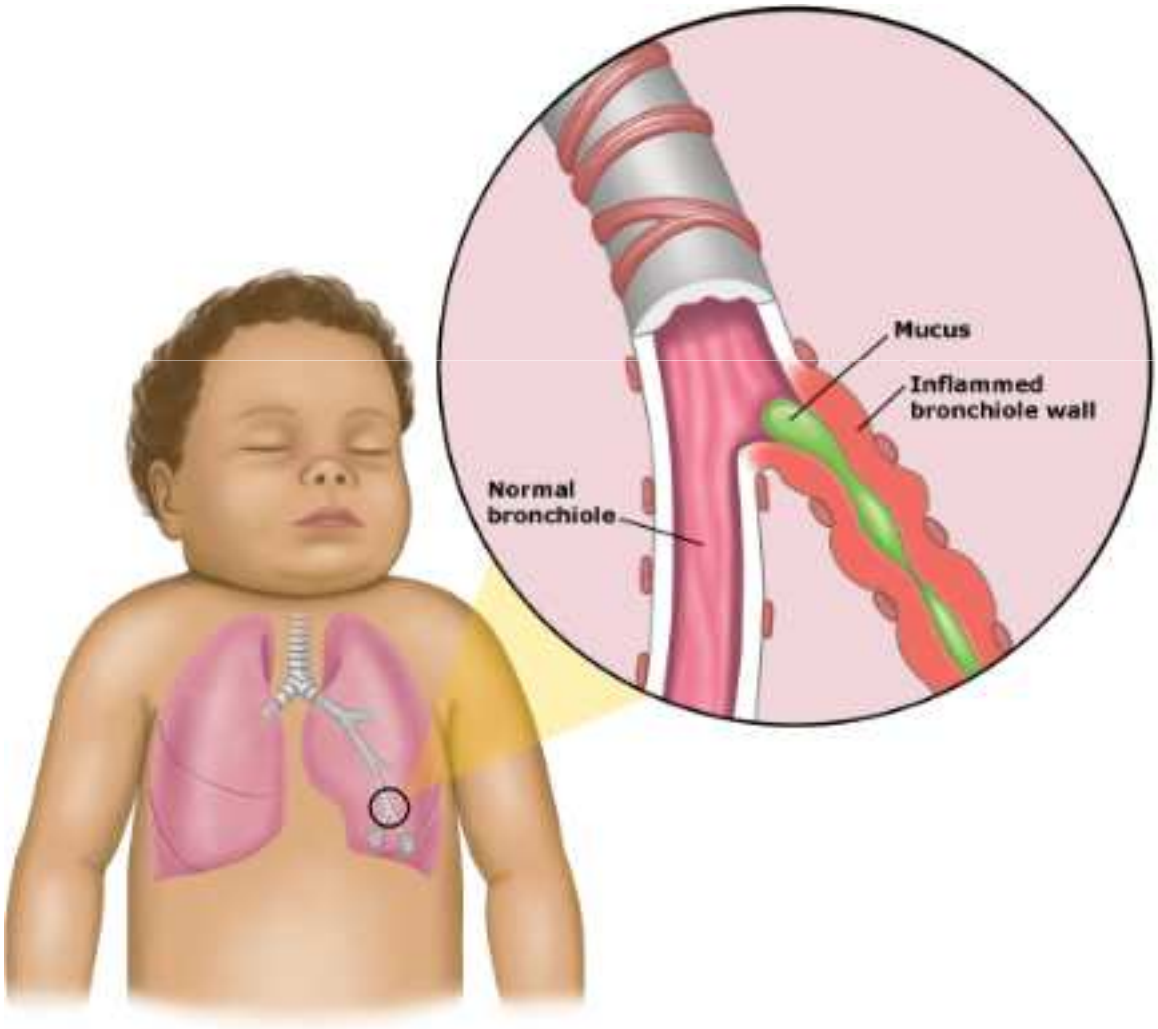
RSV Disease

- Respiratory syncytial virus (RSV) is the leading viral cause of severe lower respiratory tract disease in infants and young children worldwide.
- WHO has estimated that the global annual burden of infections and mortality due to human RSV are 64 million and 160,000, respectively [WHO 2009].
- Almost all children will have had an RSV infection by their second birthday.

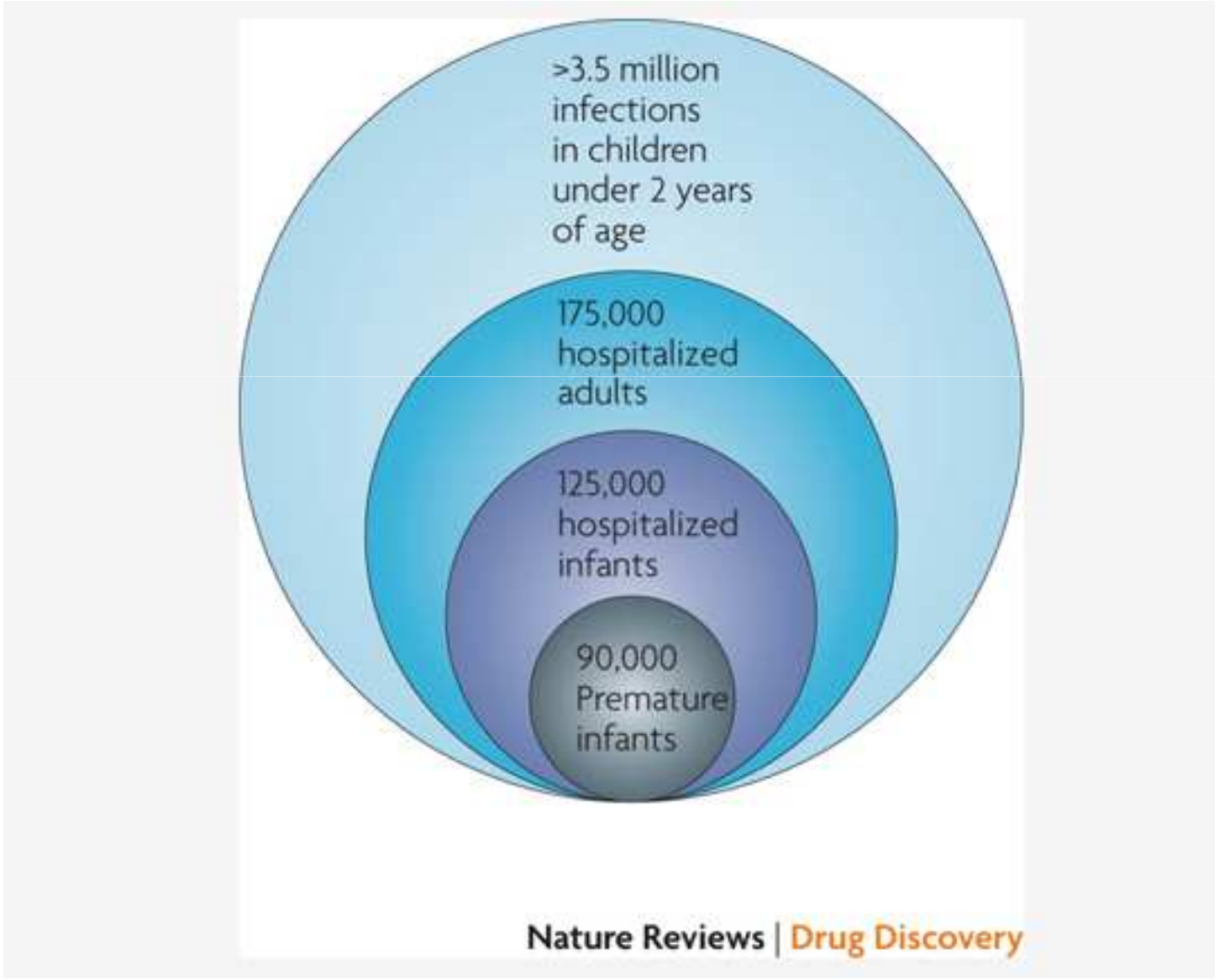
RSV Disease(2)

- When infants and children are exposed to RSV for the first time,
  - 25 to 40 out of 100 of them have signs or symptoms of bronchiolitis or pneumonia.
  - Children hospitalized for RSV infection are usually younger than 6 months of age. The most severe disease occurs within the first 2 to 6 months of life, particularly in infants born prematurely and infants with underlying chronic lung and congenital heart diseases.
  - **Highest morbidity and mortality in the first two months of life**
- RSV bronchiolitis in early life is associated with an increased risk of reactive airway disease later.

RSV Impact on the Lung



RSV Disease Burden in the US



Risk of Hospitalization and Gestational Age

TABLE 1

Average RSV Hospitalization Rates Among Children Younger Than 24 Months (2000–2005)[34]

Children <24 mo	N[a]	RSV Hospitalization Rate/1000	95% CI
All infants regardless of gestational age	559[b]	5.2	4.8–5.7
All term infants (≥37 wk gestation)	479	5.3	4.9–5.8
All preterm infants (<37 wk gestation)	56	4.6	3.4–5.8
≥35 wk gestation	494	5.1	4.7–5.5
32–34 wk gestation	23	6.9	4.3–10.1
29–31 wk gestation	6	6.3	2.0–12.4
<29 wk gestation	12	19.3	8.4–34.0
All very preterm (<30 wk gestation)	15[c]	18.7	10.0–30.0

[a] Among 2149 enrolled hospitalized children from a birth cohort of 132 085 children.

The burden of respiratory syncytial virus (RSV) and the value of prevention. Welliver in Journal of Pediatrics

Volume 143, Issue 5, Supplement, November 2003, Pages 112–117

RSV Hospitalization and Underlying Risk Favors

TABLE 2

RSV Hospitalizations per 1000 Children From >248 000 Child-Years of Follow-up[38]

Age Stratum/Risk Group	0 to <6 mo	6 to <12 mo	12 to <24 mo	IRR (95% CI) for 0 to <6 mo	Adjusted IRR (95% CI) for first 12 mo
Low-risk infants	44.1	15.0	3.7	Comparator	Comparator
Infants with CHD	120.8	63.5	18.2	2.7 (2.2–3.4)	2.8 (2.3–3.3)
Infants with CLD	562.5	214.3	73.4	12.8 (9.3–17.2)	10.7 (8.4–13.6)
≤28 wk gestation	93.8	46.1	30.0	2.1 (1.4–3.1)	2.4 (1.8–3.3)
29 to <33 wk gestation	81.8	50.0	8.4	1.9 (1.4–2.4)	2.2 (1.8–2.7)
33 to <36 wk gestation	79.8	34.5	10.8	1.8 (1.5–2.1)	1.8 (1.6–2.1)
Other condition[a]	122.3	55.2	24.1	2.8 (2.5–3.1)	2.3 (2.1–2.6)

IRR, incidence rate ratio.

[a] Asthma, cystic fibrosis, cancer, HIV infection, immunodeficiency, steroid therapy, chronic renal disease, diabetes mellitus, congenital anomalies of the respiratory tract, or respiratory distress syndrome.

Source AAP RSV Report 2014

RSV in Adults

TABLE 3

RSV pneumonia in adults

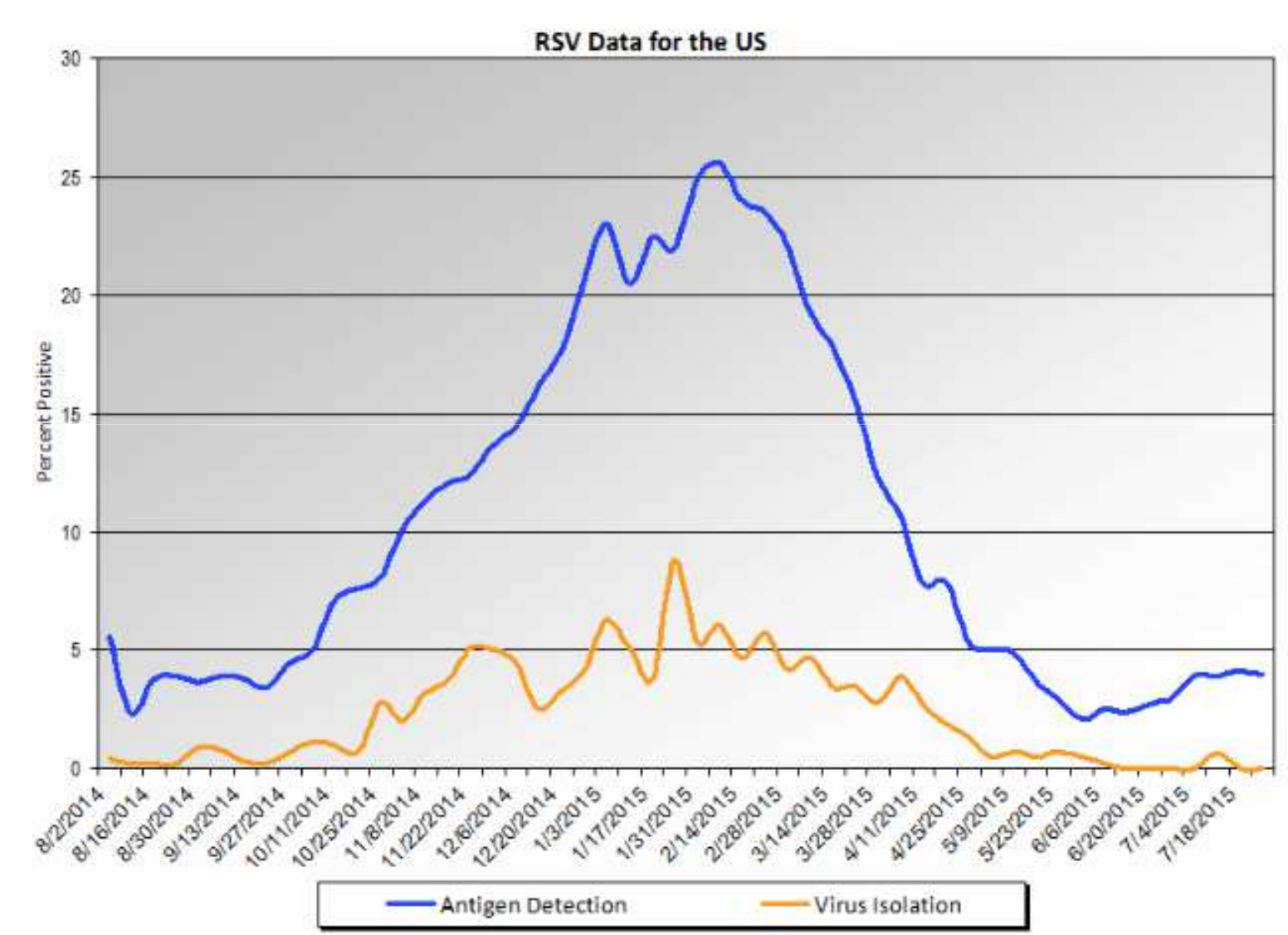
Study (reference)	Location, dates	Diagnostic test(s)[a]	No. positive/no. tested (% positi
Fransen et al. (54)	Sweden, 1963–66	CF	31/598 (5.2)
Hers et al. (96)	Netherlands, 1967–68	CF	10/207 (4.3)
Vikerfors et al. (178)	Sweden, 1971–80	CF, Ag, IgM	57/2,400 (2.0)
Kimball et al. (109)	USA, 1980–81[b]	Culture, CF	2/100 (2.0)
Stanek and Heinz (169)	Czechoslovakia, 1983–85	Culture, CF	2/74 (2.7)
Zaroukian and Leader (194)	USA, 1987–88[b]	IAH, Ag, culture	3/55 (5.4)
Melbye et al. (128)	Norway, 1988–89[b]	CF	5/36 (13.9)
Falsey et al. (42)	USA, 1989–92[b]	Culture, Ag, EIA	69/483 (14.3)
Marrie (121)	Canada, 1991–94	CF	0/149 (0)
Dowell (27)	USA, 1990–92	EIA	53/1,195 (4.4)
Ruiz et al. (159)	Spain, 1996–97	Serology not specified	5/204 (2.4)

[a]CF, complement fixation; Ag, antigen; IAH, immune adherence hemagglutination.
[b]Winter seasons only evaluated.

Clin Microbiol Rev. 2000 Jul; 13(3): 371–384.

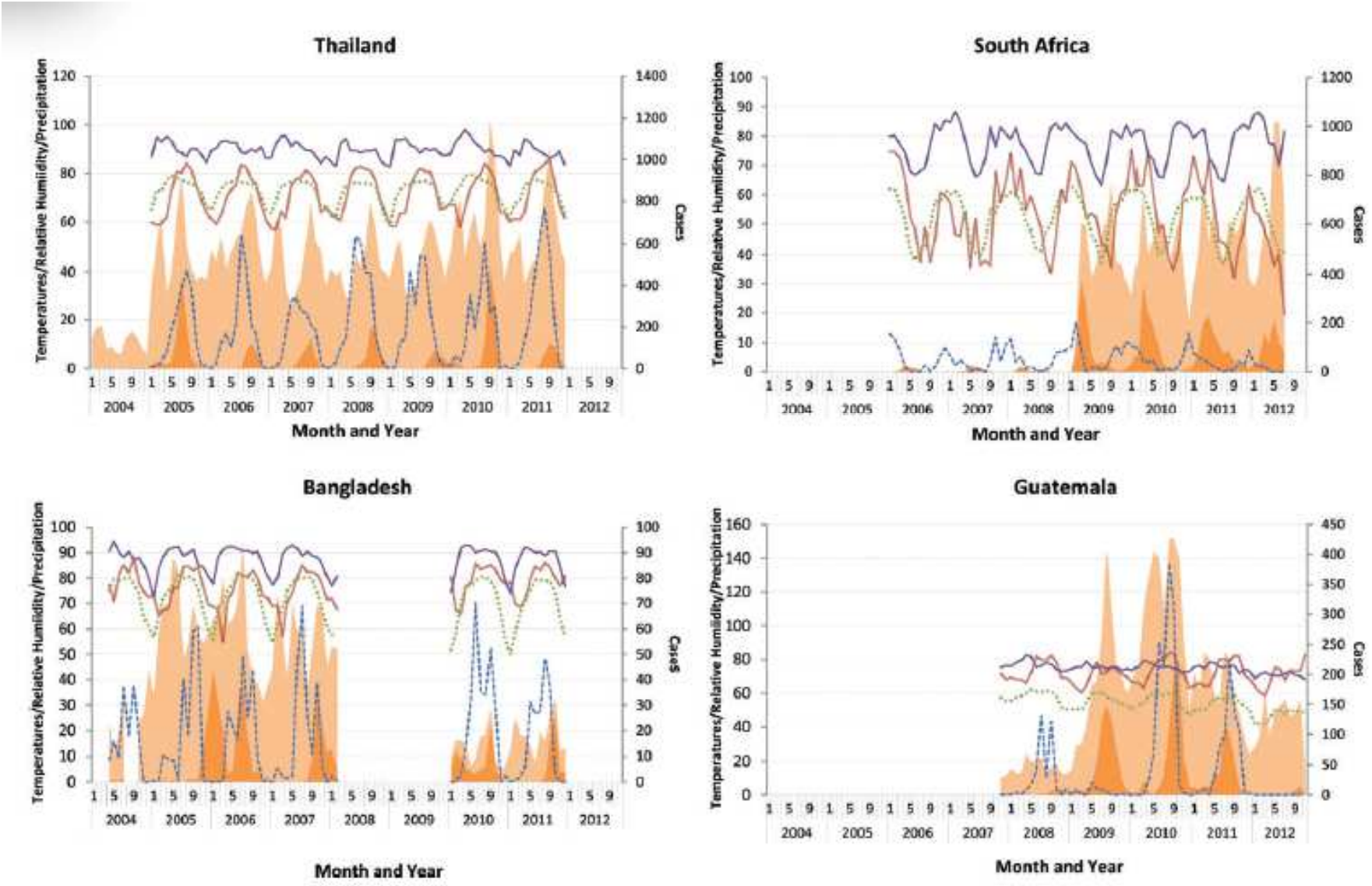
RSV Seasonality

Respiratory Syncytial Virus (RSV)



CDC Viral Disease Surveillance Network

RSV is a Global Problem



JID 2013:208 (Suppl 3) • Haynes et al

RSV in Argentina

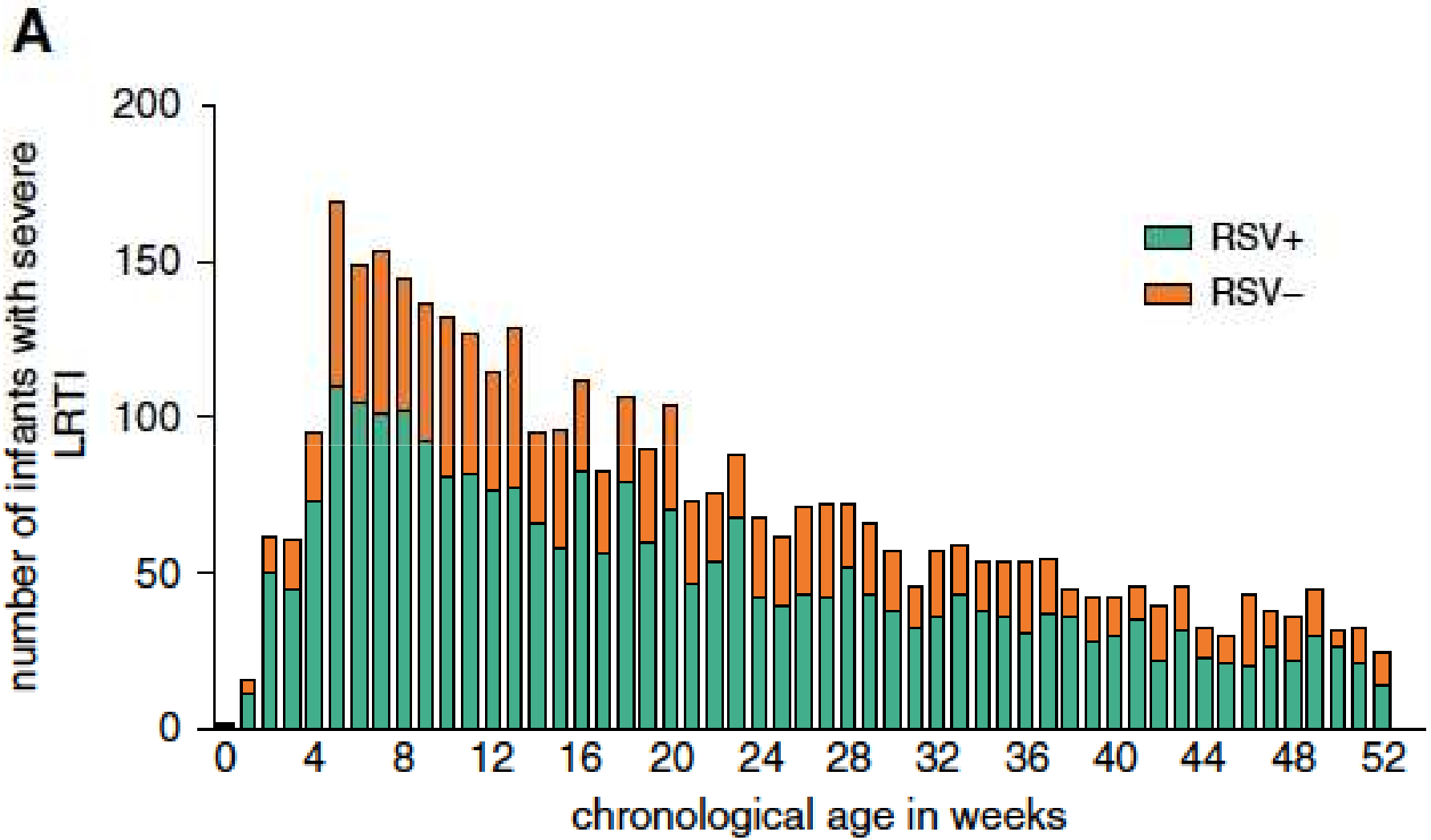
- Lower respiratory tract infections, in which RSV is a frequent pathogen in children under 2 years of age [Marguet 2009], are the second leading cause of death in children under 5 years of age in Argentina [Marconi 2010].
- Ferolla and coworkers confirmed the incidence of severe RSV infections as a major burden of respiratory illness among young children in Argentina [Ferolla 2013], in agreement with similar studies [Moisi 2011, Nair 2010], and stressed the central role of RSV in hospital admissions among children younger than 2 years.

RSV in Argentina (2)

- Specifically, this study revealed that over 60% of the respiratory infections in 1,293 hospitalized children in Buenos Aires within a catchment population of over 360,000 children, were due to RSV.
- Almost 20% of these children had life-threatening disease (as assessed by oxygen saturations below 87%), a finding that helps explain the high mortality rates associated with RSV.
- The attributable mortality rate for RSV was estimated to be 7% in this study sample.
- In the Buenos Aires metropolitan area, the burden of illness due to RSV in 2011 outweighed that of 2009 H1N1 influenza A virus during the pandemic year: 14-fold in hospitalizations and 4-fold in virus-confirmed deaths

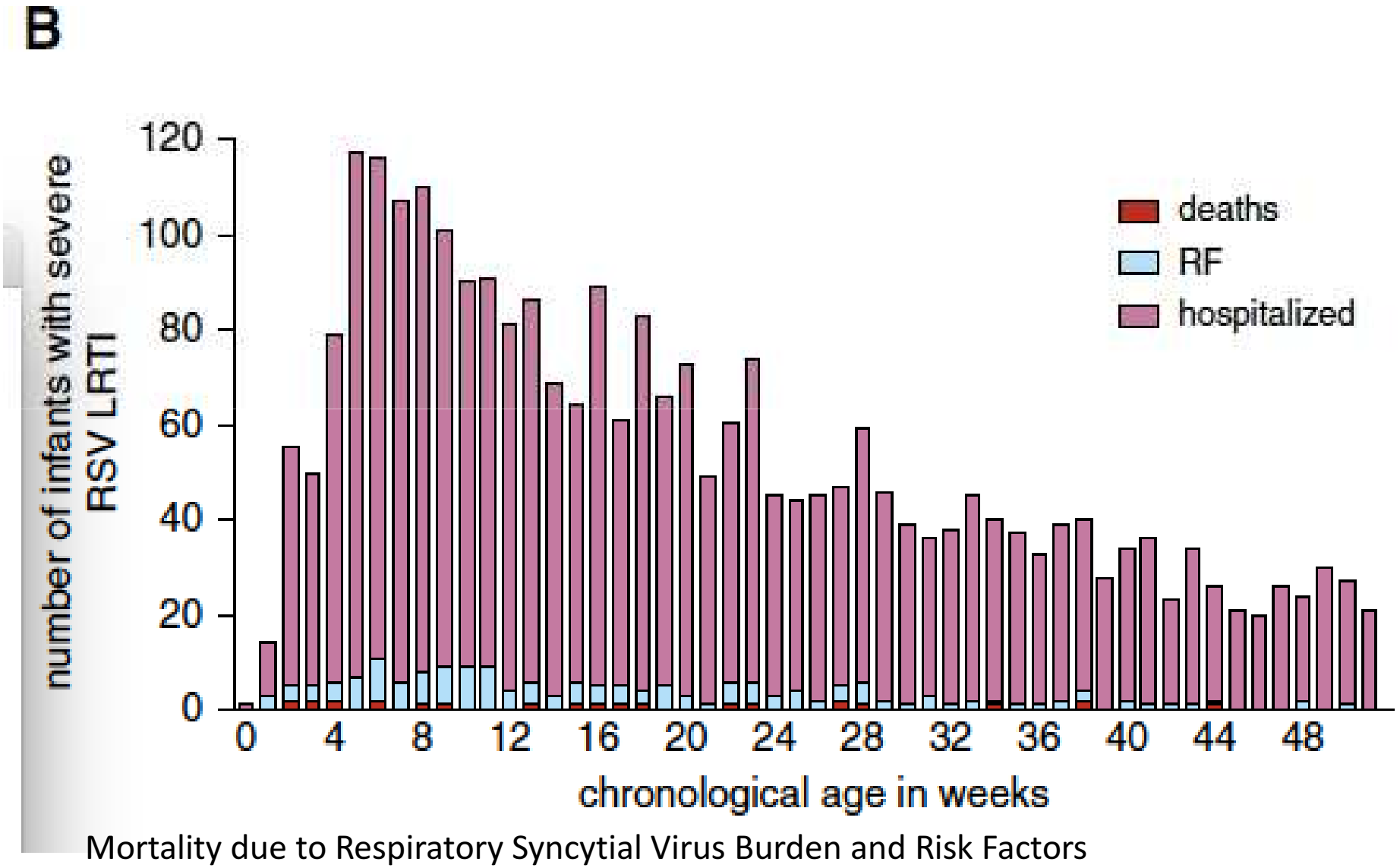
[Libster 2010].

RSV & Severe LRTI in Argentina



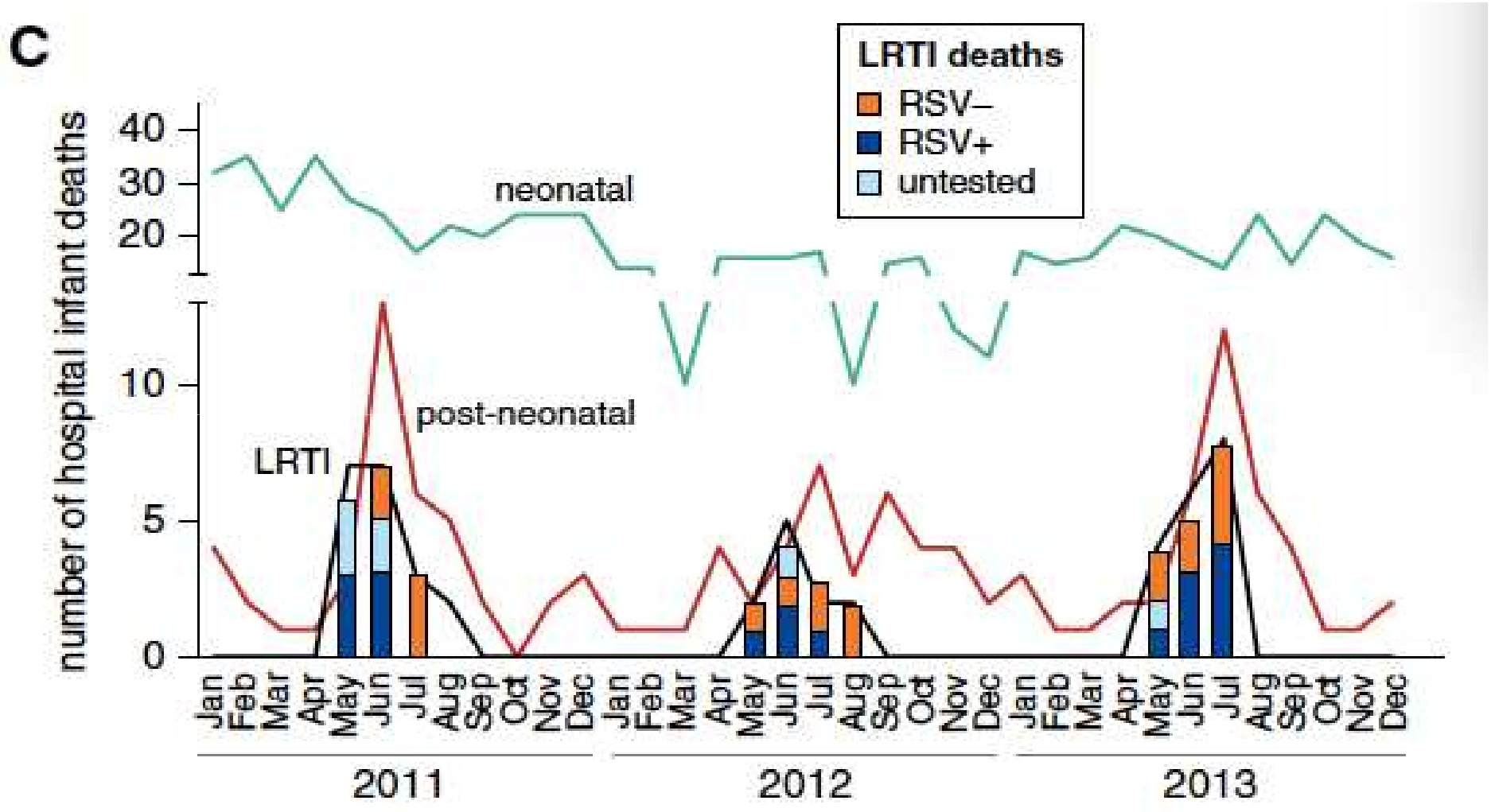
Mortality due to Respiratory Syncytial Virus Burden and Risk Factors
Sarah Geoghegan et al American Journal of Respiratory and Critical Care Medicine
January 1 2017

RSV in Argentina



Mortality due to Respiratory Syncytial Virus Burden and Risk Factors
Sarah Geoghegan et al American Journal of Respiratory and Critical Care Medicine
January 1 2017

RSV Mortality in Argentina



Mortality due to Respiratory Syncytial Virus Burden and Risk Factors
Sarah Geoghegan et al American Journal of Respiratory and Critical Care Medicine
January 1 2017

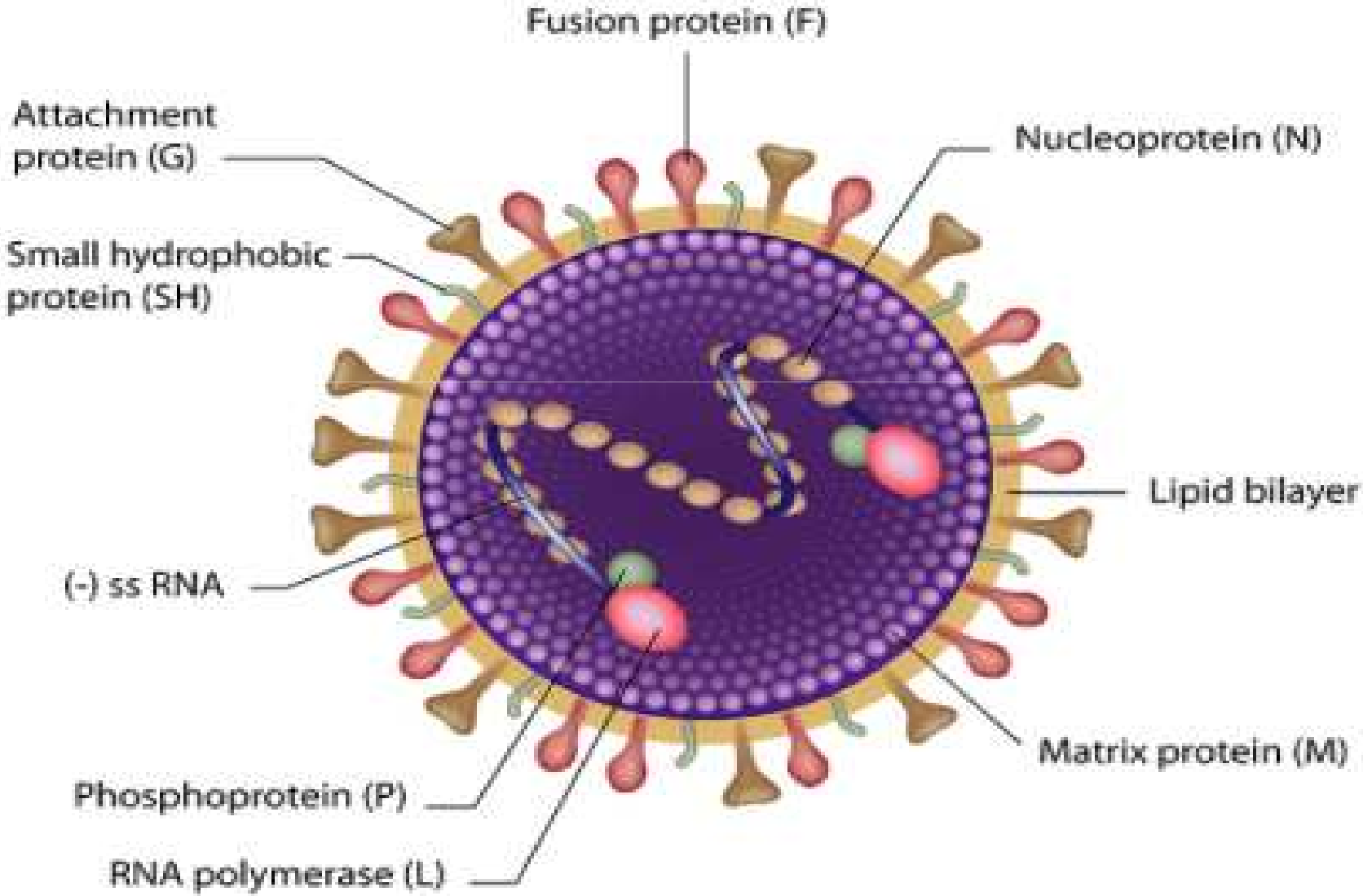
The RSV Virus

RSV: The Virus

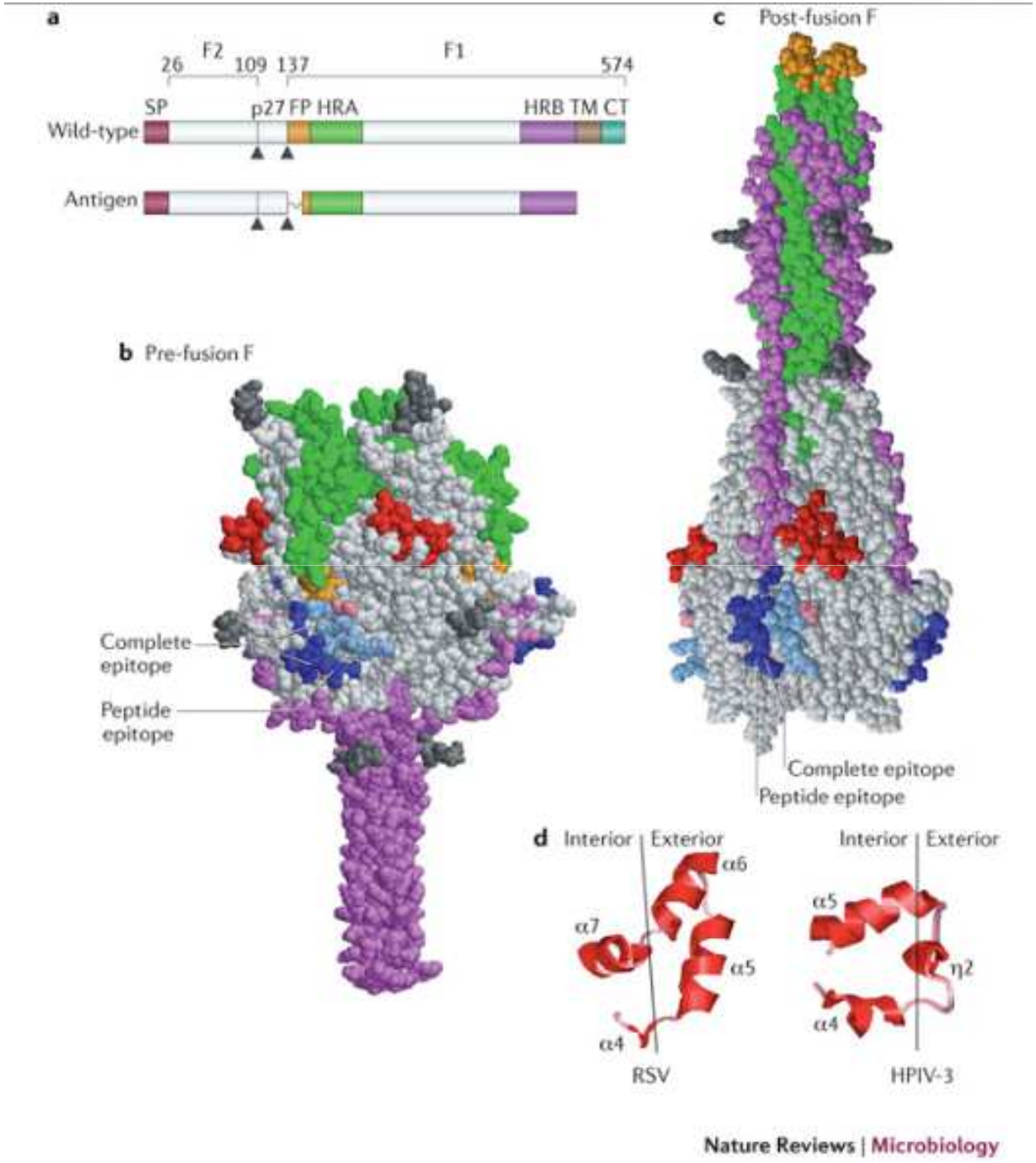
- RSV is a pleomorphic virus belonging to the *Paramyxoviridae* family.
- Two major subtypes, A and B, that co-circulate.
  - The two major surface glycoproteins of RSV, F and G, are the primary targets of neutralizing antibodies, which are associated with protection [Graham 2011]
  - The F protein mediates fusion of the viral envelope with the plasma membrane and syncytium formation.
    - There is a high degree of genetic and antigenic homology in the F proteins across RSV/A and B
  - G protein is essential for viral attachment and is much more variable.

[Johnson 1987].

Respiratory Syncytial Virus



RSV Pre and Post Fusion Structure



Prevention and Treatment of RSV

The Past, the Present and the Future

RSV Therapy

- Supportive care
- Antibodies as therapeutic agents
- Antivirals

Therapy: Less is More for Most Children

	Recommended	Not recommended
American Academy of Pediatrics, 2014[4]	Supplemental oxygen optional if SpO_2 is greater than 90%, nebulised hypertonic saline optional for hospitalised children with expected length of stay longer than 72 h, nasogastric or intravenous fluids if oral hydration cannot be maintained	Albuterol, epinephrine, nebulised hypertonic saline in emergency department, systemic corticosteroids, antibacterial medicine (unless concomitant bacterial infection), chest physiotherapy, continuous pulse oximetry
Royal Australian College of General Practitioners, 2008[28]	Supplemental oxygen, saline nasal drops, nasal suctioning, comfortable positioning (prone or supine if unable to position self), continuous pulse oximetry monitoring if in prone position, oral feeding can continue unless respiratory distress increases, trial of β_2 agonist bronchodilators for children older than 9 months (discontinue if no response), antibiotics if clinical signs or symptoms of bacterial infection, paracetamol or ibuprofen can be used if pyrexia is present	Chest physiotherapy, routine mist, routine steam, routine nebulised saline, routine nebulised adrenaline, routine β_2 agonist bronchodilators, routine ipratropium bromide, routine antibiotics, routine corticosteroids, routine ribavirin, routine immunoglobulin, routine oral antitussives, oral expectorants or oral decongestants
Scottish Intercollegiate Guidelines Network, 2006[29]	Supplemental oxygen if SpO_2 is less than 92% or if severe respiratory distress or cyanosis, nasogastric feeding if child cannot maintain hydration or oral intake, nasal suction for hospitalised infants showing respiratory distress, pulse oximetry 8 to 12 h after supplementary oxygen is discontinued	Nebulised ribavirin, antibiotic therapy, inhaled β_2 agonist bronchodilators, nebulised ipratropium or epinephrine, inhaled or oral corticosteroids, chest physiotherapy

Therapy: Antibodies

***Lancet Respir Med* 2015**

Antivirals: antibodies								
RI-001	ADMA Biologics	NCT00632463, NCT01814800	Various viral epitopes	Polyclonal RSV neutralising antibody	Intravenously	Phase 2c	Significant improvement in RSV titre from baseline to D18; 9·24x in high dose group (n=21)[57] compassionate use (n=13): 4-fold rise in antibody titres RI-002 Ph3c for indication PIDD	..
Motavizumab (MEDI-524)	MedImmune	NCT00421304, NCT00435227	F	RSV neutralising monoclonal antibody	Intravenously	Interrupted	No effect on viral load, difference in hospital stay duration or severity score, more intensive care admissions in motavizumab arm[75]	..
MEDI-8897 (derived from AIMM D25)	MedImmune	NCT02114268, NCT02290340	Prefusion F	RSV neutralising monoclonal antibody with extended half-life	Intramuscular or intravenously	Phase 2	Target population healthy infants. Ongoing RCT in healthy preterm infants	..
ALX-0171	Ablynx	NCT02309320	F	Antibody nanobody	Inhalation	Phase 2	In healthy male volunteers: no dose-limiting toxicity, no significant change lung function, opportunity for once daily dose[61,63] Phase 1 and phase 2a ongoing in toddlers and infants with RSV LRTI	..
REGN-2222	Regeneron	NCT02325791	F	Monoclonal antibody anti-RSV F	Intramuscular	Phase 1	Recruitment to start June, 2015	..

Therapy: Antivirals

- Antisense
  - Small interfacing RNAs
  - In phase 2 with moderate effect
- Fusion inhibitors
  - Prohibits cell entry by virus
  - Lower viral load in phase 1-2 trials
- RSV RNA polymerase inhibitors
  - In phase 1 and 2
  - Rapid decline in viral load and symptoms in adults
  - Studies in children ongoing

***Lancet Respir Med* 2015**

Approaches to Prevention

- Passive antibody
- Immunization of young infants
- Maternal immunization

Approaches to Prevention

- Passive immunization with monoclonal antibody to F protein
  - Highly effective
  - Very expensive
  - Currently limited to high risk infants
  - **Demonstrated that anti-F protein antibodies are protective**
- Immunization of young infants
  - Fusion protein vaccines have required multiple doses for immunogenicity – misses the high risk period
- Maternal immunization
  - Offers the most promise for protection early in life.

Passive Antibody for Prevention and Treatment

- Palivizumab (Synagis) has been shown to be effective to prevent disease
  - Prevents hospitalization by ~ 45% in high risk infants
  - Due to its cost, use is limited to high risk infants
  - Requires monthly dosing during RSV season.
  - High risk includes:
    - Infants younger than one year of age with hemodynamically significant congenital heart disease
    - Children younger than one year of age with neuromuscular disorders
    - Children younger than two years of age who are immunocompromised (e.g. those with severe combined immunodeficiency; those younger than two years of age who have undergone lung transplantation or hematopoietic stem cell transplantation) during the RSV season.
    - Children with Down syndrome

- Motavizumab not approved for licensure due to concerns related to hypersensitivity. It required lower dose and potentially lower cost.
- Although Motavizumab is not being further developed for prophylaxis of severe RSV disease, its therapeutic potential in young children is under evaluation.[1]
- MEDI-557, a high-affinity anti-F monoclonal antibody with an extended half-life, recently completed phase 1 clinical therapeutic evaluation[2].

1. (ClinicalTrials.gov; identifier# NCT00435227)
2. ClinicalTrials.gov; identifier# NCT01562938

Another Possible Approach

Biosimilar palivizumab – WHO and University of Utrecht

- Palivizumab off patent in 2015
- Plan to develop a 'biosimilar' of palivizumab and reduce costs through:
  - Using latest technologies (i.e. high expression cell line)
  - A novel development and financing plan[1]
    - Coordinated by the Utrecht Center of Excellence for Affordable Biotherapeutics for Public Health
    - Funded through a consortium of manufacturers
      - Agreement signed on 9 March 2016
  - Estimated price $US 250 per child for full 5 courses
  - First market authorization expected end 2017
  - Roll out the product in LMICs

World Health Organization

[1] http://www.uu.nl/en/news/first-consortium-of-local-manufacturers-to-make-affordable-biosimilars-available-for-low-income

MEDI8897 Clinical development overview

Phase 1a FTIH (healthy adults)

- Double-blind placebo controlled study (3:1) **(N = 136)**
- Evaluated multiple IV and IM dose levels
- Subjects followed for 1 year

Safety

- AEs: MEDI8897 62% vs placebo 63%
- 2 SAEs: Gun shot & appendicitis

Pharmacokinetics

- Bioavailability 87%
- Half-life extended to 85-117 days

Anti-drug antibody

- Incidence of ADA similar (MEDI8897 14% vs placebo 15%) , titers were low, no observed impact on safety or PK

Phase 1b/2a in 32-35 week GA infants

- Double-blind placebo controlled study (4:1) in USA, SA, Chile **(N=89)**
- Three IM dose levels evaluated
- Subjects followed for 1 year

Safety

- Day 30 safety and tolerability profile reassuring

Pharmacokinetics

- Day 30 interim PK models support single 50mg intramuscular dose administration

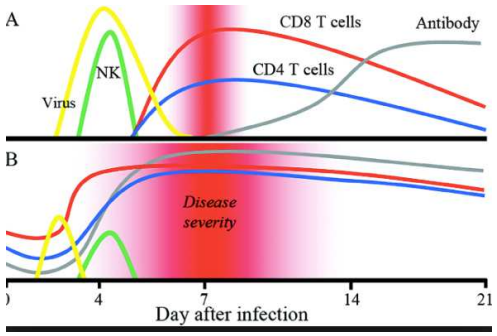
Anti-drug antibody

- Day 30 incidence of ADA was low and balanced between groups, no observed impact on safety or PK

Vaccines

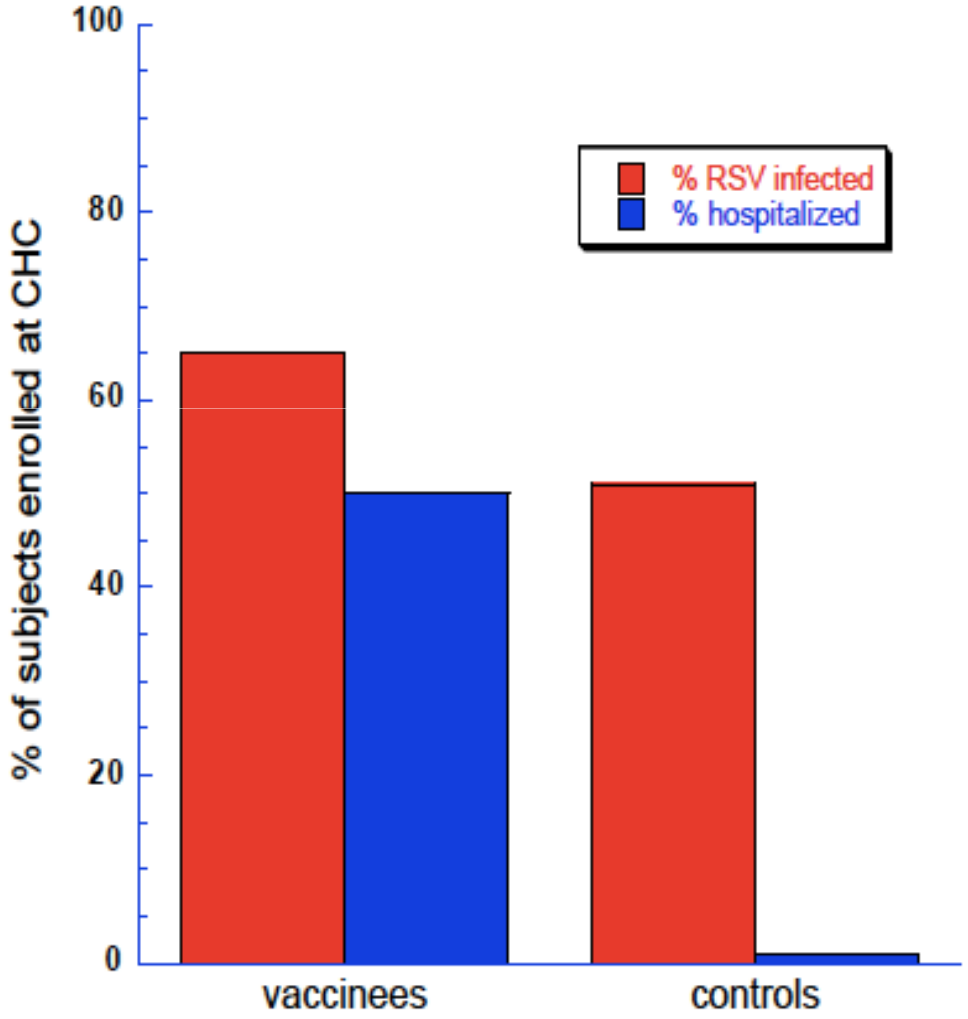
It has been a long road

Prior Vaccine Development History

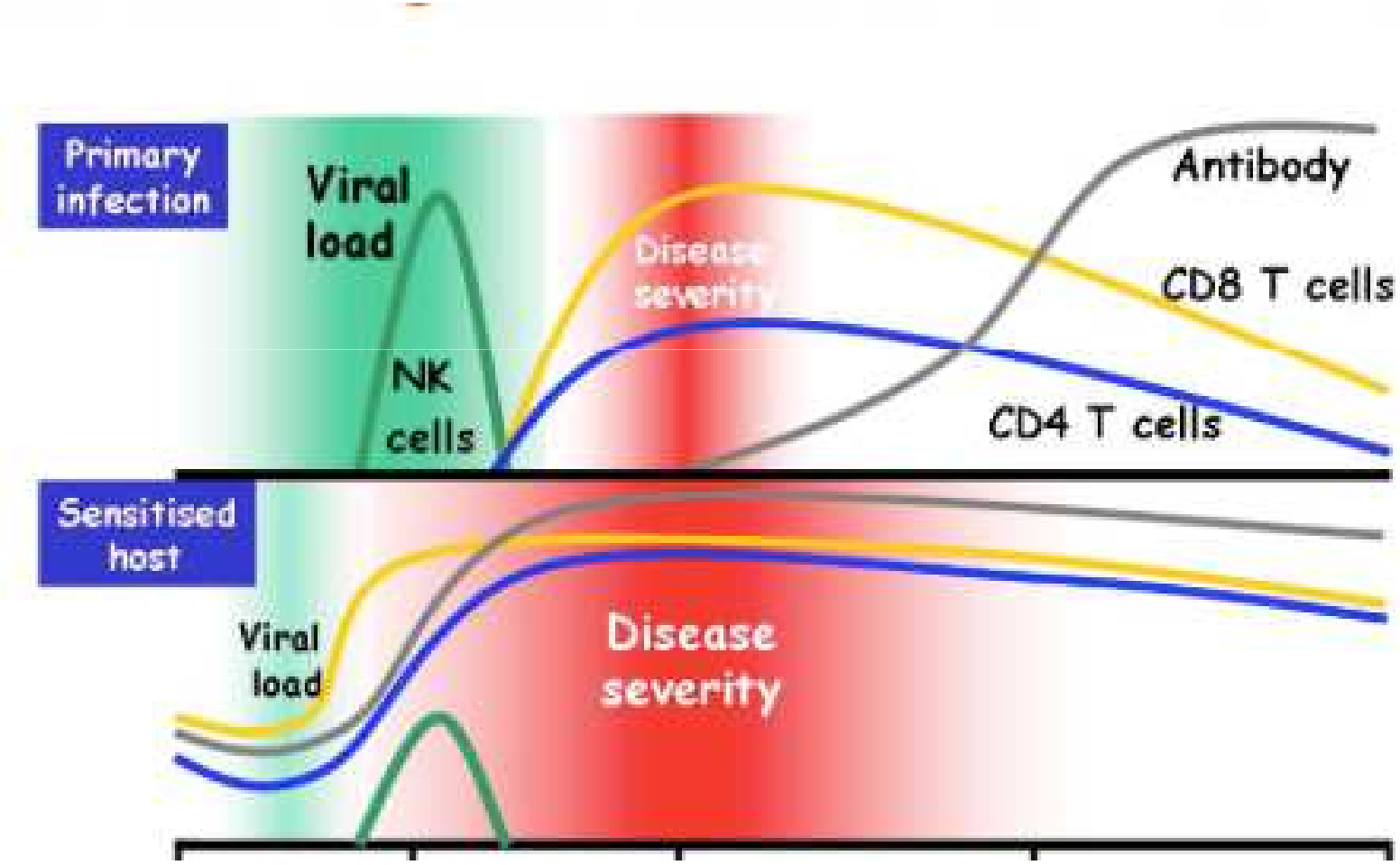


- In the 1960s, a formalin activated F protein vaccine was given to naïve children.
  - This vaccine was associated with an increased risk of severe disease and mortality in vaccine recipients.
  - Subsequently a cotton rat model of this enhanced disease has been used to screen vaccine candidates
  - This prior history has slowed development of vaccines.

Potentiation of RSV LRI following formalin inactivated vaccine



Formalin Killed RSV Vaccine: Impact of Prior Vaccine History



Implications of enhanced RSV disease for RSV vaccine development

- Vaccines for active immunization of RSV-naïve infants should induce neutralizing antibodies, CD4 and CD8 responses

- Different vaccines in development for maternal and infant immunization:

  - Non-replicating (subunit) RSV vaccines for maternal immunization
    - Also for other non-naïve populations (older children, elderly)

  - Replicating RSV vaccines (live-attenuated or vectored) for infant immunization
    - Safest alternatives for active immunization of RSV-naïve populations
    - Live-attenuated RSV candidate vaccines have been administered to hundreds of RSV-naïve children and have never been associated with enhanced disease.[1]

New Vaccines in Development

Obstacles to successful RSV vaccine development

- Difficult to induce protective immunity in the very young infant
  - Suppression of the immune response by maternal Ab
- Heterogeneous at-risk populations require different vaccines
  - Newborns
  - Older infants and young children
  - Elderly
- Imperfect animal models; adult RSV challenge (reinfection) model does not recapitulate RSV infection in naïve infants
- Specter of enhanced disease

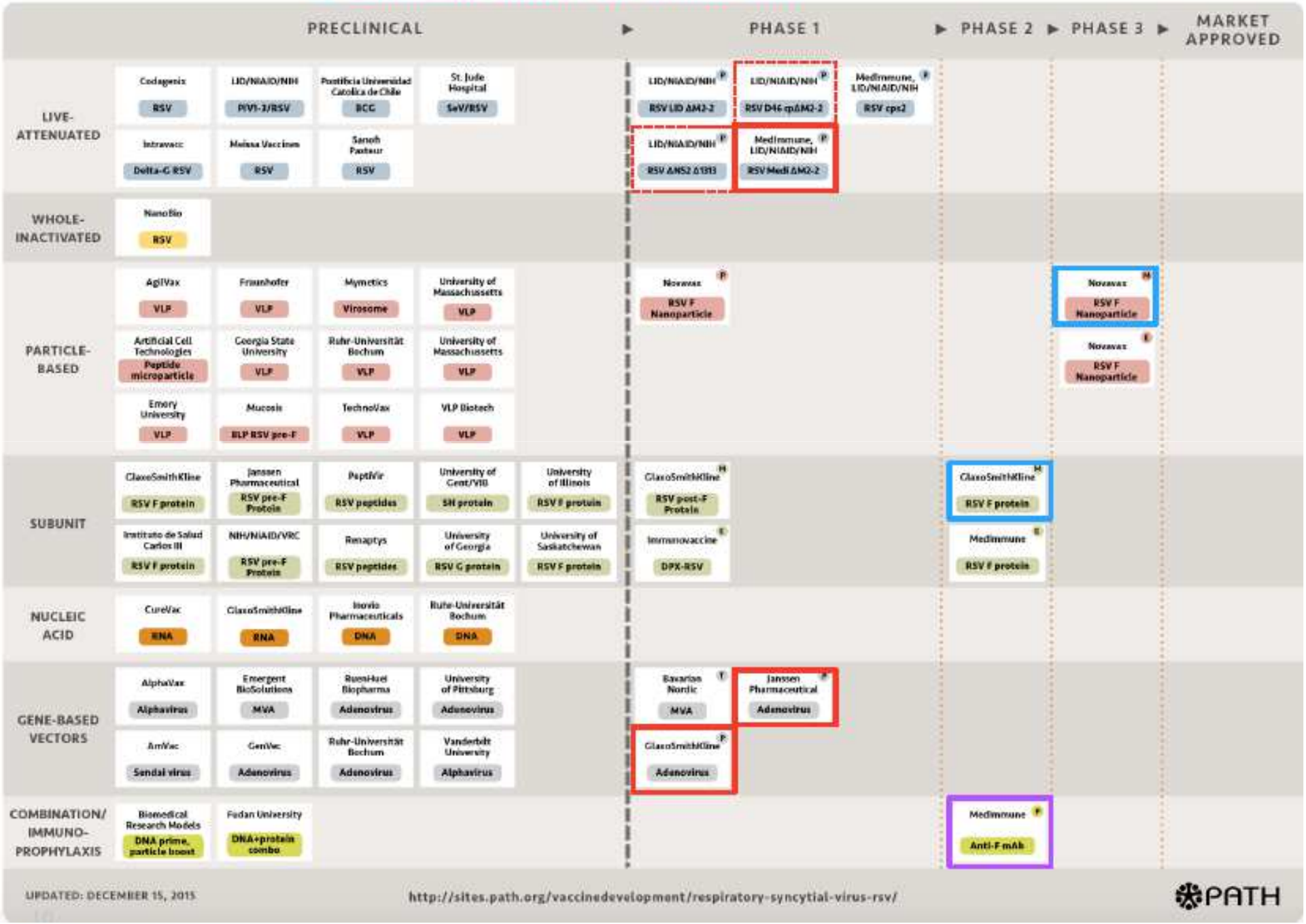
Assessing Toxicity Prior to Use in Humans

- Because of the excess mortality and toxicity seen after the formalin inactivated vaccine, safety assessment prior to use in humans has been an important challenge
- The cotton rat model of RSV disease has been used as the enhanced toxicity seen with formalin inactivated vaccine is also seen in this model.
- All current candidates have been evaluated in this model prior to use in humans.

RSV Vaccine Snapshot

62 candidates total;16 in clinical trials

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



Two vaccine programs are the most advanced

- Novavax recombinant near full-length RSV fusion (F) glycoprotein.

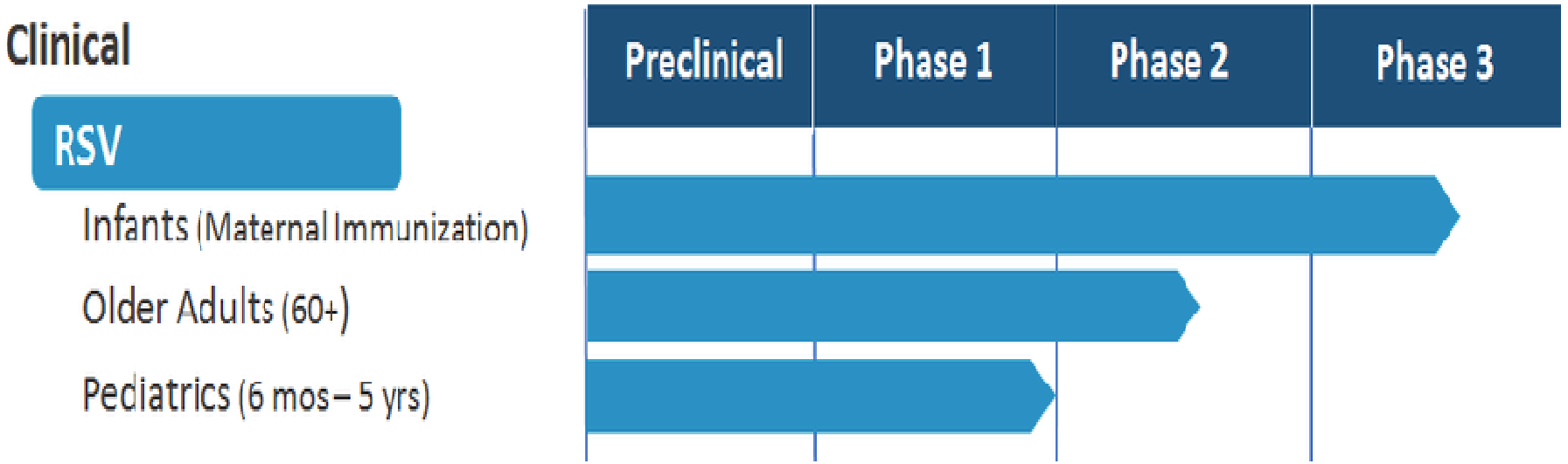
- GSK candidates
  - Recombinant pre-F protein vaccine
  - Self replicating RNA vaccine producing F fusion protein.

Candidate:

Novavax F protein vaccine

- Novavax' has developed an RSV F vaccine.
  - Based on a purified, recombinant near full-length RSV fusion (F) glycoprotein.
  - The RSV F is produced using the baculovirus/*Spodoptera frugiperda* (*Sf9*) insect cell system, and assembles into trimers, which further associate via hydrophobic interactions into nanoparticles resembling the previously-described 40nm protein-protein micelles of isolated RSV F protein [Calder 2000].
  - The purified F protein is adsorbed to aluminum phosphate and contains 120µg of RSV F protein and 0.4mg of aluminum per 0.5mL injection.
  - The vaccine contains no viable viruses.

Novavax F protein vaccine



Novavax RSV F Nanoparticle Vaccine: Phase 2 safety, immunogenicity, and transplacental antibody transfer

Protocol RSV-M-203

- Well-tolerated
- High and sustained titers of RSV F IgG and palivizumab competing antibody (binding to postfusion RSV F in ELISA)

Trial Overview

- **Phase 2 trial** randomized, observer-blinded
- **50 pregnant women in 3rd trimester**
  - Singleton pregnancies
- **120µg dose** with aluminum adjuvant

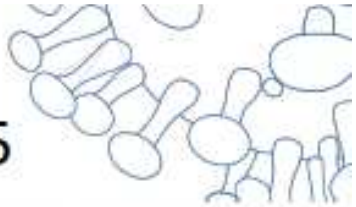
Goals

- **Describe** the safety of the RSV F vaccine women and infants
- **Describe** the immunogenicity of the vaccine in the 3rd trimester
- **Characterize** antibody transfer and decay kinetics

Method

- **Detailed collection of third trimester safety endpoints**
- **Cord blood** and infant sera
- **Maternal** and **infant RSV surveillance** through RSV season

RSV F Vaccination to Protect Infants via Maternal Immunization: Global P3 Trial **Prepare™** launched 4Q 15



Prepare™

Timeline

- Phase III trial initiated Dec 2015
- Group sequential design with enrollment 2 - 4 years

Trial Objectives

- **Primary: Prevention** of RSV lower respiratory tract infection (LRTI) with hypoxemia in infants during the first **90 days of life**
- **Secondary endpoints:** LRTI with severe hypoxemia, persistent efficacy to measure out to 120, 150, 180 days

Trial Design

- **Pregnant women in 3rd trimester**
- 5,000 – 8,255 participants
- Randomized, placebo-controlled
- DSMB oversight and iterative futility analyses to ensure safety
- **Global sites**
  - Both hemispheres

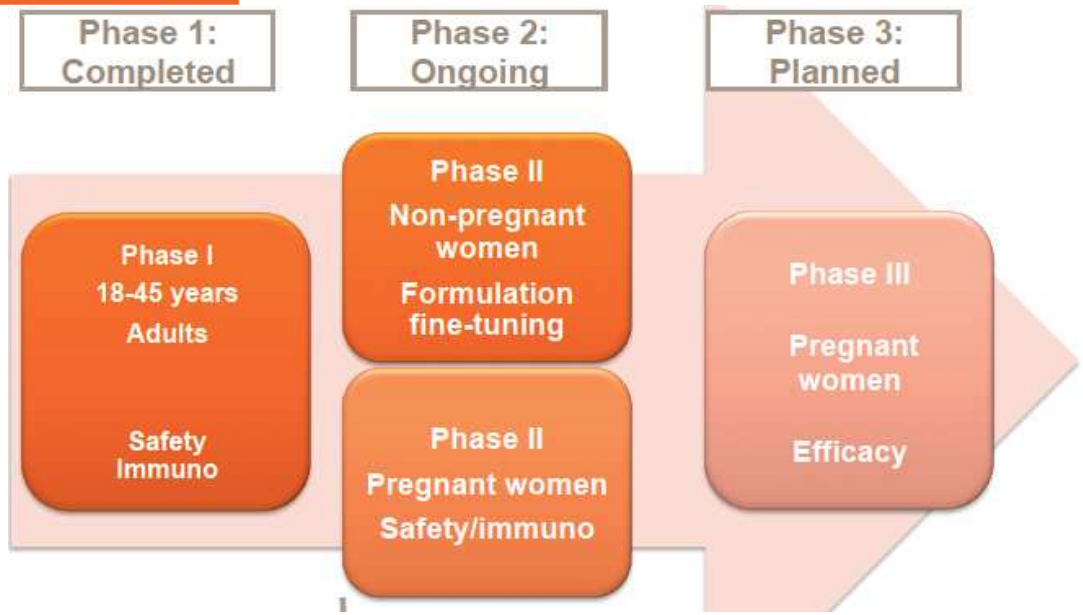
NOVAVAX

GSK RSV Vaccines

- More than one candidate in development
  - One candidate utilizes a self replicating RNA platform to induce early immunity to post fusion F protein
  - Also recombinant subunit vaccine of pre-fusion F protein

naternal RSV vaccine candidate

	Maternal
Global intent	Active immunization of pregnant women during the 3rd trimester of pregnancy to prevent RSV-associated LRTI in infants
Vaccination regimen	• Single dose to boost pre-existing immune response • Immunization in the third trimester
Vaccine Composition	Recombinant subunit PreF antigen (Dosage TBD, with or without Alum)
Stage of development	Phase II: ongoing



Other vaccines in development

Current & upcoming clinical studies in NIAID program

National Institute of Allergy and Infectious Diseases

Laboratory of Infectious Diseases/NIAID (Peter Collins, Ursula Buchholz, et al*)

1. Attenuated RSV strains

- A number of gene deletion candidates in phase 1 studies in RSV seronegative infants and children in 2016-2017 to identify a lead candidate from the following:
  - A virus comparable to RSV MEDI ΔM2-2
  - Additional ΔM2-2 backbones to evaluate potential for increased immunogenicity
  - One or more backbones based on deletion of NS2 or NS1 (interferon antagonist) genes

2. Human parainfluenza type 3 virus vectors expressing RSV F protein

- Bivalent RSV/HPIV3 vaccine (protection against both viruses)
- Improved growth and stability to facilitate manufacture & distribution in LMIC
- Expression of stabilized pre-fusion F protein enhances quality of RSV-neutralizing Ab-- potential to increase the quality of anamnestic responses
- Clinical trial seed under development, clinical study in 2017

*Collaborators: Ruth Karron et al, CIR/JHU, Elizabeth McFarland, Coleen Cunningham et al, IMPAACT/NIAID, NICHD

RSV Summary & Questions for the future

- RSV is a very significant cause of respiratory disease morbidity and mortality globally
- Current treatment and prevention strategies are suboptimal
- Toxicity with a prior vaccine candidate has slowed the field as has the need to provide protection to very young infants.
- Remaining questions:
  - Will maternal immunization provide protection in the first months of life for infants?
  - Can an effective infant immunization strategy be developed?
  - Will vaccines work for older children and adults

RSV Virus Structural Proteins

TABLE 1

RSV structural proteins in order of gene sequence, 3′ to 5′

Protein	Size (kDa)	Designation	Comments
N[a]	44	Nucleocapsid protein	Major target of CTL in humans
P[a]	34	Phosphoprotein	
M	28	Matrix protein	
SH	7.5–30	Small hydrophobic protein	Glycosylated transmembrane protein; no neutralizing epitope known; participates in cell fusion (91)
G	90	Attachment protein	Antigenic variation between strains; neutralizing epitopes; truncated secreted form (Gs) from second open reading frame (158)
F	70	Fusion protein	Sequence conserved between strains; contains neutralizing epitopes
M2-1, M2-2	22	Transcription regulation	Two open reading frame products (ORF1 and ORF2) important for full-length mRNA production by polymerase and transcription regulation (23)
L[a]	~200	Polymerase protein	

[a]N, P, and L together constitute the viral replicase.

Clin Microbiol Rev. 2000 Jul; 13(3): 371–384.