

VACCINATION IN PREGNANCY: RSV VACCINES ARE WE THERE YET?

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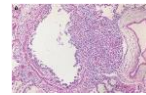
Objectives

- RSV epidemiology and burden of disease in infants and pregnant women
- Rationale for maternal immunization with RSV vaccine
- Goals and challenges in the development of RSV vaccines for administration during pregnancy to protect young infants.

Respiratory Syncytial Virus



Multinucleated RSV syncytium in cell culture



Peribroncholar and interstitial lymphocytic infiltrates with airway trapping (Bronchiolitis)

http://www.nature.com/natpath/journal/22/11/fig_146-280372513.html#fig_146

- Neg sense, **ssRNA Paramyxovirus**
- Two main types – **A, B co-circulate**
- 11 proteins, of which 2 are NS
- **F** (fusion – viral penetration, spread) and **G** (attachment) surface glycoproteins induce **Neutralizing Antibodies**

Features of Respiratory Syncytial Virus

- Mucosally restricted pathogen in the immunocompetent host
- Causes **LRTI –Bronchiolitis**
- **Co-circulation of subgroups (A and B) during winter outbreaks**
- Illness burden and disease severity is greatest in **infants, young children and elderly adults**
- **Recurrent infections** occur throughout life and are milder except for people with chronic medical conditions
- **Virus-specific serum neutralizing antibody** (infection-induced, maternally derived or passively administered) protects against severe RSV LRTI

Impact of RSV Disease in Children

- Most important cause of LRTI in infants and young children
- Nearly all children are infected at least once by age 2
- Recurrent infections common
- **30% to 40% of primary infections result in LRTI**
- **2-3% of infected children require hospitalization** – one of the most important causes of hospitalization in US and other HIC
- **Higher mortality than influenza in infants**
- **Associated with chronic reactive airways/asthma in the long term**

RSV Infection Rate in Children Less Than Five Years of Age by Treatment Site in U.S.

Treatment Site	Infection rate per 1000 children (95% CI)			
	0-5 months	6-11 months	12-23 months	24-59 months
Hospital	16.9 (15.3-18.5)	5.1 (4.6-5.5)	2.7 (2.3-2.7)	0.4 (0.3-0.4)
Emergency department	55 (24-126)	57 (20-161)	32 (11-92)	13 (4-41)
Pediatric practice	132 (46-383)	177 (61-511)	66 (18-245)	57 (19-167)

CB Hall et al., NEJM 2009;360:588

All Cause Mortality Associated With Respiratory Syncytial Virus and Influenza: 1989-1999

Age, Y	Incidence per 100,000 person-years	
	RSV	Flu
<1	5.4	2.2
1-4	0.9	1.1
5-49	2.6	1.5

Age, Y	Incidence per 100,000 person-years	
	RSV	Flu
<1	8.4	6.7
1-4	0.9	0.8
5-14	0.15	0.3

WW Thompson et al. NEJM 2003;289:179-86.

DM Fleming et al. J Epidemiol Community Health. 2005;59:586-90.

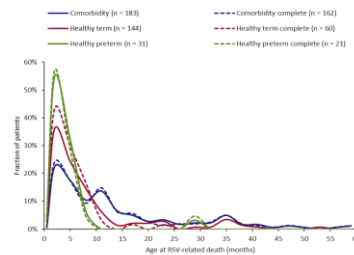
Global Burden of RSV Disease In Children Under 5 Years Of Age

Mortality estimates suggest RSV is an important cause of death in children after pneumococcal pneumonia and *Haemophilus influenzae* type b.

- RSV is a major global pathogen
- 33.8 (19.3-46.2) million cases annually of RSV-ALRI
- 3.4 (2.8-4.3) million cases annually of severe RSV-ALRI
- 60,000 to 199,000 deaths annually attributed to RSV
 - Most of the deaths in developing countries occur in young children

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

Very young infants are most at risk for RSV-related death



- Case series hospital data from 23 countries
- Median age for RSV-related deaths in LMICs is **5 months**, with more than 40% occurring in **under 3 months**
- RSV deaths from community higher

Schellekens NM et al. Lancet Glob Health 2017

RSV in infancy and subsequent asthma

- Retrospective cohort analysis using linked population-based administrative data in New South Wales, Australia.
- **Primary outcome measure:** Risk of development of severe asthma in different subgroups of children who had RSV hospitalization in the first 2 years of life compared with those who did not.
- Cohort: 847,516 children born between 2000 and 2010.
- 3 subgroups:
 - (1) non-Indigenous high-risk children (preterm or low birth weight);
 - (2) Indigenous children (Aboriginal and/or Torres Strait Islander)
 - (3) non-Indigenous standard risk children: all other non-Indigenous term children.
- **Results:**
 - Asthma hospitalization beyond age 2 yr – 7.5% in children with RSV prior hospitalization vs. 2% in those without RSV
 - High risk for asthma hospitalization persisted up to 7 years of age in children with history of severe RSV in all groups (HR 3-4)

Homaira N, et al. BMJ Open 2017

RSV in Children Current Prevention Strategies

- **No licensed vaccine for children or adults**
- **Passive Antibody**
 - RSV-Specific IgG (RSV-IG or RespiGam®)
 - Monoclonal antibody (Palivizumab or Synagis®)
 - Licensed 1998 US
 - Effective: Reduces mortality and severity of RSV disease
 - Restricted to:
 - Preterm infants < 29 weeks of gestation
 - Preterm infants with chronic lung disease (O2 requirement > 28 days)
 - Infants with hemodynamically significant/cyanotic congenital heart disease
 - Requires monthly IM administration
 - Costly
 - Most infants who are at risk for RSV are excluded (term)

RSV Antibody Type	Age	Assay Method	Article
Human IgG	198.1	Membrane Fluorescent Antibody Test	Ogihara, J Med Vi 1981 7:263
Human IgG	92	Neutralizing Ab	Mohamed Ali & Sanyal
Human IgG	40.00	IFA	Stevens, J Ped 1981 95:108
Human IgG	44.14	Neutralizing Ab	Roux, J Med Vi 2002 67:416
Human IgG	208.9	Neutralizing Ab	Probst, Vaccine 2003 21:3479
Human IgG	302.1	Neutralizing Ab	Black, Ped Inf Dis J 2008 27:207
Human IgG	1947	ELISA	Ogihara, J Med Vi 2008 67:416

A two- to four-fold lower concentration of RSV-specific antibody titers is seen in infants with RSV disease compared to infants with no disease.

Why don't we have a RSV vaccine for children?

- Primary target population, the very young infant (0-4 months of age), has a **suboptimal immune response to vaccination** in part due to presence of **maternal antibody**
- **Incomplete immunity to natural RSV infection**, especially in younger patients
- Enhanced pulmonary disease/death in very young seronegative infants receiving **formalin-inactivated RSV vaccine in the 1960's**
- Subunit vaccines safe but not immunogenic enough
- Live attenuated vaccines administered intranasally pose challenges to balance between immunogenicity and reactogenicity

Rationale for Maternal Immunization to Protect Infants Against RSV

- Reduced incidence of RSV disease in neonates during the first several months after birth correlates with higher concentrations of RSV-specific maternal antibody.
- Passive anti-F IgG (e.g., Palivizumab) reduces incidence of severe disease.
- Adults (mothers) are primed from previous infections and vaccine will boost antibodies
- RSV-specific IgG transfer from mothers to neonates is efficient
- Potential protection from breast milk antibodies
- Success of similar strategies for Tetanus, Pertussis, Influenza



Goals of a Maternal Vaccination Program Against RSV

- Prevent infant death and hospitalization
- Prevent and/or reduce severity of lower respiratory illness in young infants
- Delay onset of first RSV infection in infants
- Reduce infection / transmission in the household and community
- Indirect benefits
 - Reduce secondary complications of RSV in infants - otitis media, bacterial infections
 - Reduce antibiotics usage for the treatment of ARI
 - Reduce virus-associated wheezing in the first decade of life
 - Improve maternal health and pregnancy outcomes (?)

Maternal Effects of RSV Infection during Pregnancy

Wheeler, et al. *Em Infect Dis*, Nov 2015 – Duke – Winter 2014

	Case 1	Case 2	Case 3
Age, GA at Dx	26 yr / 33 wk G1	27 yr / 34 wk G2P0	21 yr / 32 wk G1
Infection	RSV	RSV and H1N1	RSV and GAS/trep
Diagnostic tool	PCR - BAL	PCR – NP aspirate	PCR – NP aspirate
Disease	Bronchitis Pneumonia-VAP	Pneumonia	Pharyngitis
Complications	Mechanical Vent 6 d C-section delivery at 34 weeks b/c LRTI. Hospitalization 14 d	Preterm labor and delivery at 34 weeks Mechanical Vent 1 d	None Outpatient treatment Delivery at 39 weeks
Symptoms	5 d malaise, cough, wheezing, 1 d fever	5 d cough, congestion 3 d fever, chills	3 d sore throat, congestion, fever
Treatment	Broad Abtx	Broad Abtx, steroids	Penicillin
Underlying cond.	Asthma Smoker	Asthma Smoker	Mild aortic coarctation Cognitive delay
Exposures	Young child URI	-	-

RSV infection in pregnancy: Clinical presentation and birth outcomes in Nepal. - Chu et al. *PLOS one* March 2016

- Prospective, randomized **trial of influenza** immunization in pregnancy in rural Nepal, 2011-2014
- Enrollment and immunization in 2nd trimester (~ 17 weeks of gestation)
- Weekly home-based surveillance for **febrile respiratory illness in mothers** from enrollment until 180 days post-partum
- Mid nasal swabs during illness tested for RSV by PCR
- **Maternal illness = Fever** (> 38°C) *plus* at least one of cough, myalgia, sore throat, rhinorrhea
- Infant illness = any of – fever, cough, wheeze, difficult or rapid breathing, draining ear.

RSV infection in pregnancy: Clinical presentation at birth outcomes in Nepal. Chu et al. *PLOS one* March 2016

Outcome	Description
Incidence RSV	14 (0.4%) RSV positive febrile illness episodes in 3693 women over 3554 person-years of surveillance 3.9/1000 person-years overall 11.8/1000 person-years between September and December
Morbidity	7/14 (50%) women sought medical care Median 2 (total 4) days of fever, myalgia, cough, rhinorrhea, sore throat No deaths
Pregnancy effects	7/14 (50%) infected during pregnancy All live births – median BW 3060 g [vs. 2790 g in women w/o RSV] 2 (29%) preterm births 34 and 36 weeks [vs. 469 (13%) in women w/o RSV]
Post-partum effects	7/14 (50%) infected post-partum RSV was detected in 4 (47%) of their infants
Exposures	No difference in number of children in household, indoor cook stove or smoking between RSV pos and RSV Neg
Conclusion	RSV is uncommon cause of febrile respiratory illness in mothers during pregnancy and post-partum in Nepal

Burden of RSV in Pregnant Women – Mongolia

Chaw L, et al. PLOS One. Feb 2016

Outcome	Description
Study design	Prospective, observational, open cohort of 1260 unvaccinated pregnant women and their infants, 2013-2015 ILI and severe ARI identified by bi-weekly call Flu and RSV point of care test
Maternal Incidence rate	ILI – 174 episodes in 160 PW or 11.8/1000 person days Severe ARI – 0.1 (0.0 – 0.4)/ 1000 person days Among 165 ILI cases tested: - 26 (15.8%) = influenza A (1.7 [1.5-1.9]/1000 person days) - 2 (1.2%) = influenza B (0.1 [0.1-0.2]/1000 person days) - 4 (2.4%) = RSV (0.3 [0.2-0.4]/1000 person days) - 2 women tested pos for both flu and RSV from separate ILI episodes in 2014/15
Illness	Testing within 5 days of onset Mean interval to resolution 8.1 days (3-20) No deaths

RSV in Pregnant and Post-partum Women South Africa.

Madhi et al. Burden of RSV in SA HIV+/HIV- pregnant women. CID, 2018

- 2011-2012 **study of influenza vaccine efficacy in pregnant women**
- 1060 and 1056 HIV Neg; 194 HIV Pos
- **Incidence of RSV illness:**
 - HIV Neg 1.2 – 4.0 per 1000 person-months
 - HIV Pos: 3.4 per 1000
- Maternal RSV infection was associated with respiratory symptoms including cough (72.1%), rhinorrhea (39.5%), sore throat (37.2%), and headache (42%), but fever was absent.
- RSV infection during pregnancy was **not associated with adverse pregnancy outcomes**.
- Postpartum, RSV infection in mothers was associated with **concurrent infection** among 51.9% of **their infants** and, conversely, 29.6% of mothers investigated within 7 days of their infants having an RSV illness also tested positive for RSV.

RSV In Pregnancy – PREVENT* Study

Regan A, et al. RSV hospitalization in PW in four high income countries. CID May 2016

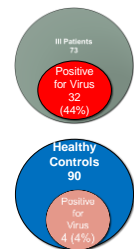
- 2010-2016 **Hospitalizations** for Acute Respiratory or Febrile Illness (ARFI) AND PCR testing for RSV
- Total population: **1,604,2016 pregnant women in US, Canada, Israel, Australia**
- RESULTS**
 - (0.9%) 15,287 \geq 1 ARFI related hospitalization
 - **Only 6% (846/13,694 unique admissions for ARFI) were tested for RSV**
 - **2.5 % (21) POS for RSV (range: 1.9 – 3.1%);** positivity by year: 0 to 4% (2013-14)
 - 51% pos for influenza; < 1% pos for both RSV and influenza
 - **63% tests and 67% detections in the 3rd trimester of pregnancy**
 - **38% women had pre-existing health condition** (19% was asthma)
 - **Pneumonia was more common in RSV POS vs. neg women** (38% vs. 19%, P=0.046)
 - **48% of RSV POS women were admitted for \geq 3 days**
 - No difference in preterm, SGA, and LBW births between RSV-pos and RSV-neg women.
 - Among ARFI admissions where no delivery occurred, there was **association between RSV-positivity and subsequent preterm birth** (RSV-pos: 29% and RSV-neg: 15%; P=0.034).

*Pregnancy Influenza Vaccine Effectiveness Network (CDC-Abt)

RSV Pregnancy Houston.

Hause A. ARI among Pregnant Women. JID May 2018

- Aim: Incidence and impact of RSV infection in pregnant women
- 2015-16 season (October – April)
- Cross sectional cohort of pregnant women receiving routine prenatal care at private OB practice
- Enrolled when healthy or ill
- Mid turbinate nasal swab for PCR viral diagnosis
- Symptom history and follow up for outcomes 2 weeks after enrolment if ill
- **RSV identified by PCR in 10% of women, and attributed cause of ARI in 14% of women (PCR + serology)**



RSV Positive Patients

	Case 53	Case 72	Case 102	Case 111	Case 121	Case 163
Date of Enrollment	Nov. 10	Nov. 16	Nov. 25	Dec. 12	Dec. 22	Mar. 31
Maternal Age	26 years	28 years	33 years	31 years	37 years	28 years
Gestational Age	39 weeks	24 weeks	37 weeks	15 weeks	26 weeks	34 weeks
Days Post-Onset	2 days	1 day	5 days	1 day	25 days	8 days
Symptoms	Congestion Sneezing Cough	Congestion Sore throat Cough	Congestion Sore throat Cough	↓ Activity ↓ Appetite Sore throat	Fever ↓ Activity ↓ Appetite Congestion Sore throat Cough Chest pain Short of breath Wheezing	Congestion Sore Throat Cough Short of breath
Duration of Illness	11 days	7 days	18 days	9 days	30 days	34 days

RSV Vaccine Trials in the 1990-2010s

- **Subunit vaccine**
 - PFP with low concentration of G (PFP-1)
 - Purified fusion protein (PFP-2, PFP-3)
 - F/G/M
 - **F nanoparticle (phase II and III trials)**
- **Live attenuated vaccine**
 - Cold passaged, temperature sensitive - cpts 248/404
 - Genetically engineered vaccines – rABcp248/404ΔSH, rA2cp248/404/1030ΔSH (**Medi-559, phase II trials**)
- **Polypeptide vaccine**
 - BBG2Na (aa130-230 of G protein fused to albumin binding domain of streptococcal G protein)
- **Vector vaccine**
 - bPIV3-hHN_{PIV3}-hF_{PIV3}-hF_{RSV} (**Medi-534**)

Munoz, Piedra, Glezen. *Vaccine* 2003;21:346.

*Munoz, et al. Vaccine 2003

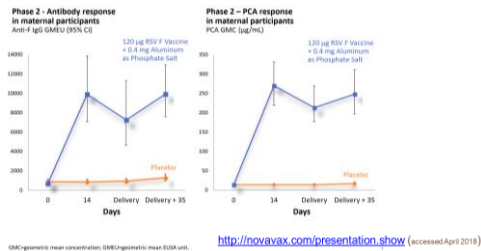
Beran J, et al. JID, May, 2018; GSK Investigational vaccines: Purified Recombinant F-protein, prefusion, Prepared in Chinese Hamster Ovary cells

Beran J, et al. JID, May, 2018; GSK Investigational vaccines: Purified Recombinant F-protein, prefusion, prepared in CHO cells

All formulations of RSV-PreF boosted preexisting immune responses in 18–45-year old women with comparable immunogenicity. The RSV-PreF safety profile was similar to that of Tdap vaccine.

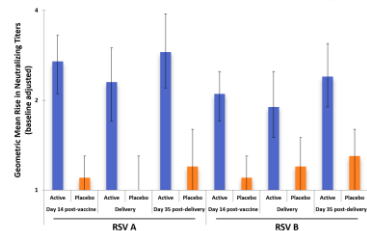
Serological determination of RSV infection before and after RSV season

RSF F-nanoparticle vaccine in clinical development in Pregnant Women – Phase 2 study



<http://novavax.com/presentation.show> (accessed April 2018)

RSV F-nanoparticle vaccine in Pregnant Women – Phase 2 study



http://novavax.com/presentation_show (accessed April 2018)

RSV F protein vaccine is in phase 3 trials in pregnant women

- ✓ **First-in class vaccine**
- ✓ **First vaccine with a specific maternal indication**
- ✓ **First near-concurrent launch in HIC and LMIC**



<http://novavax.com/presentation.show> (accessed April 2018)

RSV Vaccine for Pregnant Women – Are we there yet?

- Understanding the burden of disease
 - Mothers and infants
 - High and LMIC settings
 - Diagnosis and Surveillance of RSV disease
 - Safety
 - Obstetric vs. vaccine associated adverse events (background rates)
 - Vaccine enhanced disease upon natural infection under 2 years of age is NOT a significant consideration when vaccine is given to mother
 - Efficacy + Endpoints (eg. LRI (bronchiolitis), severe LRI, hospitalization, death)
 - Immunologic correlates of protection
- Nair et al. BMC Public Health 2011, 11(Suppl 3):S20
(<http://www.biomedcentral.com/10.1186/1471-2334-11-S3-S20>)

Nair et al. BMC Public Health 2011, 11(Suppl 3):S30
Polatti et al. BMC Medicine (2015) 13:49
Kasajik et al. Human Vaccines & Immunotherapeutics
2015, 12:63-1267; June 2013

RSV Prevention Strategies

- Long lasting monoclonal antibody (1-2 doses per season) (Phase II-III clinical trials)
- Infant vaccination (vaccines in development / phase II-III trials)
 - Vaccine for 0-6 months
 - Vaccine for 6 mo – 23 month olds

Implementation approach Strategies:

- **Maternal**
- Infant vaccination in combination with maternal Immunization
 - **MOM + INFANT at 2 – 6 months**
 - **MOM + Toddler at 12 - 24 months**
- Monoclonal antibody + Infant vaccination

Perceived benefit-risk is a key consideration for the development of novel vaccines for use in pregnancy

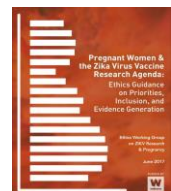
PUBLIC HEALTH
 711 *Journal of Public Health Medicine and Practice* 2010, 14(6):711-714
 DOI: 10.1093/jphmp/14.6.711

Zika rewrites maternal immunization

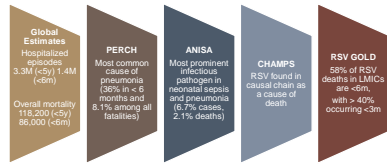
Dr. John C. S. Brown

[illegible]

The RGV and GRS vaccines attempt to address a biological constraint in newborns: their immature immune systems do not



Why pursue a maternal RSV vaccine?



ANISA = Aetiology of Neonatal Infection in South Asia; PERCH = Pneumonia Etiology Research for Child Health; RSV GOLD = Respiratory Syncytial Virus Global Database; CHAMPS = Child Health and Mortality Prevention Surveillance Network.

Schmeltzer MB et al. Lancet Glob Health. 2017; 5(7):e1-10. doi:10.1016/S2468-2667(17)30201-0. Copyright 2017. RSV: 2017. Copyright 2017. RSV: 2017. Copyright 2017. RSV: 2017.

Comparison of Deaths from MI-Preventable Diseases

According to GBD 2016 estimates, LCM is 5 million globally, including 2.1 million deaths in neonates. Amongst these, a total of 895,565 deaths were due to lower respiratory tract infection (LRTI) and neonatal sepsis.

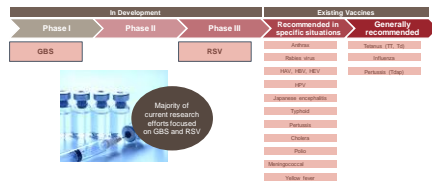
- LRTI remains the leading cause of mortality in children in LMICs (852,572)
- Neonatal sepsis is ranked as the 8th (from 10th last year) cause of death (242,992)

	OUTCOMES PER YEAR		
	Stillbirths	Neonatal or other deaths related to maternal infection or non-injury	Neonatal or infant cases
Group B Streptococcus	57,000 (10,000-100,000)	90,000 ^a (8,000-180,000)	319,000 (116,000-417,000)
Respiratory Syncytial Virus	NA	86,000 ^b (80,000-90,000)	1.4 million
Syphilis	200,000	62,000 ^c	102,000
Tetanus	NA	34,000 (10,000-60,000)	1,996 ^d

^a Missing values (30-40 days) ^b Global of monthly (30 days) ^c neonatal or other deaths in hospital (30 days) ^d Neonatal (30 days) ^e WHO Joint Reporting Form, 2016. Data not available.

Source: WHO, 2016. Data not available. GBD 2016 Diseases and Injuries Collaborators.

Current and pipeline vaccines for pregnant women



Source: Philip Landwehr, World Health Organization, "Integration of clinical and industrial immunization - a global strategy" WHO 2017, Geneva, Belgium. David R. Davis, "Maternal Immunization" 2016.

Prospects for an RSV Vaccine for Pregnant Women to Protect Infants Worldwide

- Maternal immunization is an **accepted strategy** for the prevention of maternal and infant disease (e.g Tetanus, Influenza, Pertussis)
- Active development** of RSV vaccines for pregnant women by industry
- Support from regulatory agencies** (FDA, EMA, others) to establish path for licensure of first vaccine indicated for pregnant women
- Support from funders** (BMGF, private, others) to study RSV vaccines in pregnancy, including the burden of disease in pregnant women and infants, safety and efficacy, as well as implementation strategies

Thank you



Baylor
College of
Medicine

Texas Children's Hospital