RSV infection in the elderly

troubled past, dark present, bright future ?

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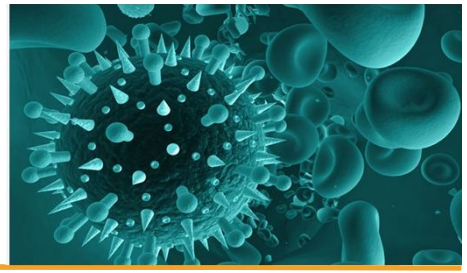
Infectious Diseases Department - CHU Saint Pierre
4th April 2019 – SBIMC-SBP-BSGG Symposium

In collaboration with Valérie Martinet MD, PhD, Geriatrics, CHU Saint Pierre

Outline

1. Introduction
2. Mechanisms of RSV disease in elderly
3. Epidemiology and burden
4. Future therapeutical intervention
5. Prevention : vaccination

Respiratory syncytial virus (RSV)

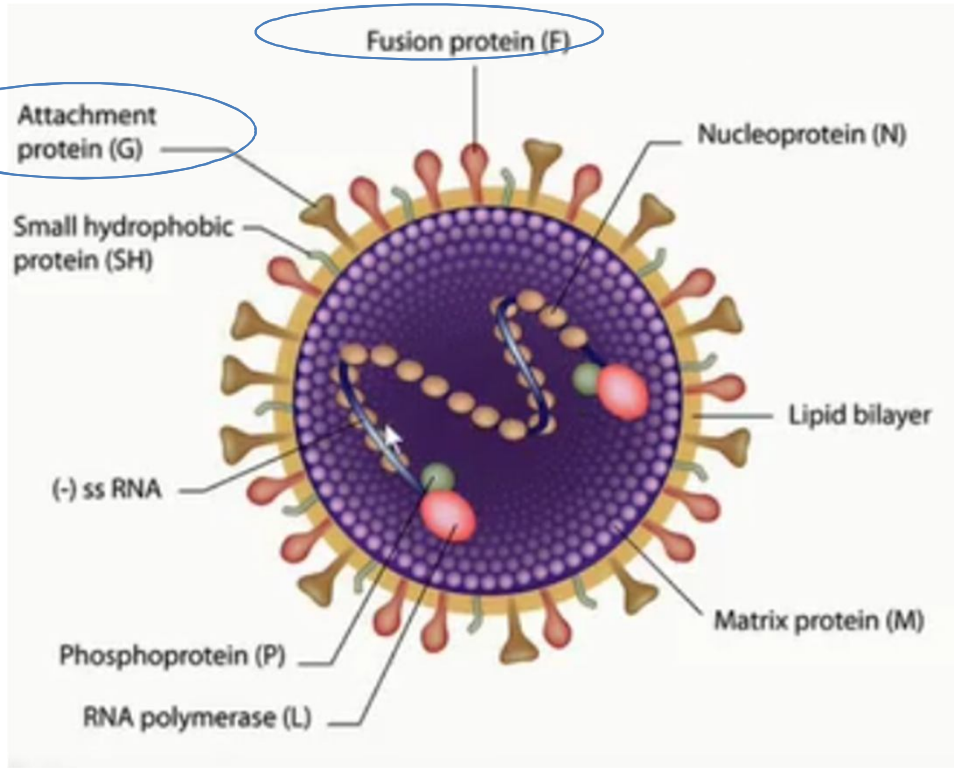


- Discovered in 1956
- Enveloped RNA virus

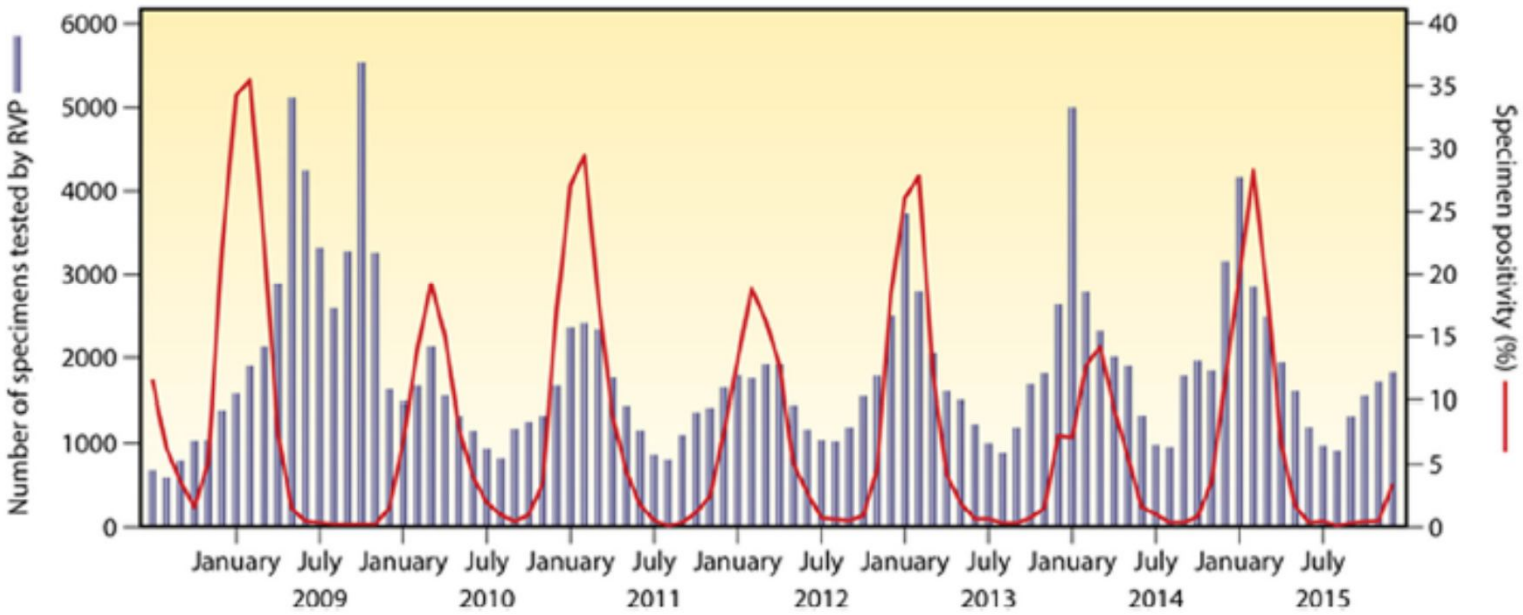
- Common & ubiquitous respiratory virus

- North hemisphere : Annual epidemics during the cold season (nov-march)

- A & B subtypes



Seasonality of RSV infection

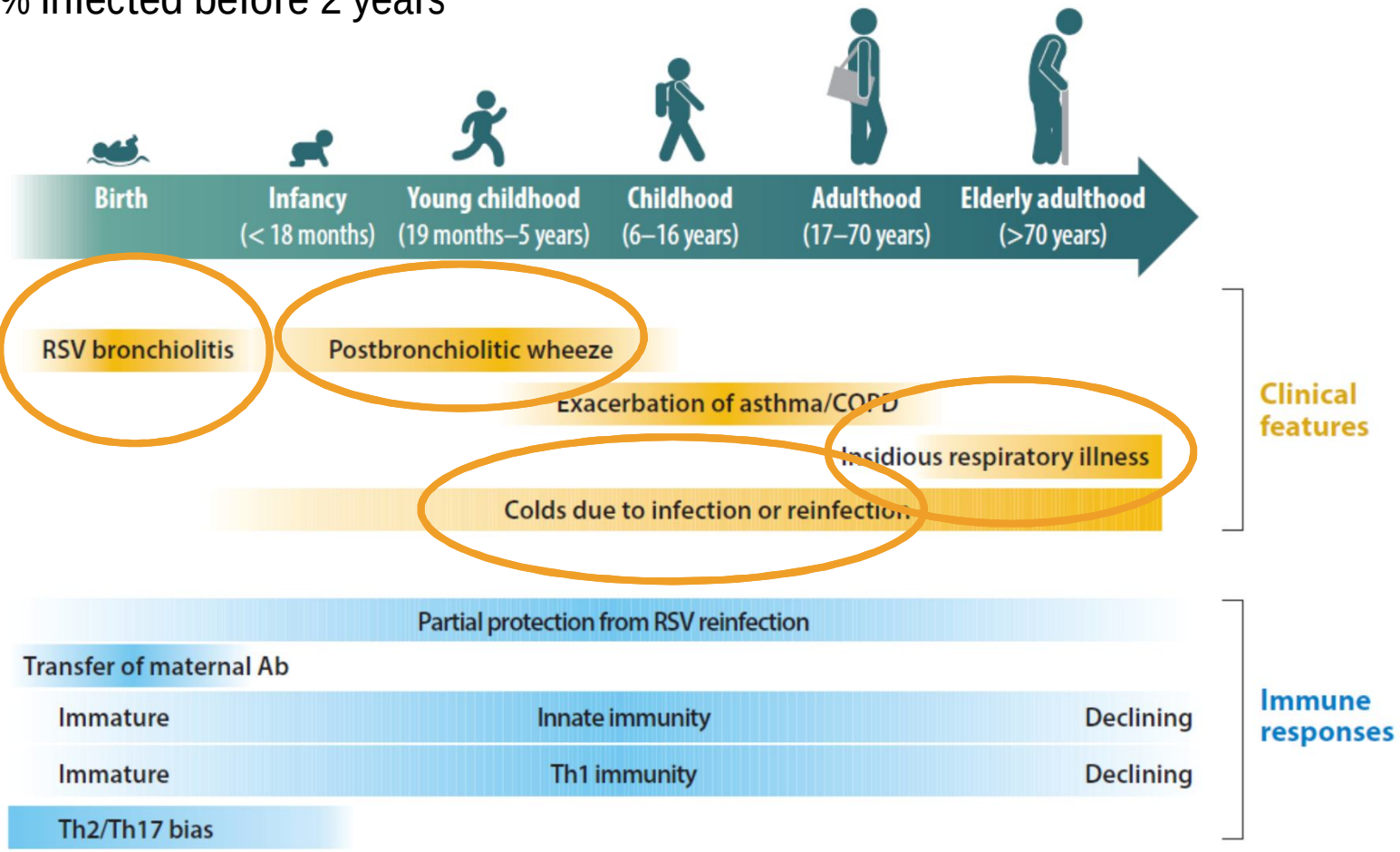


Alberta, Canada
2008-2015
Proportion of RSV positive assay by luminex Assay

Griffiths *CMR* 2017

Age as a major determinant of RSV disease

Most common respiratory infection in infants
95% infected before 2 years



Openshaw *Annual Rev Immunol* 2017

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2. **Mechanisms of RSV disease in elderly**
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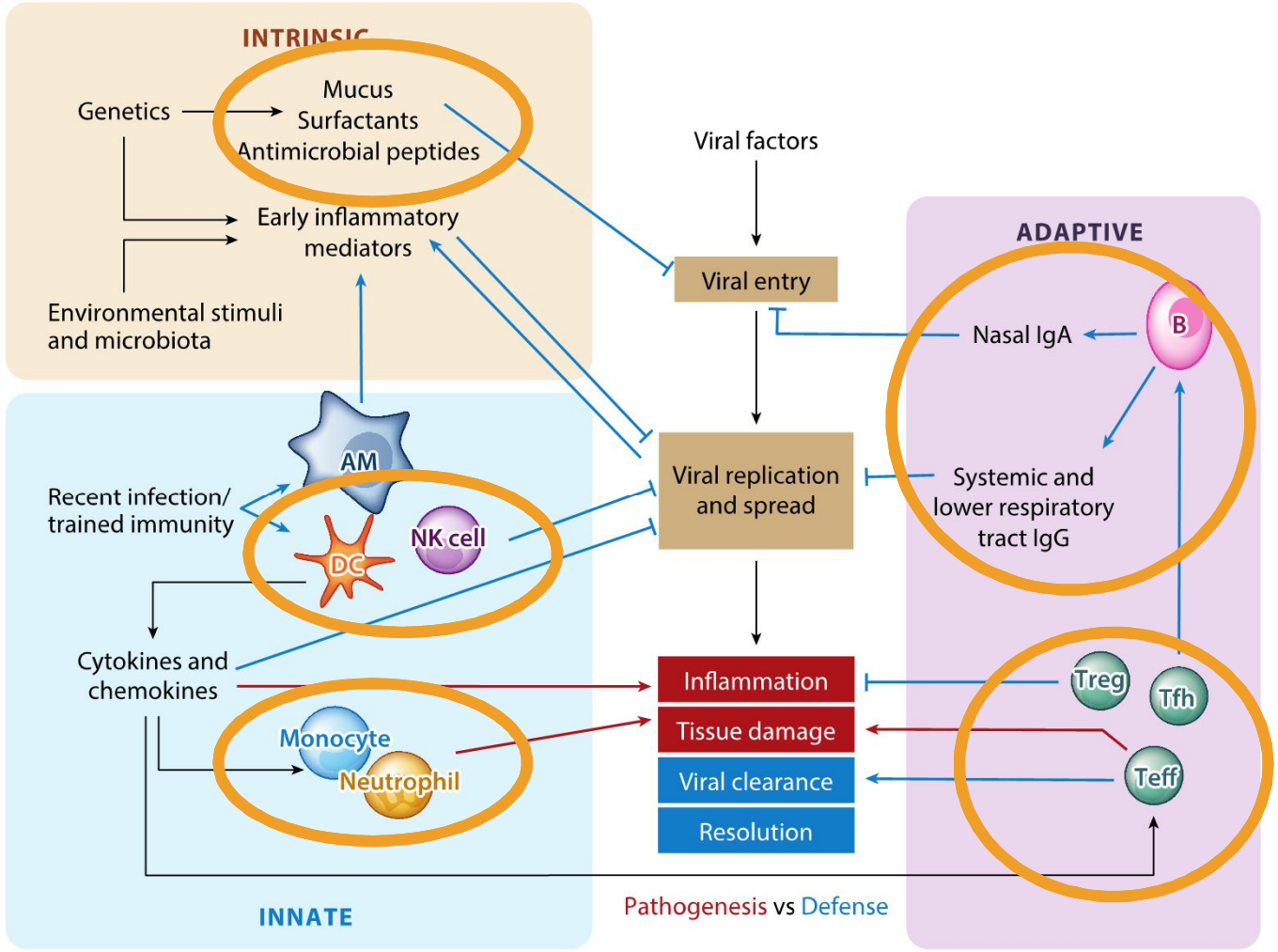
Pathways leading to antiviral defense & immunopathology during RSV infection
Protective vs Harmful immunity



Openshaw, Annual Rev Immunol 2017

Impact of aging on systemic immune functions

Early Life		Late Life
↓ Chemotaxis ↓ Intracellular and extracellular killing ↑ Numbers ↓ Response to chemokines	Neutrophil	↓ Chemotaxis ↓ Intracellular killing ↓ Phagocytosis
↓ TLR response ↓ Antigen presentation ↑ Th2/Th17 polarization ↓ Th1/proinflammatory cytokines ↓ Number of monocytes	Macrophage	↓ Expression of TLR1 ↑ Phagocytosis ↓ MHCII expression
↓ Cytotoxicity ↓ Numbers ↔ Proliferation capacity in response to IL-2 ↓ or ↔ IFN-α depending on stimulus	NK	↓ Cytotoxicity ↑ Numbers ↓ Proliferation ↓ IFN-α
↓ Phagocytosis ↓ TLR responses ↓ Numbers ↓ IL-12, IFN-α/β production ↓ Antigen presentation ↓ Costimulatory molecules	Dendritic Cells	↓ Phagocytosis ↓ TLR esponses ↓ Numbers in skin ↑ Inflammatory cytokines
↑ IL-6 ↑ IL-10 ↑ IL-23 ↑ Adenosine/cAMP	Cytokines and Soluble Mediators	↑ IL-6 ↑ IL-1β ↑ TNF-α ↑ TGF-β
↓ Antibody specificity ↓ Antibody affinity ↓ Signaling ↑ Naive ↑ Memory/plasma cell ratio ↑ Maternal antibody	B-Cell Humoral	↓ Antibody specificity ↓ Antibody affinity ↓ Signaling ↓ Naive ↑ Memory ↓ Switched memory ↑ Auto antibodies ↓ Proliferation
CD4 ↓ Th1 ↑ Th2 ↑ Th17 ↑ Tregs ↑ Naive ↓ Memory ↓ Help for IgG synthesis CD8 ↓ CTL response ↓ IFN-α production	T Cell Cellular	↓ Th1 ↑ Th2 ↑ Th17 ↑ Tregs ↓ Naive ↑ Memory ↓ Proliferation ↑ Chemotaxis

Defective phagocytosis

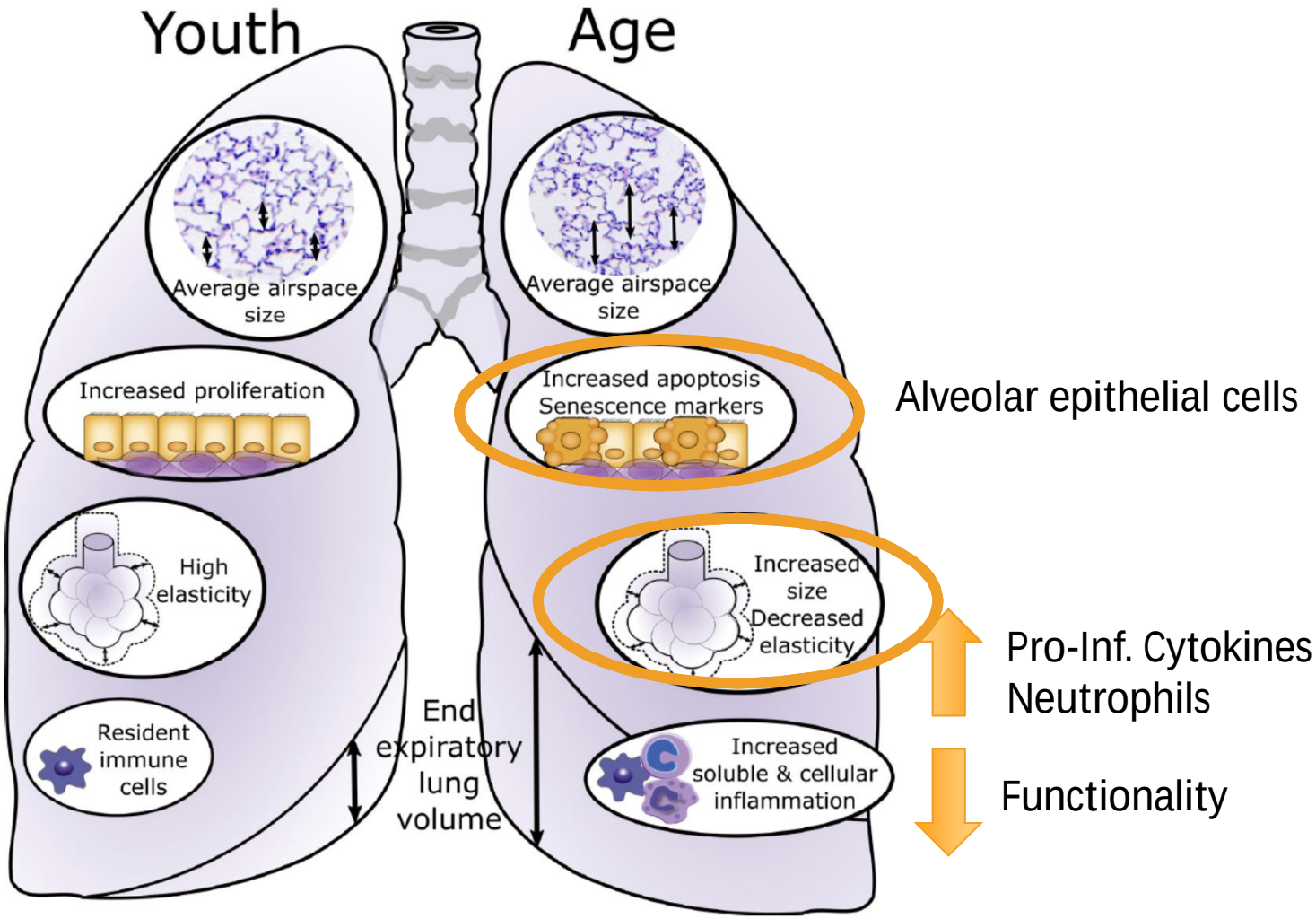
Defective phagocytosis

Reduced functions

Inflammaging

Lower effector functions
Reduced proliferation

The ageing lung



CHEST

Bowdish *Chest* 2019

Mechanisms of diseases in the elderly

- Lower frequency of RSV-specific CD8 T cells
  - Associated with higher viral load in animal models
- Lower frequency of IFN-gamma producing T cells
- Higer production of IL-10 and IL-13
- Low concentration of neutralizing antibodies
  - Higher risk of infection
  - Higher severity
- Inflammaging of the elderly
  - High IL-6 and MIP1-alpha associated with severe RSV disease

Openshaw, Annual Rev Immunol 2017

Mechanisms of diseases in the elderly

RSV neutralizing IgG
RSV mucosal IgA

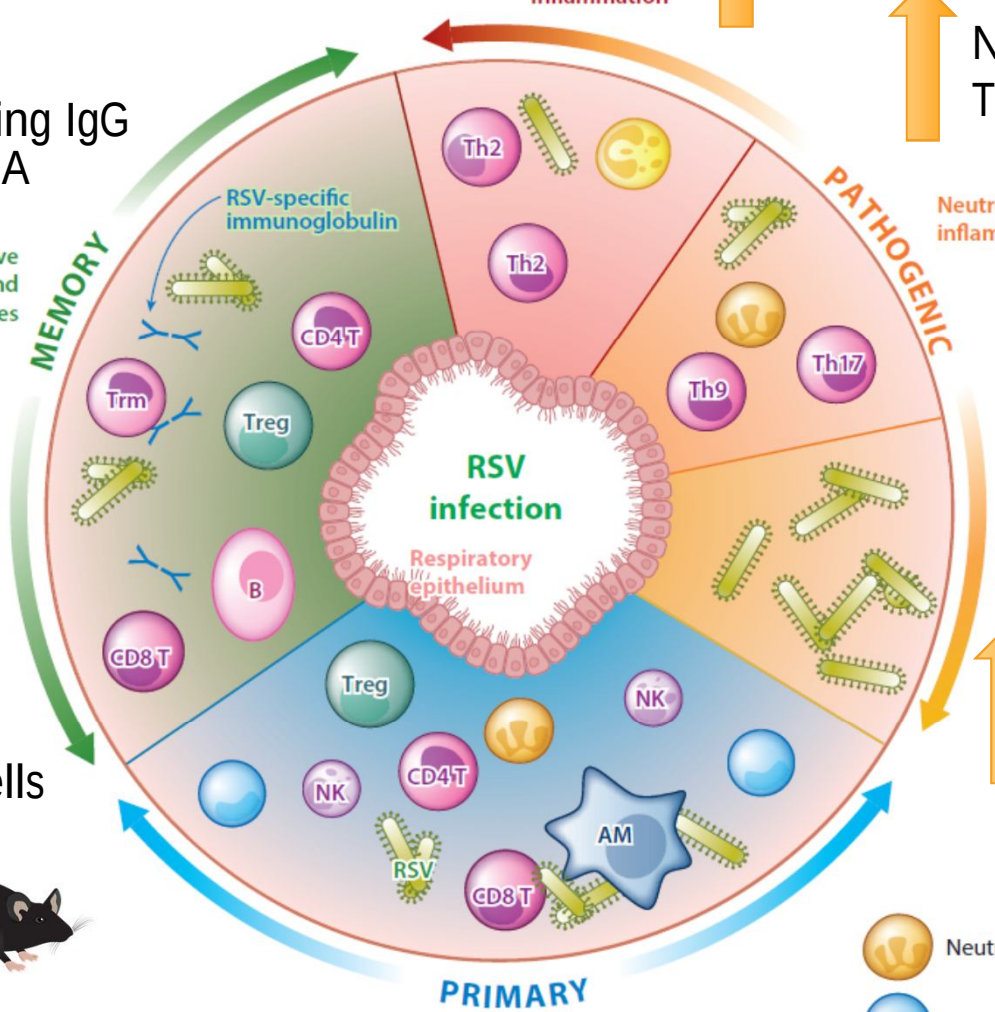
IFN-γ production
by CD4+ T cells

RSV-specific CD8+ T cells

IL-13

Neutrophil infiltration
Tissue Inflammation

IL-6 and MIP1-α



Openshaw, Annual Rev Immunol 2017

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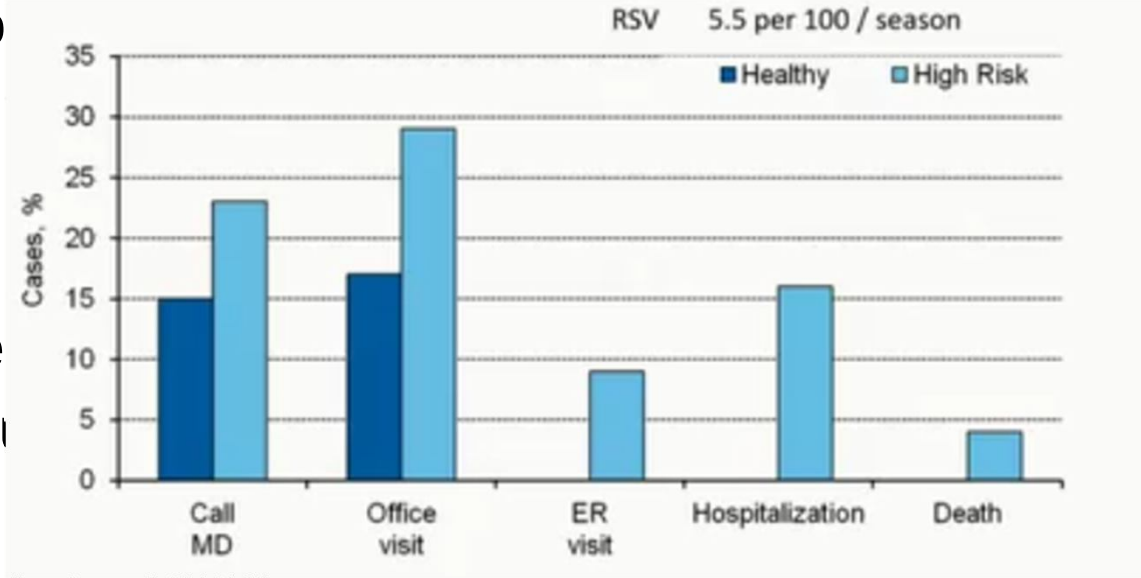
RSV infection in the Elderly & High-Risk adults

Prospective study during 4 consecutive winters (New York)

- Healthy elderly patients (>65 y)
- High risk adults (chro
- Patients hospitalized



RSV infection annually :

- 3-7 % of healthyelde
- 4-10% of high risk ad

- In hospitalized subjects (n=1388) :
- 142/1471 cases of illness (9,6%)
- Similar LOS, ICU admission (15% vs 12%), pneumonia, intubation & mortality (8% vs 7%) as compared to influenza

Falsey *NEJM* 2005

Clinical Infectious Diseases

MAJOR ARTICLE

Severe Morbidity and Mortality Associated With Respiratory Syncytial Virus Versus Influenza Infection in Hospitalized Older Adults

Bradley Ackerson,[1] Hung Fu Tseng,[1] Lina S. Sy,[1] Zendi Solano,[1] Jeff Slezak,[1] Yi Luo,[1] Christine A. Fischetti,[1] and Vivek Shinde[2]

[1]Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena; and [2]Clinical Development, Novavax Inc., Gaithersburg, Maryland

Observational retrospective cohort study

01/2011-06/2015

15 hospitals insurance-owned (KPSC) in South-California

- 4.4 10^6 members

Comparison of RSV (n=645) and influenza (n=1878) positive hospitalized adults > 60 years (PCR)

Ackerson, *CID* 2018

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	RSV (%)	Influenza (%)	P-value
Length of stay > 7 days	**34,4**	**25**	**0,001**
Pneumonia	**47,4**	**25,8**	**<0,001**
Antibiotic use	**94,1**	**88,9**	**<0,001**
Steroids use	**64,5**	**47,9**	**<0,001**
Complications cardiovasculaires	37,7	32,8	0,084
Bacteremia/sepsis	29,1	30	0,75
Acute renal failure	18,9	19,9	0,73
ICU admissison	**18,1**	**14,1**	**0,023**
Mortality 30 days	8,7	7,1	0,49
Home health service	**31**	**25.9**	**0,037**

Ackerson, *CID* 2018

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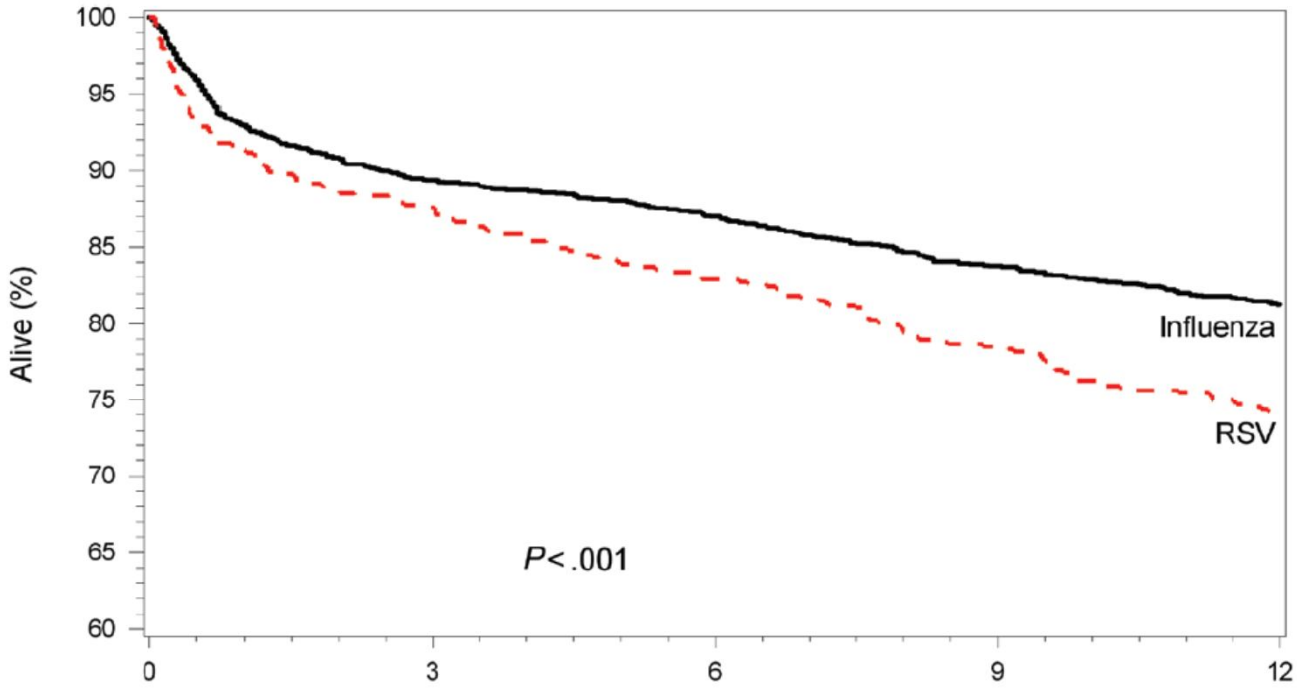
Higher rate of respiratory complication in RSV-infected older adults

	RSV (%)	Influenza (%)	P-value
Highest measured respiratory rate >22 / min	**77.7**	**67.7**	**<0.001**
Greatest level of O2 supplementation >5L	**23.3**	**20.7**	**<0,001**
Lowest oxygen saturation <93%	**74.9**	**65.7**	**<0,001**
Exacerbation of COPD	**16.9**	**10.6**	**<0,001**
Exacerbation of asthma	**16.9**	**10.6**	**<0,001**

Ackerson, *CID* 2018

Long term consequence of RSV infection in older hospitalized adults



Group	Survival Estimate (Number at Risk)				
Influenza	100% (1878)	89.4% (1665)	87.0% (1610)	83.8% (1543)	81.2% (1478)
RSV	100% (645)	87.6% (564)	82.9% (528)	78.5% (495)	74.2% (463)

Mortality 1 year	**25,6%**	**15,9%**	**0,019**

Ackerson, *CID* 2018

Estimates of global burden of RSV

Global burden of disease, 2016

- Number of deaths globally (>70 years)
  - RSV : 22,009
  - Influenza : 24,803
  - *S. pneumoniae* : 494,340

GBD 2016 LRI Collaborators *Lancet Inf Dis* 2018

Systematic review of laboratory-confirmed RSV cases, 2015 :

- 1,5 10^6 cases worldwide
- 336,000 cases hospitalized (186,000-614,000)
- 14,000 in-hospital deaths (5000-50,000)
- Higher hospitalization rate >65 years

Shi et al *JID* 2019

RSV infection in hospitalized adults with severe acute respiratory infection during four influenza seasons in Belgium: prevalence, subtype distribution, risk factors & outcome

Nicolas Dauby[1], Michèle Gérard[1], Marc Bourgeois[2], Bénédicte Delaere[2], Koen Magerman[3], Door Jouck[3], Marijke Reynders[4], Evelyn Petit[4], Patrick Lacor[5], Xavier Holemans[6], Bénédicte Lissoir[6], Isabelle Thomas[7], Cyril Barbezange[7], Nathalie Bossuyt[8]

ECCMID 2019 Amsterdam 04/2019

The Belgian « SARI » network

Aim :

- Surveillance of severe influenza infection (NRC Influenza, Sciensano)

Case definition

- Acute respiratory syndrome in the last 7 days with fever >38°C and cough or dyspnea and requiring hospitalization >24h – no age restriction

Exclusion :

- Noscomial cases

Surveillance begins from the start of the epidemic and ends at least 3 weeks after the end of the epidemic

All subjects underwent nasopharyngeal swab after oral consent

Prospective collection of clinical data : severity, duration of symptoms, vaccinal status, complications, death, LOS, antiviral & antibiotic treatment

Testing for influenza & multiples respiratory viruses (including RSV)

The Belgian « SARI » network

Network of sentinel hospitals located in the 3 regions

- Brussels Capital Region
  - CHU Saint-Pierre
  - UZ Brussel
- Flanders
  - Jessa Ziekenhuis Hasselt
  - AZ Sint-Jan Brugge-Oostende
- Wallonia
  - CHU UCL Namur site Godinne
  - Grand Hôpital de Charleroi

Estimated catchment population : 908.910 (8%)

Aims of the study

1. Assess the prevalence of RSV among SARI cases
2. Substype distribution

3. Risk factors & outcome of RSV cases with comparision with influenza confirmed cases

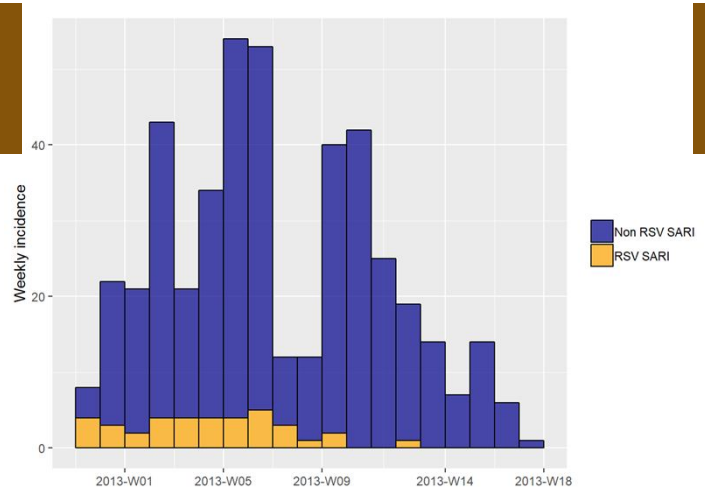
Contribute to report the burden of RSV infection in adults & provide prevaccination data

Results

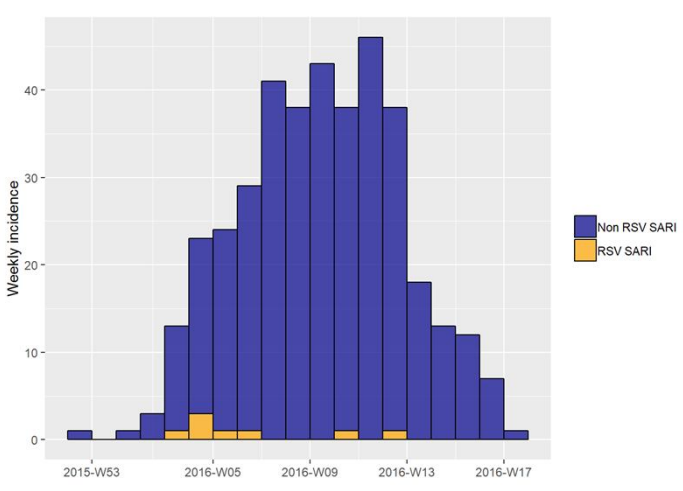
Four seasons analysed :
2012-2013, 2015-2016, 2016-2017 & 2017-2018

Overall RSV prevalence during the 4 seasons :
5.5% (165/3001)

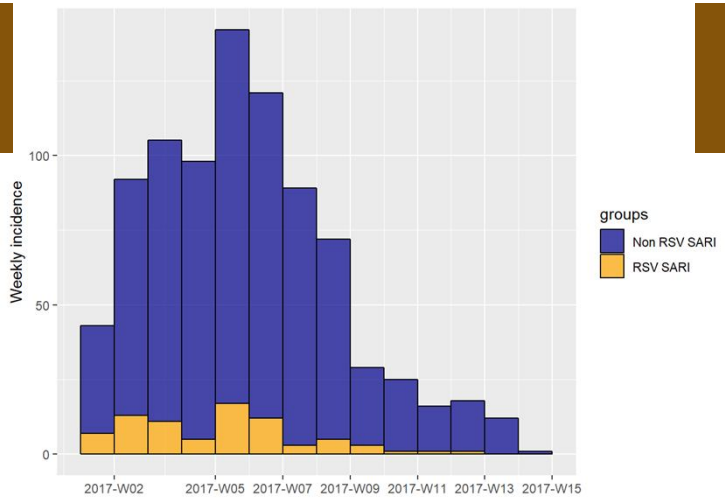
2012-2013
37/448
8.3%



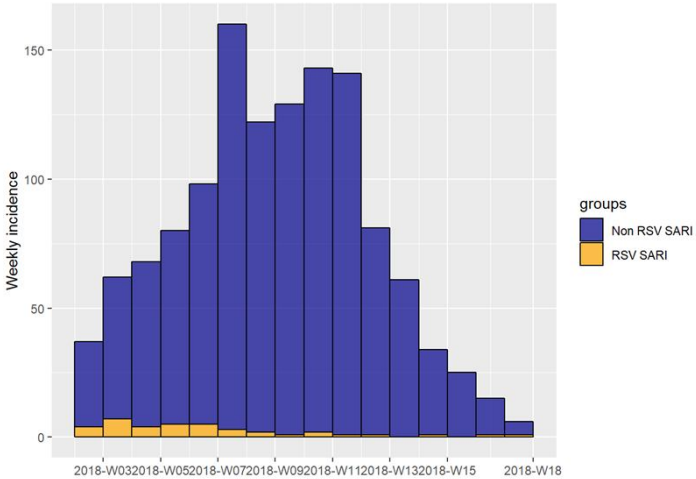
2015-2016
8/389
2.1%



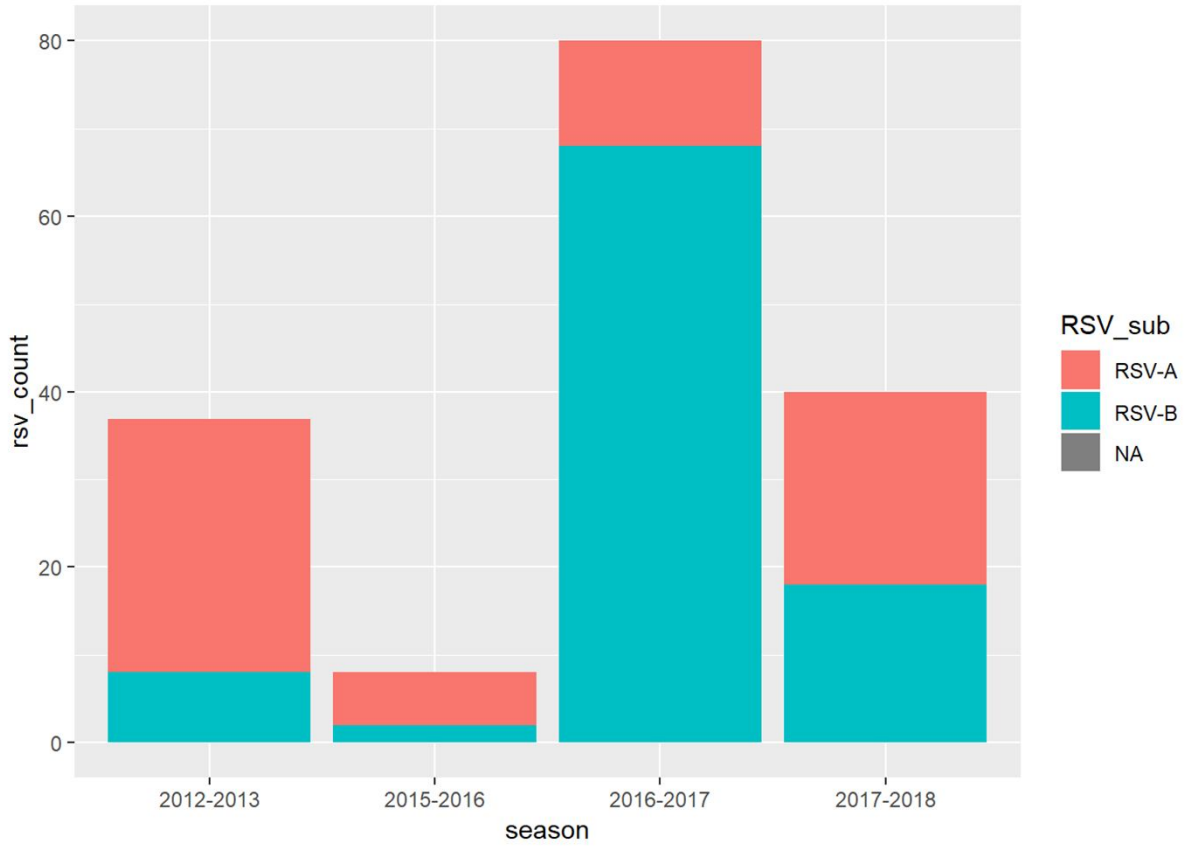
2016-2017
79/863
9.2%



2017-2018
38/1262
3%



RSV subtype distribution accross seasons (absolute numbers)



Risk factors and clinical features

	Influenza No. 1,354	RSV No. 148	P-value
Age	70.0 (±17.5)	71.8 (±16.4)	0.32
Age over 65	432 (32.0%)	37 (25.0%)	0.093
Sex			0.93
NA	57 (4.2%)	5 (3.4%)	
Female	655 (48.4%)	71 (48.0%)	
Male	642 (47.4%)	72 (48.6%)	
Time since symptoms	2.9 (±2.2)	2.6 (±2.1)	0.11
Fever at admission	257 (19.0%)	32 (21.6%)	0.44
History of Fever	**1,118 (82.6%)**	**104 (70.3%)**	**0.0005**
Cough	1,142 (84.3%)	127 (85.8%)	0.72
Dyspnea	**869 (64.2%)**	**110 (74.3%)**	**0.014**
Diabetes	175 (12.9%)	22 (14.9%)	0.52
Obesity	122 (9.0%)	17 (11.5%)	0.30
Lung disease	371 (27.4%)	46 (31.1%)	0.34
Heart Disease	**427 (31.5%)**	**59 (39.9%)**	**0.042**
Immunosuppression	269 (19.9%)	27 (18.2%)	0.74
Asthma	100 (7.4%)	13 (8.8%)	0.51

17 cases co infected excluded

Outcome : higher LOS in RSV-infected subjects

	Influenza No. 1,354	RSV No. 148	
Pneumonia on Rx	318 (23.5%)	37 (25.0%)	0.68
ARDS	46 (3.8%)	5 (3.5%)	1.0
ICU Admission	140 (10.3%)	14 (9.5%)	0.89
LOS	**11.6 (± 12.9)**	**12.7 (± 12.0)**	**0.042**
Death			0.73
Yes	99 (7.3%)	11 (7.4%)	
No	1,167 (86.2%)	115 (77.7%)	
Missing	88 (6.5%)	22 (14.9%)	

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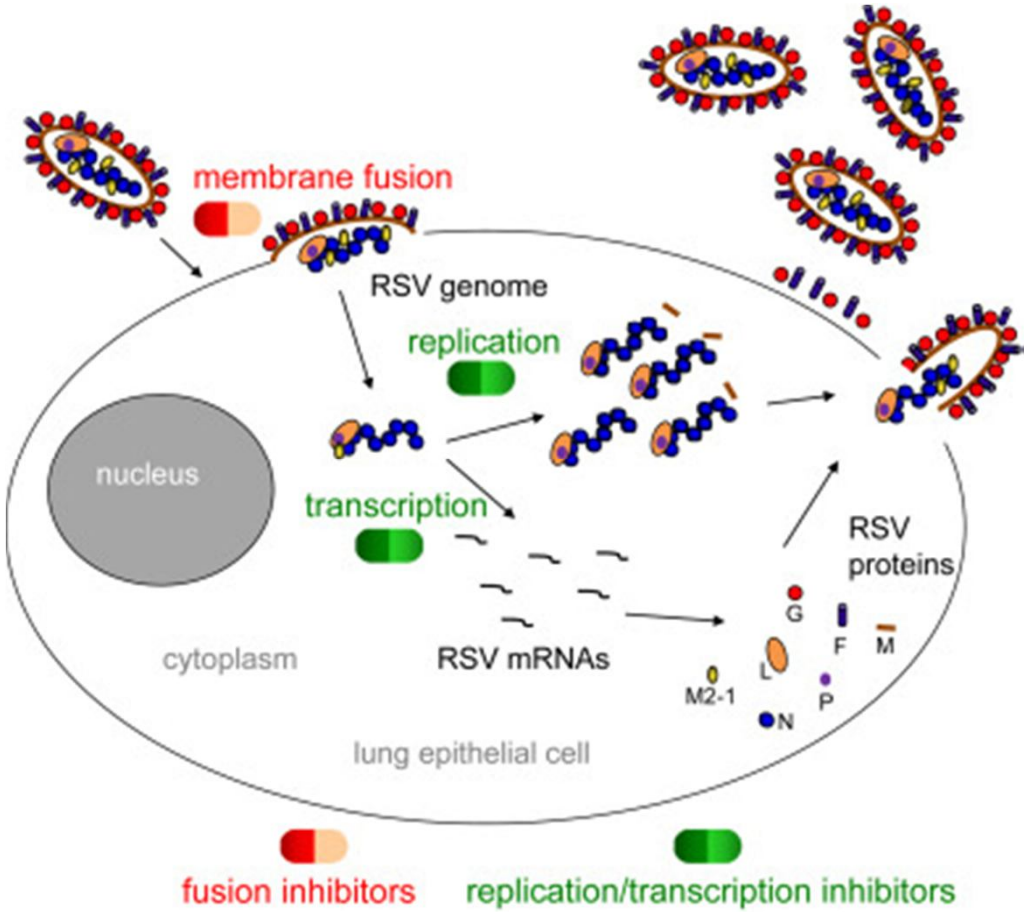
Global Respiratory Syncytial Virus (RSV) Therapeutics Market to Reach US$ 2120.0 Million by 2025, Says TMR

NEWS PROVIDED BY
Transparency Market Research →
Apr 23, 2018, 08:00 ET

RSV replication cycle & therapeutics targets



Fearns & Deval *Antiviral Res* 2016

EMA Guidelines on the clinical evaluation of medicinal products for the treatment of RSV disease

- Antiviral activity should be documented in vitro
- Specific activity (vs other viruses)

- Safety & pharmacokinetics evaluated in healthy adults

- **Human challenge study should be considered in healthy adults**
  - Relatonship between dose, plasma exposure, effect on clinical signs and symptoms
- Confirmatory trials should demonstrate superiority over untreated control group

Oral JNJ-53718678

- Targets Fusion protein (prefusion F)
- Animal model (cotton rats & lambs)

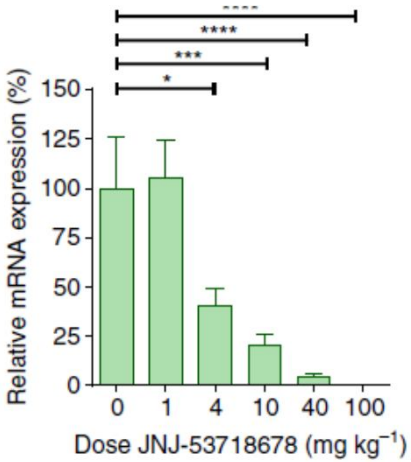
nature COMMUNICATIONS

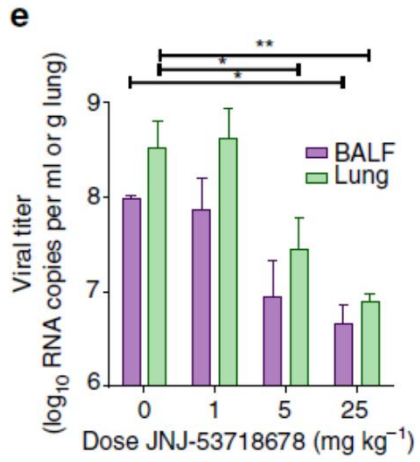
ARTICLE

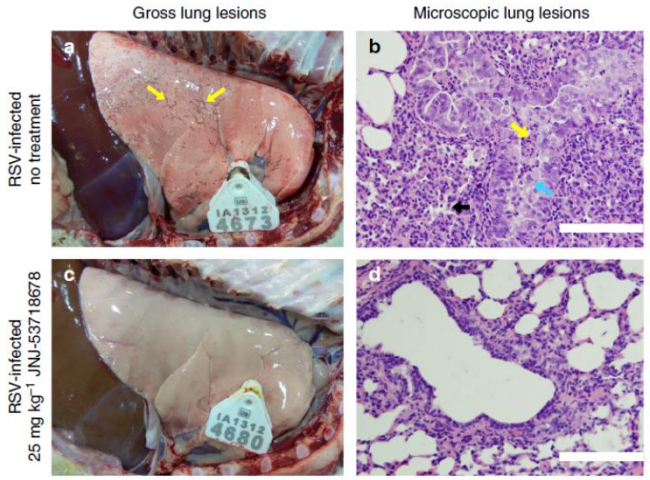
DOI: 10.1038/s41467-017-00170-x OPEN

Therapeutic efficacy of a respiratory syncytial virus fusion inhibitor

Dirk Roymans[1], Sarhad S Alnajjar[2], Michael B Battles[3], Panchan Sitthicharoenchai[2], Polina Furmanova-Hollenstein[4], Peter Rigaux[1], Joke Van den Berg[1], Leen Kwanten[1], Marcia Van Ginderen[1], Nick Verheyen[1], Luc Vranckx[1], Steffen Jaensch[5], Eric Arnoult[6], Richard Voorzaat[4], Jack M. Gallup[2], Alejandro Larios-Mora[2], Marjolein Crabbe[7], Dymphy Huntjens[8], Pierre Raboisson[1], Johannes P. Langedijk[4], Mark R. Ackermann[2], Jason S McLellan[3], Sandrine Vendeville[1] & Anil Koul[1]







Oral JNJ-53718678

- Challenge study (phase 2a) Stevens *JID* 2018
- Three doses (75mg, 200mg, 500mg) vs placebo, orally, 7 days

- Mean VL, duration of viral shedding and mean overall symptom score lower in each group

- Ongoing multicentric phase 2b in RSV infected non hospitalized adults (ROSE study)

rose

RSV Outpatient Subject Exploratory Study

Presatovir - GS-5806 (Gilead)

- Allosteric inhibitor of F protein
  - Block viral entry by inhibiting fusion of the viral enveloppe with host cell membrane

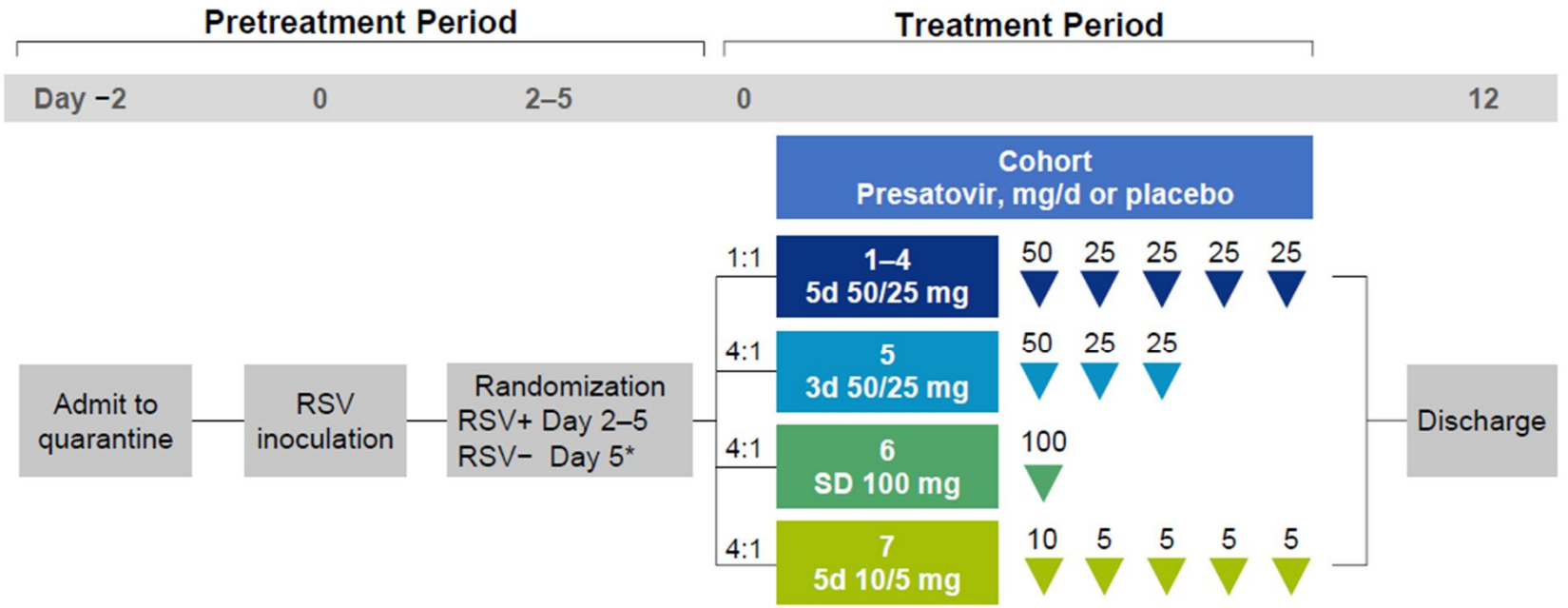
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

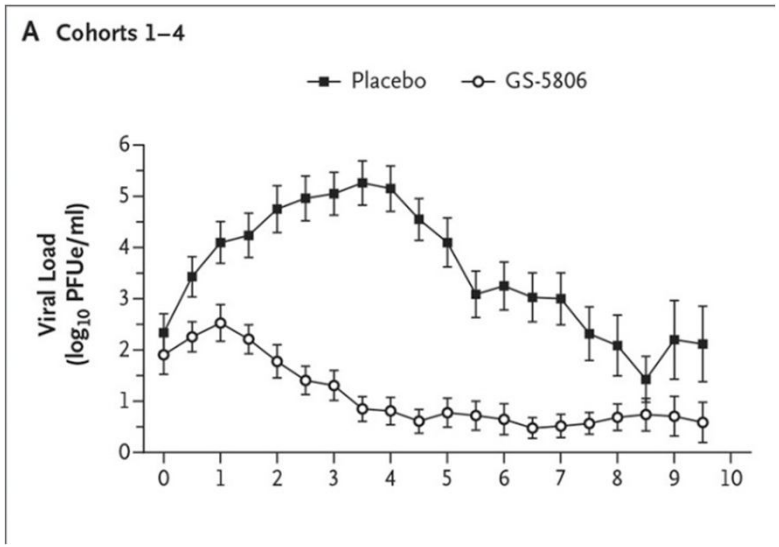
Oral GS-5806 Activity in a Respiratory Syncytial Virus Challenge Study

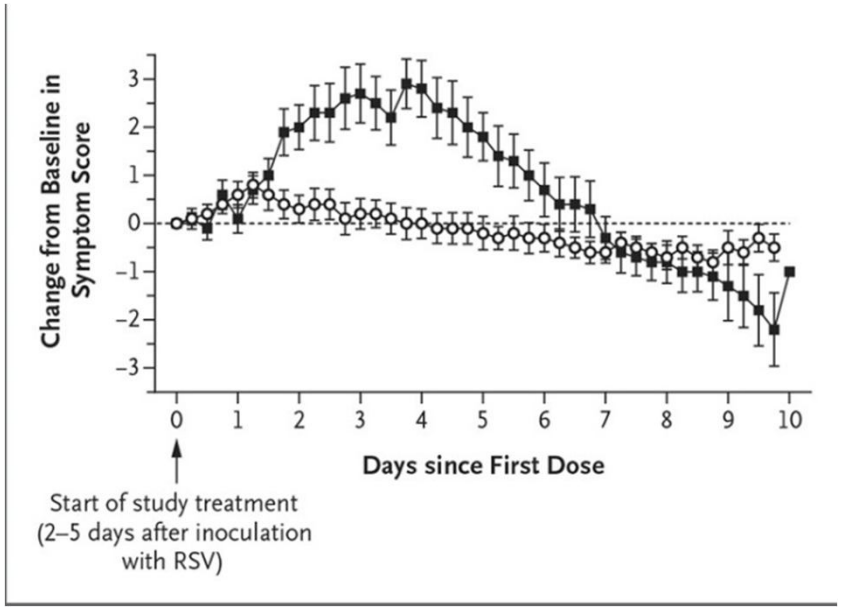
John P. DeVincenzo, M.D., Richard J. Whitley, M.D., Richard L. Mackman, Ph.D., Cecilia Scaglioni-Weinlich, M.D., Lisa Harrison, M.L.T., Eric Farrell, B.S., Stephen McBride, B.S., Robert Lambkin-Williams, Ph.D., Robert Jordan, Ph.D., Yan Xin, Ph.D., Srini Ramanathan, Ph.D., Thomas O'Riordan, M.D., Sandra A. Lewis, M.S., Xiaoming Li, Ph.D., Seth L. Toback, M.D., Shao-Lee Lin, M.D., Ph.D., and Jason W. Chien, M.D.

Challenge Study in Adults: Treatment Model



Slide from Gilead





Doses : 50 mg D1 then 25 mg/d during 4 days
Mean age (all cohorts) : 25 years

Presatovir – Trials (NCT02135614)

A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Trial of Presatovir (GS-5806), a Novel Oral RSV Fusion Inhibitor, for the Treatment of Respiratory Syncytial Virus (RSV) in Hospitalized Adults

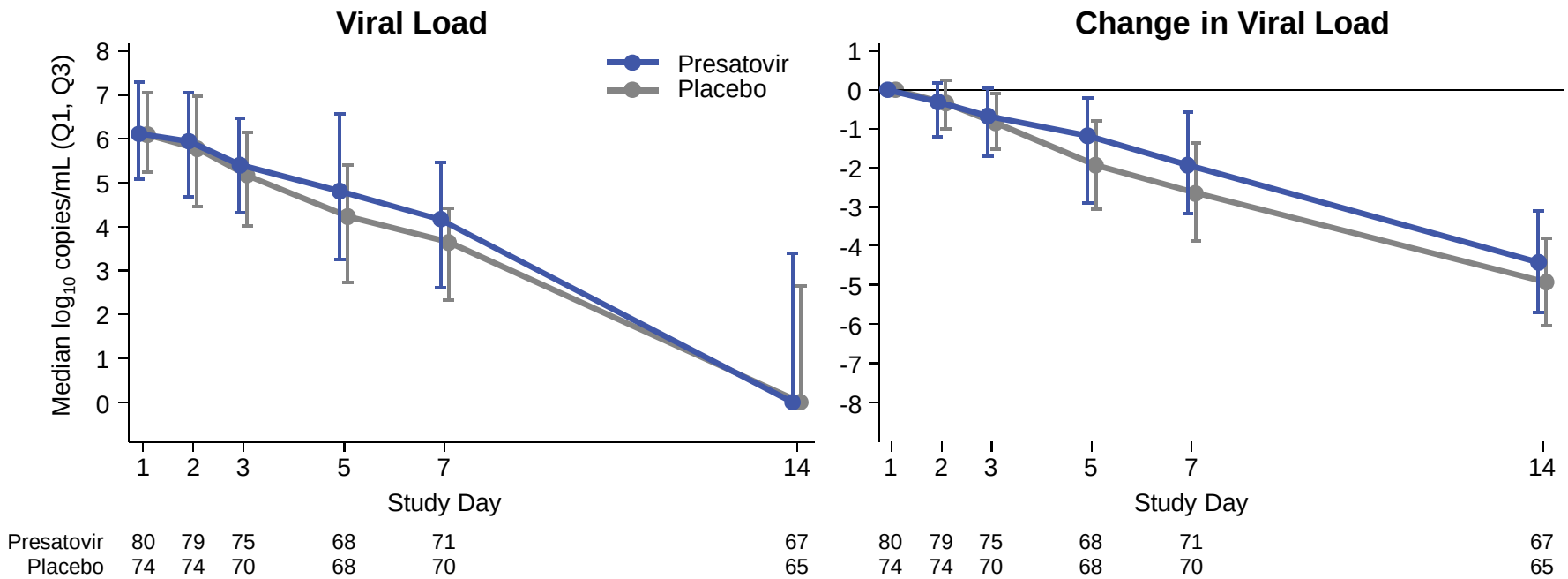
189 subjects worldwide

- 3 days after symptoms
- 200 mg vs placebo (one dose)
- Plasma levels above 4-fold PaEC95 up to day 5
- *No effect on viral load or clinical outcome*

Baseline Demographics & Key Characteristics

	Presatovir, n=92	Placebo, n=94
Mean age, y (SD)	69.4 (14.24)	65.9 (13.87)
Male, n (%)	42 (46)	42 (45)
Lung disease classification, n (%)		
No chronic lung disease	31 (34)	31 (33)
Asthma	22 (24)	22 (23)
COPD	27 (29)	30 (32)
Other chronic lung disease	12 (13)	11 (12)
Mean baseline O_2 saturation %, (SD)	93 (3.5)	93 (3.7)
Mean baseline Flu-PRO Score, (SD)	1.11 (0.553)	1.04 (0.566)
Smoking history, n (%)		
Current smoker	10 (11)	17 (18)
Former smoker	42 (46)	35 (37)
Never	39 (42)	39 (42)
Missing	1 (1)	3 (3)
Median duration of hospitalization prior to 1st study drug dose, days (Q1, Q3)	2.0 (2.0, 3.0)	2.0 (1.0, 3.0)

Primary Endpoint: DAVG5



	Presatovir, n=80	Placebo, n=74	p-Value
Mean DAVG5 (SD)	-0.78 (1.069)	-0.90 (0.872)	p=0.46
Treatment difference	0.12		

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AMERICAN JOURNAL OF EPIDEMIOLOGY
Vol. 89, No. 4

Printed in U.S.A.

RESPIRATORY SYNCYTIAL VIRUS DISEASE IN INFANTS DESPITE PRIOR ADMINISTRATION OF ANTIGENIC INACTIVATED VACCINE[1, 2]

HYUN WHA KIM, JOSE G. CANCHOLA[3], CARL D. BRANDT, GLORIA PYLES, ROBERT M. CHANOCK, KEITH JENSEN, AND ROBERT H. PARROTT[4]

(Received for publication August 8, 1968)

Kim, H. W., J. G. Canchola, C. D. Brandt, G. Pyles, R. M. Chanock, K. Jensen and R. H. Parrott (Children's Hosp. of D.C., Wash., D.C. 20009). Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. *Amer. J. Epid.*, 1969, 89: 422–434.—In response to three injections of alum precipitated, 100X concentrated, formalin inactivated RS vaccine (lot 100), 43% of infant vaccinees displayed a 4-fold or greater rise in serum neutralizing antibody and 91% displayed a 4-fold or greater rise in serum CF antibody. When RS virus became prevalent in the community, the rate of RS virus infection in infants who received this vaccine was not remarkably different from that in control infants who received parainfluenza vaccines. However, 80% of RS vaccinees required hospitalization at the time of RS infection whereas only 5% of such infections among parainfluenza vaccinees resulted in admission to the hospital. Illnesses among the RS vaccinees who underwent natural infection included pneumonia, bronchiolitis, and bronchiolitis with pneumonia in a majority and rhinitis, pharyngitis and bronchitis in a few. It seems clear that infants who received this vaccine were not protected against natural infection and also, when they became naturally infected their illness was more severe than that seen in cohorts who received a similar parainfluenza type 1 vaccine. These findings indicate that vaccine-induced RS virus serum antibody alone does not protect against illness and suggest that serum antibody without local respiratory antibody may play a part in the production of disease. We have also observed that the highest incidence of serious RS virus illness occurring naturally is under six months of age when maternally derived serum antibody is present. These findings together suggest that RS virus illness in infants is an immunologic phenomenon wherein the virus and serum antibody interact to produce severe illness.

The severity of illness in the RS vaccinees was greater than in unvaccinated infants and children who were admitted to the hospital during the community wide outbreak of RS virus infection. The mean period of hospitalization of the RS vaccinees was 10.5 days, whereas the mean period of 30 age-matched unvaccinated infants with RS bronchiolitis and/or pneumonia was 6.7 days.

Two infants died, one at age 14 months, the other at age 16 months. Each had received three inoculations, one beginning at

RSV Discovered in 1957
During 50 years : only 2 products licensed to prevent RSV

- RSV-IVIG
- Palivizumab

The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates

Natalie I Mazur, Deborah Higgins, Marta C Nunes, José A Melero, Annefleur C Langedijk, Nicole Horsley, Ursula J Buchholz, Peter J Openshaw, Jason S McLellan, Janet A Englund, Asuncion Mejias, Ruth A Karron, Eric AF Simões, Ivana Knezevic, Octavio Ramilo, Pedro A Piedra, Helen Y Chu, Ann R Falsey, Harish Nair, Leyla Kragten-Tabatabaie, Anne Greenough, Eugenio Baraldi, Nikolaos G Papadopoulos, Johan Vekemans, Fernando P Polack, Mair Powell, Ashish Satav, Edward E Walsh, Renato T Stein, Barney S Graham, Louis J Bont; in collaboration with Respiratory Syncytial Virus Network (ReSViNET) Foundation

What immunological endpoints for RSV vaccine studies ?

- Critical role of serum neutralizing antibodies
  - Variability of neutralisation assay

- Protective role of mucosal IgA

- No definitive treshold of protection defined
  - Only clinical trials will inform !

Mazur *Lancet Inf Dis* 2018

Science Translational Medicine

INFECTIOUS DISEASE

Prefusion F–specific antibodies determine the magnitude of

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Julie E. Ledgerwood,[1] Jas

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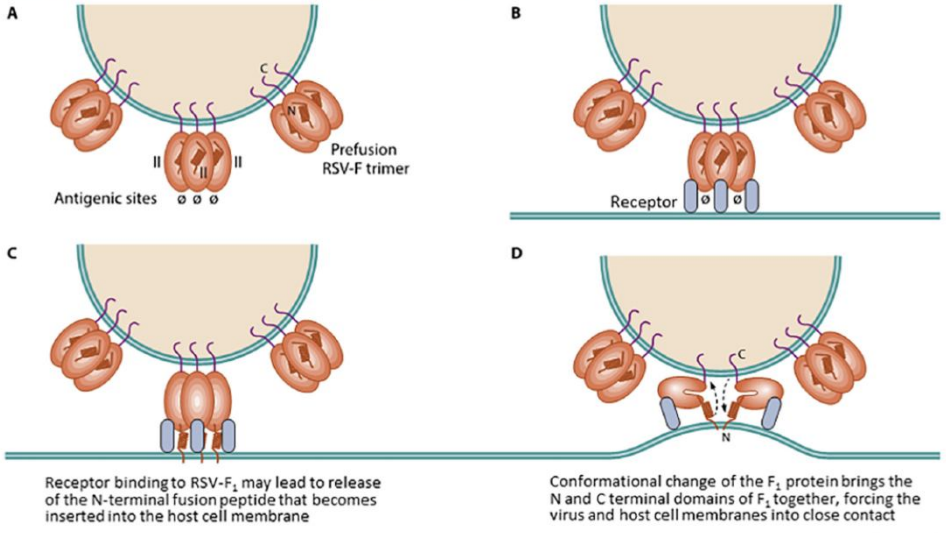

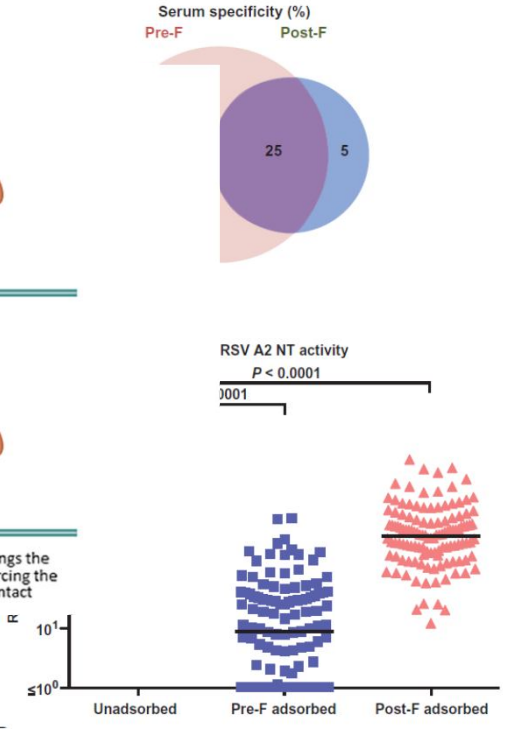

Ngwuta *STM* 2015

	Target Population	Pre-F Immunity[35]	Immune response	Mucosal/systemic
Particle-based				
RSV F nanoparticle (Novavax)	M	Pre-F<post-F	Broadly neutralising antibodies	Systemic
RSV F nanoparticle (Novavax)	O	Pre-F<post-F	Broadly neutralising antibodies	Systemic
RSV F nanoparticle (Novavax)	P	Pre-F<post-F	Broadly neutralising antibodies	Systemic
SynGEM (Mucosis)	O and P	Unclear F conformation	Activation of B and T cells; local secretion of neutralising IgA in the nose; production of IgG neutralising IgG in the blood	Mucosal and systemic
Vector-based				
MVA-BN RSV (Bavarian Nordic)	O	Pre-F<post-F	B and T cell response; antibodies against 5 RSV antigens	Systemic
ChAd155-RSV (GSK)	O	Pre-F>post-F	B and T cell response; neutralising antibodies against F antigen; CD8 T cells against F, N and M2-1 antigens	Systemic
VXA-RSVf oral (Vaxart)	O	Pre-F<post-F	B and T cell immunity, protection at mucosal surface	Mucosal>systemic
Ad26.RSV.preF (Janssen)	P	Pre-F	B and T cells	Systemic
Ad26.RSV.preF (Janssen)	O	Pre-F	B and T cells	Systemic
Subunit				
GSK RSV F (GSK)	M	Pre-F	B and T cell response	Systemic
DPX-RSV (Dalhousie University, Immunovaccine, and VIB)	O	None	B cell response specific to SHe antigen	Systemic
RSV F DS-Cav1 (NIH/NIAID/VRC)	O and M	Pre-F	Pre-F-specific serum neutralising antibodies, and CD4 T cells	Systemic
Live-attenuated				
rBCG-N-hRSV (Pontificia Universidad Catolica de Chile)	P	Pre-F and post-F	B and T cell response; Th1 polarised response; antibodies against N, F, G	Systemic
RSV D46 cp ΔM2-2 (Sanofi Pasteur/LID/NIAID/NIH)	P	Pre-F and post-F	B and T cell response; enhanced antibody production due to increased antigen production from M2-2 deletion	Mucosal and systemic
RSV LID ΔM2-2 1030s (Sanofi Pasteur/LID/NIAID/NIH)	P	Pre-F and post-F	B and T cell response; enhanced antibody production due to increased antigen production from M2-2 deletion	Mucosal and systemic
RSV ΔNS2 Δ1313/I1314L (Sanofi Pasteur/LID/NIAID/NIH)	P	Pre-F and post-F	B and T cell response	Mucosal and systemic
RSV D46 ΔNS2 N ΔM2-2-HindIII (Sanofi Pasteur/LID/NIAID/NIH)	P	Pre-F and post-F	B and T cell response; enhanced antibody production due to increased antigen production from M2-2 deletion	Mucosal and systemic
RSV LID cp ΔM2-2 (Sanofi Pasteur/LID/NIAID/NIH)	P	Pre-F and post-F	B and T cell response; enhanced antibody production due to increased antigen production from M2-2 deletion	Mucosal and systemic

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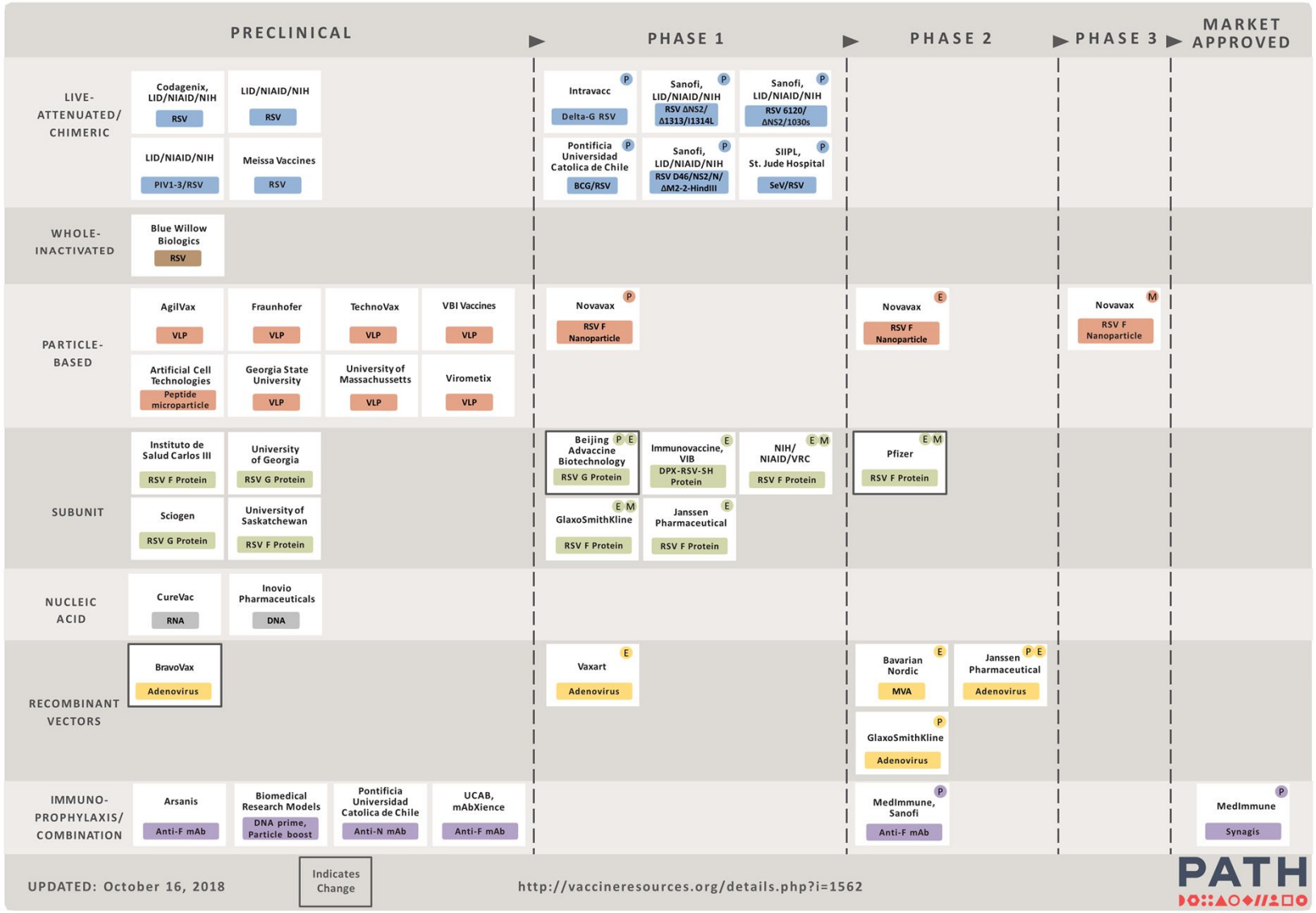
RSV Vaccine and mAb Snapshot

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



UPDATED: October 16, 2018

Indicates Change

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

PATH

	Vaccine type
Pregnant mothers	
RSV F nanoparticle (Novavax)	Particle-based
GSK RSV F (GSK)	Subunit
RSV F DS-Cav1 (NIH/NIAID/VRC)	Subunit
Paediatric	
RSV F nanoparticle (Novavax)	Particle-based
ChAd155-RSV (GSK)	Vector-based
SynGEM (Mucosis)	Particle-based
Ad26.RSV.preF (Janssen)	Vector-based
rBCG-N-hRSV (Pontificia Unversidad Catolica de Chile)	Chimeric
RSV D46 cp ΔM2-2 (Sanofi Pasteur/LID/NIAID/NIH)	Live-attenuated
RSV LID ΔM2-2 1030s (Sanofi Pasteur/LID/NIAID/NIH)	Live-attenuated
RSV ΔNS2 Δ1313 I1314L(Sanofi Pasteur/LID/NIAID/NIH)	Live-attenuated
RSV D46/NS2/ N/ΔM2-2-HindIII (Sanofi Pasteur/LID/NIAID/NIH)	Live-attenuated
RSV LID cp ΔM2-2 (Sanofi Pasteur/LID/NIAID/NIH)	Live-attenuated
MEDI8897 (MedImmune)	Monoclonal antibody
Older adults	
RSV F nanoparticle (Novavax)	Particle-based
SynGEM (Mucosis)	Particle-based
MVA-BN RSV (Bavarian Nordic)	Vector-based
VXA-RSVf oral (Vaxart)	Vector-based
Ad26.RSV.preF (Janssen)	Vector-based
DPX-RSV-Protein (Immunovaccine, VIB and Dalhousie University)	Subunit
RSV F DS-Cav1 (NIH/NIAID/VRC)	Subunit

Recent vaccine candidates that failed...

	Company/ sponsor	Vaccine type	Mechanism of action	Clinical trial phase	NCT	Trial design, name	Dates	Study population	Administration/ dosing	Location	Clinical endpoint
REGN2222 (suptavumab)	Regeneron	mAb	mAb against antigenic site V	3	NCT02325791	Double-blind, placebo-controlled trial (NURSERY)	July, 2015–July, 2017	1149 healthy preterm infants<6 months of age with a gestational age ≤35 weeks, not eligible to receive palivizumab prophylaxis	Administered once or twice during the RSV season	250 sites in 19 countries	Medically attended RSV infections through day 150 of life
RSV F nanoparticle for older adults	Novavax	Particle-based	Aggregates of full-length post-F	3	NCT02608502	Double-blind placebo-controlled trial (RESOLVE, RSV-E-301)	Nov, 2015–Dec, 2016	11 850 participants ≥60 years of age	135 µg via IM injection	60 US sites	RSV ms-LRTD for 182 days follow-up
MEDI-7510	MedImmune	Subunit	Soluble (unaggregated) postfusion (post-F) conformation of the F protein with a TLR4 agonist adjuvant	2b	NCT02508194	Double-blind placebo-controlled trial	Sept, 2015–Nov, 2016	1900 adults ≥60 years	Single IM injection	61 study sites in 7 countries (North America, Europe, South Africa, and Chile)	RSV-associated respiratory illness between 14 days post vaccination throughout the end of the surveillance period, approximately 7 months

IM=intramuscular. ms-LRTD= moderate-severe lower respiratory tract disease. RSV=respiratory syncytial virus. mAb=monoclonal antibody.

Table 1: Recent vaccine candidates that failed to meet efficacy endpoints in late-phase clinical trials

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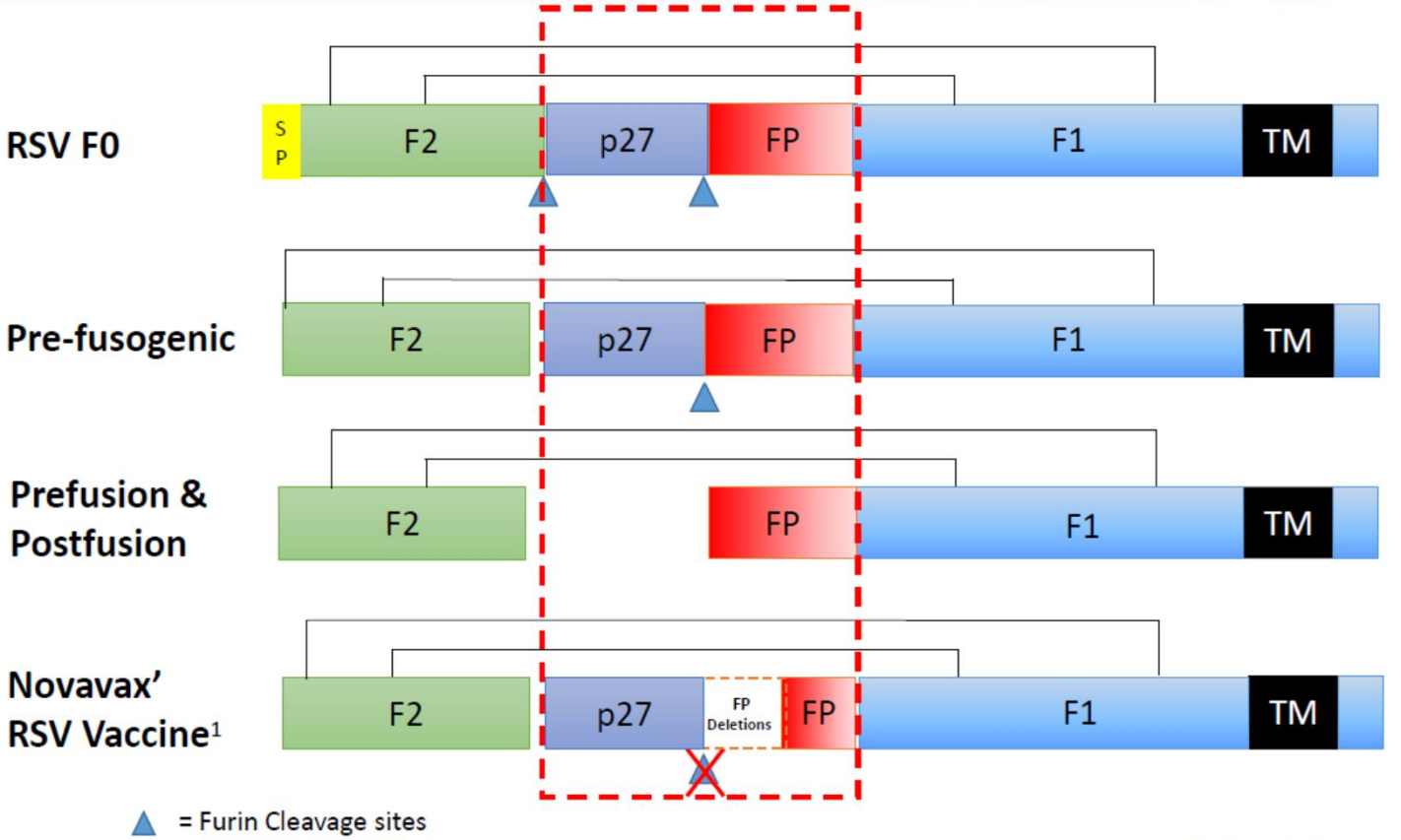
F Protein States Found in Nature: The Novavax RSV Vaccine is Similar to the Prefusogenic F



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Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Respiratory syncytial virus fusion nanoparticle vaccine immune responses target multiple neutralizing epitopes that contribute to protection against wild-type and palivizumab-resistant mutant virus challenge

Brian E. Gilbert [a], Nita Patel [b], Hanxin Lu [b], Ye Liu [c], Mimi Guebre-Xabier [b], Pedro A. Piedra [d], Gregory Glenn [b], Larry Ellingsworth [b], Gale Smith [b,*]

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E-205 RSV Phase 2 trial (2017)

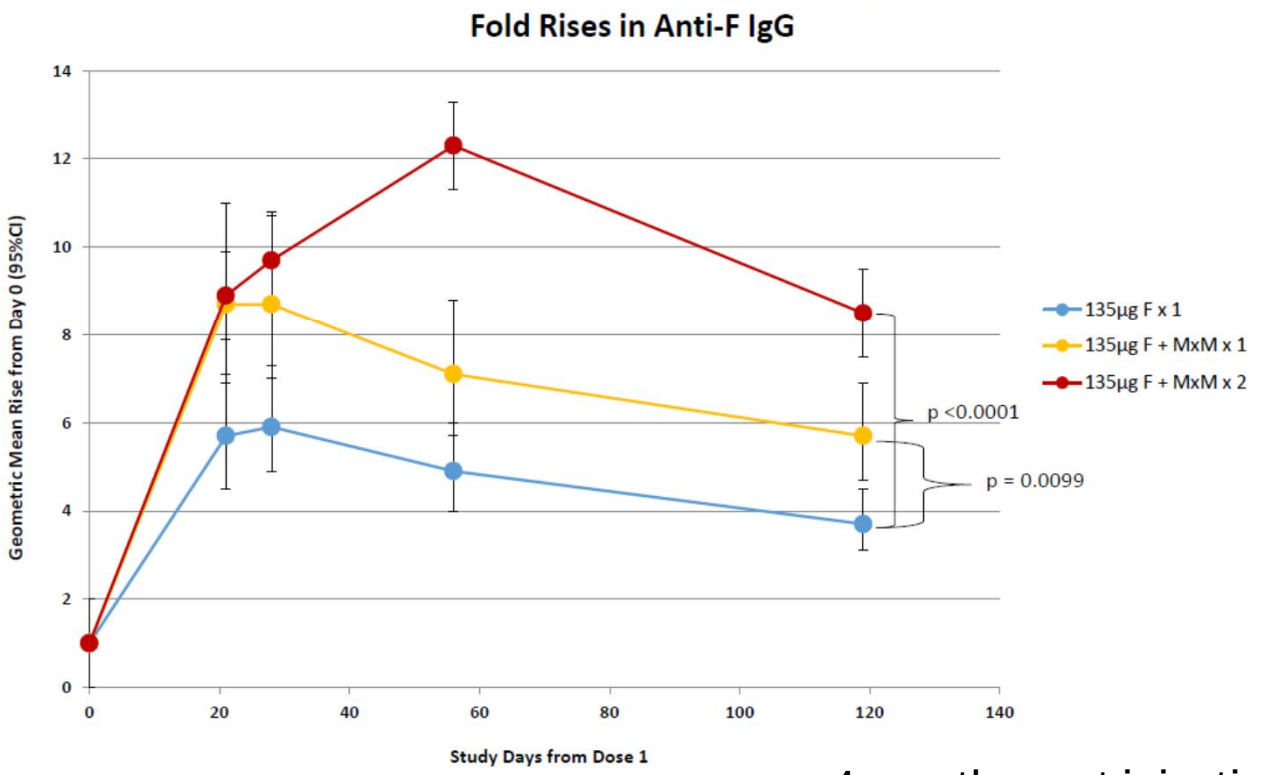
- 300 healthy older adults
- Effect of doses & adjuvant on immune responses

E-205 Treatment Groups

	Study Day	Day 0			Day 21		
Treatment Group	Subjects Per Group	RSV F Dose	Aluminum Dose	Matrix-M1 Dose	RSV F Dose	Aluminum Dose	Matrix-M1 Dose
A	25	135 µg	0	0	0	0	0
B	25	95 µg	0.3 mg	0	0	0	0
C	25	95 µg	0.3 mg	0	95 µg	0.3 mg	0
D	25	120 µg	0.4 mg	0	0	0	0
E	25	120 µg	0.4 mg	0	120 µg	0.4 mg	0
F	25	135 µg	0	50 µg	0	0	0
G	25	135 µg	0	50 µg	135 µg	0	50 µg
H	25	65 µg	0	50 µg	0	0	0
J	25	65 µg	0	50 µg	65 µg	0	50 µg
K	25	35 µg	0	50 µg	0	0	0
L	25	35 µg	0	50 µg	35 µg	0	50 µg
M (Placebo)	25	0	0	0	0	0	0
Total	300 Subjects						

E-205 RSV Phase 2 trial (2017)

Kinetics of Anti-F IgG in Representative Groups:
Adjuvant Effect, 2nd Dose Effect and Durability of Responses Enhanced



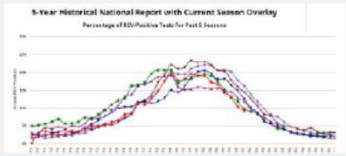
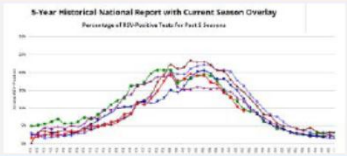
4 months post injection

Resolve Trial (E-301, Novavax)

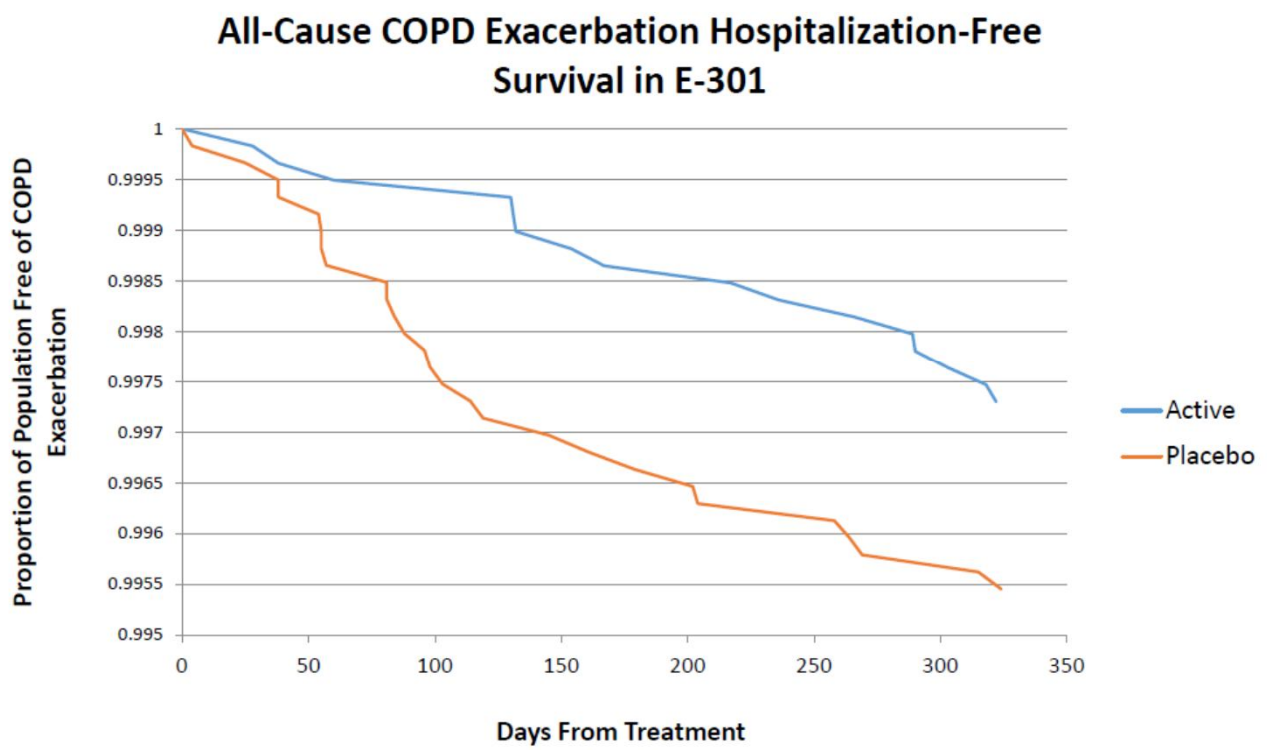
Summary of Primary and Secondary Objectives – Vaccine Efficacy				
	Number of Participants - ITT Population (11,856)			
Primary and Secondary Objectives	**Placebo (5,935)**	**Vaccine (5,921)**	**Vaccine Efficacy (CI)**	**P-Value**
Primary: RSV msLRTD, N(%)	26 (0.44%)	28 (0.47%)	-7.9 % (-84, 37)	0.78
Secondary: RSV ARD, N(%)	117 (1.97%)	102 (1.72%)	12.6 % (-14, 33)	0.32

135µg IM

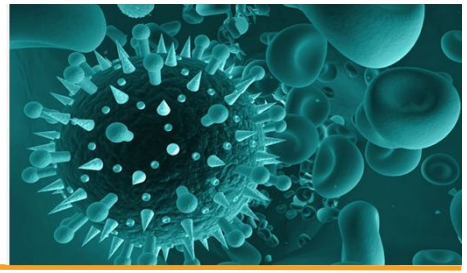
Hypothesis for Outcomes

		2014-2015		2015-2016
RSV OA Attack Rates	RSV ARD RSV msLRTD	**E-201** 4.9% 1.8%	Lower in 2015/16 on basis of trial data; confirmed by external data	**E-301** 2.0% 0.4%
RSV Circulation			Similar on basis of RSVAlert® data	
RSV Susceptibility	MN-B (GMT) baseline	**E-201** 267	Lower in 2015/16 on basis of RSV/B MN data	**E-301** 447
Vaccine Efficacy	RSV ARD RSV msLRTD	**E-201** 41% 64%	Lower in 2015/16 on basis of trial data	**E-301** 12.6% -7.9%

COPD Hospitalizations in E-301



RSV : Conclusions



- Frequent in elderly adults
- Burden similar to influenza infection
- High morbidity & mortality in subjects with risk factors
  - Heart diseases
  - COPD-Asthma

- Probably still underdiagnosed
  - Molecular testing are required !
  - Antigenic test only validated for children !

- Treatment & prophylactic vaccines soon available
  - Critical to identify high-risk gourp
  - Use appropriate diagnosis tests
- Upcoming vaccine trials should include various seasons

Acknowledgements

Dr S. De Breucker
Dr M. Surquin

Pr A. Marchant

Dr V. Martinet
Dr J. Caillet
Pr JP Praet

Dr C. Barbezange
Dr I. Thomas
Dr N. Bossuyt
SARI Network collaborators

Dr L. Busson
Dr. C. Montesinos