Imperial College London

CRI

MRC & Asthma UK Centre in Allergic Mechanisms of Asthma

*Early life infections and asthma risk*
**Monday 9th January 2012**

# RSV

## – a cause of recurrent wheeze?

Peter Openshaw
p.openshaw@imperial.ac.uk

wellcome trust

## Outline

**Background:** why RSV is special
- Epidemiology and clinical features
- Global importance

**The mouse model**
- Fundamental insights
- Plausible and relevant mechanisms

**Evidence** that that RSV does cause long-term disease

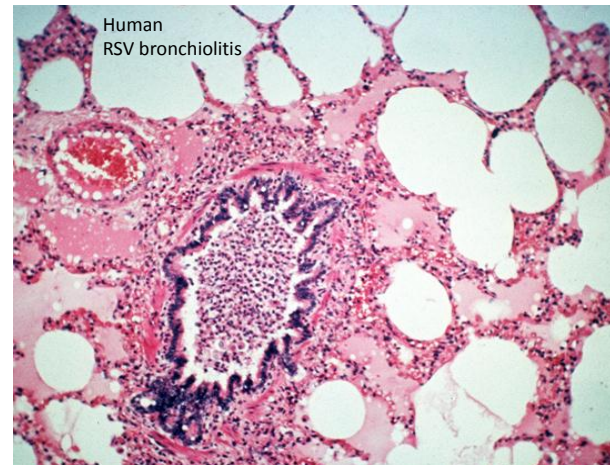
## Respiratory Syncytial Virus (RSV)

- World-wide distribution, winter epidemics
- Infects 65% of children in first year of life
- Two serogroups, but reinfects with ease

**Causes:**

- Hospital admission in 2-3% of infants
- 70% of bronchiolitis in infancy
- Coughs and colds in adults
- Wheezy RTI in kids <5 years, asthmatics *etc*

3




## Global impact of RSV disease

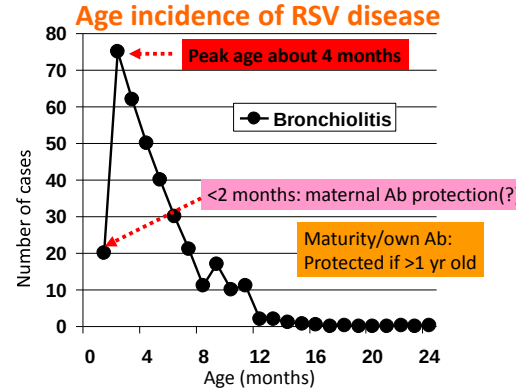
*WHO estimates*

– 1 in 5 of all childhood ALRIs
– 64 million episodes of ALRI in under 5s
  • Twice the impact of *Pneumococcus*
  • Four times the impact of *Haemophilus*
– 3-4 million RSV hospitalisations
– 160,000 child deaths

**99% of RSV deaths are in developing countries**

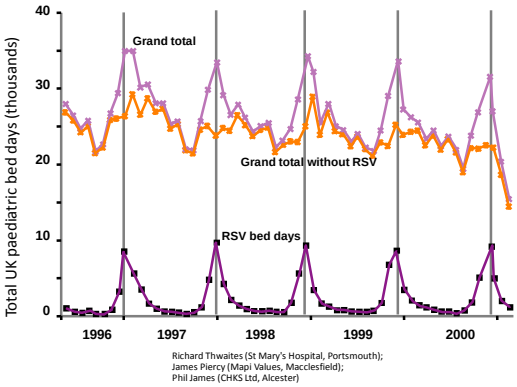
www.thelancet.com Published online April 16, 2010 DOI:10.1016/S0140-6736(10)60206-1

## Age incidence of RSV disease




Data from Parrott et al *Am J Epidemiol* 1973; **98**:289

## Bed days for RSV and all paediatric admissions




## Age-Specific Annual Deaths in USA

| Age | All Flu | RSV |
|---|---|---|
| <1 | 39 | 335 |
| 1-4 | 91 | 32 |
| 5-49 | 1 061 | 641 |
| 50-64 | 3 084 | 1 816 |
| ≥65 | 39 977 | 11 199 |
| **Total** | 44 252 | 14 028 |

Thompson et al JAMA 2003

**Anne Falsey, Rochester USA**

## RSV in the over 65s

Each year, RSV causes:

- 3-10% of colds in the elderly
- Progresses to wheezing, progressive hypoxia
- 300,000 US hospitalisations (30% with CXR 'pneumonia')

**Pathogenesis:** Similar to the FI-RSV disease

- Strong Th2 response
- Innate response is prolonged (high IL-6 levels at day 28)
- Prolonged low-level viral presence

**Risk factors:**

- COPD/heart failure
- exposed to young children
- Low serum neutralising antibody

*Boosting antibody with vaccination might be beneficial.*

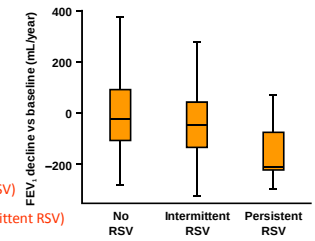
*RSV global symposium, 2nd December 2010, Rotterdam*

**Respiratory Syncytial Virus, Airway Inflammation, and $FEV_1$ Decline in Patients with Chronic Obstructive Pulmonary Disease** Am J Resp Crit Care Med (2006) 173: 871

Tom M. A. Wilkinson, Gavin C. Donaldson, Sebastian L. Johnston, Peter J. M. Openshaw, and Jadwiga A. Wedzicha

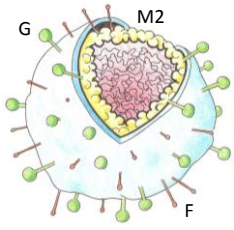
Academic Unit of Respiratory Medicine, University College London; and Department of Respiratory Medicine, National Heart and Lung Institute, Imperial College, London, United Kingdom

- 88 COPD patients (from East London)
- Prospective study, 14-month duration
- Daily diary cards
- Sputum samples every 3 months
  - 272 samples collected
    - quantitative microbiology
    - RSV by qualitative PCR




- 12 RSV + in all samples ('persistent' RSV)
- 42 RSV +, but not not all sputa (intermittent RSV)
- 34 patients were RSV negative throughout (RSV free)

## RSV




- Re-infects despite serum antibody
- Formalin treated vaccine made disease worse
- Ex-bronchiolitics often wheeze/asthma Dx
- May persist in some children/COPD patients

*Can respiratory viral infections initiate the process of airway inflammation that leads to asthma?*

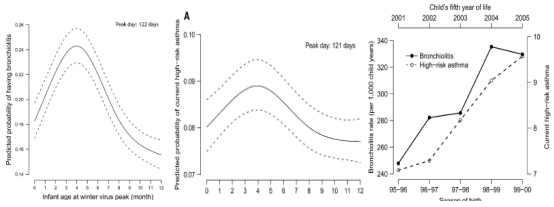
## The evidence :

- Epidemiology
- Plausible mechanisms
- Interventional clinical studies

Am J Respir Crit Care Med 178:1123-1129 (2008)

## Evidence of a Causal Role of Winter Virus Infection during Infancy in Early Childhood Asthma

Pingsheng Wu[1,2,3], William D. Dupont[3,6], Marie R. Griffin[2,4,5,6], Kecia N. Carroll[7], Edward F. Mitchel[6], Tebeb Gebretsadik[3], and Tina V. Hartert[1,2,4,3]

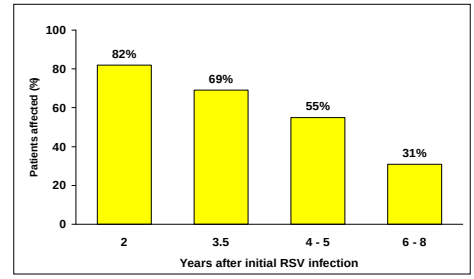



*95,310 children 5 winter seasons*

*Asthma risk peaked in those aged 4/12 at height of winter colds season*

*Age at winter virus peak was = or >any other known risk factor for asthma*

## Recurrent Lower Respiratory Symptoms After RSV Bronchiolitis




Henry, et al. *Arch Dis Child*. 1983; 58:713
Webb, et al. *Arch Dis Child*. 1985; 60:1064
Hall, et al. *J Pediatr*. 1984;105:358

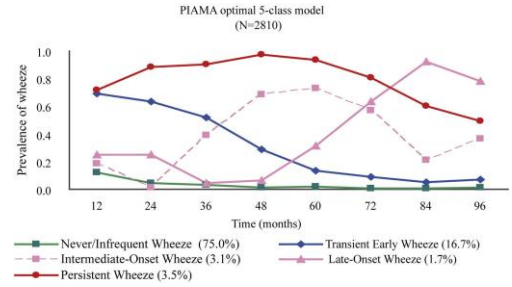
## Epidemiological links between RSV and asthma

9 controlled studies (mostly retrospective) 1978-2000

Follow-up from 2 to 13 years

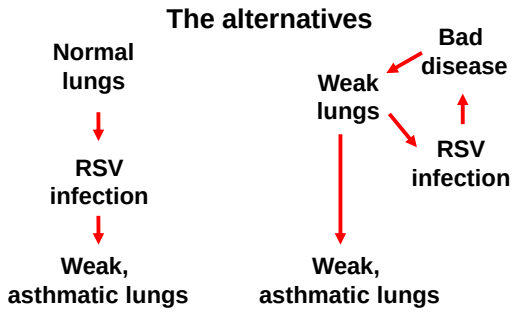
All demonstrate increased frequency of intermittent obstructive disease in post-bronchiolitcs

## Four types of childhood wheeze




Olga E. Savenije, Raquel Granell, ... Dirkje S. Postma, John Henderson and Marjan Kerkhof **(2011)** Comparison of childhood wheezing phenotypes in 2 birth cohorts: ALSPAC and PIAMA . J Allergy Clinical Immunol (2011) **127**:1505-1512.e14

## Do infantile viral infections cause "asthma"?



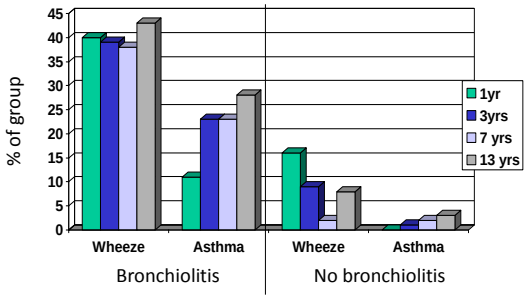

## The Sigurs study

- Longitudinal prospective study
- 47 children hospitalized for RSV <1yr old
- 93 non-hospitalized controls
- Surveyed at 1, 3, 7 and 13 years of age

- Definitions
  - Wheeze: >3 episodes of wheezing / 1 yr
  - Asthma: >3 episodes of physician diagnosed wheeze in one year

Sigurs N et al. *Pediatr* 1995; 95:500-05., Sigurs N, et al. *Am J Respir Crit Care Med* 2000;161:1501-07. Sigurs N, et al. *Am J Respir Crit Care Med* 2005;171:137-41.

## Wheezing and asthma after RSV hospitalisation




Sigurs N et al. *Pediatr* 1995; 95:500-05., Sigurs N, et al. *Am J Respir Crit Care Med* 2000;161:1501-07. Sigurs N, et al. *Am J Respir Crit Care Med* 2005;171:137-41.

## Plausible mechanisms of delayed effects

- Viral chronicity, persistence or latency
- 'Hitchhike' of other chronic pathogen
- Remodeling (altered lung growth)
- Permanent epithelial damage
- Immunological priming or tolerance
- Bystander antigenic sensitization

## Evidence for Persistence of RSV

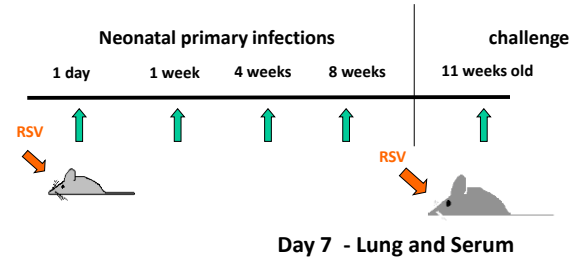
1. Occurs in T cell immunodeficiency
2. Closely related to measles
3. Persistence occurs *in vitro*
4. Seen in:
   - Cattle
   - Guinea pig
   - Mouse

*Schwarze J et al. Am.J.Respir.Crit.Care Med. 2004;169:801-5*

**Wilkinson, Donaldson, Johnston, Openshaw and Wedzicha *ATS*, 2004; AJRCCM 173: 876 (2006)**

**Age at First Viral Infection Determines the Pattern of T Cell–mediated Disease during Reinfection in Adulthood**

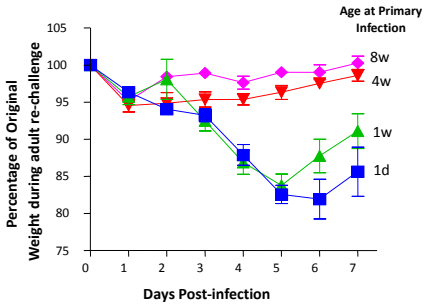
Fiona J. Culley, Joanne Pollott, and Peter J.M. Openshaw




J. Exp. Med. © The Rockefeller University Press • 0022-10
Volume 196, Number 10, November 18, 2002 1381–1386

**Age at First Viral Infection Determines the Pattern of T Cell–mediated Disease during Reinfection in Adulthood**

Fiona J. Culley, Joanne Pollott, and Peter J.M. Openshaw



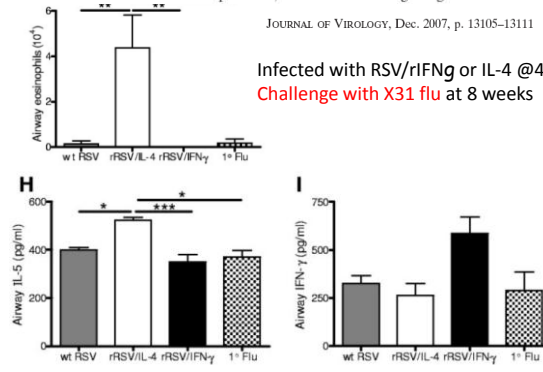

J. Exp. Med. © The Rockefeller University Press • 0022-10
Volume 196, Number 10, November 18, 2002 1381–1386

Virally Delivered Cytokines Alter the Immune Response to Future Lung Infections▽

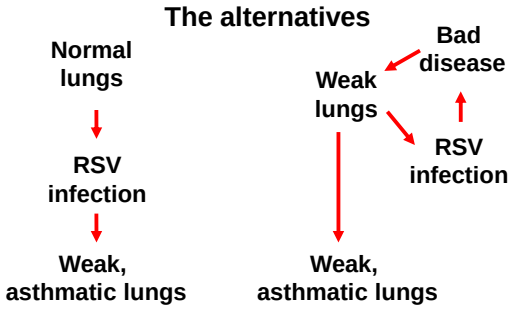
James Harker,[1] Alexander Bukreyev,[2] Peter L. Collins,[2] Belinda Wang,[1] Peter J. M. Openshaw,[1]* and John S. Tregoning[1]

JOURNAL OF VIROLOGY, Dec. 2007, p. 13105–13111

Infected with RSV/rIFNg or IL-4 @4/52
Challenge with X31 flu at 8 weeks



## Does RSV cause 'asthma'?

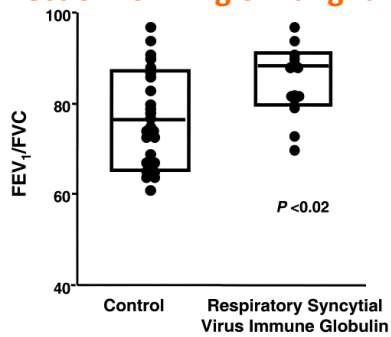



## Effect of RSV-IVIG on lung function

- Long-term follow-up study compared
  - **13 children with BPD who received RSV-IVIG for RSV LRI in infancy**
  - **26 age-matched controls with BPD who did not receive RSV-IVIG (not matched for history of documented RSV infection)**
- 6/13 treated cases had history of RSV infection vs 21/26 controls

Wenzel SE, Gibbs RL, Lehr MV, Simoes EAF. Respiratory outcomes in high-risk children 7-10 years after prophylaxis with respiratory syncytial virus immune globulin. Am J Med 2002;112:627-33.

## Effect of RSV-IVIg on lung function




Wenzel SE, Gibbs RL, Lehr MV, Simoes EAF. Respiratory outcomes in high-risk children 7-10 years after prophylaxis with respiratory syncytial virus immune globulin. Am J Med 2002;112:627-33.

## Effect of RSV-IVIg on lung function

- FEV1/FVC and airway conductance significantly better ($p < 0.02$)
- Less atopy ($p < 0.04$)
- Missed school ($p = 0.01$), colds ($p < 0.03$), and asthma attacks ($p < 0.04$) less likely

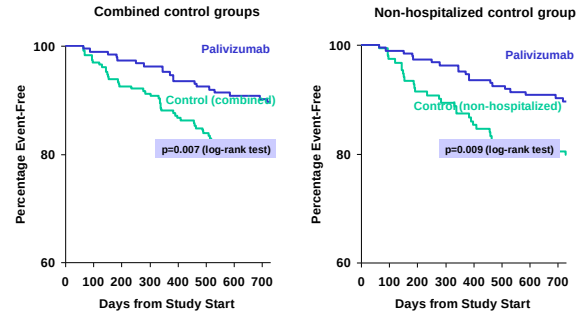
Wenzel SE, Gibbs RL, Lehr MV, Simoes EAF. Respiratory outcomes in high-risk children 7-10 years after prophylaxis with respiratory syncytial virus immune globulin. Am J Med 2002;112:627-33.

## Palivizumab prevention study

- **Multicenter, multinational trial at 27 sites**
  - Matched double-cohort design
- **Preterm infants ≤35 wGA**
  - ≤3 years of age at time of enrollment
  - No CLD/CHD
- **Two cohorts**
  - 'Palivizumab' group (prophylaxis ≤6 months of age)
  - 'No palivizumab' controls
- **Two-year prospective follow-up**
- **Intention to treat analysis**

Simões, Groothius, Kimpen *et al* (J Pediatr 2007; 151:34-42)

## Time to Onset of Physician -Documented recurrent wheeze

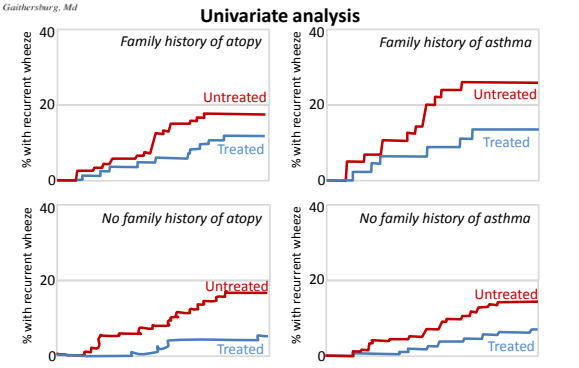



Simões, Groothius, Kimpen *et al* (J Pediatr 2007; 151:34-42)

**The effect of respiratory syncytial virus on subsequent recurrent wheezing in atopic and nonatopic children**

JACI 126:256-282, 2010 doi:10.1016/j.jaci.2010.05.026

Eric A. F. Simões, MB, BS, DCH, MD,[a] Xavier Carbonell-Estrany, MD, PhD,[b] Christian H. L. Rieger, MD,[c] Ian Mitchell, MA, MB, ChB,[d] Linda Fredrick, MS,[e] and Jessie R. Groothuis, MD,[f] on behalf of the Palivizumab Long-Term Respiratory Outcomes Study Group* *Aurora, Colo, Barcelona, Spain, Bochum, Germany, Calgary, Alberta, Canada, Abbott Park, Ill, and Gaithersburg, Md*




## Not perfect studies…

- Industry-funded
- Non-randomised, physician allocated
- Retrospective
- Non-blinded from families
- Reported wheeze by parents

*It should probably not have worked…*

- Only delayed RSV, did not prevent it

## Delaying RSV infection in infants

- Would reduce the severity of RSV disease
- Might reduce subsequent wheeze

## Reducing RSV infections in adults

- Would reduce community circulation
- Would be cost effective in high risk groups
- Would especially benefit the elderly