Respiratory viruses:

in the community and the hospital

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Never Stand Still | Medicine

Dr Nusrat Homaira, MBBS, MPH, PhD
Discipline of Paediatrics, School of Women's and Children's Health
UNSW Medicine

Viruses in May
12 May 2017

The Problem

- ALRI is the leading cause of childhood morbidity and mortality
  - 152 million new cases every year
  - 90-95% in low-income countries
  - 4 million cases in high-income countries
  - Worldwide ≈2 million deaths per year
  - 70-80% of childhood ALRI associated with viruses

Etiology of community-acquired childhood pneumonia

- In children aged <5
  - **Viral**

    Respiratory syncytial virus (RSV)
    Influenza
    Rhino virus
    Parainfluenza
    Human metapneumovirus
    Adeno virus
  - **Bacterial**

    S. Pneumoniae
    Staphylococcus aureaus
    Group A Streptococcus
    H. Influenzae type b
    Chlamydophila pneumoniae

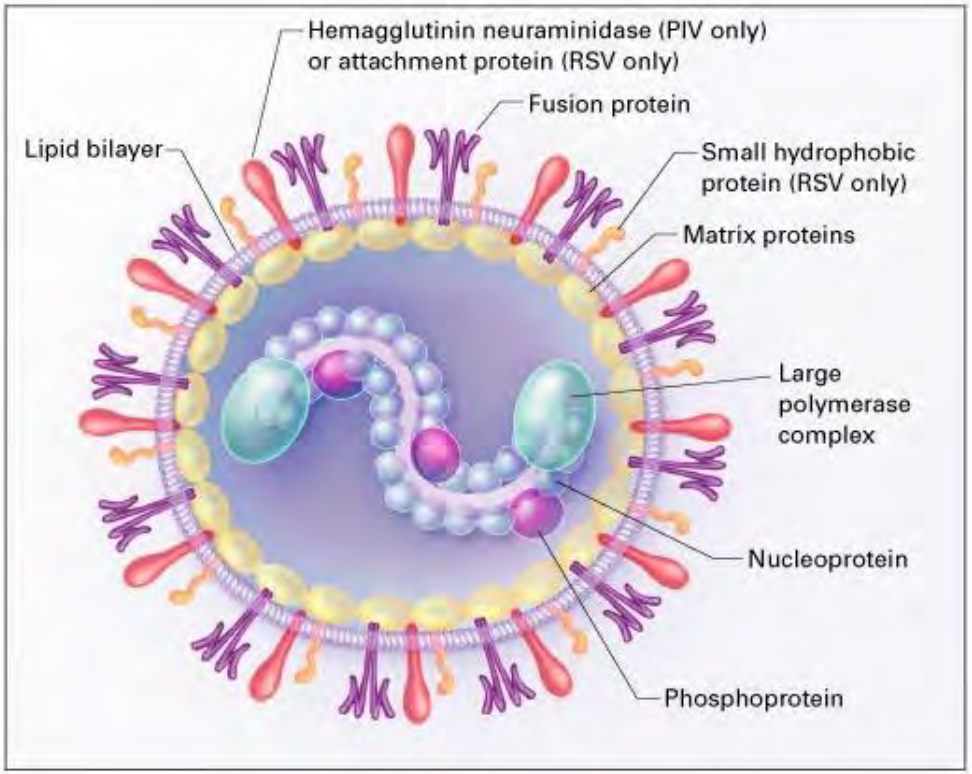
- In children aged >5
- **Bacterial**

  Mycoplasma pneumoniae
  Chlamydophila pneumoniae
  S. Pneumoniae
  Staphylococcus aureaus
  Group A Streptococcus
  Legionella pneumophila

- **Viral (same)**

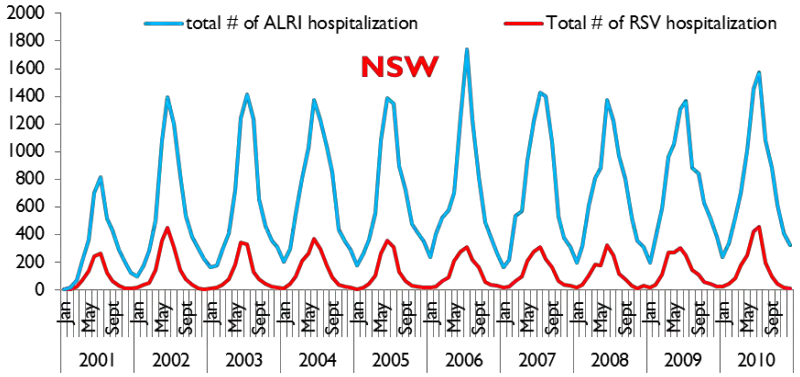
RSV: The virus

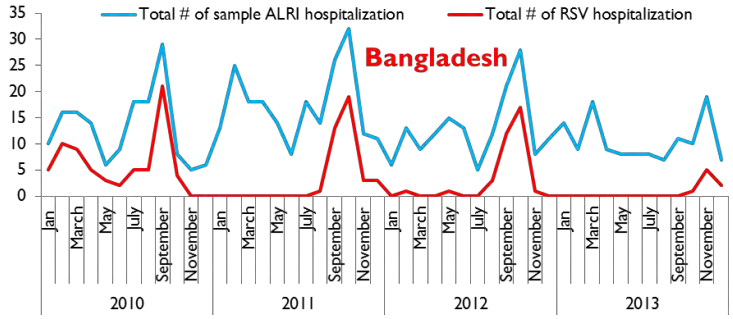
- Single-stranded RNA virus
- Family: Paramyxoviridae
- Two main large envelope glycoproteins
  - F and G proteins
  - F protein cause cell membranes on nearby cells to merge, forming syncytia
- Two main subtypes
  - RSV A
  - RSV B



RSV: Epidemiology

- Global distribution
- Winter epidemics
  - Temperate zone: epidemics occur during late fall, winter and spring
  - Tropical zone: common during rainy season





- Infects 65% of children in infancy
- Re-infects at ease

Global Burden of RSV

- Major cause of LRTI and hospital visits in children
  - 3.4 million episodes of under 5 hospitalizations
  - 66,000-199,000 under 5 deaths
    - 99% of these in low income countries
  - USA 2000-04:
    - 11.7-21.7/1000 infants 0-5 months
    - 86,000 hospitalization
    - Direct cost US$ 394 million/year
  - NSW 2001-2010:
    - 25.6/1000 infants
    - 1200-2000 hospitalization
    - Direct cost AUD$ 9 million/year

Transmission

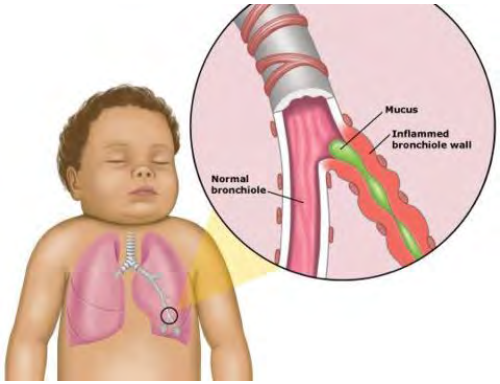
- Shed in nasopharyngeal secretions
- Infected patients can shed virus up to 21days
- Can survive on
  - nonporous surfaces such as countertops or crib rails up to 7 hours
  - porous surfaces, such as clothing up to 4 hours
  - Can be present in your NICU
- Can be transmitted by
  - direct contact
  - indirect contact
- Incubation period: 2-8 days

Respiratory Syncytial Virus is Present in the Neonatal Intensive Care Unit

Nusrat Homaira,[1] Joanne Sheils,[2] Sacha Stelzer-Braid,[3,4] Kei Lui,[1,2] Ju-Lee Oie,[2] Tom Snelling,[5] Adam Jaffe,[1] and William Rawlinson[3,4,6]*

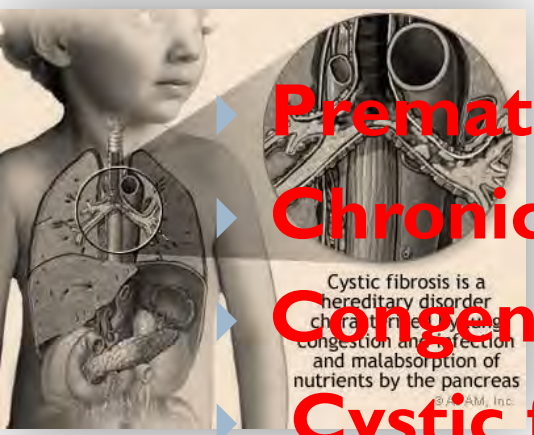
Journal of Medical Virology

The Disease

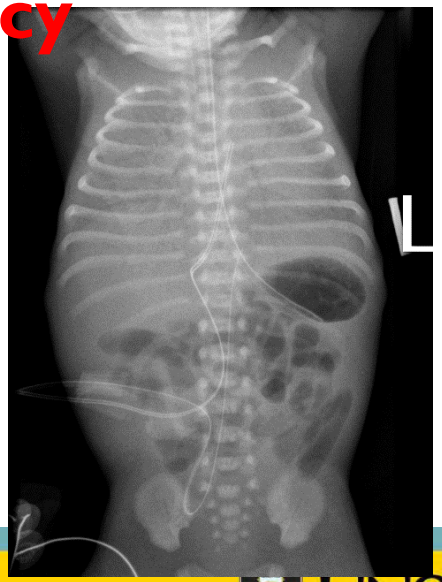


- Generally infects the URT and the eyes
- Cause cold-like symptoms
- Replicates in the nasopharyngeal epithelium
- Moves to lower RTI in 1-3 days
- Necrosis and sloughing of epithelium, edema, increased mucus secretion blocking the small airway
- Causing bronchiolitis and pneumonia
- Complete restoration in 4-8 weeks
- Cough and cold in adults

RSV and High-risk children



- **Prematurity or with low birth weight**
- **Chronic lung disease (BPD/CLD)**
- **Congenital heart disease (CHD)**
- **Cystic fibrosis (CF), multiple congenital anomalies and immunodeficiency**

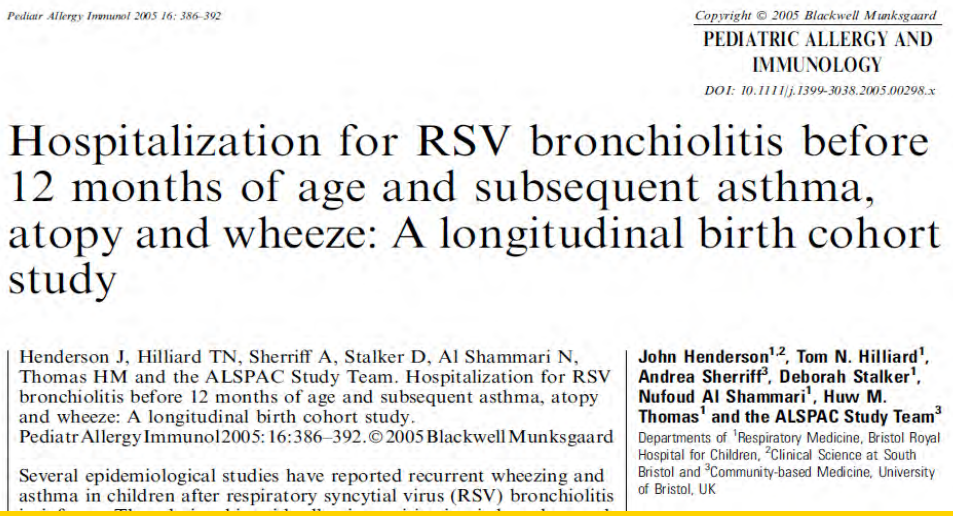


RSV and subsequent chronic respiratory morbidity

- NSW
  - Risk of subsequent first asthma hospitalization double and persisted beyond seven years

Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years

Renato T Stein, Duane Sherrill, Wayne J Morgan, Catharine J Holberg, Marilyn Halonen, Lynn M Taussig, Anne L Wright, Fernando D Martinez



Pediatr Allergy Immunol 2005 16: 386–392

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PEDIATRIC ALLERGY AND IMMUNOLOGY

DOI: 10.1111/j.1399-3038.2005.00298.x

Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy and wheeze: A longitudinal birth cohort study

Henderson J, Hilliard TN, Sherriff A, Stalker D, Al Shammari N, Thomas HM and the ALSPAC Study Team. Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy and wheeze: A longitudinal birth cohort study. Pediatr Allergy Immunol 2005: 16: 386–392. © 2005 Blackwell Munksgaard

Several epidemiological studies have reported recurrent wheezing and asthma in children after respiratory syncytial virus (RSV) bronchiolitis

John Henderson[1,2], Tom N. Hilliard[1], Andrea Sherriff[3], Deborah Stalker[1], Nufoud Al Shammari[1], Huw M. Thomas[1] and the ALSPAC Study Team[3]

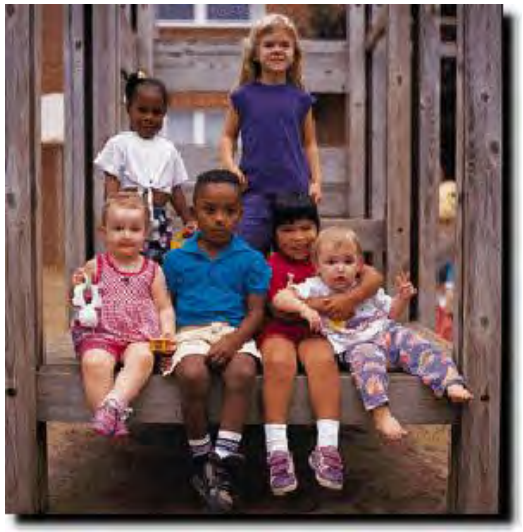
Departments of [1]Respiratory Medicine, Bristol Royal Hospital for Children, [2]Clinical Science at South Bristol and [3]Community-based Medicine, University of Bristol, UK

RSV in the elderly

- Diagnosis is problematic
- 3-10% of colds
- 10% death rates
- Causes wheeze and hypoxia
- Risk groups
  - COPD/ Heart failure
  - Exposure to young children
  - Immunocompromised
  - Living in community dwellings

RSV at different stages of life

Bronchiolitis
Subsequent asthma/wheeze
Primary spreaders



Exacerbation of chronic lung diseases
Excess deaths

https://www.google.com/url?sa=i&rct=j&q=&esrc=s&source=images&cd=&cad=rja&uact=8&ved=0ahUKEwi-sY2EmNDTAhXHH5QKHaOeDEMQjRwIBw&url=http%3A%2F%2Fwww.dailymail.co.uk%2Ffemail%2Farticle-2440113%2FBrooklyns-Geezer-Project-lets-elderly-connect-children-community.html&psig=AFQjCNHW9hUJAsSyYTSV3GakycDI4Q0rUA&ust=1493779356178476

Repeated cough
Transmitters

https://www.google.com/url?sa=i&rct=j&q=&esrc=s&source=images&cd=&ved=0ahUKEwivr7iUl9DTAhVBHZQKHRKgC00QjRwIBw&url=http%3A%2F%2Fwww.waynegov.com%2F282%2FWomen-Infants-Children-Program-WIC&psig=AFQjCNH_SDgCD6FJgk9G6ascip1SWWyO4Q&ust=1493779155353045&cad=rjt

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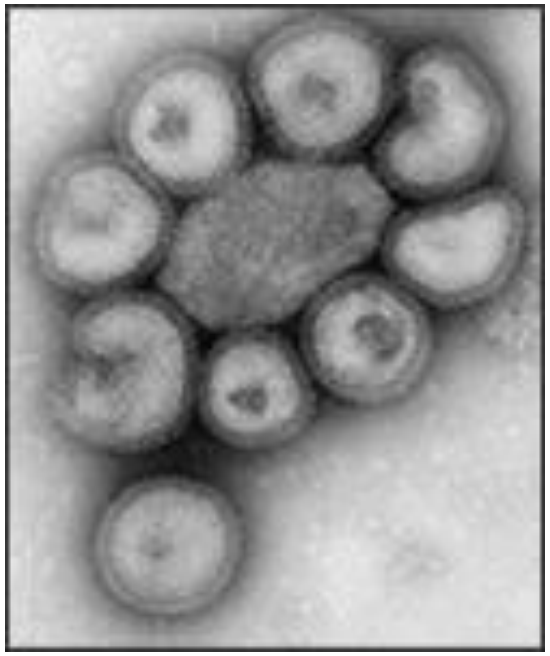
Prevention &Treatment

- No effective vaccine
  - Yet!!!!!!
- Hand washing
- Covering cough and sneeze
- Cohorting
- Supportive treatments
- Palivizumab

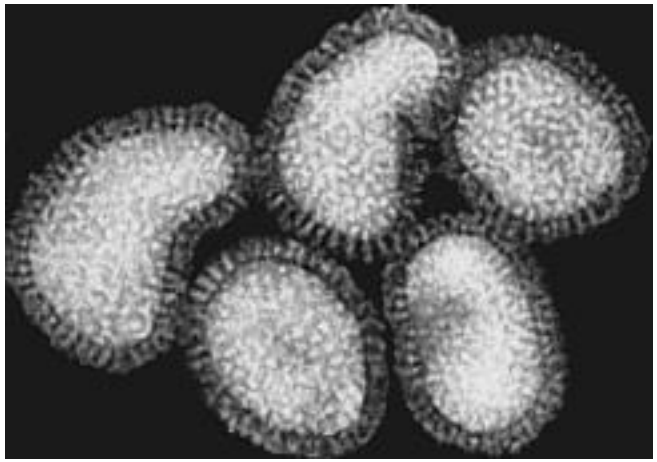
Influenza: The Virus



- Family *Orthomyxoviridae*
- Single-stranded RNA virus
  - Two major glycoprotein on the surface
    - Neuroaminidase (NA)
    - Hemaglutinin (HA)
- Virus can only replicate in living cells
- Virus undergoes continuous mutation and reassortment
  - Antigenic drift
  - Antigenic shift

Influenza Virus Types

- Influenza A
  - Most virulent type
  - Different serotypes
  - Animal reservoir
- Influenza B
  - Exclusively infects humans
  - Less common and less diverse
- Influenza C
  - Infects humans, dogs and pigs
  - Most uncommon
  - Mild illness in children



Influenza Epidemiology

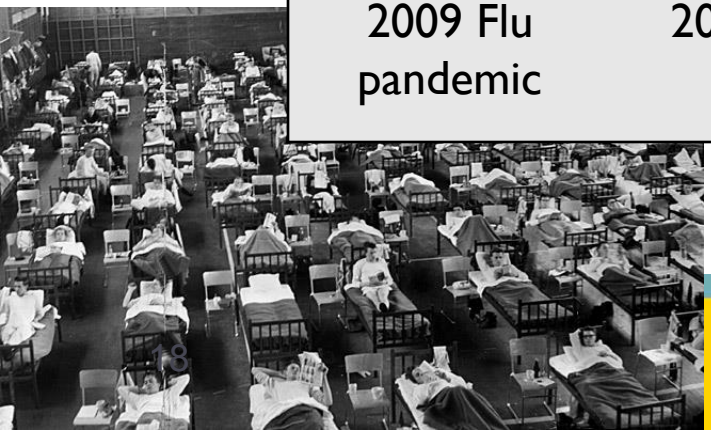
- Seasonality
  - Northern Hemisphere
    - Cool season (November – March)
  - Southern Hemisphere
    - Cool season (April – October)
  - Tropics?
    - Year-round
    - Two distinct influenza A seasons; (Pre-Monsoon H3, Monsoon H1)
    - Peak season compliment of Northern Hemisphere
    - B virus isolated year-round

Global burden of Seasonal Influenza

- 250K – 500K deaths per year globally
- Australia
  - 13,000 hospitalised/year
  - 3000 deaths/year
- At-risk subpopulations
  - Elderly
  - Young children
  - People with underlying conditions (chronic)
    - Lung (e.g. asthma, chronic obstructive pulmonary dysplasia)
    - Heart (congestive heart disease)
    - Endocrine (diabetes)
  - Pregnant women

Influenza Pandemics

Name of Pandemic	Date	Death	Subtypes involved
Asiatic (Russian) flu	1889-1890	1 mill	Possibly H3N8
Spanish flu	1918-1920	20-100 mill	H1N1
Asian flu	1957-1958	1-1.5 mill	H2N2
Hong Kong Flu	1968-1969	0.75-1 mill	H3N2
2009 Flu pandemic	2009-2010	>200,000	H1N1



Influenza : Transmission

- Transmission (human seasonal influenza)
  - Person to person
  - Droplet (aerosolised) spread
  - Very efficiently transmitted through the air
  - Highly contagious
- Children are the best transmitters
  - School-aged vs preschool aged

C Viboud, P Boëlle, S Cauchemez, *et al*

Risk factors of influenza transmission in households

Cécile Viboud, Pierre-Yves Boëlle, Simon Cauchemez, Audrey Lavenu, Alain-Jacques Valleron, Antoine Flahault and Fabrice Carrat

British Journal of General Practice, September 2004

Conclusion: Our results support the major role of children in the dissemination of influenza in households. Vaccination of children or prophylaxis with neuraminidase inhibitors would prevent, respectively, 32–38% and 21–41% of secondary cases caused by exposure to a sick child in the household.

Keywords: antivirals; children; epidemiology; influenza; prospective udies; risk factors; vaccination.

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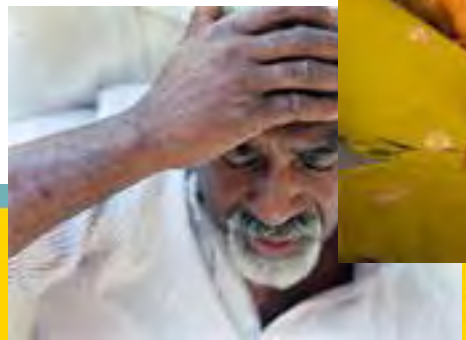
Nosocomial transmission

- Staff-patient cross-infection common
  - Elderly long-term patients
  - Renal, transplant and oncology units
  - Neonatal and paediatric intensive care units

Influenza: Clinical Presentation

- Often assumed mild 'cold' symptoms = flu
- Influenza is more severe than a 'cold'
- Initial symptoms (2 – 3 days) include abrupt onset of
  - Fever (high)
  - Muscle ache
  - Sore throat
  - Non-productive cough
- At peak (catarrhal phase) 2 – 3 days
  - Fever, lassitude, pain
  - Progresses to lower respiratory symptoms
- Recovery (2 – 3 days)+
  - Longer if complications



Influenza : Complications

- Primary Pneumonia
- Secondary bacterial pneumonia
- Otitis media
- Reye's syndrome
- Encephalitis (Parkinson's disease after the 1918 pandemic)

Influenza: Disease Control

- Treatment
  - Adamantanes (e.g. Amantadine, Ramantadine)
    - High rates of resistance
  - Neuraminidase inhibitors (e.g. Oseltamivir 'Tamiflu', Zanamivir)
    - Lower rates of resistance
    - Can also be used to control pandemic flu

- Prevention
  - Vaccines
    - Quadrivalent inactivated vaccine (6 months – any age)
    - Live attenuated (healthy, non-pregnant , aged 2-49 y)

Recommendations for Australia

- Adults aged ≥65 years
- Abori
  - agec
  - agec
- Pregl
- Indiv :al
  condi uenza
  comp
- All in

Asthma Australia
Working with your local Asthma Foundation

Home › News › National

Survey shows high impact of flu on people with asthma but low vaccination rate amongst children

MEDIA RELEASE
31 March 2017

Prevention of transmission

Annals of Internal Medicine | ARTICLE

Facemasks and Hand Hygiene to Prevent Influenza Transmission in Households

A Cluster Randomized Trial

Benjamin J. Cowling, BSc, PhD; Kwok-Hung Chan, BSc, PhD; Vicky J. Fang, BSc, MPhil; Calvin K.Y. Cheng, BSc, MMedSci; Rita O.P. Fung, BNS; Winnie Wai, BNS; Joey Sin, BNS; Wing Hong Seto, MBBS; Raymond Yung, MBBS, MPH; Daniel W.S. Chu, MBBS; Billy C.F. Chiu, MBBS; Paco W.Y. Lee, MBBS; Ming Chi Chiu, MBBS; Hoi Che Lee, MBBS; Timothy M. Uyeki, MD, MPH; Peter M. Houck, MD; J.S. Malik Peiris, MBBS, DPhil; and Gabriel M. Leung, MD, MPH

Vol 437|8 September 2005|doi:10.1038/nature04017 nature

ARTICLES

Strategies for containing an emerging influenza pandemic in Southeast Asia

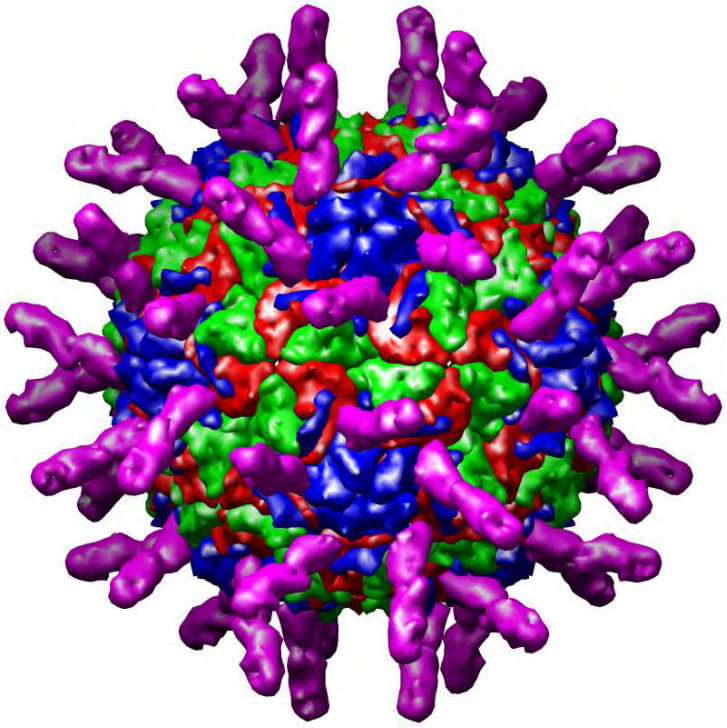
Neil M. Ferguson[1,2], Derek A.T. Cummings[3], Simon Cauchemez[4], Christophe Fraser[1], Steven Riley[5], Aronrag Meeyai[1], Sopon Iamsirithaworn[6] & Donald S. Burke[3]

Rhino Virus: newly recognized etiology of ALRI

- Why not recognised before
  - URTI
  - Difficult to culture
  - Highly variable genomes
  - Diagnostic tests not sensitive

Rhino Virus

- Family : *Picornaviridae*
- Genus: *Enterovirus*
- Single stranded RNA virus
- Three genetically distinct species
  - hRV-A
  - hRV-B, and
  - hRV-C (at least 168 serotypes and genotypes)



Epidemiology of Rhino virus

- Most common cause of URTI and LRTI in infants and children
  - By age of two 90% children have antibodies against hRV
- Although majority infections produce mild disease, overall impact on morbidly and significant economic burden
- hRV C>>hRV-A>>hRV-B
- hRV-C identified in patients with pneumonia and severe asthma exacerbations

Transmission

- Seasonal peaks
  - Year long circulation
  - Autumn and spring peaks
  - "Back to school" period peaks
  - Transmission via
    - hand-hand followed by direct inoculation
    - fomites
    - aerosolized transmission less efficient

The disease

- Incubation period 1-3 days
- Classic common cold symptoms
  - Sneezing, headache, malaise, chills, nasal discharge, nasal obstruction, sore throat, and cough
  - 6-8 episodes of cold p.a
- In children associated with bronchiolitis, wheezing and asthma exacerbations severe enough to require hospitalization

Rhinoviruses significantly affect day-to-day respiratory symptoms of children with asthma

Euan R. Tovey, PhD,[a] Sacha Stelzer-Braid, PhD,[b,c] Brett G. Toelle, PhD,[a,d] Brian G. Oliver, PhD,[a,e] Helen K. Reddel, MBBS, PhD,[a] Christiana M. Willenborg, BSc (Hons),[b] Yvonne Belessis, MBBS, PhD,[f,g] Frances L. Garden, MBiostat,[a,h,i] Adam Jaffe, MBBS, MD,[f,g] Roxanne Strachan, BN,[g] Darryl Eyles, PhD,[j,k] William D. Rawlinson, PhD,[b,g] and Guy B. Marks, PhD[a,i] *Sydney and Brisbane, Australia*

J ALLERGY CLIN IMMUNOL
MARCH 2015

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Rhino virus and asymptomatic infection

- 75% infection asymptomatic

RESEARCH ARTICLE

Respiratory Viruses Associated Hospitalization among Children Aged <5 Years in Bangladesh: 2010-2014

Nusrat Homaira[1]*, Stephen P. Luby[1,2], Kamal Hossain[1], Kariul Islam[1], Makhdum Ahmed[1], Mustafizur Rahman[1], Ziaur Rahman[1], Repon C. Paul[1], Mejbah Uddin Bhuiyan[1], W. Abdullah Brooks[1,3], Badrul Munir Sohel[1], Kajal Chandra Banik[1], Marc-Alain Widdowson[2], Melisa Willby[2], Mahmudur Rahman[4], Joseph Bresee[2], Katharine-Sturm Ramirez[1,2], Eduardo Azziz-Baumgartner[1,2]

Respiratory viral pathogens	Frequency (%)									
	Hospitalized children with respiratory symptoms						Hospitalized children without respiratory symptoms			
	2010 n = 155	2011 n = 209	2012 n = 153	2013 n = 128	2014 N = 184	2010–2014 n = 829	2012 n = 246	2013 n = 174	2014 n = 119	2012–2014 n = 540
Any positive	143 (92)	145 (69)	106 (69)	106 (83)	121 (66)	**621 (75)**	117 (47.5)	94 (53)	22 (18)	**233**
Respiratory syncytial virus	69 (44.5)	39 (19)	35 (23)	8 (6)	46 (25)	**197 (24)**	9 (4)	0 (0)	3 (2.5)	**12 (2)**
Rhinovirus	40 (31)	37 (18)	21 (14)	51 (40)	Not tested	**Not applicable**	41(17)	47 (27)	Not tested	**Not applicable**
Adenovirus	9 (6)	8 (3)	4 (3)	5 (4)	5 (3)	**31 (4)**	38 (15)	19 (11)	7 (6)	**64 (12)**
Parainfluenza viruses1-3	6 (4)	16 (8)	8 (5)	6 (5)	9 (5)	**45 (5)**	4 (2)	4 (2)	5 (4)	**13 (2)**
Human metapneumovirus	4 (2.5)	14 (7)	3 (2)	7 (5)	6 (3)	**34 (4)**	0 (0)	3(2)	0 (0)	**3 (0.5)**
Influenza viruses	4 (2.5)	6 (3)	3 (2)	4 (3)	8 (4)	**25 (3)**	3 (1)	1 (0.5)	1 (1)	**5 (1)**
Viral co-infections	11 (7)	25 (12)	32 (21)	25 (19.5)	31 (17)	**95 (15)**	22 (9)	19 (11)	6 (5)	**47 (9)**
Negative	12 (8)	64 (31)	47 (53.5)	22 (17)	63 (34)	**208 (25)**	129 (52)	81 (46.5)	97 (81.5)	**307 (57)**

doi:10.1371/journal.pone.0147982.t001

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Tracking the viruses

- Notifiable disease
- Virus and causation of disease
- The implications of viruses on clinical practice
- Limited use of antivirals and vaccine

Conclusion

- Respiratory viral infections associated with significant morbidity , mortality and economic burden
- Children , immunocompromised and elderly most at risk
- 40-60% infections are not diagnosed
- Need for well designed epidemiological investigations to determine which viruses are common
- Molecular diagnostic methods that can detect all causes of ALRTI in cost-effective manner

???????