Paediatric Virology: *Gastroenteritis* *Respiratory Disease*

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Childhood Gastroenteritis

- Greatest cause of death in the developing world.
- Up to 10 million children die p.a.
  - mainly due to rotavirus infections in malnourished infants.
- An increasing range of viruses are identified as true GE pathogens
- A diagnostic revolution targeting viral GE pathogens is essential
  - In USA aetiology of GE known in <10% of cases
- A safe, cheap and effective rotavirus vaccine is urgently required

- Rotavirus
- Norovirus
- Astrovirus
- Adenoviruses
- Others
  - Sapovirus
- Co-infections not unusual

Viral Gastroenteritis[a]

Causative agent	Patient age groupings	Selected symptoms[b]		Incubation period	Duration of illness	Mode of transmission[c]
		Vomiting	Fever			
Rotavirus, group A	Infants and toddlers	Common	Common	1–3 days	5–7 days	Water, PTP, ?food, ?air, nosocomial, fecal–oral
Rotavirus, group B	Children and adults	Variable	Rare	56 hours (average)	3–7 days	Water, PTP, fecal–oral
Rotavirus, group C	Infants, children, and adults	Unknown	Unknown	24–48 hours	3–7 days	Fecal–oral
Adenovirus (enteric)	Young children	Common	Common	7–8 days	8–12 days	Nosocomial, fecal–oral
Calicivirus	Infants, young children, and adults	Common for infants; variable for adults	Occasional	1–3 days	1–3 days	Food, water, nosocomial, fecal–oral
Calicivirus (Norwalk virus)	Older children and adults	Common	Rare or mild	18–48 hours	12–48 hours	Food, water, PTP, ?air, fecal–oral
Astrovirus	Young children and elderly people	Occasional	Occasional	1–4 days	2–3 days; occasionally 1–4 days	Food, water, fecal–oral

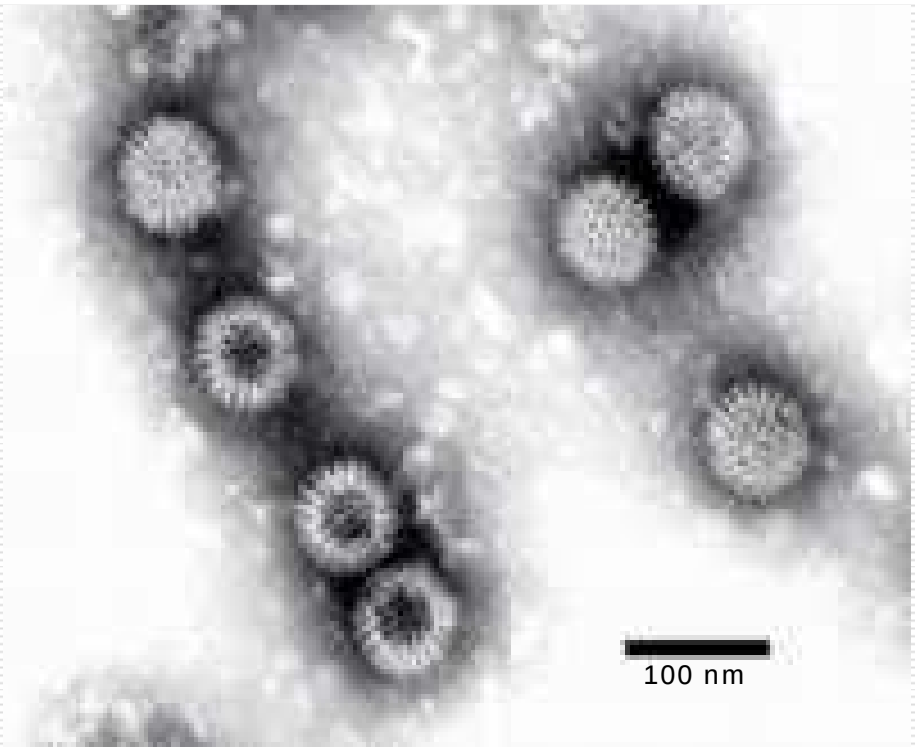
[a] From Centers for Disease Control, Recommendations for collection of laboratory specimens associated with outbreaks of gastroenteritis, *Morb. Mortal. Wkly. Rep.* **39**, RR-14 (1990).

[b] Diarrhea is common and is usually loose, watery, and nonbloody when associated with gastroenteritis.

[c] PTP, Person-to-person; ?, not confirmed.

Medical Virology, Fenner & White, 4th Edition, 1994

Rotavirus



- Properties *(Reoviridae)*
  - dsDNA, 18 Kb, 11 segments
  - 6 serogroups A-F (VP6)
- Epidemiology
  - Ages 6-24 mths (12 mths)
  - Asymptomatic infections
  - Faecal oral & water spread
  - Seasonality
  - Nosocomial outbreaks
- Pathogenesis
  - Incubation 1-3 days
  - Shed for 3-7 days
  - 10^{10} particles/g/faeces
- Clinical Features
  - VD 4-5 days, fever
  - Death rare in well child
- Diagnosis
  - EIA, Latex agglutinination
  - IEM
  - PCR

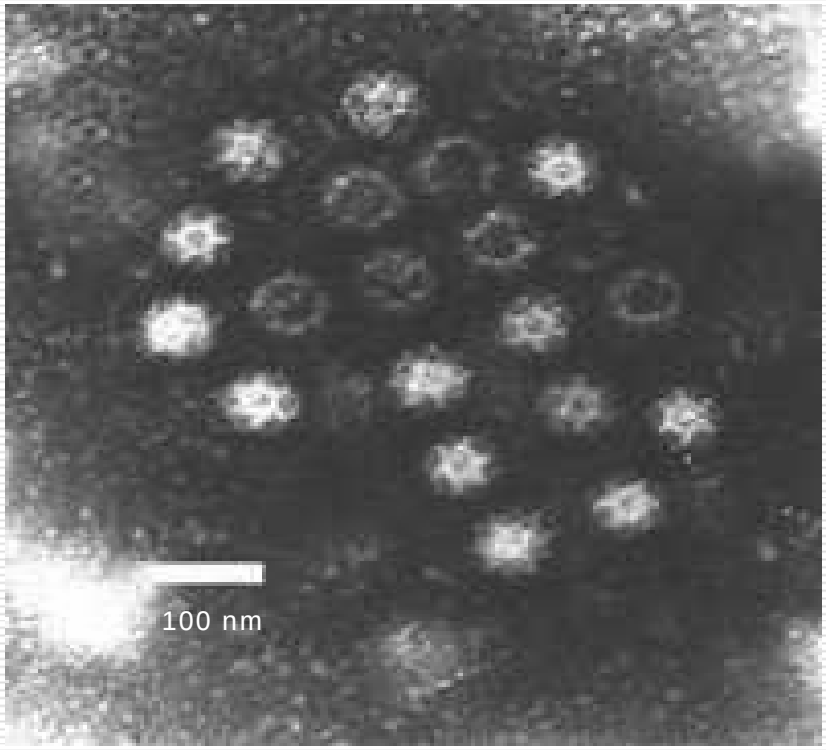
Current Status of Rotavirus Vaccines

	Company	Concept	Status of vaccine
Licensed vaccines			
Rotashield	Wyeth Ayerst, USA	Tetravalent rhesus-human reassortants	Licensed in USA (1998), withdrawn following intussusception (1999)
LLR	Lanzhou Institute of Biological Products, China	Monovalent lamb strain (P[12],G10)	Licensed in China (2001)
Late-stage development			
Rotateq	Merck, USA	WC-3-based pentavalent bovine-human reassortants	Phase III
Rotarix	GlaxoSmithKline, Belgium	Monovalent human strain (P1A[8],G1)	Phase III
Early-stage development			
RV3	University of Melbourne, Australia	Neonatal strain (P2A[6],G3)	Phase II
UK-reassortant strain	US National Institutes of Health (pending)	Tetravalent bovine-human reassortants	Phase II
Neonatal strains 116E and I132	Bharat Biotech Ltd, India	Neonatal strains – 116E (P8[11],G9); I-321 (P8[11],G10)	Phase I
Rhesus tetravalent	BIOVIRx, USA	Tetravalent rhesus–human reassortants	Original Rotashield licensed to another group

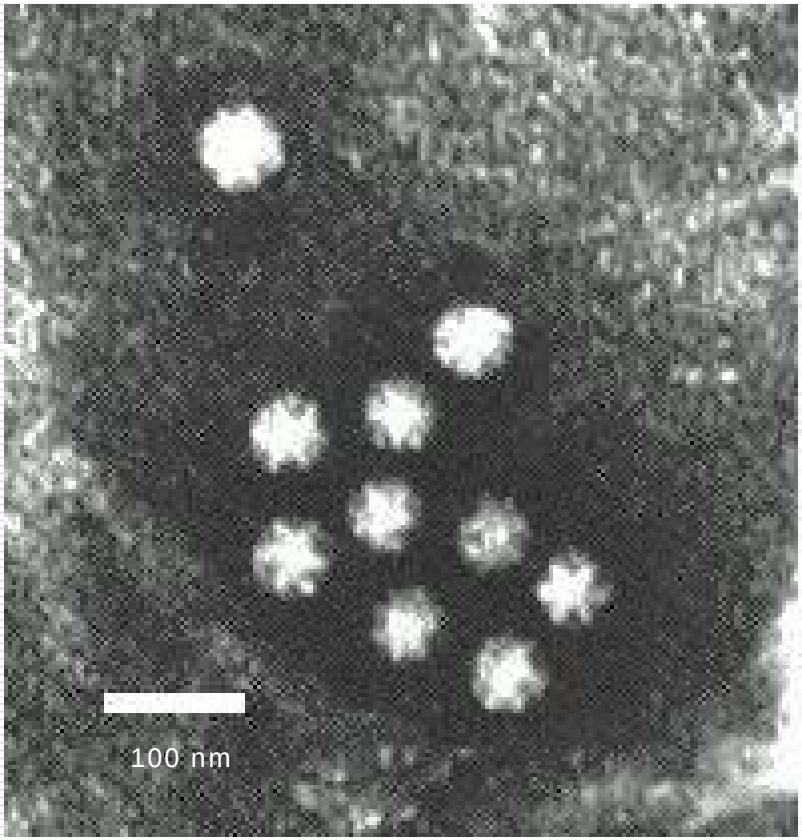
Vaccines currently licensed or in clinical trials

Norovirus

- Properties *(Calciviridae)*
  - +ssRNA 7.5 kb, 3 ORF
  - 3 major antigenic groups
- Epidemiology
  - Ubiquitous & year round with winter peak
  - 19-42% of non-bacterial GE outbreaks
  - 5-17% community incidence
  - 5-7% requiring medical Rx
- Pathogenesis
  - SI villi tips infected
  - Immunity short-lived
- Clinical Features
  - Incubation 18-36 hrs
  - NVD, abdo cramps, headache, myalgia, fever, “winter vomiting”
- Diagnosis
  - Non-culturable
  - EIA, RT-PCR, IEM



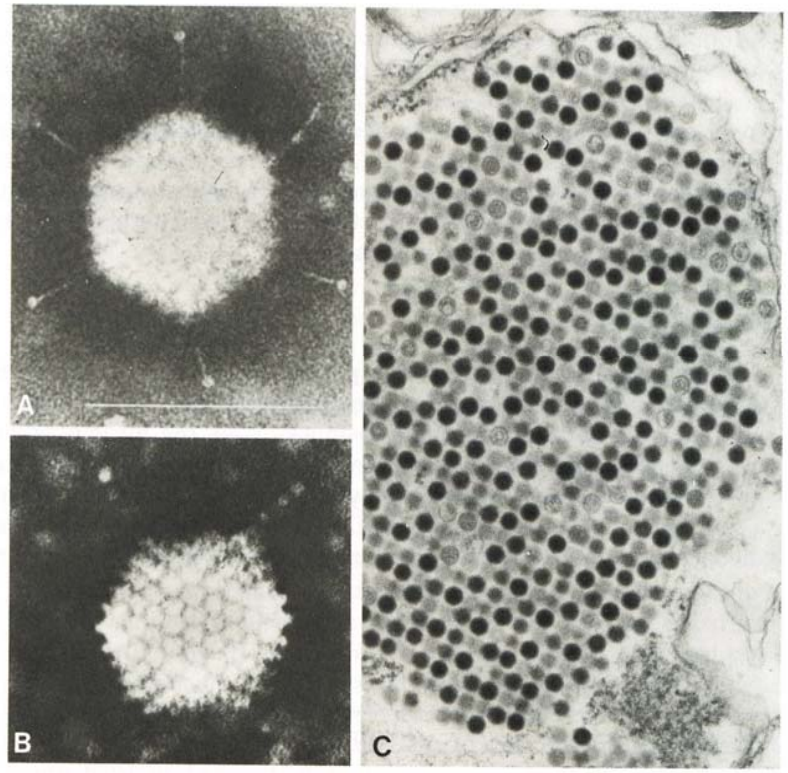
Astrovirus



- Properties *(Astroviridae)*
  - +ssRNA, 7.2 kb, 8 serotypes
- Epidemiology
  - 2-17% infantile GE
  - 2% asymptomatic carriage
  - Year-round with winter peak
  - Community epidemics
  - Co-infections; rotavirus (3-19%), adenoviruses (2-4%)
- Pathogenesis
  - Cytoplasmic replication
  - [High particle] faeces ~10^8/g
- Clinical Features
  - Mild GE, incubation 1-4 days,
  - Long term immunity
- Diagnosis
  - EIA, PCR
  - Culture (trypsin)-HEK, CaCo2

Adenoviruses

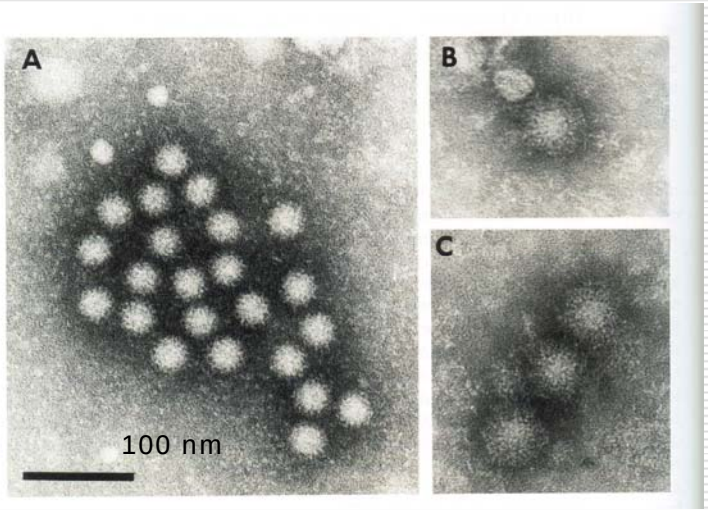
- Properties *(Adenoviridae)*
  - Genus: *Mastadenovirus*
  - dsDNA, 38 kb, 12 s. proteins
- Epidemiology
  - GE (serotypes 31,**40,41)**
  - Infantile diarrhoea (~10%)
- Pathogenesis
  - Incubation 3-10 days
  - Prolonged excretion (wk-mth)
- Clinical Features
  - Variable
  - Diarrhoea 6-9 days
- Diagnosis
  - EIA, IEM
  - Cultivable (Graham-293)



Sapovirus

- Properties
  - Family: *Calciviridae,* +ssRNA
  - 3 major genomic & antigenic diverse groups (genogroups)
    - I,II,III (GI, GII,GIII)
  - 3 ORF but genomic organisation differs from Norovirus
    - Polyprotein and capsid genes are fused into a single ORF (ORF1), open reading frame (3'-ORF), ORF overlapping capsid gene (capsid overlap, only in the GI strains) and 3' untranslated region (3'-UTR)
- Epidemiology
  - Causative agent of GE in children & adults worldwide
  - Infection occurs less frequently than Norovirus
  - Appears in sporadic cases but also in outbreaks
  - No seasonality reported
  - Transmission: person-to-person, foodborne
- Diagnosis
  - IEM, RT-PCR (Non-culturable)

Diagnostic Revolution?



- PCR for viral GIT pathogens
  - O'Neill, H.J. et al. (2002). Clinical utility of nested multiplex RT-PCR for group F adenovirus, rotavirus and norwalk-like viruses in acute viral gastroenteritis in children and adults.

    J. Clin. Virol. 25:335–343.
  - Han, Y et al. (2003). Detection of norovirus (GI, GII), Sapovirus and astrovirus in fecal samples using reverse transcription single-round multiplex PCR.

    J. Virol. Methods 114:37–44

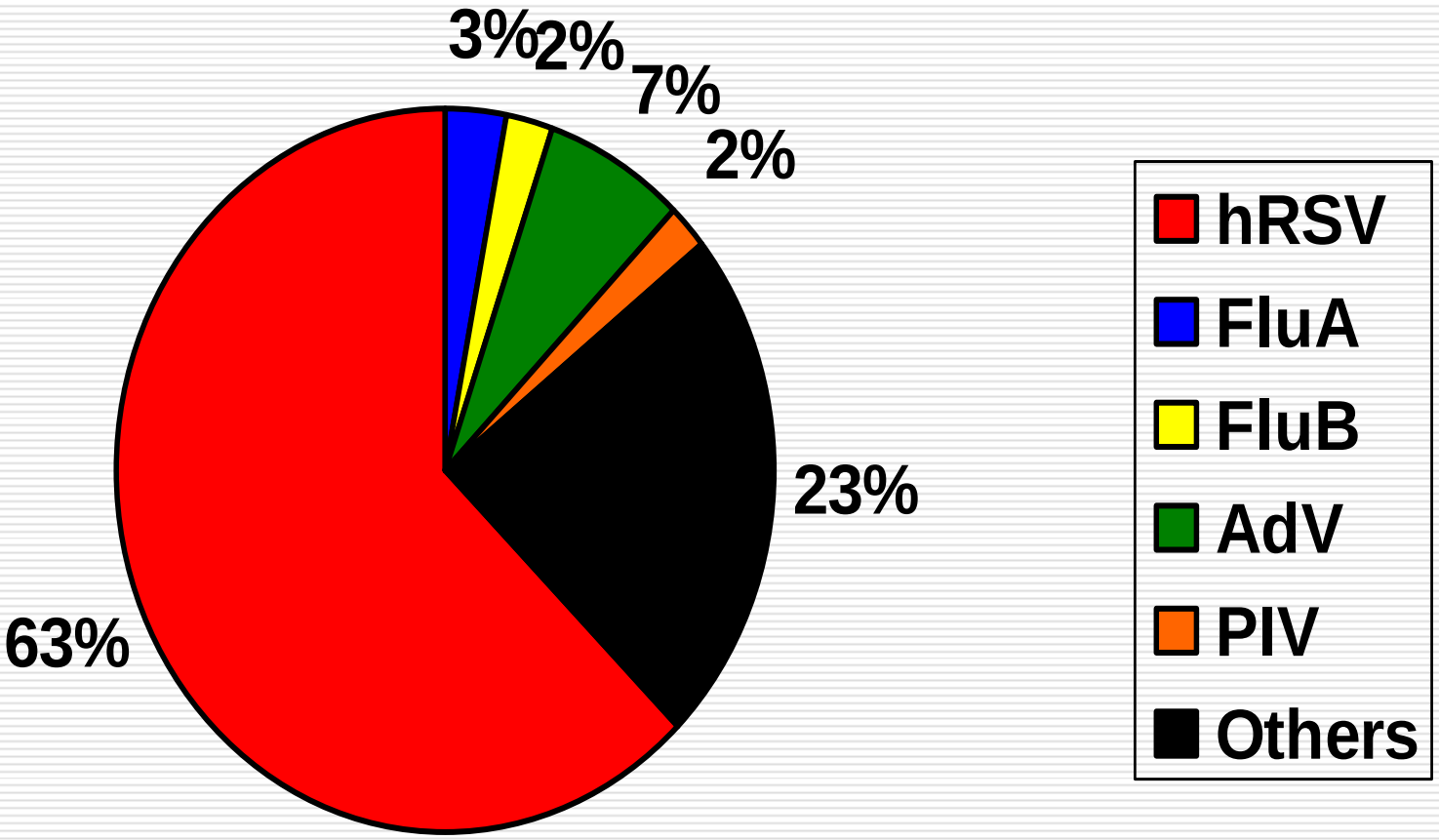
Childhood Respiratory Disease

- Respiratory infections are the most common afflictions of humans, and most are caused by viruses
- Estimated 5 million deaths from respiratory infections in children p.a. worldwide, at least 1 million are viral in origin
- Children, on average, contract 6-9 respiratory illnesses p.a.
  - significant proportion of all health care visits, and
  - unnecessary antibiotic use within the community.
- Serious viral lower respiratory tract infections due to RSV and influenza occur in the very young and elderly
  - increasing recognition of their role in immunocompromised individuals
- Respiratory viral disease has been revolutionised by;
  - molecular diagnostics, and
  - discovery and emergence of several “new” pathogens such as avian influenza, metapneumovirus, and the coronaviruses (HCoV-SARS, HCoV-NL63).

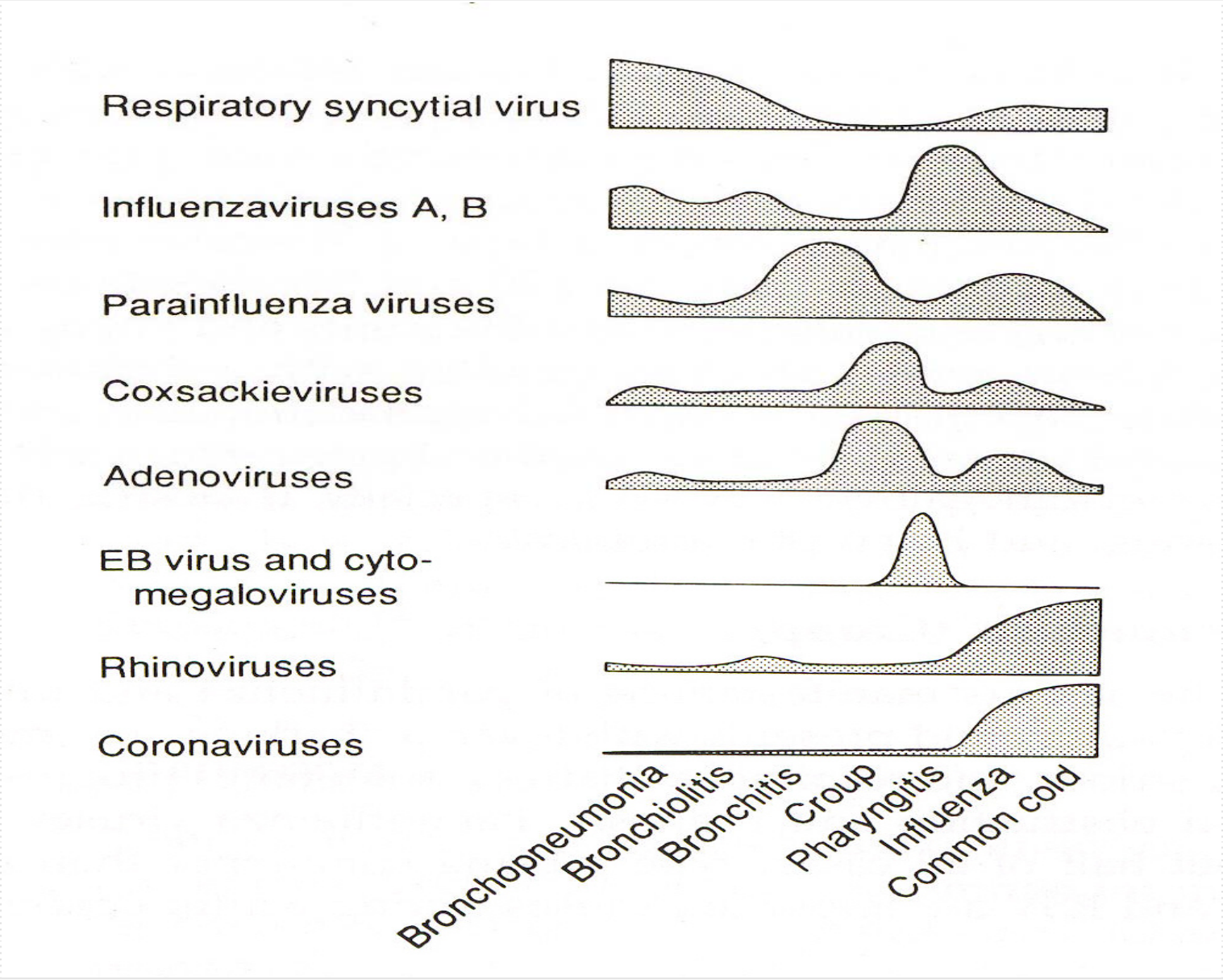
Childhood Respiratory Disease

- hRSV
- Influenza A & B
- Parainfluenza 1,2,3,4
- Adenoviruses
- Rhinoviruses
- Coronaviruses
- Enteroviruses
  - Coxsackie
  - Echo
- HSV/VZV
- EBV/CMV
- Measles
- Emerging Viruses
  - hMPV
  - HCoV-SARS
  - H5N1 influenza
  - HCoV-NL63

PAEDIATRIC VIRAL RESPIRATORY DISEASE



Simoes et al (2003) Pediatr.Infect.Dis.J.;22(2):S13-S20



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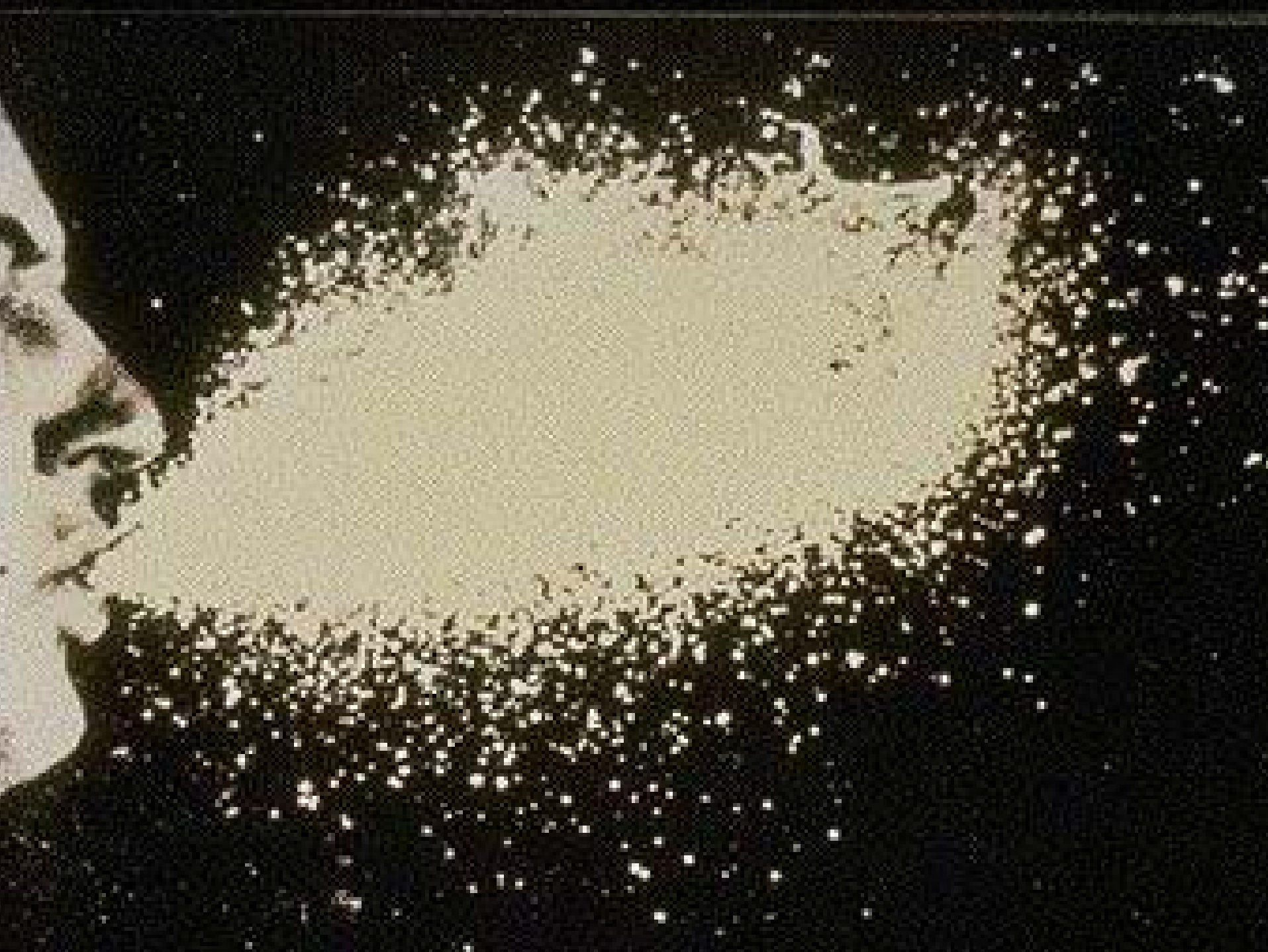
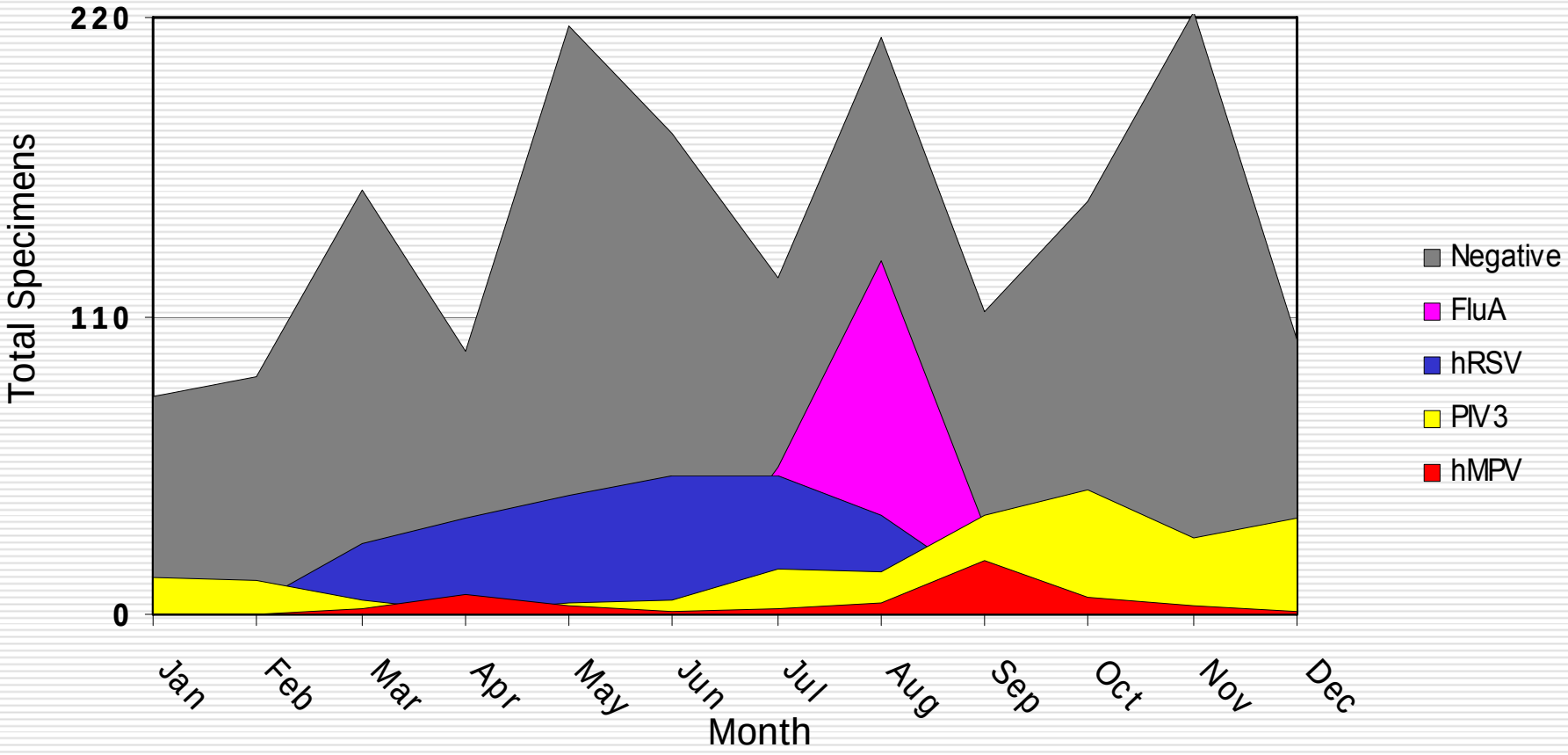
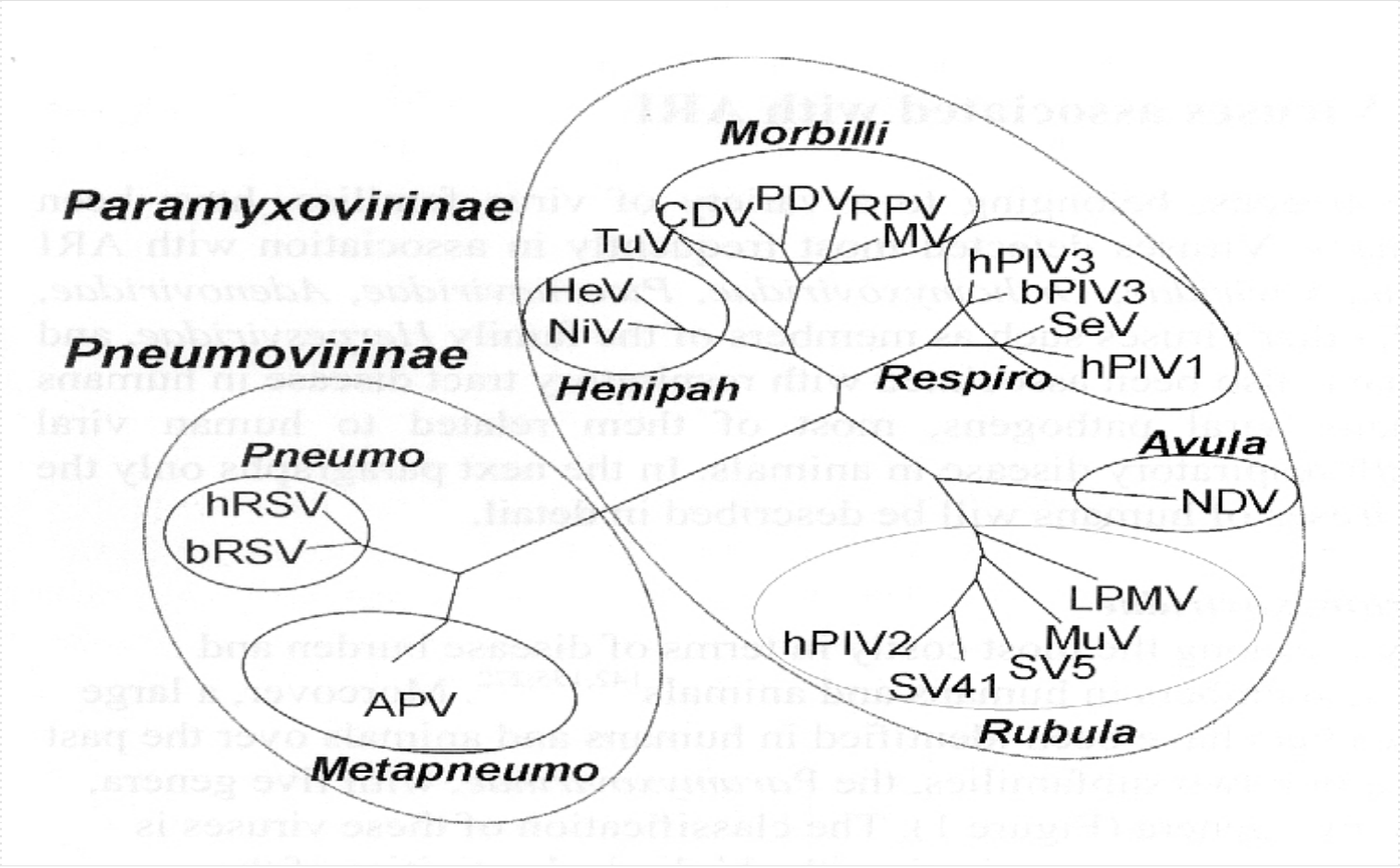


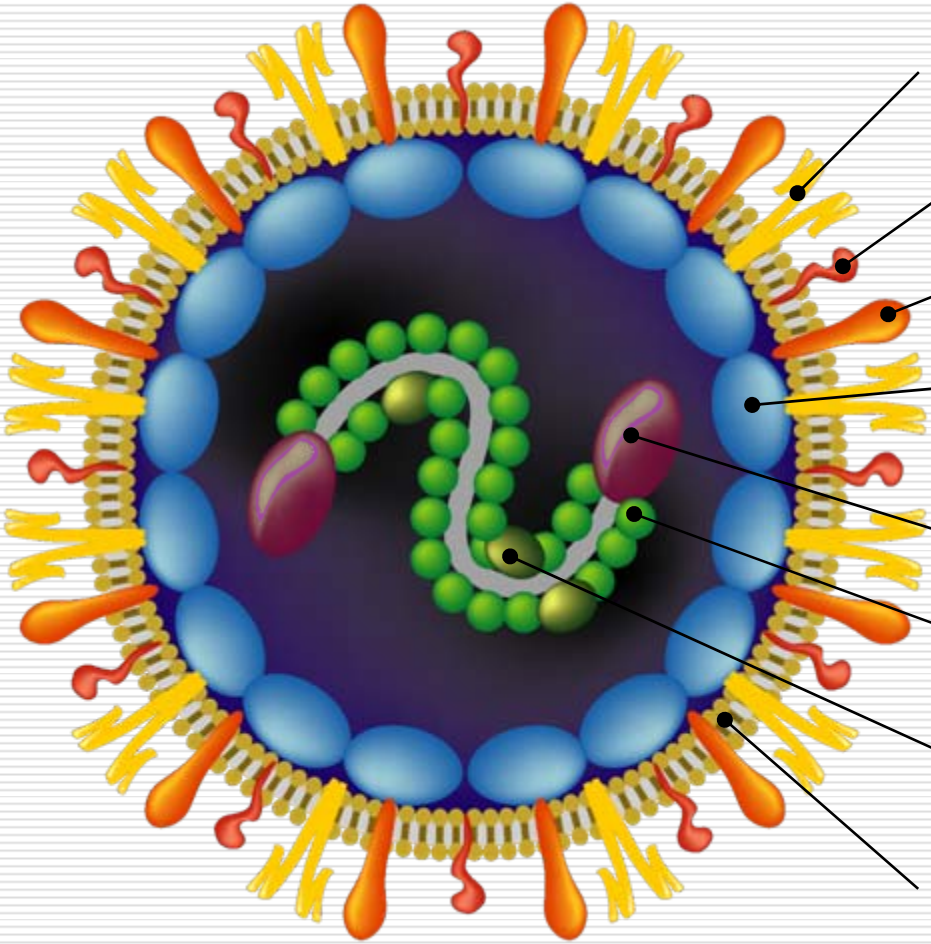
VIRAL INFECTIONS RCH 2001



Paramyxoviridae-Classification



Paramyxoviridae
General Morphology



Fusion protein (F)

SH protein

Attachment protein (G)

Matrix protein (M)

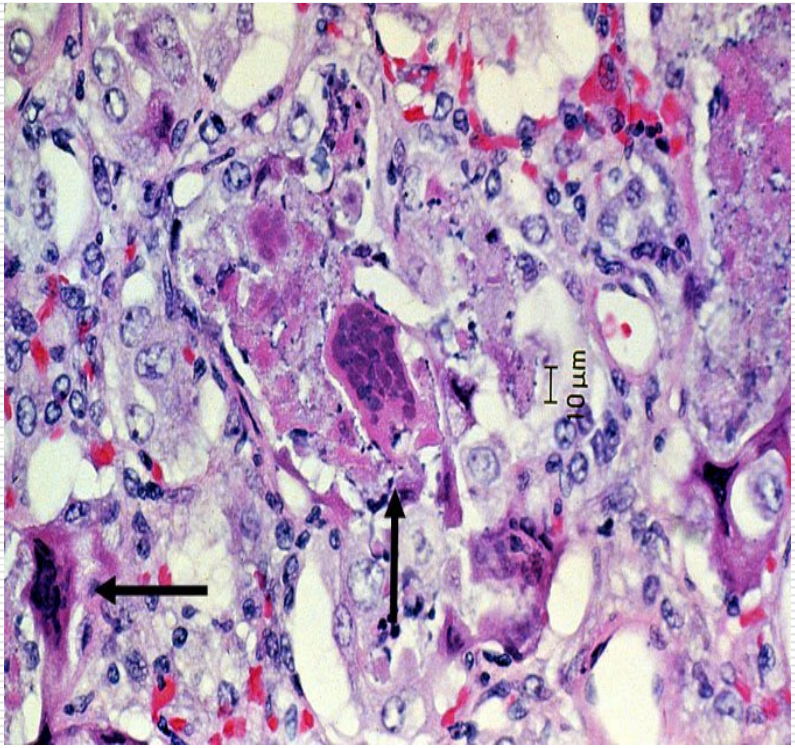
Polymerase (L)

Nucleoprotein (N)

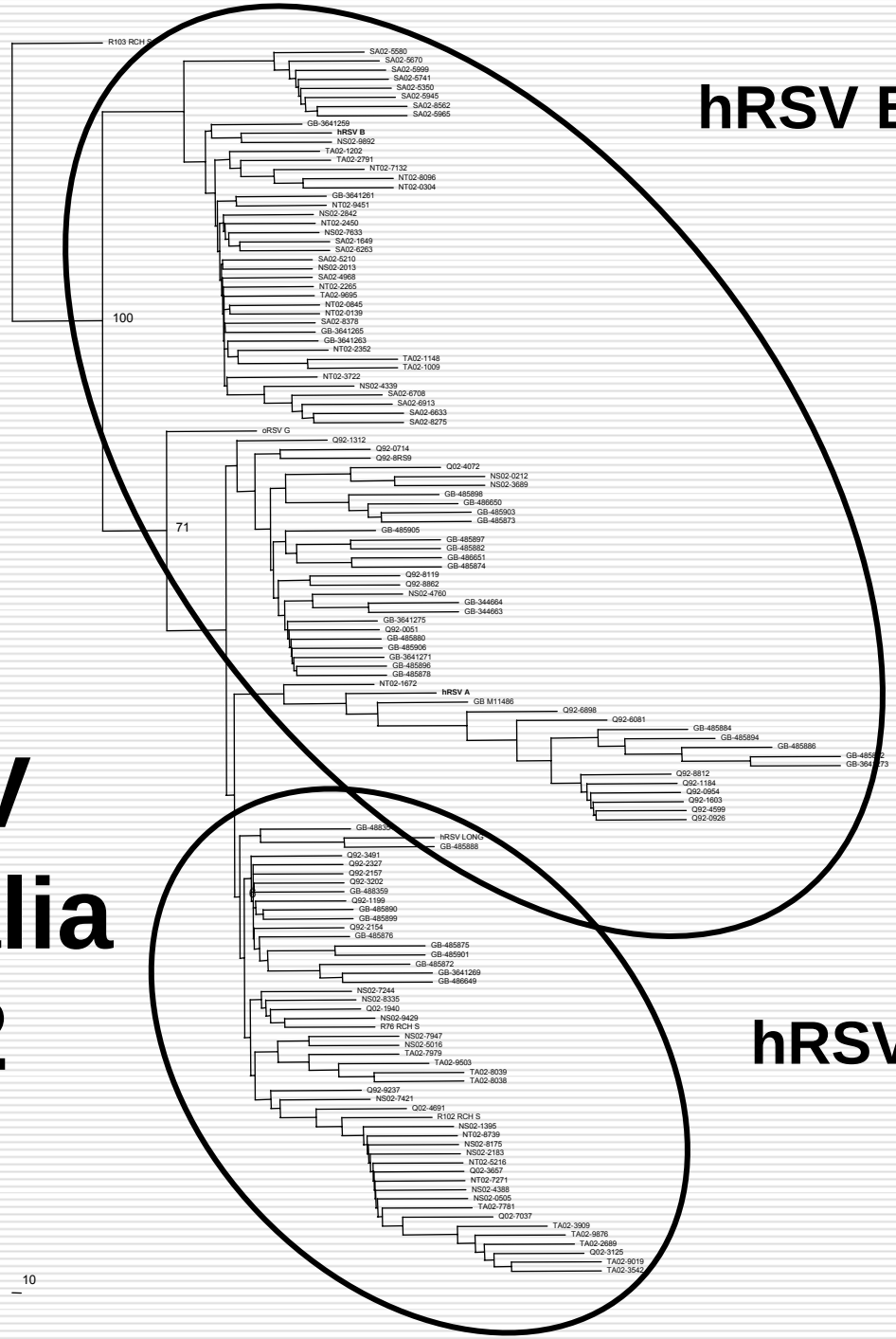
Phosphoprotein (P)

Lipid bilayer

hRSV



- Epidemiology
  - Principal cause of LRTI in infants worldwide
  - Annual seasonal variation
  - 2 major antigenic lineages: types A & B
- Pathogenesis
  - RT incubation 4-5 days
- Clinical Features
  - Acute bronchiolitis
  - Infections continue to occur throughout life
  - ↑ recognition in elderly & immunocompromised



hRSV Australia 2002

Qld

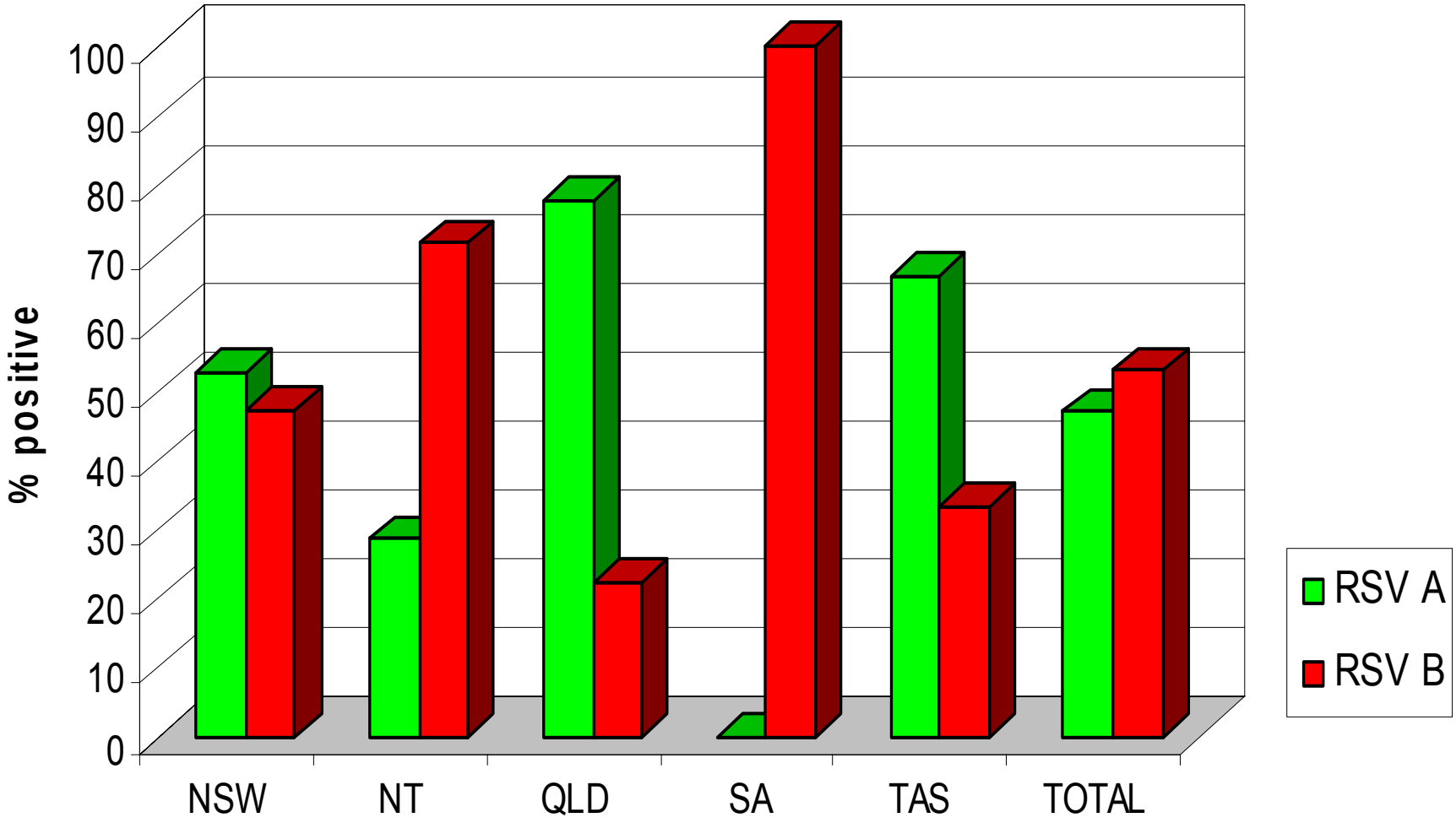
Tas

NT

NSW

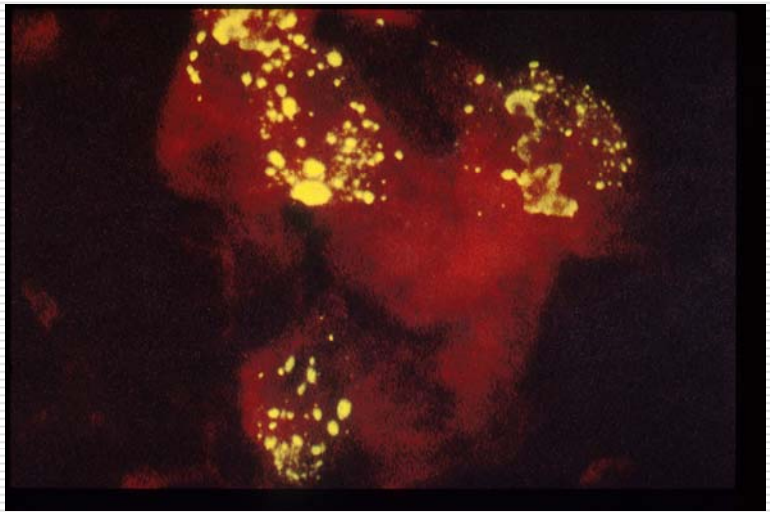
SA

Distribution of hRSV A and B in Australia

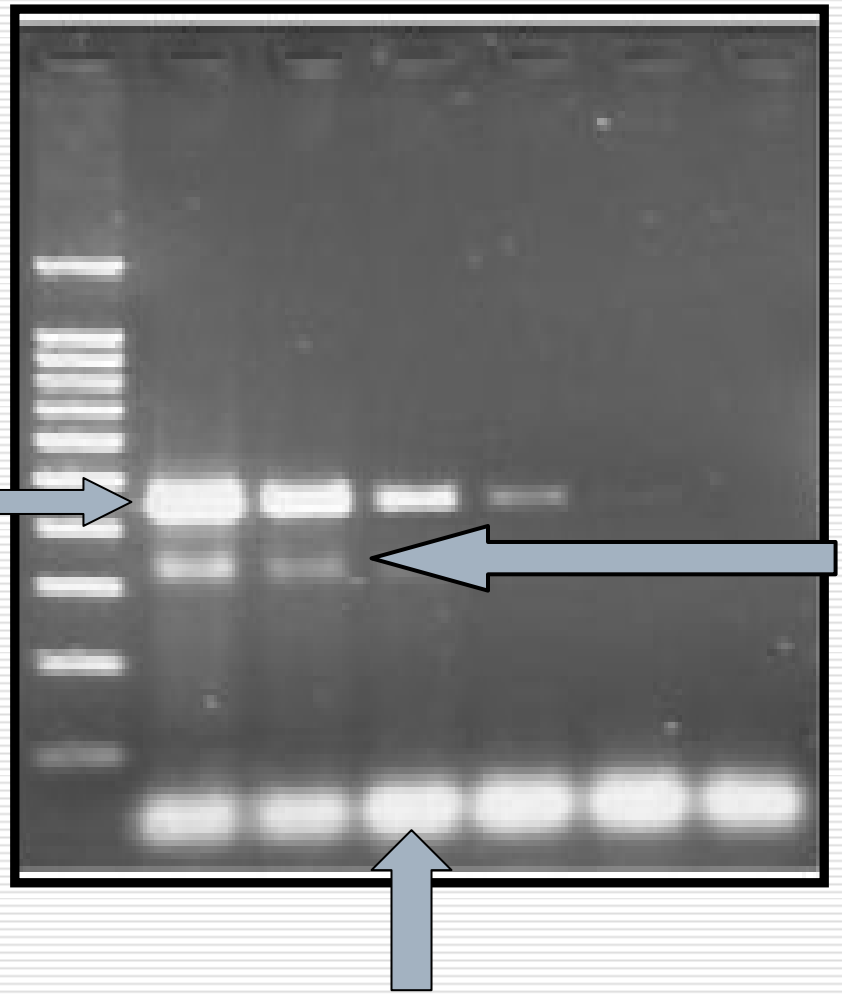


hRSV

- Diagnosis
  - DFA
  - Culture
  - RT-PCR
- Treatment
  - Supportive
  - ? Ribavirin
- Prevention
  - IVIG
  - Monoclonal IG (Palivizumab)
  - ? vaccine



Gel Electrophoresis



Subjective reading of band size

Non-specific bands

Primer-dimer

Respiratory Multiplex

Respiratory Multiplex

PROBES

SAMPLES / CONTROLS

1 2 3 4 5 6 7

RSV

PIV 1

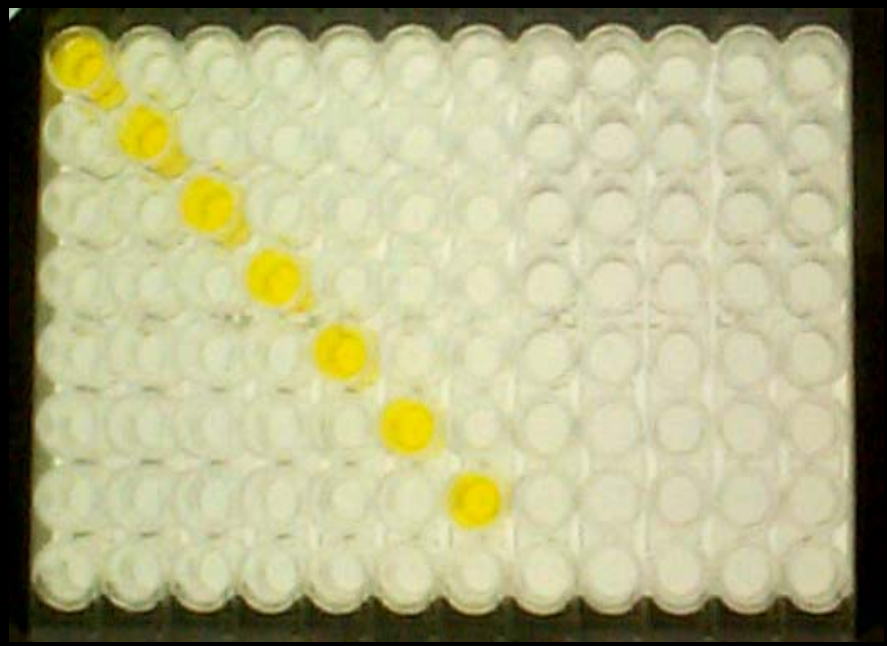
PIV 2

PIV 3

Flu A

Flu B

ADV



1: RSV + Control
2: PIV 1 + Control
3: PIV 2 + Control
4: PIV 3 + Control
5: Flu A + Control
6: Flu B + Control
7: ADV + Control

Respiratory Multiplex PCR

n=598	DFA/CADFA Positive	DFA/CADFA Negative
Multiplex Positive	**179**	**23**
Multiplex Negative	**0**	**396**

CA-DFA: Culture Amplified- Direct Fluorescent Antibody

Sensitivity=89%, Specificity=100%

PPV=100%, NPV=95%

Respiratory Multiplex PCR

n=598	DFA +		DFA -/CADFA +		DFA/CADFA -		m-RT-PCR-ELAHA +
	No.	(%)	No.	(%)	No.	(%)	No. (%)
ADV	11	**(65)**	3	**(18)**	3	**(18)**	**17 (100)**
Flu A	5	**(36)**	4	**(29)**	5	**(36)**	**14 (100)**
Flu B	2	**(100)**	0	**(0)**	0	**(0)**	**2 (100)**
PIV 1	1	**(17)**	4	**(67)**	1	**(17)**	**6 (100)**
PIV 2	5	**(71)**	1	**(14)**	1	**(14)**	**7 (100)**
PIV 3	29	**(88)**	0	**(0)**	4	**(12)**	**33 (100)**
RSV	108	**(88)**	6	**(5)**	9	**(7)**	**123 (100)**
Total	161	**(80)**	18	**(9)**	23	**(11)**	**202 (100)**

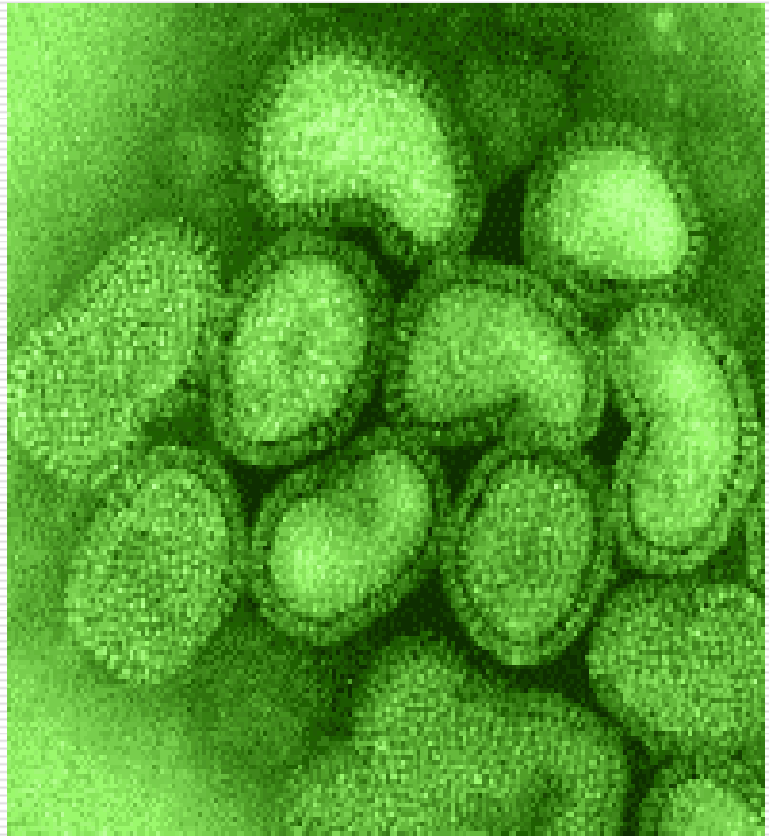
CA-DFA: Culture Amplified- Direct Fluorescent Antibody

Advantages of multiplex PCR

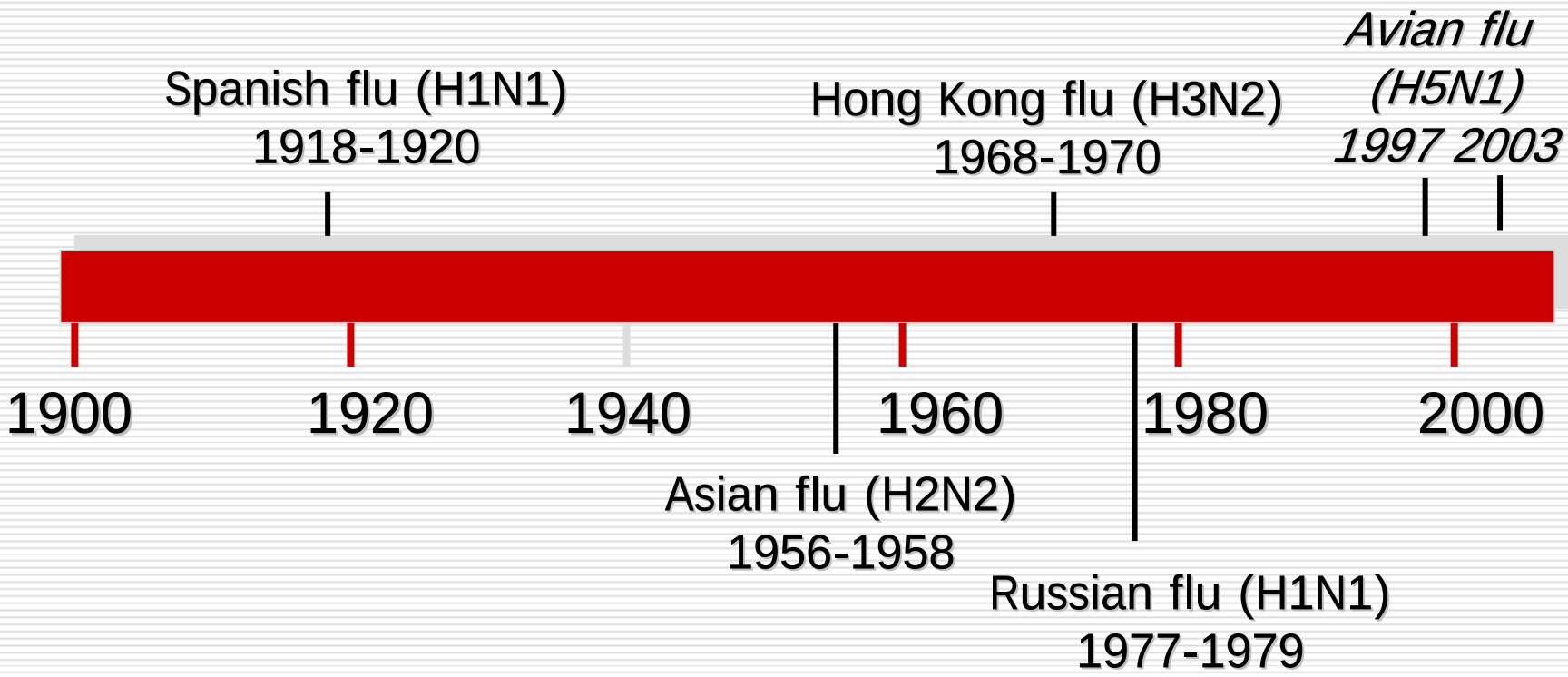
- Increased sensitivity over DFA and CA-DFA.
- High specificity equaling DFA and CA-DFA.
- Same day result turnaround time (~5 hrs)
- Reduced cost of diagnosis (PCR $18 v/s CA-DFA $35)
- Improved patient management & limit unnecessary antibiotic use
- Cost-effective
  - Reduced hands on time
  - Reduced use of consumables
  - Can detect up to seven virus types in one reaction

Influenza

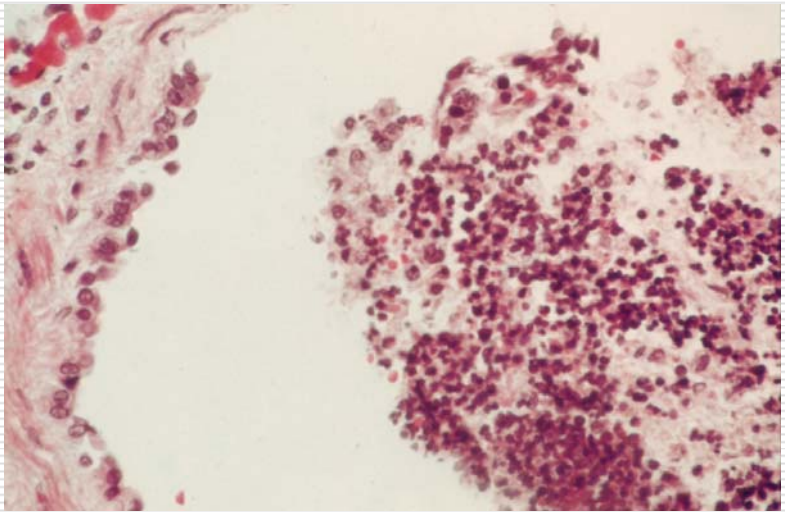
- Properties *(Orthomyxoviridae)*
  - 3 genera A,B,C
  - -ssRNA, 13.6 kb, 8 segments
- Epidemiology
  - Antigenic “drift” & “shift”
  - Seasonality
  - B less pathogenic
- Pathogenesis
  - Transcription/replication in cell nucleus
  - Incubation 1-4 days
  - Large no. of virions shed

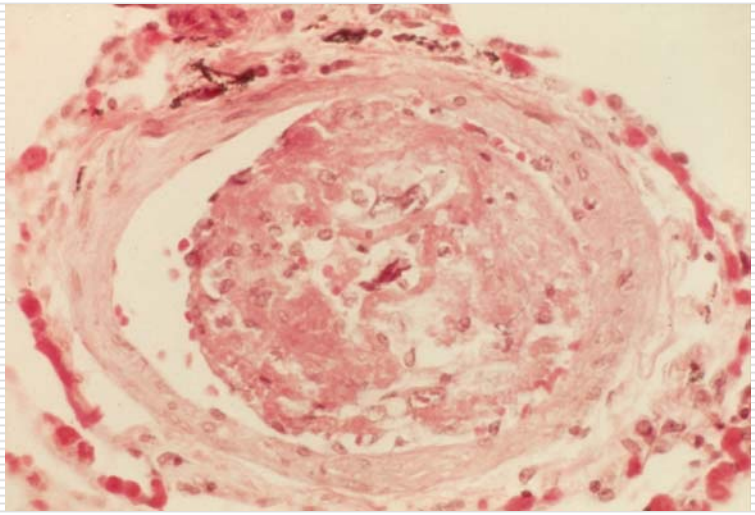


Influenza Epidemics



Influenza





- Clinical Features
  - Abrupt onset of fever, sore throat, cough, myalgia, headache, malaise.
  - Duration 3-7 days
  - Complications vary with age: croup, pneumonia, OM
  - 2^0 bacterial pathogens: *S. aureus, S. pneumoniae, H. influenzae.*

Influenza

- Control
  - Surveillance
  - Vaccination

Influenza trivalent vaccine (2004)

A/New Caledonia/20/99

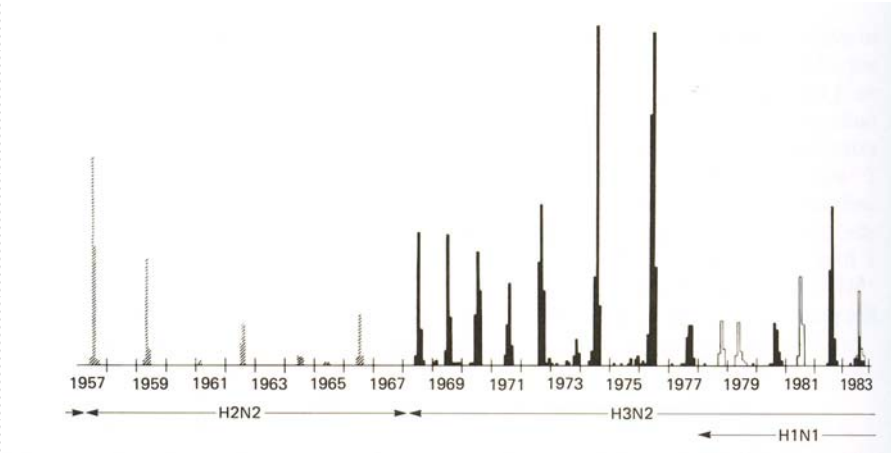
H1N1

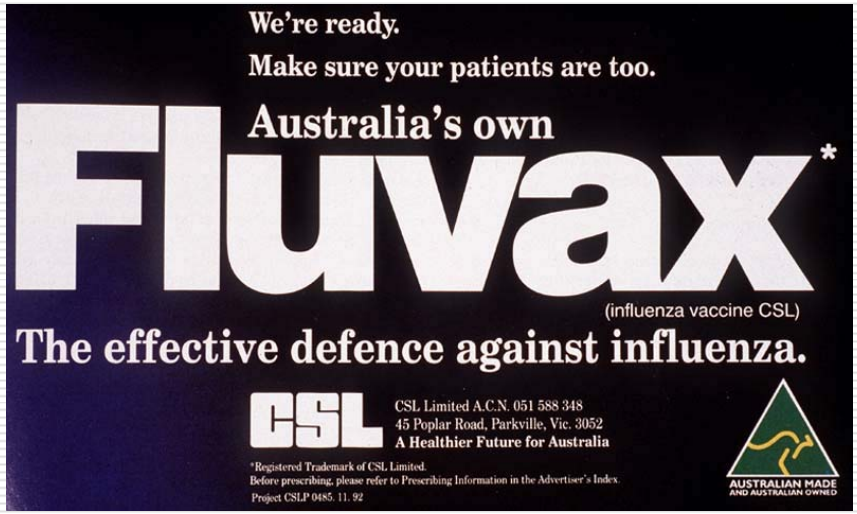
A/Fujian/411/2002

H3N2

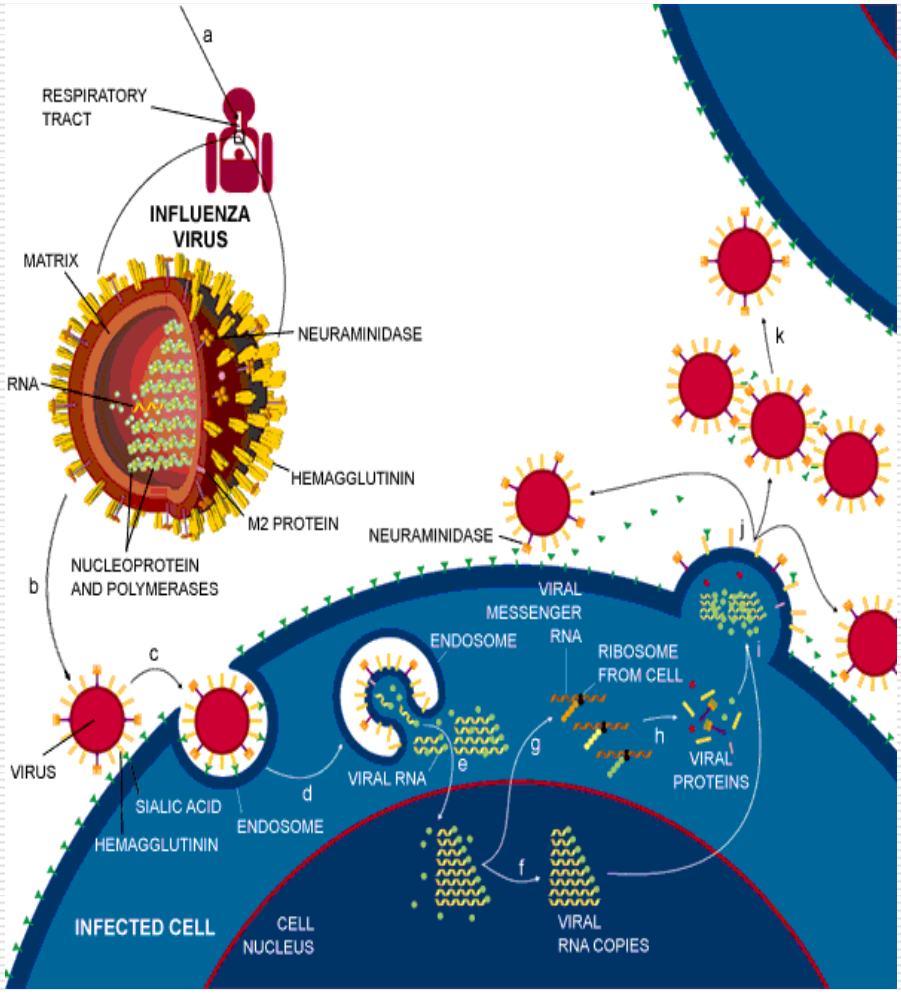
B/Hong Kong/330/2001

- Is it time to immunise kids?



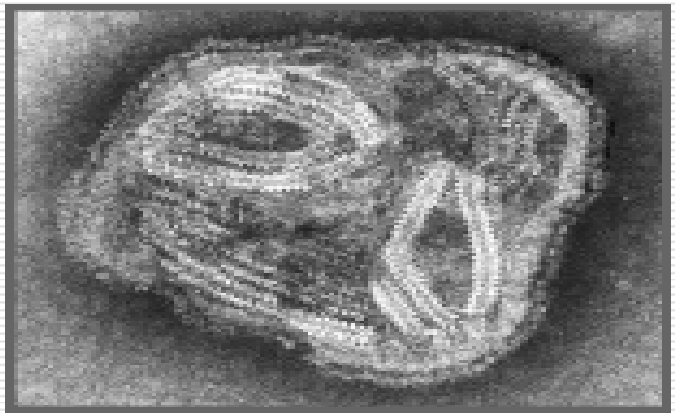


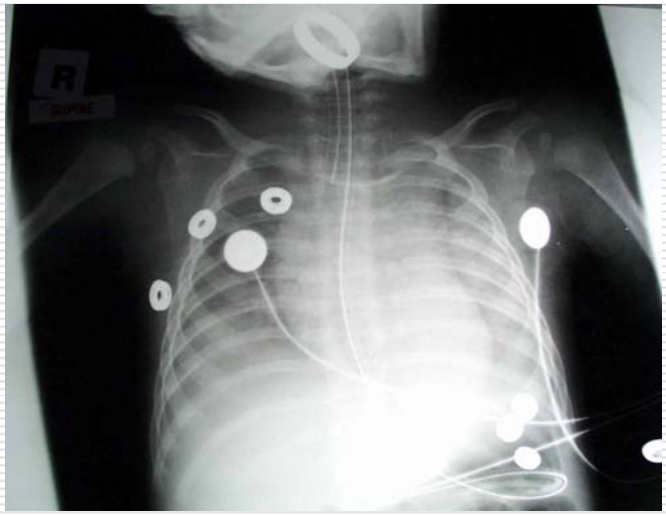
Influenza



- Treatment
  - Neuramidase inhibitors
  - Commence within 24-48 hrs of symptoms
  - Oseltamivir (Tamiflu™)
    - Capsules/powder
    - ≥ 1yoa
  - Zanamivir (Relenza™)
    - Rotadisc powder
    - ≥ 5 yoa
  - ? Prophylactic use

Parainfluenza Viruses





- Properties *(Paramyxoviridae)*
  - -ssRNA, 15 kb, 6-7 genes encoding 10-12 proteins
  - Types 1 & 3-*Respiriovirus*
  - Types 2, 4a & 4b-*Rubulavirus*
- Epidemiology
  - Types 1 & 2-"croup"
  - Type 3 infects majority by 2 yoa
- Pathogenesis
  - Incubation 2-6 days
  - Shedding ~7 days
- Clinical Features
  - <6 mth-acute bronchiolitis
  - 6mth-5 yoa: croup
- Diagnosis
  - DFA, Culture, RT-PCR
- Treatment
  - Symptomatic, PNSL

Diseases Caused by Human Adenoviruses

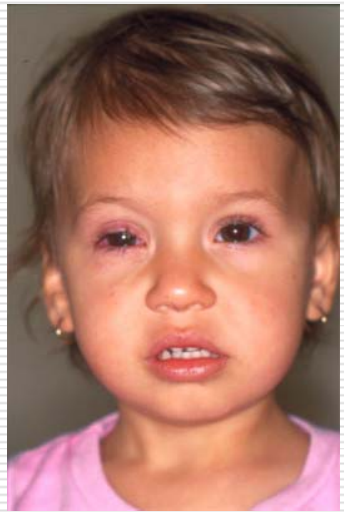
Disease	Age	Common serotypes[a]	Major subgenus	Major source
Respiratory infections				
Pharyngitis	Young children	**1, 2,** 3, **5,** 6, 7	B, C	Throat
Acute respiratory disease	Military recruits	3, **4, 7,** 14, 21	B, E	Throat
Pneumonia	Young children	1, 2, **3,** 4, 5, **7,** 21	B, C	Throat
	Military recruits	**4, 7**	B, E	Throat
Ocular infections				
Pharyngoconjunctival fever	Children	1, 2, **3, 4,** 6, **7**	B, C, E	Throat, eye
Epidemic keratoconjunctivitis	Any age	**8,** 19, **37**	D	Eye
Genitourinary infections				
Cervicitis, urethritis	Adults	19, **37**	D	Genital secretions
Hemorrhagic cystitis	Young children	**11,** 21	B	Urine
Enteric infections				
Gastroenteritis	Young children	31, **40, 41**	A, F	Feces
Infections in immunocompromised individuals				
Encephalitis, pneumonia,	Any age, including AIDS patients	7, **11, 34, 35**	B	Urine, lung
Gastroenteritis	AIDS patients	Many D including 43–47	D	Feces
Generalized	AIDS patients	2, 5	C	Blood

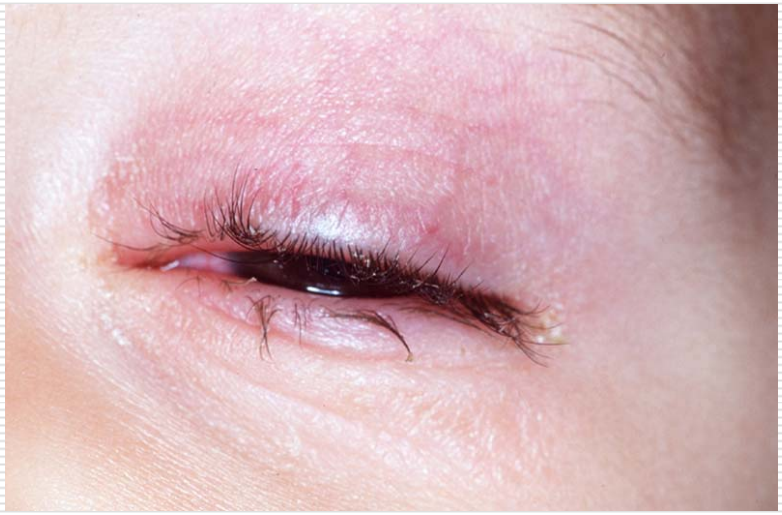
[a] Only the commonly occurring serotypes are listed; those most commonly associated with particular syndromes are in bold type.

Medical Virology, Fenner & White, 4th Edition, 1994

Adenoviruses

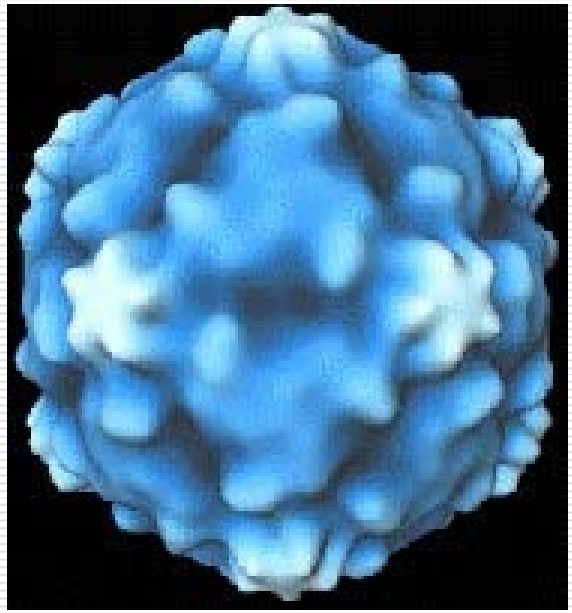
- Clinical syndromes
  - Cold-like syndrome
  - Pharyngo-conjunctival fever
  - Pertussis-like illness
  - Acute respiratory distress
  - Rapidly fatal haemorhagic pneumonia in immunocompromised
- Diagnosis
  - DFA, Culture, PCR, Serology
- Treatment
  - ? Ribavirin
- Control
  - Vaccination is available to certain populations for ARD
  - live & virulent virus
  - serotypes 4 & 7





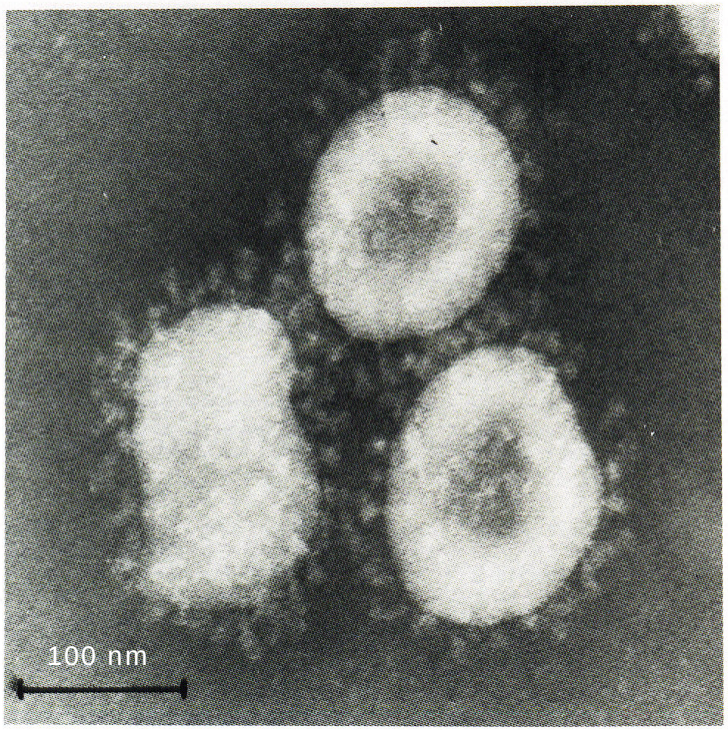
Rhinovirus

- Properties *(Picornaviridae)*
  - +ssRNA, 7-8 kb
  - Virion acts as mRNA, transcribed as a polyprotein and cleaved progressively to yield S & NS proteins
  - Acid-labile (ph<5)
  - Rhinoviruses 1-100
- Epidemiology
  - Year-round infection
  - Peaks in autumn & spring
  - 3-4 serotypes circulate simultaneously
- Pathogenesis
  - Predilection to replicate @ 33^{o}C
  - Acquired immunity type specific and correlates with locally synthesized IgA antibodies
- Clinical Features
  - "common cold"
  - ↑ recognition in LRTI & wheezing/asthma
- Diagnosis
  - EIA, PCR, culture



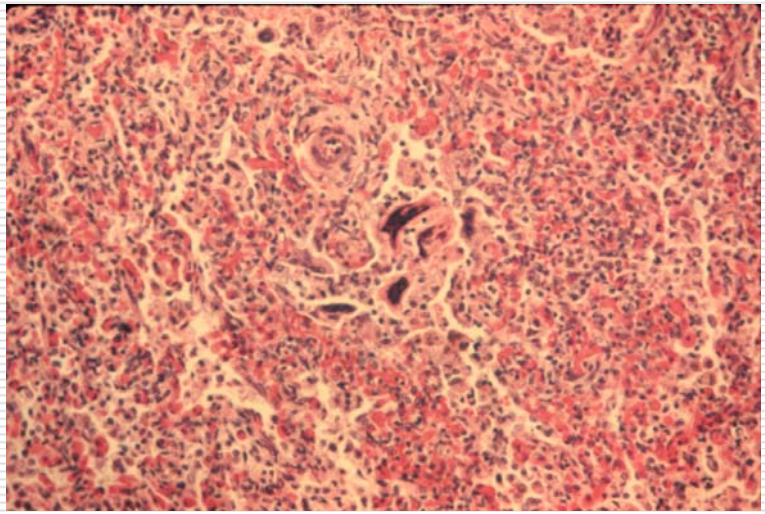
Rhinovirus 14

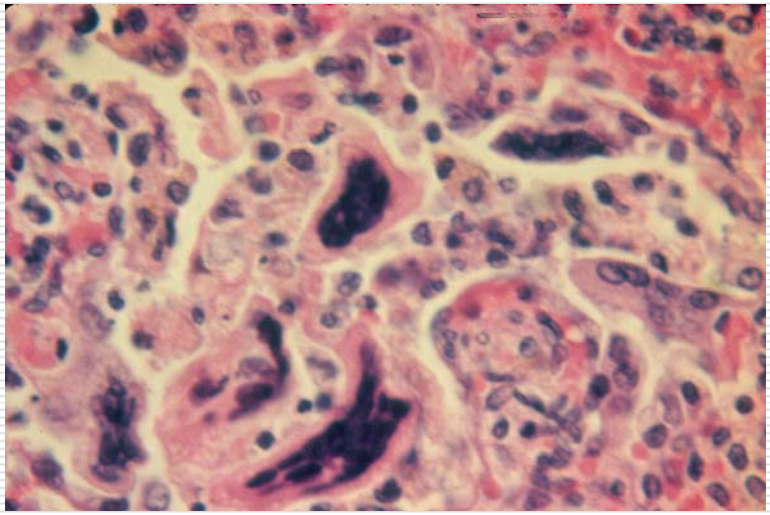
Coronaviruses



- Properties *(Coronaviridae)*
  - +ssRNA, 30 kb
  - 3-4 struct. proteins (N, S, M, HE)
  - 4 serotypes:
    - HCoV-229E, OC43, SARS, NL63
- Epidemiology
  - Incubation of 2-5 days
  - Viral shedding ~ 1week
  - Peaks in winter & early spring
  - Outbreaks ~ every 2-4 years
- Pathogenesis
  - Unique replication strategy
- Clinical Features
  - “common cold” (~15%)
  - Nosocomial infections
- Diagnosis
  - EIA
  - PCR
  - Difficult to grow (organ cultures)

Measles





- Measles pneumonia with lymphocytic infiltration and large multinucleated cells
- High power of measles pneumonia. Note the large multinucleated giant cells, named Warthin-Finkeldey cells

hMPV

Human metapneumovirus (hMPV) is a novel respiratory tract pathogen

First known mammalian MPV

Avian metapneumovirus (APV) is the only other known MPV

hMPV is now considered ubiquitous

- PCR detection
- Seroprevalence

} studies

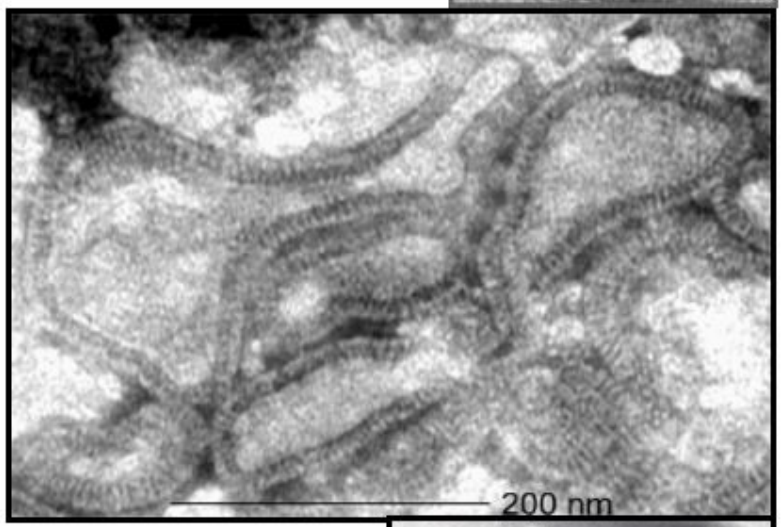
Features are thought to be similar to
human respiratory syncytial virus (hRSV)

ULTRASTRUCTURE

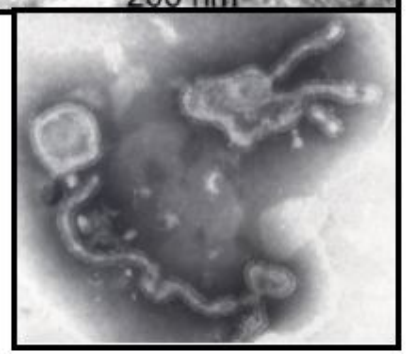
Nature Medicine 2001 7(6):719-724

Nucleocaspid
– single stranded negative sense RNA

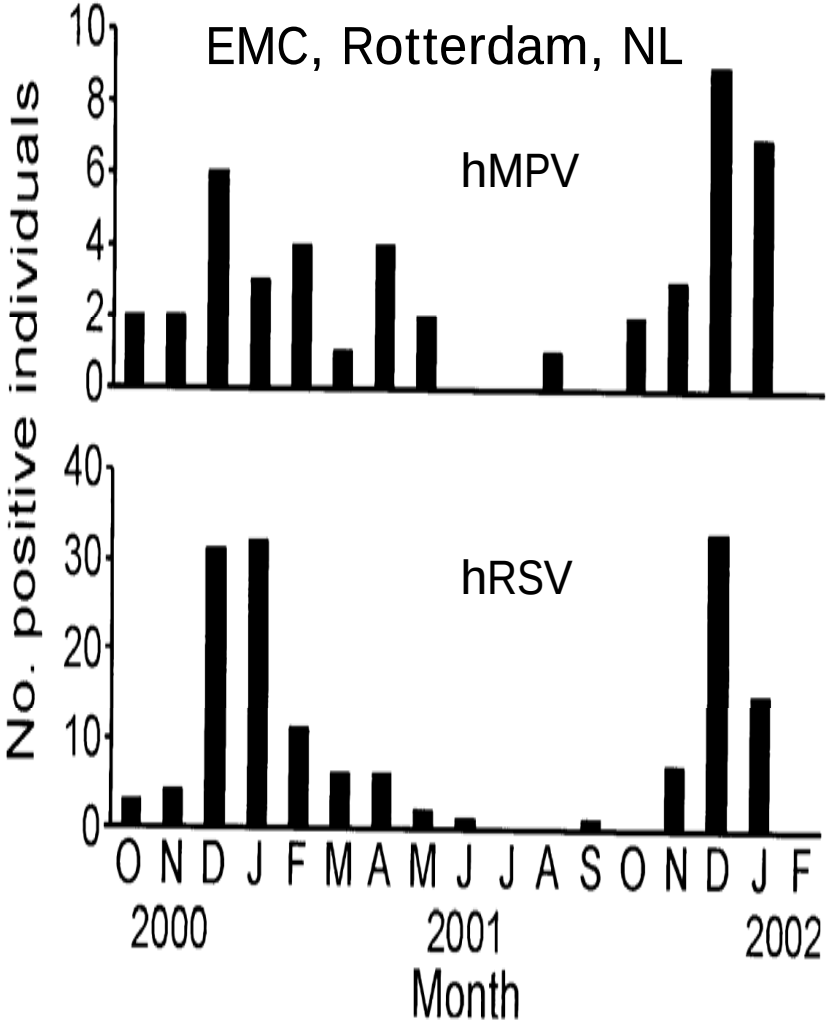
Viral particles as seen by EM
– spherical, pleomorphic
& filamentous
- 150 – 600 nm diameter
- short envelope projections
13-17 nm



Nucleocaspid
- average diameter 17 nm
- length range <200 - >1000 nm
- filamentous particles average 282 x 62 nm



hMPV Seasonality



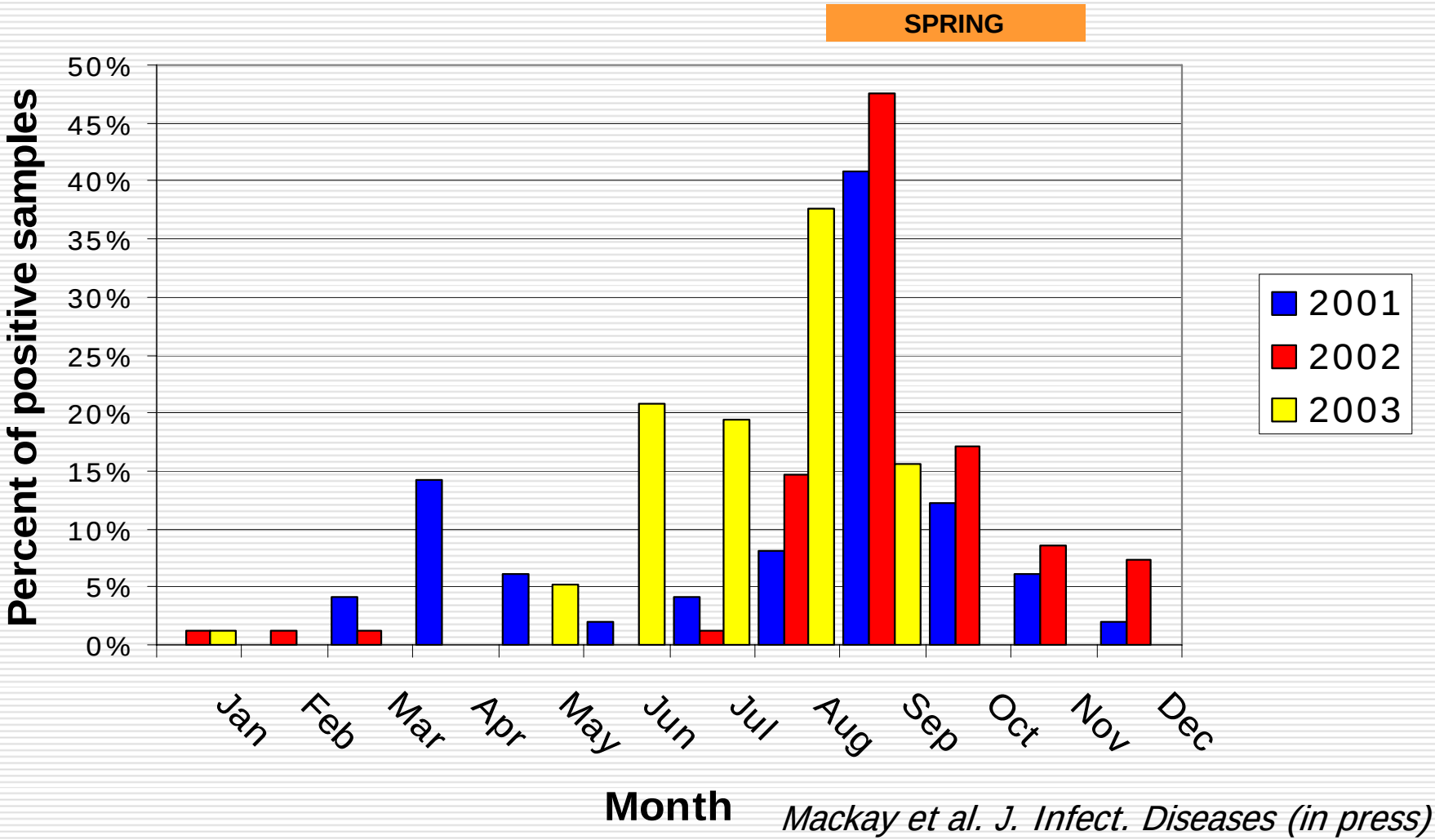
Nature Medicine 2001 7:719

Qld hMPV Testing

	Tested	hMPV PCR positive	Incidence (%)
2001	915	58	**6.3**
2002	2121	82	**3.9**
2003	1972	73	**3.7**
TOTALS	5008	213	**4.2**

Mackay et al. J. Infect. Diseases (in press)

Qld hMPV Monthly Incidence



Mackay et al. J. Infect. Diseases (in press)

Qld hMPV Seasonal Incidence

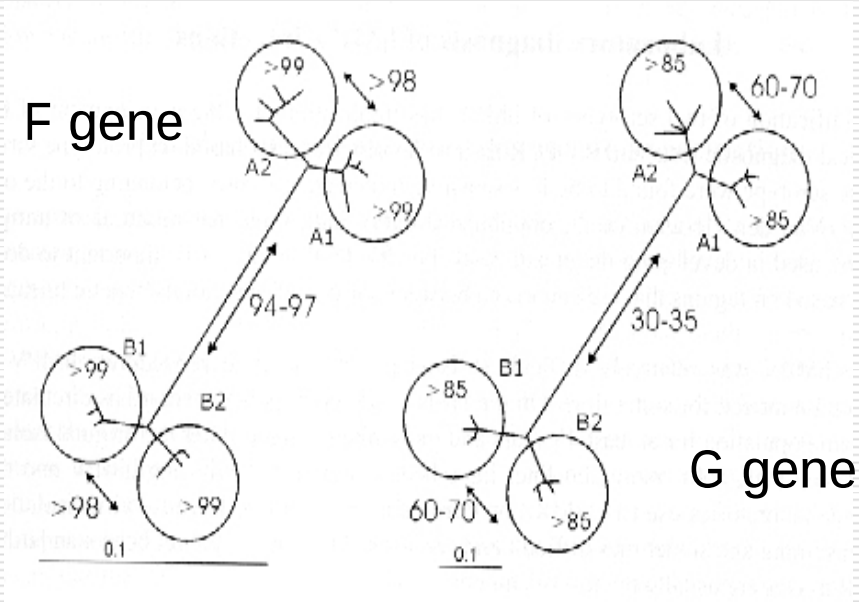
	Summer	Autumn	Winter	Spring
2001	2.9	34.3	17.1	**45.7**
2002	9.8	1.2	15.9	**73.2**
2003	1.4	5.5	**80.8**	12.3
Totals	5.7	9.7	30.3	**54.3**

Mackay et al. J. Infect. Diseases (in press)

hMPV Heterogeniety

- 2 hMPV lineages
- 4 hMPV sub-lineages

- F protein (95% conserved) between lineages
- G protein (30 % conserved)

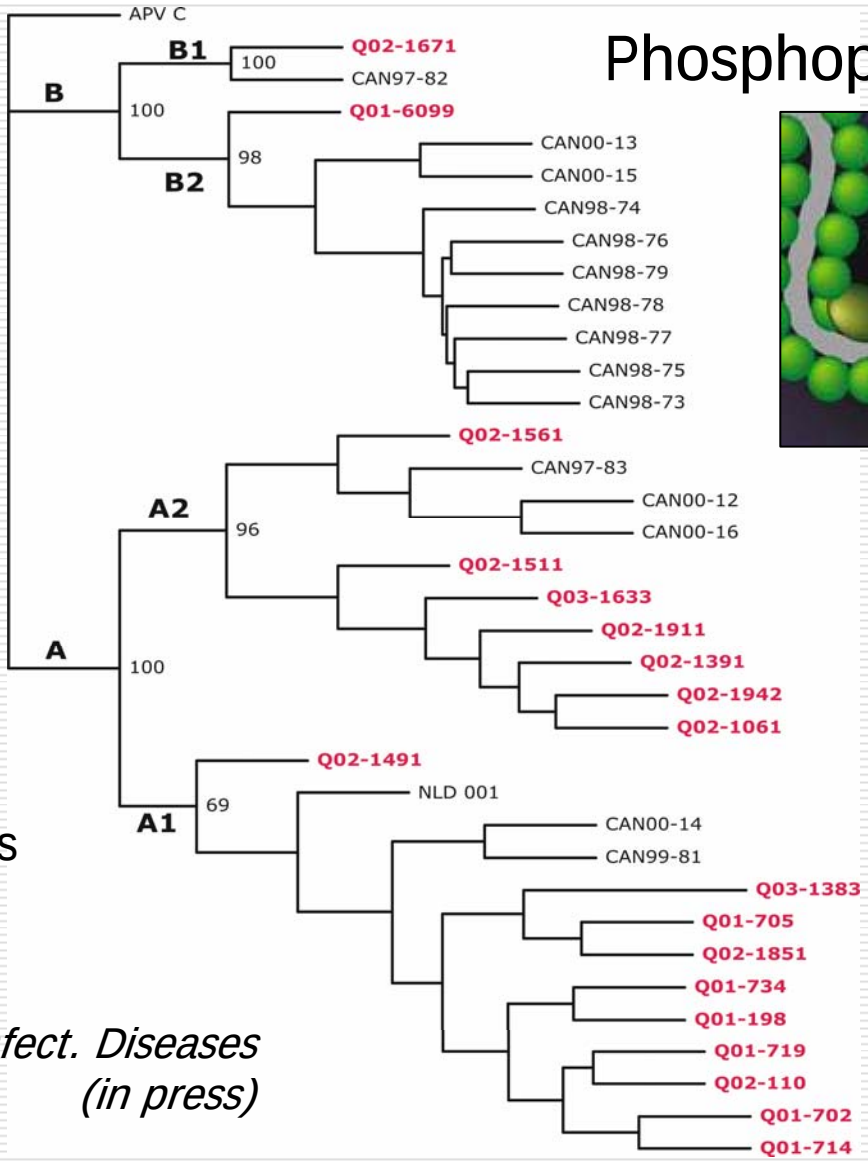


- Overall 80-81% whole genome nt identity between lineages

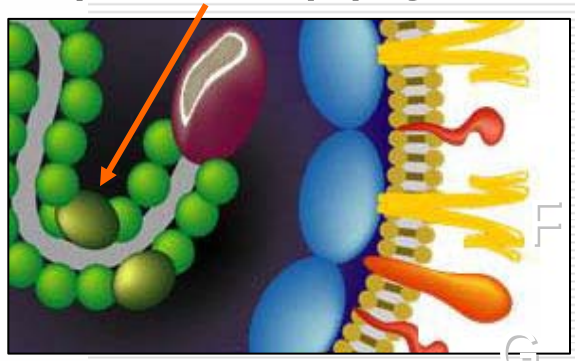
- 92-93% identity between strains belonging to same lineage

van den Hoogen BG, PhD thesis, 2004

Australian hMPV Phylogeny



Phosphoprotein (P) gene



2 virus types

4 virus subtypes

exist in Australia

Mackay et al. J. Infect. Diseases (in press)

Coinfections with hMPV

2001 (n=58)	**Number**	**Incidence (%)**
Influenza A	5	8.6
Adenovirus	4	6.9
PIV 3	1	1.7
RSV	1	1.7
Total virus	**11**	**19**
S. pneumoniae	1	1.7
B. pertussis	1	1.7
Total bacteria	**2**	**3.4**
Total pathogens	**13**	**22.4**

HCoV-SARS

- Newly recognised and highly contagious respiratory infection by a novel coronavirus
  - Progressive respiratory failure in adults
  - Mortality rate 8–15%
  - Droplet & faecal transmission
  - Role of hMPV?
- Children acquire SARS through close household contact exposure with adults...less infective?
- Disease severity is milder in children
  - No case fatalities recorded
  - Air space consolidation is commonly seen though chest radiographs are normal in 50% of the cases
  - Neonates of infected mothers not affected....reasons?

H5N1 Influenza

- Recent outbreaks of avian influenza A (H5N1) in poultry throughout Asia have had major economic and health repercussions.
- 10 Human infections identified in Vietnam in January 2004
  - Mean age, 13.7 years (range
  - None had preexisting medical conditions
- **Clear history of direct contact with poultry**
  - Median time before onset of illness=3 days
- All presented with;
  - Fever (T 38.5-40.0°C)
  - Respiratory symptoms,
  - Marked abnormalities on CXR, and
  - Clinically significant lymphopenia (median count 700)
- Nine (9) thrombocytopaenic (median count 75,500)
- Seven (7) patients had diarrhoea
- **No definitive evidence** of human-to-human transmission
- Eight (8) patients died

HCoV-NL63

- Identification and characterization of a novel coronavirus
  - *Van der Hoek et al. (2004) Nature Medicine (on-line 21 March 2004)*
  - *Fouchier RM et al. (2004) PNAS 101(16):6212*
- Isolation from 2 children with LRTI (7 & 8 mths) then further 11 cases
- Distinctive full genome sequence revealed a new Group 1 HCoV (43-67% id)
  - Unique N-terminal fragment within spike protein
  - Closest relatives:HCoV-229E & porcine epidemic diarrhea virus
- Replication *in-vitro:* tertiary MK & LLC-MK2

Table 3. Patients suffering from RTI associated with HCoV-NL infection

Age	Gender	Sample date	Symptoms	Underlying disease
5 mo	Male	January 12, 1988	Pneumonia	Unknown
3 mo	Female	November 1, 2000	Fever (39.4°C) Runny nose	Giant cell hepatitis
4 mo	Female	December 19, 2000	Subfebrile (37.6°C) Runny nose	Trisomy-21 AVSD
4 mo	Female	January 18, 2001	Subfebrile (37.8°C) Sever cough	Pertussis
10 yr	Female	January 18, 2001	Fever (38.6°C) Runny nose Dry cough	Rett syndrome Epilepsia

AVSD, atrioventricular septum defect.

Fouchier RM et al. (2004) PNAS 101(16):6212


Acknowledgements to CVRU & MMRU, SASVRC, RCH
Unofficially sponsored by Lowes

Thank you
Questions?

Table 1. Hospitalisation rates due to acute respiratory disease in children without high-risk conditions

Period and age group	Rate/100 000 person-months (95% CI)	
	Northern California Kaiser, 1998–1997	Group Health Cooperative, 1992–1997
Period when influenza virus predominated		
0–1 year	231 (197–271)	193 (154–238)
2–4 years	53 (38–72)	21 (11–38)
5–17 years	19 (15–24)	16 (12–22)
Period when respiratory syncytial virus predominated		
0–1 year	309 (278–343)	372 (321–428)
2–4 years	51 (40–64)	44 (29–65)
5–17 years	23 (19–27)	10 (7–13)
Periseasonal baseline period		
0–1 year	120 (108–133)	107 (85–133)
2–4 years	38 (32–44)	24 (14–37)
5–17 years	14 (12–16)	10 (7–13)
Summer baseline period		
0–1 year	81 (72–90)	66 (49–87)
2–4 years	27 (23–32)	16 (8–25)
5–17 years	19 (17–21)	12 (9–14)

CI=confidence interval. Adapted from reference 10.

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Table 2. Effect of illness episodes on school and family in 313 schoolchildren monitored during an influenza season

Variable	Influenza-attributable events per 100 children
Illness episodes	27·8
Missed school days	62·9
Febrile illnesses	28·1
Antibiotic courses	–0·64
Analgesics used	24·0
Health-care visits	4·2
Working days missed by parent	19·8
Household members ill in the 3 days after absence	21·7

Values calculated by subtracting expected from reported outcomes during an influenza season. An excess event rate per 100 children was generated by dividing by the number of children in the cohort (n=313) and multiplying by 100. Adapted from reference 14.

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Table 3. Social effect of influenza among the household contacts of otherwise healthy children with respiratory-tract infections

	Household contacts of children with influenza diagnosis	
	Positive (n=915)	Negative (n=9128)
Hospitalisation (%)	3 (0·3)	11 (0·1)
Parents (%)	2/704 (0·3)	7/6838 (0·1)
Siblings (%)	1/211 (0·5)	4/2290 (0·2)
Additional medical visits, mean (SD)	0·39 (0·76)*	0·14 (0·47)
Parents (%)	0·28 (0·55)*	0·07 (0·25)
Siblings (%)	0·48 (0·98)*	0·22 (0·73)
Lost working days (parents), mean (SD)	1·39 (3·09)*	0·59 (2·02)
Lost school days (siblings), mean (SD)	1·27 (2·47)*	0·49 (2·33)
No of days help was needed to care for ill children, mean (SD)	1·10 (1·76)*	0·85 (1·63)

*p<0·0001 *vs* influenza-negative children; no other significant differences. Adapted from reference 12.

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Table 4. Estimated rates of influenza-associated hospitalisation by age group and risk group from selected studies*

Study years	Population	Age group	Hospitalisations/ 100 000 people with high-risk conditions	Hospitalisations/ 100 000 people without high-risk conditions
1973–1993	Tennessee	0–11 mo	1900	496–1038
1973–1993	Medicaid	1–2 yr	800	186
		3–4 yr	320	86
		5–14 yr	92	41
1992–1997	Two health-maintenance organisations	0–23 mo		144–187
		2–4 yr		0-25
		5–17 yr		8–12

*Rates estimated in years and populations with low vaccination rates. Hospitalisation rates can be expected to decrease as vaccination rates increase. Adapted from reference 1.

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Table 5. Reactogenicity rates in studies of T-CAIV in healthy children aged 1–8 years

Events*	After dose 1		After dose 2	
	T-CAIV (%)	Placebo (%)	T-CAIV (%)	Placebo (%)
Cough	26·9	28·7	27·4	29·0
Runny nose/nasal discharge	57·6	48·0	42·9	42·2
Congestion	10·0	8·6	6·6	7·4
Sore throat	9·5	7·1	6·1	6·4
Headache	4·2	4·1	3·6	2·3
Chills	6·8	4·4	6·0	4·4
Vomiting	16·1	13·1	12·5	11·8
Fever				
Grade 1†	16·4	12·3	11·3	10·1
Grade 2‡	2·9	3·5	2·3	3·5
Grade 3§	0	0·1	0·3	0·5

*Days 0–10 after immunisation. †Oral temperature >37·8°C, rectal or aural temperature >38°C, or axillary temperature >37·5°C. ‡Oral temperature >39·9°C, rectal or aural temperature >39·2°C, or axillary temperature >38·7°C. §Oral temperature >40°C, rectal, or aural temperature >38·7°C, or axillary temperature >39·6°C.
Adapted from reference 3.

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Table 6. Effectiveness of influenza vaccine among household contacts of influenza vaccinated healthy children and unvaccinated controls

Event	Household contacts of vaccinated children (n=728)	Household contacts of unvaccinated controls (n=370)	Vaccine effectiveness %*	p value
Respiratory tract infections	3·03 (1·68)	4·27 (1·68)	30	0·0005
Medical visits for respiratory illness	2·18 (1·37)	3·16 (1·77)	32	0·002
Lost maternal working days	3·22 (1·86)	4·78 (2·34)	33	0·001
Lost paternal working days	0·56 (0·46)	0·98 (2·24)	43	0·001
Days at home to care for ill children	0·57 (0·37)	3·22 (2·24)	83	<0·0001

Mean values (SD). *Vaccine effectiveness=1 minus attack rate (defined as rate of illness divided by the total population) among household contacts of vaccinated children divided by attack rate among household contacts of controls. Adapted from reference 12.

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Table 7. Pharmacoeconomic studies of influenza vaccination in children

Country/author	Population	Conclusions regarding influenza vaccination	Comments
US/OTA[41]	Children aged <3 and 3–14 years	Cost effective	Net costs per year of healthy life gained were US$1122 and 853 ($2000) for children aged <3 and 3–14 yr, respectively
US/Cohen and Nettleman[42]	Preschool children	Cost saving	
US/White et al[43]	School-aged children	Cost saving	
US/Luce et al[44]	Children aged 15–71 months	Probably cost effective	Break-even costs for vaccination were US$5–28
US/Meltzer et al[45]	Children aged 0–19 years	Cost saving (for vaccination cost of US$21)	Model: pandemic influenza
Hong Kong/Fitzner et al[46]	Children aged 0–19 years	Not cost saving	Cost benefit ratio for vaccination of children was HK$3·81 in costs for every HK$1 saved
Argentina/Dayan et al[47]	High-risk children aged 6 months–15 years	Cost saving	

Adapted from reference 80.

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