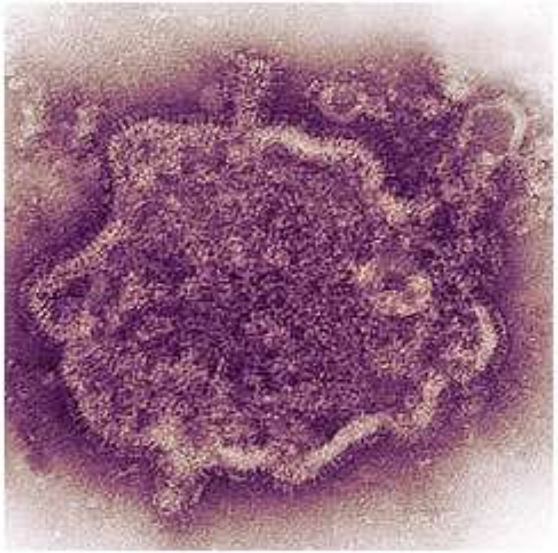
Human Metapneumovirus: recent experience in Hunter New England region, NSW, Australia

A significant cause of morbidity in infants and adults



hMPV virus responsible for many respiratory infections in children.

John Ferguson

IM/ID Meeting 3/2/14

Metapneumovirus
Virus classification
Group: Group V ((-)ssRNA)
Order: *Mononegavirales*
Family: *Paramyxoviridae*
Genus: ***Metapneumovirus***
Type species
Avian metapneumovirus
Species
Human metapneumovirus

Case 1: M, 8 mths

Type 1 respiratory failure secondary to bronchiolitis

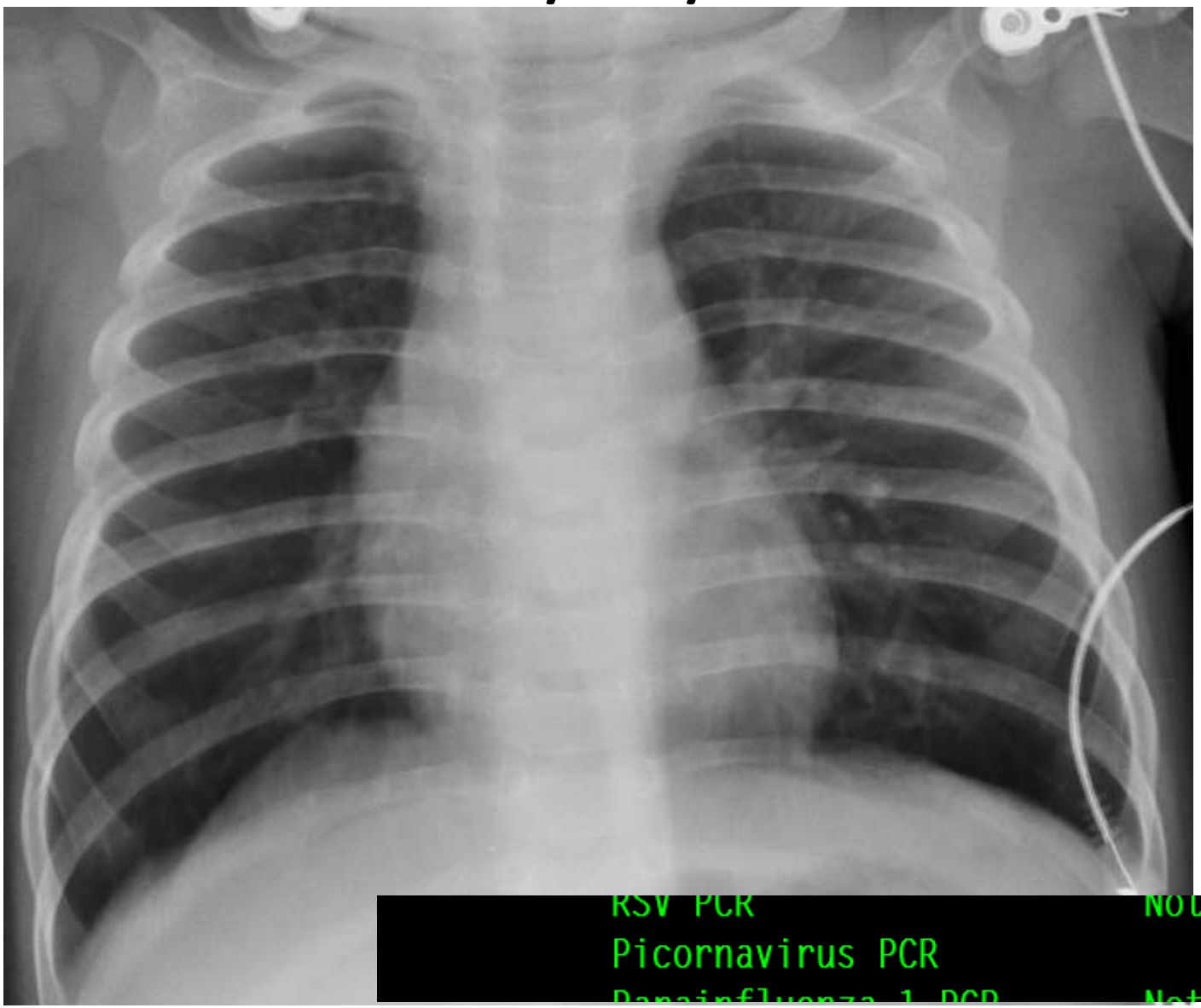
- Full term, NVD
- Nil significant medical / development issues
- Minor eczema; strong family history of asthma

HPI

URTI symptoms for 1/52. Worsening moist cough, increased work of breathing and grunting over past 2/7.

- Hypoxic in ED. Admitted to ICU 25/10/12
- Intermittent bubble CPAP during the day - weaned to room air overnight.
- Restarted breast feeds whilst off CPAP > 4 hours
- BSL stable

25/10/12



Haematology case 1

DOB 21-Feb-2012 Wd ICU (JHH) Dr DR M LONERGAN 10:25 26-Oct-12

HAEMATOLOGY - FULL BLOOD COUNT Film :

WBC :	21.8 H	(6.0 - 17.5)	Neut :	11.2 H		Aty Lymphs :	0.0
RBC :	4.34	(3.70 - 5.30)	Lymph :	8.6		Smear cells:	0.0
HGB :	118	(105 - 135)	Mono :	1.1		Plasma cell:	0.0
HCT :	0.341	(0.330 - 0.390)	Eos :	0.6 H		Hairy cells:	0.0
MCV :	78.6	(70.0 - 86.0)	Baso :	0.0		Abn Lymph :	0.0
MCH :	27.2	(23.0 - 31.0)	Bands :	0.2		Abn Mono :	0.0
MCHC:	346	(300 - 360)	Meta :	0.0	:		
RDW :	14.5	(9.0 - 14.5)	Myelo :	0.0			
PLT :	739 H	(150 - 400)	Promyelo:	0.0			
MPV :	8.5	(7.2 - 11.1)	Blasts :	0.0		NRBC/100 WBC:	0

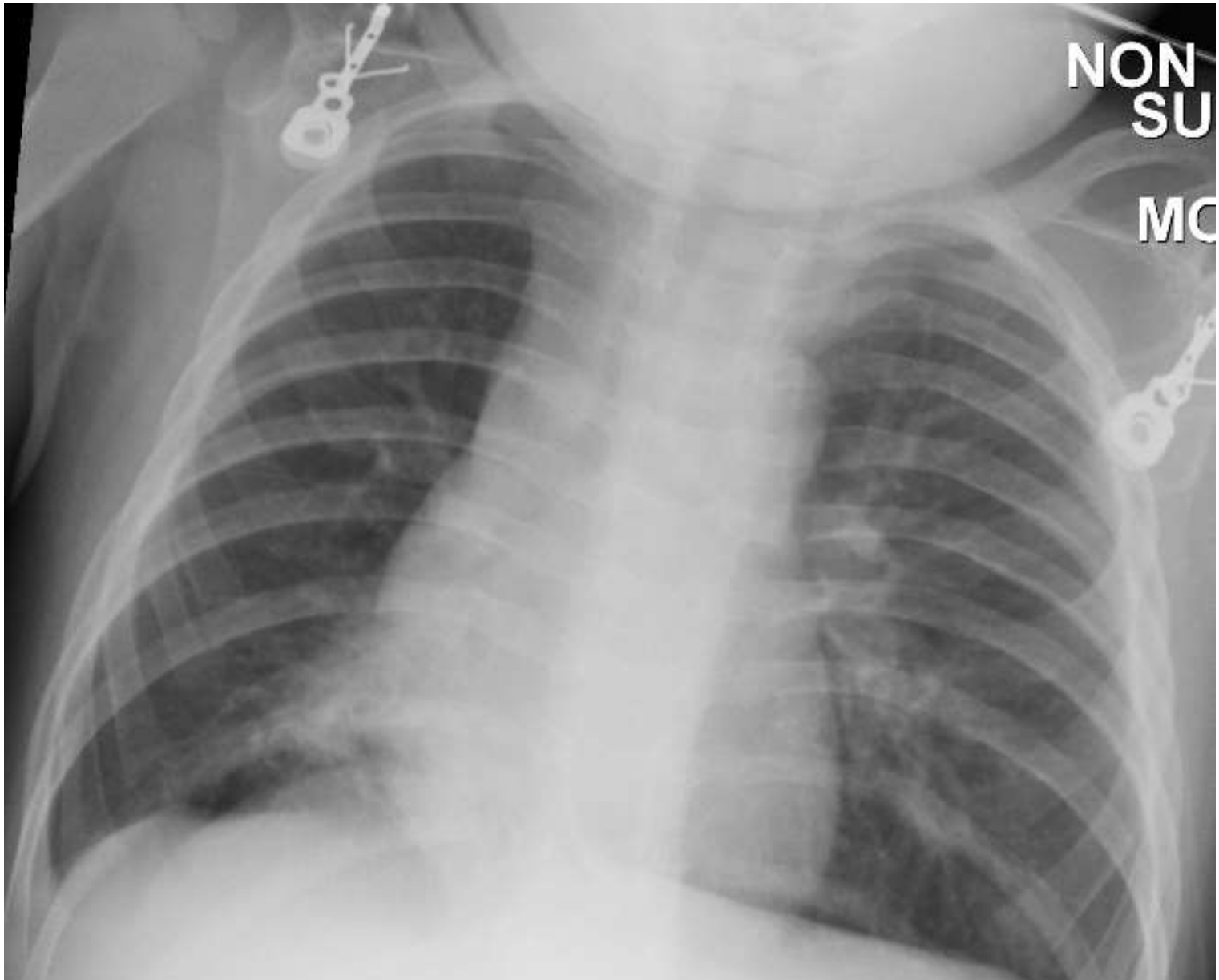
Analyser WBC:

Comment <F8>: Neutrophilia with a left shift and mild toxic changes.
Thrombocytosis.

27/11/12 re-presentation with pneumonia

- Became unwell at home on 27/11/12 and brought to ED by ambulance with fevers, cough, runny nose.
- Hypoxic in ED with Sats 85% room air, increased work of breathing
- Admitted to ICU
  - Initially put on bubble CPAP - requiring Fi02 90% to maintain Sats.
  - CPAP for ~6 hours, but minimal improvement and ongoing high work of breathing-> intubated

27/11/13



DOB 21-Feb-2012 Wd Emergency (JHH)Dr DR J HILTON ??:?? 27-Nov-12

HAEMATOLOGY - FULL BLOOD COUNT Film :

WBC :	24.0 H	(6.0 - 17.5)	Neut :	15.8 D	Aty Lymphs :	0.0
RBC :	4.41	(3.70 - 5.30)	Lymph :	5.5	Smear cells:	0.0
HGB :	116	(105 - 135)	Mono :	1.9 H	Plasma cell:	0.0
HCT :	0.343	(0.330 - 0.390)	Eos :	0.2	Hairy cells:	0.0
MCV :	77.7	(70.0 - 86.0)	Baso :	0.0	Abn Lymph :	0.0
MCH :	26.2	(23.0 - 31.0)	Bands :	0.5	Abn Mono :	0.0
MCHC:	337	(300 - 360)	Meta :	0.0	:	
RDW :	14.6 H	(9.0 - 14.5)	Myelo :	0.0		
PLT :	579 D	(150 - 400)	Promyelo:	0.0		
MPV :	8.3	(7.2 - 11.1)	Blasts :	0.0	NRBC/100 WBC:	0

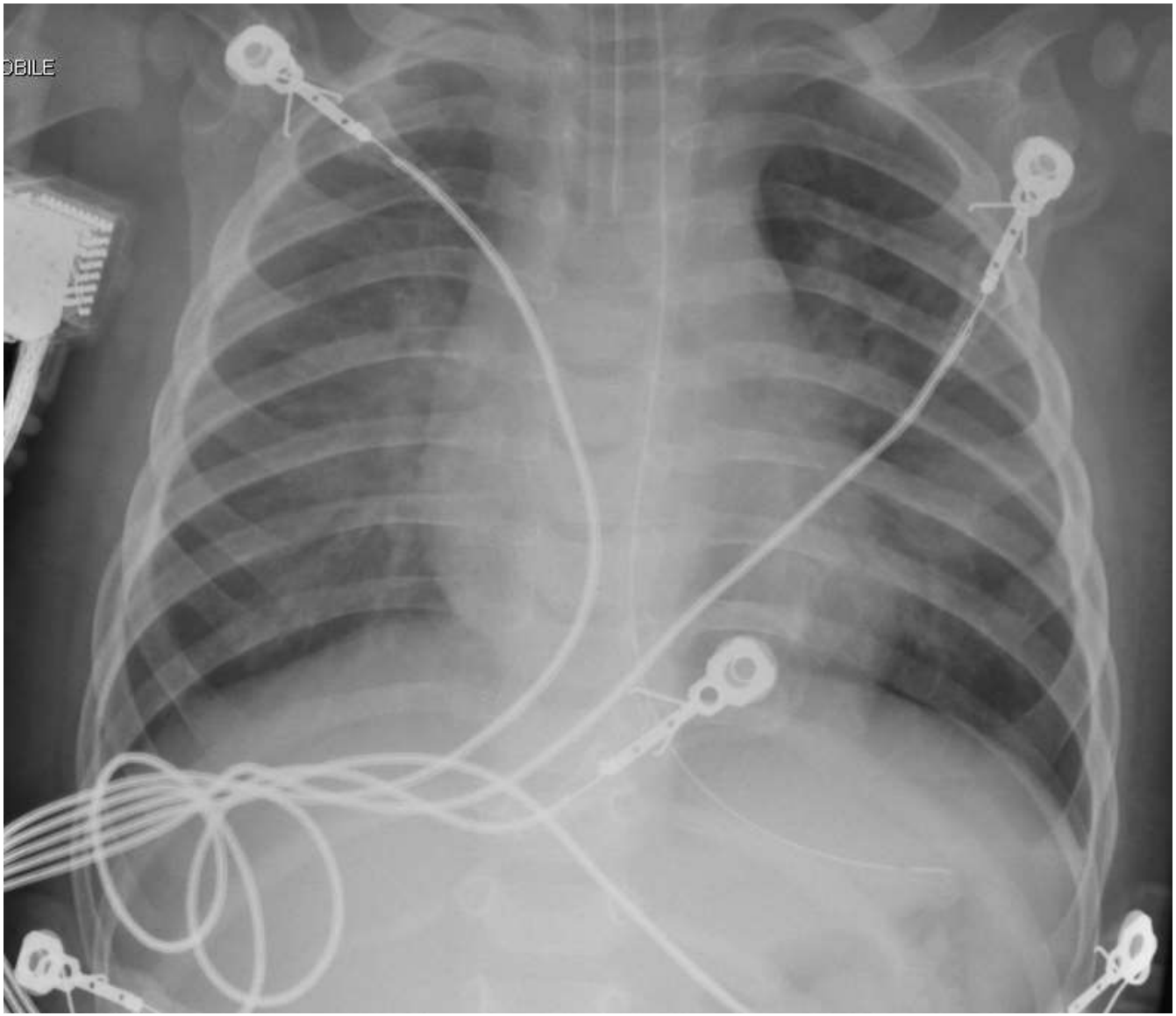
Analyser WBC:

Comment <F8>: Neutrophilia with a left shift and mild toxic changes. Monocytosis. Thrombocytosis.

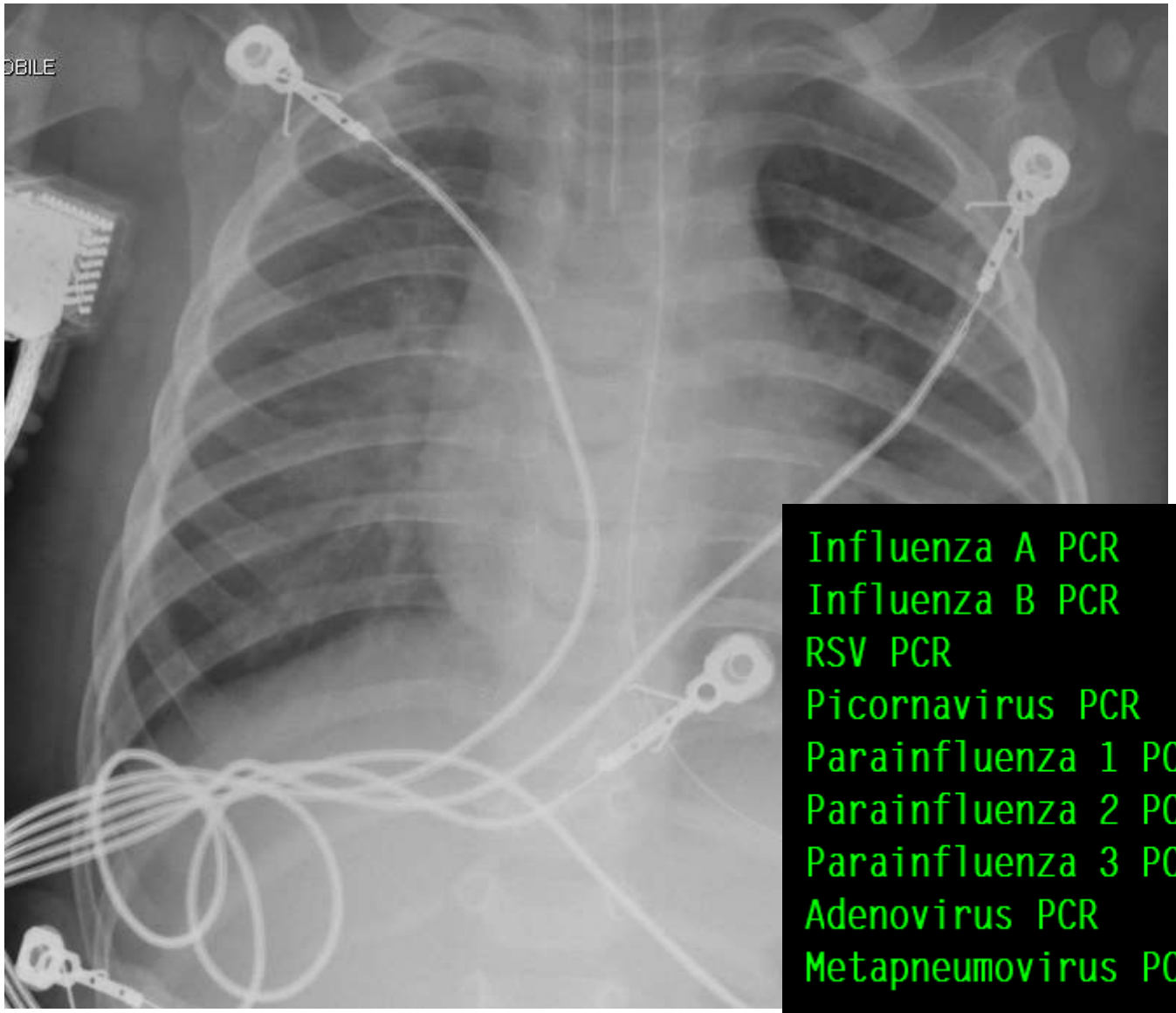
CRP relatively low

Labno	148071344	148673845	148051841
Date	29Nov12	28Nov12	27Nov12
Time	c08:55	c05:00	c??:??
zLactate			
zCRP - C*		22.3 H	<3.1

29/11/13



29/11/13



Influenza A PCR	Not Detected
Influenza B PCR	Not Detected
RSV PCR	Not Detected
Picornavirus PCR	Detected
Parainfluenza 1 PCR	Not Detected
Parainfluenza 2 PCR	Not Detected
Parainfluenza 3 PCR	Not Detected
Adenovirus PCR	Not Detected
Metapneumovirus PCR	Detected

Case 1 8m M: Progress (4 days in ICU)

- Required high pressures to achieve acceptable tidal volumes.
  - Managed with bronchodilators and steroids
- Benzylpenicillin, azithromycin and gentamicin – benpen. and gent ceased 30/11.
- Extubated 30/11/12.
- Ongoing thick secretions; baby miserable and hungry. Some increased WOB with wheeze and stridor --> remained on WHO 2L/kg flow, then weaned to 1 L/kg with FiO2 30%.
- Commenced feeds, increased as tolerated.
- Steroids ceased 01/12.

Nature Medicine **7**, 719 - 724 (2001)
doi:10.1038/89098

A newly discovered human pneumovirus isolated from young children with respiratory tract disease

Bernadette G. van den Hoogen[1], Jan C. de Jong[1], Jan Groen[1], Thijs Kuiken[1], Ronald de Groot[2], Ron A.M. Fouchier[1] & Albert D.M.E. Osterhaus[1]

From 28 young children in the Netherlands, we isolated a paramyxovirus that was identified as a tentative new member of the *Metapneumovirus* genus based on virological data, sequence homology and gene constellation. Previously, avian pneumovirus was the sole member of this recently assigned genus, hence the provisional name for the newly discovered virus: human metapneumovirus. The clinical symptoms of the children from whom the virus was isolated were similar to those caused by human respiratory syncytial virus infection, ranging from upper respiratory tract disease to severe bronchiolitis and pneumonia. Serological studies showed that by the age of five years, virtually all children in the Netherlands have been exposed to human metapneumovirus and that the virus has been circulating in humans for at least 50 years.

LETTERS

Evidence of human metapneumovirus in Australian children

Michael D Nissen,* David J Siebert,† Ian M Mackay,‡ Theo P Sloots,§ Stephen J Withers¶

Three isolates from random selection of 200 NPAs collected throughout 2001 from children presenting to the Royal Children's Hospital, Brisbane, or the Logan Hospital with clinical respiratory tract disease.

Clinical features of human metapneumovirus in three Australian children

	Case 1 (Girl, 12 months)	Case 2 (Boy, 5 years 11 months)	Case 3 (Boy, 20 months)
Date of nasopharyngeal aspirate collection	17/2/01	21/3/01	11/5/01
Presenting symptoms	Rhinorrhoea, cough, tachypnoea, wheeze, vomiting	Rhinorrhoea, cough, pharyngitis, conjunctivitis	Rhinorrhoea, cough, fever
Symptom duration before presentation (days)	4	3	4
Clinical signs	Respiratory distress with hypoxia, rhinorrhoea, pharyngitis, chest wheeze with crackles	Pharyngitis, chest wheeze	Rhinorrhoea, pharyngitis, chest wheeze, cervical lymphadenopathy
Chest X-ray	Not performed	Bilateral parahilar pneumonic infiltrates	Bilateral parahilar pneumonic infiltrates
Clinical diagnosis	Bronchiolitis	Viral lower respiratory tract infection	Viral lower respiratory tract infection
Outcome	Admitted for oxygen therapy and nasal suctioning for three days	Symptomatic treatment at home	Symptomatic treatment at home

Symptoms and clinical diagnoses assoc. with childhood hMPV infections

TABLE 2. Symptoms and clinical diagnoses associated with human metapneumovirus infection of children

Parameter	Value[a] in reference:							
	29	235	72	248	253	173	63	19
No. of patients	12	25	53	49	118	26	50	26
% of patients with symptom or diagnosis								
Fever	67	61	77	52	54	73	44	13
Rhinorrhea	92	80	64	88	82	77	90	2
Cough	100	72	68	90	66	92	90	16
Wheezing	83	24	51	52	*	*	56	6
Vomiting	25	*	*	10	20	*	36	4
Diarrhea	8	*	*	17	14	*	14	1
Rash	0	*	*	4	3	*	2	5
Abnormal chest radiograph	*	62	56	50	*	85	67	*
Bronchiolitis	67	*	*	59	*	23	48	*
Pneumonia	17	*	*	8	*	23	34	9
Croup	0	*	*	18	*	*	4	*
Asthma	*	*	*	14	*	27	*	*
Acute otitis media	50	*	*	37	50	15	6	*

[a] *, not reported.

CLINICAL MICROBIOLOGY REVIEWS, Oct. 2011, p. 734–754

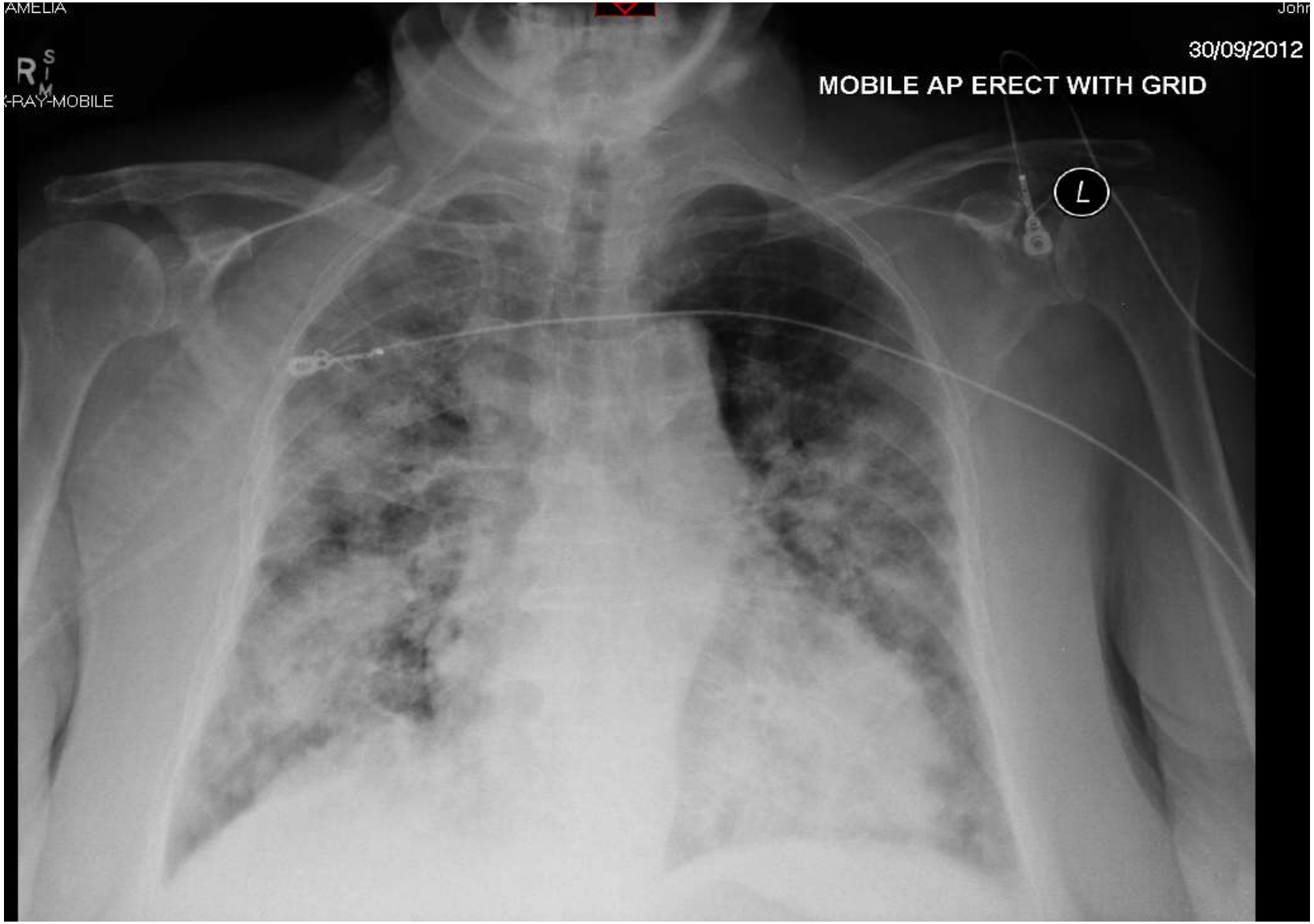
Case 2: 82 yr old female

- Unwell 4 days prior to presentation with increasing SOB and non-productive cough
- ED 30/9/12 : tachypnoea, sats 66% RA, HR 120

PMX

- Type 2 diabetes on metformin
- SVT investigated in 2010-Incessant multifocal ventricular ectopics
- Right tibial plateau #, ORIF 2001
- Ex smoker, quit 40 years ago
- Independent , lived with husband

30/9/12



Day 0

- ABG, pH 7.4, pCO2 32.6, pO2 72.7, Lac 2.2 (Non re-breather, FiO2 100%)
- CXR consistent with multilobar pneumonia +/- APO
- Bedside cardiac ECHO showed preserved LV function
- Commenced on BIPAP in ED with good effect, sats > 92% on 0.7 FiO2
- Admitted to HDU for NIV and management of CAP
- Antibiotics and oseltamivir commenced

DOB 04-Oct-1929 Wd ICU (JHH) Dr Dr N SALTOS 16:45 30-Sep-12

HAEMATOLOGY - FULL BLOOD COUNT Film :

WBC :	18.1 H	(4.0 - 11.0)	Neut :	16.1 H	
RBC :	4.07	(3.80 - 5.80)	Lymph :	0.6 D	
HGB :	127	(115 - 165)	Mono :	1.4 H	
HCT :	0.365	(0.320 - 0.460)	Eos :	0.0	
MCV :	89.6	(80.0 - 100.0)	Baso :	0.0	
MCH :	31.2	(27.0 - 32.0)	Bands :		
MCHC:	348	(310 - 360)	Meta :		
RDW :	13.8	(9.0 - 14.5)	Myelo :		
PLT :	240	(150 - 400)	Promyelo:		
MPV :	8.6	(7.2 - 11.1)	Blasts :		

Hyponatraemia (124) c/w SIADH

Procalcitonin remained low (< 1)

(Below right)

BIOCHEMISTRY - GENERAL Fasting: ?

				(result)	(range)
Sodium	124 C	(136 - 144)	T.Protein	73	(63 - 78)
Potassium	3.4 L	(3.4 - 4.8)	Albumin	29 L	(33 - 41)
Chloride	90 L	(98 - 108)	Calc.Glob.	44 H	(29 - 40)
Bicarb.	23 D	(24 - 30)	Total Bilirubin	15	(< 20)
Urea	9.1 H	(3.5 - 7.2)	GGT	72 H	(< 38)
Creatinine	77	(60 - 100)	Alk.Phos.	77	(40 - 115)
GFR Est.	62	(> 60)	ALT	38	(1 - 40)
Anion Gap	14	(7 - 17)	AST	59 H	(1 - 30)

Lab No	Time/Date	PCTMT
146248809	c 14:30 02-Oct-12	0.61
145386687	c 16:45 30-Sep-12	0.36
145405746	c 12:55 30-Sep-12	0.29

Case 2 progress

- Following change to HFNP, tired significantly, dropping Sats to 80% on a FiO2 of 100%
- With consent obtained, patient intubated and transferred to ICU
- Metapneumovirus positive (30/10) ; all other micro cultures and antigens negative
- Troponin leak (max 13) thought secondary to RV strain: clexane and aspirin given
- Initially slow to wake following cessation of sedation ; generalised global weakness noted
- Increasingly agitated with some ventilatory dysynchrony
- Respiratory failure continued to worsen
- After discussion with the family , care withdrawn and patient died 9/10/13

8/10/13

10 yrs of research hPMV

- Recognised as one of the main viral pathogens responsible for acute respiratory tract infections in children and in elderly and immunocompromised patients.
- hRSV is most closely related to hMPV is human respiratory syncytial virus (hRSV). Classified into two main viral groups A and B.
- Seasonal distribution in temperate countries with most cases occurring in winter and spring
- hMPV has a negative-sense single-stranded RNA genome that includes 8 genes coding for 9 different proteins. The genomic organization and functions of surface attachment and fusion glycoproteins are relatively similar to those of hRSV; many questions remain unanswered concerning the exact roles of the viral proteins in the attachment, fusion and replication of hMPV
- no effective treatment available
- Some innovative approaches based on RNA interference and on fusion inhibitors have shown efficacy in vitro and in animal studies and could be beneficial in treating human hMPV disease.
- Difficulties faced inducing a durable immune response represent the biggest challenge in the development of an effective hMPV vaccine. Live-attenuated viruses generated by reverse genetics or recombinant proteins, have been tested in animals with encouraging results

Journal of Clinical Virology 53 (2012) 97–105

Other findings

- Reinfection occurs: repeated infections more likely to be limited to the upper respiratory tract in otherwise healthy children
- Association between HMPV infection and asthma is not clear
- HMPV infections remain restricted to respiratory tract - primary tropism limited to respiratory epithelia; no spread to other internal organs
- Histopathology studies of infected macaques and infected cotton rats : infection associated with disruption of epithelial architecture, sloughing of epithelial cells, loss of ciliation, and presence of inflammatory infiltrates in the lungs
- HMPV-infected mice develop parenchymal pneumonia and neutrophilic infiltrates during infection

CLINICAL MICROBIOLOGY REVIEWS, Oct. 2011, p. 734–754

Transpl Infect Dis. 2011 June ; 13(3): 324–328. doi:10.1111/j.1399-3062.2010.00575.x.

The human metapneumovirus: a case series and review of the literature

- Lung transplant patients:
  - hMPV common cause of respiratory illness
  - increases risk of acute and chronic graft rejection
  - increase risk of developing bronchiolitis obliterans with significant impact on survival
- HSCT recipients and patients with hematologic malignancies:
  - High risk of severe respiratory viral infections including hMPV.
  - MPV-infected patients : minimal symptoms or remain asymptomatic over a period of time. In others, signs of respiratory failure and complicated course may occur with fatal pulmonary infection

HAPS all viruses 2012-2013 ch < 5 yrs

Viruses detected	Age - years 0-1	1-2	2-3	3-4	4-5	Grand Total
aden	17	14	7	5	8	51
aden mp	3	1	2			6
InfA	18	9	9	12	4	52
InfA aden	3	1				4
InfA pico	6	3	1	3	1	14
InfA RSV	1					1
InfA RSV pico	2	2				4
InfA RSV pico aden		1				1
InfA RSV pico mp	1					1
InfB	4		2	2	2	10
InfB p1	1					1
InfB pico	1	2		1		4
InfB pico aden			1			1
mp	47	22	7	4	6	86
p1	3					3
p2	6	4	1	1		12
p2 aden		3	1			4
p2 aden mp	1					1
p3	32	15	3	1		51
p3 mp	2					2

Viruses detected	0-1	1-2	2-3	3-4	4-5	Grand Total
pico	367	161	57	25	13	623
pico aden	29	43	12	5	2	91
pico aden mp	1	6				7
pico mp	20	12	3	3	1	39
pico p1	2	2				4
pico p1 aden					1	1
pico p2	3		1	1		5
pico p3	23	8	3			34
pico p3 aden	4	4	1	1		10
pico p3 aden mp		1				1
RSV	120	35	32	8	6	201
RSV aden	6	9	1	1		17
RSV aden mp		1				1
RSV mp	1	1				2
RSV p3	2	1				3
RSV p3 aden		1				1
RSV pico	55	20	4	3	1	83
RSV pico aden	8	6				14
RSV pico aden mp		1				1
RSV pico mp		1				1
RSV pico p2	1	1				2
RSV pico p3	1	3	2			6
RSV pico p3 aden			1			1
(blank)						
Grand Total	**791**	**394**	**151**	**76**	**45**	**1457**

R10 PCR assay implemented June 2012

P1= parainfluenza 1, pico=picornavirus, adeno=adenovirus

Proportion of multiple virus detections

Children <=2yr	
2012	2013
140	**171**
531	654
26%	26%

Others > 2 yrs	
2012	2013
52	**64**
744	822
7%	8%

Debiaggi *et al. Virology Journal* 2012, **9**:247
http://www.virologyj.com/content/9/1/247

VIROLOGY JOURNAL

REVIEW **Open Access**

The role of infections and coinfections with newly identified and emerging respiratory viruses in children

Maurizia Debiaggi[1†], Filippo Canducci[2*†], Elisa Rita Ceresola[2] and Massimo Clementi[2]

Abstract

Acute respiratory infections are a major cause of morbidity in children both in developed and developing countries. A wide range of respiratory viruses, including respiratory syncytial virus (RSV), influenza A and B viruses, parainfluenza viruses (PIVs), adenovirus, rhinovirus (HRV), have repeatedly been detected in acute lower respiratory tract infections (LRTI) in children in the past decades. However, in the last ten years thanks to progress in molecular technologies, newly discovered viruses have been identified including human Metapneumovirus (hMPV), coronaviruses NL63 (HcoV-NL63) and HKU1 (HcoV-HKU1), human Bocavirus (HBoV), new enterovirus (HEV), parechovirus (HpeV) and rhinovirus (HRV) strains, polyomaviruses WU (WUPyV) and KI (KIPyV) and the pandemic H1N1v influenza A virus. These discoveries have heavily modified previous knowledge on respiratory infections mainly highlighting that pediatric population is exposed to a variety of viruses with similar seasonal patterns. In this context establishing a causal link between a newly identified virus and the disease as well as an association between mixed infections and an increase in disease severity can be challenging. This review will present an overview of newly recognized as well as the main emerging respiratory viruses and seek to focus on the their contribution to infection and co-infection in LRTIs in childhood.

? RSV and HMPV co-infections may be associated with more severe disease- conflicting evidence

Coinfections

Many studies evaluating HMPV infection have tested for other viruses by using sensitive methods and have detected RSV in 5 to 17% of patients infected with HMPV (10, 17, 29, 31, 38, 49, 63, 67, 72, 81, 84, 119, 133, 159, 168, 173, 182, 189, 225, 235, 238, 248, 253). Most studies have not described exacerbated disease in patients with codetection of multiple viruses. Note that highly sensitive RT-PCR techniques may detect viruses for several weeks after an acute infection. A few studies of hospitalized patients have described much higher coinfection rates (30 to 60%) (87, 119, 130, 238), raising the question of whether HMPV infections are more severe if another virus is present. One group addressed this question by using a nested RT-PCR assay to test BAL fluids from 30 intubated infants with RSV infection, and they detected HMPV in 21/30 (70%) infants (98). They subsequently used the same nested PCR assay to test specimens from children admitted to the intensive care unit and the general wards. HMPV and RSV coinfections were detected in 18/25 (72%) intensive care patients and in 15/171 (9%) general ward patients, leading the authors to conclude that dual infection with RSV and HMPV was associated with severe bronchiolitis (205). However, a study of 46 inpatients with either mild or severe RSV disease found no coinfections with HMPV (141). Also, a Dutch study did not find any HMPV-RSV coinfections in children with severe RSV bronchiolitis (236). Whether these conflicting findings are due to methodological differences or to variability in circulating viruses is unknown. Further studies are needed to clarify the nature of disease associated with codetections; however, it is clear that the majority of HMPV infections are not associated with other viruses and that HMPV is a primary respiratory pathogen.

RSV- antigen test is inferior to PCR

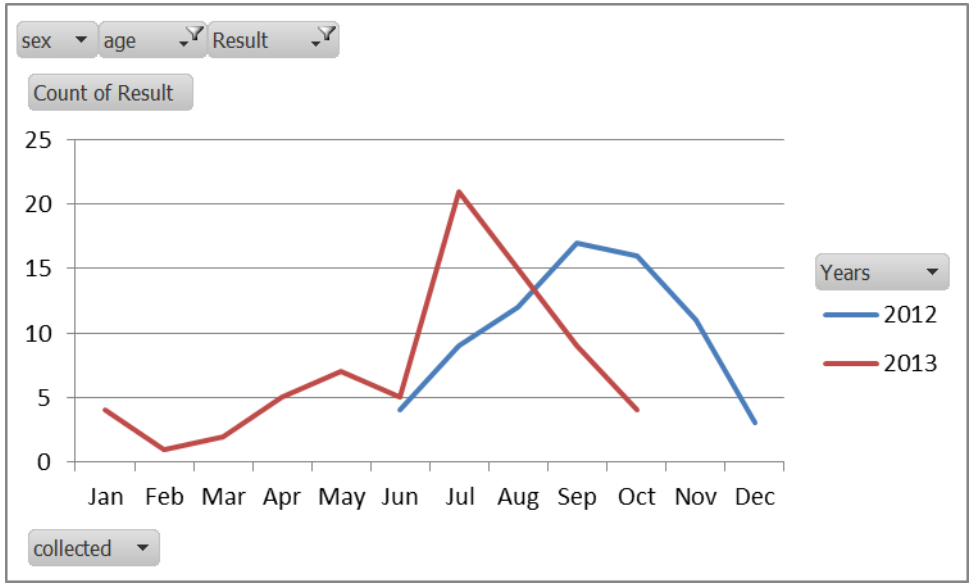
PCR result		RSV antigen result			
		Negative	**Positive**	**See comment**	**Grand Total**
DET	1	111	33		145
INHIBS		6			6
ND	1	1035		1	1037
Grand Total	**2**	**1152**	**33**	**1**	**1188**
	RSAG test sensitivity	23%			

HMPV infections , ch < 5yrs

Row Labels	0-1	1-2	2-3	3-4	4-5	Grand Total
aden mp	3	1	2			6
InfA RSV pico mp	1					1
mp	47	22	7	4	6	86
p2 aden mp	1					1
p3 mp	2					2
pico aden mp	1	6				7
pico mp	20	12	3	3	1	39
pico p3 aden mp		1				1
RSV aden mp		1				1
RSV mp	1	1				2
RSV pico aden mp		1				1
RSV pico mp		1				1
Grand Total	**76**	**46**	**12**	**7**	**7**	**148**

Seasonality- HPMV (all) Ch< 5y

Row Labels	2012	2013
Jan		4
Feb		1
Mar		2
Apr		5
May		7
Jun	4	5
Jul	9	21
Aug	12	15
Sep	17	9
Oct	16	4
Nov	11	
Dec	3	
Grand Total	**72**	**73**



2012-2013: Adults 16y+

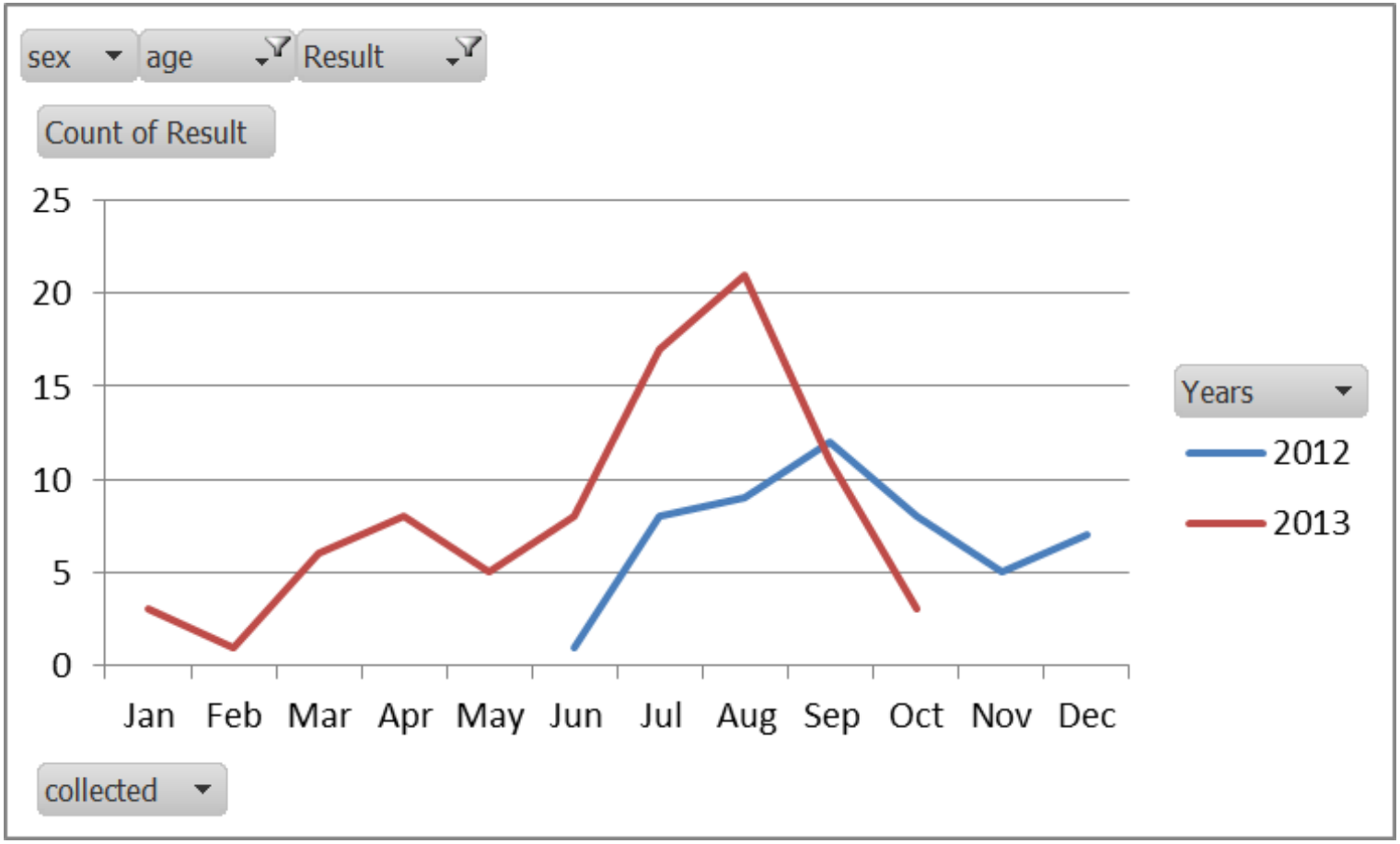
Row Labels	15-35	35-55	55-75	75-95	95-115	Grand Total
aden	18	12	16	5		51
InfA	52	77	79	69	4	281
InfA aden				1		1
InfA pico	6	3	3	1		13
InfA RSV			1	1		2
InfB	17	18	20	8		63
InfB pico		1				1
mp	12	16	43	44		115
p1	1	1	1	1		4
p2	1	3	2	1		7
p2 aden			1			1
p3	7	8	14	16	3	48
p3 mp		1				1
pico	122	81	110	77	3	393
pico aden		2	2			4
pico mp	3			2		5
pico p2				1		1
pico p3			1			1
RSV	6	15	33	52	2	108
RSV aden			1			1
RSV mp		1				1
RSV pico	1	4	2	1		8
(blank)						
Grand Total	**246**	**243**	**329**	**280**	**12**	**1110**

2012-2013: Adults 16y+

Row Labels	15-35	35-55	55-75	75-95	95-115	Grand Total
aden	18	12	16	5		51
InfA	52	77	79	69	4	281
InfA aden				1		1
InfA pico	6	3	3	1		13
InfA RSV			1	1		2
InfB						
InfB pico						
mp						
p1						
p2						
p2 aden						
p3						
p3 mp						
pico						
pico aden						
pico mp	3			2		5
pico p2				1		1
pico p3			1			1
RSV	6	15	33	52	2	108
RSV aden			1			1
RSV mp		1				1
RSV pico	1	4	2	1		8
(blank)						
Grand Total	**246**	**243**	**329**	**280**	**12**	**1110**

Row Labels	15-35	35-55	55-75	75-95	Grand Total
mp	12	16	43	44	115
p3 mp		1			1
pico mp	3			2	5
RSV mp		1			1
Grand Total	**15**	**18**	**43**	**46**	**122**

> 5 yr hPMV


sex
age
Result
Count of Result
25
20
15
10
5
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Years
2012
2013
collected

Recent ICU cases

age	sex	labno	collected	ward	Result
0.7	M	154094412	15/07/13	ICU~JHH	pico mp
0.8	M	148074994	27/11/12	ICU~JHH	pico mp
5.8	M	145565464	23/08/12	ICU~JHH	pico mp
20.1	F	152635549	7/05/13	3ICU~MMI	mp
39.4	F	141387992	28/08/13	ICU~JHH	mp
53.7	M	141203667	11/09/13	3ICU~MMI	mp
63.4	F	152413123	4/06/13	ICU~JHH	mp
72.8	F	147896061	22/10/12	3ICU~MMI	mp
78.2	F	148735086	22/11/12	3ICU~MMI	mp
83.0	F	146228337	30/09/12	ICU~JHH	mp