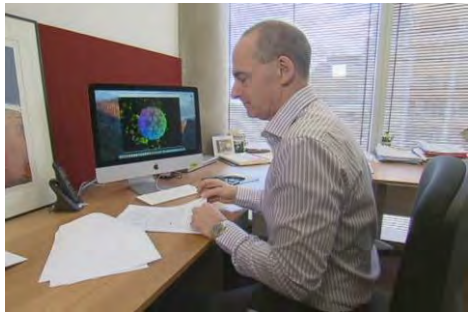
Principles of clinical virology

Structure, Pathogenesis, New Diagnostics

Bill Rawlinson

SAViD Serology and Virology Division, NSWHP

May 2018



Viruses in May 2018

The Diagnostic Specialist

RCPAQAP

The Royal College of Pathologists of Australasia
Quality Assurance Programs

RCPA

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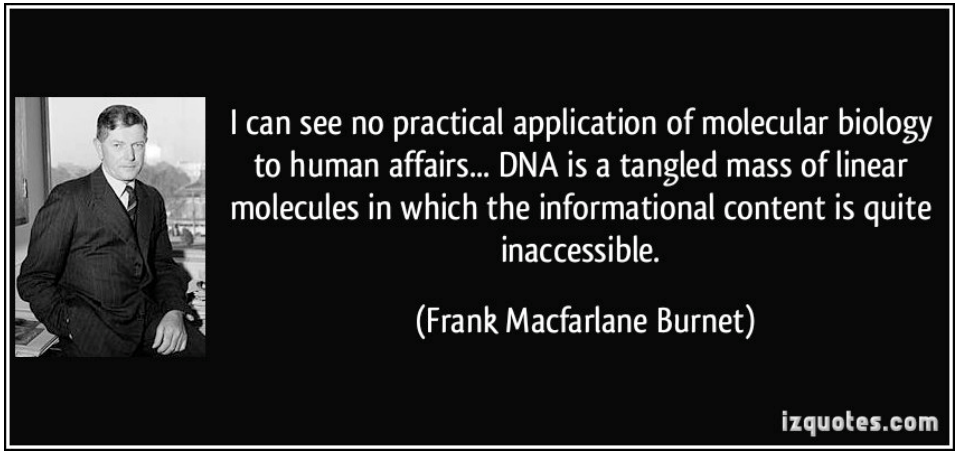
Acknowledge financial support for attendance at NRL (DiaSorin),
advisory boards (MSD Letermovir, GSS), diagnostic trials (Abbott, Meridian)

"With 7.4 billion people, 20 billion chickens and 400 million pigs now sharing the earth, we have created the ideal scenario for creating and spreading dangerous microbes."

[The real threat to national security, Michael Osterholm 2017]

Virology

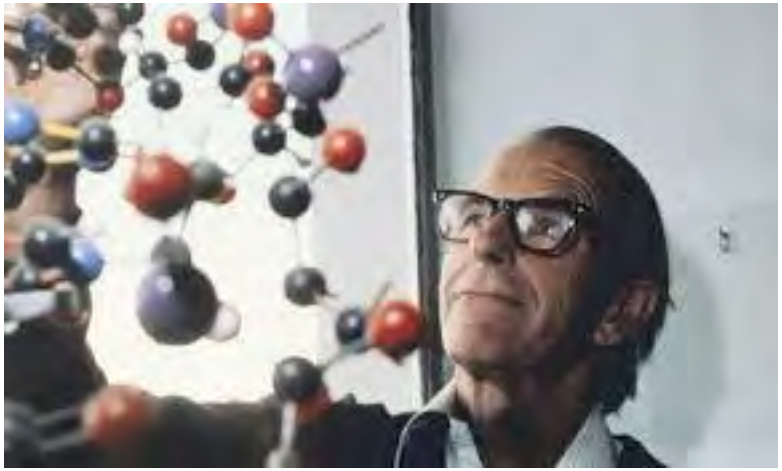


Virology has become an integral part of molecular biology because it deals with subcellular entities, the viruses, whose entire structure and organization belong in the macromolecular domain

(Salvador Luria, 1953)

Molecular biology is the practice of biochemistry without a licence

(Fred Sanger)



OUTLINE

1. Virus definitions
   - Characteristics
   - Structure, Replication
   - Some useful definitions

2. Pathogenesis - how viruses cause disease
   - Molecular principles
   - New ways of examining virus pathogenesis

3. Clinical virology and diagnosis
   - Principles
   - Surveillance
   - Applications – outbreaks, antiviral resistance

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OUTLINE

1. Virus definitions
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Viruses

Strictly intracellular, and potentially pathogenic entities with an infectious phase, one type of nucleic acid, multiplying in form of genetic material, unable to grow and undergo binary fission, devoid of enzymes for energy production

(Lwoff 1957)

Viruses

Elements of genetic material that can determine, in the cells where they reproduce, the biosynthesis of a specific apparatus for their own transfer into other cells

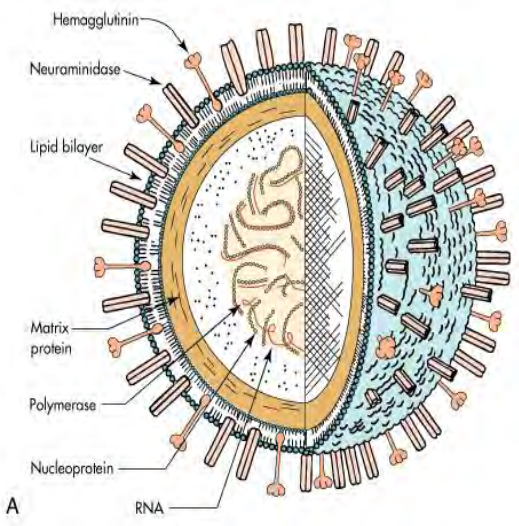
Two elements – genetic material of its which inside a cell behaves as part of the cell, and extracellular infective state

(Luria 1953)

A virus is a molecular genetic parasite that uses cellular systems for its own replication

(Villareal 2005)

Filtrable agents



Delivery system to deliver nucleic acid

ICTV Definition

- “a virus species is a polythetic class of viruses that constitute a replicating lineage and occupy a particular ecological niche”
- “polythetic class” members have several properties in common, although not necessarily all share a single common defining property

- Members of a virus species defined collectively by a consensus group of properties

- Virus species differ from higher viral taxa, which are “universal” classes defined by properties

Viruses

- Viruses are the simplest organisms, containing DNA or RNA, but not both
- RNA viruses are more diverse and replication often error prone

- Enveloped (environmentally unstable) and non-enveloped (environmentally stable)

Viruses have life

- Can be killed
- Can become extinct
- Undergo Darwinian selection
- Subject to evolutionary biology
- But
  - Have no sexual exchange process
  - Species is defined by its lineage
  - Species is a class that occupies a replicating lineage and occupies an ecological niche

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Classification and phylogeny

- Viral nucleic acid + virus capsid + envelope
- Other characteristics:
  - Genomic makeup e.g: Caliciviruses
  - Virion structure – EM appearance e.g: herpes
  - Replication strategy
  - Virion antigenicity e.g: adenoviruses, serological distinction MVE / JE / WNV
  - Virion chemical characteristics, stability
  - Diseases caused in the host e.g: hepatitis
- Phylogeny only uses nucleic acid or aa sequence

Steps in phylogenetic analysis

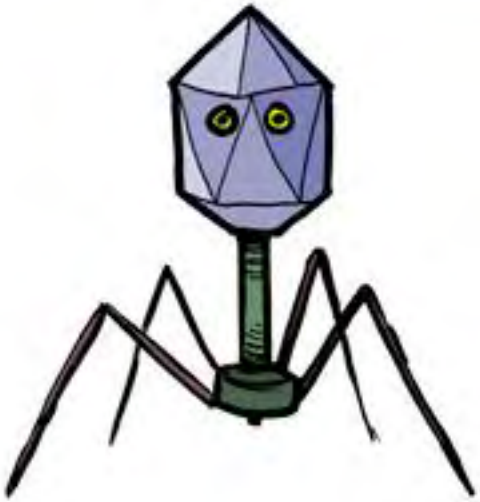
- Determine or obtain previous online sequences
- Align sequences so homologous nt (or aa) are in line with each other
- Perform calculations to make a tree, with branches determined by similarity of sequences
- Test trees for best fit of the data

Alignments and trees

- Align
  - AAACTGAATG
  - AAACCGATTG
  - Differences real or sequence errors
- Construct trees based on computer-search for tree most consistent with the data set
  - Evolutionary distance
  - Maximum parsimony
  - Maximum likelihood

Things that may interfere

- Nucleotide biases (G+C)
- Rapidly evolving lineages
- Misalignment and slippages of sequence from multiple repeats, hompolymeric runs
- Taxon selection affecting outcomes – wrong outliers



Virus

Retrovirus

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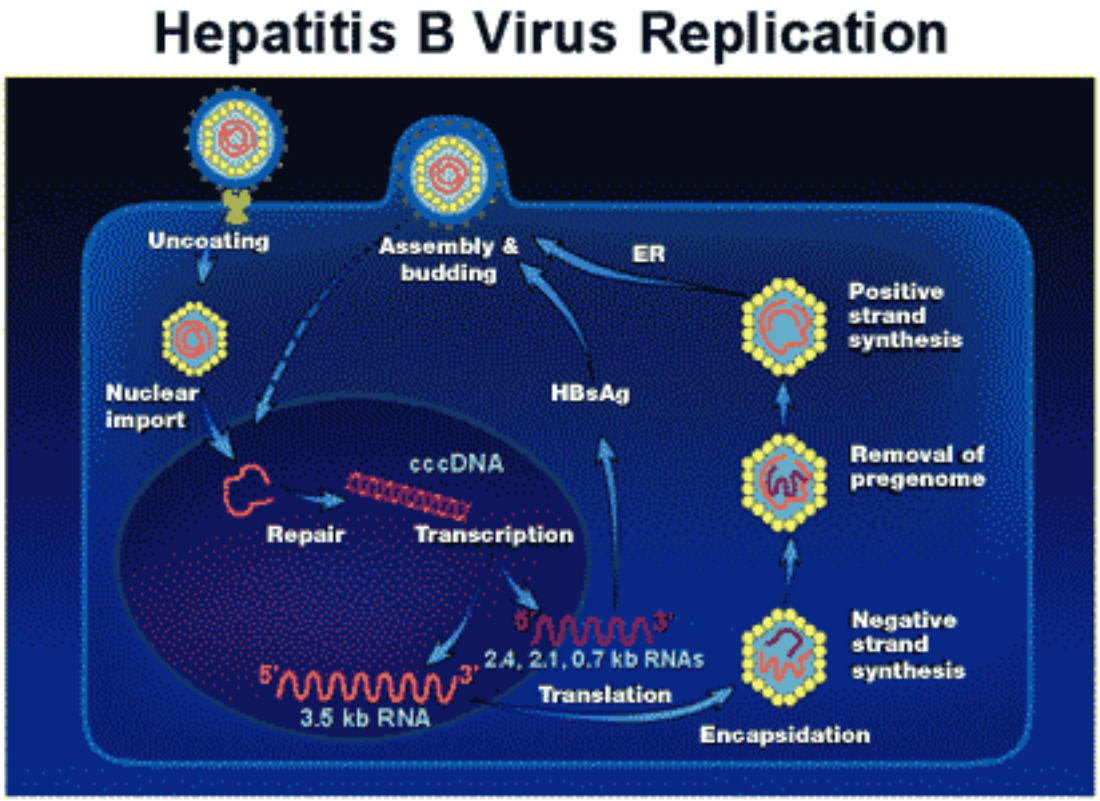
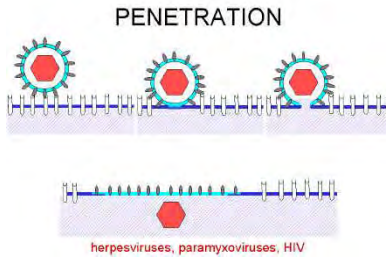
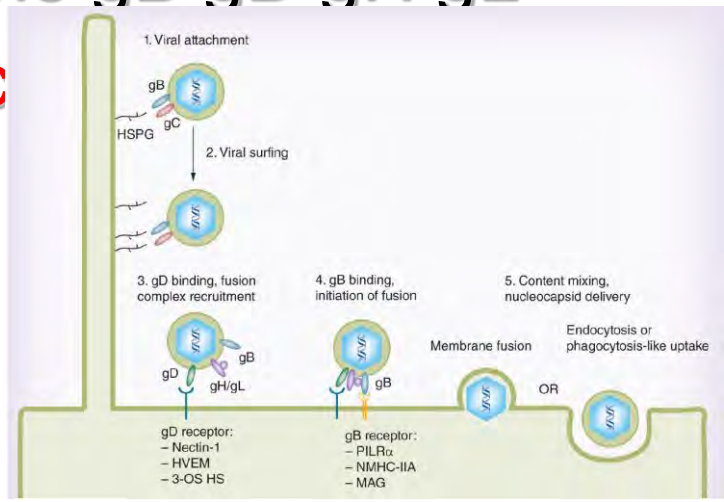
Virus replication
The delivery system and the payload



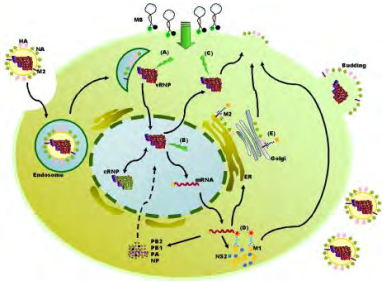
Virus replication
The delivery system and the payload

- Differs between viruses
- HVs
  - ➢Attachment to cell surface gB gC
  - ➢Viral gp + receptors
  - ➢Capsid penetration of membrane gB gD gH gL
  - ➢Nucleocapsid moves along mic
  - ➢Membrane fusion multiprotein





Virus Receptors



DNA

- CMV
  - PDFGRalpha (gHgLgO)
  - Heparan sulfate glycosaminoglycans (gB)
- HSV
  - gB gD gH gL sufficient
  - Heparan sulfate
  - Nectin -1
  - HVEM
  - 3-O-sulfated heparan sulfate
  - Integrins (gH)
  - PILRalpha NMHC-IIA MAG (gB)
  - ENDOCYTOSIS alternative
  - Cell type dependent

(Vanarsdall AL 2012, Agelidis AM 2015)

RNA

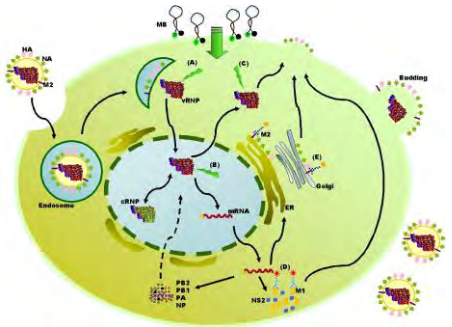
- Enteroviruses
  - CAR (CB3 Pentameric vertex)
  - Ig superfamily CD155 (PV1-3), ICAM1 (CA21, hRV), CAR (CB3)
  - CD55 (EV7)
  - Integrin aVb6, avb3
  - LDLR family (hRV)
  - PSGL1, SCARB2 transmembrane (EV71)

(Liu Y 2014)

Virus Receptors

So multiple receptors, differ between viruses, different receptors utilised by different strains, still more to be found

Interaction with other viral proteins



Virion Architecture
The delivery system

Architecture of virions regardless of host is based on two simple themes:

Sphere – normally in the form icosahedron (cubical)
- Best way of producing a shell of equivalently bonded identical structures
- Minimum free energy state
- Strong structure that can enclose a maximal volume

Helix – cylindrical shape (spiral staircase)

Classification

- Viral nucleic acid + virus capsid + envelope
- Other characteristics:
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  - Virion structure – EM appearance e.g: herpes
  - Replication strategy
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  - Virion chemical characteristics, stability
  - Diseases caused in the host e.g: hepatitis

Viruses as a molecule

- ssRNA – most diverse Noro, HCV, HIV
- dsDNA – Adeno, CMV, HSV, Variola
- dsRNA – Rota
- ssDNA – least diverse PVB19


I think I need antibiotics for my co...
It's a virus!
FOUND AT VERYFUNNYPICS.EU
www.veryfunnypics.eu

OUTLINE

2. Pathogenesis - how viruses cause disease
   - Molecular principles
   - New ways of examining virus pathogenesis

Acute and persistent virus life strategies

- No persistence in individual host
- Often disease associated
- High mutation rates (RNA viruses)
- Virus replicates in more than one species
- Little coevolution with host
- Horizontal transmission
- Highly dependent on host population structure
- Seldom evolves to persistence

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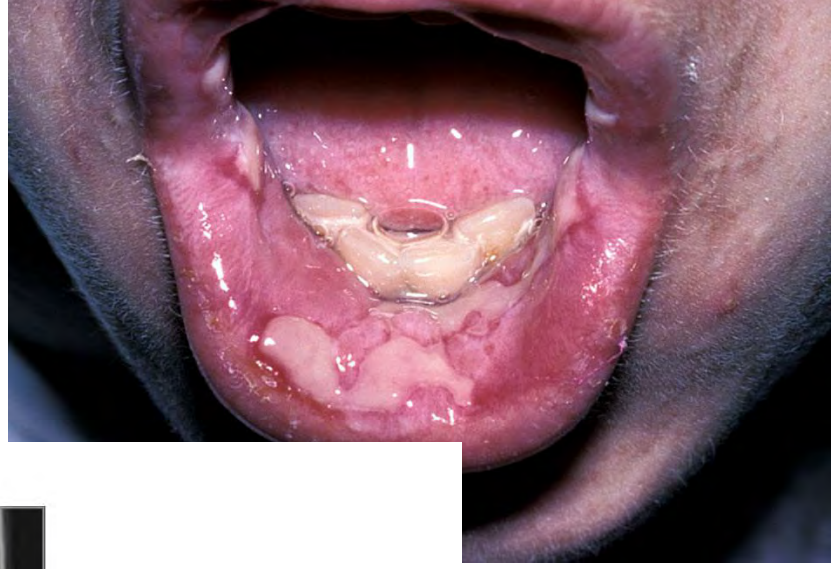
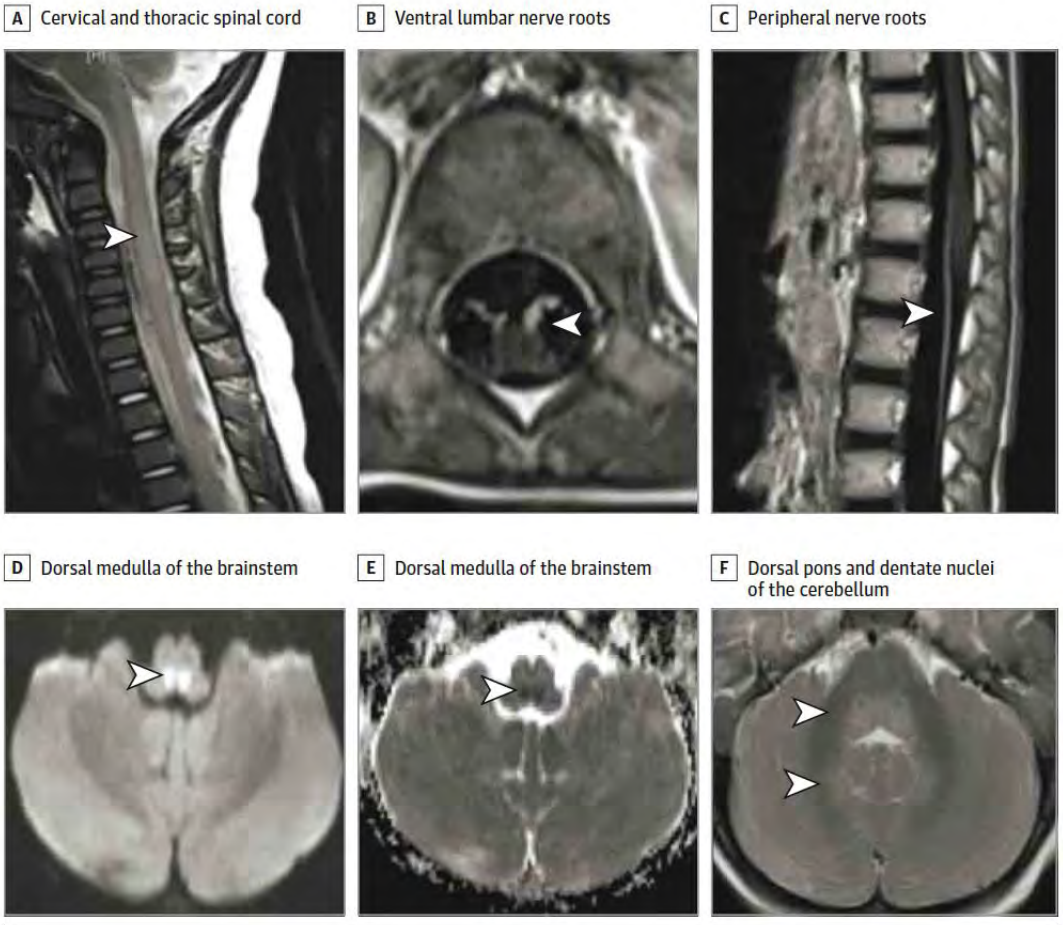
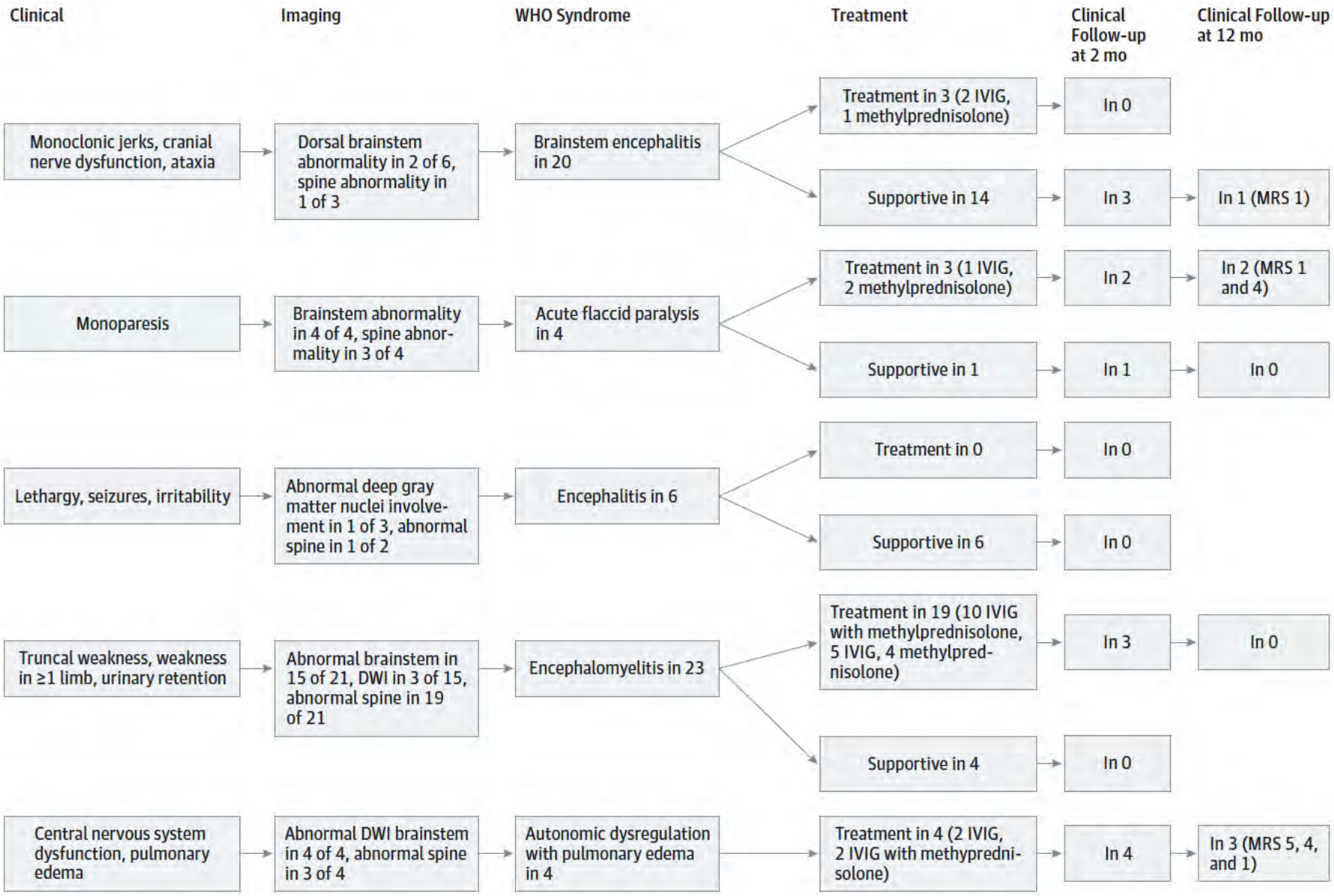
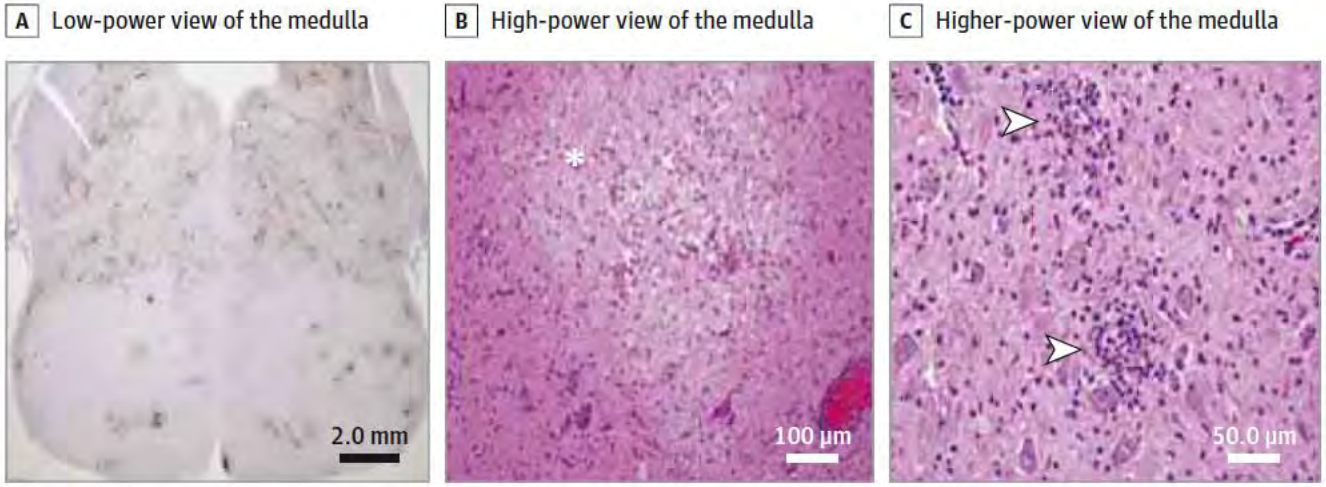
EV71 Acute meningoencephalitis





The arrowheads point to the findings in A through F. A, T2-weighted signal hyperintensity and expansion. B, Gadolinium enhancement. C, Gadolinium enhancement. The arrowhead is sitting over the L2/L3 intervertebral space. D, Restricted diffusion. E, Apparent diffusion coefficient map. F, T2-weighted signal hyperintensity.


Clinical
Imaging
WHO Syndrome
Treatment
Clinical Follow-up at 2 mo
Clinical Follow-up at 12 mo
Monoclonic jerks, cranial nerve dysfunction, ataxia
Dorsal brainstem abnormality in 2 of 6, spine abnormality in 1 of 3
Brainstem encephalitis in 20
Treatment in 3 (2 IVIG, 1 methylprednisolone)
In 0
Supportive in 14
In 3
In 1 (MRS 1)
Monoparesis
Brainstem abnormality in 4 of 4, spine abnormality in 3 of 4
Acute flaccid paralysis in 4
Treatment in 3 (1 IVIG, 2 methylprednisolone)
In 2
In 2 (MRS 1 and 4)
Supportive in 1
In 1
In 0
Lethargy, seizures, irritability
Abnormal deep gray matter nuclei involvement in 1 of 3, abnormal spine in 1 of 2
Encephalitis in 6
Treatment in 0
In 0
Supportive in 6
In 0
Truncal weakness, weakness in ≥1 limb, urinary retention
Abnormal brainstem in 15 of 21, DWI in 3 of 15, abnormal spine in 19 of 21
Encephalomyelitis in 23
Treatment in 19 (10 IVIG with methylprednisolone, 5 IVIG, 4 methylprednisolone)
In 3
In 0
Supportive in 4
In 0
Central nervous system dysfunction, pulmonary edema
Abnormal DWI brainstem in 4 of 4, abnormal spine in 3 of 4
Autonomic dysregulation with pulmonary edema in 4
Treatment in 4 (2 IVIG, 2 IVIG with methyprednisolone)
In 4
In 3 (MRS 5, 4, and 1)



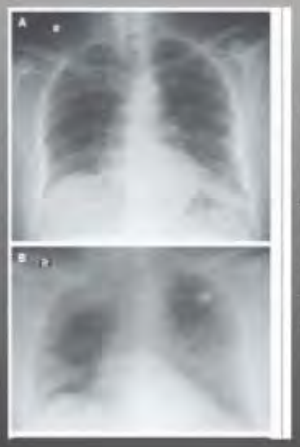
An 18-month-old patient was seen at the hospital with a 2-day history of fever, anorexia, and vomiting. On examination, she was in shock, with supraventricular tachycardia (225 beats/min). There was ptosis and rightward deviation of the left eye, as well as right eye nystagmus. She had cardiac arrest in the emergency department and was unable to be resuscitated. A, Shown are marked and widespread microglial activation and microglial nodules (immunostained for major histocompatibility complex class II antigens [CR3/43]). B, Foci of necrosis (asterisk) with perivascular lymphocytes (hematoxylin-eosin) are shown. C, Shown are microglial nodules (arrowheads) (hematoxylin-eosin).

At the severe end of the clinical spectrum, all patients with pulmonary edema (which was strongly associated with an adverse Clinical outcome) demonstrated restricted diffusion within the dorsal brainstem on MRI. Histopathology correlated with the imaging findings among deaths associated with fulminant disease. These findings support the concept that inflammation may be an important modifiable pathophysiological process, corroborate observations immunological therapies such as IVIG may be beneficial in EV71 neurological disease

(Teoh 2015)

First Case: Chest Radiographs

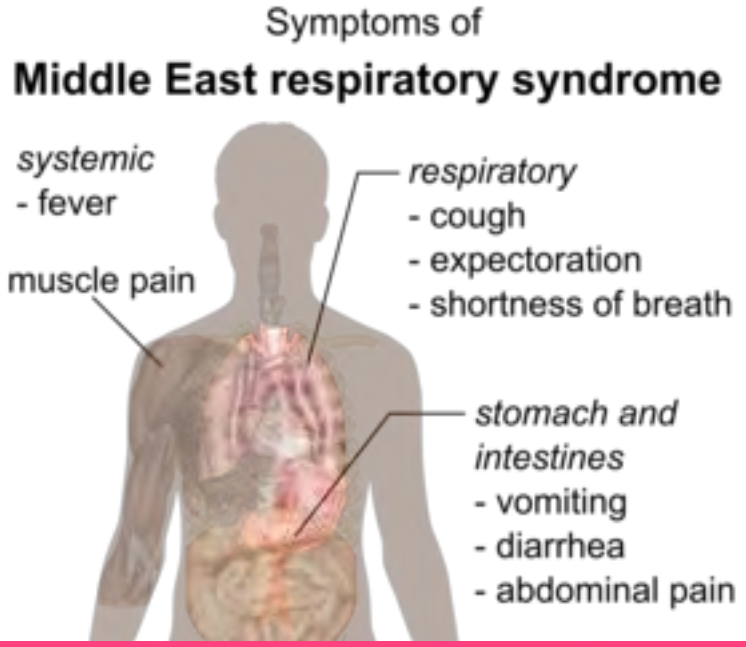
A: On admission

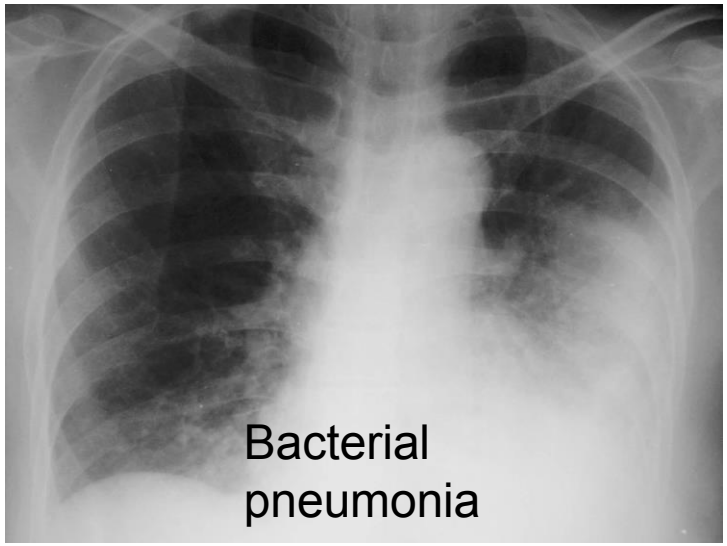


B: 2 days later

Bilateral enhanced pulmonary hilar vascular shadows (more prominent on the left) and accentuated bronchovascular lung markings. Multiple patchy opacities in middle and lower lung fields Opacities more confluent and dense

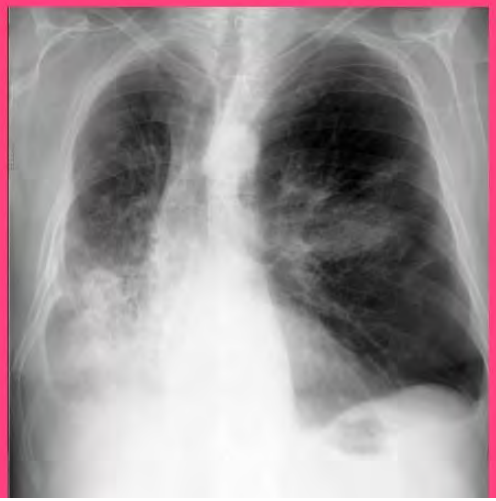
MERS CoV



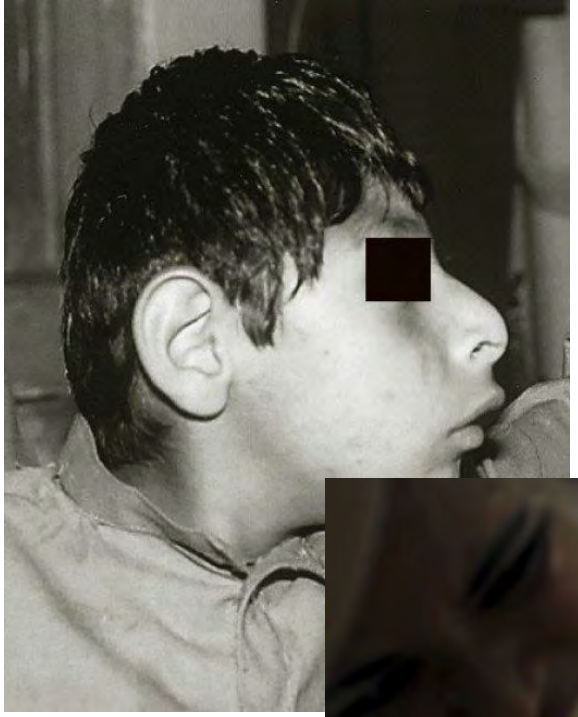


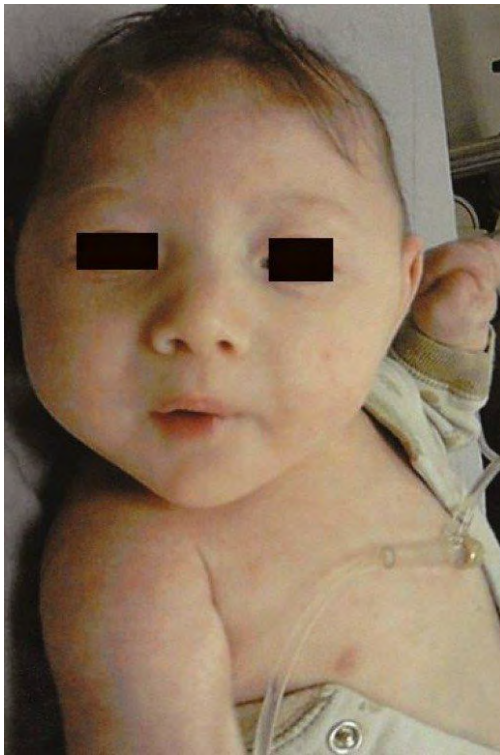
Bacterial pneumonia

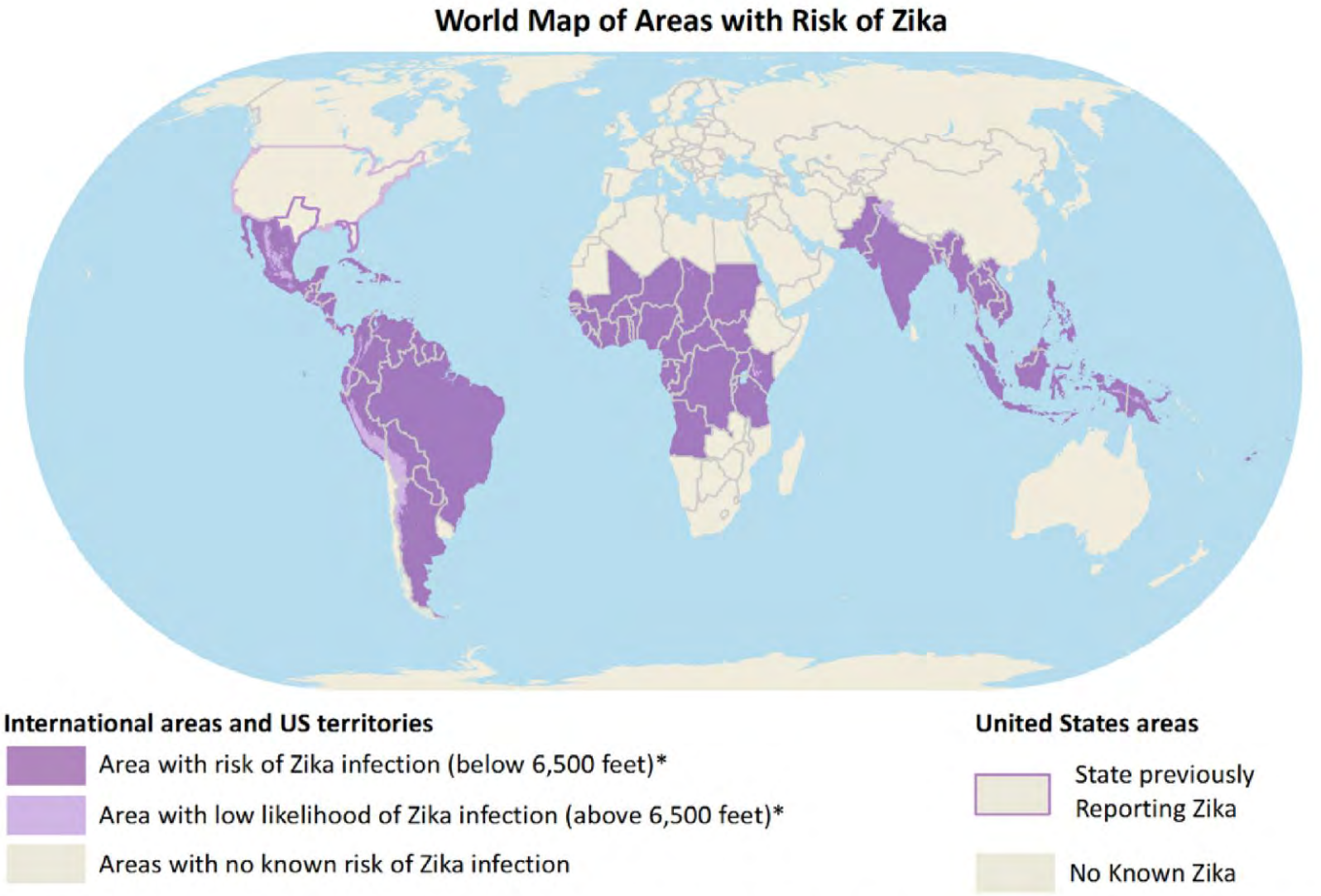
Post-lung transplant, CMV pneumonia



Zika Virus







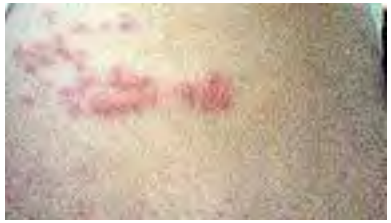
96 countries involved

[CDC 2018]

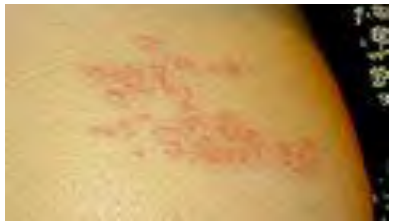
Acute and persistent virus life strategies

- Persistent in individual host
- Acute disease often inapparent
- Genetically stable
- Highly species specific
- Coevolution with host
- Transmission is often from parent to offspring (vertical) or through sexual contact
- Less dependent on host population structure
- Often the source of emerging acute disease in new host species

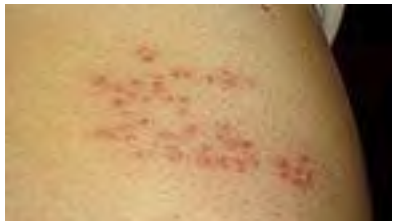
VZV



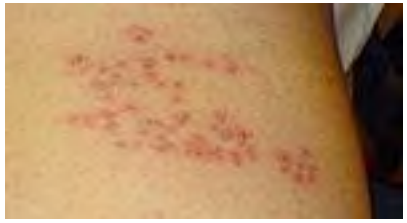
Day 1



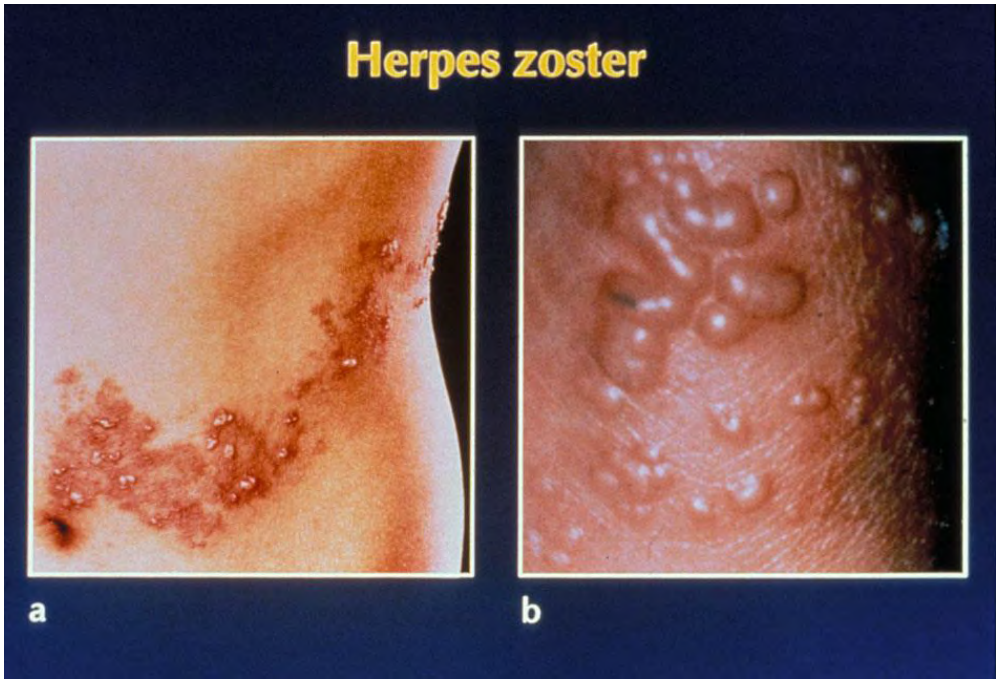
Day 2

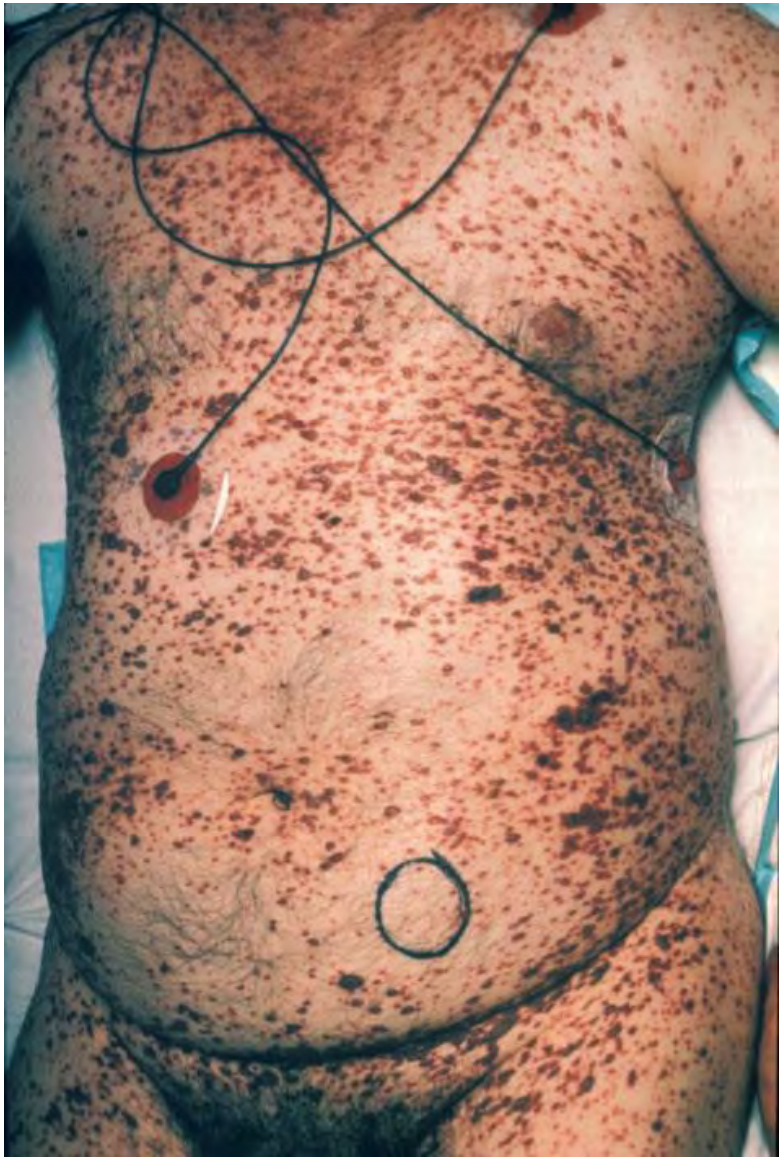


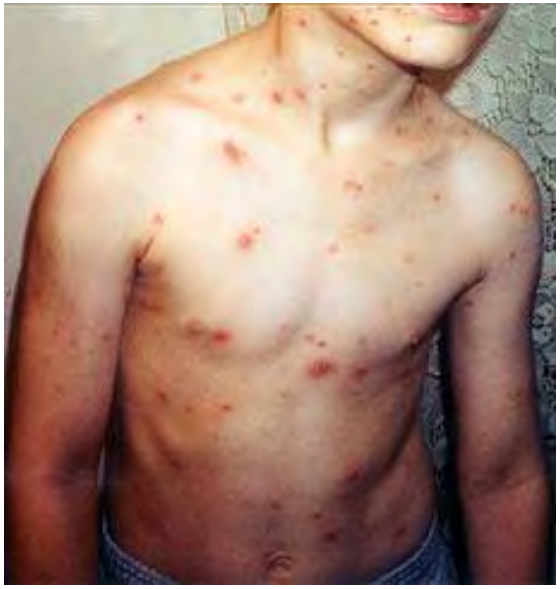
Day 5

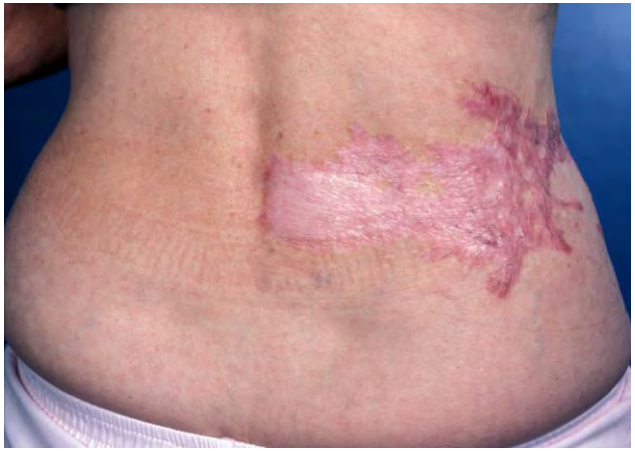


Day 6









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Some numbers

- Whales often infected with caliciviridae, transmit to humans, excrete >10^{13} per day

- There are ~ 10^{16} HIV genomes on the planet, with resistance likely to every antiviral now or in the future
- HERVs make up ~5% of human DNA
- Tobacco mosaic virus discovered 1892 (Ivanov) and further 1898 (Beijerinck)

OUTLINE

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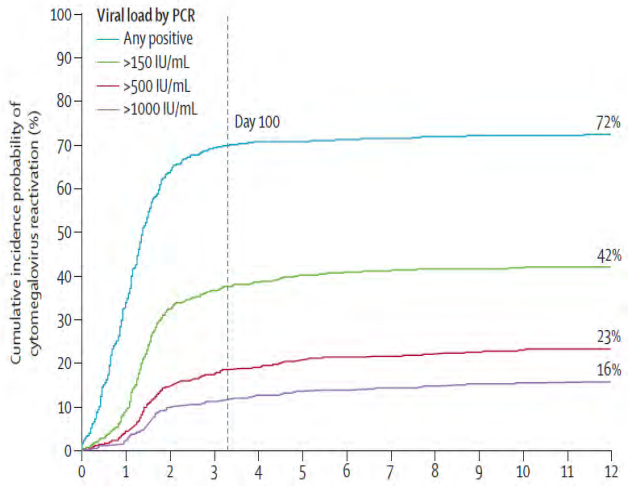
CMV in HSCT recipients

- Higher Viral Load [Howden 2003, Green 2016]
- Concomitant HHV6



- Antiviral resistance
  - Higher if D+/R-
  - Higher persisting VL
  - Multiple CMV disease episodes
  - High level of immunosuppression include OKT3
  - Lung, kidney-pancreas
  - Prolonged antiviral administration, with Prophylaxis>Pre emptive
  - Low antiviral concentrations with ValGCV 450 > 900 [Stevens 2015]

Q-NAT use in transplant recipients

- Initiation of therapy in SCT
  - High risk allogeneic SCT 10,000 c/ml whole blood
    - Alternative 418 cp/104 PBL [Peres 2010]
  - Pre emptive therapy with GCV 5mg/kg/dy
  - Dose escalation of GCV if no VL response
- Initiation of therapy in renal transplants
  - Lower risk SOT 30,000 c/ml plasma
- Initiation of therapy in liver transplants
  - Moderate risk SOT 1,000 c/ml plasma, PPV 47%, NPV 83%
  - Moderate risk SOT 5,000 c/5x106 cells, PPV 40%, NPV 90%

[Li 2003; Martin-Davila 2005; Rayes 2005; Verkruyse 2006, Peres 2010]

Viruses in childcare settings

TABLE II. Predictors of Symptomatic Illness and hRV Detection

Outcome construct	Overall corrected % predicted	Nagelkerke R^2	Significant predictor constructs	Odds ratio (95% CIs)	*P*-value
Detection of hRV RNA on clothing (evening sample)	97.1	0.233	Detection of hRV RNA on clothing (morning sample)	39.7 (8.5–185.6)	<0.001
Detection of hRV RNA on clothing (morning or evening sample)	95.2	0.112	Self-recognition of symptomatic illness, 2 days previously	8.2 (1.3–53.1)	0.028
			Worked at center 2	0.07 (0.07–0.6)	0.018

Journal of Medical Virology 87:925–930 (2015)

Personal Clothing as a Potential Vector of Respiratory Virus Transmission in Childcare Settings

Jan Gralton,[1,2] Mary-Louise McLaws,[1] and William D. Rawlinson[2,3,4]*
[1]UNSW Medicine, UNSW Australia, Australia
[2]Virology Division, Prince of Wales Hospital, Australia
[3]School of Medical Sciences, UNSW Australia, Australia
[4]School of Biotechnology and Biomolecular Sciences, UNSW Australia, Australia

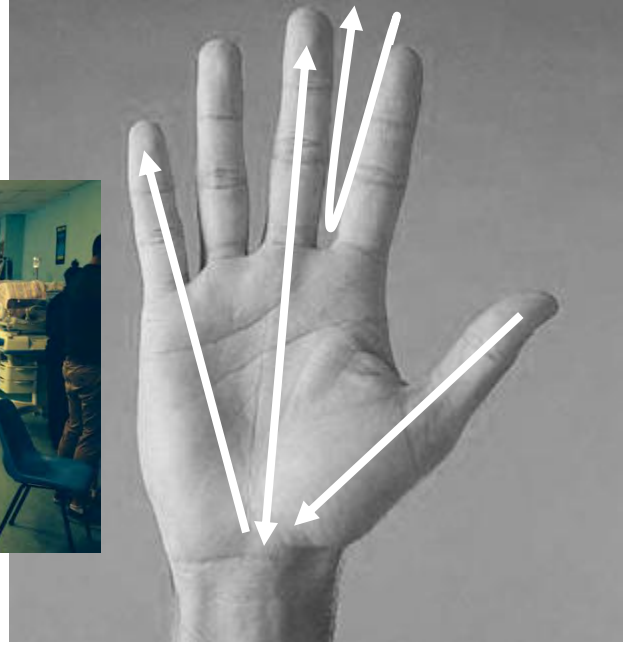
CMV in childcare settings

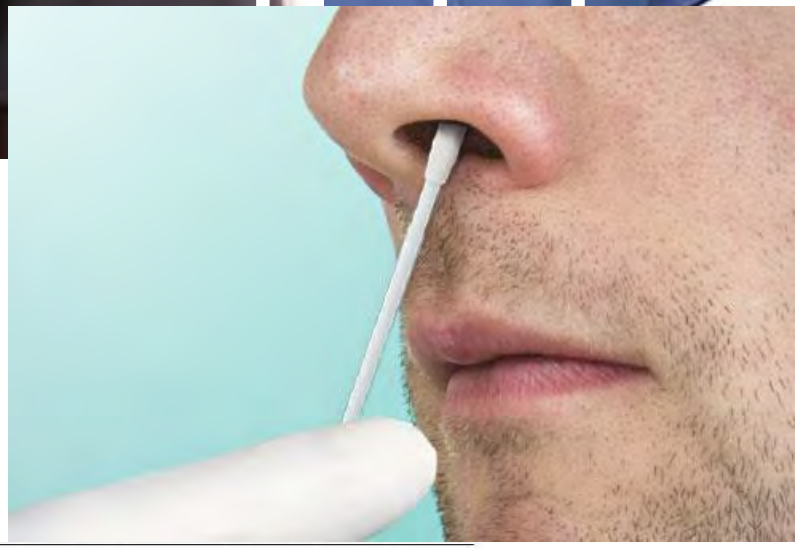
Risk

- Infection through high levels of CMV in saliva and urine in children
- Exposure of childcare staff through changing nappies, feeding, contaminated environmental surfaces
- higher rates of paediatric shedding in childcare (50% in childcare versus 20% in controls in Emergency for subjects 3 months to 6 years age) [Grosjean 2014]

CMV excretion among childcare staff from two childcare centres in Sydney

- 114 clothing samples + 125 nasal samples from 20 trained childcare staff, Sydney 5 weeks in 2011
- 6/125 nasal swabs +ve CMV DNA
- CMV excretion rate 30% (6/20) among childcare staff
- 0/114 clothing swabs +ve [van Zuylen 2017]





- Sampling days: once every week for 8 weeks
- Sampling procedure: nasal, hand and personal clothing specimens
- Environmental samples :"point prevalence"

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]

[1]*School of Women's and Children's Health, UNSW, Randwick, Australia*
[2]*Department of Newborn Care, Royal Hospital for Women, Randwick, Australia*
[3]*Serology and Virology Division (SAViD), SEALS Microbiology, Prince of Wales Hospital, Randwick, Australia*
[4]*School of Medical Sciences, UNSW, Australia*
[5]*Telethon Institute for Child Health Research, Institute for Child Health Research, University of Western, Australia*
[6]*School of Biotechnology and Biomolecular Sciences, UNSW, Australia*

Background

- "Colds" trigger asthma exacerbations (1927)
- Multiple "triggers" for asthma symptoms
  - allergens, smoke/pollution, Weather
  - Infection
- Other factors increase symptoms with colds
  - allergic, allergen exposure, ?low Vit D
- Childhood rhinovirus hRVC > A > B > others
- Back to school asthma - more & different viruses
- Infants, severe RSV+ hRV increases risk of asthma in childhood 5-10 X, typically allergic children

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Results – virus overall in study

25.5 % nasal hRV +ve

11.5 % exhaled breath hRV +ve

33.3 % either nasal wash or breath hRV +ve

32.4 % breath / nasal concordant +ve for hRV

2.3 % nasal +ve for other viruses*

1.5 % breath +ve for other viruses*

56 % hRV sequenced (231 nasal, 24 breath)

*Influenza A, Influenza B, RSV, PIV1, 2, 3, hMPV

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Conclusions

The detection of nasal hRV was associated with a small significantly increased risk of day-to-day asthma symptoms in children.

Host, virus genotype, and environmental factors each had only a small or no effect on the relationship of viral infections to asthma symptoms.

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]

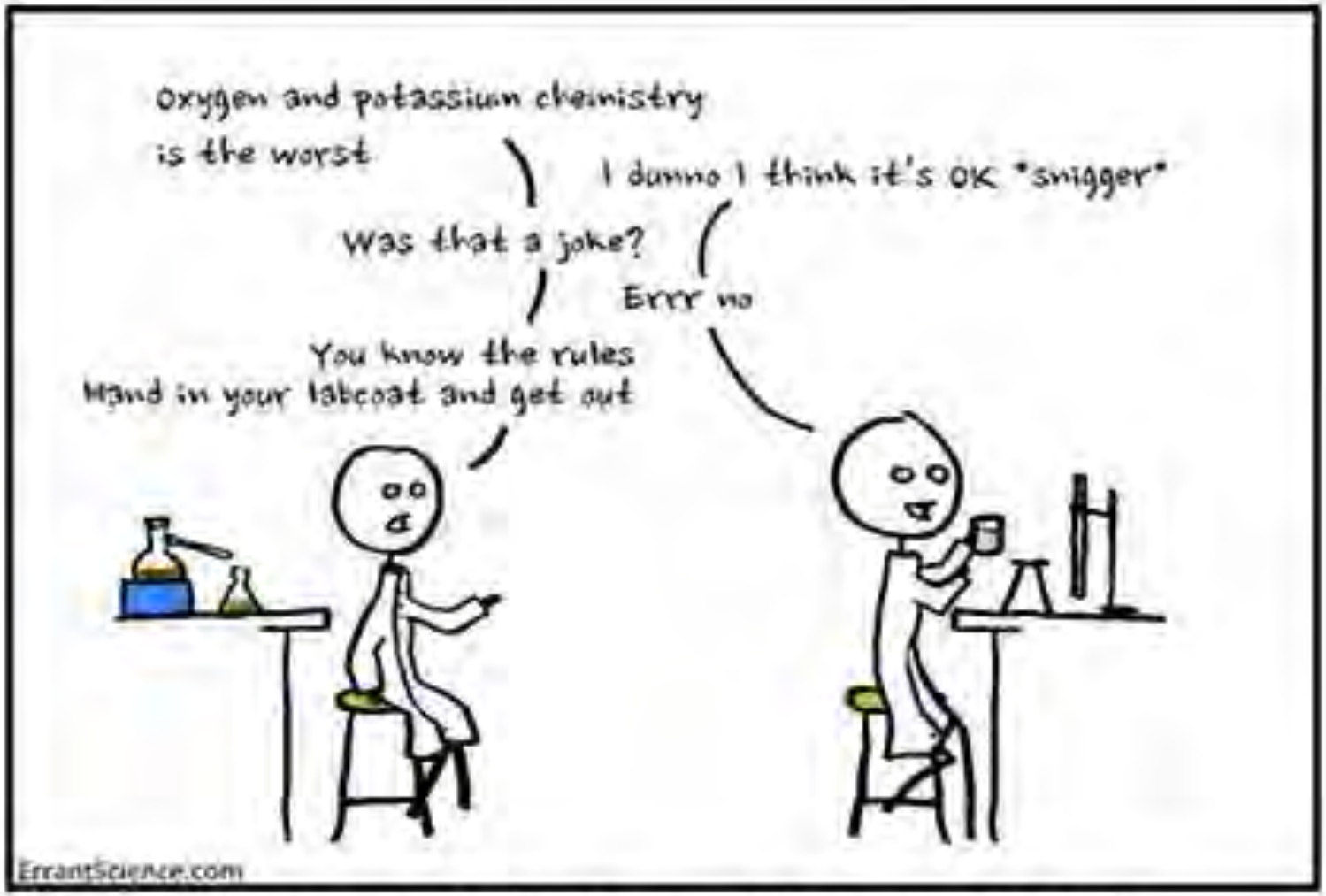
Sydney and Brisbane, Australia

Background: Viruses are frequently associated with acute exacerbations of asthma, but the extent to which they contribute to the level of day-to-day symptom control is less clear.

Objective: We sought to explore the relationship between viral infections, host and environmental factors, and respiratory symptoms in children.

Methods: Sixty-seven asthmatic children collected samples twice weekly for an average of 10 weeks. These included nasal wash fluid and exhaled breath for PCR-based detection of viral RNA, lung function measurements, and records of medication use and asthma and respiratory symptoms in the previous 3 days. Atopy with sampling and 3 to 4 days later. No differences were found between the 3 hRV genotypes (hRV-A, hRV-B, and hRV-C) in symptom risk. A history of inhaled corticosteroid use, but not atopic status, mite allergen exposure, or vitamin D levels, modified the association between viruses and asthma symptoms.

Conclusion: The detection of nasal hRV was associated with a significantly increased risk of day-to-day asthma symptoms in children. Host, virus genotype, and environmental factors each had only a small or no effect on the relationship of viral infections to asthma symptoms. (J Allergy Clin Immunol 2015;135:663-9.)



The zero-tolerance policy on jokes claimed its first victim

OUTLINE

3. Clinical virology and diagnosis
   - Principles
   - Surveillance
   - Applications – outbreaks, antiviral resistance

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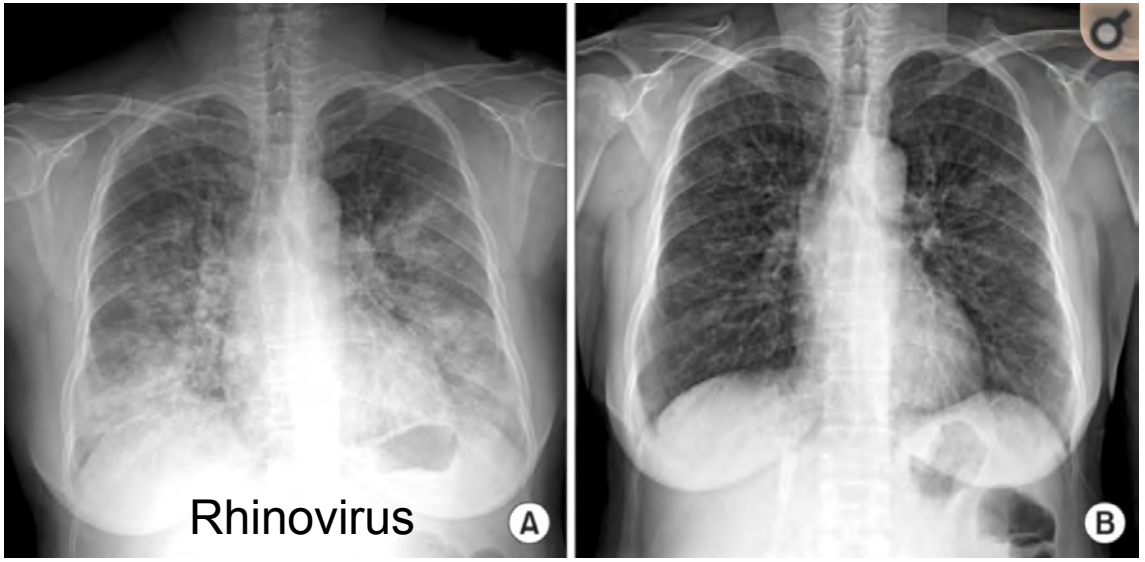
Viral Syndromes

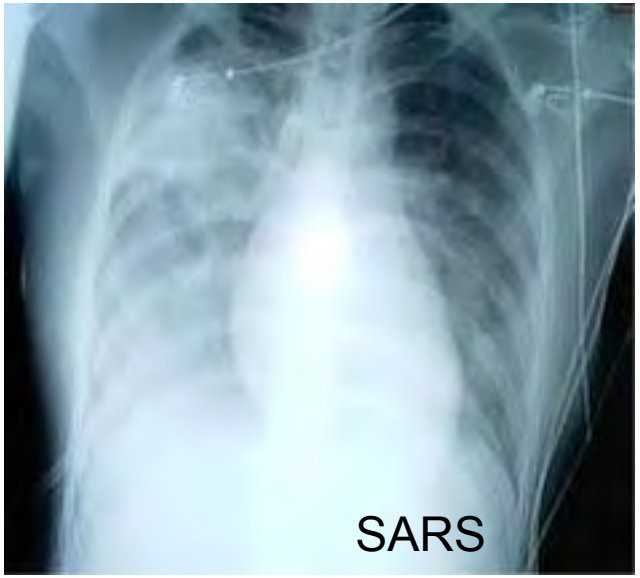
- Adenopathy and glandular fever
- Arthritis
- Carditis
- Chronic Fatigue Syndrome
- Congenital and perinatal disease
- Exanthemata and skin disease
- Eye disease
- Gastroenteritis

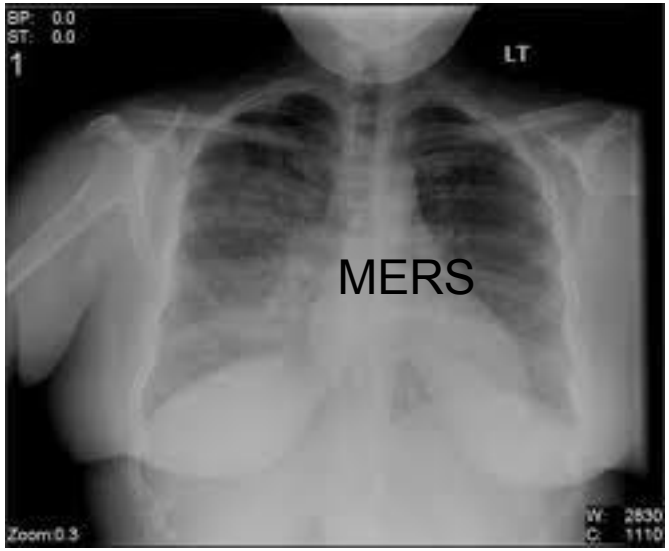
Viral Syndromes

- Haemorrhagic fevers
- Hepatitis
- Immunocompromised infections
- Neurological disease
  - encephalitis and meningitis
- Pancreatitis and diabetes
- Respiratory disease
- Sexually Transmitted Infections (STD, STI)

ACUTE PNEUMONITIS



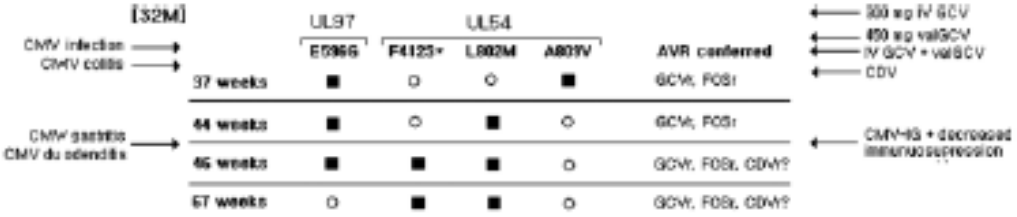


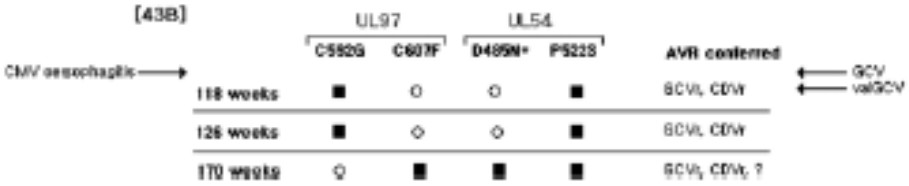


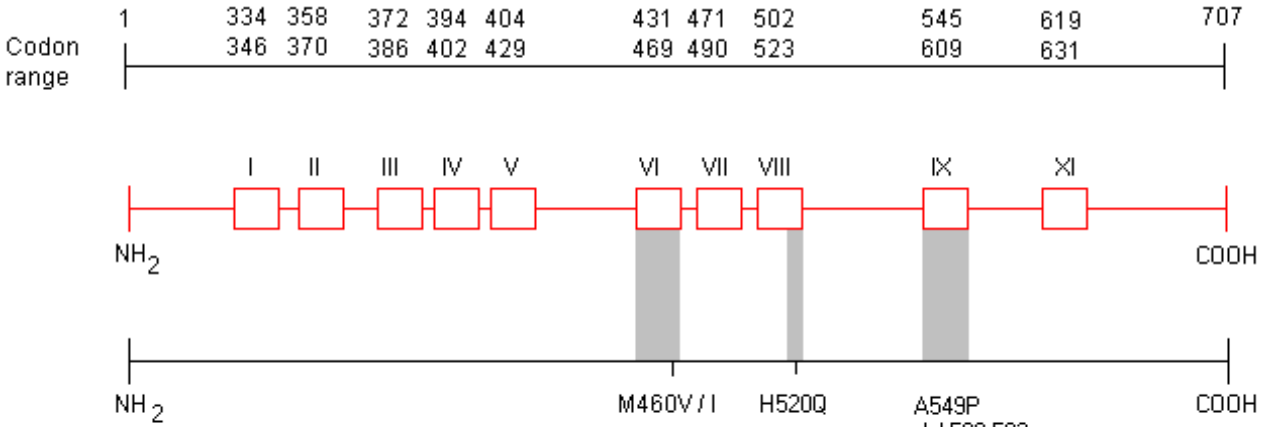
Diagnostic Methods

- Serology - retrospective
- Ag
  - Protein based
  - IFA (Respiratory)
  - WB (HIV)
  - Protein function (HIV-RT)
- Culture – some viruses non-cultivable
- Molecular
  - Virion nucleic acid
  - HIV RNA, HCV RNA
  - CMV DNA
- Detection of viruses in different/new situations
- Emerging Microarray different formats, HPLC, Protein amplification, MALDI-TOF
- Deep sequencing and multiple sequence determinations

CMV







A549P
del 590-593
del 591-594
del 591-607
A591D/V
C592G
A594T/V
del 595
del 595-603
L595F/S/W
E596D/G
N597D
G598S
del 600
C603W
D605E
C607F/T

Diversity of antiviral-resistant human cytomegalovirus in heart and lung transplant recipients

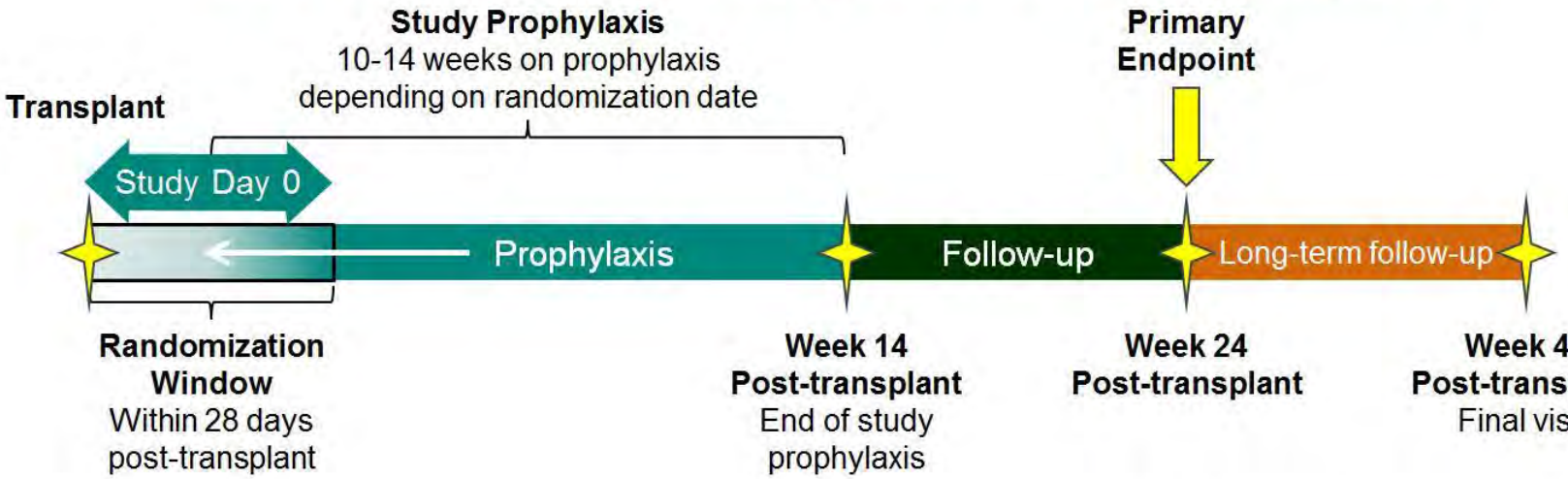
J.M. Iwasenko, G.M. Scott, Z. Naing, A.R. Glanville, W.D. Rawlinson. Diversity of antiviral-resistant human cytomegalovirus in heart and lung transplant recipients.
Transpl Infect Dis 2010. All rights reserved

Abstract: Immunocompromised transplant recipients are at high risk for human cytomegalovirus (CMV)-related infection and disease. Antiviral prophylaxis and treatment have reduced CMV morbidity and mortality, but at times promote development of antiviral-resistant CMV strains that can significantly contribute to adverse clinical outcomes in transplant recipients. We have investigated CMV genotypes in transplant recipients (bone marrow, stem cell, kidney, heart, lung, and

J.M. Iwasenko[1,2,4], G.M. Scott[1,2], Z. Naing[1], A.R. Glanville[3,4], W.D. Rawlinson[1,2,4]

[1]Virology, Department of Microbiology, South Eastern Area Laboratory Services (SEALS), Prince of Wales Hospital, Randwick, New South Wales, Australia, [2]School of Biotechnology and Biomolecular Sciences, Faculty of Science, University of New South Wales, Kensington, New South Wales, Australia, [3]Lung Transplant Unit, St Vincent's Hospital, Darlinghurst, New South Wales, Australia, [4]School of Medical Sciences, Faculty of Medicine, University of New South Wales, Kensington, New South Wales, Australia

P001 Clinical Trial Design for CMV Prophylaxis



- 565 adult CMV seropositive HSCT recipients (R^+) randomized and received study medication
- Prophylaxis with letermovir or placebo (2:1 ratio)
  - 67 centers in 20 countries
  - Dose: 480 mg once daily; 240 mg once daily with cyclosporine (CsA)
- PET was initiated if subject experienced clinically significant CMV infection

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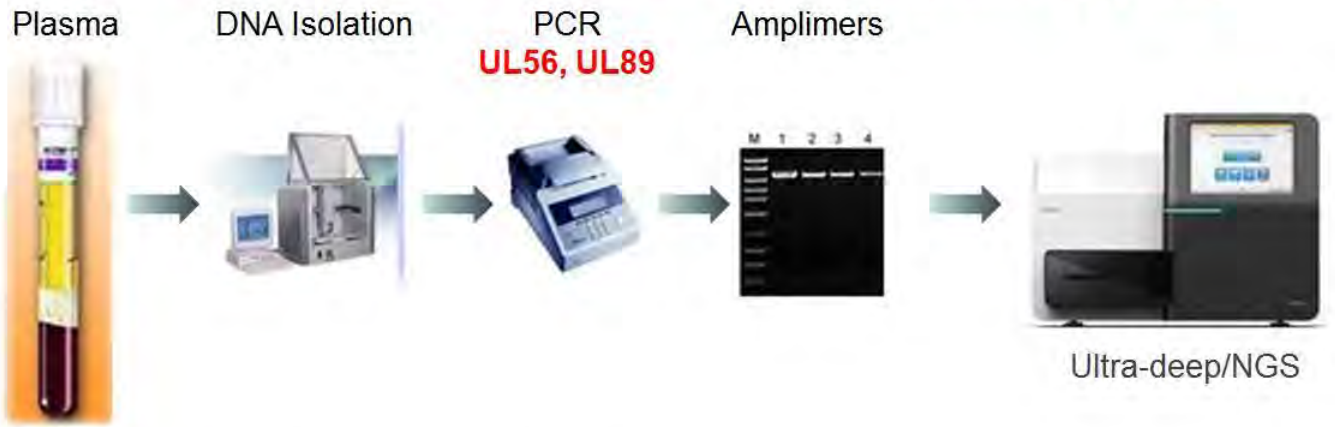
Methodology for Resistance Genotyping



- Plasma collected at the time of csCMVi from LET and PBO subjects was used for resistance genotyping
  - Low copies of CMV DNA required a highly sensitive assay (LOD < 151 copies/mL)
- Compare deduced AA sequences to references and identify substitutions
- Genotypic variants (GVs)
  - Detected in ≥ 5% of sample sequence data at given position
  - If detected in ≥ 5% but < 99% of NGS reads, replicate tested to rule out artifacts

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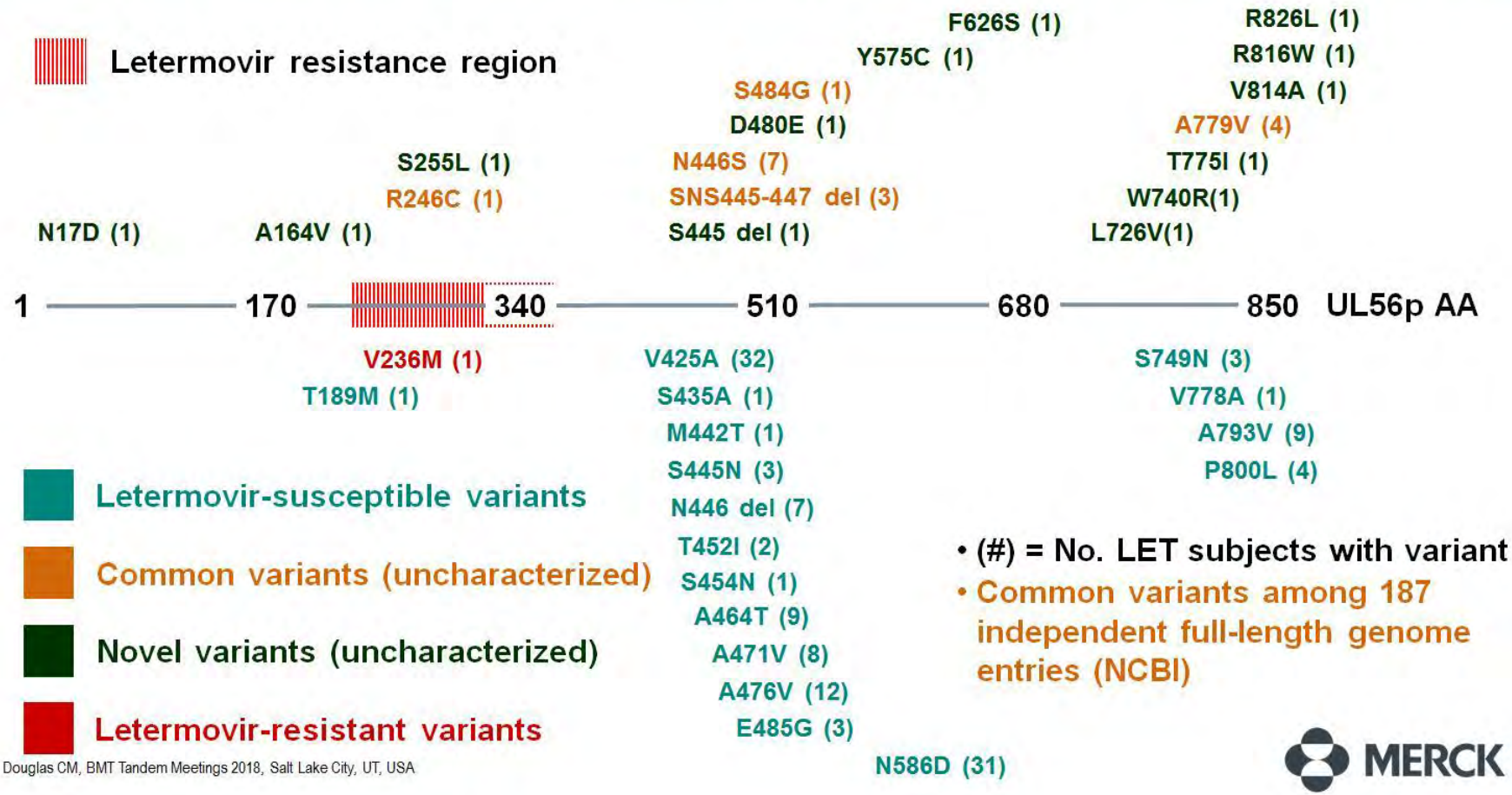
UL56p Variants in Letermovir Subjects Who Failed Prophylaxis



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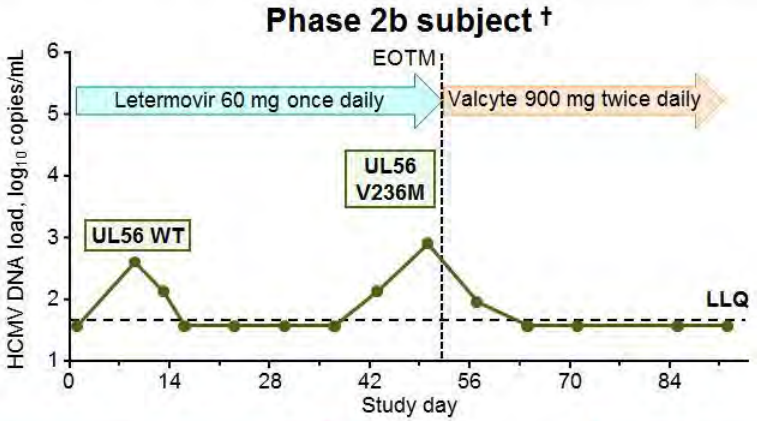
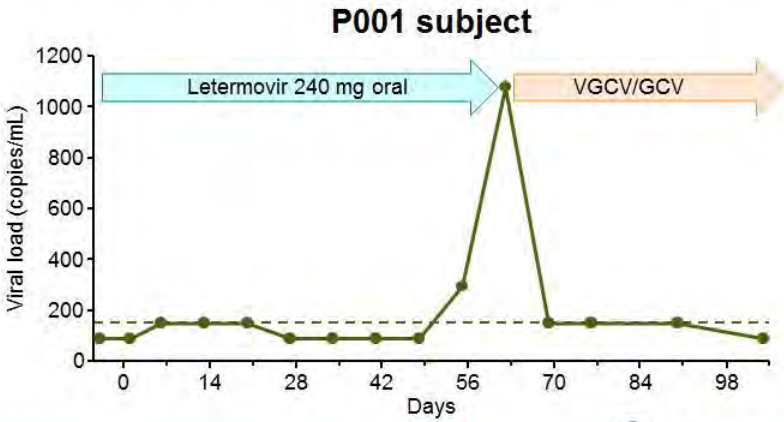
The UL56p V236M Letermovir-Resistance Mutation

- The UL56p V236M mutation confers a 30 to 50-fold shift in the EC_{50} for letermovir in a cell-culture model of CMV infection
  - There is no impact on susceptibility to other anti-CMV agents (cidofovir, foscarnet, and ganciclovir)*
- UL56p V236M was not observed in subjects who received placebo or among CMV UL56p sequences in public databases
- One subject in a Phase 2b study of letermovir also failed with the UL56p V236M mutation
- Infections with a CMV UL56p V236M mutant resolved with GCV/VGCV pre-emptive therapy





6 J Infect Dis 213: 23-30

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* 2017 Antimicrob Agents Chemother 61: e01044-17

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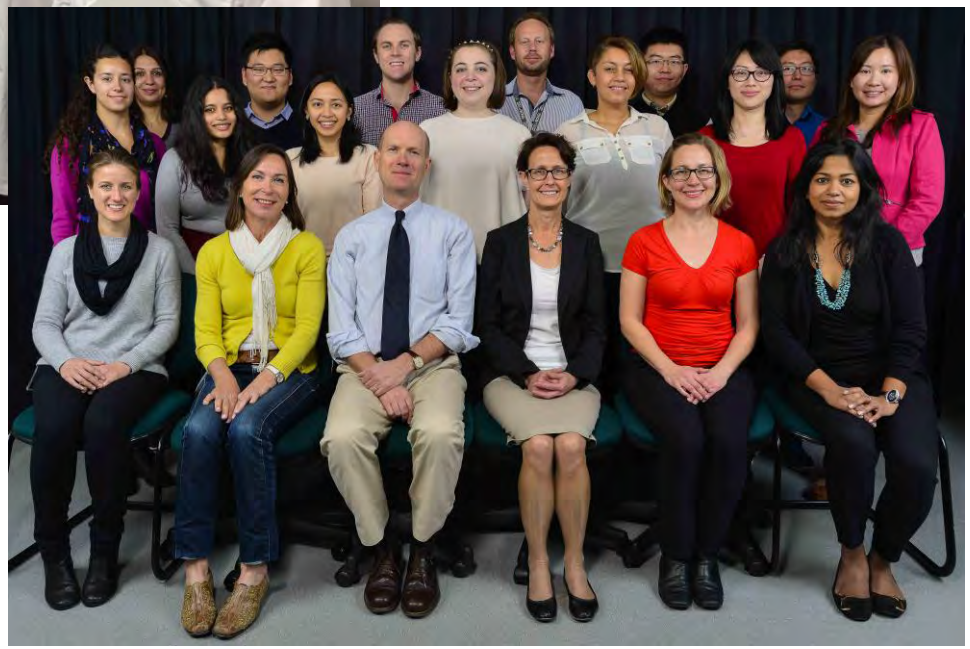

Viruses in May 2018

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