

Trends in human virology

New viruses from animals

Nipah virus
Hendra virus
SARS coronavirus
Avian (H5N1) influenza

New human viruses

Metapneumovirus
Bocavirus

Changing epidemiology

Measles
Varicella
Dengue
Chikungunya

Newer diagnostic techniques

Molecular
Serological
Imaging

Common viral syndromes

Mucosal	Respiratory tract infection Gastroenteritis
Systemic	Fever/rash/lymphocytosis
Organ-related	Meningitis/encephalitis Acute flaccid paralysis Arthritis Hepatitis HIV
Special groups	Fever after travel Viral infections in immunodeficiency

Is this a viral illness ?

0200 – 0300 hrs

Female, age 20, lives in a university college
Attended A&E with malaise, aching upper limbs
Had been horse riding the day before

T 38.4 WCC 6.5; Neutrophils 4.5, lymphocytes 2.0
Probable viral infection; given Voltaren

1630-1700 hrs

Feeling worse
Noticed a skin rash
Attended the university medical service
T 39.0; several macules on thighs and legs

1800 hrs

Returned to A&E

Blood culture grew *Neisseria meningitidis*

Clinical recognition of meningococcal sepsis

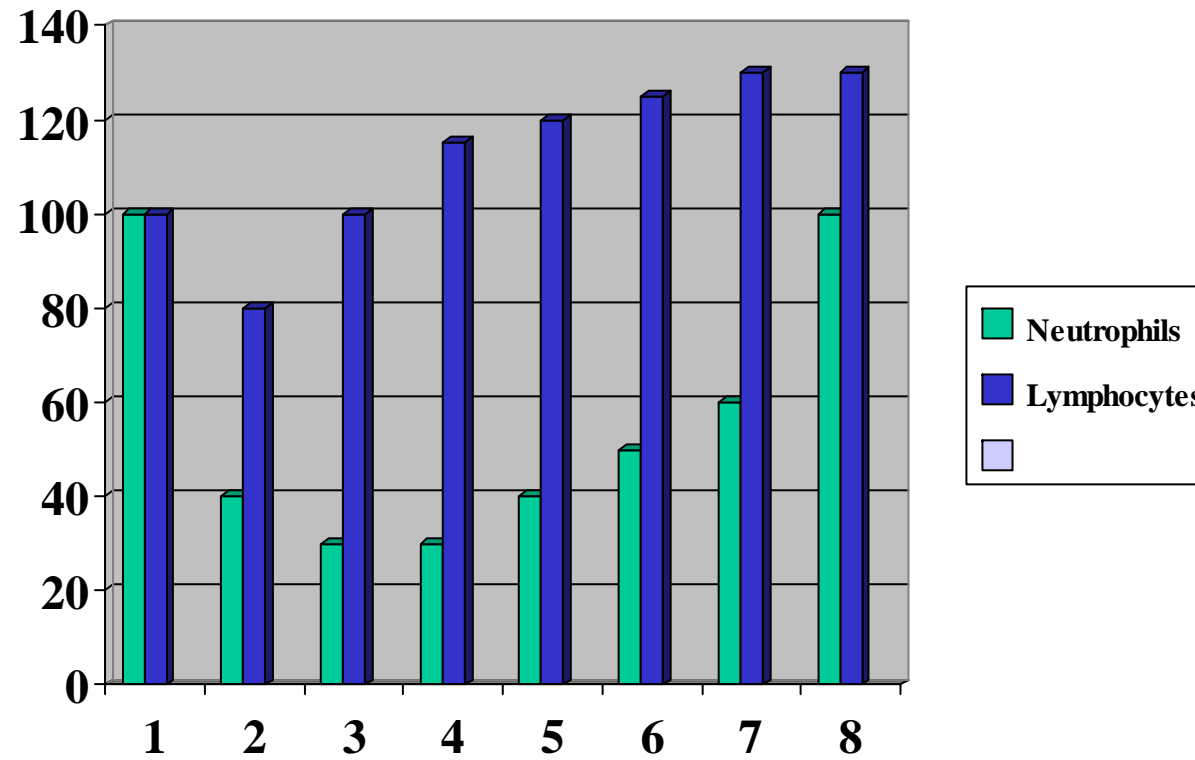
Thompson, et al, Lancet, 4/2/06, p.397

4-6 hrs Non-specific flu-like symptoms

8 hrs Leg pains
Cold hands and feet
Abnormal skin colour

13-22 hrs Rash, meningism

Leucocyte response in acute viral infections
(expressed as % of normal counts)



Acute phase reactants as markers of sepsis

Simon L et al. *Clinical Infectious Diseases*, 2004;39:206-17

	Begins to rise at:	Peaks at:
C-reactive protein (CRP)	4 – 6 hours	36 hours
Procalcitonin (PCT)	4 hours	8 hours

Is this a viral illness ?

Farmer, age 60, developed malaise and arthralgia
PH of aortic murmur (bicuspid valve)

February	Hb	105
	CRP	46
	Ross River IgM	POSITIVE

March	Petechial rash on shins	
	Rheum. factor	2420 IU/ml
	Ross River IgM	POSITIVE

.....commenced prednisone 5mg/day

April	No improvement	
	Creatinine	220
	Urine microscopy	White cells 10-100, red cells > 100 + red cell casts

Multiple blood culture grew viridans streptococci

Beware of making a viral diagnosis when.....

- WCC, or CRP, or ESR are elevated
Neutrophils are vacuolated
- Fever has persisted more than a week
- The patient is over 50
- The patient is at high risk of sepsis, eg
 - Puerperium
 - IVDU's
 - Following surgery
 - Immunodeficiency
 - Previous splenectomy
 - Abnormal heart valve

Female, age 71, with fever, headache and dysphasia

Wednesday afternoon	Severe headache
Wednesday evening:	Trouble following the football score on TV Did some chores and went to bed
Thursday morning:	Woke unwell; would not make breakfast Trouble speaking
Thursday midday:	Brought to A&E by her husband

T 38.1 BP 140/90

Disoriented according to RMO who first saw her

Oriented according to neuro reg, who saw her 2 hours later

Dysphasia, mostly expressive

No neck stiffness

No cranial nerve or long tract signs

Na 131

Hb 152

WCC 10.4

CXR: clear

CT head (without contrast) normal

Neuro registrar: No risk factors for CVA

Discussed the case with AMO

Commenced treatment with aciclovir and ceftriaxone

The next day.....

CSF	White cells	7 cells/ul, not characterised
	Red cells	Nil
	Protein	0.48 (N = 0.15-0.45)
	Glucose	4.2

Herpes simplex PCR **positive**

MRI

F 1568186
07-Jul-2006
12:12:31

R
A

P
L

I
A
L

W: 560, C: 280
MAG: 227%
2.6:1

User ID : bennri, Team : All Users



pacsweb.cs.nsw.:

00:05

Agfa WEB1000 - Mi...

WEB1000



15:06

Progress

EEG, day 2:

Bilateral temporal slow waves

During the procedure, there was an episode of left temporal 5 Hz slow wave activity accompanied by speech disturbance, ie, a partial seizure

Commenced on phenytoin

Discharged on day 15, substantially improved

Features of herpes simplex encephalitis

- Caused by (recurrent) HSV-1
- Occurs at any age; the commonest cause of fatal sporadic encephalitis
- 2-4 cases per million persons per year
- Acute onset, fever, focal neurological signs, then obtundation
- Temporal lobes are most frequently involved
- CSF cell count and/or protein content are mildly elevated
- CT scans are normal in the first week; MRI is very sensitive
- Detection rate of CSF HSV DNA approaches 100% in first week
- Prompt aciclovir reduces mortality to 20% (but sequelae are common)

Molecular tests for HSV - RPAH, 1992-2006

	Extraction	Primers	Detection
1992	Boiling	Glycoprotein D	Gel
1996	Quiagen	Glycoprotein D	Gel
2000	Quiagen	Duplex Glycoprotein B	Probes/real-time + melt curve
2006	Quiagen	Tests X 2 Glycoprotein B	Probes/real-time

Cases of suspected herpes encephalitis, Central Sydney, 2005-2006

All patients were treated presumptively with aciclovir

All had MRI scans

Sex/age	Cells	Protein	PCR	Final diagnosis
F71	7	0.48	Pos	Encephalitis
M67	18	1.34	Pos	Encephalitis
M27	90	NT	Pos	Encephalitis
M67	72	1.15	Pos	Encephalitis
M48	90	1.65	Pos	Encephalitis
M76	2	0.40	Equivocal	No cause found
F82	9	0.63	Pos	Vascular disease

Causes of encephalitis

California Encephalitis Project *Clinical Infectious Diseases* 2003;36:731-42

Common causes of fever + obtundation included the following:

Infectious (53)

Herpes simplex
Varicella-zoster
Epstein-Barr
Enterovirus
HHV6
Bartonella henselae (cat-scratch disease)

Infection-associated (41)

Mycoplasma pneumoniae
Influenza
Endocarditis
Sepsis (staphylococcal, gram negative, brucella, etc)

Non-infectious (32)

Psychosis
Lymphoma
Autoimmune diseases
Vascular disease

Could this be a rare zoonotic viral encephalitis?

Travel to rural Asia

Japanese encephalitis

Nipah virus

Travel to rural Australia

Murray Valley encephalitis

Association with horses, bats

Hendra virus

Lyssavirus

Travel to rural USA

West Nile encephalitis

Other arthropod-borne viruses

Dog bite in certain countries

Rabies

Aseptic meningitis

Female, age 24

Presented with fever and headache of 12 hour's duration

Has had dysuria for the last week

O/E T38.5

Mild neck stiffness

U/A White cells ++, protein ++

Labs WCC normal

CRP 25

CSF: 35 cells, all mononuclear. Protein 0.55, glucose 3.8

Herpes simplex PCR (type 2) **positive**

Causes of viral meningitis in young adults

Enteroviruses

Herpes simplex, type 2

Epstein-Barr virus

Varicella-zoster

HHV 6

Consequences of oral poliovirus vaccine (OPV)

Risk

Outcome

Administration
of vaccine

Flaccid paralysis in 2-4 persons per
million vaccinated

High rate of OPV
carriage and transmission
in an urban community

Outbreaks of flaccid paralysis

B-cell deficiency

Encephalopathy

Fever and rash in a returning traveller

Male, age 21, Australian resident born in New Zealand (Polynesian)
Travelled to Kuala Lumpur with a soccer team for one week
On returning to Sydney presented to Emergency with malaise and rash
No recent medications

O/E T 38^C
 Widespread maculopapular rash
 Looks unwell

Labs WCC: 3.8
 Neutrophils 2.8
 Lymphocytes 0.8
 Monocytes 0.2
 Platelets: 80
 CRP 15
 Thick film: Negative

Inspection of the oral cavity revealed Koplik's spots

Measles vaccination in Australia

Before 1968 most of the population had been infected with the wild virus

1968 One-dose vaccination introduced

1994 Two-dose schedule introduced

1998 “catch-up” campaign for those born between 1968 and 1994

People now aged between 13 and 39 may not have received a second dose of measles vaccine and may not be immune

Morbidity among ill travellers returning to the USA from Southeast Asia
NEJM 2006; 354:119-230

(number per 1000 ill returned travellers)

Fever, cause not determined	104
Diarrhoea	97
Dengue	80
Larva migrans	36
Malaria	22

Features of dengue haemorrhagic fever (DHF)

In Asia, primarily a disease of children (but of all ages in the Americas)

Defined as:

- Bleeding
- Platelets < 10
- Haematocrit increased by $> 20\%$
- Pleural effusions or hypoalbuminaemia

Pre-existing dengue antibodies are the most significant risk factor for spontaneous bleeding

Question: Should Australians who have had dengue fever travel to high risk areas?

Fever + rash in returned travellers

Dengue

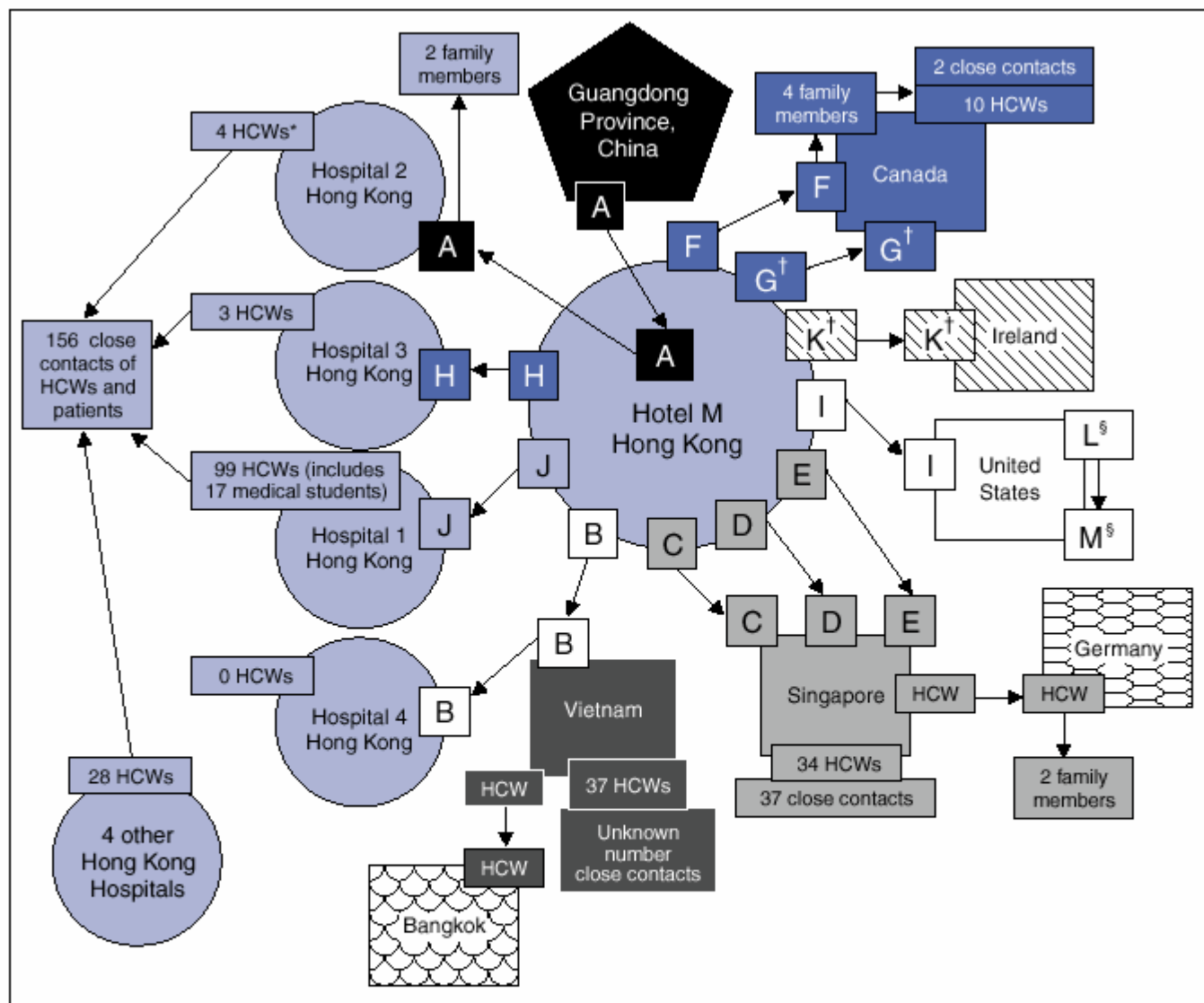
Measles

Chikungunya

Tick typhus

Drugs

FIGURE 1. Chain of transmission among guests at Hotel M — Hong Kong, 2003



* Health-care workers.

[†] All guests except G and K stayed on the 9th floor of the hotel. Guest G stayed on the 14th floor, and Guest K stayed on the 11th floor.

[§] Guests L and M (spouses) were not at Hotel M during the same time as index Guest A but were at the hotel during the same times as Guests G, H, and I, who were ill during this period.

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Figure 2

FIGURE 2. Number of suspected cases* of severe acute respiratory syndrome, by exposure category and date of illness onset — United States, 2003

Curbing the spread of SARS

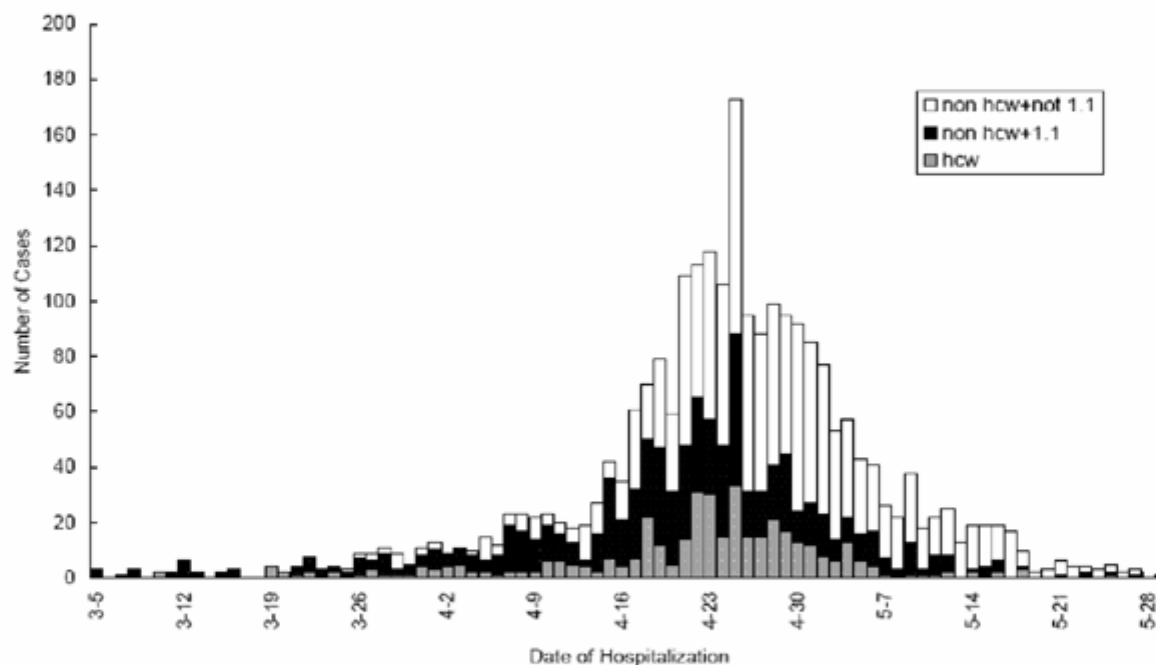
- Create a case definition
- Enhance detection
- Isolate suspected cases
- Establish the diagnosis
- Trace contacts

er 1, January 2004

se Respiratory Syndrome, Beijing, 2003

* Zonghan Zhu, * Jiyong Guo, * Zejun Liu, * Xiong He, * Weigong Zhou, † Daniel P. Chin, ‡ and Anne Schuchat† for the Beijing Joint SARS Expert

l Health Bureau and Beijing Municipal Centers for Disease Prevention and Control, Beijing, China; †Centers for Disease Control and Prevention, Atlanta, d ‡World Health Organization, Beijing, China



ic curve—severe acute respiratory syndrome (SARS) probable case-patients by date of hospitalization and type of exposure, Beijing, 2003. Open bars care workers without contact with a SARS patient; dark bars (“1.1”) indicate nonhealthcare workers with contact with a SARS patient; light filled bars indicate s.

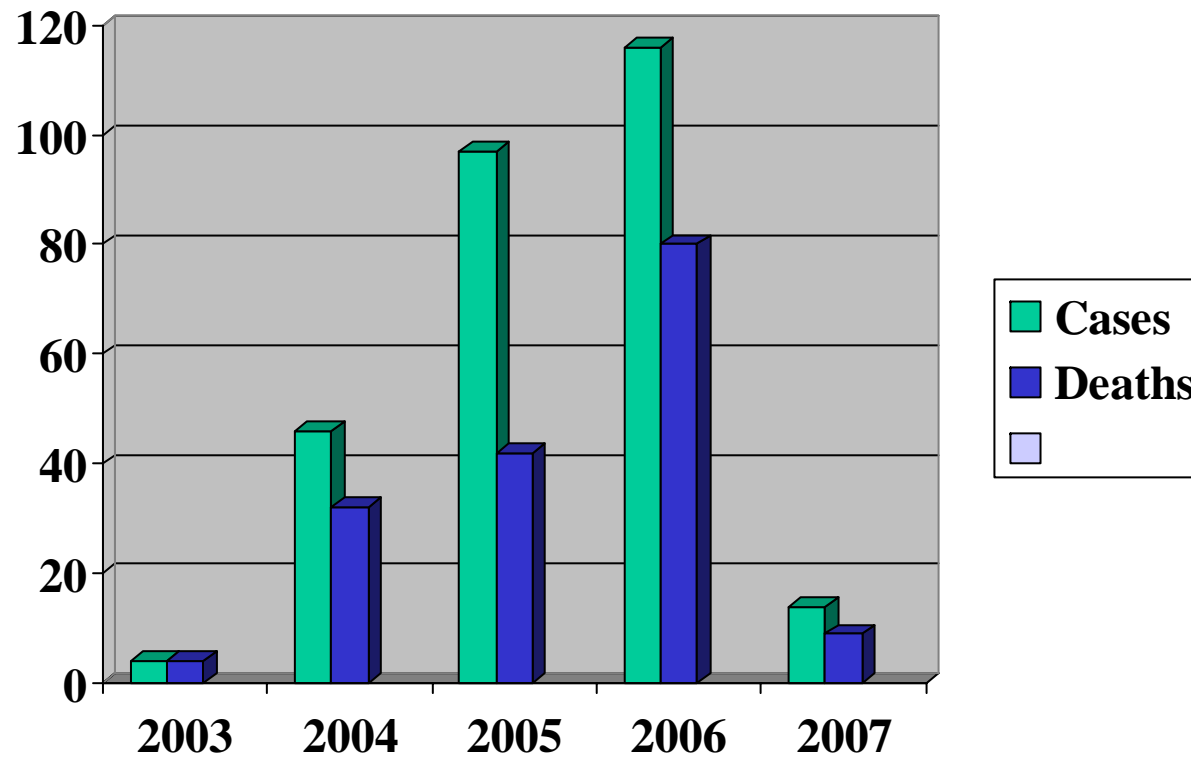
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viewed November 26, 2003

Epidemiology of SARS and avian influenza

	SARS	Influenza
Origin	S.China	S.China
Reservoir	? Bats	? Water birds
Amplified in	civets	poultry, pigs
Main transmission	Human-to-human	Poultry-to-human
Mode of transmission	Contact, droplets	Contact, droplets, ?air

Confirmed cases of avian influenza (worldwide, to 1 March 2007)



Avian influenza: The global situation

Asia	Most countries in SE Asia have had outbreaks Indonesia continues to be a problem
Africa	Illegal poultry imports and transport have promoted spread in Nigeria and Egypt
Europe	13 EU countries have been affected. Outbreak in Suffolk turkeys in February led to slaughter of 160,000 birds
America	Small outbreaks. Sophisticated monitoring
AUSTRALIA	No H5N1 outbreaks despite migrating Asian birds

Viruses as opportunists

Herpesviruses

CMV, HSV, EBV, VZV, HHV6, HHV8

Polyomaviruses

JC and BK viruses

Papillomaviruses

Respiratory viruses

Influenza, RSV, parainfluenzae 3

Parvovirus B19

A cluster of parvovirus infections in renal transplant recipients.

Rochester, USA Am.J.Transplant. 2006;6:225

3 cases of PVB19 were detected in 52 RTP's with EPO-resistant anaemia
(Hb <100)

All had PVB19 DNA in blood

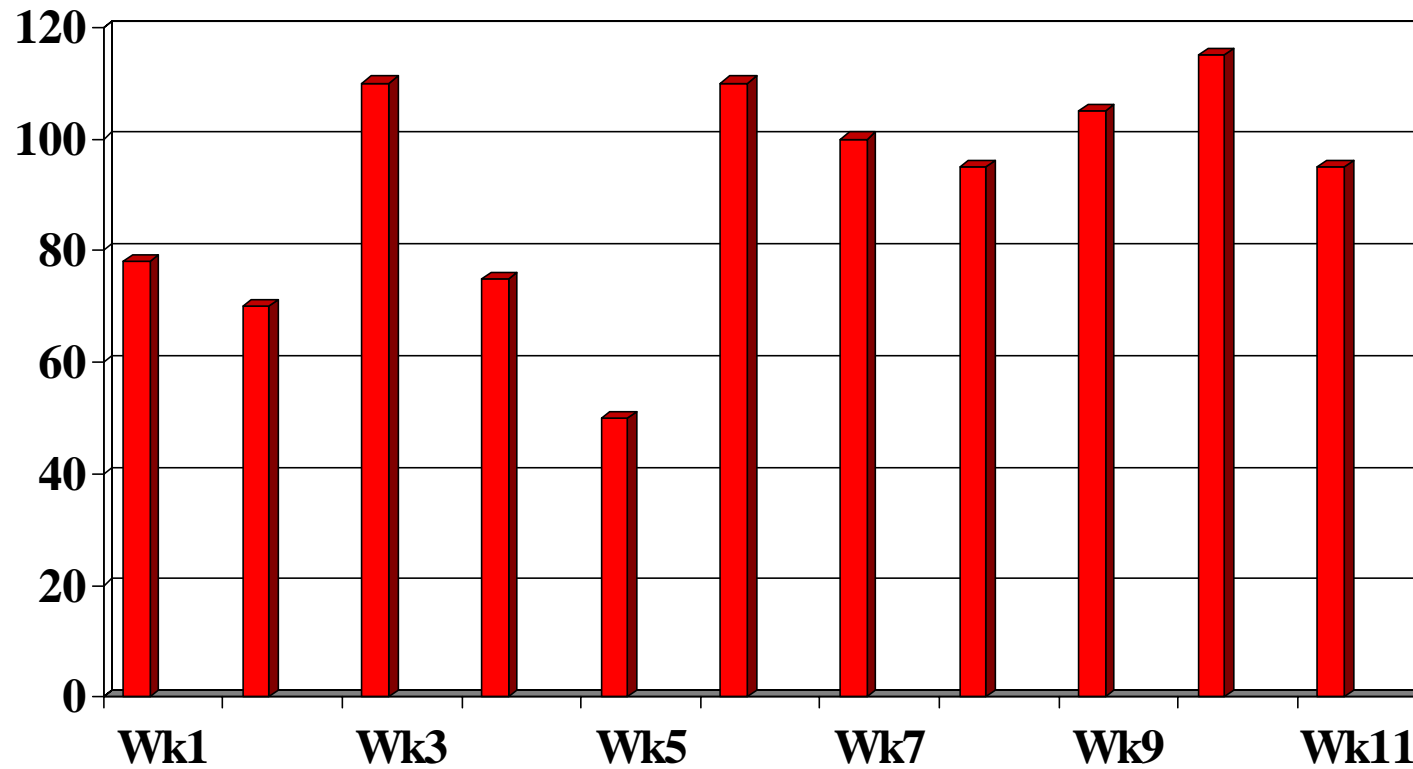
Serology and bone marrow biopsies were inconclusive

All were given 4 doses of IVIG

All responded but 1 relapsed

Case: Persistent anaemia after renal transplant

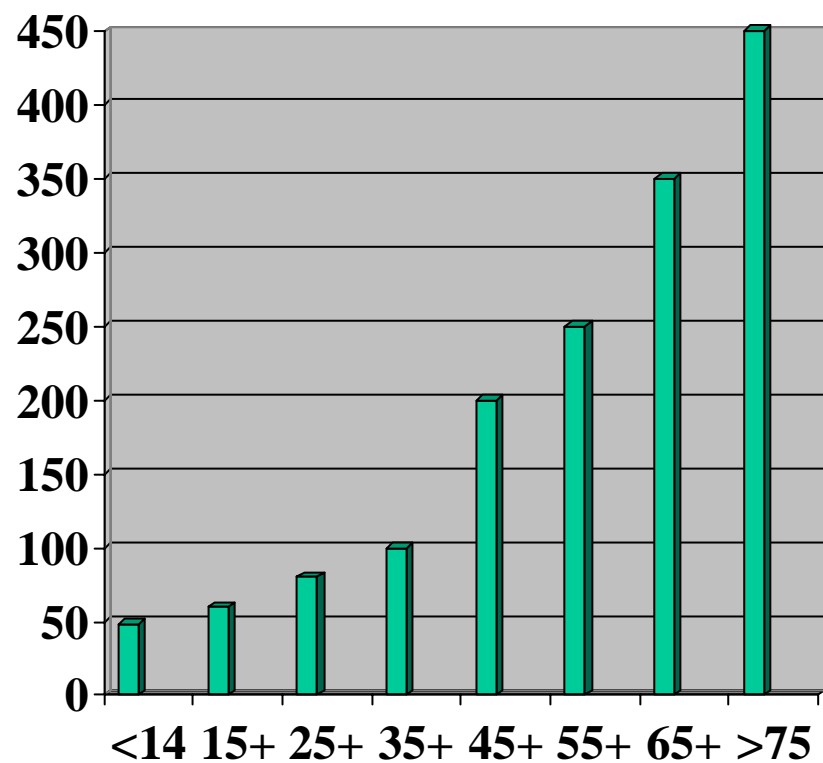
(Parvovirus PCR was positive but serology was negative)



Viral vaccines

	Children	Adults
Killed	Hepatitis B Poliovirus HPV	Influenza Hepatitis A Japanese encephalitis Rabies
Live, attenuated	Measles Mumps Rubella Varicella	? varicella

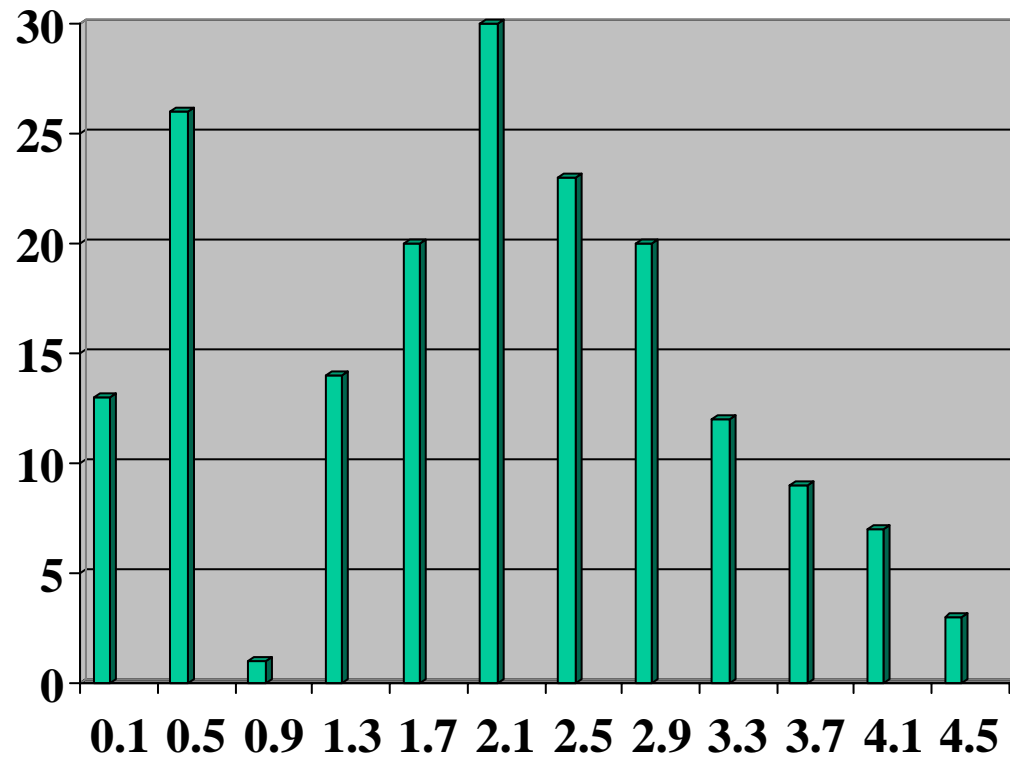
Age-related incidence of herpes zoster (per 100,000 persons per year)



..



Frequency distribution of varicella titres – RPAH - 2000



Does exposure to varicella prevent shingles?

Lancet

2/7/02

244 recent cases of zoster were matched with controls
Protection was associated with exposure to varicella*

Vaccine

2002;20:250

A large prospective study of adult morbidity included 1,595
cases of zoster
Exposure to varicella* was highly protective

* Living with children

Serological response to varicella vaccination in a male, age 59, with a history of varicella at the age of 10

	IgG EIA	CFT
Pre-vaccination	1.18*	< 4
Day 7	1.78	4
Day 14	3.08	32

Conclusion: there was a swift anamnestic response to vaccination

* cut-off = 0.9