The 2009 swine flu pandemic – 10 years on

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2009 Influenza pandemic – 10 years on

Reflections on 2009 – what have we learned since?

Influenza is multidimensional

A bad seasonal year is good practice

It’s hard to work out who has influenza

Infection control is important

Influenza complications are more than bacterial pneumonia

We need to know that vaccines work

We need to know that vaccines are safe

We still don’t know if antivirals work in hospitalized patients

Timeline

18 March, 2009 - first cases detected in Mexico

14 April, 2009 – first case detected in US (onset of illness 30 April)

25 April 2009 – WHO declares “public health emergency of international concern”

8 May, 2009 – first case in Australia (returned traveller from LA)

20 May, 2009 – first Melbourne case (11 year old)

21 May 2009 – Clifton Hill Primary School closed for 2 days

National | World | Lifestyle | Travel | Entertainment | Technology | Finance | Sport

news

Melbourne the swine flu capital of the world

MELBOURNE is now the swine-flu capital of the world, with the H1N1 virus twice as prevalent in the Victorian population as it is in Mexico, where the pandemic began.

Lauren Wilson

AUGUST 17, 2009 **4:29AM**

The Singapore Government posted a health warning on its website advising residents to defer non-essential travel to Victoria. And it is warning Singaporeans returning from Victoria to be alert for any flu-like symptoms.

Victorian Premier John Brumby yesterday questioned Singapore's stance.

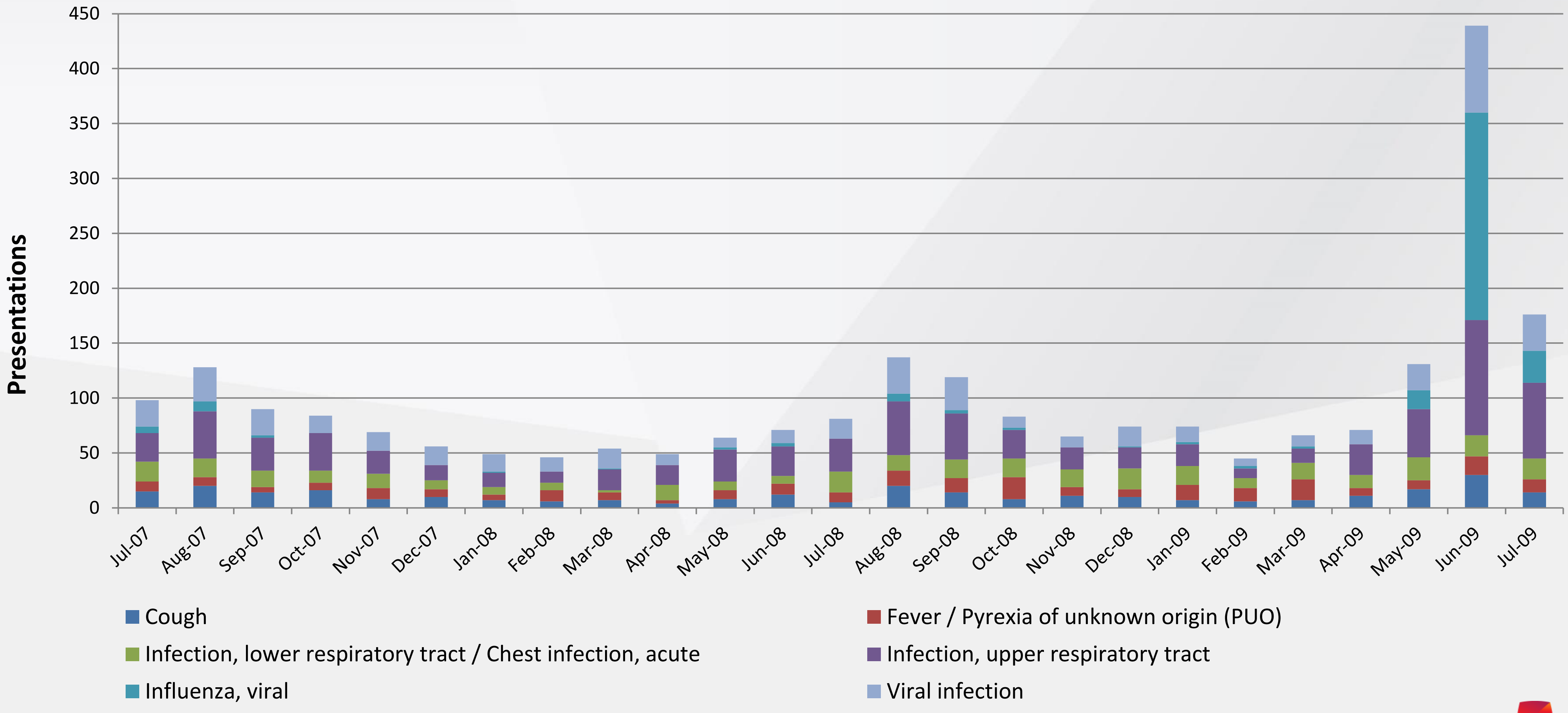
"I think it's an inappropriate decision," he said. "It's unfortunate they have singled out Victoria, because we are no different to the rest of Australia.

"The fact is we have been testing in a more vigorous way, and so it would appear the number of cases are higher."

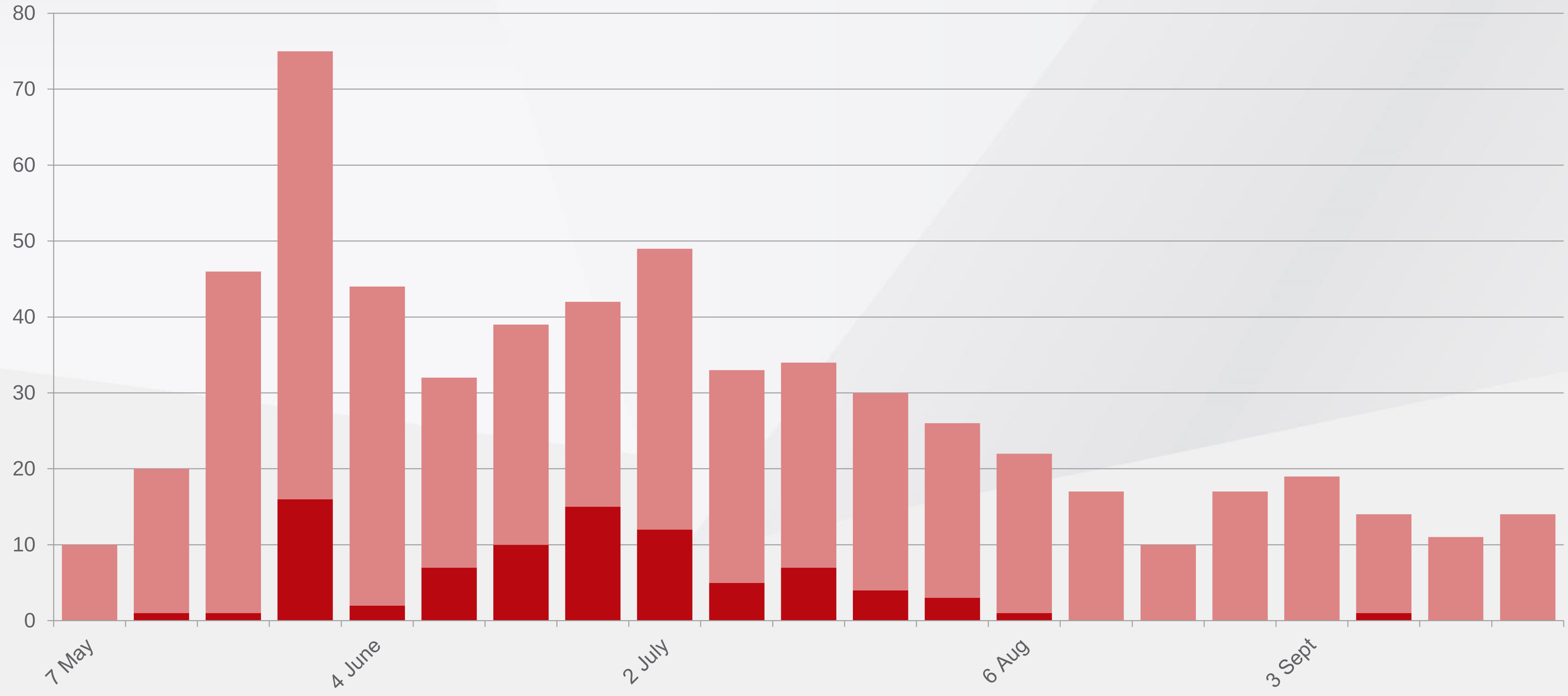
A spokesman for the Victorian Department of Human Services said it was now logistically impossible for the state's infectious disease laboratories to test every Melburnian with flu-like symptoms for the H1N1 virus.

"There is a limit to how much contact tracing we can do," the spokesman added.

Presentations to Alfred ED



Weekly flu tests/positives



Case 1- 44 year old F, June/July 2009

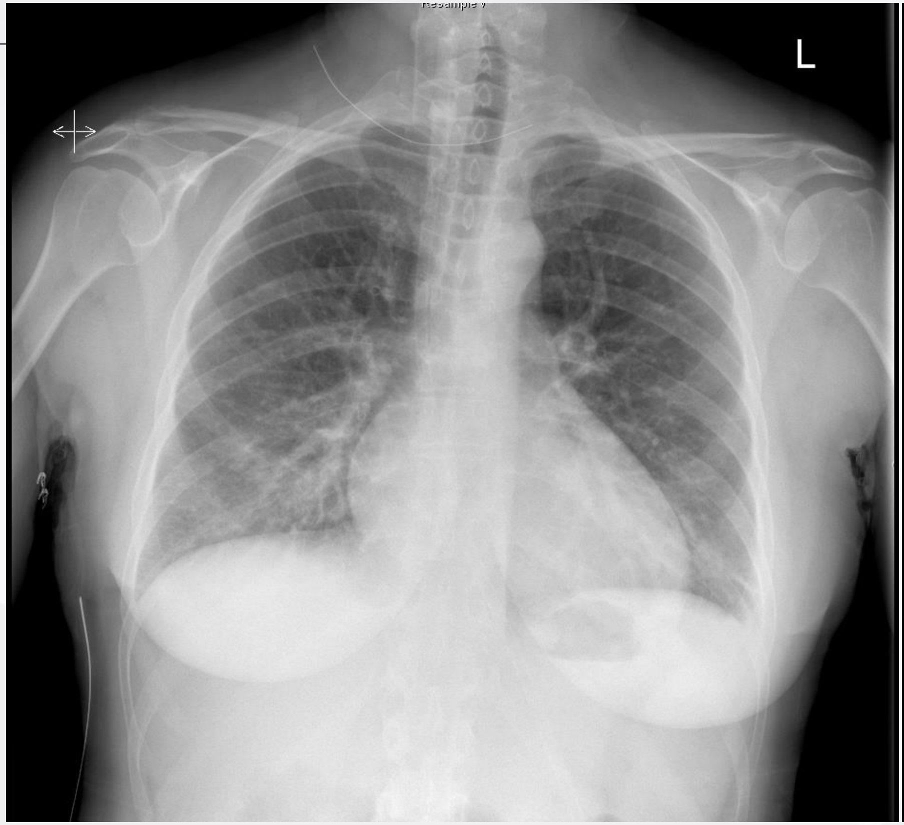
Presented to ED with fevers, tachycardia, dyspnoea, coryza
SaO2 86% RA on arrival

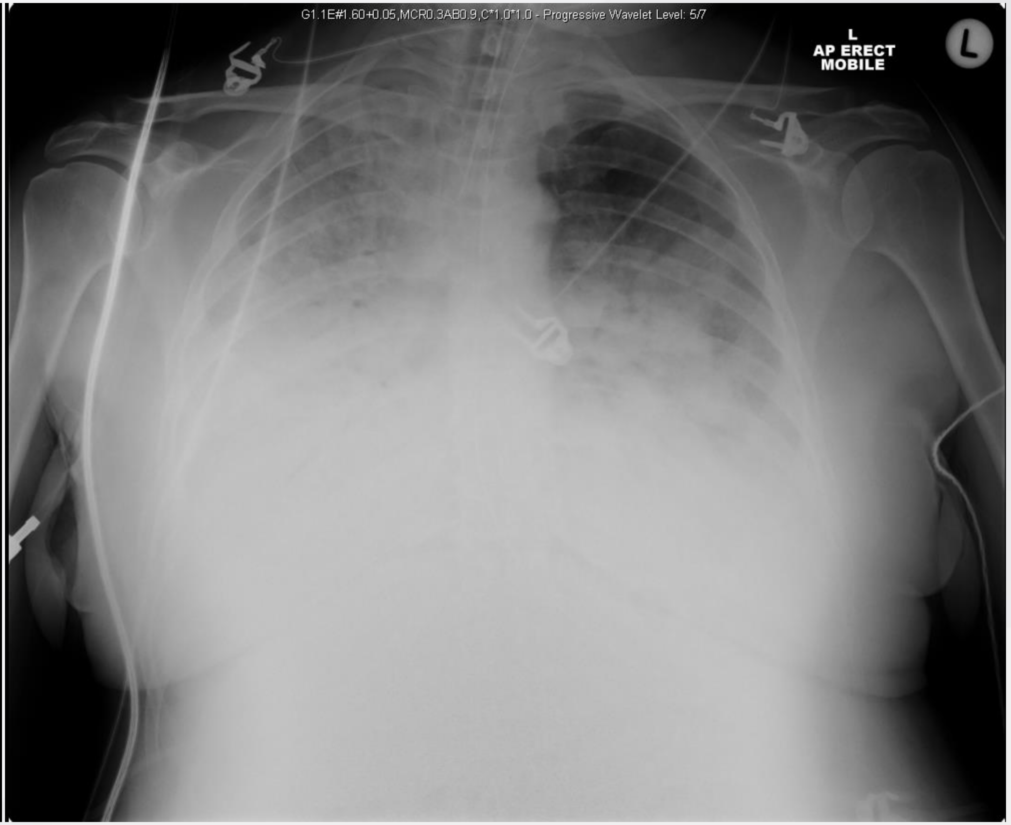
Respiratory viral NPA: **H1N1 Influenza A RNA PCR positive**

Day 9 admission: MET call for hypoxia
Admitted to ICU: intubated, severe type 1 respiratory failure, possible ARDS

Background
T- cell pro-lymphocytic leukaemia diagnosed May 2008
Treatment: chemo/radiotherapy, allogeneic SCT Oct 2008

Complications: Grade I cutaneous GvHD (hands), CMV viraemia (Feb 2009), bilateral AVN femoral head due to steroids



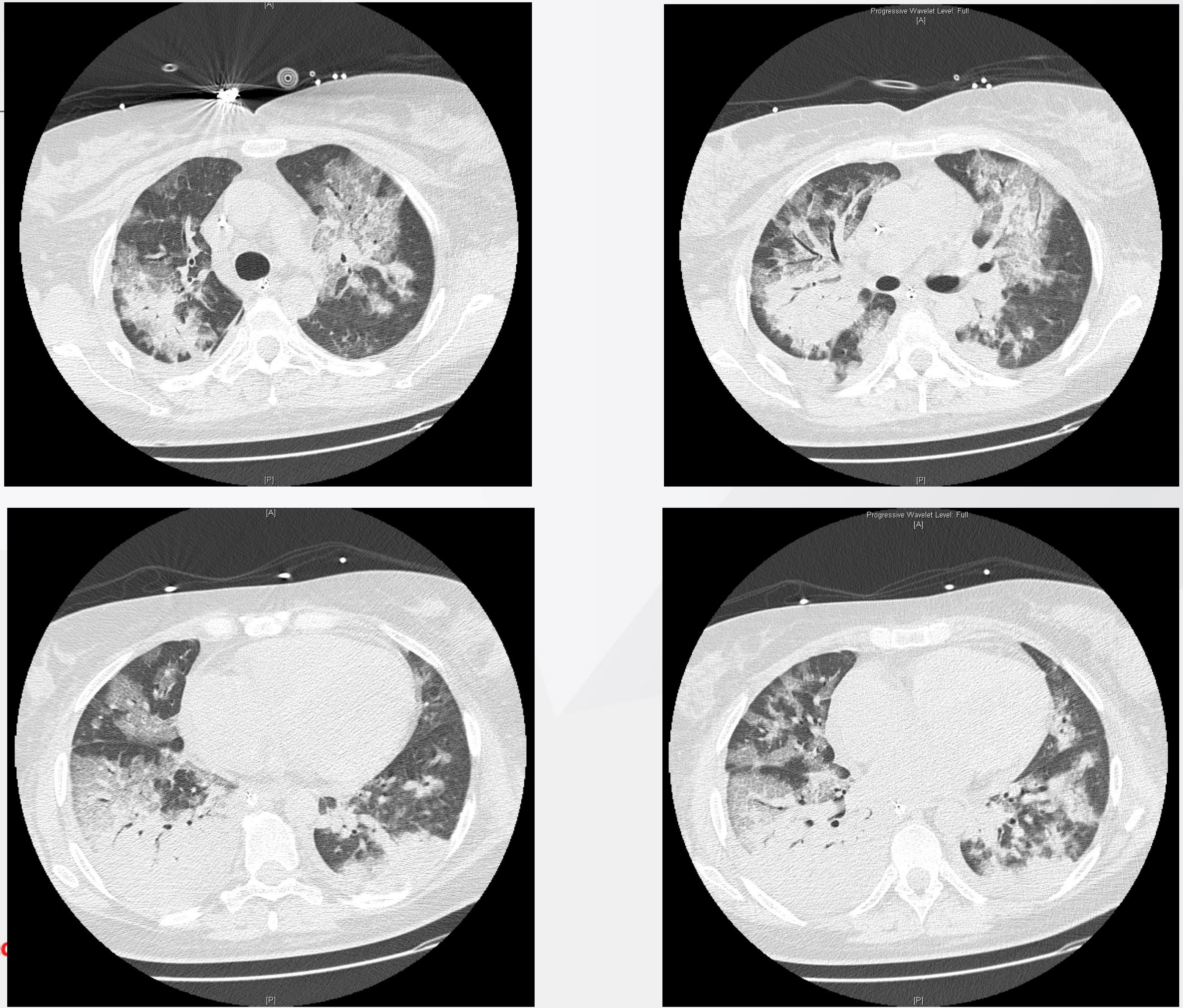


Day 0 in ED

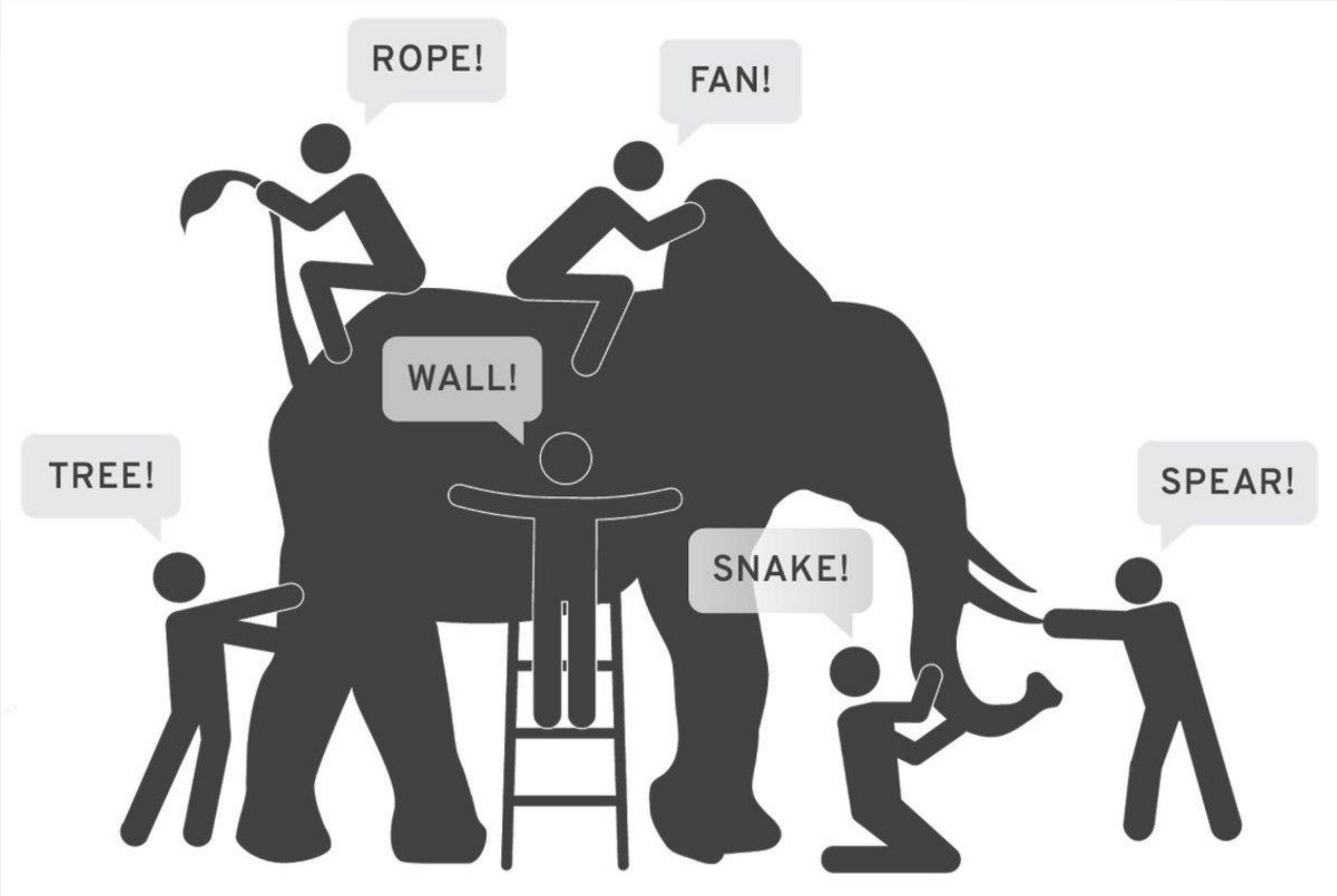
Day 9 admission to ICU

Multiple issues: ARDS, secondary bacterial bronchopneumonia, anuric AKI/ fluid overload, hyperglycaemia, PR bleeding, pneumothorax, diarrhoea/faecal incontinence

Day 21 admission



1. Influenza is multidimensional



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 12, 2009 VOL. 361 NO. 20

Critical Care Services and 2009 H1N1 Influenza in Australia and New Zealand

The ANZIC Influenza Investigators*

722 ICU admissions

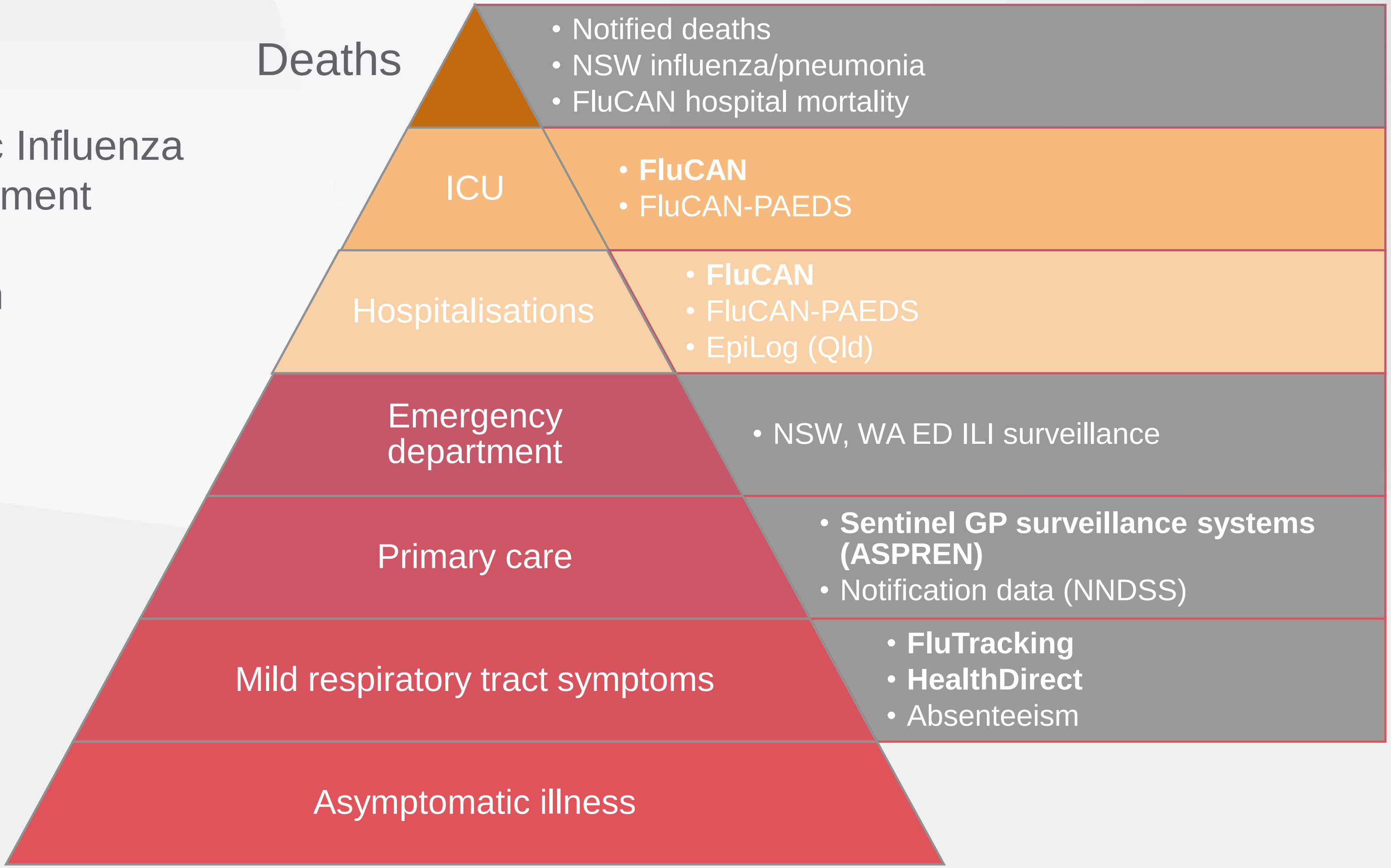
350 bed days per million population (June-Aug 2009)

Maximum occupancy 7.4 per million

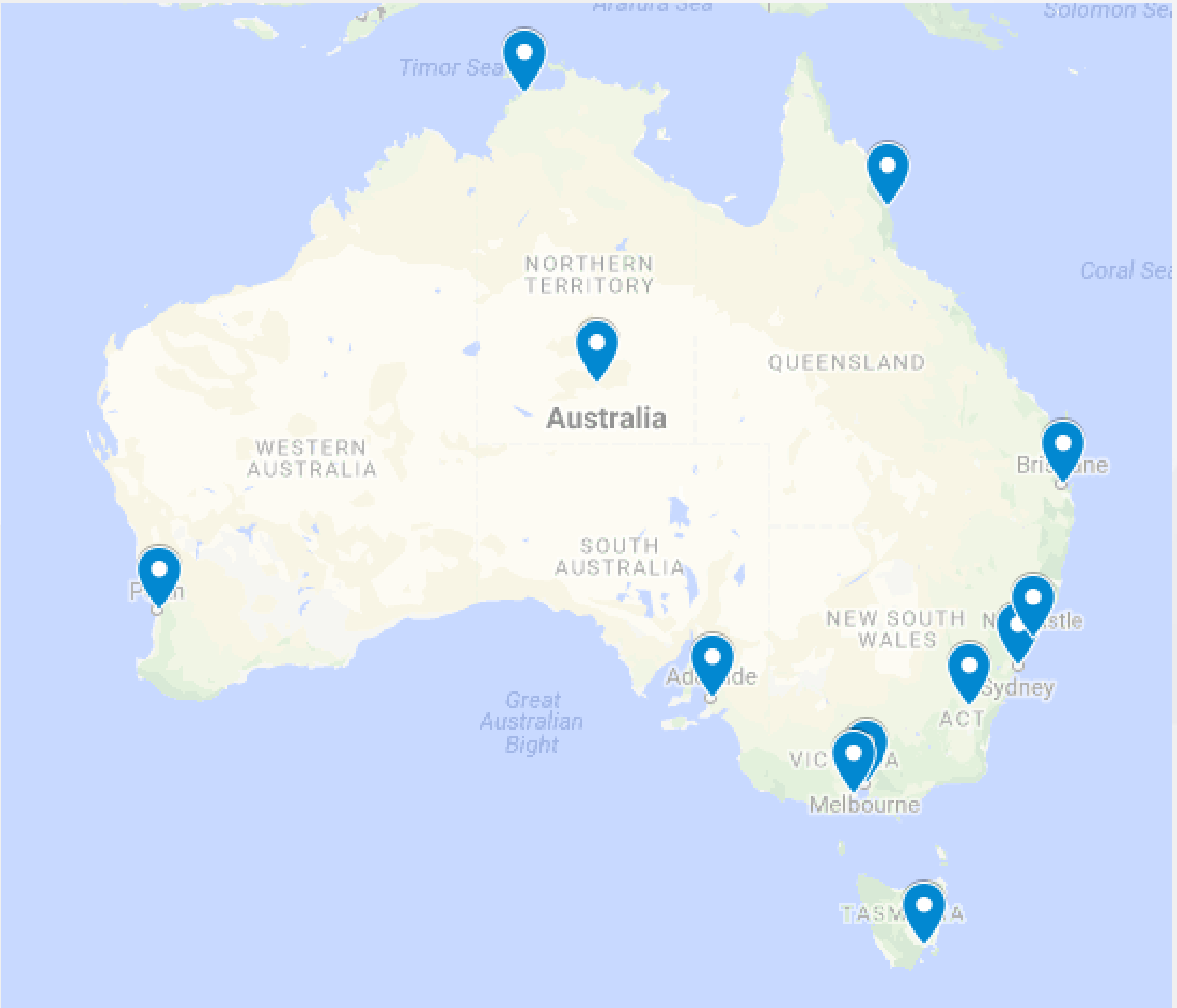
Surveillance pyramid

WHO Pandemic Influenza Severity Assessment (PISA)

- Transmission
- Severity
- Impact



FluCAN 2012-18



21 hospitals (incl 6 paediatric hospitals)

17 hospitals used for surveillance

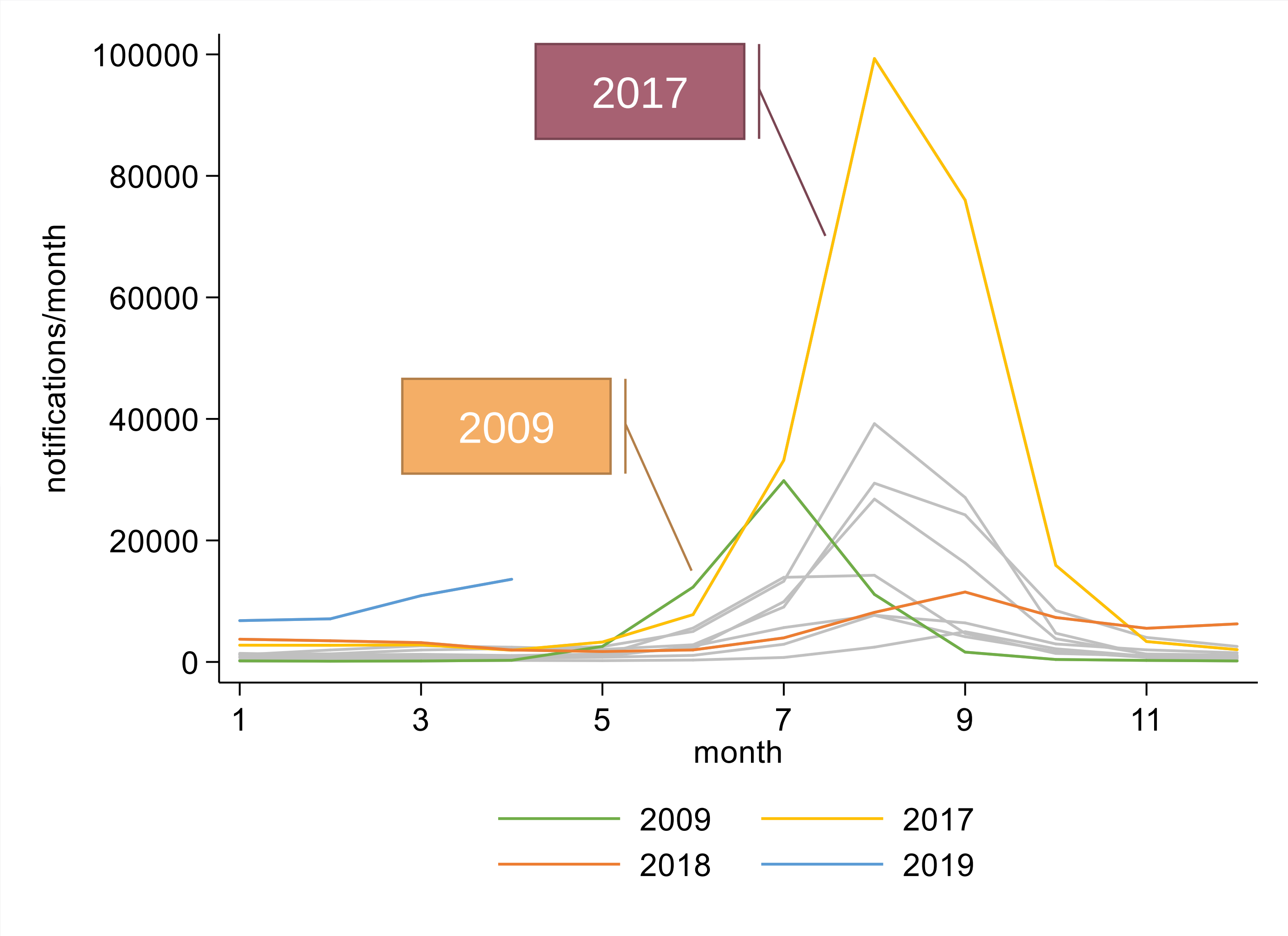
All states/territories

Metropolitan/regional
Temperate/tropical

>14% of national bed capacity

(TSANZ/ASID collaboration 2009)

2. A bad seasonal year is good practice for a pandemic



2017 impact

Mean duration of hospital stay: 6.2 days

At peak, 5.2% of Australian hospital beds occupied by patients with confirmed influenza

At Royal Hobart – 12.8% peak occupancy

3. It's difficult to work out who has influenza

DOI:10.1111/j.1750-2659.2012.00398.x
www.influenzajournal.com
Original Article

Diagnosing swine flu: the inaccuracy of case definitions during the 2009 pandemic, an attempt at refinement, and the implications for future planning

Andrew A. Mahony,[a] Allen C. Cheng,[b,c] Karen L. Olsen,[a] Craig A. Aboltins,[d] James F. P. Black,[e] Paul D. R. Johnson,[a,f] M. Lindsay Grayson,[a,b,f] Joseph Torresi[a,f]

Definition	Symptoms/signs	Epidemiology	Sensitivity	Specificity	Predictive values
Suspected case	**1.** Acute febrile respiratory illness, with at least one of rhinorrhea, nasal congestion, sore throat, or cough	Onset within 7 days of travel to Mexico, USA, Canada (and other countries with evidence of local transmission)	85% (80–89%)	43% (39–48%)	PPV 44% (40–48%) NPV 84% (79–88%)
	2. As above	Onset within 7 days of close contact with a person who is a confirmed case Close contact of a confirmed case within that case's infectious period	89% (85–93%)	27% (23–31%)	PPV 39% (35–43%) NPV 83% (76–88%)
Probable case	**3.** As above, for which no other cause is identified	–	93% (89–96%)	23% (19–27%)	PPV 39% (35–43%) NPV 86% (79–91%)

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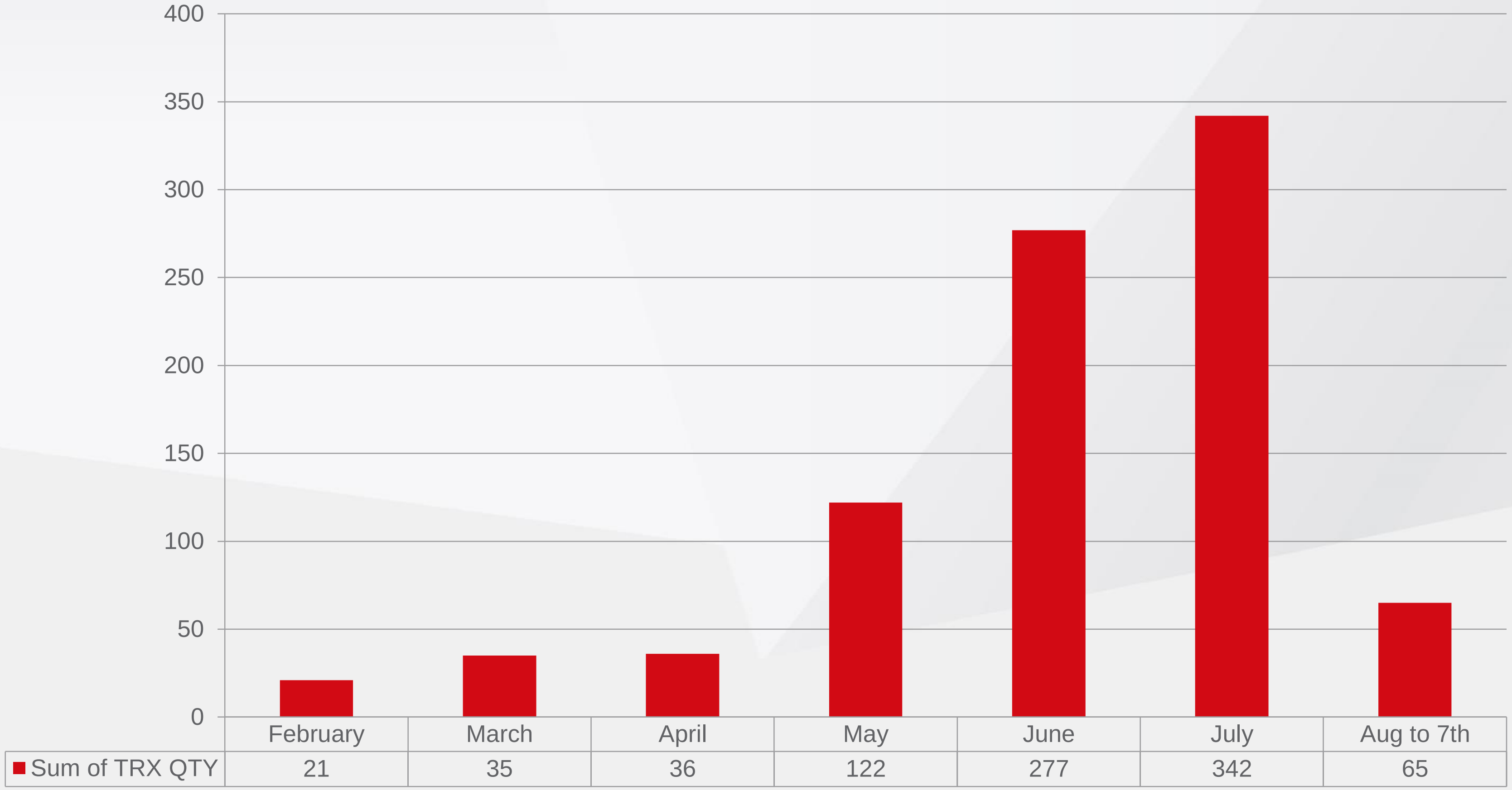
Influenza diagnostics

Who to treat?	Antiviral use
How to test?	Lab capacity
Who to isolate?	Hospital infection control
How to measure?	Public health surveillance; case definitions
How to control?	Quarantine
How to understand spread?	Research
What to communicate?	Public health actions and messaging

3. Infection control is important for staff and patients

N95 mask use


400
350
300
250
200
150
100
50
0
February
March
April
May
June
July
Aug to 7th
Sum of TRX QTY
21
35
36
122
277
342
65

Ebola 2014

Examples of PPE

5. Influenza complications are much more than secondary bacterial pneumonia

Severe paediatric complications

Acute Necrotising Encephalopathy

Acute encephalopathy with biphasic seizures

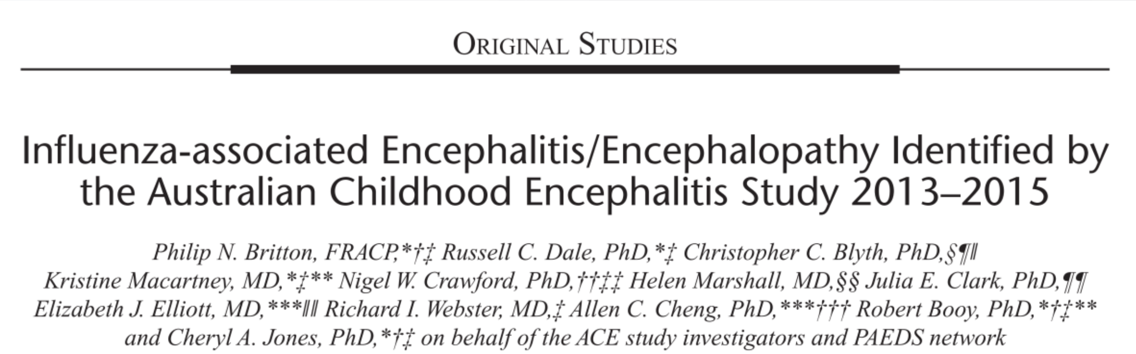
Status epilepticus

Febrile seizures

Acute ataxia

Post-infectious myelitis,

Ospoclonus myoclonus

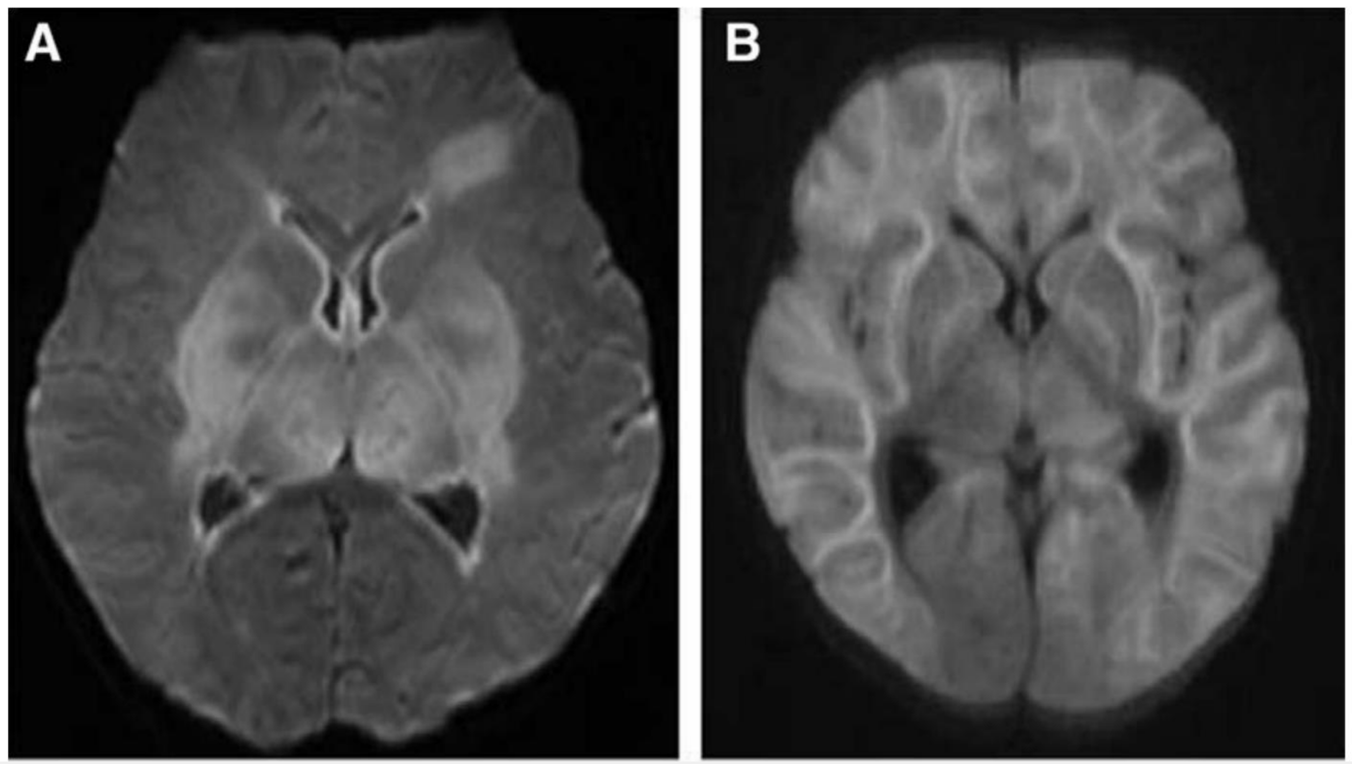


ORIGINAL STUDIES

Influenza-associated Encephalitis/Encephalopathy Identified by the Australian Childhood Encephalitis Study 2013–2015

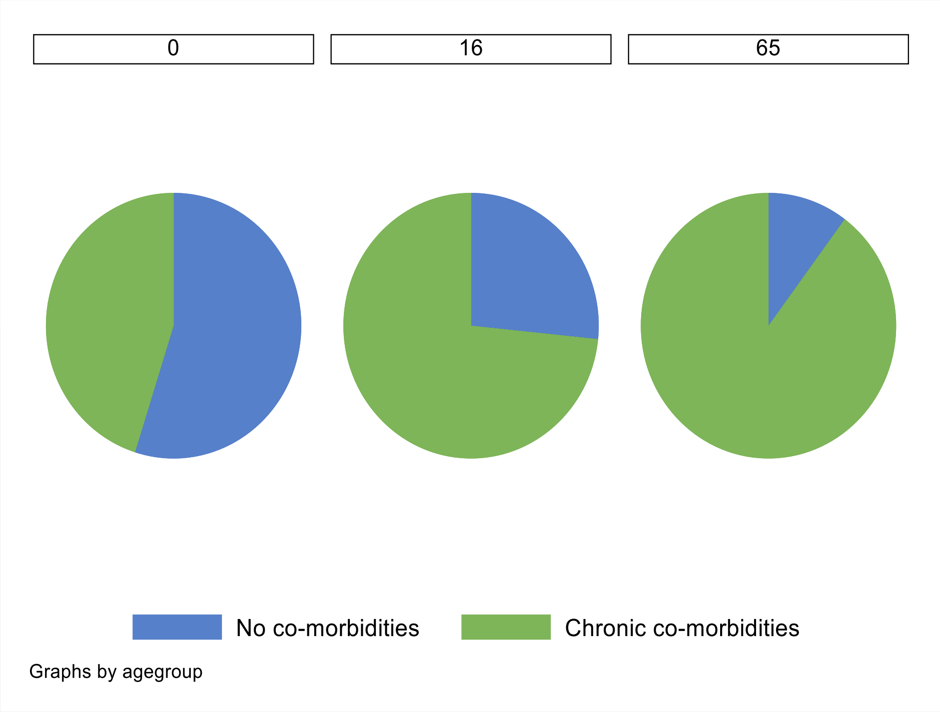
Philip N. Britton, FRACP,†‡ Russell C. Dale, PhD,*‡ Christopher C. Blyth, PhD,§¶‖ Kristine Macartney, MD,*‡** Nigel W. Crawford, PhD,††‡‡ Helen Marshall, MD,§§ Julia E. Clark, PhD,¶¶ Elizabeth J. Elliott, MD,***‖‖ Richard I. Webster, MD,‡ Allen C. Cheng, PhD,***††† Robert Booy, PhD,*†‡** and Cheryl A. Jones, PhD,*†‡ on behalf of the ACE study investigators and PAEDS network*

ANE AESD



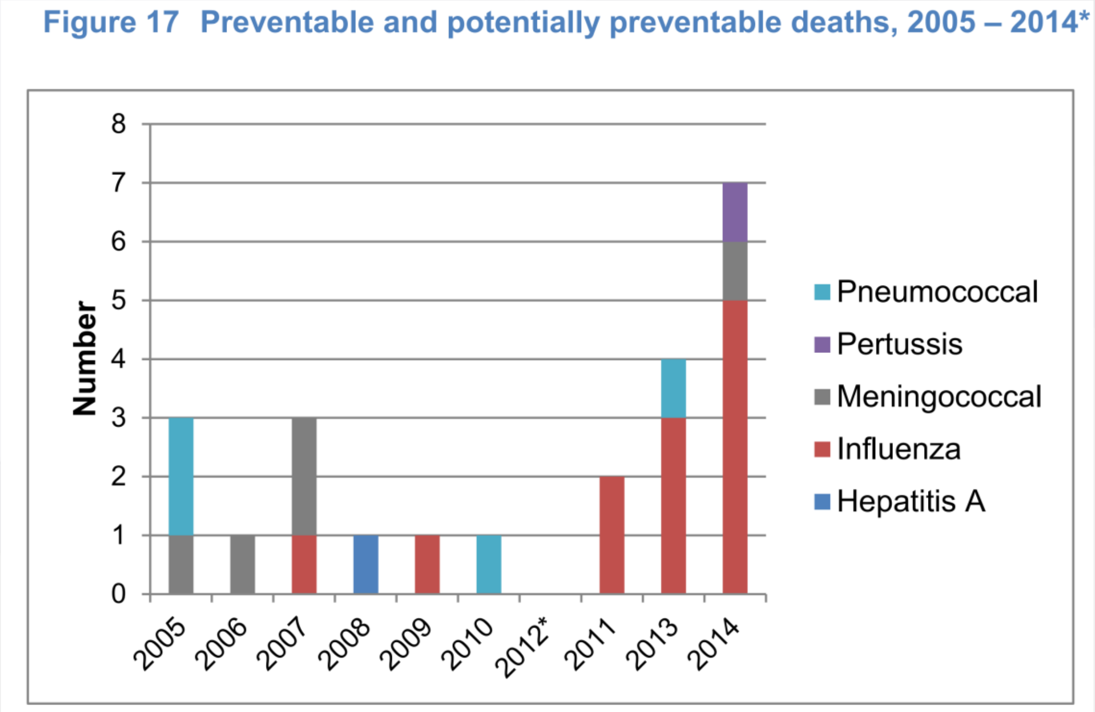
Paediatric influenza

Risk factors by age group



FluCAN hospitalisations

Paediatric deaths from vaccine preventable diseases, NSW



NCIRS NSW report, 2016

Case 2- 51 year old M, May 2019

Transfer to the Alfred for consideration VV-ECMO
6/5/19: Presented in extremis – intubated, bilateral chest infiltrates

1 week of coryzal symptoms, fever, cough – family all unwell

BAL 9/5: atypical pneumonia PCR, flu PCR, PJP PCR negative, cultures no growth

Repeat BAL 11/5 AH: Influenza A RNA PCR positive

Background

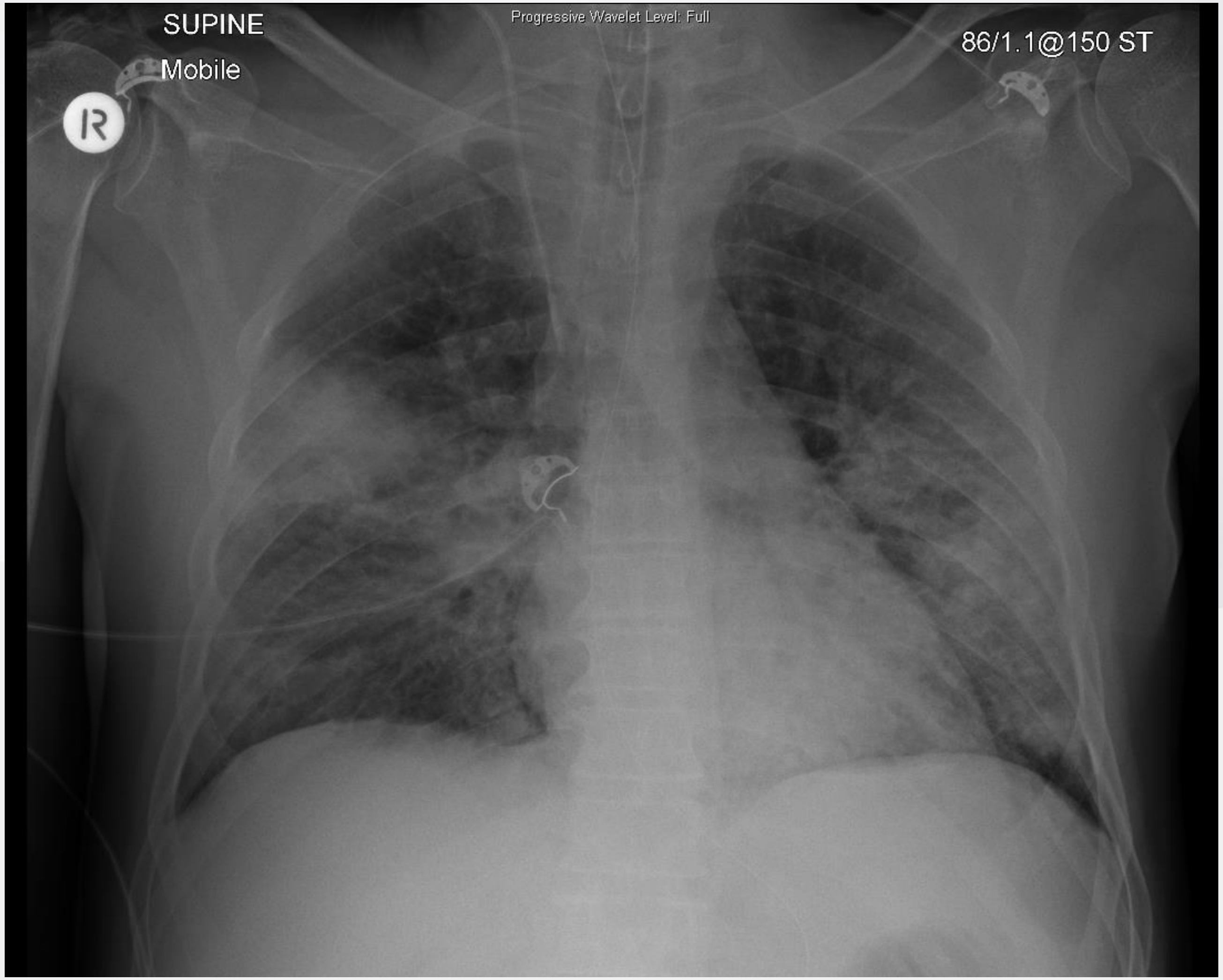
1. **Pyoderma gangrenosum diagnosed March 2019**

   Single R lower limb ulcer; improving with 20mg prednisolone and MMF 1g daily, PJP prophylaxis. No influenza vaccination.

   Avid gardener

2. **Hypertension, hypercholesterolemia**
3. **Smoker – 15 cigs/day, occasional alcohol**

Day 0 admission



Progress in the ICU

BAL fungal MCS 9/5 – positive *Aspergillus fumigatus complex*, galactomannan index 9.0
Caspofungin 70mg IV d added to voriconazole

Severe influenza respiratory infection with secondary invasive pulmonary aspergillosis

Repeat BAL MCS 17/5 and 20/5

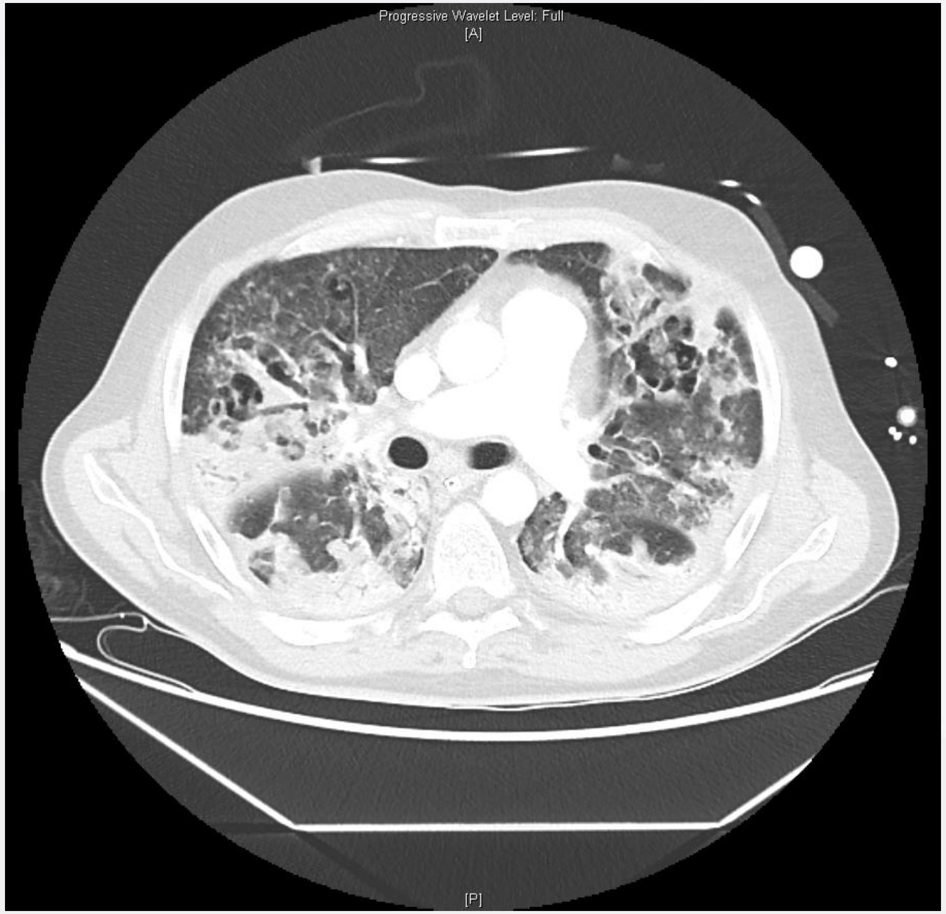
Positive *Aspergillus fumigatus complex* culture and high galactomannan/aspergillus PCR positive

17/5: VV ECMO

21/5: Nebulised amphotericin B added

Day 14 admission

Day 14 admission



Invasive pulmonary aspergillosis (IPA) as complication of IAV infection

Prevalence
2% – 29%[2-6]

European multi-centre cohort study of 220 ICU patients with severe influenza A infection[5]
36% hospital-acquired pneumonia

- *Aspergillus* was 5th top common pathogen

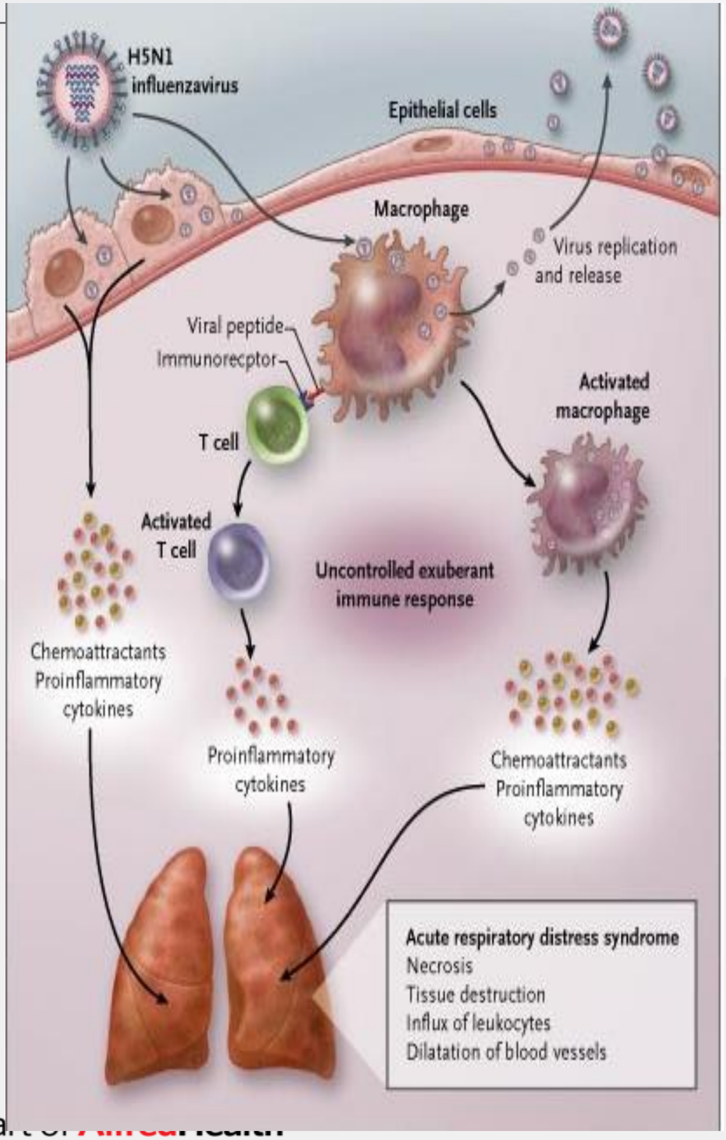
Study did not define IPA by EORTC/MSG criteria

Prospective observational study from 2009-2015 in Spanish ICUs[6]
2901 ICU patients with influenza infection

Aspergillus was 4th top common pathogen

Independent risk factor for ICU mortality

Influenza-related factors can predispose to the development of invasive aspergillosis[7-10]



- Diffuse alveolar damage
- Impaired local phagocytosis by macrophages and NK cells
- Disruption of normal ciliary clearance
- Cytokine imbalances
- Immunodysregulation
- Viral induced apoptosis of T-cells
- Affect on the Th1/Th2 response→lymphopenia
- Alterations in T-cell subsets
- Diminished T-cell function

Invasive Aspergillosis

Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study

Alexander F A D Schauwvlieghe, Bart J A Rijnders*, Nele Philips, Rosanne Verwijs, Lore Vanderbeke, Carla Van Tienen, Katrien Lagrou, Paul E Verweij, Frank L Van de Veerdonk, Diederik Gommers, Peter Spronk, Dennis C J J Bergmans, Astrid Hoedemaekers, Eleni-Rosalina Andrinopoulou, Charlotte H S B van den Berg, Nicole P Juffermans, Casper J Hodiamont, Alieke G Vonk, Pieter Depuydt, Jerina Boelens, Joost Wauters, on behalf of the Dutch-Belgian Mycosis study group*

Lancet Respir Med 2018; 6: 782–92

Published Online
July 31, 2018
http://dx.doi.org/10.1016/S2213-2600(18)30274-1

- Retrospective multicentre cohort study, adult patients with severe influenza – 7 ICUs across Belgium & Netherlands Jan 2009 – June 2016
- Admitted to ICU > 24 hours with acute respiratory failure, pulmonary infiltrates
- Cases of IPA defined by *AspICU* algorithm (Blot et al, *Am J Respir Crit Care Med* 2012)
- Influenza cohort = confirmed influenza infection (+ PCR) vs control cohort = (- PCR)

- IPA diagnosed in 83/432 (19%) patients with influenza
- Immunocompromised – IPA incidence 32% (38/117); non-immunocompromised 14% (45/315) patients vs non-influenza patients 5% (16/315, control cohort)
- 90 day mortality 51% in influenza cohort with IPA vs 28% in influenza cohort without IPA (p= .0001)
- Influenza infection independently associated with IPA (OR 5.19, CI 2.63-10.26, p<0.0001)

There are influenza and ICU-related/critical illness factors that can influence the development of IPA

Influenza related factors[7-10]

ICU related/critical illness related factors[11,12]

Invasive Aspergillosis

Antibiotic use → alteration in URT flora

Steroids

Severe structural lung disease

Mechanical ventilation

ECMO

Immunodysregulation

Severe organ dysfunction

Clinical Microbiology and Infection
Available online 16 May 2019
In Press, Accepted Manuscript

Narrative Review

Intensive Care management of influenza-associated pulmonary aspergillosis

Philipp Koehler [1, 2], Matteo Bassetti [3], Matthias Kochanek [1], Alexander Shimabukuro-Vornhagen [1], Oliver A. Cornely [1, 2, 4, 5]

- Overview of influenza and IPA co-infection
- Evidence-based advice for optimal ICU management

- **"Management algorithm"** = BAL, CT imaging, sophisticated ventilator-management, rescue ECMO, early and appropriate antifungal and antiviral therapy

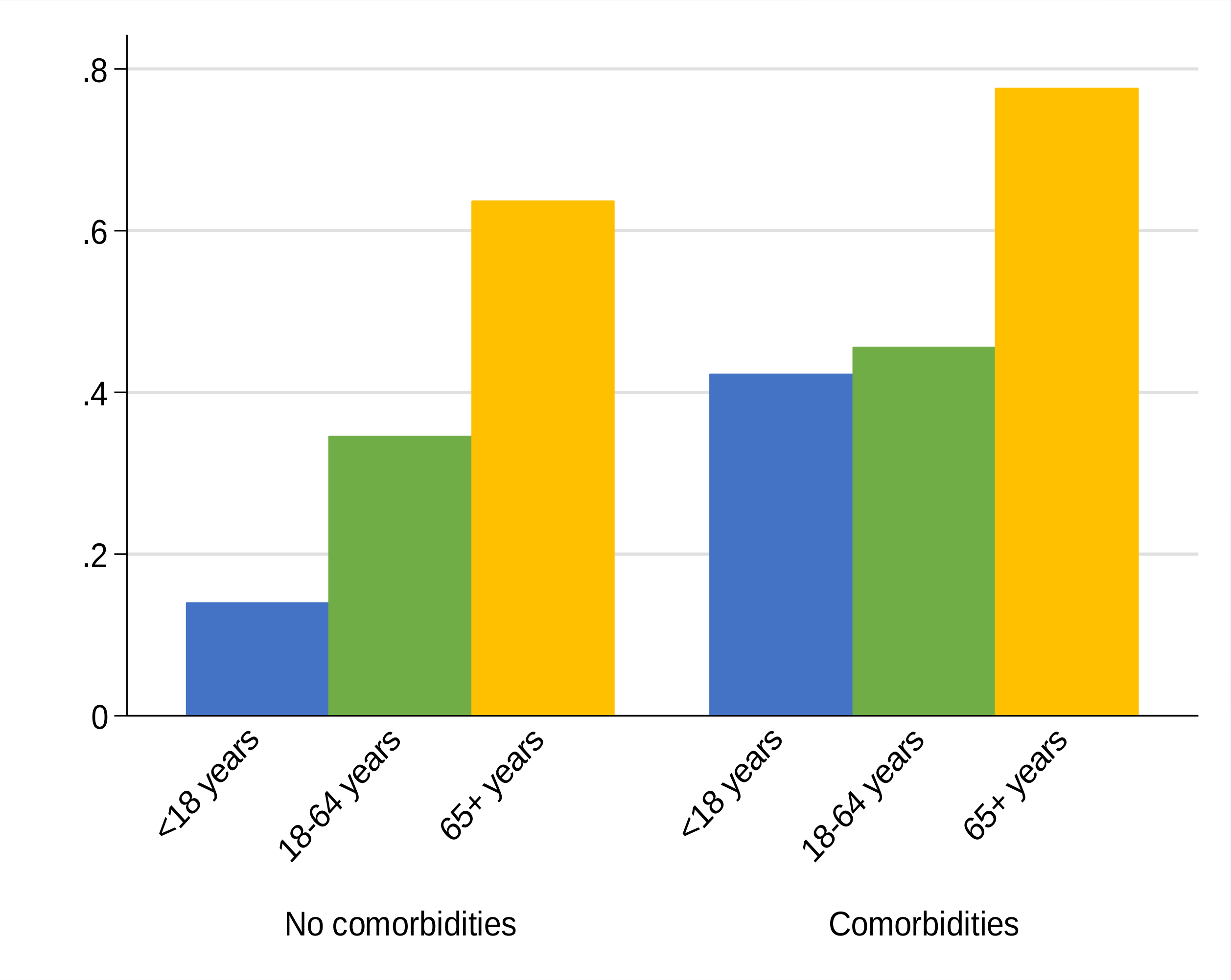
- **Bronchoscopy mandatory** -> 15% develop tracheobronchitis with plaques and invasive and obstructive growth
- Chest CT imaging modality of choice – variable yield, may be as low as 29%
- Can be difficult to define invasive fungal disease in a non-neutropenic, non-haematological population -> consensus project underway
- **Early administration of antifungal therapy** reduces mortality and improves clinical outcomes

- **Vaccination** still the most important method of reducing the burden of influenza-related illness

6. We need to know that vaccines are safe and effective

Case = influenza
Control = non influenza ILI matched for date of presentation
Case/control status assigned when test result known
Adjust for confounders

Vaccine coverage

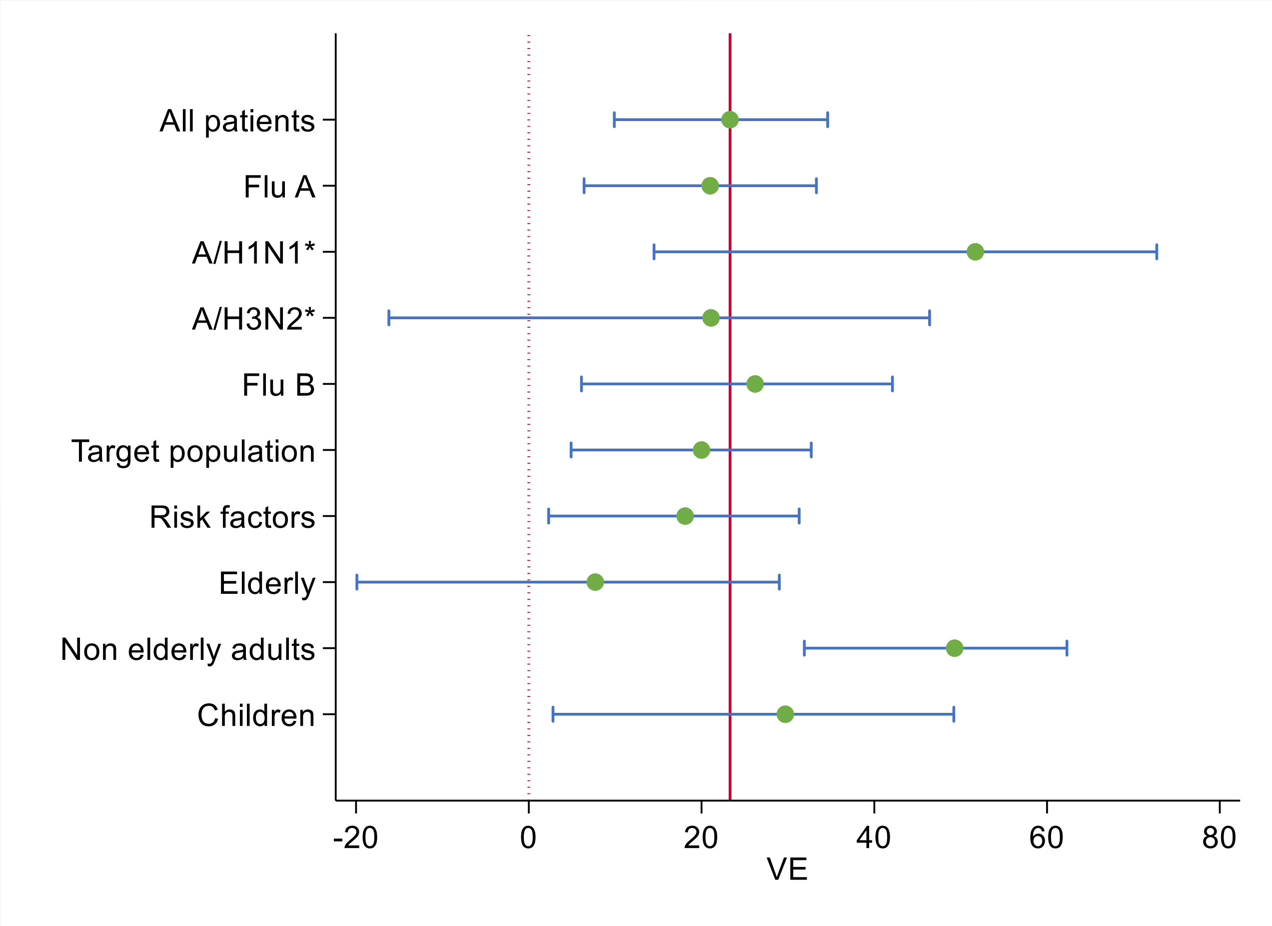


Moderate coverage in elderly

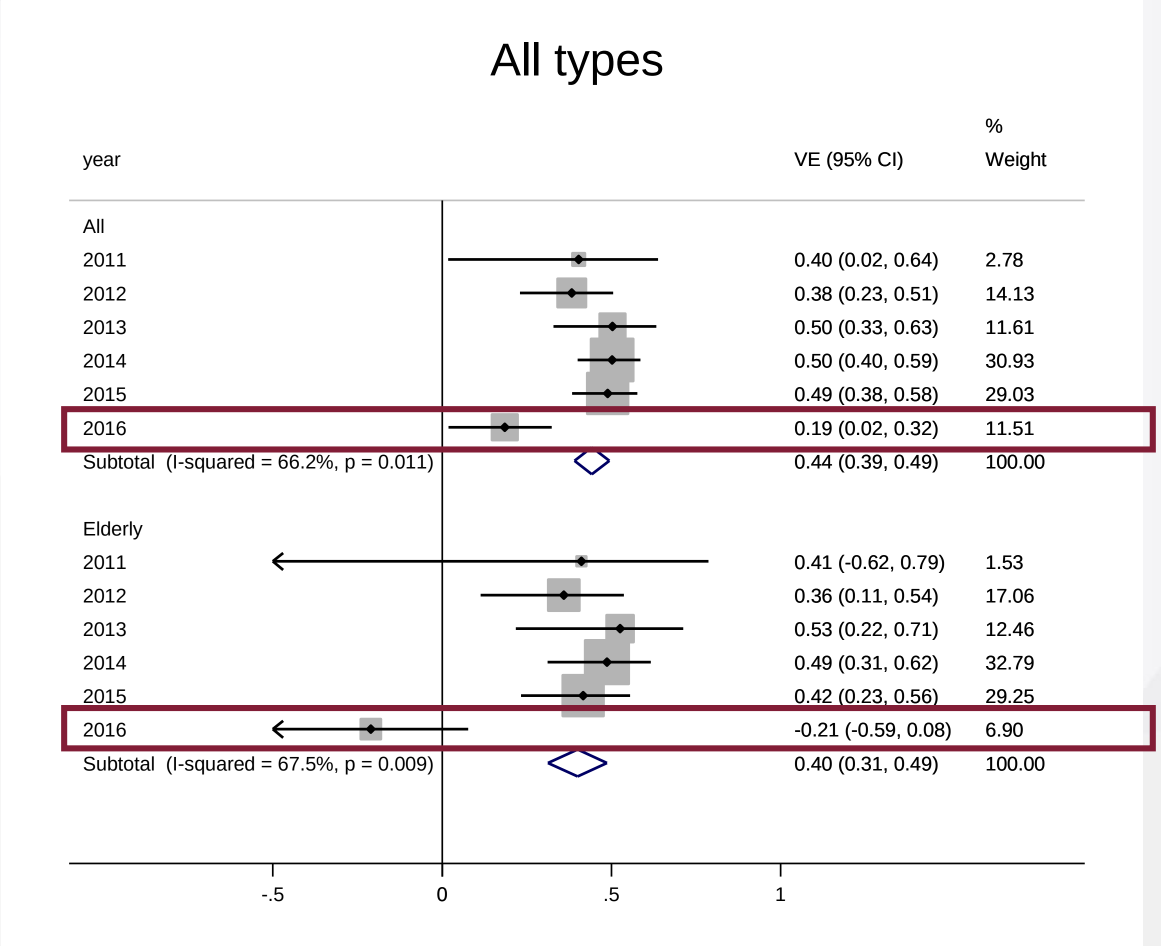
Poor coverage in younger target groups

Increase in coverage with paediatric programs

Vaccine effectiveness (FluCAN 2017)



Historical context



Influenza vaccine effectiveness moderate until 2016

Particularly low in elderly in 2016

Why had recent vaccine effectiveness been lower than usual?

A/H3 subtype predominating
Tends to affect elderly

Genetically diverse subtype compared to A/H1 and B

Egg adaptation of H3 vaccine strain
Fewer vaccine candidates

Difficult to match against diverse H3 strains

Poorly protective vaccine-induced antibodies
Vaccine poorly immunogenic in high risk groups

A/H3 vaccine issues

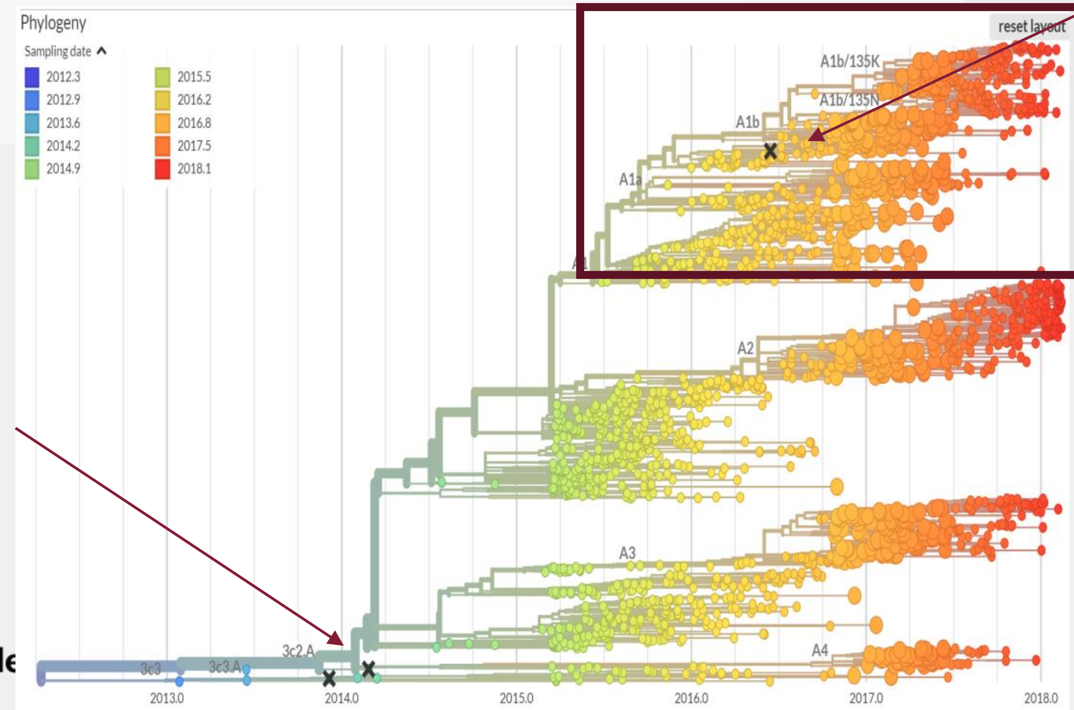
H3N2 diversity

Significant genetic diversity within H3N2 circulating strains
Various clades – recent strains in 3C.2a1
Recent diversification in 2a1 clade

Singapore vaccine strain (2018)

3C.2a1 clade

Hong Kong vaccine strain (2016-17)



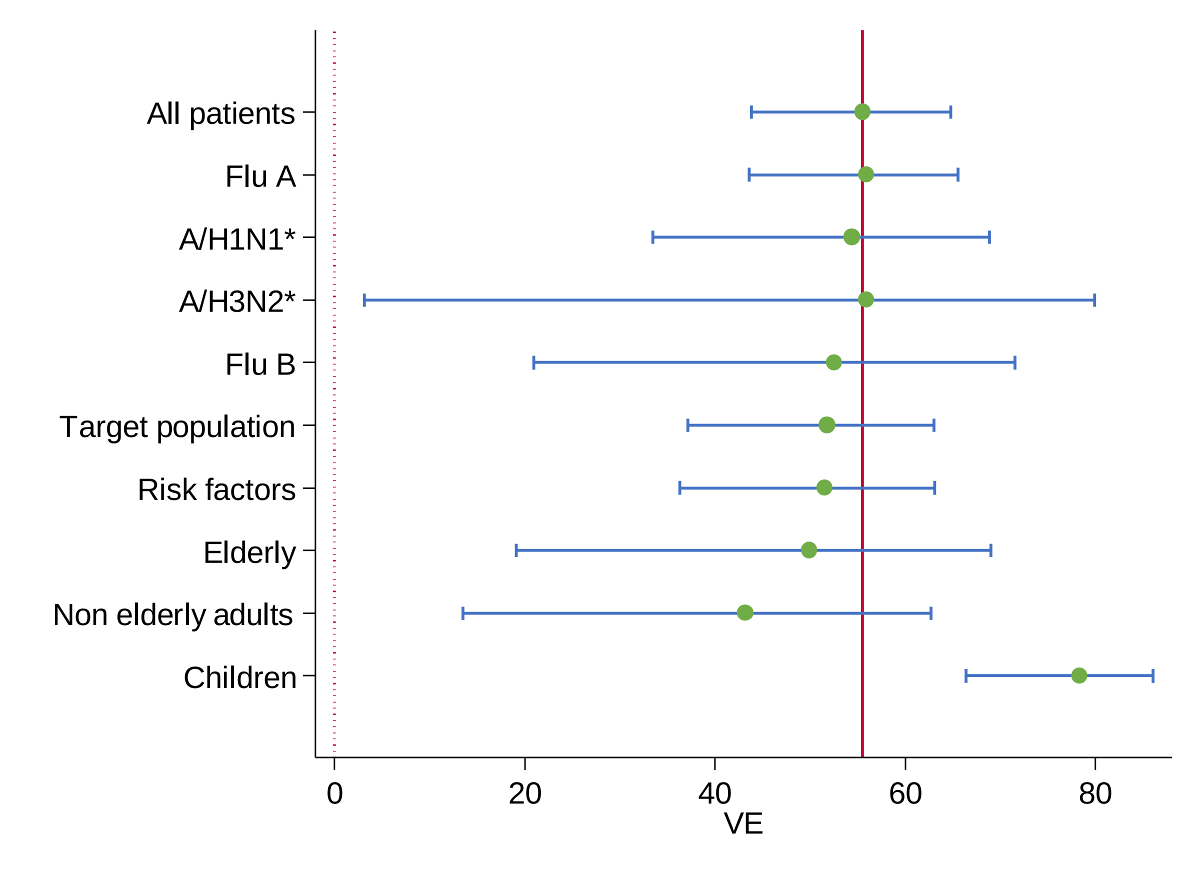
Vaccine effectiveness (FluCAN 2018)

H1 dominant season

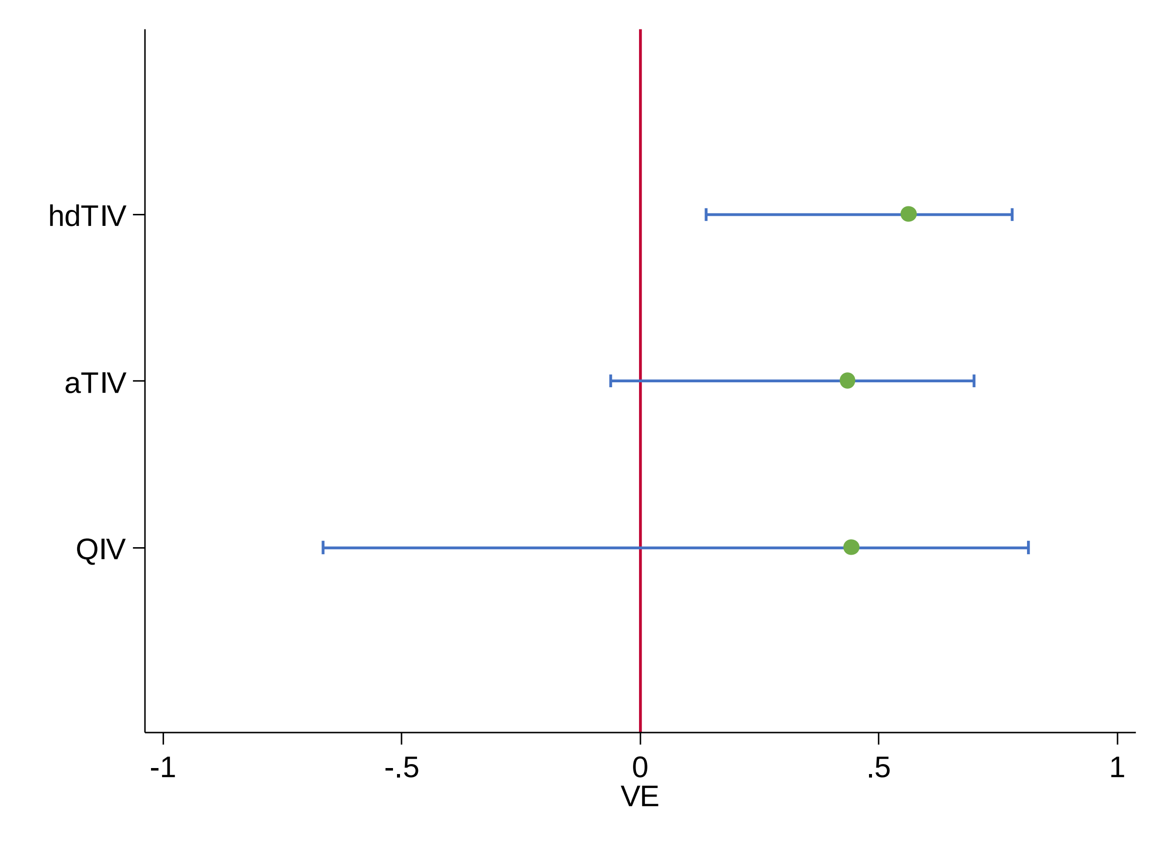
Overall VE 55.5%

Higher in children: VE 78%

Similar in elderly to non-elderly adults (50% vs 43%)



VE: enhanced vaccines (elderly)

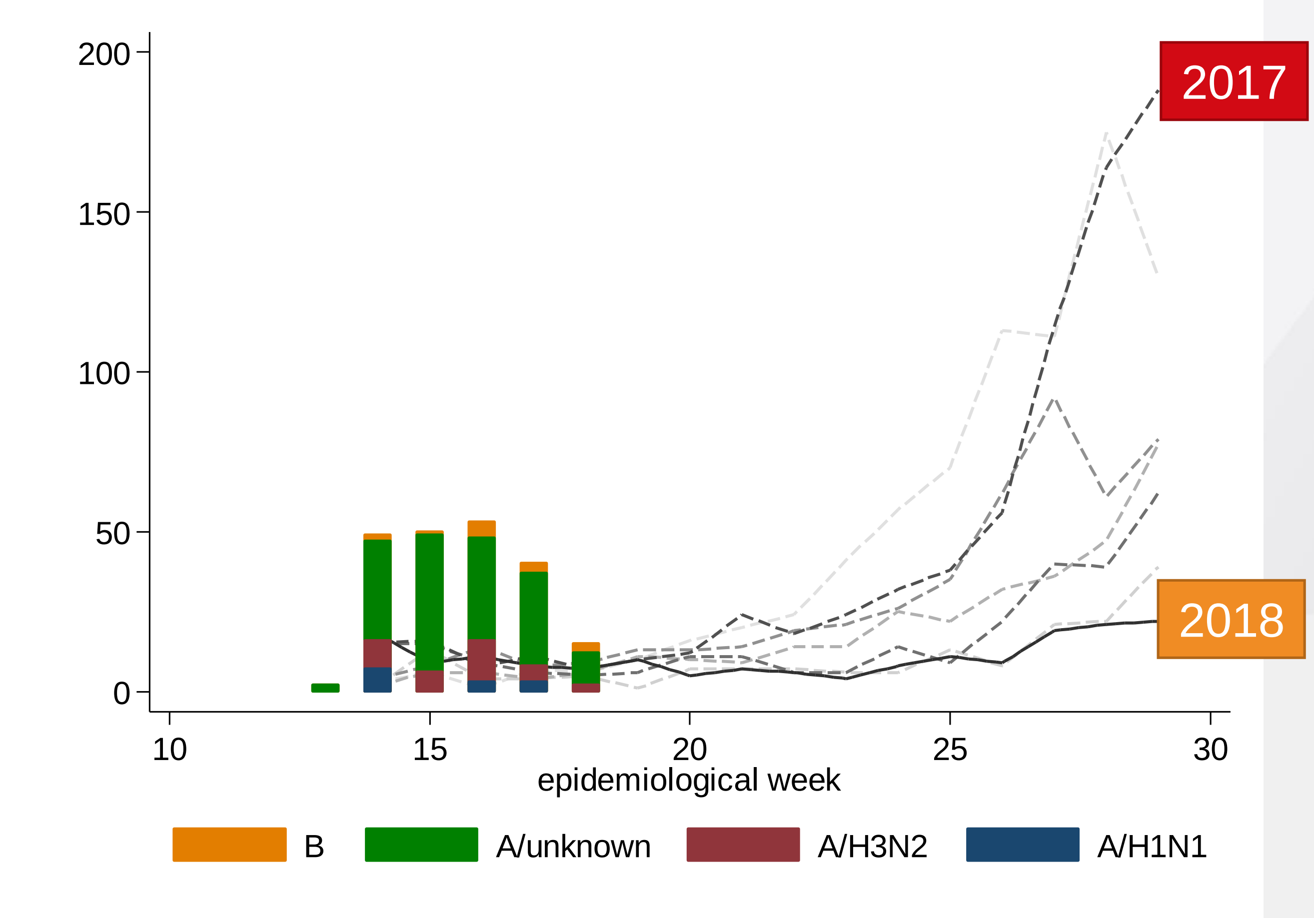


hdTIV: VE 56% (14%, 78%)
aTIV: VE 44% (-6%, 70%)
QIV: VE 44%, (-66%, 81%)

hdTIV-aTIV, p=0.44

Many limitations- small numbers, incomplete ascertainment

2019 season to date



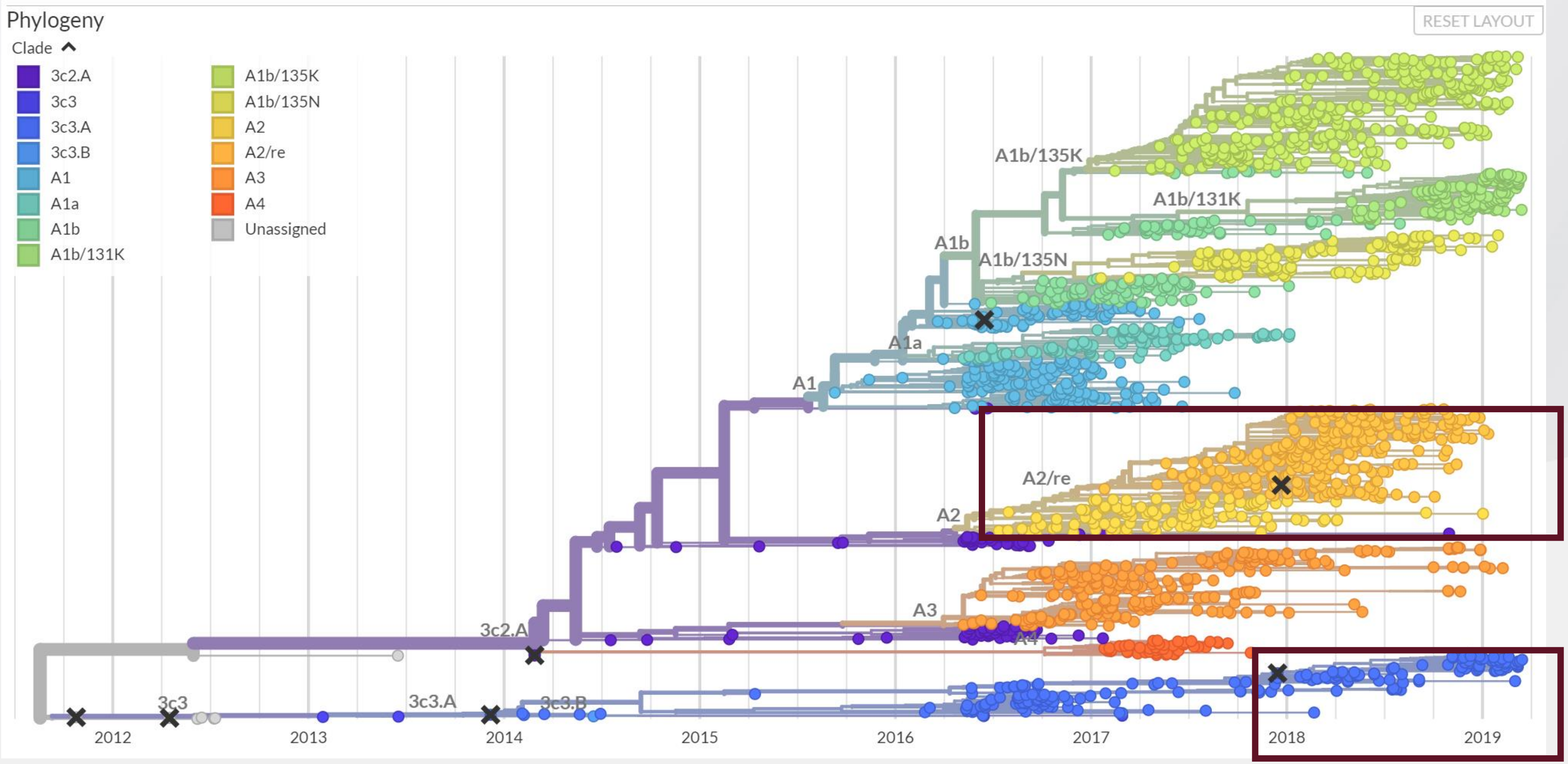
Unusually high interseasonal activity esp Qld

Emergence of new A/H3 clade
Change in 2019/20 NH vaccine strain

A/H3>A/H1

ICU 7.4%

New A/H3 clade



Clade 3C.2a1b

3C.2a2

3C.3a

Vaccine safety

Febrile convulsions related to Fluvax Jr – 2010

WA paediatric program – febrile convulsions in 1%

Higher rates of fever (57% Fluvax vs 17% Influvac)

Several cases of severe neurological outcomes

Saba Button (Photo: PerthNow)

Safety

Partially unsplit products

Insufficient content of TDOC for two new viruses

(Marakvosky, Rockman Vaccine 2012)

Program suspended

Stokes report (WA); Horvath report (TGA)

ACSOV established

WA: fall in vaccine coverage from >50% (2008-09) to <20% (2010-12)

Safety

Combination of active and passive surveillance

AusVaxSafety and associated systems

Jurisdictional surveillance – SAEFVIC, WAVSS

TGA DAEN

International data

Specific safety studies eg Guillain Barre syndrome in 2009/10

Sponsor data - PSUR

7. We still don't know if antivirals work in hospitalized patients

Clinical Infectious Diseases

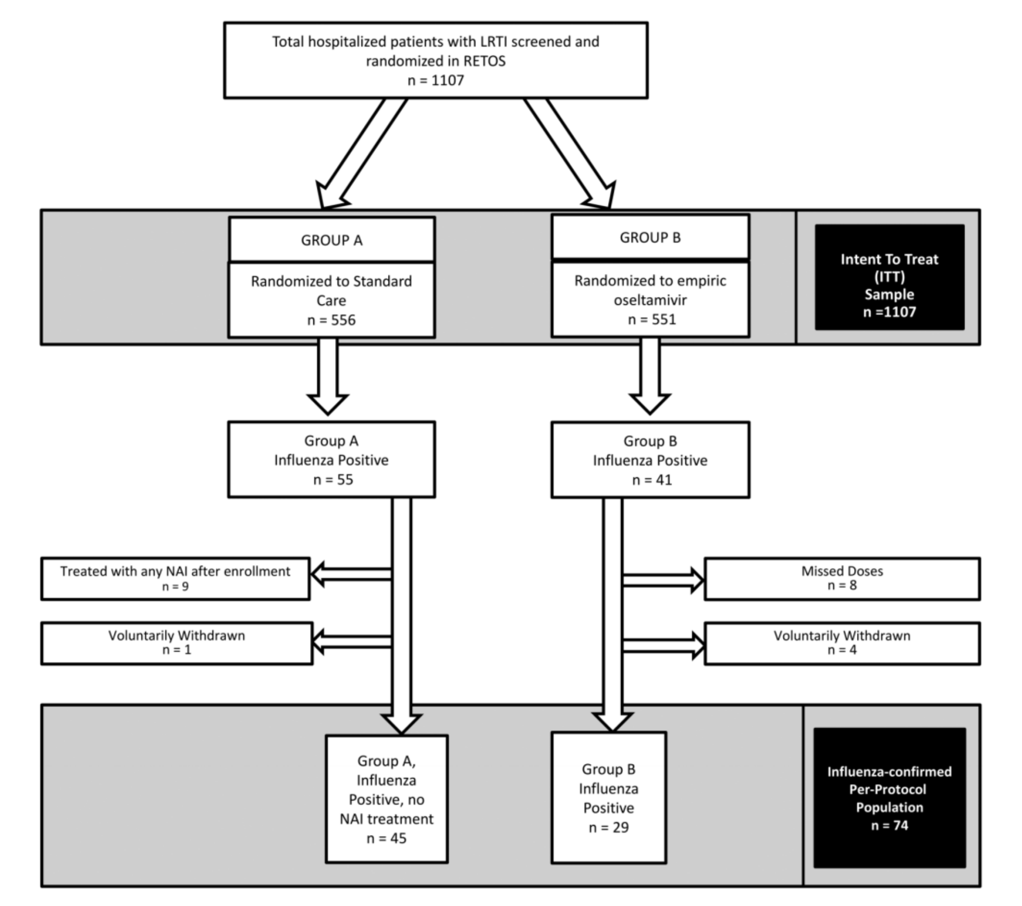
MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

A Randomized Study Evaluating the Effectiveness of Oseltamivir Initiated at the Time of Hospital Admission in Adults Hospitalized With Influenza-Associated Lower Respiratory Tract Infections

Julio Ramirez,[1] Paula Peyrani,[1] Timothy Wiemken,[2] Sandra S. Chaves,[3] and Alicia M. Fry[3]

[1]Division of Infectious Diseases, School of Medicine and [2]Department of Epidemiology and Population Health, School of Public Health and Information Sciences, University of Louisville, Kentucky; and [3]Centers for Disease Control and Prevention, Atlanta, Georgia



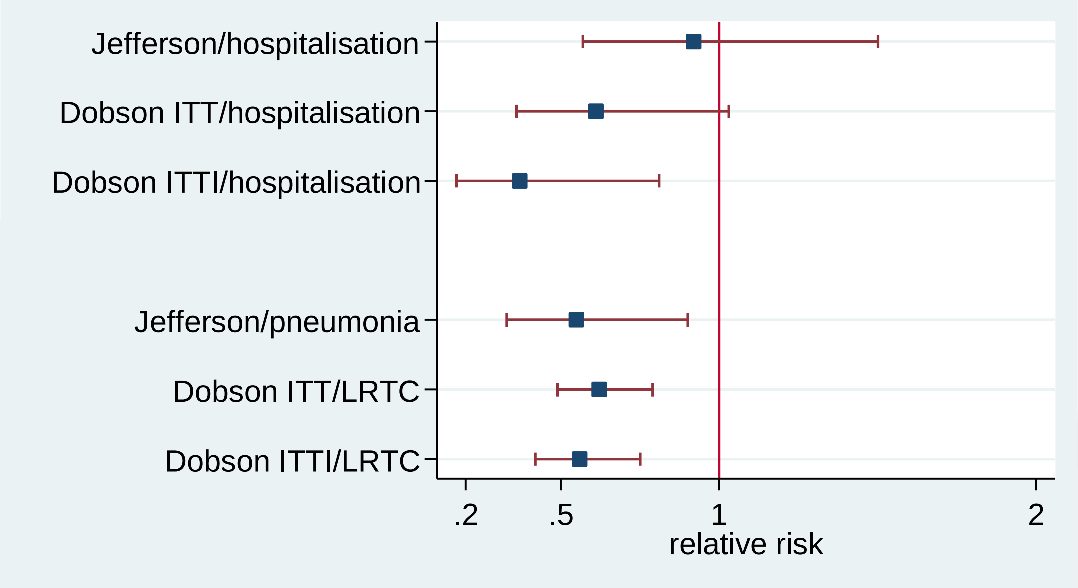
N>1000; only 96 flu positive; only 74 in PP analysis

Clinical failure 24% vs 14%; similar LOS, mortality

Ramierez CID 2018

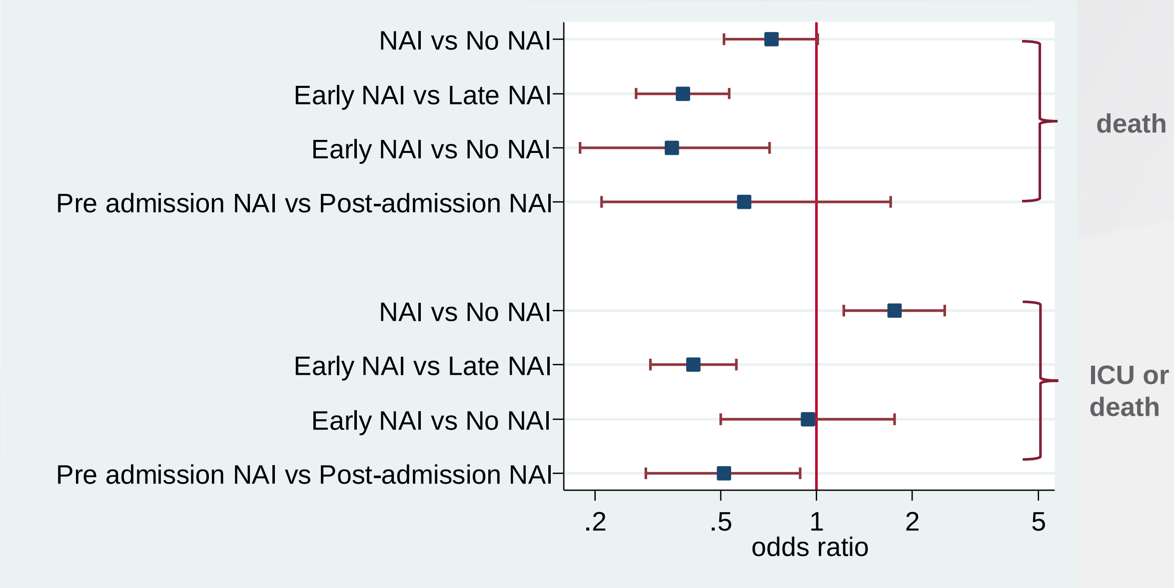
Do NIs have an effect in non-hospitalized patients?

RCTs on NIs in seasonal years in healthy adults



Jefferson 2014
Dobson 2014
(Ebell 2013)

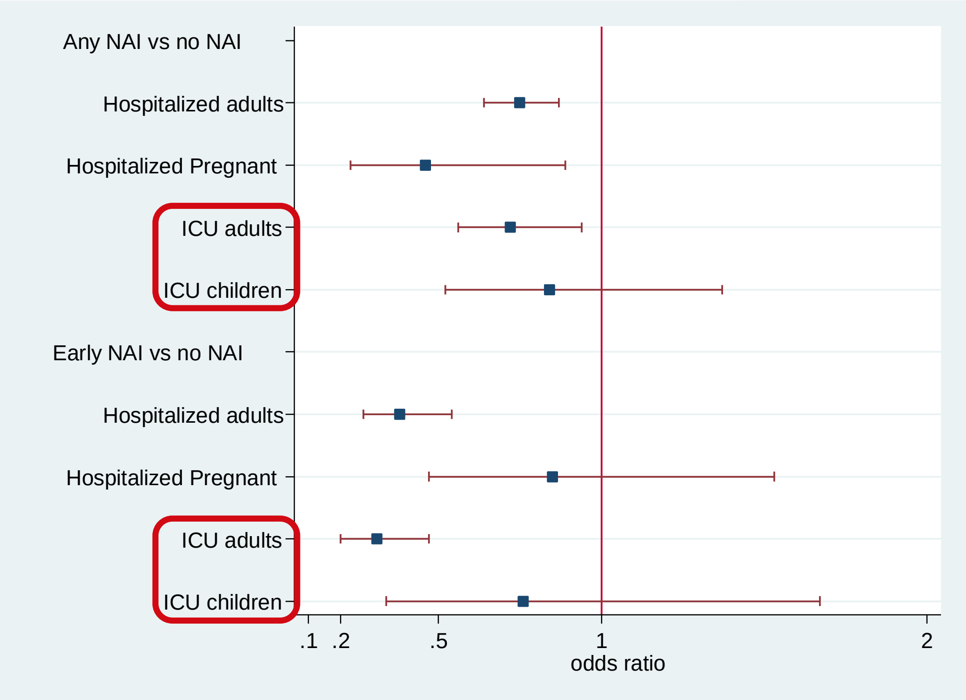
Effect of NIs on mortality in observational studies



Muthuri 2013;
(Hsu 2012)

Do NIs have an effect in hospitalized patients?

Effect of NIs on mortality in hospitalized patients – observational data



Muthuri 2014

Conclusions

NIs are effective at reducing pneumonia in adults

NIs are probably effective in reducing mortality in hospitalized patients

NIs are may reduce hospitalisation in non-hospitalized adults

Better quality evidence is needed but unlikely

REMAP-CAP

REMAP trial for community-acquired pneumonia

Randomized allocation

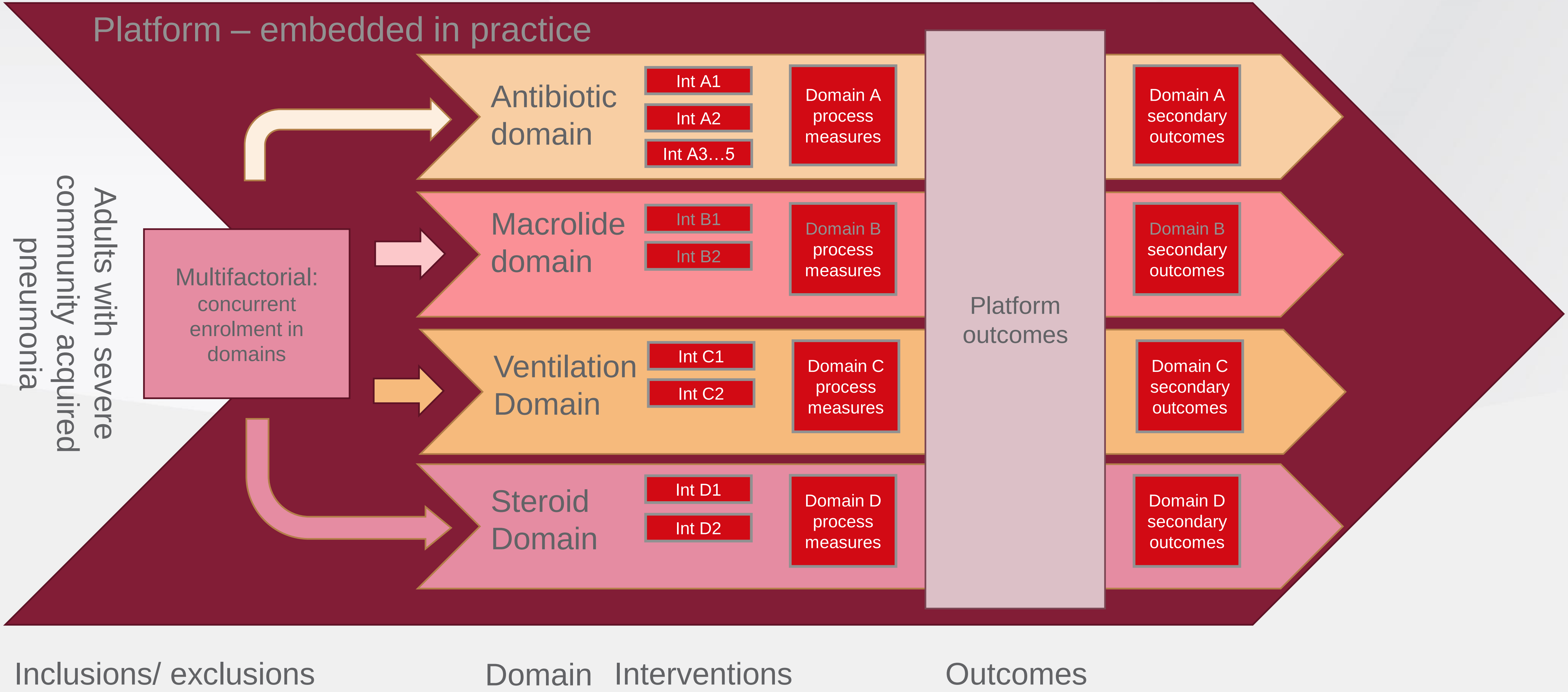
Embedded in clinical practice

Multifactorial interventions

Adaptive design - based on Bayesian analysis

Platform for evaluation of interventions

Multiple interventions within multiple domains


Platform – embedded in practice
Adults with severe community acquired pneumonia
Multifactorial: concurrent enrolment in domains
Antibiotic domain
Int A1
Int A2
Int A3…5
Domain A process measures
Domain A secondary outcomes
Macrolide domain
Int B1
Int B2
Domain B process measures
Domain B secondary outcomes
Ventilation Domain
Int C1
Int C2
Domain C process measures
Domain C secondary outcomes
Steroid Domain
Int D1
Int D2
Domain D process measures
Domain D secondary outcomes
Platform outcomes
Inclusions/ exclusions
Domain
Interventions
Outcomes

Proposed influenza stratum

P: patients with community-acquired pneumonia and suspected or proven influenza infection

I/C:
no antivirals vs

oseltamivir 75mg bd for 5 days vs

oseltamivir 75mg bd for 10 days

O: 90-day mortality

Significance

Few trials of antivirals in hospitalized patients

“Placeholder” domain to permit rapid pivot to new respiratory pathogen

Future interventions (eg baloxavir, pimodivir)

New severe respiratory infection syndromes (eg hyperimmune immunoglobulin, ribavirin)

Conclusions

We have better surveillance systems for influenza

New diagnostic technologies (and models of lab support) are important

Influenza can be a very nasty disease in some people

We have systems to monitor vaccine effectiveness

We have better systems to warn of potential vaccine problems

Existing research studies can “pivot” to new respiratory pathogens

Acknowledgements

FluCAN investigators, including Paul Kelly, Tom Kotsimbos

PAEDS investigators, including Kristine Macartney, Chris Blyth

AuxVaxSafety – Catherine Glover

Steve Webb, Colin MacArthur and REMAP-CAP Investigators

Alfred Health Infection Prevention & Healthcare Epidemiology Unit

Asma Sohail