

Development of antivirals and treatments for Influenza



Paul Ananth Tambyah

Unfortunate Singaporean mother

- 39 year old woman
- No past medical history, no travel
- Presented to hospital with a one week history of worsening productive cough, dyspnea, chest pain, fever and multiple episodes of non-bloody diarrhea
- Examination; BP 90/50, HR 120, T 39C, in respiratory distress, with lung crackles and left sided bronchial breath sounds

In ED

- Collapsed
- Intubated
- Resuscitated
- Augmentin +
- Ceftazidime



Initial labs

Location: NCA&L
 Receipt Date: 16/06/2010 09:09

Procedure	Results	Unit	Expected Range
Full Blood Count			
White Blood Cell	7.66	x10 ⁹ /L	3.26 - 9.28
Red Blood Cells	4.60	x10 ¹² /L	3.77 - 4.92
Haemoglobin	14.1	g/dL	11.7 - 14.7
MCV	90.6	fL	80.1 - 96.7
MCH	30.8	pg	24.5 - 34.3
MCHC	33.9	g/dL	30.8 - 38.4
Haematocrit	41.6	%	33.5 - 43.8
Platelets	281	x10 ⁹ /L	160 - 398
MPV	6.6	fL	6.6 - 9.9
RDW	12.7	%	10.5 - 15.9
Differential Counts			
Neutrophils %	95.1	%	
Neutrophils	7.29	> x10 ⁹ /L	1.41 - 6.83
Lymphocytes %	2.2	%	
Lymphocytes	0.17	< x10 ⁹ /L	0.53 - 3.98
Monocytes %	1.4	%	
Monocytes	0.10	x10 ⁹ /L	0.10 - 0.80
Eosinophils %	0.3	%	
Eosinophils	0.02	x10 ⁹ /L	0.00 - 0.72
Basophils %	0.3	%	
Basophils	0.02	x10 ⁹ /L	0.00 - 0.11
LUC %	0.7	%	
LUC	0.06	x10 ⁹ /L	0.02 - 0.29

Hematology - Common - Reviewed by Dr. Eusebio Hernandez

Renal Panel (w/Glu)

Sodium	130	<	mmol/L	135 - 150
Potassium	3.4	<	mmol/L	3.5 - 5.0
Chloride	91	<	mmol/L	98 - 107
Carbon Dioxide	20	<	mmol/L	22 - 31
Creatinine	64		umol/L	50 - 90
Urea	7.0	>	mmol/L	2.0 - 6.5
Glucose	8.3	>	mmol/L	4.0 - 7.8
Anion Gap	22	>	mmol/L	10 - 18

Liver Panel

Protein, Total	61	<	g/L	65 - 82
Albumin	31	<	g/L	38 - 48
Globulin	30		g/L	
Bilirubin, Total	13		umol/L	5 - 30
Bilirubin, Conj	8	>	umol/L	0 - 5
Bilirubin, Unconj	5		umol/L	5 - 25
AST	216	>	U/L	10 - 50
ALT	117	>	U/L	10 - 70
ALP	69		U/L	40 - 130
LDH	1367	>	U/L	250 - 580
GGT	34		U/L	10 - 80

PEA Collapse again in MICU

- No response to HFOV
- Placed on V-V ECLS
- V-Fib after femoral cannulation

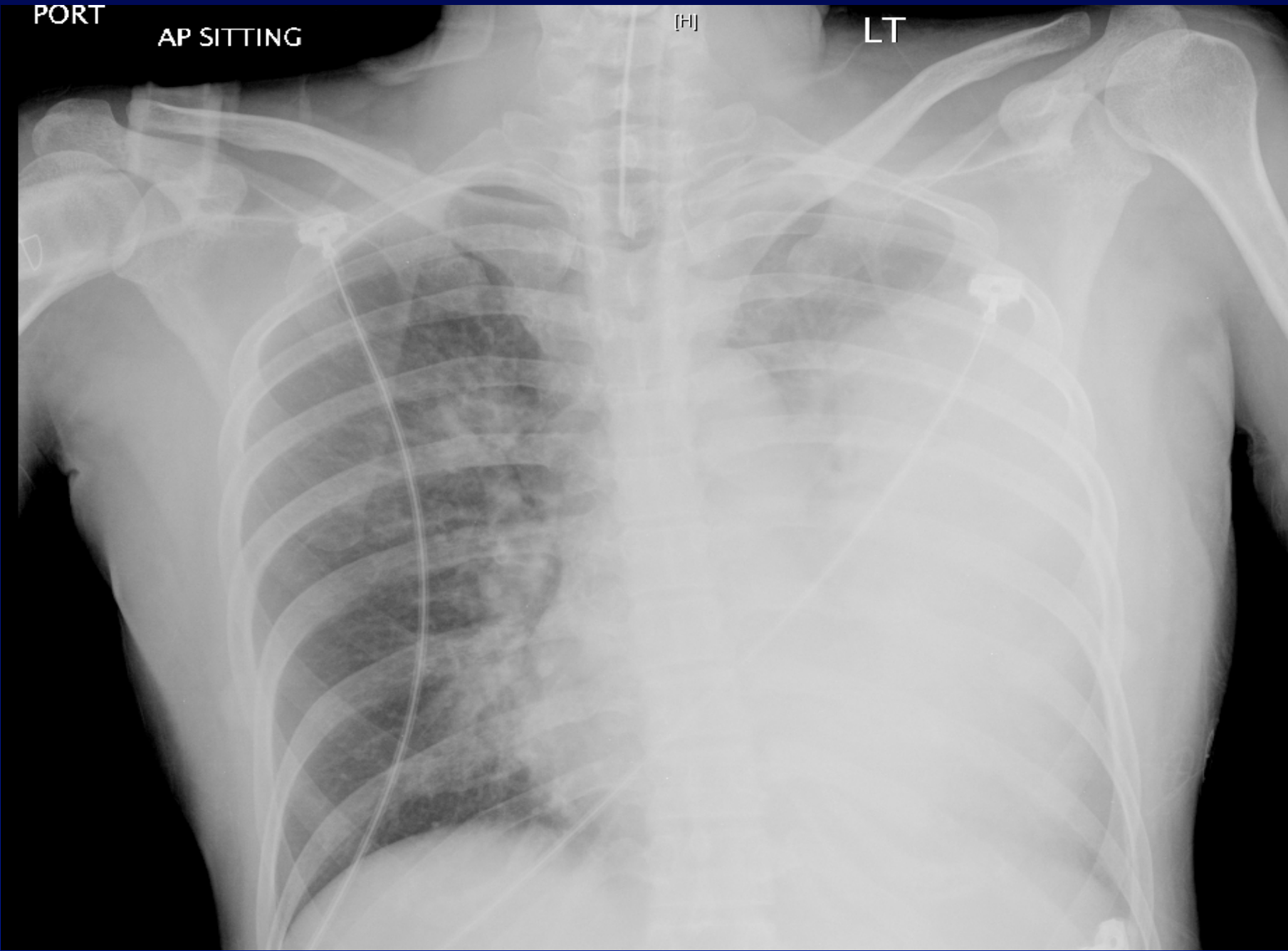
Location	NCA&E		
Receipt Date	16/06/2010 11:44		
Procedure	Results	Unit	Expected Ranges
Blood Gases, POCT			
pH, POCT	7.21	<	7.35 - 7.45
pCO2	48.1	> mmHg	35.0 - 45.0
pO2	70.0	< mmHg	75.0 - 100.0
Bicarbonate	19.3	< mmol/L	23.0 - 33.0
Base Excess	-9.0	< mmol/L	-2.0 - 2.0
O2 Saturation(calc)	90.0	< %	96.0 - 100.0
Sodium, POCT			
Sodium, POCT	137	mmol/L	135 - 150
Ionised CA, POCT			
Ionised CA, POCT	0.89	< mmol/L	1.15 - 1.35
Potassium, POCT			
Potassium, POCT	3.1	< mmol/L	3.5 - 5.0

PORT

AP SITTING

[H]

LT



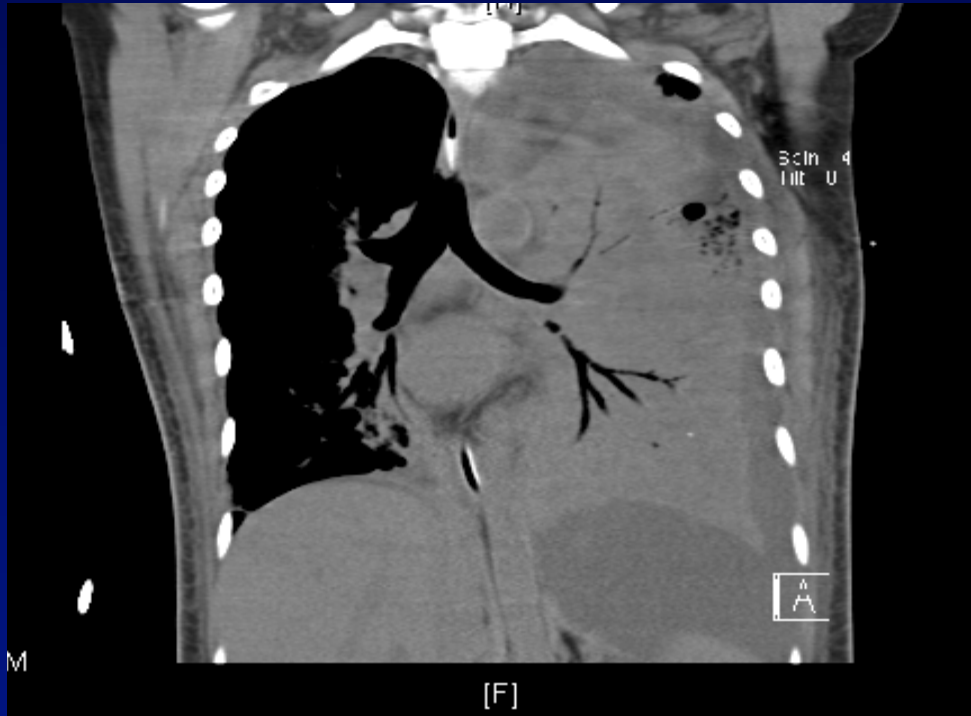
Location	NCA&E
Receipt Date	16/06/2010 10:53
Procedure	Results Unit Expected Ranges
Influenza A B RT-PCR	
Influenza A RT-PCR	Detected
Influenza B RT-PCR	Not Detected
Influenza A Subtypng	H3
InfluenzaA(H1N1-2009)	Not Detected
Assay information	Strategy for detection (rule in/rule out) of influenza A (H1N1-2009) at NUH: 1) Screening for influenza (includes seasonal + novel A) and influenza B 2) Subtyping for seasonal H1 and H3 3) Subtyping for specific swine-origin A (H1N1/2009), targeting NP and HA gene segments Please contact the undersigned for further clarifications if needed.
Specimen	Nasal swab
Reported by	A/Prof Evelyn S.C. Koay, Director, Molecular Diagnosis Centre Dr Julian Tang, Consultant (Virology), Department of Laboratory Medicine

Lab Results

	Results	Unit
AnO2 c/s		
igin	Blood, vein	
comment	SFJT3CRF SGHF925M	

Request status		
Direct Exam	.	
Comment	S. pneumoniae with reduced susceptibility to beta-lactams.	
Identification	.	
Organism 1	Streptococcus pneumoniae	
Germ Comment	Isolated from aerobic bottle only	
Sensitivity 1	.	
Organism 1	Streptococcus pneumoniae	
Penicillin	Intermediate	
1.500		mg/L
Vancomycin MIC	Sensitive	
0.380		mg/L
Ceftriaxone MIC	Intermediate	
0.750		mg/L
Cotrimoxazole	Resistant	
Erythromycin	Resistant	
Clindamycin	Resistant	

Unable to wean off ECLCS



21 June: both pupils fixed and dilated



often...
ECMO
does work

Graeme MacLaren
Kollengode R. Ramanathan
Vitaly Sorokin

Extubation to facilitate mother–baby bonding in refractory acute respiratory distress syndrome

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G. MacLaren
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The Royal Children's Hospital, University of Melbourne,
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A 25-year-old pregnant woman presented at 37 weeks gestation with worsening respiratory distress. A diagnosis of influenza A (H1N1) pneumonitis with acute respiratory distress syndrome (ARDS) was established. Following tracheal intubation, emergency Cesarean section, and delivery of a healthy baby boy, she developed progressive, severe respiratory failure with a PaO₂/FiO₂ ratio of 50. She was referred to our centre and cannulated onto venovenous extracorporeal membrane oxygenation (ECMO).

The ARDS persisted and the patient was unable to be weaned from ECMO after 7 days of extracorporeal support (Fig. 1). However, influenza was no longer detectable on repeat polymerase chain reaction testing

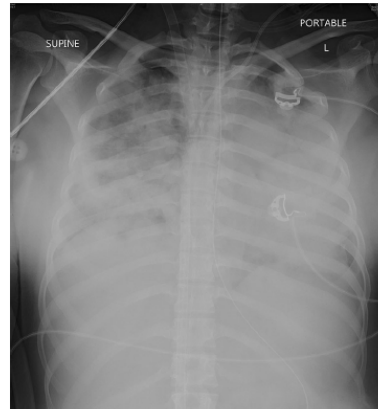


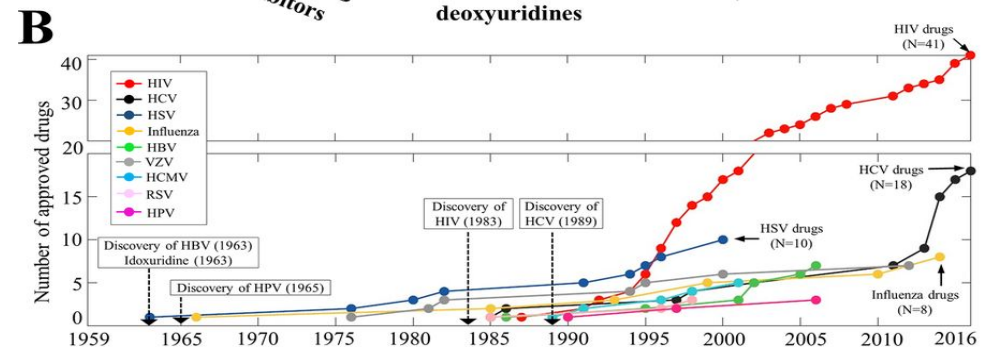
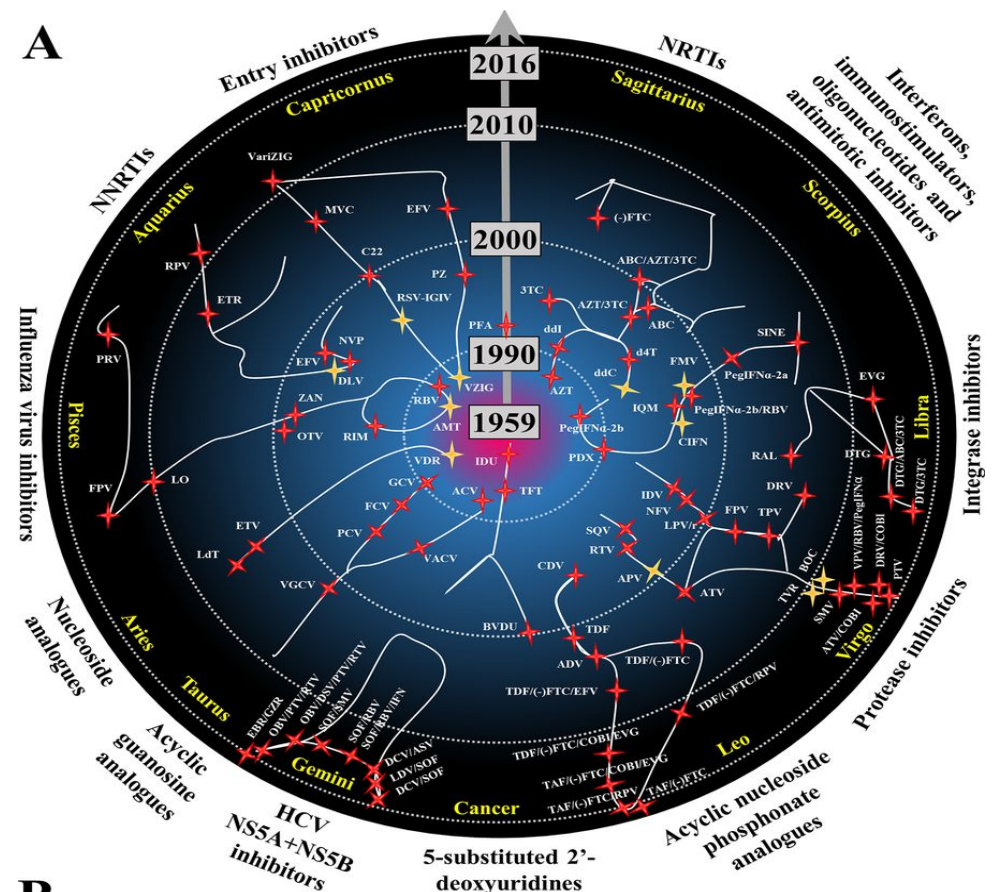
Fig. 1 Chest X-ray after one week of ECMO



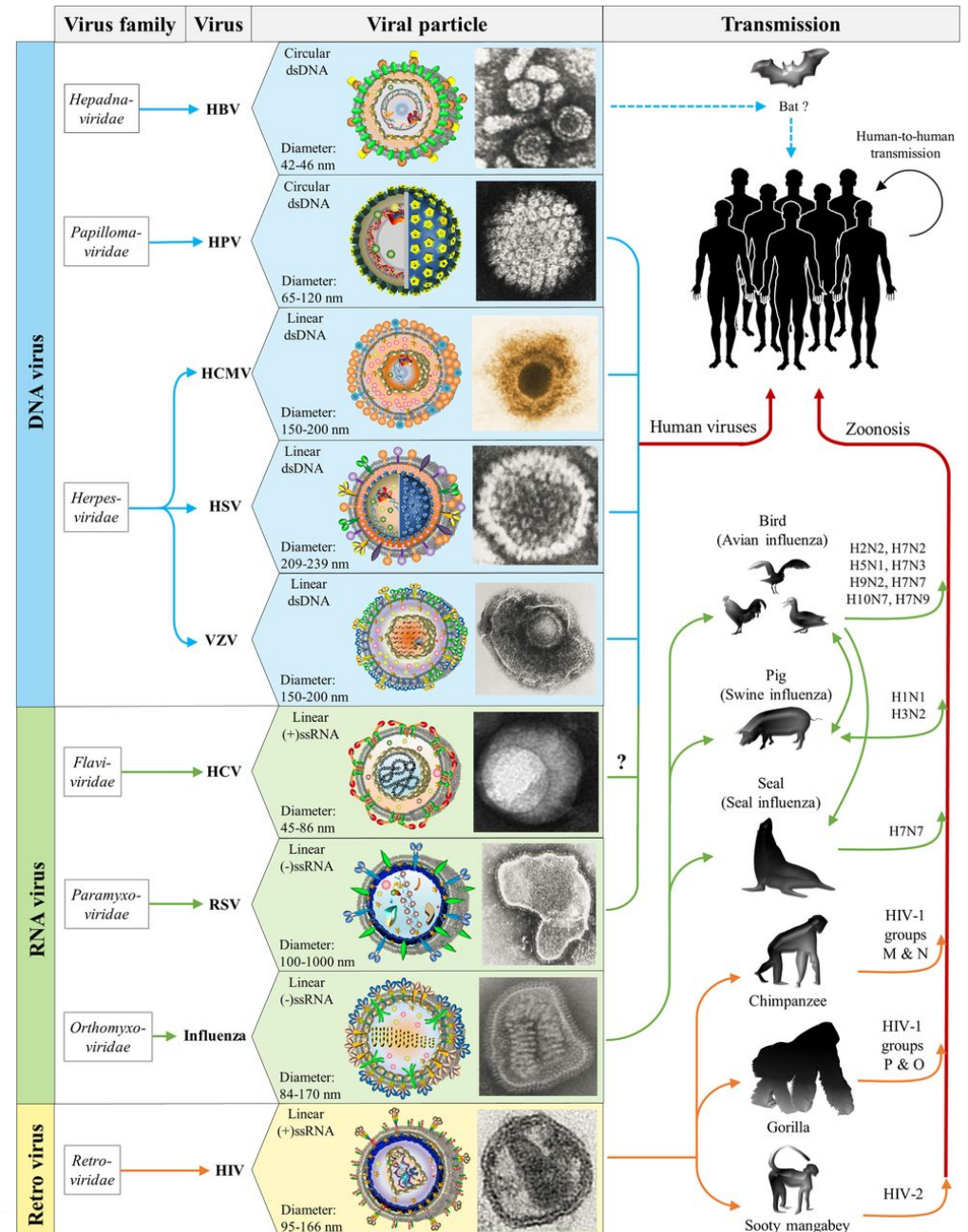
Fig. 2 Photograph of the patient and her son taken on the same day

History of antiviral drugs approved between January 1959 and April 2016.

Erik De Clercq, and Guangdi Li *Clin. Microbiol. Rev.* 2016;29:695-747



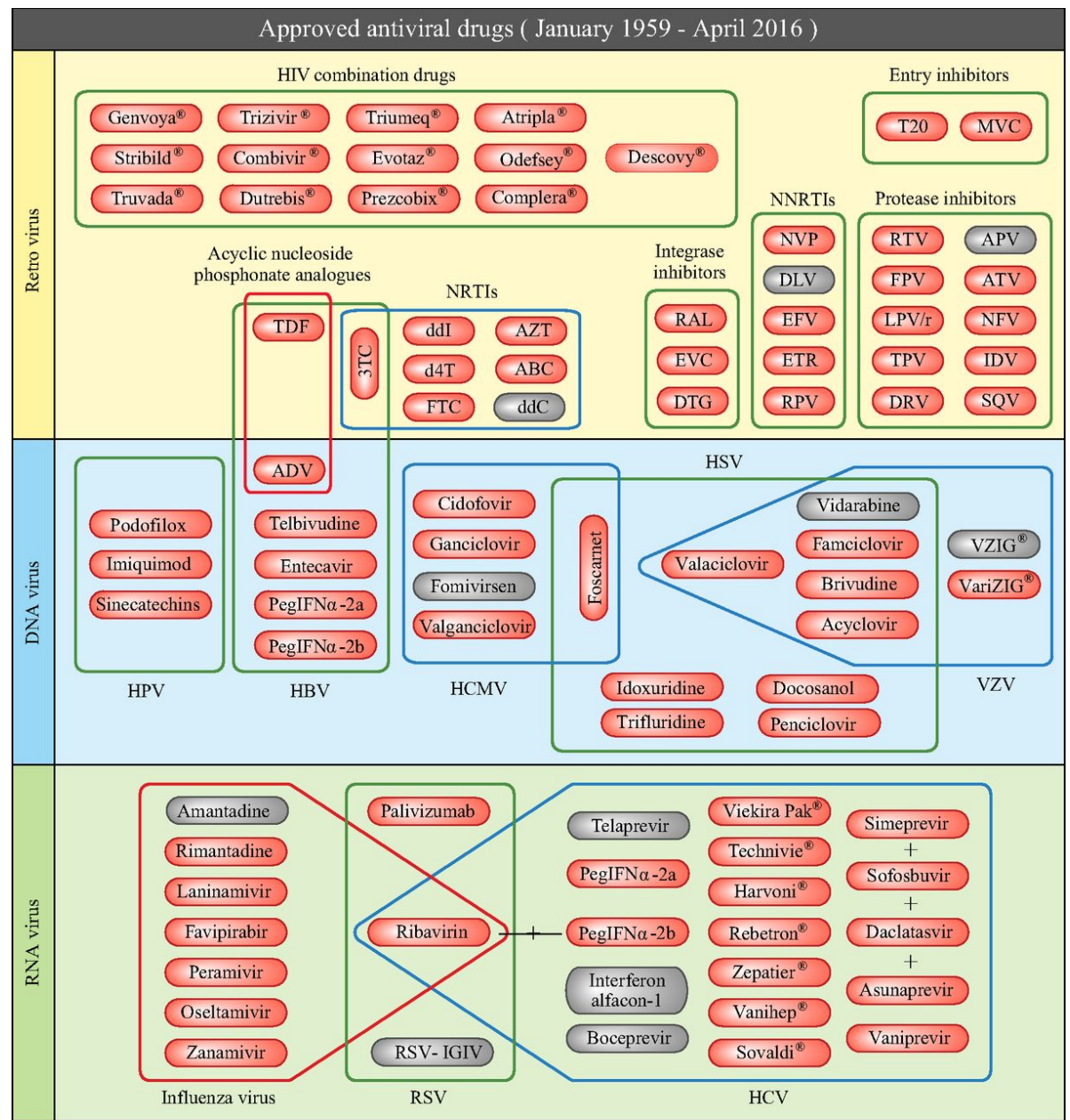
Virus family, morphology, and transmission of HIV, HBV, HCV, HSV, HCMV, HPV, RSV, VZV, and influenza virus.



Erik De Clercq, and Guangdi Li Clin. Microbiol. Rev. 2016;29:695-747

Clinical Microbiology Reviews

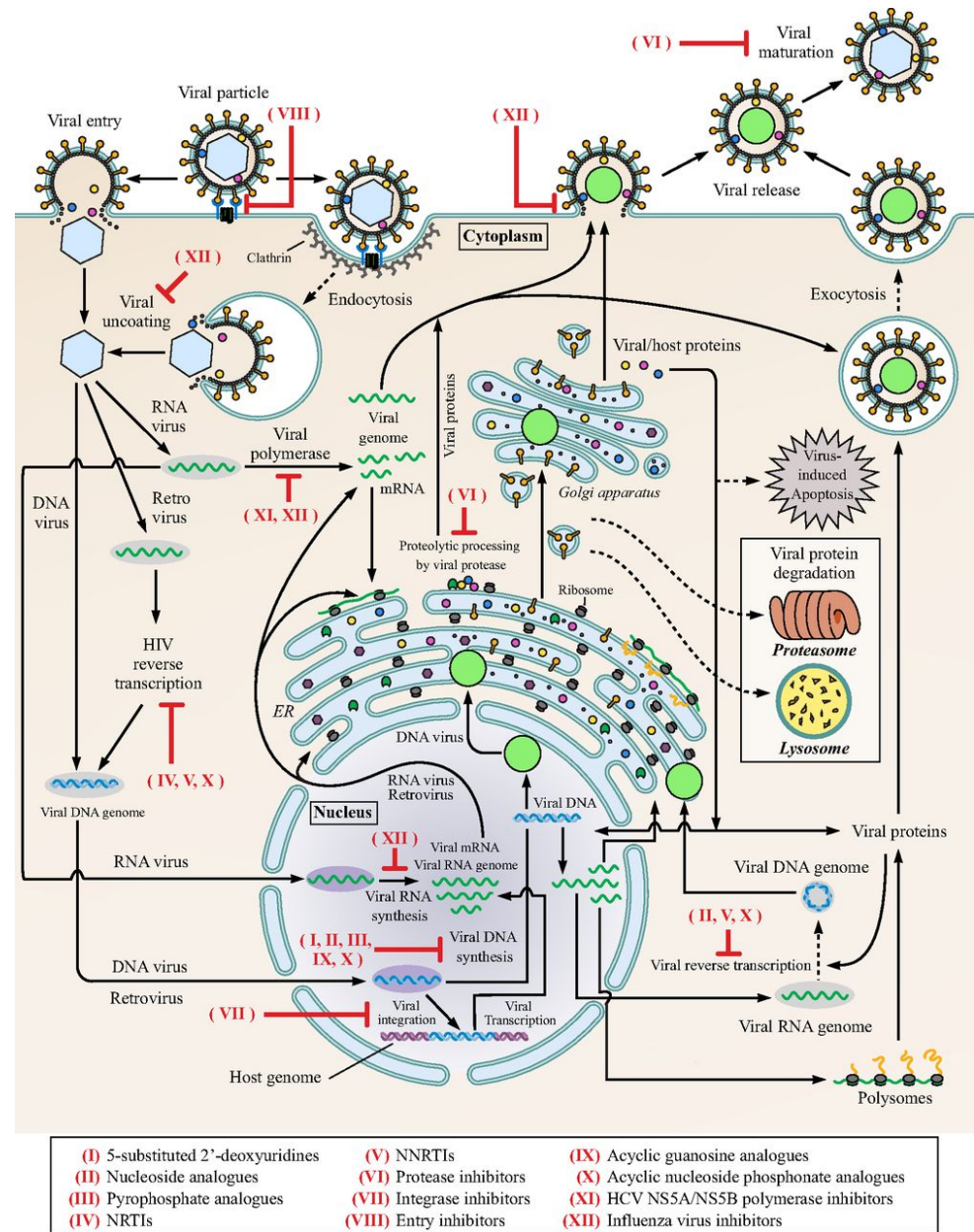
Antiviral drug groups for the treatment of 9 infectious diseases.



Erik De Clercq, and Guangdi Li Clin. Microbiol. Rev. 2016;29:695-747

Clinical Microbiology Reviews

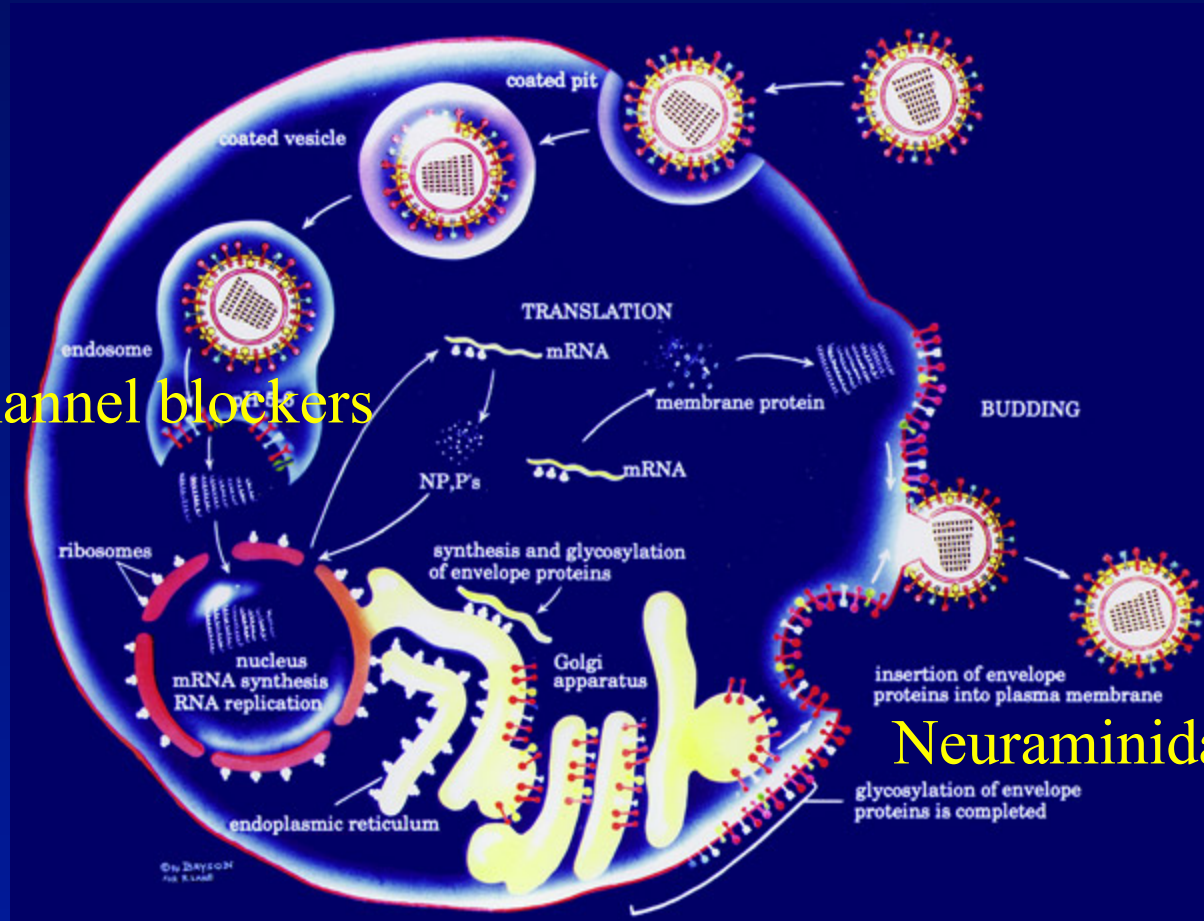
Mechanisms of drug actions during the viral life cycle.



Erik De Clercq, and Guangdi Li Clin. Microbiol. Rev. 2016;29:695-747

Clinical Microbiology Reviews

Influenza



M2 ion channel blockers

Neuraminidase inhibitors

Flu treatment has a chequered history..

To the Editors of THE LANCET.

SIRS,—I read with much interest Dr. Yeo's valuable letter on the Treatment of Influenza in last week's issue of THE LANCET, and should like to endorse what he says in reference to the deleterious effects of antipyrin in the treatment of this scourge. In comparing notes of the cases which have presented themselves for treatment during the past five years it has forcibly struck me that the mortality has been gradually diminishing, and the period of convalescence shortened in each successive epidemic. I do not consider this due to any lessened virulence of the much-maligned bacilli, but to the fact that antipyrin and similar depressants are being withheld in the treatment of this disease. During the first epidemic five years ago I noticed the great prominence given to pneumonia as a complication by all writers on influenza. My own firm conviction is, and has been all along, that the antipyrin treatment was entirely responsible in many cases for the onset of the pneumonia, and that ordinary cases of influenza with bronchitic trouble ended frequently in broncho-pneumonia when antipyrin was administered. During the past three epidemics I have not seen a single case of pneumonia complicating influenza excepting in asthenic cases in very old persons. So long as we have therapeutic agents such as quinine and alcohol we need not be afraid to combat this year's epidemic.—I am, Sirs, yours faithfully,

FRANCIS WILLIAM GRANT, M.D., B.Sc., C.M. Edin.

Elgin, March 4th, 1895.

Existing antivirals

- M2 ion channel blockers:
 - Amantadine
 - Rimantadine
- Neuraminidase inhibitors:
 - Oseltamivir
 - Zanamivir
 - (Peramivir) + (Favipiravir)

Existing antivirals are effective against influenza viruses with genes from the 1918 pandemic virus

Terrence M. Tumpey*, Adolfo García-Sastre†, Andrea Mikulasova†, Jeffery K. Tauber Peter Palese†, and Christopher F. Basler†[§]

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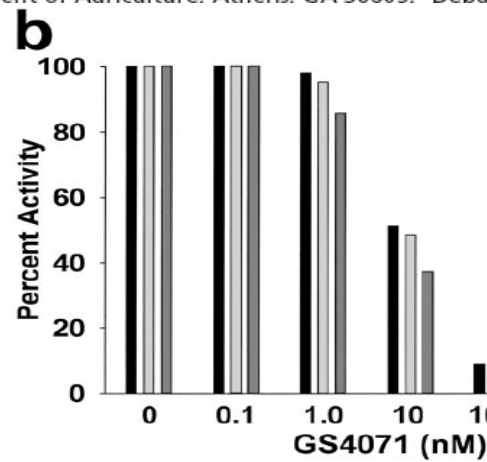
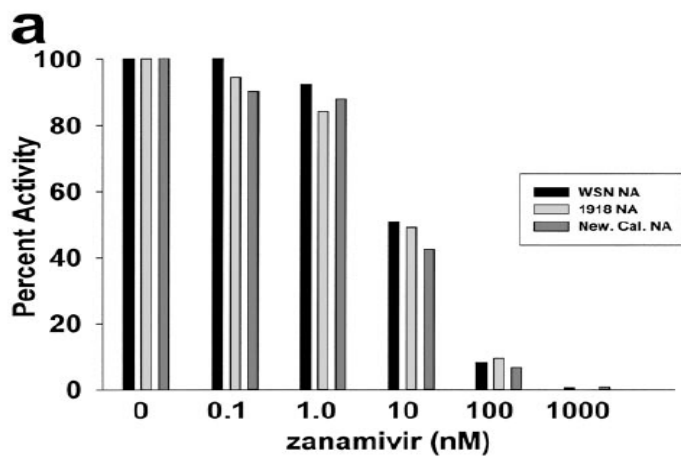
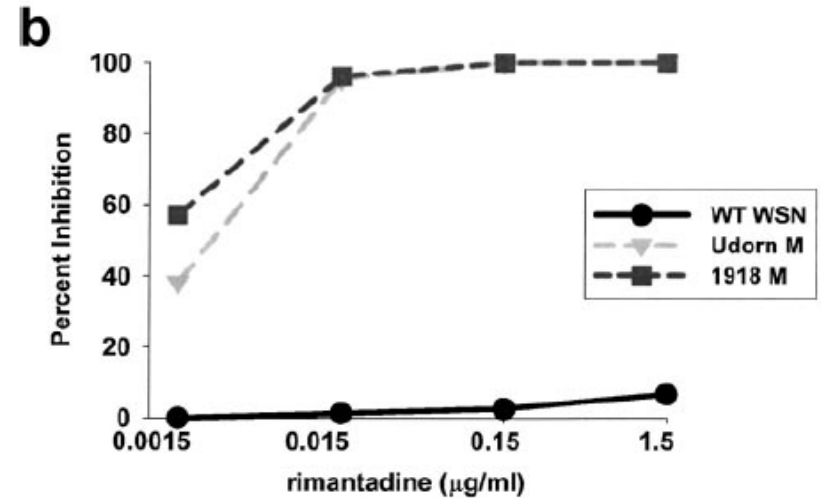
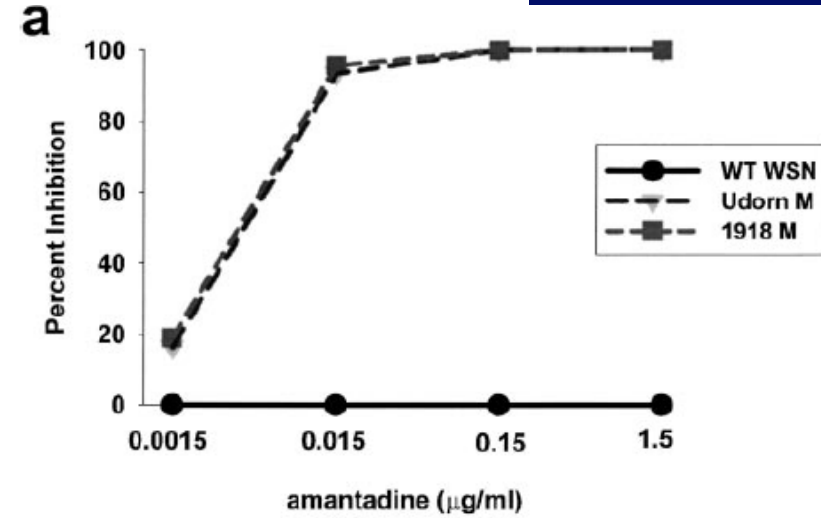


Fig. 1. Inhibition *in vitro* of the 1918 influenza virus NA by zanamivir and GS4071 (oseltamivir carboxylate). Extracts expressing WSN NA, or 1918 NA were assayed in the presence of the indicated concentrations of zanamivir (a) or GS4071 (oseltamivir carboxylate) (b). Activities activity relative to the no-drug control.



M2 ion channel blockers

- Years of experience with amantadine, rimantadine
- Effective in treatment also limited efficacy in prophylaxis
- Occasional neurotoxicity
- Problem is resistance

za A viruses isolated in Australia, New Zealand, Pacific Islands and compared these results with those regions in recent

received from WHO Collaborating Centres from Australia, New Zealand. Viruses were received from original clinical samples and immunofluorescence. The isolates were cultured by CPE and the virus was growing in turkey red blood cells (Barr et al., 2003). Positional cloning and glutination inhibition tests were used as standard reference viruses (WHO, 1982). Viruses

Table 1

Geographic origin and proportion of A(H1) and A(H3) adamantane resistant viruses isolated in 2006

Country	2006 A(H1) viruses		2006 A(H3) viruses	
	# Resistant/# tested	Resistant (%)	# Resistant/# tested	Resistant (%)
Macau (SAR)	9/11	82	1/1	100
Taiwan	1/5	20	2/2	100
Thailand	1/10	10	6/10	60
Malaysia	0/10	0	2/9	22
Cambodia	0/3	0	–	–
Singapore	1/10	10	0/1	0
Philippines	0/14	0	1/1	100
Australia	8/20	40	20/40	50
New Zealand	1/7	14	9/12	75
New Caledonia	0/5	0	0/1	0
South Africa	1/3	33	10/10	100
Solomon Islands	0/3	0	–	–
Total	22/101	21.8	51/87	58.6

NA Inhibitors

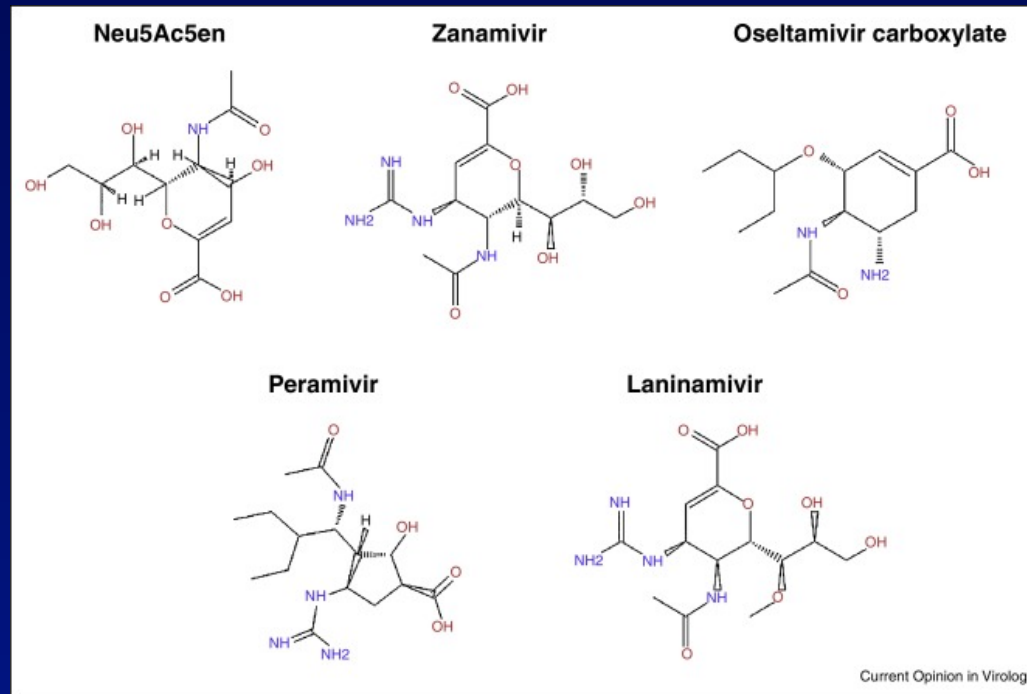


Figure 2. Chemical structures of Neu5Ac2en and the currently approved NA inhibitors. The structural base designed NA inhibitors were developed based on Neu5Ac2en, a transition state analog of sialic acid with different modifications at C4 and C6. To further im...

Hui-Ling Yen

Current and novel antiviral strategies for influenza infection

Current Opinion in Virology, Volume 18, 2016, 126–134



Next generation
therapeutics

BioCryst Research Pipeline

Peramivir (Neuraminidase Inhibitor)



More research informa

[Research Pipeline →](#)

[Peramivir
\(Neuraminidase Inhibitor\)](#)

Peramivir (Neuraminidase Inhibitor)

Peramivir is a member of the class of antiviral agents that essential for the spread of influenza virus within the host. neuraminidases and certain strains of influenza viruses th but are susceptible to peramivir in laboratory tests. BioC of acute influenza, including infection caused by highly vir 2006, BioCryst received United States Food and Drug Adr injection. The availabilily of an intravenous neuraminida: hospitalized with severe and potentially life-threatening in formulation of peramivir could ensure appropriate dosing inhaled anti-influenza agents.

In September 2007, BioCryst Reported Preliminary Result

BIOCRIST REPORTS PRELIMINARY RESULTS FROM A PHASE II CLINICAL TRIAL OF PERAMIVIR IN SUBJECTS WITH ACUTE INFLUENZA

Birmingham, Alabama - September 19, 2007 - BioCryst Pharmaceuticals, Inc. (Nasdaq: BCRX) today announced preliminary findings from a Phase II study with intramuscular (i.m.) injection of peramivir, the Company's product candidate for the treatment of seasonal and life-threatening influenza.

The study was a randomized, double-blind, placebo-controlled clinical trial designed to test whether peramivir, when administered acutely in high doses intramuscularly, could reduce the duration of symptoms during seasonal influenza. 344 patients who had a positive rapid antigen test indicating acute influenza illness were randomized to receive intramuscular injections of either placebo or one of two dose levels of peramivir (150mg and 300mg) as a single dose administered within 48 hours of symptom onset. The primary endpoint of the study was the time to alleviation of symptoms in the patients with confirmed influenza infection (n=313).

While the results indicate that in the evaluable population of 313 subjects, a single dose of peramivir demonstrated a treatment improvement over placebo, the improvement was not statistically significant. With regard to the primary endpoint of median time to alleviation of symptoms, the improvement over placebo was 22.9 hours with the 150mg dose (p=0.284) and 21.1 hours with the 300mg dose (p=0.152). Based on a preliminary review, the Company believes that due to the introduction of a shorter injection needle in the Phase II trial compared to the Phase I trial, only one-third of subjects received an adequate intramuscular injection.

In a post hoc analysis, 101 subjects showed evidence of adequate intramuscular injections as measured by a standard laboratory test, serum creatine kinase elevations over baseline. In this group of subjects, peramivir showed a larger treatment effect on the time to alleviation of symptoms. For these 101 subjects, peramivir showed an improvement of 64.8 hours over placebo at the 300mg dose, and an improvement of 44.6 hours over placebo at the 150mg dose. These differences were shown using the same measure of symptom alleviation as used for the primary endpoint, and they indicate a dose response in this group of patients.

At both doses studied, peramivir demonstrated a safety and tolerability profile similar to placebo, both in the total population and in the population showing evidence of intramuscular delivery.

"We are clearly disappointed that we did not achieve the primary endpoint across the entire study population.

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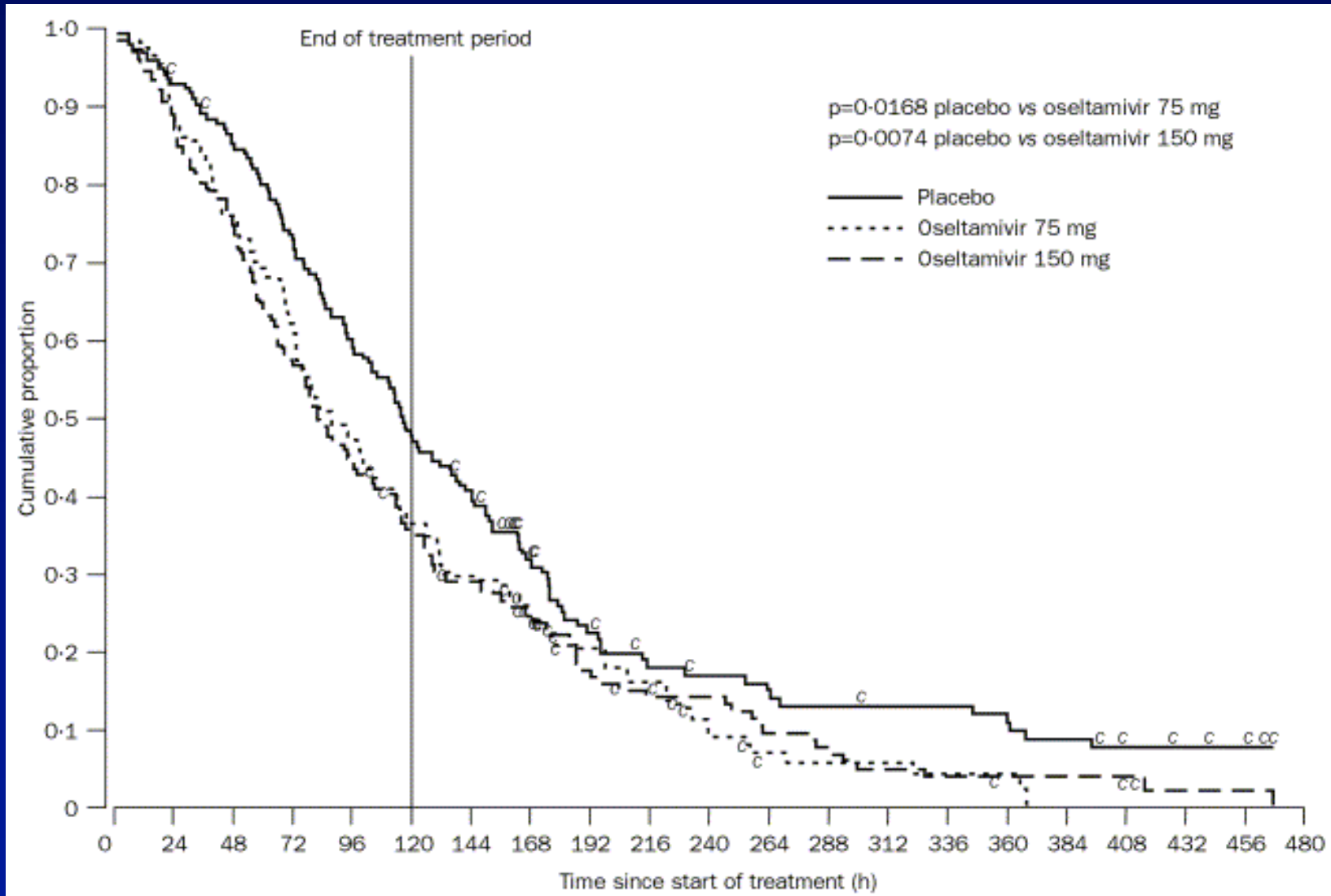
BioCryst Pharmaceuticals

2190 Parkway Lake Drive
Birmingham, Alabama 35244

Phone (205) 444-4600
Fax (205) 444-4640
info@biocryst.com

Oseltamivir vs Influenza

Regular
Flu



Nicholson et al. Lancet 2000;355:1845-50

Selected Treatment Trials of Neuraminidase Inhibitors

Table 2. Selected Treatment Trials of Neuraminidase Inhibitors.

Study	No. of Patients	Characteristics of Patients*	Time from Onset of Symptoms to Start of Therapy	Reduction in Length of Illness†
Zanamivir				
Hayden et al., ¹² Cooper et al., ¹³ Monto et al., ¹⁴ Makela et al., ¹⁵ MIST Study Group, ¹⁶ Matsumoto et al. ¹⁷	2600 (pooled number)	Healthy adults	36–48 hr	1.0–2.0 days
Cooper et al. ¹³	Pooled number (meta-analysis)	Elderly and high-risk patients	36–48 hr	2.0 days
Hedrick et al. ²¹	471	Children 5–12 yr	36–48 hr	1.0 day
Oseltamivir				
Cooper et al. ¹³	Pooled number	Healthy adults with laboratory-confirmed influenza	<48 hr	1.4 days
Treanor et al. ¹⁸	629	Healthy adults with laboratory-confirmed influenza	<36 hr	1.3 days
Nicholson et al. ¹⁹	726	Healthy adults with laboratory-confirmed influenza	24–36 hr	1.0–2.0 days
Aoki et al. ²³	1426 (total)	Healthy adults (12–70 yr) with laboratory-confirmed influenza	0–6 hr	4.1 days‡
Aoki et al. ²³	1426 (total)	Healthy adults (12–70 yr) with laboratory-confirmed influenza	6–12 hr	3.1 days‡
Cooper et al., ¹³ Kaiser et al. ²⁴	Pooled number from compiled studies	Elderly and high-risk patients with laboratory-confirmed influenza	36–48 hr	0.5 day§
Whitley et al. ²²	695	Children (1–12 yr) with influenza-like illness (65% with laboratory-confirmed influenza)	<48 hr	1.5 days¶

* In cases in which results were collected for both influenza-like illness and laboratory-confirmed influenza, data are given for laboratory-confirmed influenza.

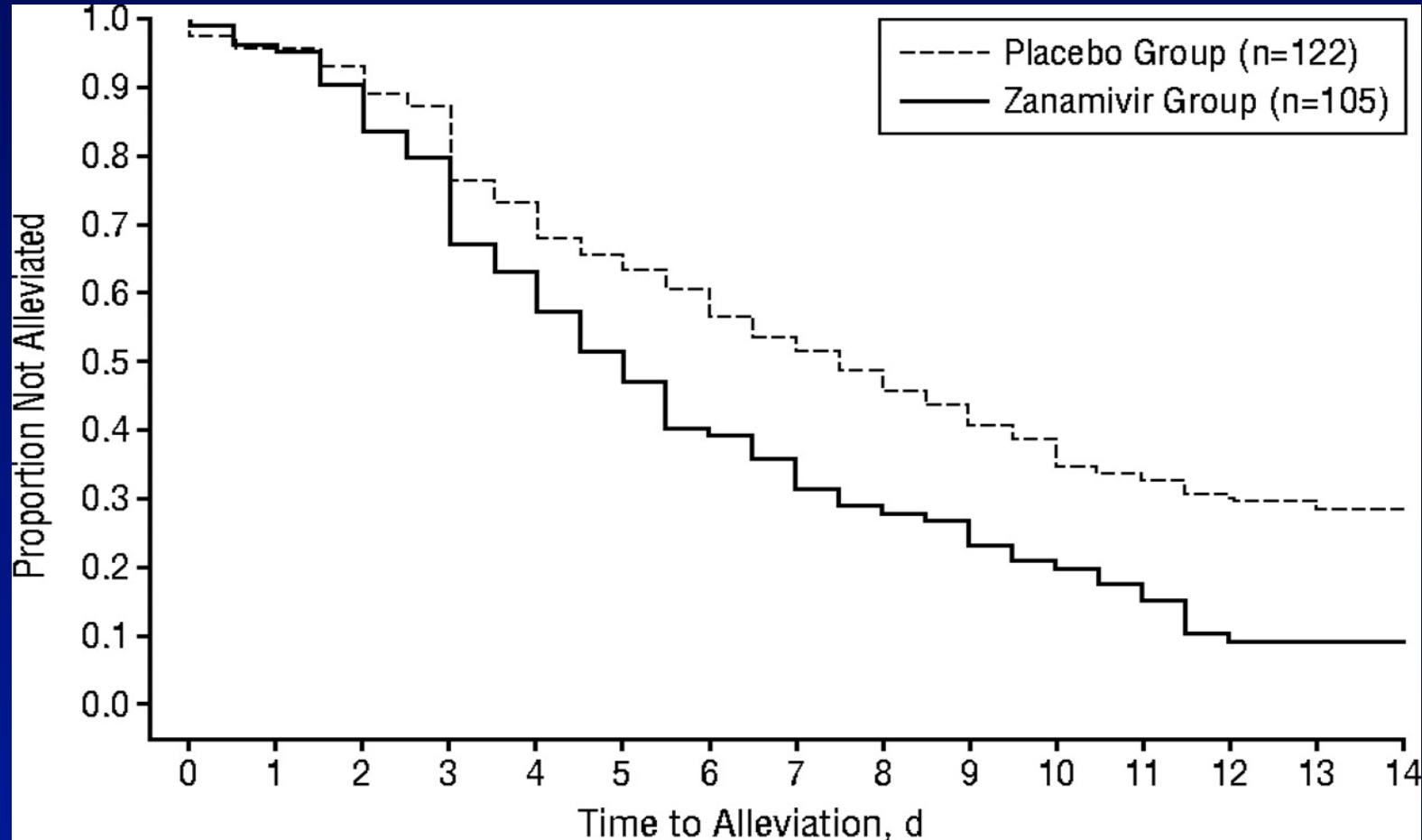
† Comparisons were between a neuraminidase inhibitor and no therapy, unless otherwise noted.

‡ Comparisons were between a neuraminidase inhibitor at the designated time and at 48 hours after the onset of symptoms, rather than no treatment.

§ Patients also had a 34 percent reduction in the use of antibiotic therapy for infections of the lower respiratory tract.

¶ Patients also had a 44 percent reduction in the incidence of otitis media.

Zanamivir in Influenza in high risk individuals



Lalezari, J. et al. Arch Intern Med 2001;161:212-217.

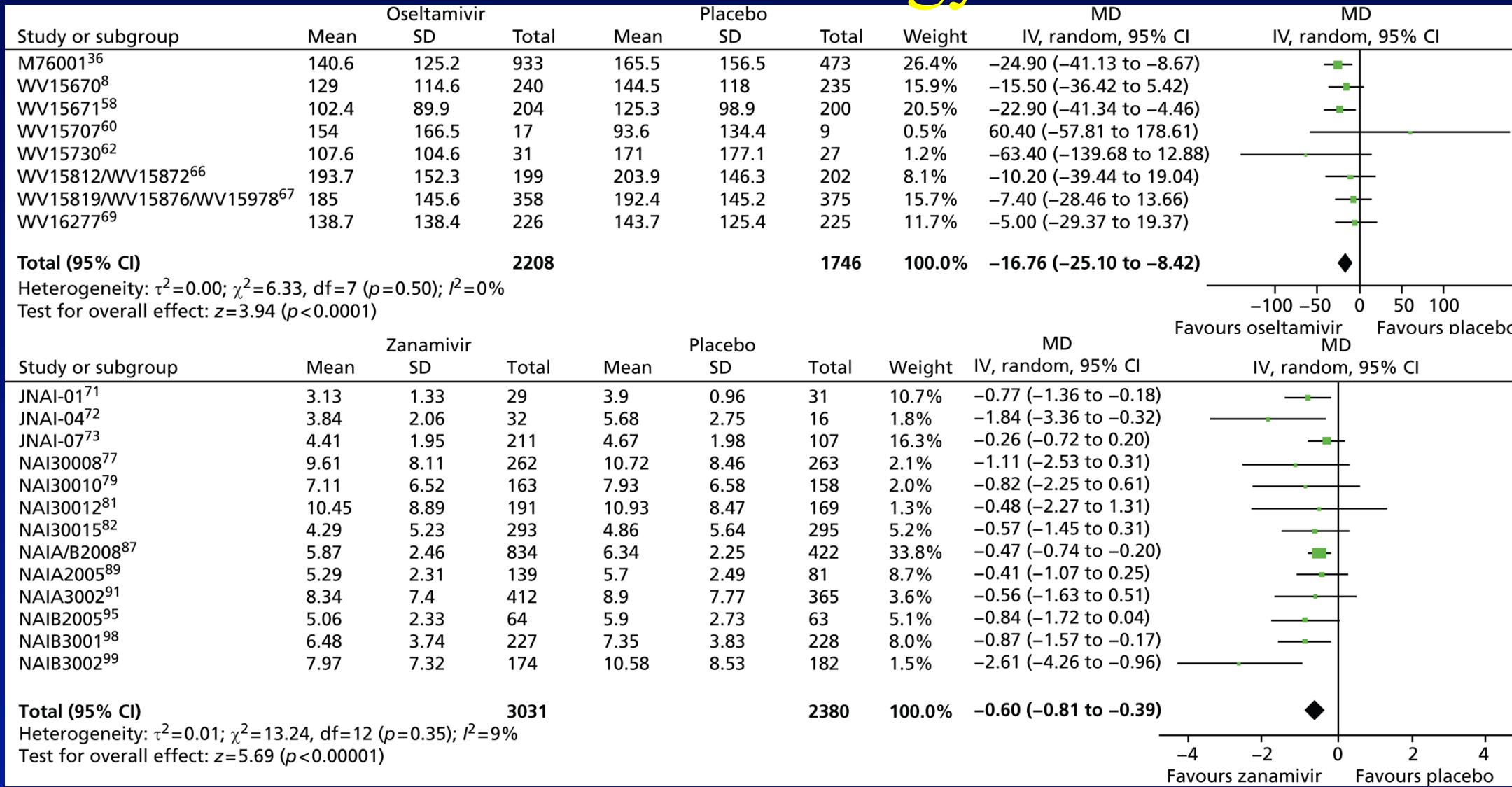
Oseltamivir

Regular
Flu

- Trials data: 849 patients: 1.3 day reduction in duration.
- “It is my opinion that a one-day reduction in the duration of moderate-to-severe symptoms, including fever, is likely to be of clinical importance to many individuals. However, it is ultimately the judgement of the healthcare provider whether use of the product, given the expectation of a modest treatment benefit, is appropriate and indicated for a given patient's circumstance. Because influenza symptoms are self-limited in the majority of individuals, it is anticipated that many persons with influenza will neither require, nor desire treatment with antiviral medication.”

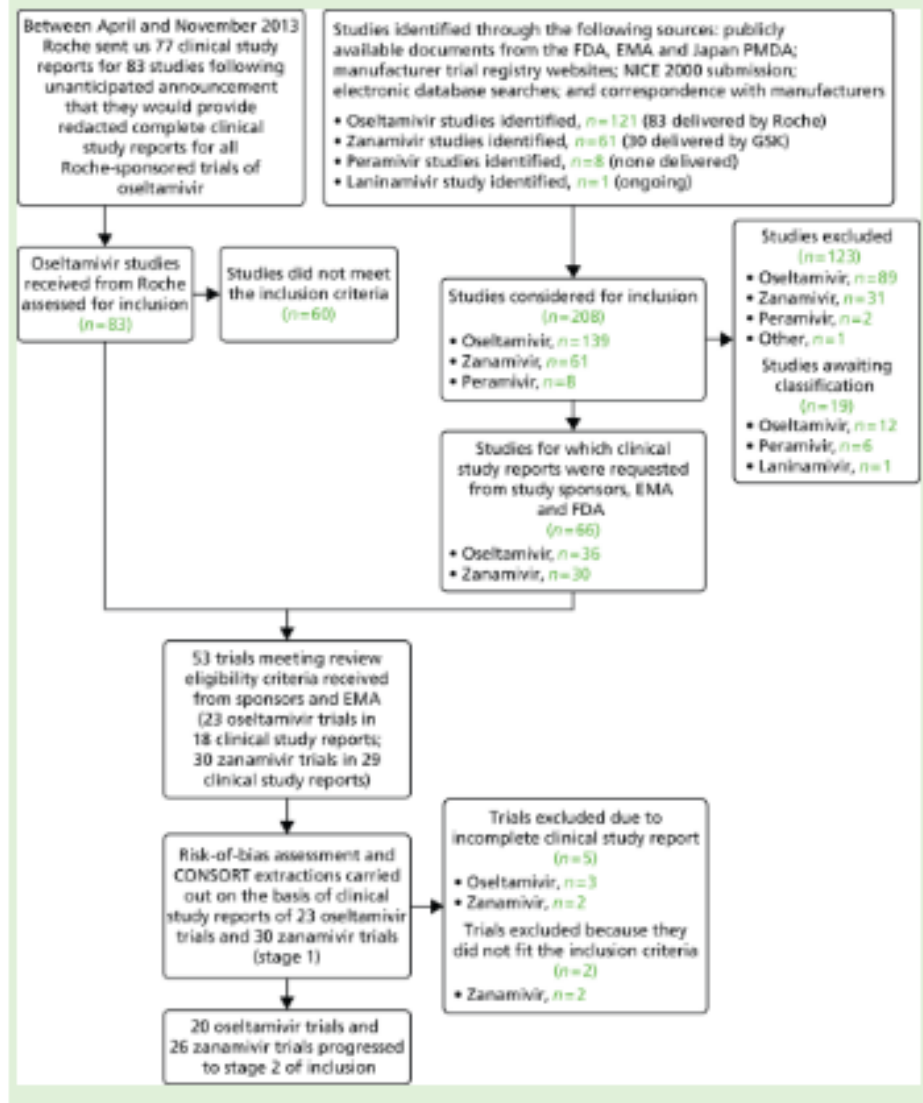
<http://www.fda.gov/cder/drug/infopage/tamiflu/directormemo.htm>

NIHR Health technology assessment



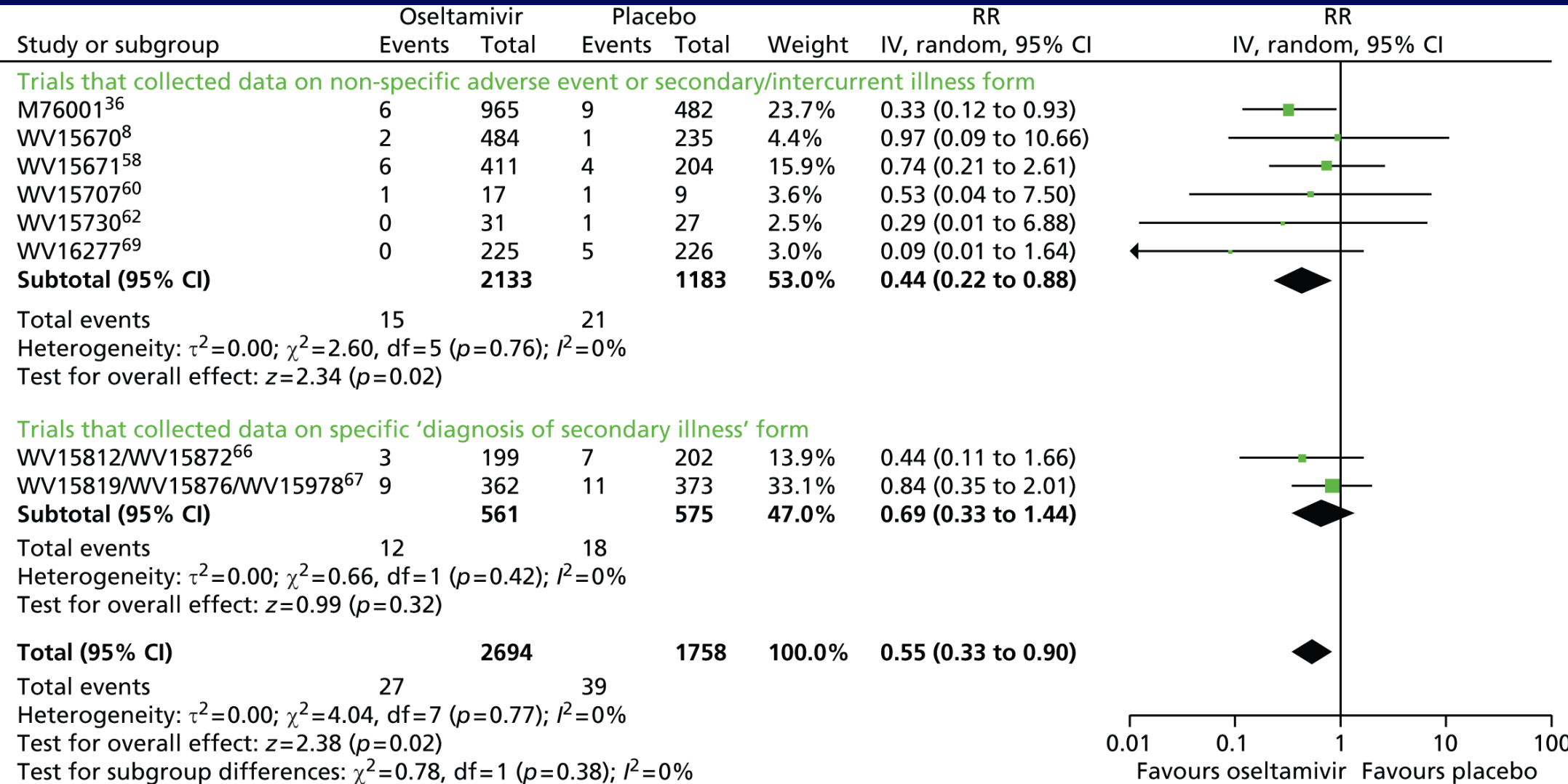
A thorough review

FIGURE 3 Flow diagram describing the number of studies identified, inclusion, exclusion and progression from identification to stage 1 to stage 2 of the review. (PMDA, Japanese Pharmaceuticals and Medical Devices Agency).

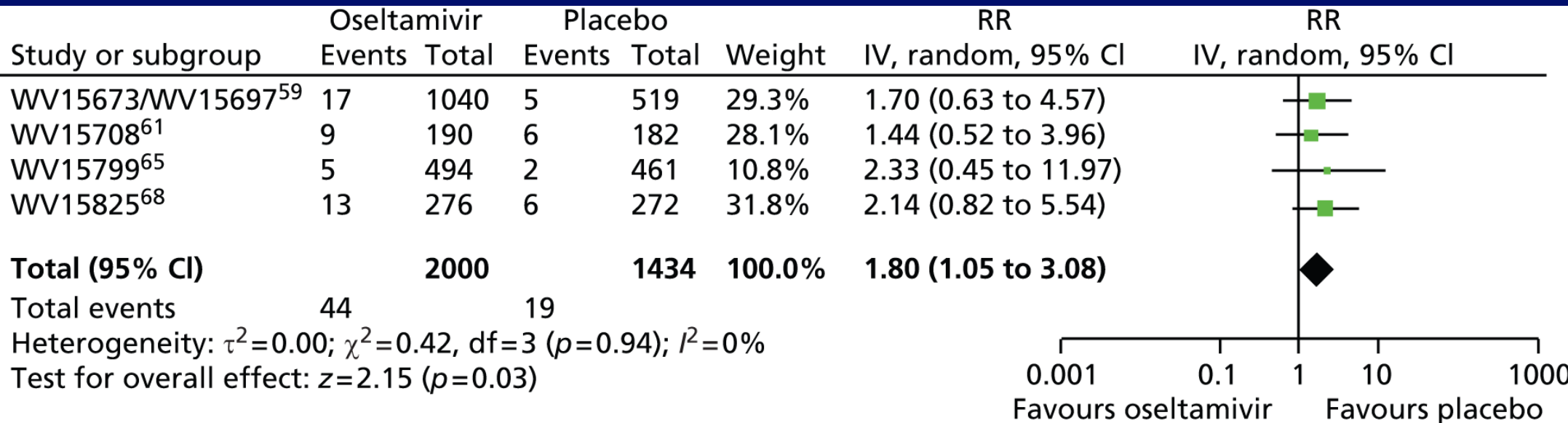


We carried out the inclusion into stage 1 using the CSRs, titles, abstracts and any other relevant information. Through this process we identified 208 potentially relevant studies (139 oseltamivir trials, 61 zanamivir trials and eight peramivir trials). We excluded 123 studies (see Appendix 10, listed in the 'characteristics of excluded studies' table) as clearly ineligible. A further 19 studies are awaiting classification (Table 6). We requested 66 trials from study sponsors, the EMA and the FDA. From these different methods, the total number of trials available for assessment for inclusion in our review at stage 1 was 53.

Prevention of pneumonia



Neuropsychiatric side effects



Adverse Drug Reaction

n e w s

Published by the Centre for Drug Administration, HSA and the HSA Pharmacovigilance Advisory Committee

Oseltamivir and neuropsychiatric events

Monitor patients on oseltamivir for signs of unusual behaviour

Oseltamivir (Tamiflu®, Roche) is an antiviral agent licensed by HSA in October 2000 for the treatment of uncomplicated acute illness due to influenza infection (influenza A & B) in adults and children ≥ 1 year old who have been symptomatic for no more than two days and for the prophylaxis of influenza in adults and children ≥ 13 years old.

Recent post-marketing reports of CNS disorders^{1,2}

The Health Sciences Authority (HSA) has reviewed the data from the 103 post-marketing reports of neuropsychiatric adverse events suspected to be associated with oseltamivir received between August 2005 to July 2006. These include events such as delirium with prominent behavioural disturbances (n=60) and suicidal events (n=6) including self-injury and suicidal ideation.

The majority of the cases were reported from Japan (92%) and were predominantly for the treatment of influenza (97%). These were primarily among paediatric patients (67%) with an age range of 1.5 to 17 years old. There were three deaths: a 14 year-old boy and two adults who fell to their deaths. The patients who died were healthy before contracting influenza



coincident p
Japan or a
Additionally
depressed I
encephalitis
to Tamiflu®

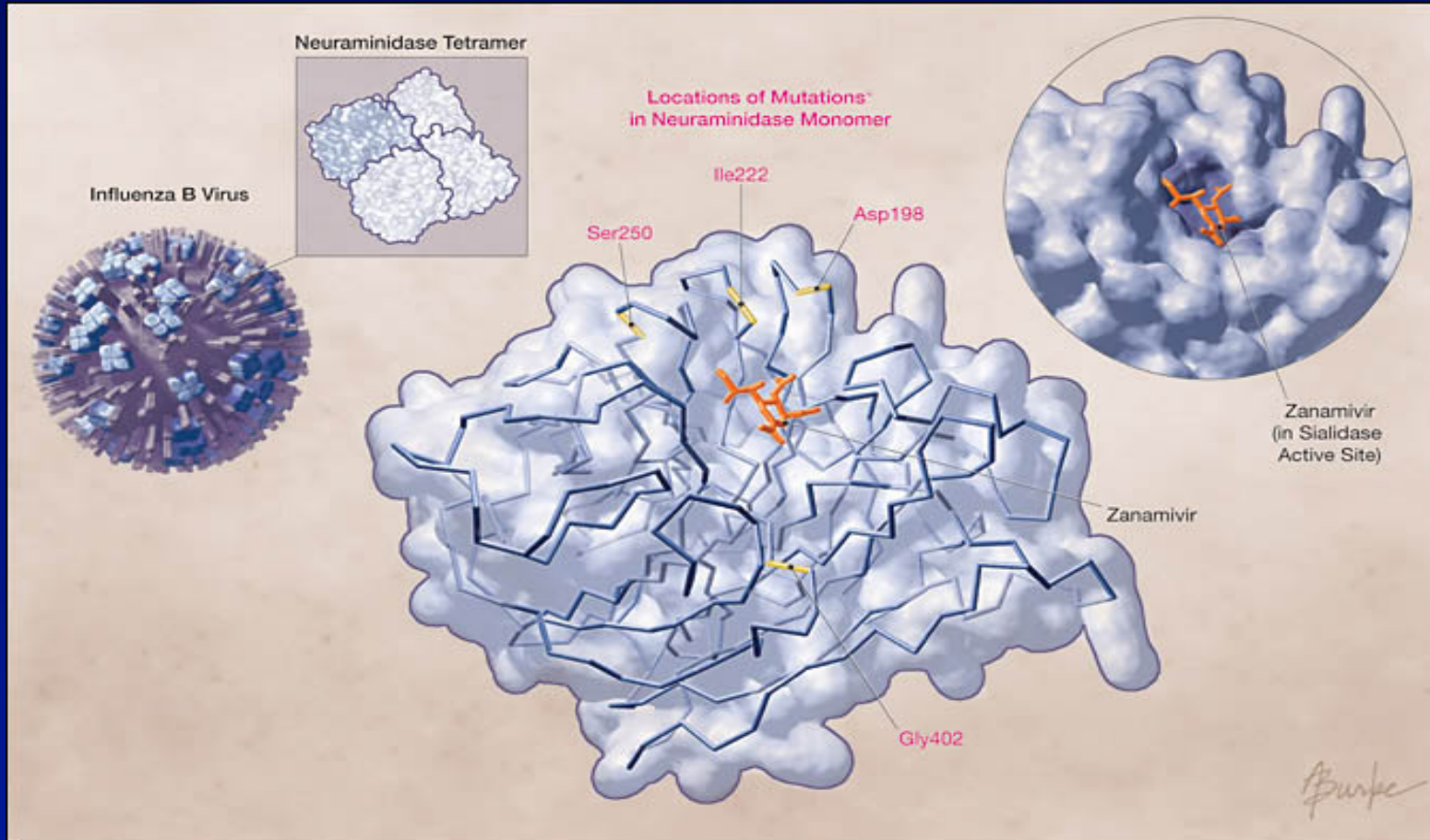
Nonetheless:
adverse eve
positive de-

recovery from neuropsychiatric adverse effects once oseltamivir was discontinued and/or lack of positive neuro-imaging findings in the reviewed reports (n=25), the local prescribing information of Tamiflu® will be updated to warn of the potential for the occurrence of neuropsychiatric adverse events. In addition, it also advised that patients with flu, particularly children may be at an increased risk of self-injury and confusion shortly after taking Tamiflu® and should be closely monitored for signs of unusual behaviour.

Local situation

HSA has received three adverse drug reactions suspected with use of oseltamivir. They are one report of hepatitis, and another of nausea and urticaria. There is also one report of a middle-aged male who committed suicide by falling to his death. He was prescribed oseltamivir at 75mg twice a day for flu and the adverse event was reported to have occurred on the 7th day. The causality however could not be established as it was reported that the patient was also taking other medications.

Locations of Mutations on the 3-Dimensional Structure of Neuraminidase



Hatakeyama, S. et al. JAMA 2007;297:1435-1442.

BRIEF REPORTS

MIXTURES OF OSELTAMIVIR-SENSITIVE AND -RESISTANT PANDEMIC INFLUENZA A/H1N1/2009 VIRUSES IN IMMUNOCOMPROMISED HOSPITALIZED CHILDREN

Mas Suhaila, MD,* Julian W. Tang, PhD, FRCPATH,†
Hong Kai Lee, BSc,† Cui Lin, PhD,‡ Paul A. Tambyah, MD,§
Hui Kim Yap, MD,* Seng Hock Ouak, MD,*
and Evelyn S. C. Koay, MD†¶ **Evelyn S.C. Koay, PhD**

Abstract: We report on 3 immunocompromised children infected with pandemic influenza A/H1N1/2009 in whom mixtures of oseltamivir-susceptible and oseltamivir-resistant viral populations developed, despite them receiving relatively short-term courses of oseltamivir. In addition, it was found that bacterial coinfections were common, indicating that empiric, broad-spectrum antibiotics should be considered in such patients when infected with influenza virus.

Key Words: influenza, oseltamivir, drug resistance, **H275Y**, children, mixture

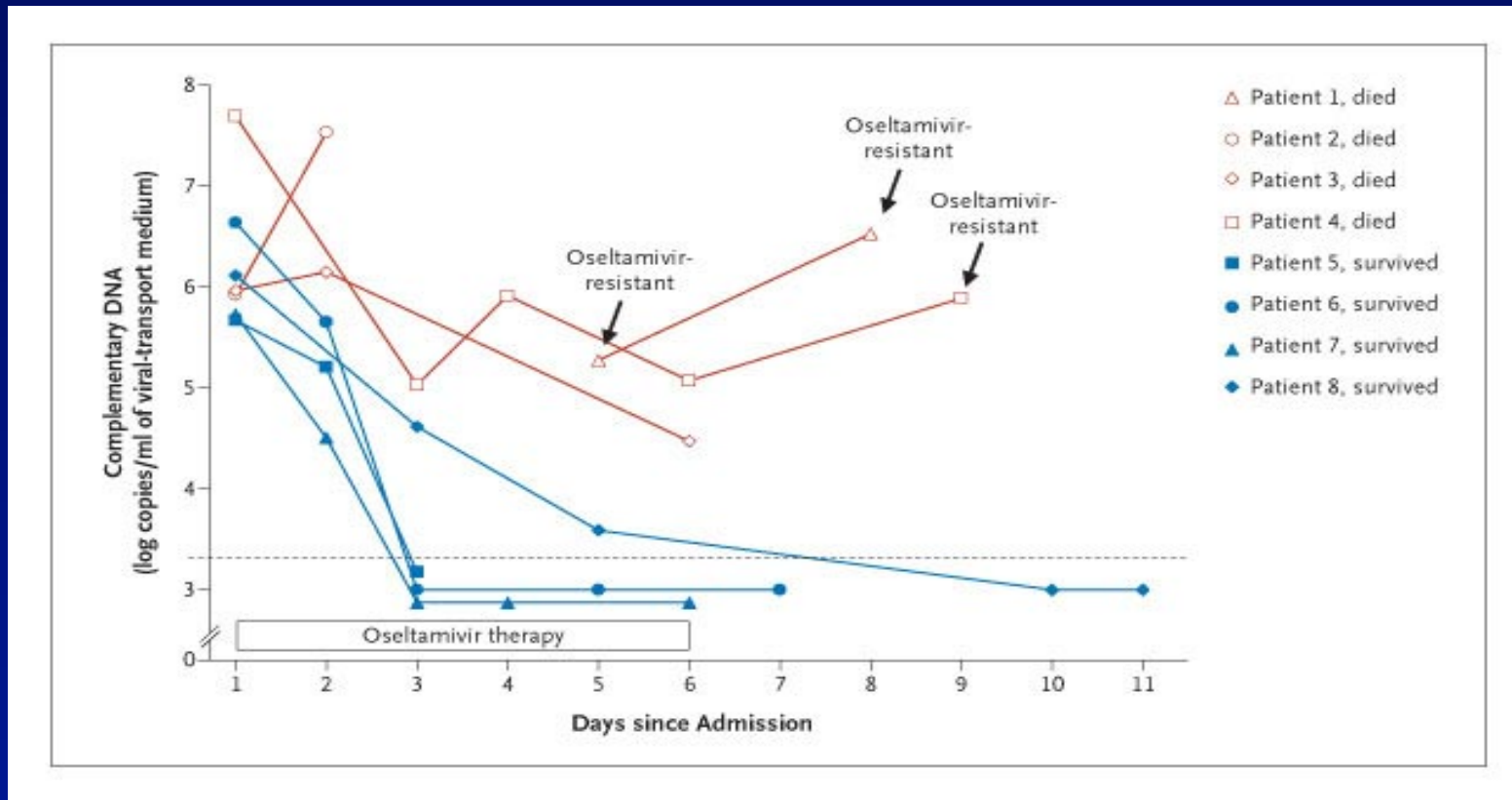
Accepted for publication November 30, 2010.

From the *Departments of Paediatrics, National University of Singapore,

samples taken for drug resistance (**H275Y**) testing while he was on oseltamivir. His infection eventually resolved and was limited to a mild upper respiratory tract infection. As his fever settled after oseltamivir was started, no screening for bacterial coinfection was thought necessary as his condition had improved.

Patient C.Y.Z. was a 4-year-old Chinese boy with common variable immunodeficiency syndrome. He was initially admitted for 5 days (January 8–12, 2010) for presumed community-acquired pneumonia for which he received ceftriaxone followed by amoxicillin-clavulanate. An influenza reverse transcription polymerase chain reaction (RT-PCR) test done during this admission (January 8, 2010) was negative for all viral subtypes. Blood cultures were also negative. He was readmitted on January 15, 2010 as he had a new onset of fever up to 40°C. On admission, his total white cell count was $11.2 \times 10^9/L$, with absolute lymphopenia ($0.47 \times 10^9/L$). His repeat chest radiograph showed further progression with additional right lung infiltrates and left lower lobe consolidation. During this time, *Pseudomonas aeruginosa* and *Streptococcus pneumoniae* (serotype 23 F) were cultured from sputum (January 15, 2010). The child had not had any previous pneumococcal vaccination. Intravenous ceftazidime and amikacin were given from January 15 to 22, 2010. He was started on a standard 5-day course of oseltamivir (20 mg twice daily, January

Oseltamivir Resistant H5N1 influenza in Vietnam



de Jong, M. D. et al. *N Engl J Med* 2005;353:2667-2672

Avian
Flu




The NEW ENGLAND
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Panic....

Top 10 Leading Products: 2005, 1st Quarter

Source: IMS Quarterly Market Brief
<http://www.imshealthasia.com/1311.html#spore>

2005, 1 st Quarter	Tamiflu
2005, 1 st Quarter	Subutex
2005, 1 st Quarter	Norvasc
2005, 1 st Quarter	Plavix
2005, 1 st Quarter	Lipitor
2005, 1 st Quarter	Propecia
2005, 1 st Quarter	Ciprobay
2005, 1 st Quarter	Recormon
2005, 1 st Quarter	Fosamax
2005, 1 st Quarter	Neupogen

 Singapore	Top 10 Corporations	Top 10 Products
	Roche Group Pfizer GlaxoSmithKline Group Sanofi-Aventis Group Merck Sharp & Dohme AstraZeneca Novartis Group Schering Plough Group J&J Group Eli Lilly	Tamiflu Norvasc Plavix Subutex Lipitor Fosamax Recormon Augmentin Gemzar Neupogen
Total Pharma Market		
	MAT 2Q 2005	MAT 2Q 2004
	LC: 516 million US: \$308 million	LC: 469 million US: \$280 million

http://www.zuelligpharma.com/ip/ip_4_7_ims_singapore.html

<http://www.imshealthasia.com/1311.html>

It turned out to be swine flu not bird flu...

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Singapore reports 12th H1N1-related death

By Rekha | Posted: 21 August 2009 20:04 hrs

SINGAPORE: A 41-year-old male foreigner is Singapore's latest H1N1-related fatality, and the 12th so far.

The Health Ministry said the man had a history of diabetes. The cause of his death at Tan Tock Seng Hospital was certified as pneumonia due to H1N1 flu infection.

The ministry added that the number of patients seeking help at polyclinics for acute respiratory infection has decreased.

The ministry, which tracks the cases on a weekly basis, said the number had dropped from some 20,435 for the week starting August 2, to 15,486 for the week starting August 9.

It added that the data from the influenza bio-surveillance programme showed that the proportion of H1N1 flu cases detected among patients with influenza-like illness seen at polyclinics, GP clinics and hospitals in the week of August 2 continued to remain above 50 per cent.

- CNA/yt



Photos 1 of 1 [<](#) [||](#) [>](#)

Special Report

- [Flu Outbreak](#)



THE BUTTER FACTORY

HOME EVENTS BLOG PHOTO GALLERY DJs VIP ART ABOUT MAILING LIST

YOU SAY PARTY! WE SAY RAVE! | 12TH MAR SAT

SAT 12 MAR YOU SAY PARTY! WE SAY RAVE! DJs: KURT, SHAWN LIVEWIRE & THE LFK. FASH One of Singapore's most infamous dance

Events



Original Article

Outbreak of Novel Influenza A (H1N1-2009) Linked to a Dance Club

Pei Pei Chan,¹BSc (Hons), Hariharan Subramony,¹MBBS, Florence YL Lai,¹MPhil, Wee Siong Tien,¹BSc (Life Sciences) (Hons), Boon Hian Tan,¹BSc (Life Sci) (Hons), Suhana Solhan,¹BSc (Phar) (Hons), Hwi Kwang Han,¹BEoHS, Bok Huay Foong,¹BA, Lyn James,¹MBBS, MMed (PH), FAMS, Peng Lim Ooi,¹MSc, MPH, FAMS

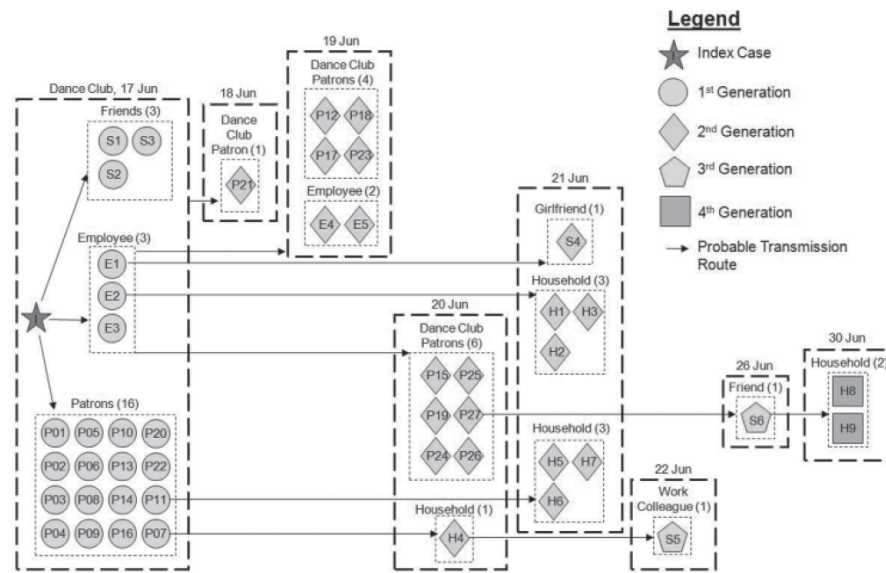
Abstract

Introduction: This paper describes the epidemiology and control of a community outbreak of novel influenza A (H1N1-2009) originating from a dance club in Singapore between June and July 2009. **Materials and Methods:** Cases of novel influenza A (H1N1-2009) were confirmed using in-house probe-based real-time polymerase chain reaction (PCR). Contact tracing teams from the Singapore Ministry of Health obtained epidemiological information from all cases via telephone. **Results:** A total of 48 cases were identified in this outbreak, of which 36 (75%) cases were patrons and dance club staff, and 12 (25%) cases were household members and social contacts. Mathematical modelling showed that this outbreak had a reproductive number of 1.9 to 2.1, which was similar to values calculated from outbreaks in naïve populations in other countries. **Conclusion:** This transmission risk occurred within an enclosed space with patrons engaged in intimate social activities, suggesting that dance clubs are places conducive for the spread of the virus.

Ann Acad Med Singapore 2010;39:299-302

Key words: Contact tracing, Control, Epidemiology, Mathematical modelling

Transmission of Influenza A H1N1 (2009) in 48 cases linked to the Dance Club outbreak, 16 – 30 Jun 09



* Numbering of each case is based on onset of illness in chronological order e.g. P01 had an onset of illness before P02.

Fig. 1. Pictogram on the transmission of the 48 cases linked to the dance club outbreak.

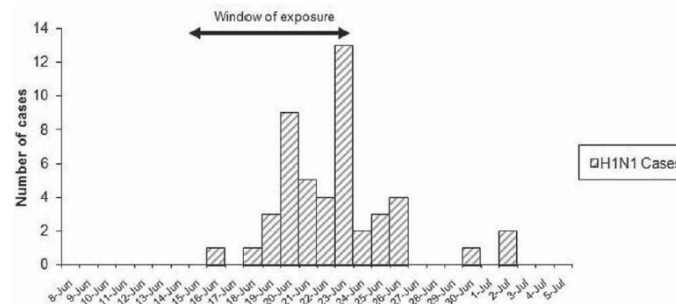


Fig. 2. Onset chart of 48 influenza A (H1N1-2009) cases linked to the dance club outbreak.

News

Press Releases

91 new confirmed cases of Influenza A (H1N1-2009)

03 Jul 2009

Situational Report

Singapore has confirmed 91 new cases (879th – 969th case) of Influenza A (H1N1-2009) today, bringing the total tally to 969 confirmed cases. Investigation are on-going for the remaining 97 cases. Of the 89 cases investigated yesterday there were 61 local cases and 28 imported cases.

Coping with Influenza A (H1N1- 2009)

2. H1N1 is now a global pandemic. It is widely circulating in all countries and communities. The virus is here to stay, just like other influenza strains. Fortunately, the current strain remains mild, except for high-risk individuals with underlying medical conditions where complications and even deaths may occur. Our focus is on caring for those with more severe illness.

3. Many countries no longer track the number of infected cases or report them. The listing of countries with reported confirmed cases is therefore becoming misleading.

4. Likewise, travel advisory is also becoming less useful as the risk of picking up the virus at home or in any other country has evened. That is why the WHO does not recommend any travel advisory.

5. Instead, the approach in managing this virus should be largely based on personal responsibility. All Singaporeans should observe good personal hygiene at all times. If they are unwell with flu-like symptoms (fever, cough, sore throat,

Breakdown of Total Confirmed Cases

DETAILS OF NEWLY INVESTIGATED CASES

Classification	New cases	Total
(1) LOCAL	61	504
A) Community clusters		
Riverlife Church	0	10
Butter Factory	0	44
Workplace	0	3
Republic Polytechnic	4	95
Fishermen of Christ Church	0	13
Maju Camp	0	23
NUS Orientation Camp	0	6
Pulau Tekong Camp	1	10
Clementi Camp	1	58
Police Coast Guard (Brani Base)	1	8
Social (Party)	0	4
Social (Tour Group)	10	16
Raffles Institution Boarding	0	4
Jurong Camp	1	7
NUH Cluster	4	5
B) Local transmission from imported case.	1	17
C) Unlinked	38	181
(2) IMPORTED	28	368
TOTAL	89	872



Press Releases



SAF STEPS UP MEASURES AGAINST H1N1 VIRUS



1. In view of the community spread of the H1N1 virus in Singapore and confirmed cases among Singapore Armed Forces (SAF) personnel, the SAF is putting in place additional measures which have been planned for against the H1N1 virus. These measures will ensure that the SAF maintains its operational readiness, our servicemen will be protected against the H1N1 virus, and the training of our servicemen will continue.
2. Measures that will be taken SAF-wide to detect cases early include active surveillance for flu-like illness as well as implementing daily temperature monitoring regime and self declaration by SAF personnel if they feel unwell. All SAF medical centres are H1N1-ready based on the criteria established by the Ministry of Health (MOH). The SAF medical centres are also stocked with the Tamiflu prophylaxis to treat infected personnel. In addition, these centres are equipped with rapid test kits to diagnose H1N1 cases.
3. Servicemen who are confirmed to be infected with the H1N1 virus will be referred to public hospitals for treatment. Personnel who have been in close contact with infected servicemen will be issued with a Home Quarantine Order in accordance to MOH policies. They will monitor their temperature twice daily and provide daily updates on their condition to their units. This is in line with existing MOH guidelines.
4. To prevent the further spread of the virus, units with infected servicemen will be physically separated from the other units in the same camp. The premises of the infected units will also be disinfected. Additional measures which will be taken include systematically screening for the H1N1 virus in all personnel exposed and nasal swabs for virus-testing, and prescription of the Tamiflu prophylaxis.
5. The SAF will continue to monitor the situation and emphasise the importance of social responsibility, vigilance and personal hygiene to all its personnel.



WAR ON SARS PARLIAMENT

Home quarantine orders

No more leniency: Tough penalties await those who break the rules

Clearly in no mood to tolerate socially irresponsible behaviour, the Government yesterday spelt out what it expects of those served with home quarantine orders — and showed just how tough it is prepared to get from now. M. NIRMALA explains:

**DO THE
RIGHT
THING**

facility in case individuals tried to outsmart the authorities.

Mr Lee said the quarantine system had to be watertight: "It takes only one undeclared contact, one irresponsible breach of a home quarantine order, to start a whole new cluster of infections.

"It is therefore absolutely essential that those served with HQOs obey the orders

and stay at home, and not put many others at risk."

DON'T TRY TO LEAVE THE COUNTRY

INDIVIDUALS on home quarantine orders cannot leave the country.

Once they are quarantined, their details will be flagged with the immigration authori-

ties, and any such person attempting to leave Singapore will be detained.

"We recognise the emotional anxiety and fear that some of these persons on home quarantine orders may be facing," said the Home Affairs Minister.

"But, to win this battle against Sars, we cannot afford any kinks in our armour," he added.

"Otherwise, we put the whole community at risk, and the consequential impact will be disastrous."

NAMING AND SHAMING IN PUBLIC

RECALCITRANTS and defaulters should definitely be named and shamed, said Health Minister Lim Hng

Kiang. "I think we should publish these names and shame them, because otherwise such Singaporeans will continue not to do what is necessary of them," he said, echoing a sentiment expressed by many Singaporeans who felt this was the only way to get irresponsible Sars-affected individuals to behave.

TAGGED IF YOU STILL LEAVE HOME

ANY individual who breaches a home quarantine order will no longer just be issued with a warning. He will be electronically tagged immediately. At last count, 14 people broke quarantine orders by venturing outside their homes.

TAGGED IF YOU DON'T PICK UP THAT PHONE

INDIVIDUALS are checked via electronic cameras installed in their homes.

They need to turn on the cameras when Cisco officers make their telephone checks. But some refuse to answer.

As of now, a quarantined person who does not pick up the telephone after a third call is made by Cisco officers will be electronically tagged.

Nine people have already been tagged as they could not be contacted after three calls.

After amendments are made to the Infectious Dis-

eases Act, those who break the rules can also be given composition fines of up to \$5,000 instead of being charged in court.

The general penalty for committing an offence under the Act will also be doubled, to a maximum of \$10,000 or six months' imprisonment for a first offence, and \$20,000 or 12 months' imprisonment for a repeat offence.

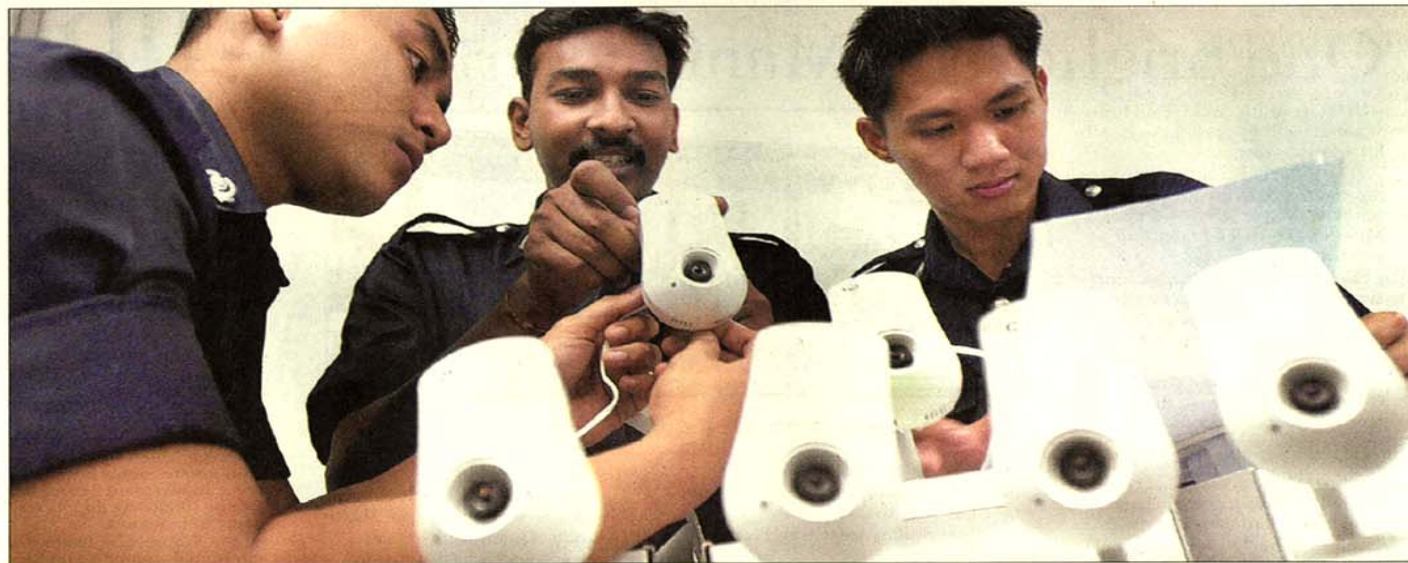
CALL-FORWARDING TRICKS ARE OUT

SMART alics who think they can use a telephone's call-forwarding facility and be somewhere else can think again.

Anyone on a home quarantine order and who has this service will have it cut for the duration of their quarantine.

"Let me tell you: Don't try," Home Affairs Minister Wong Kan Seng warned.

Deputy Prime Minister Lee Hsien Loong had said that someone had alerted him to deal with the call-forwarding



Those under home quarantine will be under watchful eyes to make sure they stay at home — with the help of electronic cameras.

WANG HUI FEN

Selected Trials of Prophylaxis with the Use of Neuraminidase Inhibitors

Table 3. Selected Trials of Prophylaxis with the Use of Neuraminidase Inhibitors.

Study and Drug	No. of Patients	Characteristics of Patients	Setting of Prophylaxis	Reduction in Incidence of Influenza*
Zanamivir				
Monto et al. ³¹	1107	Healthy adults	Seasonal prophylaxis in the community	69% (laboratory-confirmed influenza)
Cooper et al. ¹³	Pooled number	Healthy adults	Prophylaxis after exposure in household	81%
Oseltamivir				
Hayden et al. ³²	1559	Healthy adults	Seasonal prophylaxis in the community	87% (laboratory-confirmed influenza); 74% (influenza-like illness)
Welliver et al. ³⁰	955	Teenagers and adults (>12 yr)	Prophylaxis after exposure in household	89% (laboratory-confirmed influenza); 84% (disease in the household)
Hayden et al. ²⁹	812	All ages (including children >1 yr)	Prophylaxis after exposure in household	68% (laboratory-confirmed influenza) (85%, excluding patients who tested positive at start of prophylaxis); children, 55% (80%, excluding patients who tested positive at start of prophylaxis) †
Peters et al. ³⁶	548	Elderly persons (>80% vaccinated against influenza)	Seasonal prophylaxis in institutional setting	92% (laboratory-confirmed influenza)

* Influenza was defined as both laboratory-confirmed influenza and influenza-like illness, unless otherwise indicated.

† Results were compared with the treatment of index cases.

Moscona A. N Engl J Med 2005;353:1363-1373



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Adverse Drug Reaction

Published by the Centre for Drug Administration, HSA and the HSA Pharmacovigilance Advisory Committee

Oseltamivir and neuropsychiatric events

Monitor patients on oseltamivir for signs of unusual behaviour

Oseltamivir (Tamiflu®, Roche) is an antiviral agent licensed by HSA in October 2000 for the treatment of uncomplicated acute illness due to influenza infection (influenza A & B) in adults and children ≥ 1 year old who have been symptomatic for no more than two days and for the prophylaxis of influenza in adults and children ≥ 13 years old.

Recent post-marketing reports of CNS disorders^{1,2}

The Health Sciences Authority (HSA) has reviewed the data from the 103 post-marketing reports of neuropsychiatric adverse events suspected to be associated with oseltamivir received between August 2005 to July 2006. These include events such as delirium with prominent behavioural disturbances (n=60) and suicidal events (n=6) including self-injury and suicidal ideation.

The majority of the cases were reported from Japan (92%) and were predominantly for the treatment of influenza (97%). These were primarily among paediatric patients (67%) with an age range of 1.5 to 17 years old. There were three deaths: a 14 year-old boy and two adults who fell to their deaths. The patients who died were healthy before contracting influenza



Local situation

HSA has received three adverse drug reactions suspected with use of oseltamivir. They are one report of hepatitis, and another of nausea and urticaria. There is also one report of a middle-aged male who committed suicide by falling to his death. He was prescribed oseltamivir at 75mg twice a day for flu and the adverse event was reported to have occurred on the 7th day.

The causality however could not be established as it was reported that the patient was also taking other medications.

coincident p
Japan or a
Additionally
depressed l
encephalitis
to Tamiflu®

Nonetheless:
adverse eve
positive de-

recovery from neuropsychiatric adverse effects once oseltamivir was discontinued and/or lack of positive neuro-imaging findings in the reviewed reports (n=25), the local prescribing information of Tamiflu® will be updated to warn of the potential for the occurrence of neuropsychiatric adverse events. In addition, it also advised that patients with flu, particularly children may be at an increased risk of self-injury and confusion shortly after taking Tamiflu® and should be closely monitored for signs of unusual behaviour.

Ring
prophylaxis
worked
for
smallpox



REWARD - RECOMPENSE

\$ 10000

Smallpox Variole ОСПА Viruela Smittkoppor

The World Health Organization offers US \$ 1000 to the first person reporting an active smallpox case resulting from human-to-human transmission and confirmed by laboratory tests. Valid until global eradication is certified.

L'Organisation mondiale de la Santé offre une récompense de US \$ 1000 à la première personne qui signalera un cas actif de variole résultant d'une transmission d'un être humain à un autre et confirmé en laboratoire. Cette offre est valable jusqu'à la certification de l'éradication mondiale.

天花 चेचक Furuqa Ndui الجدرى

Original Article

Oseltamivir Ring Prophylaxis for Containment of 2009 H1N1 Influenza Outbreaks

Vernon J. Lee, M.B., B.S., M.P.H., Jonathan Yap, M.B., B.S., Alex R. Cook, Ph.D., Mark I. Chen, M.B., B.S., Ph.D., Joshua K. Tay, M.B., B.S., Boon Huan Tan, Ph.D., Jin Phang Loh, M.Sc., Seok Wei Chew, B.Sc., Wee Hong Koh, B.Sc., Raymond Lin, M.B., B.S., Lin Cui, Ph.D., Charlie W.H. Lee, M.Sc., Wing-Kin Sung, Ph.D., Christopher W. Wong, Ph.D., Martin L. Hibberd, Ph.D., Wee Lee Kang, M.B., B.S., M.Med., Benjamin Seet, M.B., B.S., M.P.H., and Paul A. Tambyah, M.D.

N Engl J Med
Volume 362(23):2166-2174
June 10, 2010



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Summary of the Four Outbreaks of 2009 H1N1 Influenza and Efficacy of Oseltamivir Prophylaxis and Other Interventions

Table 1. Summary of the Four Outbreaks of 2009 H1N1 Influenza and Efficacy of Oseltamivir Prophylaxis and Other Interventions.*

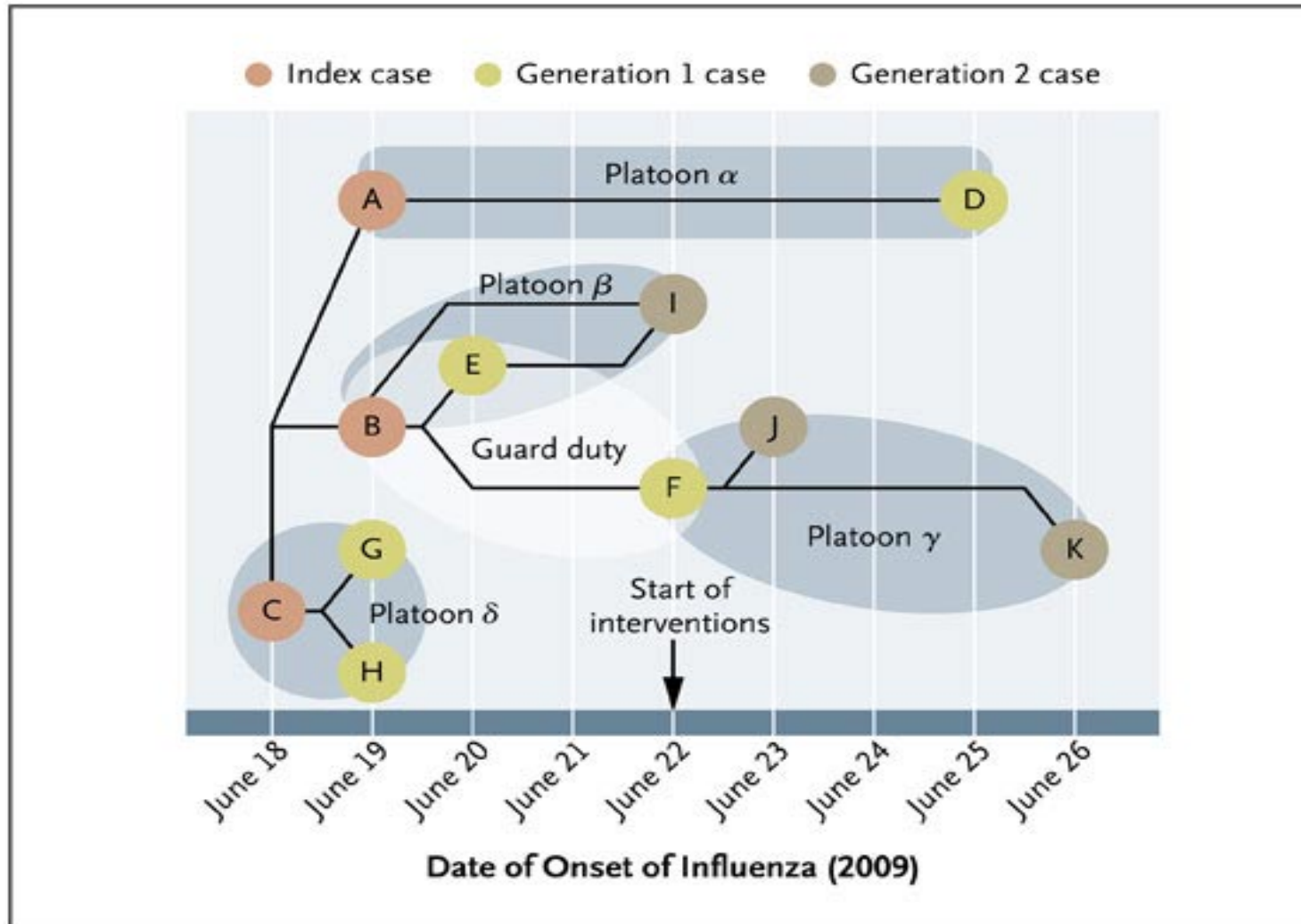
Variable	Total	Outbreak 1	Outbreak 2	Outbreak 3	Outbreak 4
Total no. of personnel	1175	216	47	219	693
Confirmed cases — no. (%)	82 (7.0)	11 (5.1)	6 (12.8)	2 (0.9)	63 (9.1)
Before intervention — no. (%)	75 (6.4)	8 (3.7)	6 (12.8)	2 (0.9)	59 (8.5)
After intervention — no. (%)	7 (0.6)	3 (1.4)	0	0	4 (0.6)
Posterior hypothesis probability	<0.001	0.11	<0.001	<0.001	<0.001
Symptomatic personnel (excluding confirmed cases)					
Tested and negative — no. (%)	23 (2.0)	11 (5.1)	0	1 (0.5)	11 (1.6)
Not tested — no. (%)	47 (4.0)	3 (1.4)	0	4 (1.8)	40 (5.8)
Mild respiratory symptoms only	40 (3.4)	1 (0.5)	0	4 (1.8)	35 (5.1)
Reported fever with respiratory symptoms	7 (0.6)	2 (0.9)	0	0	5 (0.7)
Completion of oseltamivir prophylaxis — no./total no. (%)†	929/974 (95.4)	185/205 (90.2)	41/41 (100)	186/193 (96.4)	517/535 (96.6)
Confirmed cases and symptomatic personnel who were not tested‡					
Total — no./total no.	115/1161	14/216	6/47	5/218	90/680
Before intervention — no./total no. (%)	85/1161 (7.3)	10/216 (4.6)	6/47 (12.8)	3/218 (1.4)	66/680 (9.7)
After intervention — no./total no. (%)	30/1076 (2.8)	4/206 (1.9)	0	2/215 (0.9)	24/614 (3.9)
Posterior hypothesis probability	<0.001	0.02	<0.001	0.09	<0.001

* The posterior hypothesis probabilities were calculated for the comparison of the incidence of infection before intervention and after intervention, as described in the Supplementary Appendix.

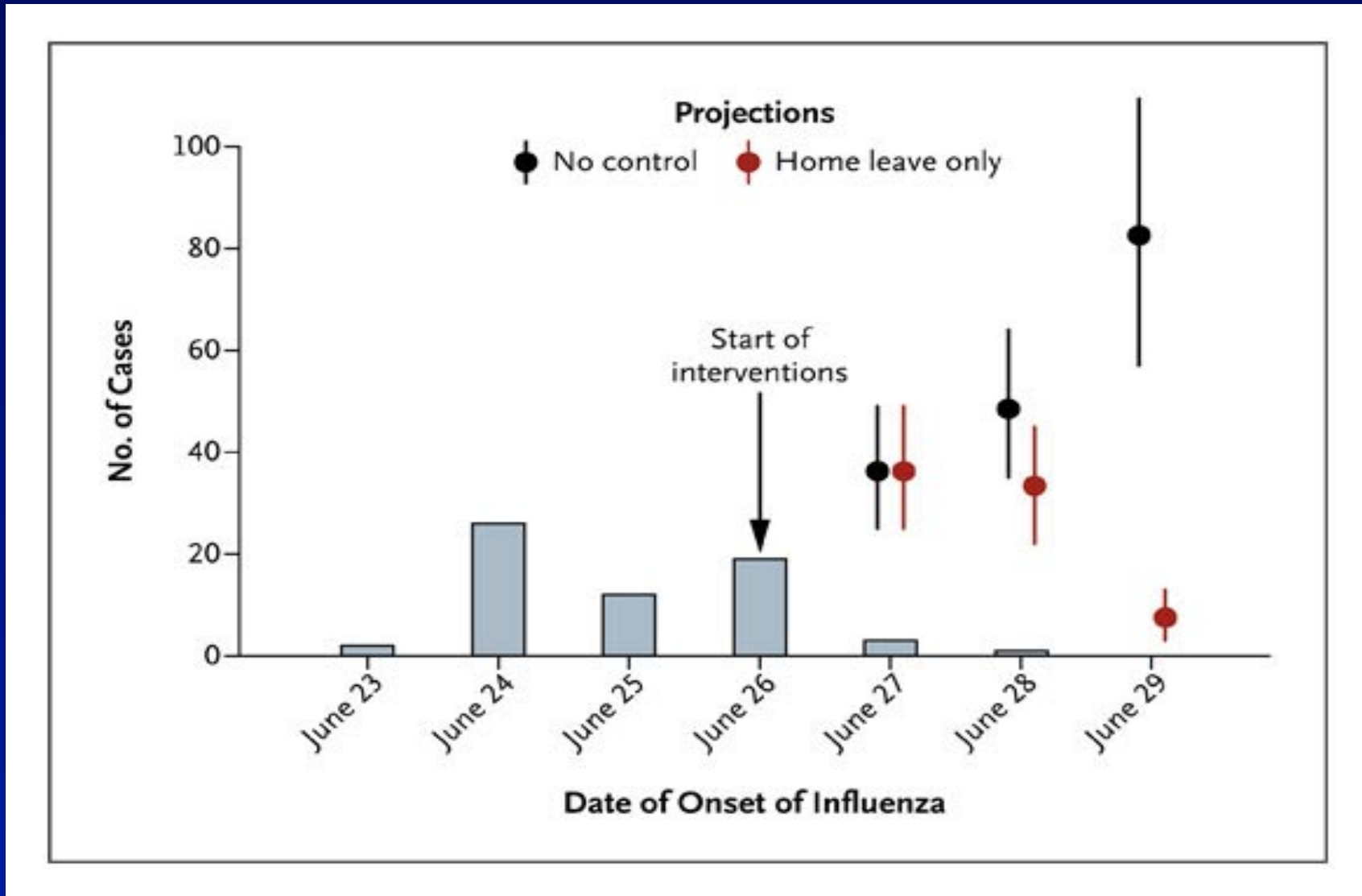
† The number of subjects who completed the oseltamivir prophylaxis regimen excludes those with confirmed infections and those who could not be contacted.

‡ The number of confirmed cases and symptomatic personnel who were not tested excludes 14 symptomatic personnel who could not remember the date of onset of their illness. The percentage of confirmed cases and symptomatic personnel who were not tested before intervention is based on the total number with data; the percentage after intervention is based on the total number with data minus the number identified before intervention.

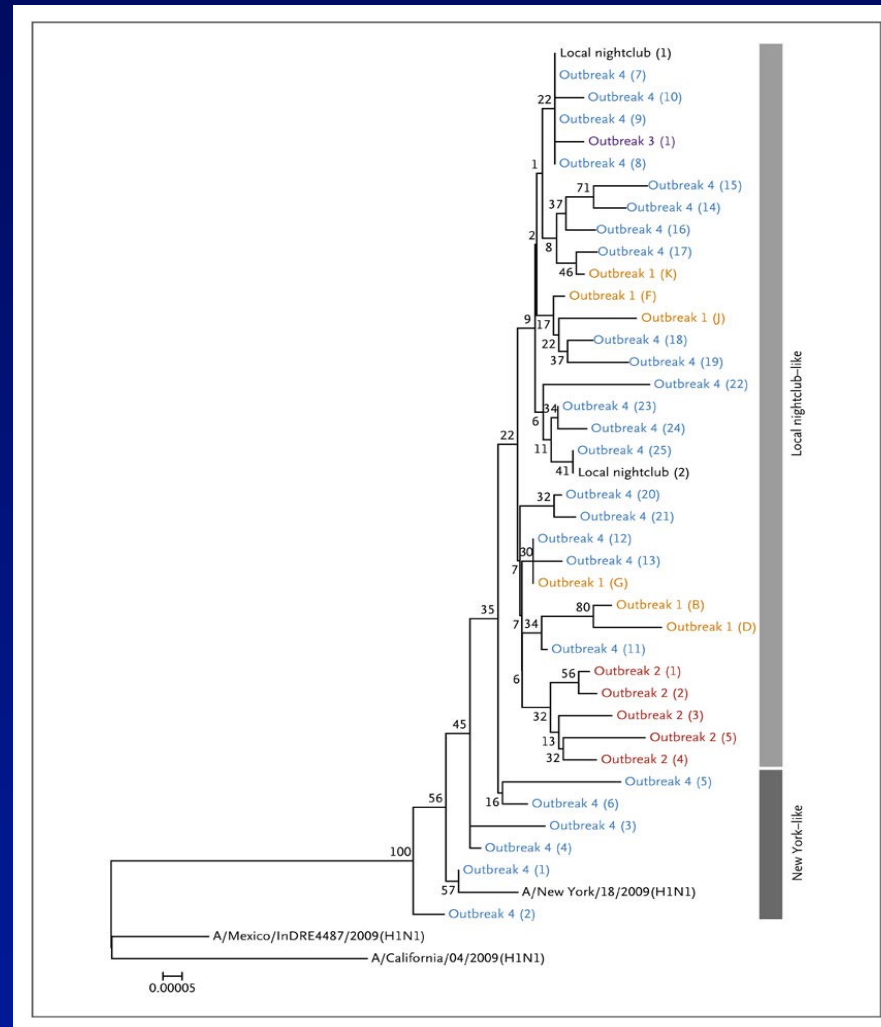
Timing of Events and Cases during Outbreak 1, According to Date of Onset of Influenza



Epidemiologic Data and Model Projections for Outbreak 4, According to Date of Onset of Influenza



Phylogenetic Relationships among the Viruses Identified during the Four Outbreaks with the Use of Whole-Genome Sequencing



Side Effects of Oseltamivir Prophylaxis

Table 2. Side Effects of Oseltamivir Prophylaxis.

Side Effect	Personnel (N = 816)
	<i>no. (%)</i>
Diarrhea	14 (1.7)
Headache	9 (1.1)
Nausea or vomiting	22 (2.7)
Dizziness	5 (0.6)
Epigastric pain	4 (0.5)
Drowsiness	8 (1.0)
Mild allergic reaction (rash)	6 (0.7)

Lee VJ et al. N Engl J Med 2010;362:2166-2174



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Conclusion

- Oseltamivir ring chemoprophylaxis, together with prompt identification and isolation of infected personnel, was effective in reducing the impact of outbreaks of 2009 H1N1 influenza in semiclosed settings



RESEARCH

Effect of double dose oseltamivir on clinical and virological outcomes in children and adults admitted to hospital with severe influenza: double blind randomised controlled

 OPEN ACCESS

South East Asia Infectious Disease Clinica

Table 4 Risk factors identified by conditional multiple logistic regression for being viral RNA negative by RT-PCR on day five. Important non-significant factors are also included. Patients with no detected influenza were excluded from analysis

Factor	No of patients*	No of events*	OR (95% CI)	P value
Nose viral load†	304	213	0.73 (0.62 to 0.86)	<0.01
Karnofsky score <50‡	35	15	0.24 (0.08 to 0.78)	0.02
Child	236	49	0.62 (0.17 to 2.22)	0.46
Double dose oseltamivir	156	112	1.27 (0.73 to 2.20)	0.39
Virus type:				
B	51	36	0.88 (0.32 to 2.41)	0.80
H3N2	132	91	0.72 (0.30 to 1.70)	0.45
H5N1	15	2	0.03 (0.00 to 0.64)	0.03
H12009	68	57	1.01 (0.34 to 2.97)	0.99
H1N1-pdm	38	27	Reference	—

RT-PCR=reverse transcriptase polymerase chain reaction.

*Total number of patients in group and total number negative for viral RNA by RT-PCR on day 5; 304 patients with 213 events were included in analysis.

†After $\log_{10}(x+1)$ transformation, odds ratio corresponds to change in odds associated with 10-fold increase in viral load.

‡Patients with score <50 require frequent medical attention.

Combinations???

- Oseltamivir and Amantadine
 - More effective in combo than alone, no emergence of resistance
 - *Gourokova et al Antivir Ther. 2007;12(3):363-70*
- ***Oseltamivir and Ribavirin***
 - ***More effective in combo***
 - *Smee DF et al Antivir Chem Chemother. 2006;17(4):185-92.*
- *Both in Mouse models*

Combination therapy with amantadine, oseltamivir and ribavirin for influenza A infection: safety and pharmacokinetics

Sachiko Seo¹, Janet A Englund², Jack T Nguyen³, Sasithon Pukrittayakamee⁴, Niklas Lindegardh^{4,5}, Joel Tarning^{4,5}, Paul A Tambyah⁶, Christian Renaud^{1,2}, Gregory T Went³, Menno D de Jong⁷, and Michael J Boeckh^{1,*}

Table 1

Pharmacokinetic parameters for AMT, OSL carboxylate and RBV administered alone or in combination in healthy volunteers

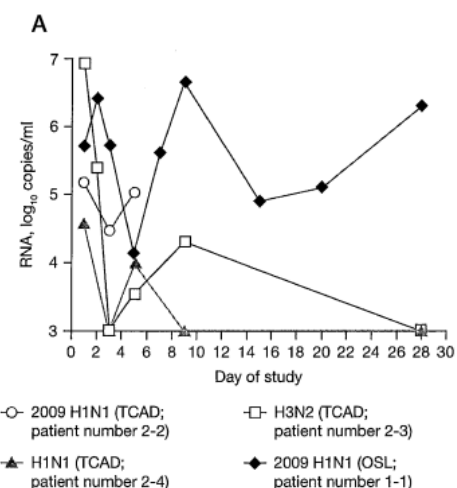
Parameter	Group 1		Group 2		Group 3	
	AMT alone 100 mg (n=14)	AMT TCAD 100 mg (n=14)	OSL carboxylate alone 75 mg (n=13)	OSL carboxylate TCAD 75 mg (n=14)	RBV alone 600 mg (n=14)	RBV TCAD 600 mg (n=14)
C _{max} , ng/ml	361 (268–482)	349 (264–402)	271 (208–386)	274 (151–375)	971 (496–2,550)	945 (364–2,220)
T _{max} , h	1.50 (0.500–4.00)	1.75 (1.00–6.00)	4.00 (2.00–6.00)	6.00 (4.00–6.00)	1.00 (0.500–1.50)	1.25 (0.500–3.00)
CL/F, l/h	19.4 (13.3–37.7)	19.1 (11.0–34.6)	20.8 (16.0–25.5)	20.5 (15.9–25.4)	26.8 (13.4–37.0)	22.0 (12.9–53.8)
V/F, l	265 (181–439)	266 (214–361)	186 (141–253)	193 (145–312)	4,050 (2,820–7,260)	3,450 (2,500–8,060)
T _{1/2} , h	8.87 (6.24–22.9)	9.04 (6.47–22.9)	6.26 (5.00–8.99)	6.57 (5.09–8.59)	111 (90.3–281)	105 (84.4–183)
AUC _{0–last} , hxng/ml	5,060 (2,630–7,330)	5,140 (2,830–8,890)	3,160 (2,580–4,130)	3,220 (2,520–4,190)	16,400 (11,800–27,000)	19,800 (8,460–25,800)
AUC _{0–inf} , hxng/ml	5,150 (2,650–7,530)	5,240 (2,900–9,140)	3,270 (2,670–4,250)	3,330 (2,680–4,280)	22,300 (16,200–44,700)	27,200 (11,200–46,600)

Values are reported as median (range).

Geometric mean ratios^a in healthy volunteers

Parameter	Group 1 amantadine (n=14) geometric mean ratio (90% CI)	Group 2 oseltamivir carboxylate (n=13) geometric mean ratio (90% CI)	Group 3 ribavirin (n=14) geometric mean ratio (90% CI)
C _{max} , ng/ml	93.8 (87.0, 101)	94.2 (87.1, 102)	97.8 (81.2, 118)
AUC _{0–last} , hxng/ml	107 (97.7, 118)	98.5 (94.2, 103)	102 (93.3, 110)
AUC _{0–inf} , hxng/ml	107 (97.8, 118)	98.3 (94.8, 102)	96.6 (82.0, 114)

Table 1 continued: Pharmacokinetic parameters (range) in patients





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Antiviral therapies on the horizon for influenza

Lieve Naesens, Annelies Stevaert and Evelien Vanderlinden



Adequate response to outbreaks requires vaccination and M2 blocker clinical efficacy in past three years pipeline and 2 trials. For anti-hemagglutinin the viral polymerase instrumental insights also influenza A polymerase therapy should

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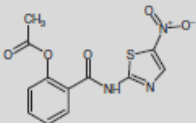
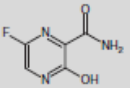
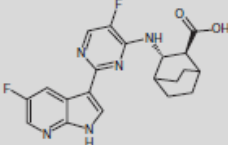
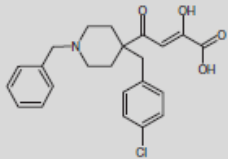
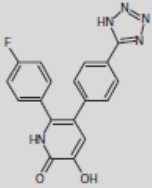
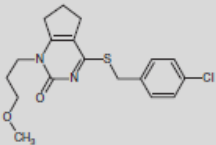
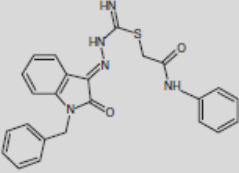
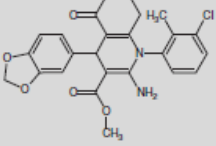
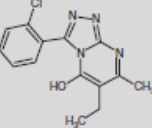
Table 1			
Prototypic influenza inhibitors in various stages of (pre)clinical development			
Name and structure	Proposed action principle ^a	Status ^b	References
Hemagglutinin inhibitors – broadly-neutralizing antibodies			
CR6261	Binds to stem region of A/group 1 HA ⁴⁵	Phase 2	[13,14]
CR8020	Binds to membrane-proximal stem region of A/group 2 HA ⁴⁵	Phase 2	[13,14]
MH1AA4549A	Binds to HA stem epitope conserved in influenza A	Phase 2a	[18,19]
VIS410	Engineered antibody; binds to HA stem epitope conserved in influenza A	Phase 2a	[64]
Hemagglutinin inhibitors – small molecules			
Nitsozanide	Interferes with virus maturation	Phase 3	[23,24]
			
Polymerase inhibitors			
Favipiravir (T-705)	Nucleobase inhibitor ^c ; causes RNA chain termination and virus mutagenesis	Approved (Japan) Phase 3 (US/EU)	[31–37]
			
VX-787 (JNJ-872)	Blocks the PB2-CBD of influenza A ⁴⁸	Phase 2b	[38 ^{**} , 40]
			
L-742,001	Metal-chelating inhibitor of PA endonuclease ⁴⁹	Experimental	[48–51]
			

Table 1 (Continued)			
Name and structure	Proposed action principle ^a	Status ^b	References
Compound 7 ^c	Metal-chelating inhibitor of PA endonuclease ⁴⁹	Experimental	[52]
			
AL-794 (structure undisclosed) S-033188 (structure undisclosed) 367	PA inhibitor PA inhibitor Unknown (PB1?) ^d	Phase 1 Phase 2 Experimental	[53]
			
ASN2	Unknown (PB1?) ^d	Experimental	[54]
			
Compound 1 ^c	Inhibits PA ₂ -PB1 ₂ assembly	Experimental	[57,58] ^e
			
ANA-1	Inhibits PA ₂ -PB1 ₂ assembly	Experimental	[59]
			

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RNA Polymerase Inhibitors

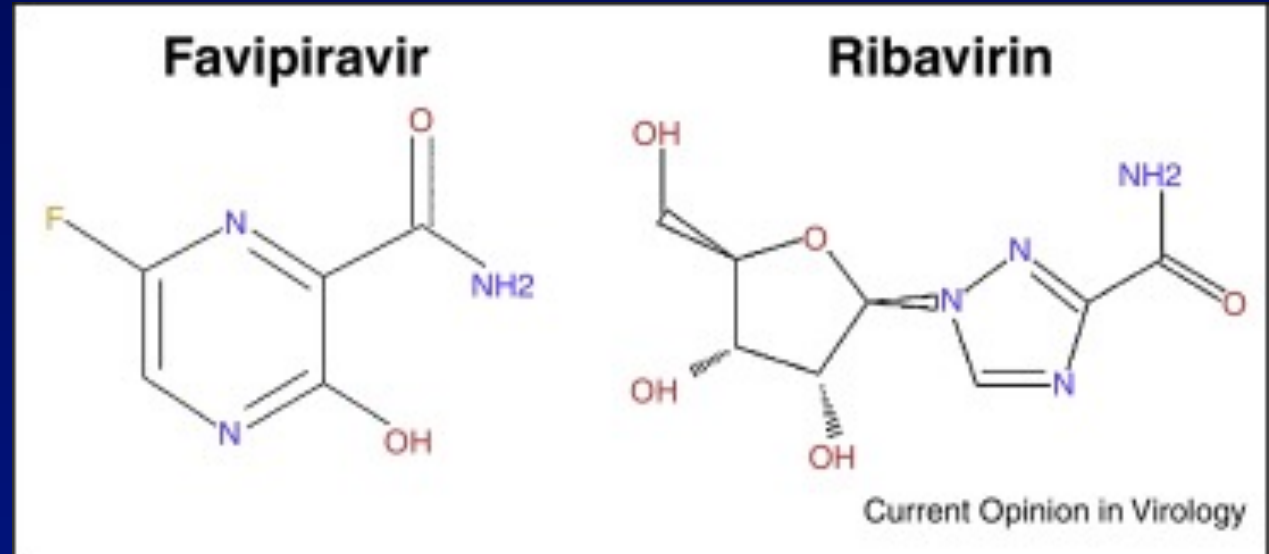


Figure 3. Nucleoside analogs that inhibit RNA-dependent RNA polymerase. Favipiravir and ribavirin are nucleoside analogs that shown broad-spectrum inhibitory activity for multiple RNA viruses.

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Current and novel antiviral strategies for influenza infection

Current Opinion in Virology, Volume 18, 2016, 126–134

NP active compounds

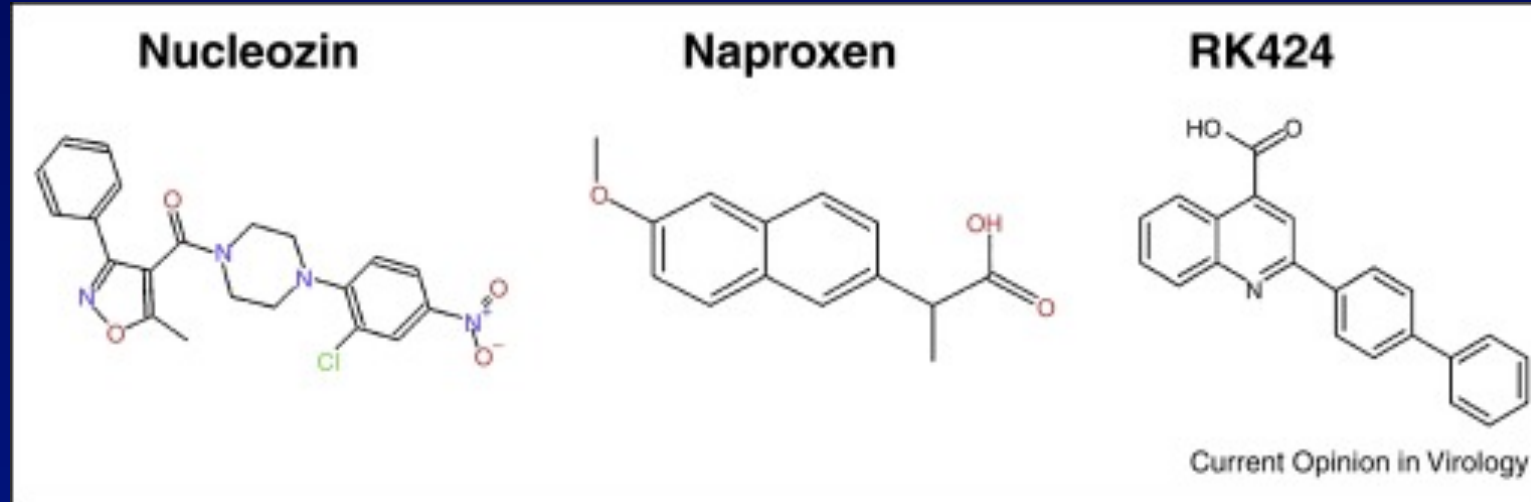


Figure 4. Inhibitors that interfere NP–NP or NP–RNA interactions. Nucleozin and RK424 were identified via high-throughput screening; naproxen that inhibits cyclooxygenase I and II were identified through virtual screening.

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Current and novel antiviral strategies for influenza infection

Current Opinion in Virology, Volume 18, 2016, 126–134

PB2/PA active compounds

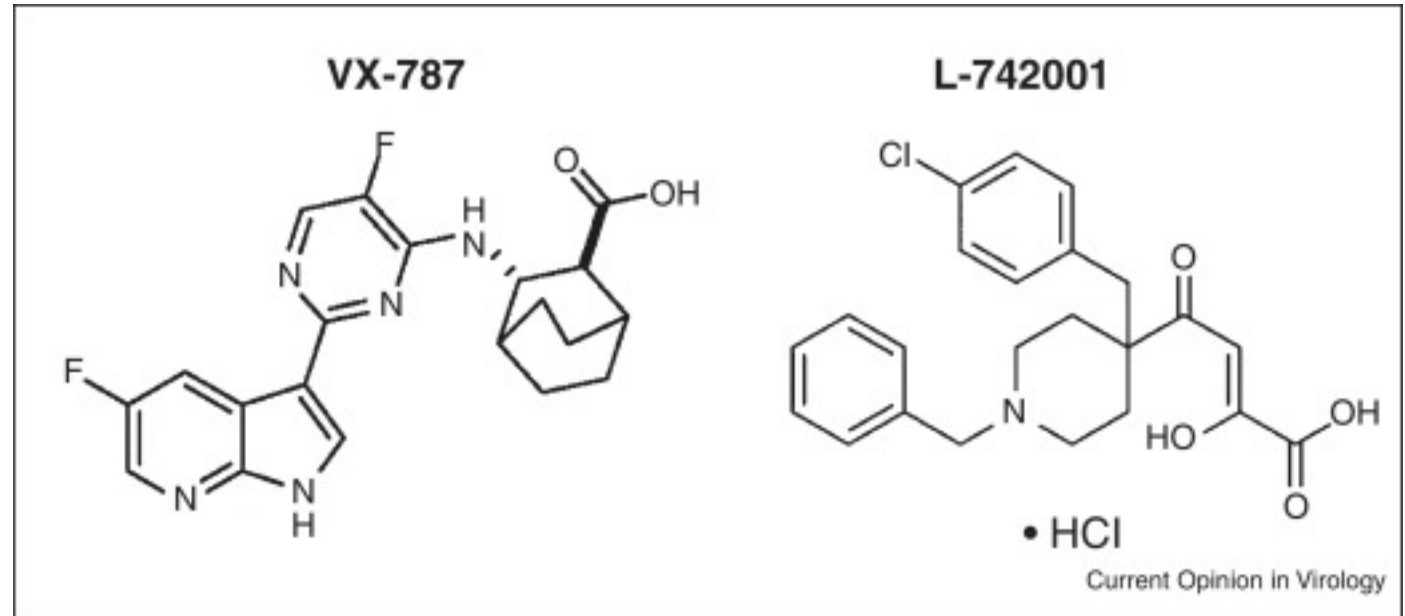


Figure 5. Small molecules that inhibits PB2 cap-binding and PA endonuclease activity.

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Current and novel antiviral strategies for influenza infection

Current Opinion in Virology, Volume 18, 2016, 126–134

Preclinical Activity of VX-787, a First-in-Class, Orally Bioavailable Inhibitor of the Influenza Virus Polymerase PB2 Subunit

Randal A. Byrn,^a Steven M. Jones,^a Hamilton B. Bennett,^a Chris Bral,^b Michael P. Clark,^c Marc D. Jacobs,^d Ann D. Kwong,^g Mark W. Ledebroer,^c Joshua R. Leeman,^a Colleen F. McNeil,^a Mark A. Murcko,^h Azin Nezami,^d Emanuele Perola,^e Rene Rijnbrand,^a Kumkum Saxena,^d Alice W. Tsai,^f Yi Zhou,^a Paul S. Charifson^c

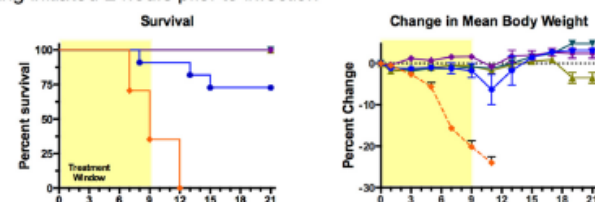
Departments of Infectious Diseases,^a Drug Safety Evaluation,^b Chemistry,^c Protein Sciences,^d Computational Sciences,^e and Drug Metabolism and Pharmacokinetics,^f Vertex Pharmaceuticals Incorporated, Boston, Massachusetts, USA; InnovaTID Pharmaceuticals, Cambridge, Massachusetts, USA^g; Disruptive Biomedical, LLC, Holliston, Massachusetts, USA^h

VX-787 is a novel inhibitor of influenza virus replication that blocks the polymerase complex. Viral genetics and X-ray crystallography studies identified VX-787 as a potent inhibitor of the 7-methyl GTP (m^7GTP) cap-binding site of PB2. VX-787 binds to the polymerase complex with a dissociation constant (K_d) of 24 nM as determined by isothermal titration calorimetry. VX-787 is active against influenza A virus (H1N1pdm09 and H5N1 strains, as well as strains with reduced susceptibility to oseltamivir, including in delayed-start-to-treat experiments, and is highly efficacious in both prophylaxis and treatment models of mouse influenza infection. VX-787 is active against influenza A virus replication in vivo in groups where the initiation of therapy was delayed up to 12 hours post-infection, resulting in a mean survival of 100% and a mean viral load reduction of >5 -log (relative to vehicle controls) in non-lethal challenge experiments. VX-787 is a novel antiviral agent for the treatment of influenza infection.

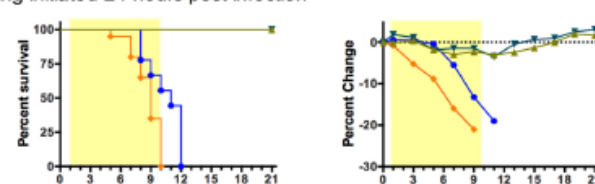
Citation: Byrn RA, Jones SM, Bennett HB, Bral C, Clark MP, Jacobs MD, Kwong AD, Ledebroer MW, Leeman JR, McNeil CF, Murcko MA, Nezami A, Perola E, Rijnbrand R, Saxena K, Tsai AW, Zhou Y, Charifson PS. 2015. Preclinical activity of VX-787, a first-in-class, orally bioavailable inhibitor of the influenza virus polymerase PB2 subunit. *Antimicrob Agents Chemother* 59:1569–1582. doi:10.1128/AAC.04623-14.

Address correspondence to Dr. P.S. Charifson, paul.charifson@vertex.com.

A. Dosing initiated 2 hours prior to infection



B. Dosing initiated 24 hours post infection



C. Dosing initiated 96 hours post infection

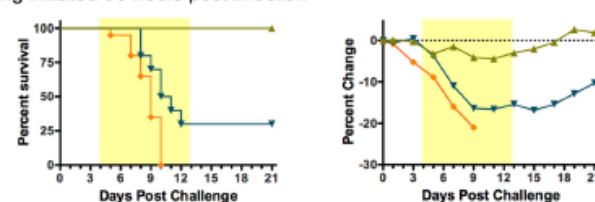


FIG 9 Prophylactic or delayed-start-to-treat effectiveness of VX-787 in the mouse influenza A/Viet Nam/1203/2004 (H5N1) virus infection model. Male BALB/c mice (8/group) were infected with a lethal challenge of influenza virus followed by administration of vehicle, oseltamivir, or VX-787 at the indicated doses and start times. The 21-day survival rate and percent BW loss (means \pm SEM) are shown. The shaded area represents the treatment period.

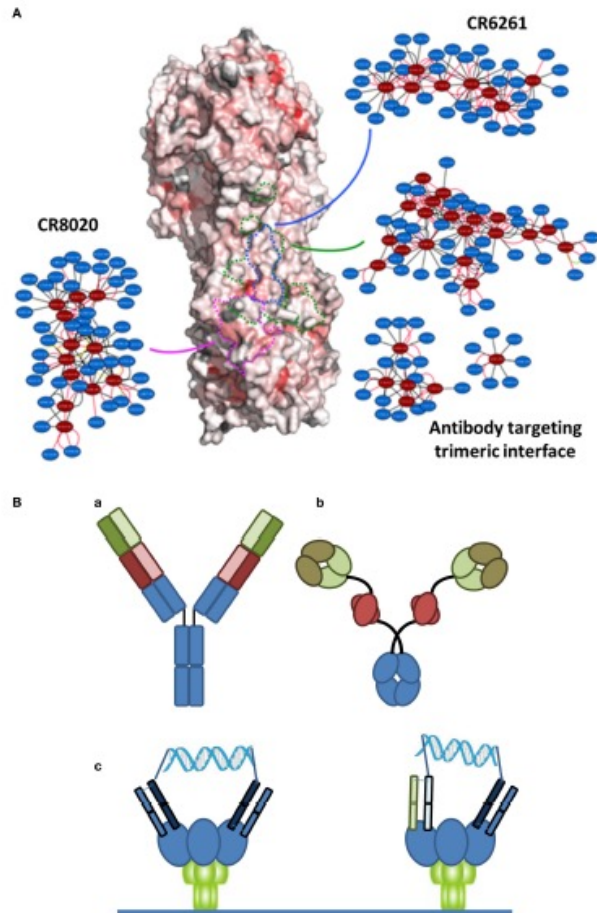


FIGURE 1 | (A) Network-view of bNAbs epitopes. HA trimer is represented in a solvent accessible surface format and colored based on normalized residue network scores. Coloring varies from white to red where white indicates poorly networked residues and red indicates highly networked residues. The three bNAbs epitopes are highlighted by dotted borderlines (green: antibody targeting trimeric interface; blue: CR6261; pink: CR8020). The 2D network map of the epitope is also shown. A network is made up of nodes and edges. Nodes colored in red indicate functional epitope residues whereas nodes colored in blue indicate residues that are in the network environment of the epitope

residues. **(B)** Different bispecific formats that have demonstrated activity against infectious disease targets. (a) A dual-variable domain immunoglobulin format containing two distinct Vh-Vl pairings (one in red and one in green) has demonstrated activity against hepatitis B. (b) A bispecific format where a single chain variable region against Pst (red) targets the antibody to the cell surface of *Pseudomonas* enables engagement of a traditional Vh-Vl paratope with the rarer PorV target. (c) Crosslinking of binding domains of variable and constant regions (NH₂-CH₁/VL-CL; Fabs), either homotypic (left) or heterotypic (right) with a defined DNA-based spacer enables more potent neutralization of HIV virus.

Antibody-based strategies to prevent and treat influenza

Zachary Shriver¹, Jose M. Trevejo¹ and Ram Sasisekharan^{2,3*}








¹ Visterra Inc., Cambridge, MA, USA, ² Department of Biological Engineering, Koch Institute of Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA, USA, ³ Infectious Diseases Interdisciplinary Research Group, Singapore-MIT Alliance for Research and Technology, Singapore, Singapore

TABLE 1 | Recent discoveries in broadly neutralizing antibodies to influenza.

Antibody	Target	Breadth	Development
CR6261	Stem region/HA	Group 1	Phase II
CR8020	Stem region/HA	Group 2	Phase II
CR9114	Stem region/HA	Group 1/group 2	Pre-clinical
F10	Stem region/HA	Group 1	Pre-clinical
F16	Stem region/HA	Group 1/group 2	Pre-clinical
TCN-032	M2	Group 1/group 2	Phase II
MHAA4549A	Stem region/HA	Group 1/group 2	Phase II
CH65	Receptor binding site/HA	H1	Pre-clinical
VIS410	Stem region/HA	Group 1/group 2	Phase II

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Funding Rounds (6) - \$75.44M

UPDATE

Date	Amount / Round	Valuation	Lead Investor	Investors
Oct, 2014	\$30M / Series B	—	Temasek Holdings Vertex Ventures	8
Dec, 2013	\$8.1M / Series A	—	—	5
Nov, 2012	\$26.1M / Series A	—	—	5
Aug, 2010	\$6M / Debt Financing	—	—	3
		—	—	0
		—	—	1

Participates in Visterra's Series B financing

Earlier this month, Temasek Holdings as well as its 100%-owned subsidiary Vertex Venture Holdings, participated in the \$30 million series B financing of biotechnology company Visterra Inc.

“The Series B financing round was co-led by new Visterra investors, Merck Research Labs Venture Fund, Vertex Venture Holdings Ltd. and Temasek. Existing investors – Polaris Partners, Flagship Ventures, Omega Funds and Alexandria Venture Investments – and a new investor, Cycad Group, also participated in this upsized financing,” Visterra had said in a statement, while adding that the proceeds would be ‘used to advance the development of multiple product candidates from the company’s pipeline of monoclonal antibodies that target infectious diseases, including VIS410 for seasonal and pandemic influenza and VIS513 for dengue fever’.

Vertex Venture Holdings Ltd, which also participated in this round of fund raising, is a wholly-owned subsidiary of Temasek, investing in emerging companies across Greater Asia and selectively in US and Europe.

Safety, potential efficacy, and pharmacokinetics of specific polyclonal immunoglobulin F(ab')₂ fragments against avian influenza A (H5N1) in healthy volunteers: a single-centre, randomised, double-blind, placebo-controlled, phase 1 study



Céline Bal, Cécile H Herbretau, Philippe Buchy, Sareth Rith, Masliza Zaid, William Kristanto, Velda Han, Charlotte Reynaud, Patrick Granjard, Bertrand Lépine, Caroline Durand*, Paul A Tambyah*

Summary

Background Human infection with the avian influenza against which antiviral treatments have limited efficacy.

	C _{max} (µg/mL)	T _{max} (h)	AUC ₀₋₂₄ (µg/mL×h)	AUC _{0-∞} (µg/mL×h)	AUC ₀₋₉₆ (µg/mL×h)	%AUC _{0-∞}	t _{1/2} (h)
Day 1, stage 1							
Number of participants	3	3	3	3	3	3	3
Mean (SD)	19.3 (3.5)	1.0 (0.0)	203.0 (20)	247.0 (88)	305.0 (76)	20.2 (10.7)	16.8 (7.9)
% CV	18.3%	0%	9.8%	35.7%	25.0%	53.0%	47.1%
Day 1, stage 2							
Participants	10	10	10	10	10	10	10
Mean (SD)	19.3 (4.7)	1.0 (0.0)	185.0 (34)	188.0 (34)	241.0(55)	21.2 (6.1)	10.9 (2.4)
% CV	24.5%	0%	18.5%	18.0%	22.7%	28.8%	22.3%
Day 5, stage 2							
Participants	10	10	10	10	10	10	Nd
Mean (SD)	23.0 (4.5)	1.0 (0.0)	298.0 (61)	678.0 (213)	804.0(288)	14.7 (6.4)	Nd
% CV	19.4%	0%	20.6%	31.5%	35.9%	43.4%	Nd

C_{max}=maximum plasma concentration. T_{max}=time of maximum plasma concentration. t_{1/2}=half-life in plasmatic compartment. AUC=area under the concentration-time curve. AUC_{0-∞}=AUC in steady state. AUC_{0-t}=AUC from administration to last observed concentration at time t. AUC₀₋₉₆=AUC area under the plasma concentration curve extrapolated to infinite time. CV=coefficient of variation. Nd=not determined.

Table 3: Pharmacokinetic data

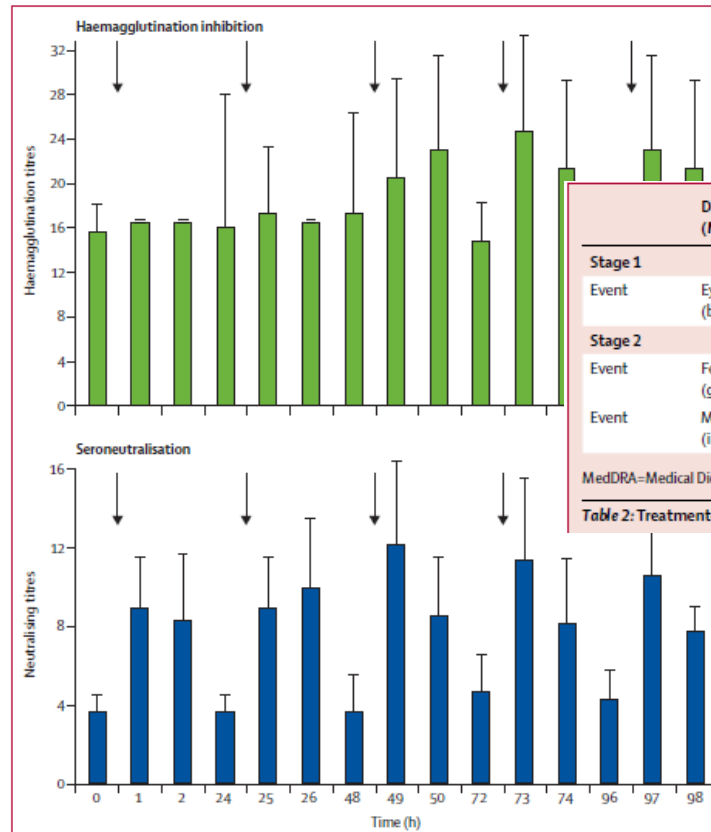


Figure 4: Haemagglutination inhibition and neutralising titres after five infusions of FBF001. Data are means (bars show SD). Titres measured in patients after five doses of FBF001 at 0 h, 24 h, 48 h, 72 h, and 96 h (arrows) in study phase 2.

Lancet Infect Dis 2015; 15: 285-92

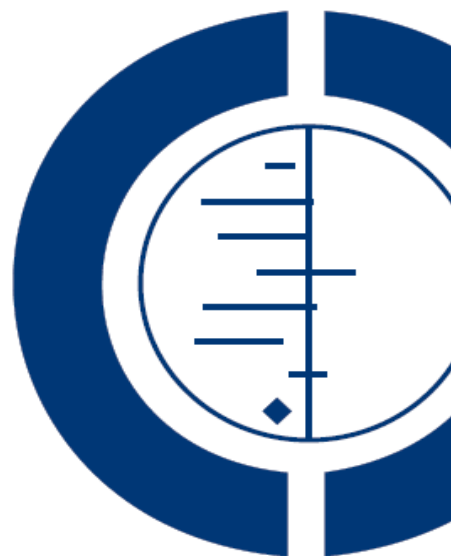
	Description (MedDRA term)	Start	Finish	Duration	Intensity	Relation with treatment?
Stage 1						
Event	Eyelid twitching (blepharospasm)	Day 4	Day 6	2 days	Mild	Unlikely
Stage 2						
Event	Febrile reaction (general disorders)	Day 3	Day 3	37 min	Mild	Probable
Event	Mild sinusitis (infections)	Day 13	Day 23	10 days	Mild	Unlikely

MedDRA=Medical Dictionary for Regulatory Activities.

Table 2: Treatment-emergent adverse events

Chinese medicinal herbs for influenza (Review)

Chen XY, Wu TX, Liu GJ, Wang Q, Zheng J, Wei J, Ni J, Zhou LK, Duan X, Qiao JQ



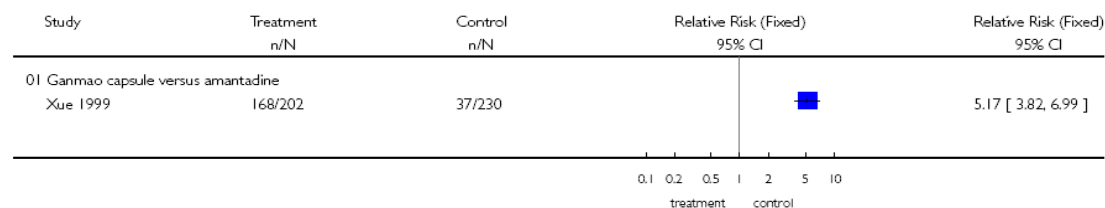
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Analysis 01.01. Comparison 01 Day 2 recovery rate, Outcome 01 Herbal medicine versus antiviral drugs

Review: Chinese medicinal herbs for influenza

Comparison: 01 Day 2 recovery rate

Outcome: 01 Herbal medicine versus antiviral drugs

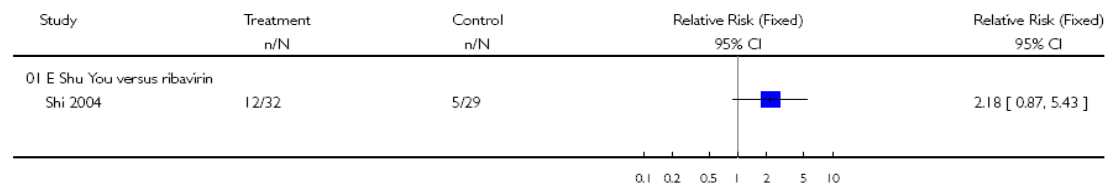


Analysis 02.01. Comparison 02 Day 3 recovery rate, Outcome 01 Herbal medicine versus antiviral drugs

Review: Chinese medicinal herbs for influenza

Comparison: 02 Day 3 recovery rate

Outcome: 01 Herbal medicine versus antiviral drugs



Compliance is an issue

A systematic review of factors affecting intended and actual adherence with antiviral medication as treatment or prophylaxis in seasonal and pandemic flu

Louise E. Smith¹ | Donatella D'Antoni² | Vageesh Jain¹ | Julia M. Pearce³ | John Weinman² | G. James Rubin¹

TABLE 6 Predictors of uptake of antivirals identified in relation to the COM-B model of behaviour change

Capability	Motivation	Opportunity
<p><i>Psychological</i></p> <ul style="list-style-type: none"> • Knowledge of the virus • Amount of information received about the virus • Information seeking behaviours • Increased attention to information about virus • Forgetting 	<p><i>Reflective</i></p> <ul style="list-style-type: none"> • Perception of virus and associated risks • Perception of antivirals and associated risks (response efficacy) • Belief of necessity of precautionary behaviour • Self-efficacy • Perceived personal consequences of flu • Positive attitude towards prevention of flu 	<p><i>Physical</i></p> <ul style="list-style-type: none"> • Losing pills • Not having enough pills
<p><i>Physical</i></p> <ul style="list-style-type: none"> • Difficulty swallowing pills 	<p><i>Automatic</i></p> <ul style="list-style-type: none"> • Habitual behaviour of previous compliance with precautions • Emotion—fear (of antivirals, and of side effects of antivirals) • Emotion—anxiety 	<p><i>Social</i></p> <ul style="list-style-type: none"> • Trust in government • Speaking to someone who has experienced side effects previously

The aim of this review was to identify factors predicting actual or intended adherence to antivirals as treatment or prophylaxis for influenza. Literature from inception to March 2015 was systematically reviewed to find studies reporting predictors of adherence to antivirals and self-reported reasons for non-adherence to antivirals. Twenty-two studies were included in the review; twenty identified through the literature search and six through other means. Of these studies, 18 assessed predictors of actual adherence to antivirals, whereas eight assessed predictors of intended adherence. The most commonly found predictor of, and self-reported reason for, non-adherence was the occurrence of side effects. Other predictors include perceptions surrounding self-efficacy, response efficacy and perceived personal consequences as well as social influences of others' experiences of taking antivirals. Predictors identified in this review can be used to help inform communications to increase adherence to antivirals for both seasonal and pandemic influenza.

KEYWORDS
 adherence, antivirals, influenza, pandemic

TABLE 5 (Continued)

Citation	Outcome measures	Intended adherence with oseltamivir	Predictors of adherence (significant results in bold)	Risk of bias
Yap et al. ¹⁴ ; Phern-Chern, personal communication	Oseltamivir as effective treatment and prevention for pandemic influenza	85.5% (970/1134) would complete a course of oseltamivir if prescribed for pandemic influenza	Univariate analysis: Female sex, older age group, exposure group (patients, contacts, HCW vs general individuals), ethnicity (Malay, Indian vs Chinese) , education, role in military, private housing, adverse events, higher knowledge score , practice score Multivariate analysis: sex, age, exposure group patients, Malay ethnicity ($\beta = 3.30$, 95% CI [0.67–5.92, $P = .014$], higher knowledge scores ($\beta = 0.21$, 95% CI [0.14–0.28], $P < .001$), practice score	B, C
Quinn et al. ²⁷	Attitudes towards pandemic influenza. Willingness to accept an EUA drug	54.5% (869/1519) probably/definitely would accept Tamiflu for self. 48.8% (276/521) probably/definitely would accept Tamiflu for child.	Refusal to accept vaccine. Ethnicity – accept drug for self ($P < .01$) and child ($P < .05$) . Age (18–34) – accept drug for child ($P < .001$) . Prior history of having flu vaccine - accept drug for self ($P < .001$). Knowledge and attitudes towards pandemic. Language from a CDC factsheet. Perceived personal consequences – accept drug for self ($P < .05$) . Trust in government – accept drug for self ($P < .001$) and child ($P < .05$) . Healthcare status. Worry about EUA drug – accept drug for self ($P < .001$) and child ($P < .001$) . Dispensed by non-health professional. Lower level of education (when dispensed by public health professional: $P = .01$)	B

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of oseltamivir "consumed" between 2009/2010 and 2012/2013, the majority of these during the pandemic.³

In an effort to gauge oseltamivir adherence in one area of the UK during the pandemic, Singer et al.⁴ measured levels of the active metabolite of oseltamivir in wastewater. When comparing these levels with the number of prescriptions collected, adherence was estimated to be in the range of 45%–60%. The repercussions of non-adherence to antiviral medication are widespread, including the monetary cost of unused antivirals,⁴ a longer duration of absenteeism from work and the potential implication of more drastic measures such as school closures, household quarantine and restrictions on travel. In the UK, the cost of school closure alone is estimated at £0.2–£1.2 billion.⁵ Other health implications of non-adherence to antivirals include possible



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Meeting report

Meeting report: 4th ISIRV antiviral group conference: Novel antiviral therapies for influenza and other respiratory viruses



Jennifer L. McKimm-Breschkin ^{a,*}, Alicia M. Fry ^b

^a CSIRO, 343 Royal Parade, Parkville, Australia

^b Influenza Division, Ctr 22

J.L. McKimm-Breschkin, A.M. Fry / Antiviral Research 129 (2016) 21–38

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Flu spreads fast The time for antivirals is short

1957 "Asian Flu" Dr Lim Kok Ann

THE LANCET] PUBLIC HEALTH [OCT. 19, 1957 7

Most of the chronic sick are elderly, but unfortunately there is a small minority of young people among them. It is, as the Minister says, "wholly unsatisfactory" for them to be nursed for, "perhaps, the greater part of a life-time in the company of older patients in all stages of terminal illness or of much greater ages." He asked regional hospital boards to consider how far these patients could be grouped together without losing touch with their own families.

The Minister reminded the local authorities that there were still many people—it had been estimated at 4500—who were occupying hospital beds but who could be in residential homes if they were available. A smaller number of people living in homes would probably benefit by being moved to hospital. These ill-used beds showed the need for closer co-operation between hospitals and the local services, which should cover not only the patients on the hospitals' waiting-lists but also the patients who had returned to their homes. Both of these groups stood in special need of the help of the domiciliary health services. These, the Minister thought, though generally adequate, were too thinly spread in some areas and he urged their continued expansion.

The advice which the Minister has offered the hospital and the local authorities was based on Dr. C. A. Boucher's report² on the survey of services for the chronic sick and elderly. This survey was carried out during 1955 in

² *Rep. publ. Hlth med. Subj., Lond.* no. 98, 1957. H.M. Stationery Office. Pp. 60, 3s.

Public Health

INFLUENZA OUTBREAK IN SINGAPORE

K. A. LIM

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ALWYN SMITH

M.B., Ph.D. Birm., D.P.H.

WORLD HEALTH ORGANISATION LECTURER IN EPIDEMIOLOGY, UNIVERSITY OF MALAYA

J. H. HALE

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PROFESSOR OF BACTERIOLOGY, UNIVERSITY OF MALAYA

J. GLASS

B.A. Edin., L.R.C.P.E., D.P.H.

SURGEON COMMANDER, R.N.; PRINCIPAL MEDICAL OFFICER, H.M. DOCKYARD, SINGAPORE

AN outbreak of influenza, which seems to have begun in North China, reached Singapore in May, 1957. Influenza is not notifiable in the island and no reliable figures for overall incidence could be obtained. Moreover, a large proportion of the population does not seek Western-type medical care. Mainly for these reasons, our detailed study of the outbreak has been confined to the civilian population in the Singapore Naval Base, consisting of Naval Base workers and their dependants. The main advantages of this include fairly complete ascertainment of cases from the working population at least, reasonable

each hospital region by teams headed by a principal regional officer of the Ministry. The teams collect opinions as well as facts, and not the least interesting part of the report is the chapter on the views on geriatrics as a specialty. At one extreme it was held that an elderly patient should be treated in the general wards of hospital, and geriatricians were regarded as "mere practitioners of a clinical calibre who could not at all claim equality with other consultants." There was considerable prejudice against geriatric appointments, some ignorance of the possibility of reablement. On the other hand those who supported these appointments were sure that, thanks to them, the pressure on beds would be relieved, and the turnover improved. Many geriatric units had been remarkably successful; some less perhaps because the geriatrician's responsibilities were limited to the daily treatment of patients and because there was lack of junior medical staff and an insufficiency of almoning, physiotherapy, and occupational therapy help. Though geriatrics offers clinical opportunities of unlimited interest and wide opportunities of research the survey found that the recruitment of junior staff remained difficult and senior staff with suitable experience were not always forthcoming. New units would entail appointment of more physicians with a clear understanding of the social and medical problems of the elderly patient, yet the number of registrar appointments in existing units did not seem to meet the demand for such appointments.

data, with certain other observations made in the Singapore Civilian General Hospital in the city.

Clinical Findings

For present purposes, the clinical observations relate to 298 patients with influenza admitted to the Singapore Civilian General Hospital in the city. Criteria of admission were difficult to specify since they depended on many factors (age of the patient, general state of health, availability of beds, &c.). Doctors were asked to assess their cases clinically in three categories—mild, moderate, and severe—but became evident that such classification was difficult and unreliable and it was accordingly dropped.

Table 1 shows the distribution of the 298 admitted cases by age and sex. At the younger ages little difference is seen between the numbers of males and females, but as age increases female cases are fewer. This is probably due to a difference in the numbers seeking treatment rather than in the numbers affected. Table 1 also shows the duration of hospital stay by age. It is clear that hospital stay was longest in the very young and the very young adults had the shortest stay.

Pyrexia

All patients had pyrexia, and they were not discharged until their temperatures had returned to normal. The mean duration of pyrexia over all ages was 2.4 ± 0.87 days and varied little with age.

The mean temperature on admission was 102.9°F and mean highest record was 103.1°F . In 41 of the 298 cases the highest record was higher than the record on admission. The patients with temperatures below 100°F on admission the temperature rose in 63% during their hospital stay.

Scientists say the flu bug is new type

HIGH PRAISE FOR COLONY DOCTOR

MELBOURNE, Thursday. SIR MacFarlane Burnet, director of the Walter and Eliza Hall Institute for Medical Research, said today that a new type of influenza virus was responsible for the epidemic now sweeping the Far East.

FLU VICTIMS BARRED ON MADRAS BOAT

PENANG, Thurs.—Five suspected influenza victims were not allowed to sail from here aboard the State of Madras today.

A family of four were also barred, after the ship's doctor, Dr. A. Rahman, found that the youngest child had measles.

These nine disappointed passengers will leave instead on May 28 for Madras by the same boat. The flu epidemic is still declining throughout Malaya.

'Bomb' protest

TOKYO, Thurs.—Students and Buddhists today began indefinite picket outside United States and British consulates in protest against clear tests.—Reuter.

...OUS AGAIN

...r General Hospital. ...ospital spokesman said ...day she was "progress...g satisfactorily." ...police spokesman told ...e Straits Times that ...as Evaratt would be

Scientists at the institute had established that the virus was a new type of influenza virus A, he said. "This means that the virus formerly known as



DR. LIM

Type A has undergone a sharp change in character," Sir MacFarlane said. He added that serums developed to combat the previously known virus would now be "useless."

'Great credit'

Sir MacFarlane said great credit must be given to Dr. Lim Kok Ann, lecturer in the University of Malaya, for isolating specimens which were examined at the institute.

Sir MacFarlane will confer tomorrow with the head of the Commonwealth Serum Laboratory on plans to produce a new serum. Commenting on reports

Dr. Lim, the flu fighter, says:

It was a case of teamwork really



DR. LIM KOK ANN, the University of Malaya virologist who isolated the virus which is causing the flu epidemic, yesterday modestly disclaimed the praise heaped on him by Australian specialists.

In his laboratory—littered with some of the 400 eggs he has used so far in his researches—Dr. Lim said: "It's really a matter of teamwork—modern research always is."

He added that first credit was due to Dr. W. K. Ng, the rural health officer, who drew his attention to the infection when it first broke out on Pulau Brani.

Dr. Lim has been working 10 hours a day since the end of April on analysing the epidemic.

He expects to continue working so for the next two or three months.

He is trying now to classify in manner in which the virus spread through the different age, social and racial groups.

A graduate of Edinburgh University, Dr. Lim is a chess fanatic in his spare time. He is champion of the Singapore Chess Club and editor of its magazine.

Vaccine on way

On Thursday, Dr. Lim was said by Sir MacFarlane, Chief Director of the Walter and Eliza Hall Institute Medical Research in Melbourne.

Sir MacFarlane said the specimens isolated by Dr. Lim had enabled scientists at the institute to establish that the epidemic sweeping the Far East was caused by a new type of influenza virus.

A vaccine is now developing...



Fish poisoned—

PENANG, Fri.—The Director of Fisheries, Mr. D. W. Le Mare, said today that poisoning of fishing waters was a "royal prerogative."

He was commenting on a report that a fish drive

will be held in the River next week to celebrate the Sultan's jubilee.

Plans for this drive for the control of the river with tubs roots which paralyse the fish. They will then be

HE WILL ADVISE RUBBER MISSION

SCHO

'HE

New rules

PARENTS here of hours which set Monday.

Under a new Federal regulation requiring a minimum number of hours for subjects, particularly schools will work an five hours a week.

To cope with this, some schools will start early as 7.30 a.m. and at 2 p.m.

Afternoon sessions...

ployee, rich or poor, it
made no difference. —
Reuter.

Formosa 'flu epidemic

TAIPEH, Thurs.—Hospitals
in Taipei and Keelung were
officially described as "crowd-
ed" today as an influenza
epidemic continued to spread
in Formosa.

There are 2,000 influenza
victims in Taipei, mostly
school children, and between
3,000 to 4,000 in Keelung. —

Leaflet raid

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WATCH ON FLU EPIDEMIC

The Singapore Minister for
Health, Mr. A. J. Braga, said
yesterday that the Ministry
was "keeping a very close
watch" on the influenza
epidemic.

Hundreds of people have
been hit by the disease be-

lieved to have been spread
by passengers from Hong
Kong.

Mr. Braga told the Straits
Times that the Ministry was
warning children to keep
away from crowded places
where germs could more easi-
ly spread.

May 6, 1957

ST May 3, 1957

May 7

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The Straits Times Newspaper

ESTD. 1845 SINGAPORE, TUESDAY, MAY 7, 1957 13 CENTS

SCHOOLS MAY HAVE TO CLOSE—25,000 PUPILS ABSENT

Health and Education Ministries making urgent review of the situation

SINGAPORE FLU SCARE

Worst ever in Colony history

...of the General ...-striking group

A 'MIRACLE' FLU CURE STARTS RUSH FOR OLIVES

From Page One
 ... last week. The number of daily severe cases was lower than those treated earlier last week.

He gave this advice: "Avoid crowded places and if you do travel, wear your surgical mask."

Meanwhile, a Singapore Chinese newspaper's report of a "miracle" cure for influenza is causing hundreds of Chinese hospitals to buy olives and olive capsules.

The report said influenza can be effectively cured if the juice of the vegetable was drunk after they had been boiled. Students have called in by increasing the price of olives and olive capsules.

Firms hit

Commercial firms were also affected by absenteeism and an extra spokesman reported a rise in the number of people attending sick parades.

A doctor with more than 30 years' experience in Singapore told the Straits Times: "I've never heard of an influenza epidemic anything like this since I've been here."

A spokesman for the Ministry of Education said: "This has sprung upon us as suddenly as lightning and there is nothing to be done."

Only about 30 teachers had reported sick. "If they too were laid up we wouldn't have a hope of carrying on classes," he said.



Malaya's
 National
 Newspaper

HALF-EMPTY CLASSROOMS AS 45,000 PUPILS FALL ILL

162,000 children freed of danger of taking disease home

FLU CLOSES SCHOOLS

Dodge the crowds' advice

SINGAPORE, Monday (By Reuters).—New Singapore Minister for Education, Mr. New Seng Lee, yesterday advised the parents of the Colony's schools from today as a cure to the influenza epidemic—those bringing their children to school from the danger of carrying disease to their homes.

Ministry's own schools will remain shut at least for a week, says a Government statement.

Review of epidemic

The review is expected to appear next Monday in view of the epidemic's progress at the end of the week provides a favourable report.

The new half-empty classrooms all over the Colony are expected to accommodate 45,000 pupils next week.

The Ministry's own schools will remain shut at least for a week, says a Government statement.

Embassy sorry about Red flag incident

JAKARTA, Tuesday.—The U.S. Embassy here today expressed its regret over the Red flag incident.

FLU PATIENTS AGAIN SWAMP CLINICS

☆ From Page One

the epidemic," said an army spokesman.

There had been a "very definite" increase in sick parade attendances by Army staff, he added.

A rumour yesterday swept Chinatown and the Queens-town area that the epidemic had been caused by radioactive fall-out from Russian hydrogen bomb tests.

It was an eager topic for discussion among the superstitious in coffee-shops and on five-foot-ways.

But the university authorities said the rumour was "utter nonsense."

Delayed cables

City Council clinics, dispensaries, private doctors and the General Hospital were again swamped yesterday by patients seeking treatment for their red eyes and feverish temperatures.

One in 25 of the army civilian workers did not turn up for work.

Seven out of eight workers in Chinatown were away with influenza and business was halted.

Cable and Wireless Ltd. appealed to business houses to collect their own cables as more than 20 of their 60 delivery boys were ill.

A spokesman said cable deliveries were heavily delayed as a result.

About 250 workers at the Singapore Harbour Board reported sick.

Six out of the 11 soccer matches scheduled for today have been postponed.

Prof. J.E. Hale, Professor of Bacteriology at the University of Malaya, is trying to discover if the epidemic is more prevalent amongst a certain age or ethnic group.

He has chosen the Naval Base as a target for a survey. St. Hilda's school has announced that its speech day and prize-giving ceremony will be held today as scheduled, but children in primary classes one to four should not attend unless they are prize-winners.

THE FLU epidemic is spreading rapidly in Singapore and the number of patients is increasing steadily.

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Malaya's Largest—Daily 100

FLU SPREADS TO JOHORE: 500 ARE HIT

THE Singapore influenza epidemic has crossed the Causeway to Johore where the number of victims is increasing steadily. The Johore Bahru General Hospital yesterday treated 515 flu patients.

Two doctors and 15 of the nursing staff at the hospital are ill. Several patients have been admitted.

Private clinics have been besieged by parents, clamouring for attention for their children.

In Singapore, as the epidemic continued to affect thousands of Malays, the 17,000 members of the Malaya European community have almost all missed it.

'Phenomenal'
 Most parents agreed that Malays were the worst sufferers owing to their resistance having been lowered by one recent touring month.

A doctor with more than 20 years' experience in the Colony said the spread of the epidemic was "quite phenomenal" the worst he's ever known. "It's so widespread I think it will burn itself out soon."

He agreed with the Minister for Health, Mr. A. J. Straag, who said the epidemic had reached its peak and his ministry had the situation well under control.

The epidemic will cause ☆ See Page 9—Col. 6

THE ROAD MOURNERS



Malaya
National
Newspaper



IN SINGAPORE A BIG POSER: IS THE WORST OVER?

No, say experts: 'It's on increase—people are fainting at work'

FLU BUGS OVER MALAYA

Schools shut in Johore Bahru

Business epidemic is being developed by schools of the State.
A confirmed epidemic of influenza is spreading in Johore Bahru, and the Government has ordered the closure of all schools in the State.
The epidemic is being spread by the schools of the State, and the Government has ordered the closure of all schools in the State.
The epidemic is being spread by the schools of the State, and the Government has ordered the closure of all schools in the State.

EXCLUSIVE TO THE STRAITS TIMES

SPY STORY

The spy story of the war will begin in the Straits Times as an exclusive serial from Monday.
Malaya was set off from the rest of the world when British air ace Leslie Howard was shot down over the Bay of Biscay in June 1940 by the Germans.
He was returning home in a Dakota from a lecture tour of Spain and Portugal.
The Germans had detailed special agents to shadow him and find out the real purpose of his mission in the neutral countries.
But when the news of Howard's death was delivered by

NOW PERL FANS OUT ALONG THE EAST COAST

Doctors fight back: Virus will be flown to London



KUALA LUMPUR, Friday.
AFTER ravaging Johore Bahru and other districts along the West Coast, the influenza epidemic is spreading along the East Coast.
Doctors here are fighting back, and a virus sample will be flown to London for further study.

...ed the bug.

Flu fear: The worst is yet to come

From Page One
having a bad time. I've had reports of them fainting at work."
Both he and Prof. Hale were cautious when asked if the present epidemic was likely to emulate the great world epidemics of the past and be succeeded by another wave of infection, more serious than the first.
Prof. Hale pointed out that this would not become obvious unless the present sickness graph declined and then sharply rose again.
He stressed that, although the epidemic produced debilitating effects for its sufferers and was "probably economically disastrous", there was no cause for alarm as its duration in the case of individuals was only about four days.
The Deputy Director of Education, Mr. R. E. Ince,

said the question of whether or not Singapore schools reopened next Wednesday would depend on the green light being given by the Ministry of Health.
He pointed out that, in any case, Tuesday was a holiday for the Buddhist festival of Wesak.
A further announcement on the schools will be made on Monday.
Some doctors had reduced their rates by using simplified dispensing methods.
Thirty-six of the Singapore Telephone Board's 182 "bell" girls are down with influenza—the highest total so far. Nineteen of the 75 male operators are also ill.
An STB spokesman said that while the service had been affected as a result, the public was adopting a sympathetic attitude, thus helping the remaining operators

who were co-operating "splendidly" under the additional burden thrust upon them.
The Convent in Johore Bahru closed yesterday with 130 of its 1,100 pupils ill. It may re-open on Monday.
Also shut-down are St. Joseph's English School with a fifth of its 500 pupils absent—and the Ngee Heng Primary School which found that, in some classes, only five out of the normal 40 students attended.
A Singapore Government statement says the Minister for Health, Mr. A. J. Braga, is satisfied with the reception and treatment of outpatients at the General Hospital "at a time when a considerable strain is being thrown on the Medical Department by the increase in the volume of work when so many members of the staff are themselves absent from duty."

Bonn insists on A-arms

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Ships. Were y keep old Pulau B Western blasting

Burning car seized



...the car was seized.

MANY INTERESTING ITEMS
HAVE JUST ARRIVED
WE SUGGEST YOU PAY US
A VISIT TO SEE WHAT
WE HAVE NEW.
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The Straits Times

Malaya's
National
Newspaper

Est'd. 1845. SINGAPORE, MONDAY, MAY 13, 1957 ★ 15 CENTS

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ST

NEW CASES REPORTED IN THREE FEDERATION CENTRES

Penang doctors can barely cope: K.L. ready for serious situation

FLU TIGHTENS ITS GRIP

**BUDDHISTS
BEGIN
1,500-YEAR
FESTIVAL**

*35 students in
training
college sick*

SINGAPORE Buddhists
last night began the
annual Vesak festival,
which this year marks
the 2,500th anniversary
of the death of
the Buddha.
Thousands of worshippers
gathered at the Sakya Muni
Buddha Gaya Temple in
Dunlop Road, which
was brilliantly illuminated.

THE influenza epidemic continued to spread
in the Federation yesterday, with new cases
reported from Kuala Lumpur, Penang and
Kota Bharu.
In Singapore the Chief Medical Officer,
Dr. R. Calderwood, said the situation yester-
day was "very much the same" as on Saturday.
In the Federation the worst-hit centre appear-
ed to be PENANG where the number of new cases
yesterday was believed to be double Saturday's.

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...with Service.
...GENERAL ELECTRIC CO. (MALAYA) LTD.

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INFLUENZA TOLL IN FEDERATION NEARS THE 3,000 MARK

Ipo latest town to be hit: Penang, Province Wellesley situation worse

SCHOOLS STAY CLOSED

More
are
struck
down

MR. LIM'S 'BODYGUARD' CHATS WITH CHINA'S PREMIER



**DEAD:
'THE MOST
HATED
MAN ON THE
SCREEN'**

12,000 DOWN WITH THE FLU

Sweeping epidemic—'this is really it'

Dr. DIN: WORSE MAY COME IN NEXT FEW WEEKS'

POLYENZA victims in the Federation have soared to 12,000, according to the latest reports received at Federal Medical Headquarters in Kuala Lumpur yesterday evening.

Yesterday morning alone there were 6,000 fresh cases.

JOHORE has the most victims, the toll rising from 3,000 on Monday to 5,000 yesterday. In SELANGOR the number rose from 1,200 to 2,000. PENANG alone had 1,000 fresh cases yesterday.

ON-SPOT PROBE IS SUGGESTED

MELBOURNE, Aust.—The Herald tonight led an on-the-spot inquiry by Australia into the epidemic sweeping Malaya.

In an editorial it said: "It would be a commendable proposition to fly a small team of medical experts to Singapore."

The Commonwealth Health Department under Mr. Macquay, due in Fremantle tomorrow from Singapore, to discover if there were any fresh cases. The ship replied no.

The department said that victims reaching Fremantle from Singapore would be quarantined to be treated in an infectious diseases hospital.

AUSTRALIA TO GET CULTURES

Department asked for the Singapore culture as a possible aid for diagnosis.

Prof. J. H. Hays, Professor of Bacteriology at the University of Malaya, was sending them.

Mr. Tolson had the department's attention.

PRETTY PEGGY MODELS A CHEONGSAM WITH A BIG DIFFERENCE



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SINGAPORE 2
Phone: The People Optical Co. 14, Selegie Street, Penang.

The Straits Times

ESTD. 1846. SINGAPORE, THURSDAY, MAY 14, 1957. 15 CENTS

Malayan National Newspaper

THE FEDERATION HAS MORE THAN 21,000 VICTIMS

Minister (he's ill himself) gives full power to close any school

UP, UP GOES FLU TOTAL

Every state is now affected

Flu—what to do if you get it

KUALA LUMPUR, Fed.—The number of influenza victims in the Federation is now 21,000, according to reports received at the medical headquarters in Kuala Lumpur late this evening.

There has been 6,000 fresh cases, bringing the total to 21,000.

Minister, Mr. Din, has today given full powers to close any school in the Federation.

From Page One

It said the 21,000 victims of influenza were reported to be in all States and Federal Territories.

The Minister has today given full powers to close any school in the Federation.

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The Minister has today given full powers to close any school in the Federation.

Students ill

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He said the 21,000 victims of influenza were reported to be in all States and Federal Territories.

The Minister has today given full powers to close any school in the Federation.

He said the 21,000 victims of influenza were reported to be in all States and Federal Territories.

The Minister has today given full powers to close any school in the Federation.



Fingers crossed

The FLU: PEAK STILL TO COME

But end in sight in Singapore: 'Over by June'

PENG GOES DOWN WITH FLU

Prolonged closure of schools is not necessary

As a teacher, I think that the prolonged closure of schools is unnecessary.

When the schools remain closed until teachers and pupils are completely free from infection, they run on longer courses. The influenza will still remain in schools for some months, and will be spread to other schools and will be spread to the general community to some extent. In this way more people get infected.

Consequently, the Ministry of Education should announce that the necessary holidays are to be granted to enable children to return to their schools. This will bring down the number of children in schools.

I think it would be better to let the teachers and pupils return to school as soon as possible.

In relation to the health of the staff, I think that the Ministry of Education should consider the health of the staff. The Ministry should consider the health of the staff and the health of the pupils.

Teachers should be given a special holiday to enable them to return to work as soon as possible. This will help to reduce the number of infected teachers.

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Teachers should be given a special holiday to enable them to return to work as soon as possible. This will help to reduce the number of infected teachers.

LETTERS TO THE EDITOR

Letters for publication in the Straits Times should be:

Short.

Written on one side of the paper.

Bear the signature and address of the writer.

A preliminary may be used provided the full name and address of the writer is also given. Preference will be given to letters bearing a proper name and not just a pen-name.

Public phone wanted

THE people of the Tanjong Pagar area would be grateful for a public telephone and a public lavatory.

J. S. S. S. S.

Letterbox heard for merdeka

IT will be some time before the Merdeka celebration, I would suggest that the Government should establish a merdeka letterbox.

A. H. S. S. S.

Teachers about

Teachers should be given a special holiday to enable them to return to work as soon as possible. This will help to reduce the number of infected teachers.

THE FIRST FREE CLINIC FOR FLU OPENS: 130 TREATED

ABOUT 130 influenza cases were treated at the first free clinic in Singapore. The clinic was held at the Tanjong Pagar Police Station. The clinic was held from 6 p.m. to 9 p.m.

Flu report goes to Assembly

EPIDEMIC IS DECLINING

THE Health Minister, Mr. A. J. Bragg, will make a full report on the influenza epidemic to the Singapore Legislative Assembly when it meets on Wednesday.

COLONY SHIP 'SEALED'

MADRAS, Sun. — Senior doctors here held hurried consultations yesterday to consider whether to extend the period of quarantine for the British liner Rajula (8,946 tons) after several cases of influenza patients reported sick.

The Rajula was placed under quarantine for five days after arriving here on Thursday from Singapore.

A team of 100 doctors, nurses and orderlies despatched to the Rajula's berth three miles off the harbour have already diagnosed 44 cases of which four are severe.

Mr. Bragg told the Straits Times yesterday that the Ministry was still keeping a close watch on the epidemic although it was "definitely on the decline."

A peak was reached on May 8 and things began to improve five days later.

The epidemic would probably peter out completely by the end of the month.

Only once

Mr. Bragg said it was normally unlikely for a person to catch the flu more than once in the same epidemic.

About 200,000 school-children will be returning to school today. Schools have been closed since May 8 due to the epidemic. To make up for this the August holidays will be cut by a week.

The situation in the Federation has not shown much improvement with a total of 75,000 reported cases on record yesterday morning, when

But disease continues its climb in Federation—to 97,000 cases

FLU FIZZLING OUT NOW

In a short time it is expected to vanish

The epidemic in Singapore is fading out. As in the Federation, the number of cases faded to 93,800.

SPORTS

Flu puts off a cricket match

FOUR of the six matches in the S.C.A. junior tournament ended decisively yesterday. The Section "B" match between R.A.P. Changi "A" and BODCA was postponed owing to the flu epidemic. Results and brief scores were:

SECTION "A"
Fraser & Neave beat Ceylon Sports Club by two wickets at River Valley Road.
C.S.C. 59 (Fernando 12, Ponnudurai 11, Martens 7-24, Chan 2-18).
F & N 51-3 (Topling 14, Perera 5-22, Fernando 3-4).
Y.M.C.A. and Singapore Recreation Club drew at Balestier Road.

FLU CLOSES ALL NEW DELHI CINEMAS, SWIM POOLS, SCHOOLS

gh 3-58) S.H.B. gnam 13, Chan- er 5-25, Kearton

Indian Associa- Balestier Road. (Ali Omar 32, ller 16, Bala- mechanical 3-6), dra 30, Arvnirai), Sullivan 3-31). B" beat Police Seletar. Harley 56 n.o., ther 5-40, OUR- Police 109 ST, Doolley 4-40,

NEW DELHI, Friday. ALL schools, swimming pools and cinemas here have been closed until further notice in an all-out government drive to stem the fast-spreading influenza epidemic.

Nearly 3,000 new cases were reported in the capital yesterday, mostly in the slum areas, bringing the total to over 6,000. Besides affecting essential services like public conveyances, police, posts and telegraphs in some sections of the city, the influenza has not spared even the Sadhus (Hindu holy men) who for the past fortnight have been praying around a sacrificial fire on the banks of the sacred Jumna river for world peace and a lessening of tensions.

Sharp increase

Nearly 100 Sadhus were laid down in tents and under trees.

30 girls enter world strip contest

PARIS, Fri. — Mr. Charles Albertos, 42-year-old Paris night club owner and organiser of the first International Strip-tease Contest, said today he had received more than 30 entries from as far afield as Mexico and Indonesia. At least 12 nations, including the United States, will be represented, he said. Mr. Albertos said the prize for the winner has been doubled to £1,000.—Reuter.

2 1/2 m. DOWN WITH FLU IN JAPAN

TOKYO, Thurs. — The influenza epidemic spread today to all of Japan with an estimated 2,500,000 Japanese suffering from coughs, fever and muscle pains. Two more Japanese died from complications resulting from the flu yesterday bringing to five the number of dead in the epidemic. The only two southern Japan prefectures which had been reported free from the wave of illness reported outbreaks today.

Mass absences

The Welfare Ministry said 505,000 school children were stricken. Mass absences were reported in 4,195 schools ranging from kindergartens to universities throughout the country. A total of 1,174 schools were closed completely and 2,514 have suspended at least some of their classes.—U.P. Epidemic news in the other world capitals:

Close check in France

PARIS: French health authorities today tightened sanitary controls at Marseilles and Orly as measures against the influenza epidemic. This followed reports from Durban that the 13,500-ton French liner Vietnam had been placed in quarantine when she arrived there from Yokohama and Singapore yesterday.—Reuter.

May 21

Singapore flu is new—now Japan is asking: 'Is ours the same?'

GENEVA, Thurs. — The World Health Organisation announced last night the discovery of a new strain of influenza in samples sent to London from Singapore. It was found in eggs as the most convenient medium. It differed from recently isolated strains and had unusual properties in its behaviour in the laboratory, said the centre. Existing influenza vaccine

which analysed the virus isolated in Singapore by Dr. Lim Kok Ann, said the strain was "a new epidemic variant of type A." The World Health Organisation said that, according to a cable today, there were now 120,000 cases of influenza in Manila, involving 50 per cent of the population. Fourteen deaths were reported in 36 hours. The Philippine Ministry of Education today closed all schools and universities in Bangkok because 2,500 students have influenza. —Reuter.

OUR BANK—SEE PAGE 7

INFLUENZA HITS MALAYA

"Influenza Hits Malaya". Take emergency measures with Aspro. Get Aspro now at the first sign of influenza, take Aspro according to directions on packet. Aspro stops influenza quickly. You can take after

INFLUENZA

Your best friend

FLU WARNING!

Many bad cases of heavy colds and 'flu have been reported. In some instances, whole families have been hit. Whether or not this is the beginning of a serious 'flu epidemic, every possible effort should be made to protect your family—children and grown-ups alike—now.

How To Protect Yourself and Your Family!



Make sure that you have plenty of Vicks VapoRub in your medicine chest. The demand is heavy. Buy Vicks VapoRub today while your drugist is still able to supply you—and be ready to treat every cold promptly.



Watch your family's health carefully, especially the children who may be exposed to infection at school. At the first sign of a cold—stuffy nose, sore throat, tight chest or cough—use Vicks VapoRub promptly.



Rub Vicks VapoRub on chest, throat and back. Then spread an extra layer of VapoRub on the chest and cover with a warm cloth. Relief comes quickly in two ways at once:

FIGHTS "FLU-COLDS" IN 2 WAYS!



1. Warmed by the body, VapoRub gives off medicinal vapors which are inhaled with every breath. These vapors soothe irritation, make breathing easier and calm coughing.



2. Like a warming poultice, VapoRub works through the skin, relieves tightness and pain in the chest and draws out congestion.

Works in the air-passages.

Works through the skin.

This double action of Vicks VapoRub—vapors and poultice combined—keeps on working during sleep, bringing relief to nose, throat and chest all at the same time. Next morning, often, the worst of the cold is over. But repeat the treatment, if necessary, until you are certain the cold is broken.



FOLLOW THESE HEALTH RULES TO HELP WARD OFF FLU

1. Keep away from crowds; avoid close contact with others who have colds or 'flu.
2. Live sensibly. Avoid overwork. Eat lightly. Drink plenty of water.
3. While 'flu is about, put a little Vicks VapoRub in each nostril every night and morning or before any unusual exposure.
4. If there is fever, a doctor should be called immediately.

VICKS VAPORUB

STOP PRESS!

FOR QUICK RELIEF FROM

'FLU

COLDS or SORE THROAT

TAKE Vinac

THE FAMOUS PINK HEADACHE TABLETS.

3 MEDICINES IN ONE
ASPRIN relieves the pain
PHENACETIN reduces the temperature
CAFFEINE stimulates the nerves
DOES NOT AFFECT THE HEART



Get quick relief from 'FLU



IF YOU HAVE HAD 'FLU'
BUILD UP VITALITY WITH **SCOTT'S EMULSION**



The essential Vitamins A & D plus hypophosphites of lime and soda in SCOTT'S EMULSION mean the sure way to build up health and vitality after Influenza. Buy a bottle now!



SCOTT'S EMULSION

BUILDS THE BODY • PROTECTS THE LUNGS

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