

Therapeutic considerations for Emerging Viral Diseases



Paul Ananth Tambyah

What is an Emerging Infectious Disease?

- "new, re-emerging or drug-resistant infections whose incidence in humans has increased within the past two decades or whose incidence threatens to increase in the near future."
 - Lederberg et al Institute of Medicine 1992

An illustrative case presentation

- 24 year old pig chaser
- Admitted February 1999
- 4 day history of fever and confusion
- Initial temperature 39C
- Neck stiff, drowsy, became comatose
- CSF showed lymphocytic meningitis
- Treated with ceftriaxone, Acyclovir, RHEZ

Progress II

- Fifth hospital day:
 - Began to improve spontaneously
 - Able to respond to simple commands
- Tenth hospital day:
 - Alert and oriented
 - Repeat CSF exam normal
- Discharged well on 14th hospital day
- Diagnosis:
 - "Viral encephalitis of unknown etiology"

Nipah Virus: A Recently Emergent Deadly Paramyxovirus

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A paramyxovirus virus termed Nipah virus has been identified as the etiologic agent of an outbreak of severe encephalitis in people with close contact exposure to pigs in Malaysia and Singapore. The outbreak was first noted in late September 1998 and by mid-June 1999, more than 265 encephalitis cases, including 105 deaths, had been reported in Malaysia, and 11 cases of encephalitis or respiratory illness with one death had been reported in Singapore. Electron microscopic, serologic, and genetic studies indicate that this virus belongs to the family *Paramyxoviridae* and is most closely related to the recently discovered Hendra virus. We suggest that these two viruses are representative of a new genus within the family *Paramyxoviridae*. Like Hendra virus, Nipah virus is unusual among the paramyxoviruses in its ability to infect and cause potentially fatal disease in a number of host species, including humans.

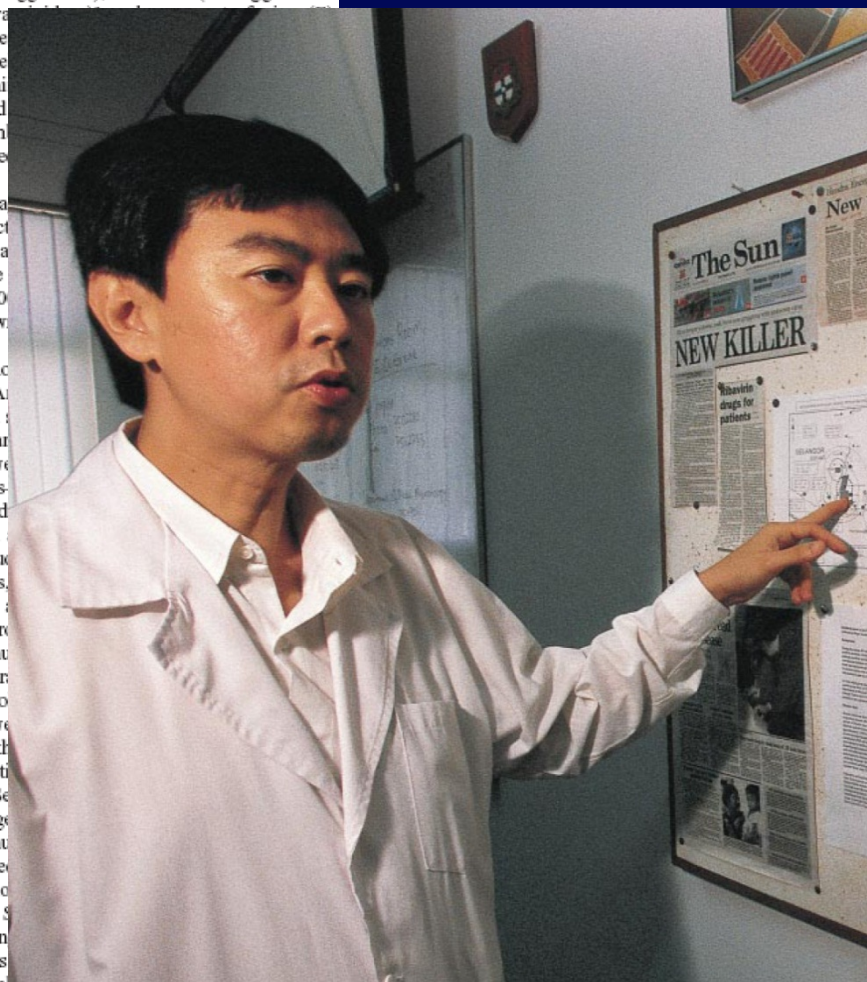

An outbreak of severe febrile encephalitis associated with human deaths was reported in peninsular Malaysia beginning in late September 1998. The outbreak was associated with respiratory illness in pigs and was initially attributed to Japanese encephalitis (JE) (1). JE is a mosquito-borne viral disease that is enzootic in the region, and pigs are among the amplifying vertebrate hosts (2). By February 1999, similar diseases in pigs and humans were recognized in other regions in Malaysia, in association with the movement of a large number of pigs from Ipoh southward into the new outbreak areas. In March 1999, a cluster of 11 cases of respiratory and encephalitis illnesses was noted in Singapore

in abattoir workers who handled pigs from the outbreak regions in Malaysia. The outbreak in Singapore ended when the importation of pigs from Malaysia was prohibited, and the outbreak in Malaysia ceased when over 1 million pigs were culled from the outbreak area and immediately surrounding areas (3). A total of 265 cases of encephalitis, including 105 deaths, were associated with the outbreak in Malaysia.

Because some of the epidemiologic characteristics of the disease in humans were distinct from those of JE [most cases occurred in adult males who worked with pigs, very few case patients were young children, and neither mosquito control nor JE vaccination programs appeared to affect the course of the outbreak (4)], investigators in Malaysia expanded attempts to isolate an agent. In early March 1999, Vero cells inoculated with cerebrospinal fluid specimens from three fatal cases of encephalitis developed syncytia.

Electron microscopic (EM) studies of the virus, named Nipah virus (5), demonstrated features characteristic of a virus belonging to the family *Paramyxoviridae* (Fig. 1). This family of viruses typically possesses a single-stranded nonsegmented RNA genome of negative polarity that is fully encapsidated by protein. The helical

nucleocapsid structure is surrounded by membrane derived from the plasma membrane from which the viruses bud. Virus particles vary in size from 120 to 500 nm. The paramyxovirus envelope contains two transmembrane glycoproteins, a cell receptor binding protein [G (glycoprotein), H (hemagglutinin), or HN (hemagglutinin/neuraminidase) glycoprotein], and a protein that is embedded in the envelope. The average size of the virus particles is 120 nm. The virus particles are spherical and have a diameter of 120 nm. The virus particles are spherical and have a diameter of 120 nm. The virus particles are spherical and have a diameter of 120 nm.



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Patient was called back for serology and an MRI review...

Internal Medicine Journal 2001; 31: 132–133

CASE REPORT

First case of Nipah virus encephalitis in Singapore

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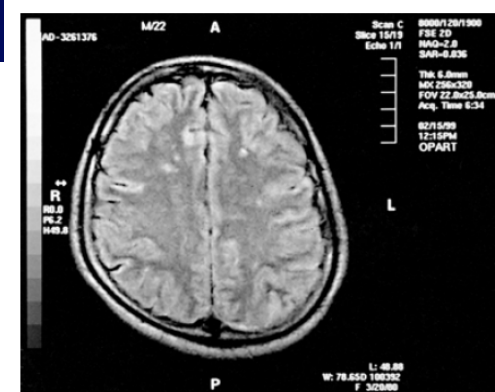


Figure 1 Axial T2-weighted fluid-attenuated inversion-recovery magnetic resonance imaging brain scan showing multiple cortical and subcortical hyperintense lesions typical of Nipah encephalitis.

Neuroradiology

In March 1999, an outbreak of Nipah virus encephalitis was recognized among slaughterhouse workers in Singapore.¹ One month prior, a 24-year-old pig auction worker presented to the National University Hospital with a 4-day history of fever and confusion. He had a temperature of 39°C, neck stiffness and drowsiness. His full blood count and

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10.1148/radiol.2221010499
Radiology 2002; 222:219–226

Nipah Virus Encephalitis: Serial MR Study of an Emerging Disease¹

PURPOSE: To report the serial magnetic resonance (MR) imaging findings of the Nipah virus.

MATERIALS AND METHODS: Twelve patients underwent serial MR imaging. Eight patients were examined at the outbreak; 11, at 1 month; and seven, at 6 months. Contrast material-enhanced MR images, diffusion-weighted images, and single voxel proton MR spectroscopic images were reviewed. Clinical and neurologic assessment, as well as analysis of the size, location, and appearance of brain lesions on MR images, were performed.

RESULTS: During the outbreak, all eight patients had multiple small foci of high signal intensity within the white matter on T2-weighted images. In six patients, cortical and brain stem lesions were also detected, and five patients had diffusio

Live pork imports from Malaysia were banned

A-PORK-ALYPSE NOW

*Passionate pork lovers
wallow in their deprivation*



ou may not believe this, but there are people out there who swear by pork. And after a month without pork and pork lard, they are exhibiting withdrawal symptoms that range from acute to barely bearable. "Life is tasteless without pork," says one who claims he is "not half the man I used to be".

The Sunday Times

March 21, 1999 • 92 Pages in four parts • MTA (P) 095/12596

A Singapore Press Holdings publication 65 cents

Chinese elite is no cause for worry

DPM Lee gives the reassurance that the Government will promote the cultures of all ethnic communities

MINORITY communities have no cause to worry about moves to develop a Chinese cultural elite and Special Assistance Plan (SAP) schools, said Deputy Prime Minister Lee Hsien Loong last night.

He said he was aware that non-Chinese were concerned that these moves might result in a shift away from the ideal of multiculturalism.

But they need not worry, he said.

The Government remains

and "squeens out other talented Singaporeans".

The reality was that non-SAP students form the majority among the top Chinese students at school, among Government scholarship holders and in the premier Administrative service.

DPM Lee began his speech to the Sikh community which celebrated the fifth harvest festival on a field off Bragie Road by praising its strong sense of identity.

"We are trying to maintain and strengthen the cultural and linguistic roots of Singaporeans in a predominantly and increasingly English language environment."

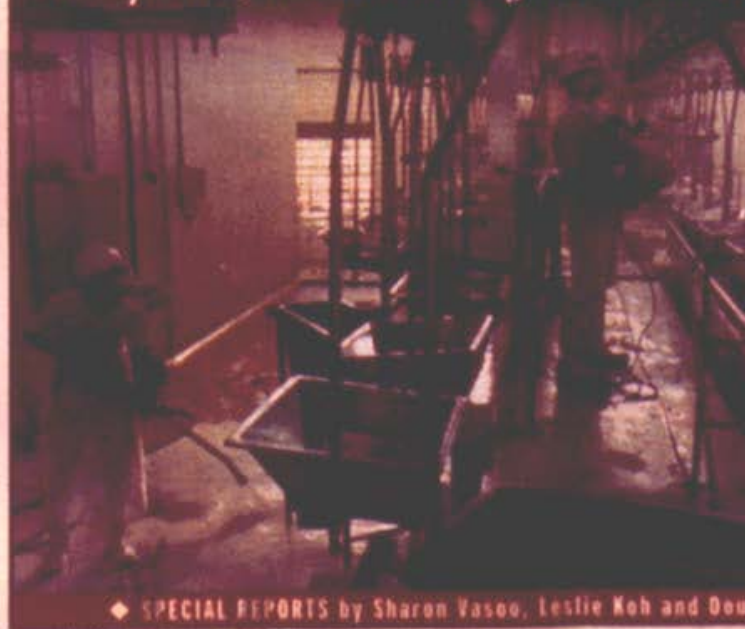
Furthermore, we are trying to do this for all ethnic groups, not just the Chinese," he said, noting that with the review of Chinese-language teaching over, the Education Ministry will start to review that of Malay and Tamil.

He said the term "elite" might have contributed to the fear that an in-group will form, squeezing out other talented Singaporeans.

But the aim was to produce a group steeped in Chinese culture, as journalists, artists, writers, who can

THE SILENCE OF THE PIGS

No squeals, no machinery noise, no workers' yells



A deathly silence fell on Jurong abattoir yesterday. Some workers and managers were there to do the clearing job, since the cleaners had refused to do it. Both the Jurong and Kim Chuan abattoirs were ordered by the Primary Production Department to cease operations. But pork is safe - you can eat your char siu rice and your bak kut teh.

◆ SPECIAL REPORTS by Sharon Vasoo, Leslie Koh and Douglas Wong: Pages 2-4

MOVE TO ENSURE NO ONE ELSE HAS ENCEPHALITIS

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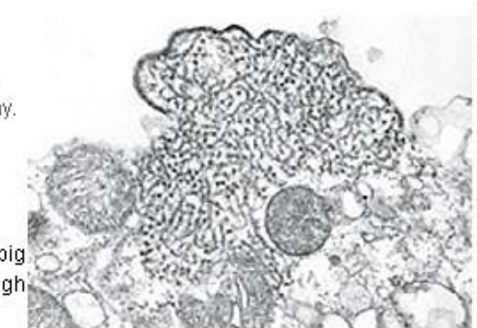
09.25.2006

Natural Selections: The Potential Pandemic You've Never Heard Of

How the connections between pigs, bats, and people could threaten your health.
by Mary C. Pearl

The mystery began when pigs on large farms in Malaysia began hacking so loudly that their owners called it a "one-mile cough." Nerve damage was also cropping up in some of the animals. No one knew why. Up to 5 percent of pigs in affected herds were dying, and the illness was spreading like wildfire. Locals named it Nipah, after the place where it was first identified.

More alarming news followed. People, most of them pig handlers, started falling ill. Nipah caused fevers so high that some victims suffered brain inflammation and seizures. Nearly half of those sickened—105 out of 265 cases—died. Through the sale of pigs, the illness continued to spread for several months throughout



Budding particles of Nipah virus assemble near the surface of a cell.



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Search results

Items: 1 to 20 of 118

<< First < Prev Page 1 of 6 Next > Last >>

- ☐ [The Matrix Protein of Nipah Virus Targets the E3-Ubiquitin Ligase TRIM6 to Inhibit the IKK \$\epsilon\$ Kinase-Mediated Type-I IFN Antiviral Response.](#)

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- ☐ [Pathogenic Differences between Nipah Virus Bangladesh and Malaysia Strains in Primates: Implications for Antibody Therapy.](#)

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Sci Rep. 2016 Aug 3;6:30916. doi: 10.1038/srep30916.

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Int J Infect Dis. 2016 Jun;47:5-9. doi: 10.1016/j.ijid.2016.06.012.

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- ☐ [Genome-wide siRNA Screening at Biosafety Level 4 Reveals a Crucial Role for Fibrillarin in Henipavirus Infection.](#)

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PLoS Pathog. 2016 Mar 24;12(3):e1005478. doi: 10.1371/journal.ppat.1005478.

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Why do we have no licensed therapeutics for Nipah, SARS, MERS, Ebola, Dengue, Zika...

- Pre-clinical issues – biosafety, animal models
- Clinical trial issues – lack of patients, infrastructure
- Ethics and Economic issues – no market ☹

CHAIN EFFECT

How one person infected more than 120 people. **SALMA KHALIK** traces the links.



SUPER SPREADER 1

was in ward 5A before she was isolated at Tan Tock Seng Hospital

* Esther Mok and two other women who stayed at Metropole Hotel in Hongkong where they got the virus from a Guangdong professor, who has since died.

Note: Esther was among seven people who were infected overseas. But she was the only one who was so highly infectious.

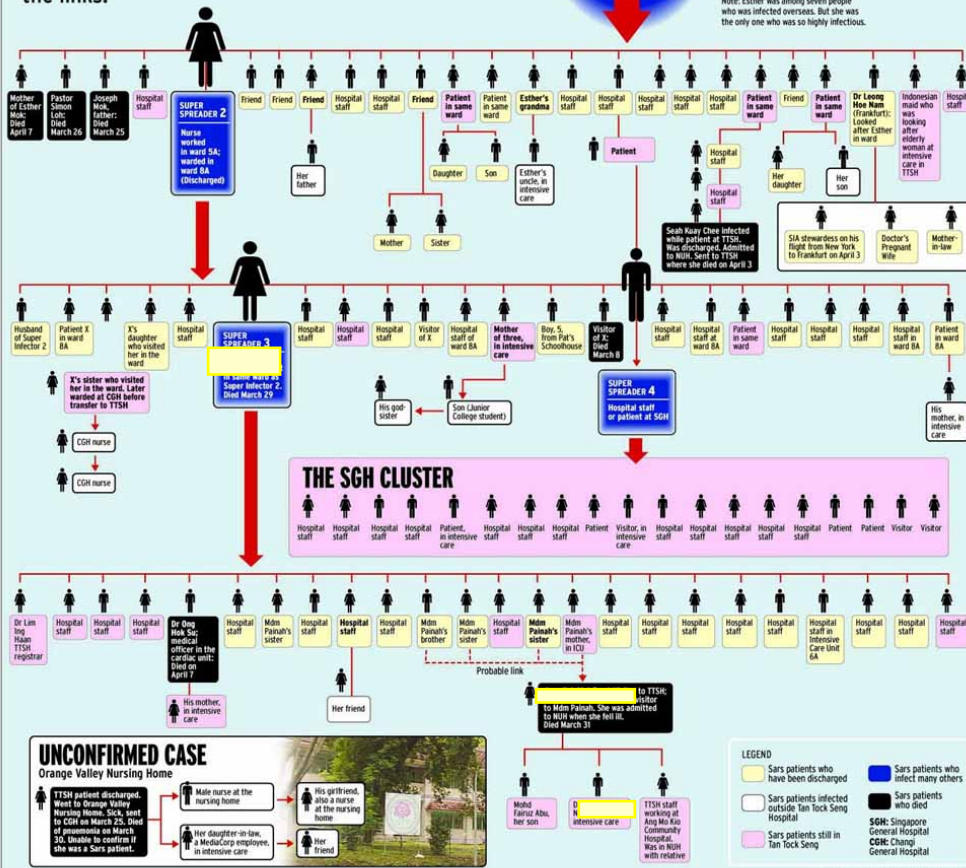
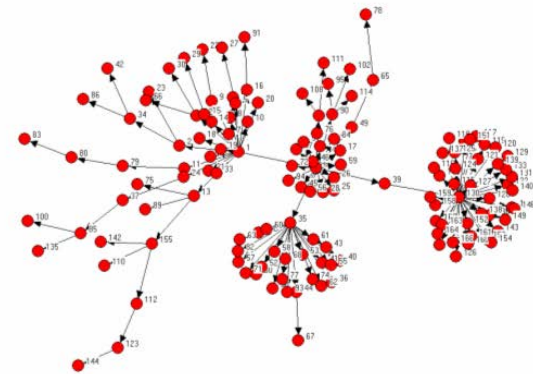
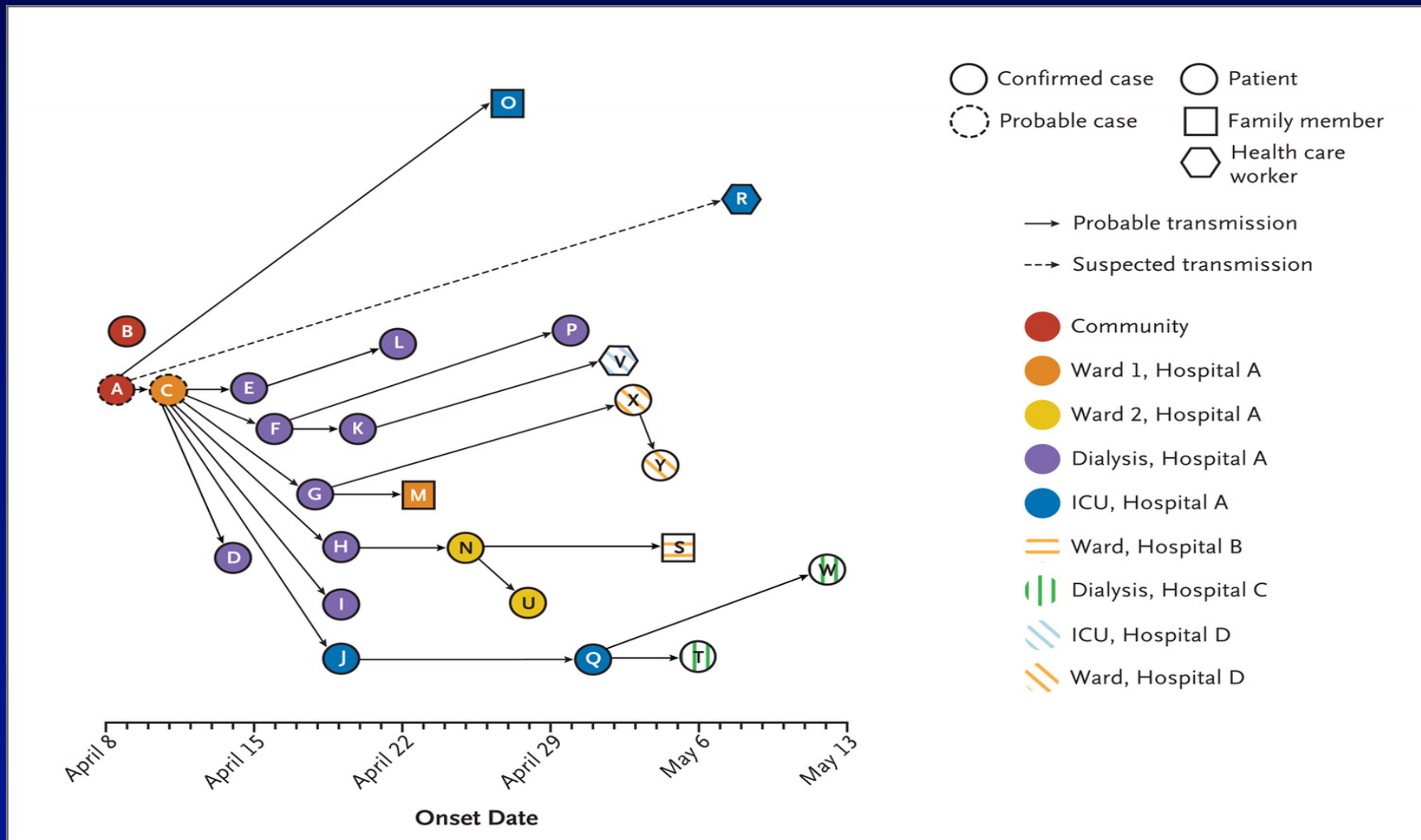


Figure 3.



MMWR 2003;52:18

Transmission Map of Outbreak of MERS-CoV Infection.



Assiri A et al. *N Engl J Med* 2013. DOI: 10.1056/NEJMoa1306742



The NEW ENGLAND
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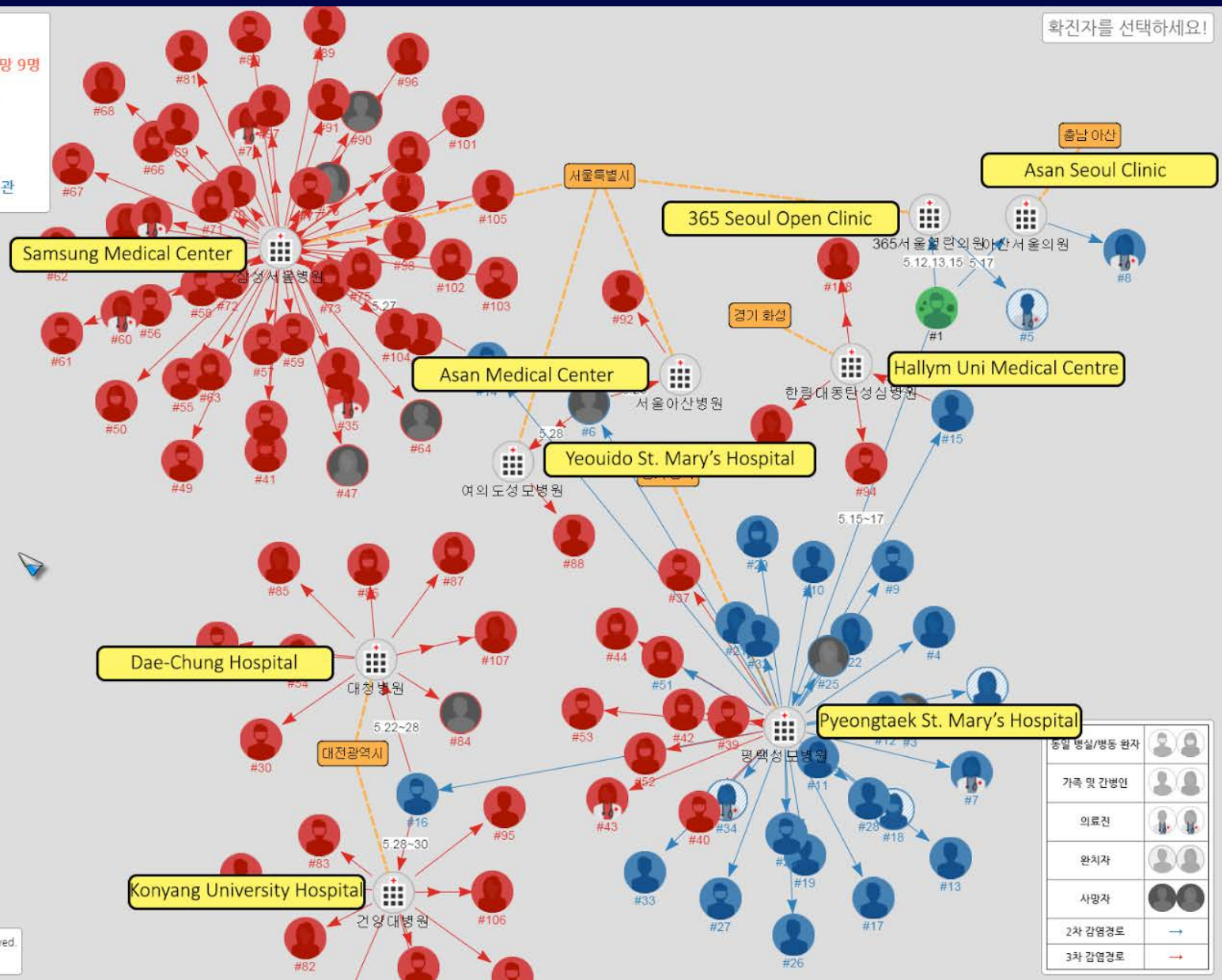
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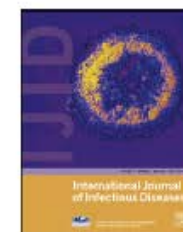


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journal homepage: www.elsevier.com/locate/ijid

Therapeutic Options for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) – possible lessons from a systematic review of SARS-CoV therapy

Hisham Momattin^a, Khurram Mohammed^a, Alimuddin Zumla^b, Ziad A. Memish^c,
Affar A. Al-Tawfiq^{d,*}

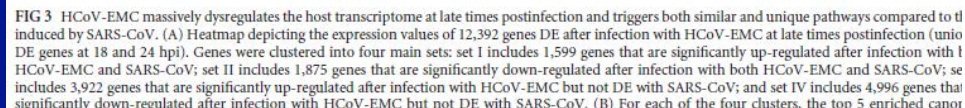
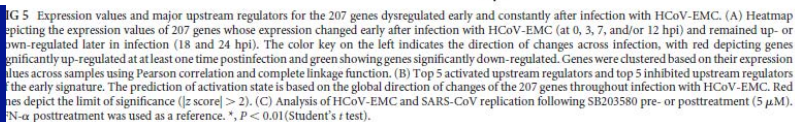
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^b Division of Infection and Immunity, University College London, London, and University College London
^c Deputy Minister for Public Health, and Director WHO Collaborating Center for Mass Gathering Medicine
^d U-Faisal University, Riyadh, Saudi Arabia
^e Specialty Internal Medicine, Saudi Aramco Medical Services Organization, Dhahran, Saudi Arabia, and Indi

Table 3
Convalescent Plasma studies

Reference #	Type of study	Regimen	# patients	Indication	Time of administration	Outcome																				
19	Cohort study (LOE, II)	Convalescent plasma (500 mL) was obtained from each of three SARS patients and transfused into the 3 infected HCW.	3 patients	SARS	No date was given	All three patients survived. One healthcare worker became pregnant subsequently, delivering 13 months after discharge.																				
20	Case report (LOE, III)	infusion of plasma collected (200ml) from a convalescent patient with SARS to treat, in combination with ribavirin and corticosteroids	One patient	SARS	On day 14 of hospitalization	The clinical outcome was successful, despite the relatively low volume of plasma infused; furthermore, no side-effects were observed																				
21	Cohort (LOE, II)	200-400ml (4-5ml/kg) of (ABO) compatible convalescent plasma	80 patients		On day 14 of starting symptoms	Mortality rate 12.5% compared to 17% of SARS patient																				
22	Retrospective cohort study (LOE, II)	ribavirin + methylprednisolone 3 doses (500 mg each) of pulsed methylprednisolone 200-400 mL of convalescent plasma (plasma group) or further pulses of methylprednisolone (steroid group) 200-400 mL of	30	SARS	At the discretion of the attending clinicians and according to the availability of convalescent plasma.	<table><thead><tr><th></th><th>Plasma group (n=19)</th><th>Steroid group (n=21)</th><th>P value</th></tr></thead><tbody><tr><td>Discharge rate by day 22</td><td>73.4% N=14</td><td>19% N=4</td><td>0.001</td></tr><tr><td>Following onset of illness</td><td>77.8% (14/18)</td><td>23% (3/13)</td><td>0.004</td></tr><tr><td>Discharge rate by day 22 after adjustment for co-morbidities</td><td>0%</td><td>23.8% (n=5)</td><td>0.049</td></tr><tr><td>Death rate</td><td></td><td></td><td></td></tr></tbody></table> Inconclusive		Plasma group (n=19)	Steroid group (n=21)	P value	Discharge rate by day 22	73.4% N=14	19% N=4	0.001	Following onset of illness	77.8% (14/18)	23% (3/13)	0.004	Discharge rate by day 22 after adjustment for co-morbidities	0%	23.8% (n=5)	0.049	Death rate			
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Death rate																										

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IMPORTANCE Identification of widespread outbreaks of disease and global transmission requires rapid assessment of the impact of the disease. CoV-EMC and SARS-CoV-2 could be more generally applicable and make rapid



Still nothing licensed

Journal of Infection (2013) xx, 1–11



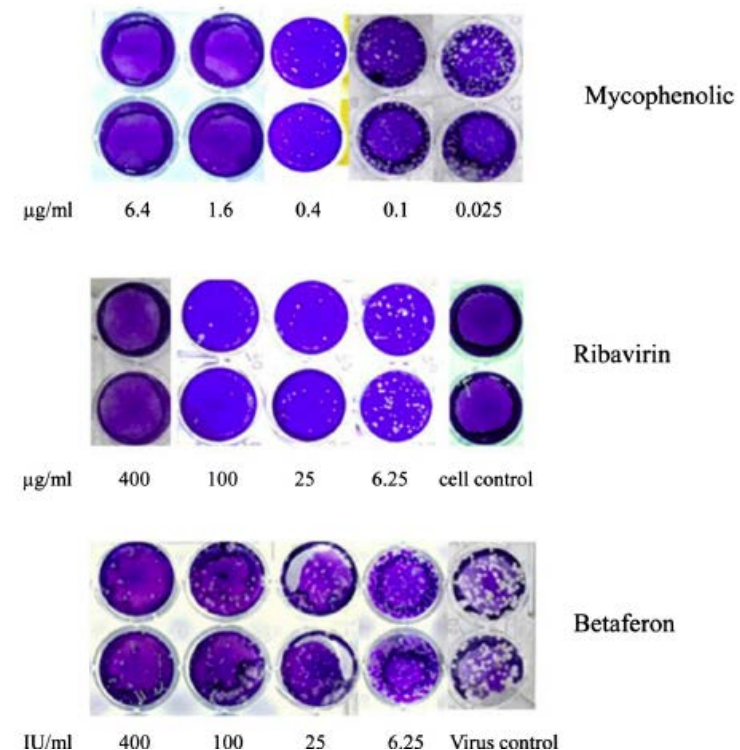
Table 2 Inhibitory effect of mycophenolic acid, ribavirin, and interferons on MERS-CoV replication in Vero cell yield reduction assay.

Drug	EC ₅₀	EC ₉₀	EC ₉₉	CC ₅₀	Selectivity index
Mycophenolic acid (μg/ml)					
Alone	0.17 ± 0.03	2.61 ± 0.34	4.86 ± 0.57	>32	>195.
With 6.25 IU/ml Betaferon	0.10 ± 0.01				
With 12.5 IU/ml Betaferon	0.06 ± 0.01				
Ribavirin (μg/ml)	9.99 ± 2.97	107.06 ± 11.24	183.17 ± 11.97	>1600	>152.
Intron A (IU/ml)	6709.79 ± 1747.97	184015.75 ± 90145.01	371242.78 ± 255482.32	>75,000	>11.
Avonex (IU/ml)	5073.33 ± 7333.86	179949.17 ± 138588.37	708919.75 ± 840503.36	>75,000	>35.
Rebif (IU/ml)	480.54 ± 183.85	2473.86 ± 576.35	3599.06 ± 778.81	15,625	27.
Betaferon (IU/ml)					
Alone	17.64 ± 1.09	93.31 ± 10.07	135.70 ± 15.96	3125	249.
With 0.016 μg/ml of mycophenolic acid	16.09 ± 4.09				
With 0.063 μg/ml of mycophenolic acid	9.80 ± 0.53				

^a Selectivity index defined as ratio of CC₅₀/EC₅₀.

Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus

²³ Jasper F.W. Chan^{a,b,c,e}, Kwok-Hung Chan^{b,e}, Richard Y.T. Kao^{a,b,c,e}, Kelvin K.W. To^{a,b,c}, Bo-Jian Zheng^{a,b,c}, Clara P.Y. Li^b, Patrick T.W. Li^b, Jun Dai^b, Florence K.Y. Mok^b, Honglin Chen^{a,b,c}, Frederick G. Hayden^d, Kwok-Yung Yuen^{a,b,c,*}



SARS was devastating to healthcare workers: One of my colleagues died of SARS

Monday, April 28, 2003 • THE STRAITS TIMES

•3



WAR ON SARS

Surgeon died of Sars, not dengue

Son of late P [redacted] may have been infected by an SGH patient before that man was found to have Sars

By WENDY TAN

SINGAPORE General Hospital surgeon [redacted], 37, who died while being treated for dengue fever, was actually a Sars patient.

Like [redacted] here so far, he had a fever that landed him in hospital.

tient", who had isolated himself from the moment he knew he was ill and had no contact with his wife, children or mother.

The last person he had unprotected contact with was a sick uncle he prayed with and sang a song for on April 11, the day before he fell ill.

Dr Balakrishnan said: "He

home to stay at his godfather's house, where he isolated himself and had meals delivered to his door.

The next day, he saw the SGH staff doctor and was given two days' medical leave.

But when he still had a fever on April 15, he was admitted to SGH and put in isolation. The diagnosis was dengue fever.

The next day, he broke out in rashes, a symptom consistent with dengue fever.

Chest X-rays on April 17 and 19 showed no problem.

"If a man is not going to see his wife, is not going to see or touch his daughters, not going to see or touch his mother, you think this is a man who is going to socialise with all and sundry in an isolation ward in a hospital on high alert, in which we have already said for isolation, no visitors?"

- Dr Vivian Balakrishnan, who was confident that others at SGH were not infected by [redacted] whom he described as "extremely responsible"

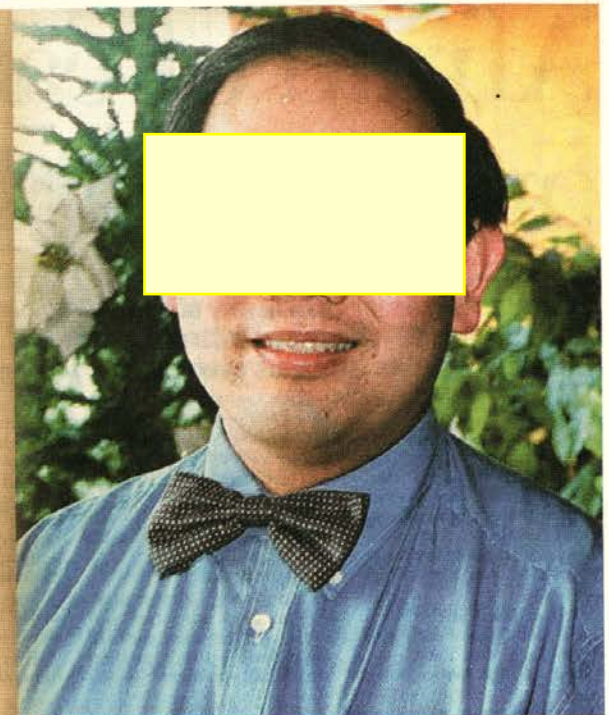
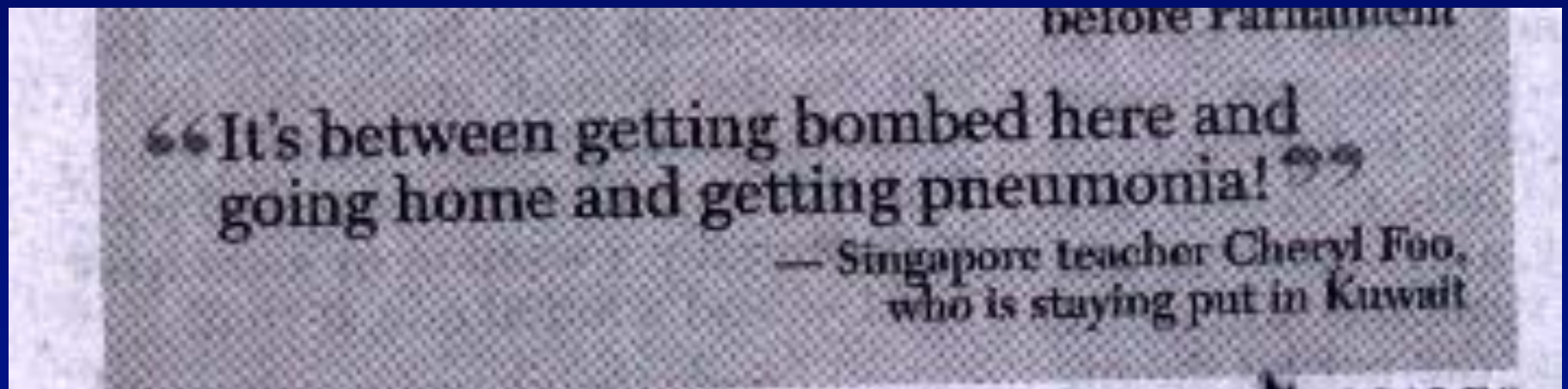


Photo: ZAOBAO

a sore throat later patient he treated between treating his patients, said now getting their masks fitted

The whole of society was affected....



Eventually, after a few months
it was over

The Straits Times

PACIFIC AREA NEWSPAPER OF THE YEAR

Established 1845

Saturday • May 31, 2003 • 182 Pages in six parts • MTA (P) 033/03/2003

A Singapore Press Holdings publication 60 Cents



**YES! SINGAPORE
IS OFF THE W.H.O
SARS LIST. BUT WE
MUST STILL KEEP
OUR GUARD UP.**

REPORTS ON SARS

- HOSPITALS' NO-VISITORS RULE EASED HOME H4
- GO AHEAD, CELEBRATE, SAYS PAUL JACOB HOME H17
- CHINA VOWS TO REVAMP HEALTH SYSTEM ASIA A4
- SINGAPORE FIRMS' GIFTS TO BEIJING PRIME 6

NUMBERS TO NOTE: 1800-333-9999 HOTLINE FOR INFORMATION ON SARS
993 TO CALL AN AMBULANCE TO SEND SOMEONE TO TAN TOCK SENG HOSPITAL

LOH JAHAN

Singapore is off WHO's Sars list

Good news comes a day early, showing confidence in action to contain Sars here

By CHANG AL-LIEN

SINGAPORE is off the list of Sars-affected countries. The decision by the World Health Organisation was announced by the Health Ministry last night.

The good news came a day ahead of the required 20-day period with no new cases of infection and demonstrated the WHO's confidence that "Singapore has contained Sars", its spokesman said.

It should have gone on the world body's website at noon yesterday, Switzerland time, but was delayed by a technical hitch.

Dr David Heymann,

highest level of vigilance".

"The possibility of a future imported case sparking off clusters of Sars cases in Singapore cannot be discounted," the ministry said, in a clear reference to Toronto in Canada which went back on the Sars list two weeks after it was removed.

"So long as there are Sars-affected areas in the region and the world, we cannot afford to let our guard down," it added, echoing the familiar caution of incoming Health Minister Khaw Boon Wan.

Since arriving in March, Sars has infected 206 people here and 31 died. Nine people are still in hospital, four of them critically ill.

director of Singapore Can Lah!, a grouping of travel and tourism companies, said: "We are excited about welcoming back our international visitors."

Part of his wish was answered yesterday when about 3,000 people turned up at four major events.

At the Shangri-La Hotel, defence chiefs from 20 countries gathered for the annual Asia Security Conference.

In the morning at Raffles City, about 500 business leaders listened to Trade and Industry Minister George Yeo describe the benefits of the newly-signed Singapore-US Free Trade Agreement.

Last night, it was time to



Almost came back

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Laboratory-Acquired Severe Acute Respiratory Syndrome

Poh Lian Lim, M.D., M.P.H., Asok Kurup, M.B., B.S., Gowri Gopalakrishna, M.Sc.,
Kwai Peng Chan, M.B., B.S., Christopher W. Wong, Ph.D., Lee Ching Ng, Ph.D.,
Su Yun Se-Thoe, Ph.D., Lynette Oon, M.B., B.S., Xinlai Bai, M.Sc.,
Lawrence W. Stanton, Ph.D., Yijun Ruan, Ph.D., Lance D. Miller, Ph.D.,
Vinsensius B. Vega, M.Sc., Lyn James, M.B., B.S., M.Med.,
Peng Lim Ooi, M.B., B.S., M.P.H., Chew Suok Kai, M.B., B.S.,
Sonja J. Olsen, Ph.D., Brenda Ang, M.B., B.S., and Yee-Sin Leo, M.B., B.S.

From the Department of Infectious Diseases, Tan Tock Seng Hospital (P.L.L., B.A., Y.-S.L.); the Departments of Medicine (A.K.) and Pathology (K.P.C., S.Y.S.-T., L.O., X.B.), Singapore General Hospital; the Ministry of Health (G.G., L.J., P.L.O., C.S.K.); the Genome Institute of Singapore (C.W.W., I.W.S., Y.R., L.D.M., V.B.V.); and DSO Na-

THE OUTBREAK OF SEVERE ACUTE RESPIRATORY SYNDROME (SARS) IN Singapore ended in late May 2003.¹ The Centers for Disease Control and Prevention (CDC) removed its travel alerts for Toronto, Hong Kong, China, and Taiwan shortly thereafter.² We report the first case of SARS to occur in Singapore after the initial worldwide outbreak ended. Our report documents the transmission of SARS in a laboratory setting.

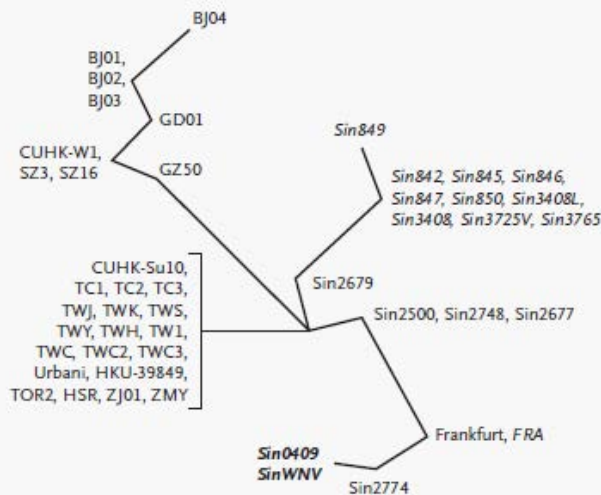


Figure 2. Molecular Relationships among 47 SARS-CoV Genomes.

A phylogenetic tree was constructed by means of a maximum-likelihood method⁹ with the use of sequence information from 13 informative positions (nucleotides 9404, 9854, 17564, 18965, 19084, 19838, 21721, 22222, 22549, 23174, 23735, 23792, and 28268 in the Urbani strain; GenBank accession number AY278741) and 1 deletion (position 27760 to 27807). Sin0409 (the strain isolated from the patient) and SinWNV (the strain isolated from the sample of West Nile virus) appear on the same branch, indicating complete equivalence at all 14 sites. All SARS-CoV sequences were obtained from GenBank except for those indicated in italics, which were from the Genome Institute of Singapore.

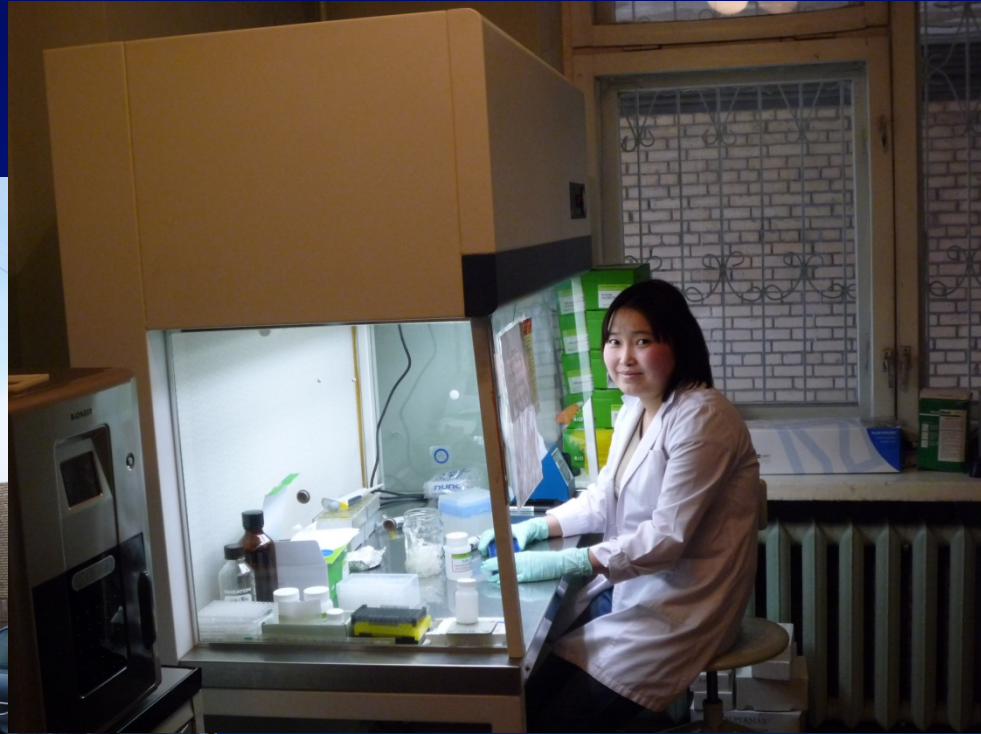
Laboratory-associated infection and relative risk of infection, compared with the risk among the general population.

Organism	No. of cases of infection	Relative risk of infection
<i>Shigella</i> species	15	1
<i>Brucella</i> species	7	8012.5
<i>Salmonella</i> species	6	0.08
<i>Staphylococcus aureus</i>		
All	6	NA
MRSA	5	NA
<i>Neisseria meningitidis</i>	4	40.8
<i>Escherichia coli</i> O157:H7	2	8.6
<i>Coccidioides</i> species	2	1.1
<i>Clostridium difficile</i>	1	0.03

NOTE. Data are for the years 2002–2004 [11]. MRSA, methicillin-resistant *S. aureus*.

Robert A. Weinstein, and Kamaljit Singh Clin Infect Dis.
2009;49:142-147

Molecular diagnostics have allowed
countries to make large leaps
Biosafety follows



Development of Animal Models Against Emerging Coronaviruses: From SARS to MERS corona

Troy C Sutton and Kanta Subbarao

Laboratory of Infectious Disease, NIAID, NIH

The FDA's
Animal efficacy
Rule:
2 animals,
1 a "non-rodent"

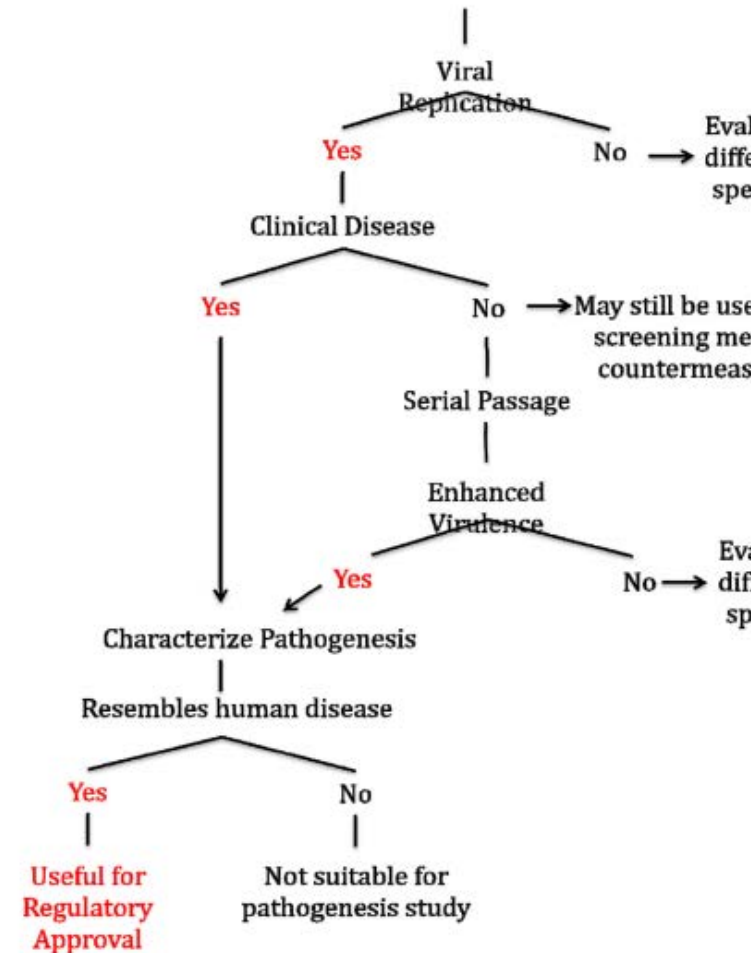


Figure 1. Schematic of strategies to develop an animal model to meet the FDA *Animal Efficacy Rule*

Under the FDA's *Animal Efficacy Rule* ("Animal Rule") therapeutics against rare, emergent or virulent agents can achieve regulatory approval provided efficacy is demonstrated in two animal models (one of which must be a non-rodent species). Animal species of interest must first be evaluated for permissiveness to viral replication and presentation of clinical disease. As an alternative, in animal species that are permissive but do not show clinical disease, serial passage can be performed. After an animal model has been developed the resulting

Why do we have no licensed therapeutics for Nipah, SARS, MERS, Ebola, Dengue, Zika...

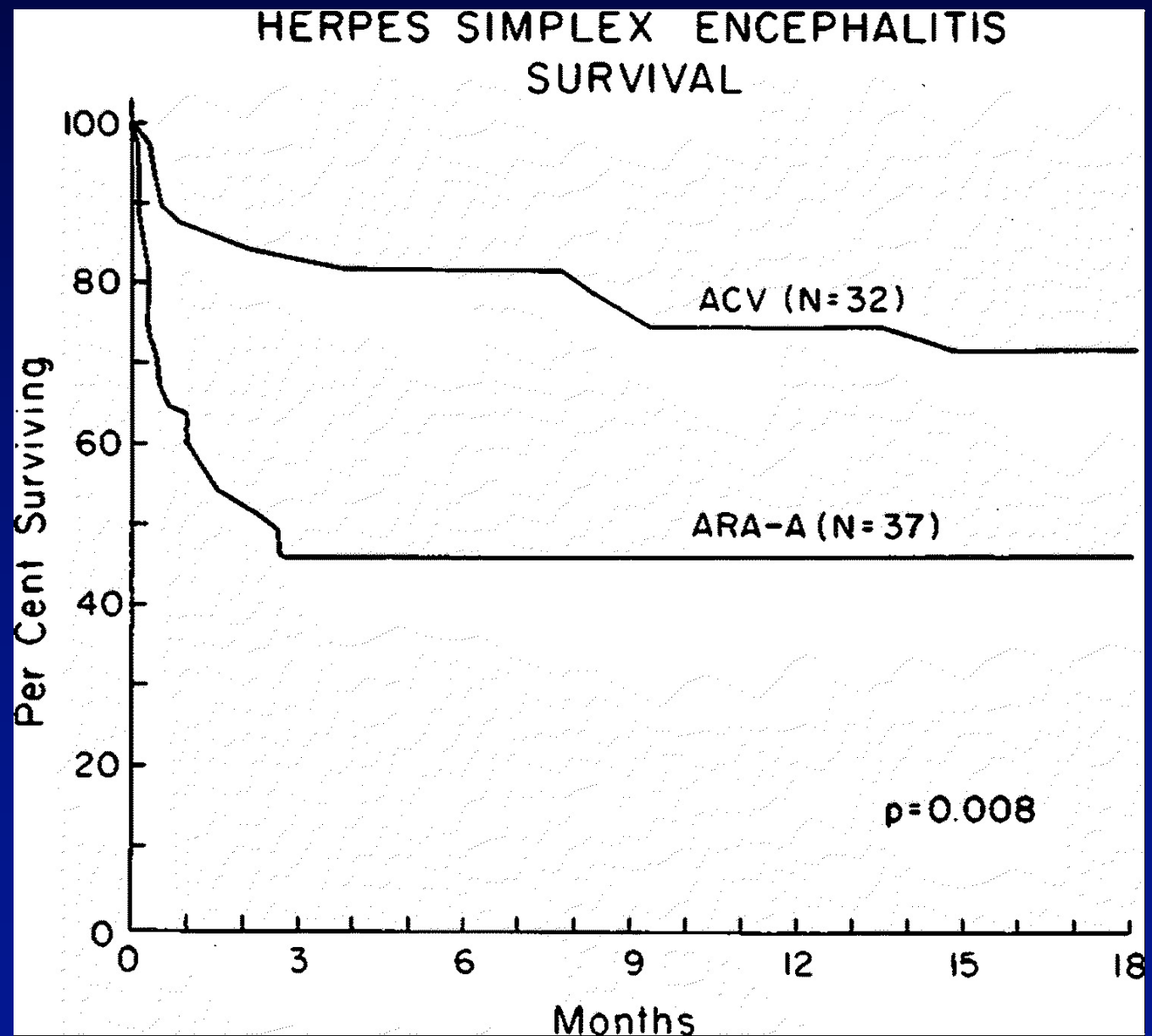
- Pre-clinical issues – biosafety, animal models
- Clinical trial issues – lack of patients, infrastructure
- Ethics and Economic issues – no market ☹

**Comparison of
Survival in Patients
with Biopsy-Proved
Herpes Simplex
Encephalitis
Treated with
Vidarabine (ARA-A)
or Acyclovir (ACV);
 $P = 0.008$.**

*Whitley RJ et al.
N Engl J Med 1986;
314:144-149.*



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Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

view strategies for development of dengue virus inhibitors

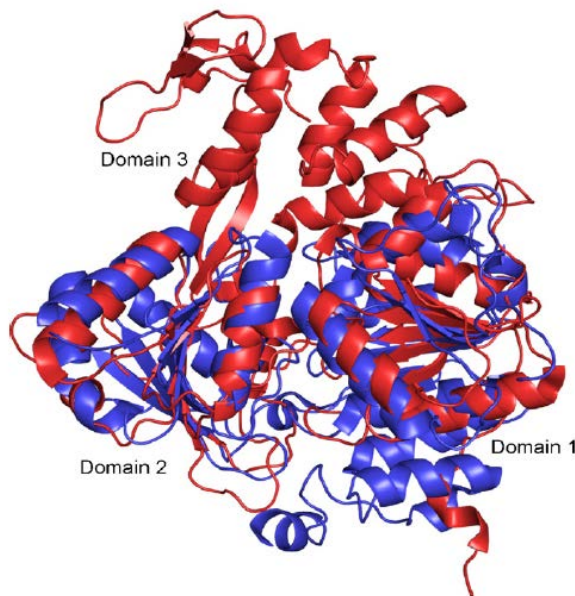
Christian G. Noble, Yen-Liang Chen, Hongping Dong, Feng Gu,
Jew Pheng Lim, Wouter Schul, Qing-Yin Wang, Pei-Yong Shi*

Artis Institute for Tropical Diseases, 10 Biopolis Road, 05-01 Chromos, Singapore 138670, Singapore

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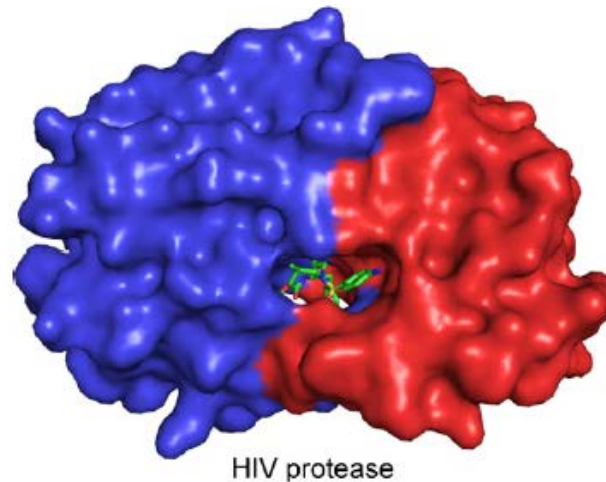
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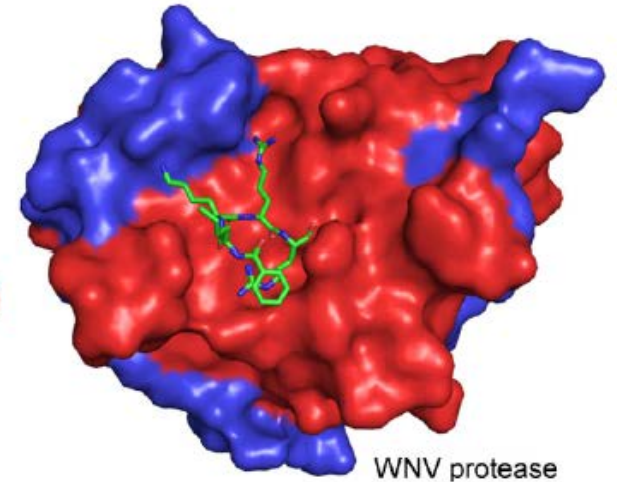
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strategies discussed in this report should be applicable to antiviral development of other



HIV protease



WNV protease

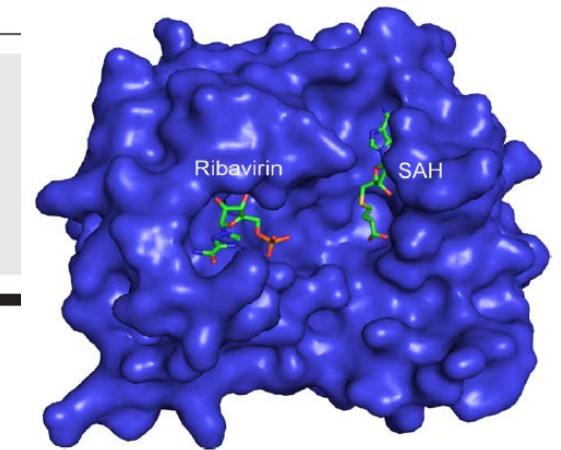


Fig. 4. Structure of the dengue methyltransferase. A surface representation of the dengue methyltransferase shows the positions of the GTP-cap binding site, here bound to Ribavirin, and of the S-adenosyl homocysteine/S-adenosyl methionine binding site. The two existing ligand-binding pockets suggest that it is possible to inhibit the enzyme with a small molecule.

Fig. 3. Alignment of the structures of the dengue helicase (in blue; Xu et al., 2005) and human DDX19B (red; von Moeller et al., 2009), showing that both helicases contain the RecA-like folds (domains 1 and 2), but that only the dengue helicase



Efficacy and safety of celgosivir in patients with dengue fever (CELADEN): a phase 1b, randomised, double-blind, placebo-controlled, proof-of-concept trial

Jenny G Low*, Cynthia Sung*, Limin Wijaya*, Yuan Wei, Abhay P S Rathore, Satoru Watanabe, Boon Hian Tan, Liying Toh, Lian Tee Chua, Yan'an Hou, Angelia Chow, Shiqin Howe, Wing Ki Chan, Kah Hin Tan, Jasmine S Chung, Benjamin P Cherng, David C Lye, Paul A Tambayah, Lee Ching Ng, John Connolly, Martin L Hibberd, Yee Sin Leo, Yin Bun Cheung, Eng Eong Ooi*, Subhash G Vasudevan

Summary

Lancet Infect Dis 2014;
14:706–15

Published Online

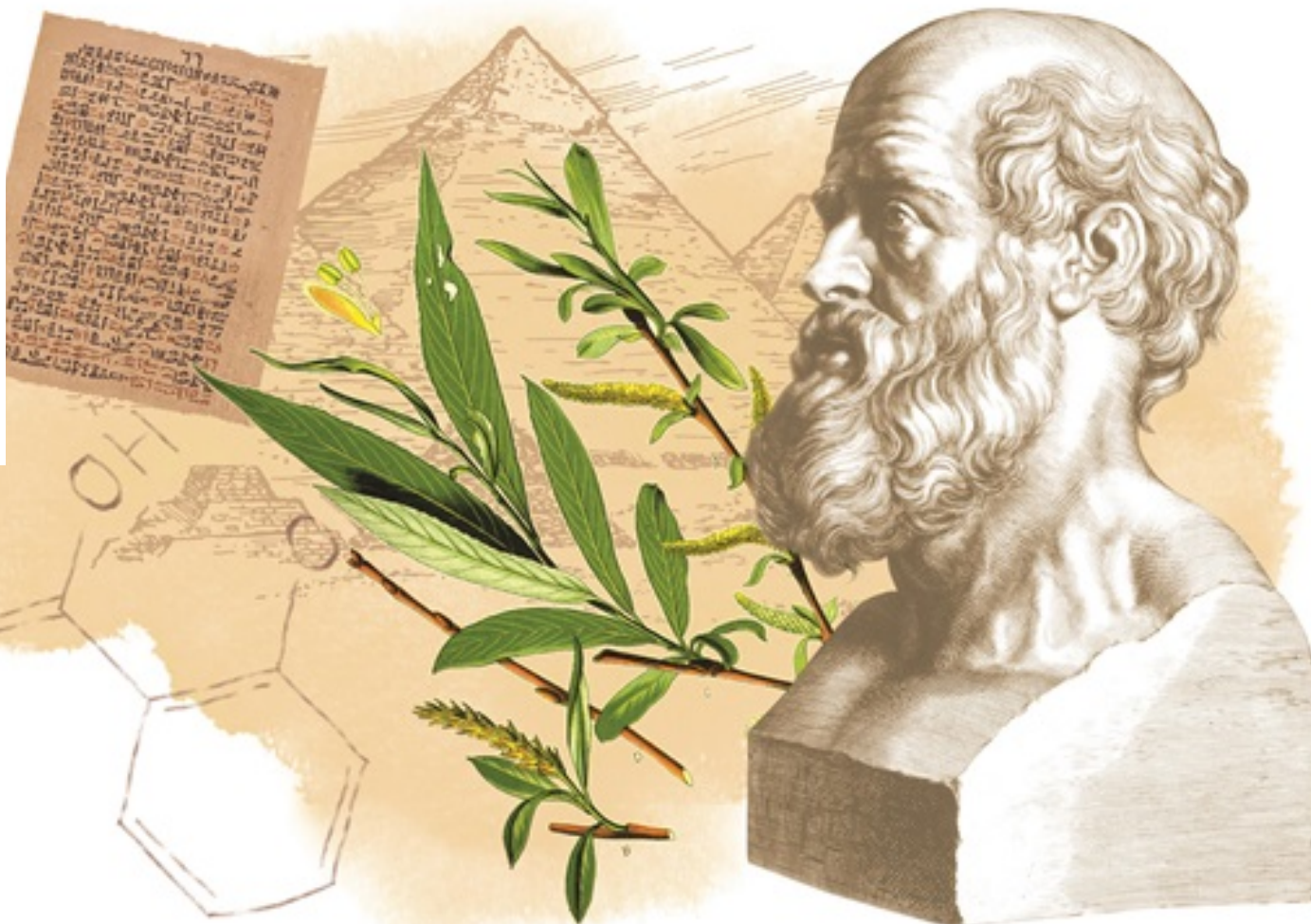
	Celgosivir group (n=24)	Placebo group (n=26)	Difference (90% CI)	p value
VLR* of all patients	–1.86 (1.07)	–1.64 (0.75)	–0.22 (–0.65 to 0.22)	0.203
VLR* of patients with primary infection	–1.37 (0.78)†	–1.51 (0.66)‡	0.13 (–0.31 to 0.58)	0.690
VLR* of patients with secondary infection	–2.27 (1.13)§	–2.22 (0.88)¶	–0.05 (–1.04 to 0.93)	0.463
AUC above 37°C (0–96 h) for all patients	54.92 (31.04)	40.72 (18.69)	14.20 (2.16 to 26.25)	0.073 (0.054)
AUC above 37°C (0–96 h) for patients with primary infection	54.41 (34.75)†	38.82 (18.62)‡	15.60 (–0.30 to 31.50)	0.947 (0.106)
AUC (0–96 h) for patients with secondary infection	55.34 (28.98)§	48.69 (18.74)¶	6.65 (–17.97 to 31.27)	0.678 (0.644)

Data are mean (SD) unless otherwise stated. VLR=virological log reduction. AUC=area under the curve for fever burden. * Mean value of VLR from day 1 at days 2, 3, and 4. †n=11. ‡n=21. §n=13. ¶n=5. ||Two-sided p value from two-sample t test.

Table 3: Mean VLR and AUC

It worked well in animal models but...

Re-purposed drugs have a long history



<http://www.pharmaceutical-journal.com/news-and-analysis/infographics/a-history-of-aspirin/20066661.article>

Volunteers needed to test a possible treatment for **DENGUE**

Join the Ketotifen as a Treatment Against Dengue **KETODEN DRUG TRIAL**

Ketotifen is a drug that is approved for the treatment of asthma and allergies. It may also be effective in limiting the damage to blood vessels that occur during dengue fever.

This is an approved medicine being tested for a new use in relieving symptoms of dengue fever caused by damage to the blood vessels.

If you are diagnosed with dengue fever and choose to participate in the **KETODEN Drug Trial**, you will be required to:

- Return to the Investigational Medicine Unit at NUH or an approved trial site for 7 visits
- Undergo an MRI on the first visit and after 5 days
- You will be paid to compensate for your time and inconveniences



CONTACT US

8591-7313
8595-2343

EMAIL US

KetodenTrial
@gmail.com

FOR MORE INFO

www.ketoden.com

Untested Ebola drug given to patients in Sierra Leone causes UK walkout

Use of amiodarone heart drug at Lakka centre in Freetown deemed 'reckless' by scientist as 14 medical staff withdraw over safety fears

Sarah Boseley in Freetown

Monday 22 December 2014 19.02 GMT



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Original Article

A Randomized, Controlled Trial of ZMapp for Ebola Virus Infection

The PREVAIL II Writing Group

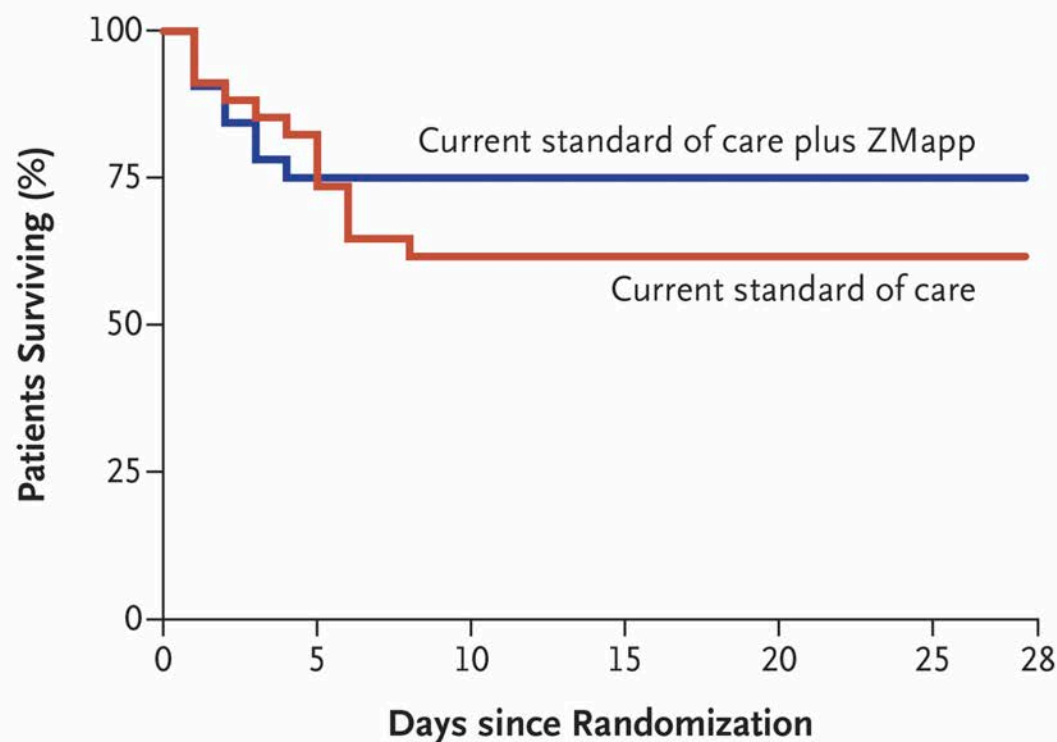
But good trials can and have been done

N Engl J Med
Volume 375(15):1448-1456
October 13, 2016



The NEW ENGLAND
JOURNAL of MEDICINE

Kaplan–Meier Plot of Survival, According to the Two Assigned Treatment Groups.

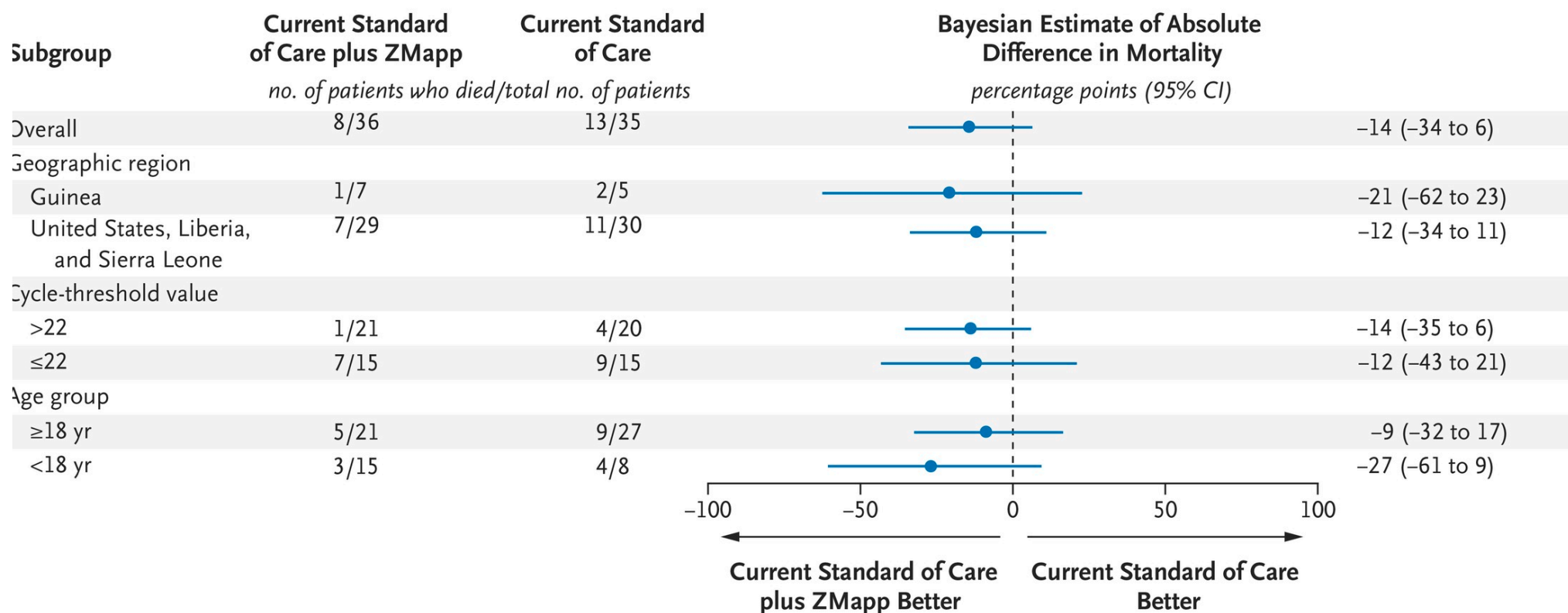


No. at Risk

Current standard of care	35	29	22	22	22	22	22
Current standard of care plus ZMapp	36	28	28	28	28	28	28



Forest Plot of Absolute Difference between Groups in 28-Day Mortality, Overall and According to Subgroup.



It pays to be Prepared

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. Import 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
Kamofsky 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 log₁₀ (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.

Can antiviral
treatment work?

There are plenty
of skeptics..

To the Editors of THE LANCET.

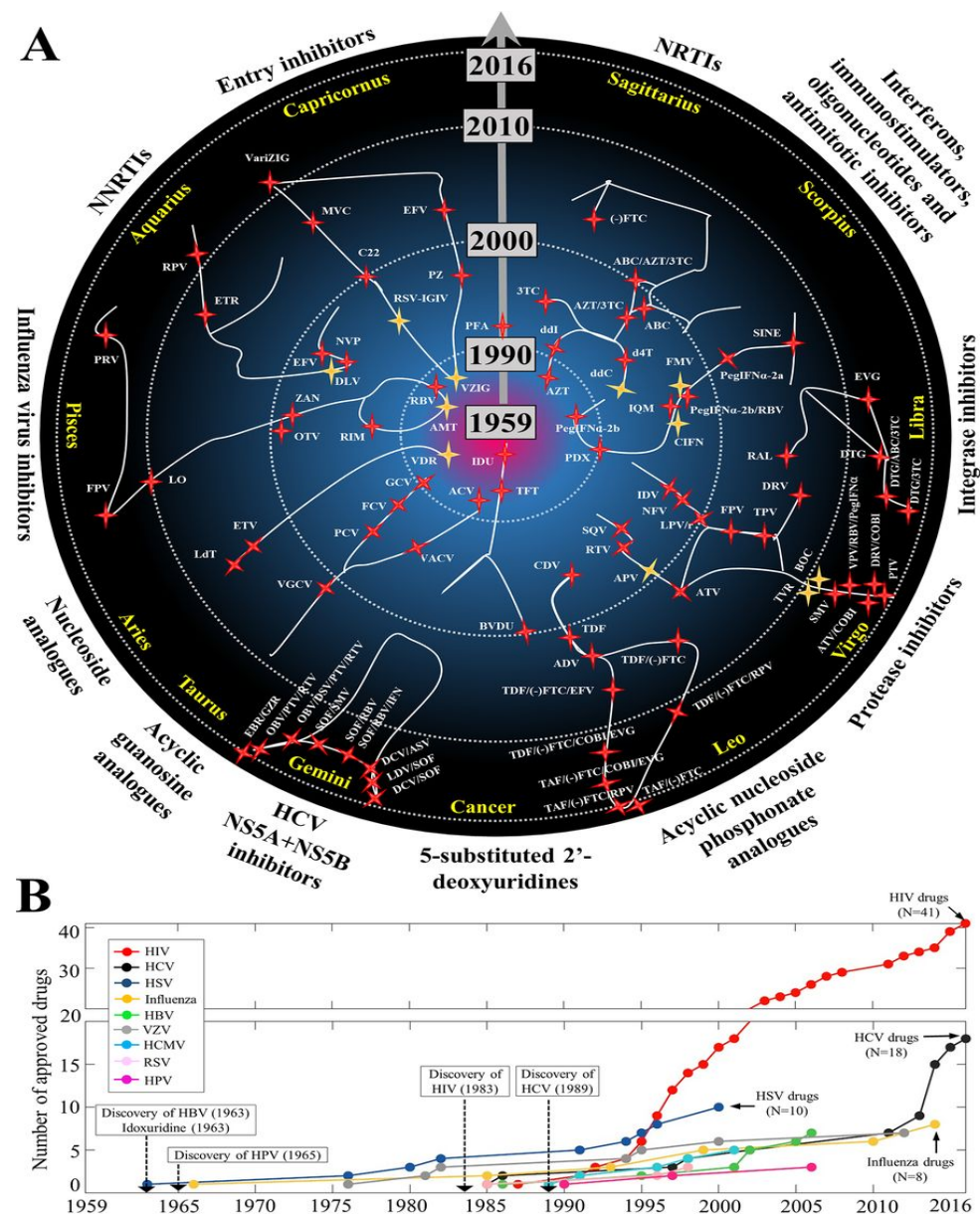
SIRS,—I read with much interest Dr. Yeo's valuable letter on the Treatment of Influenza in last week's issue of THE LANCET, and should like to endorse what he says in reference to the deleterious effects of antipyrin in the treatment of this scourge. In comparing notes of the cases which have presented 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.

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

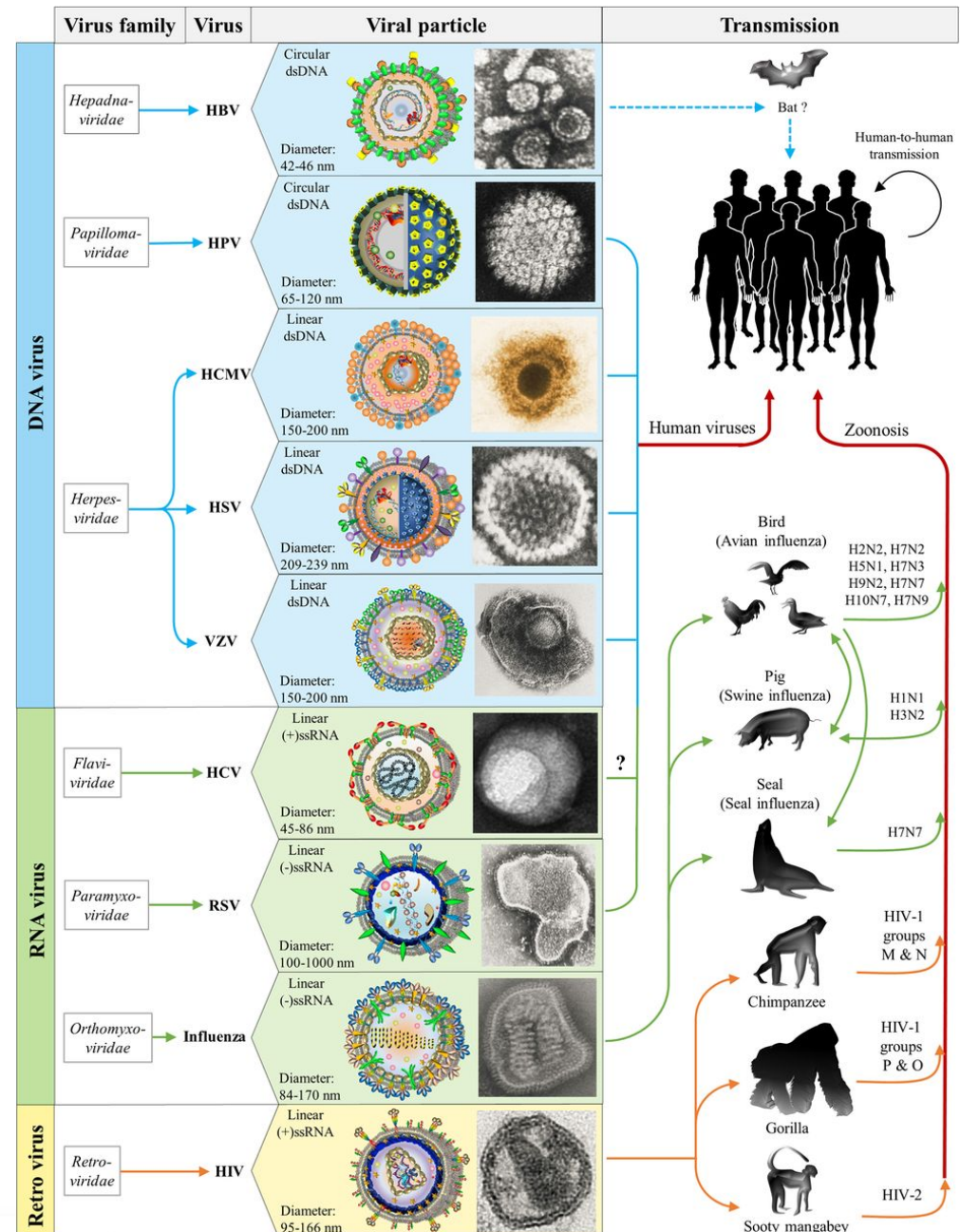
rik De Clercq, and Guangdi Li Clin. Microbiol. Rev. 2016;29:695-747



Clinical Microbiology Reviews

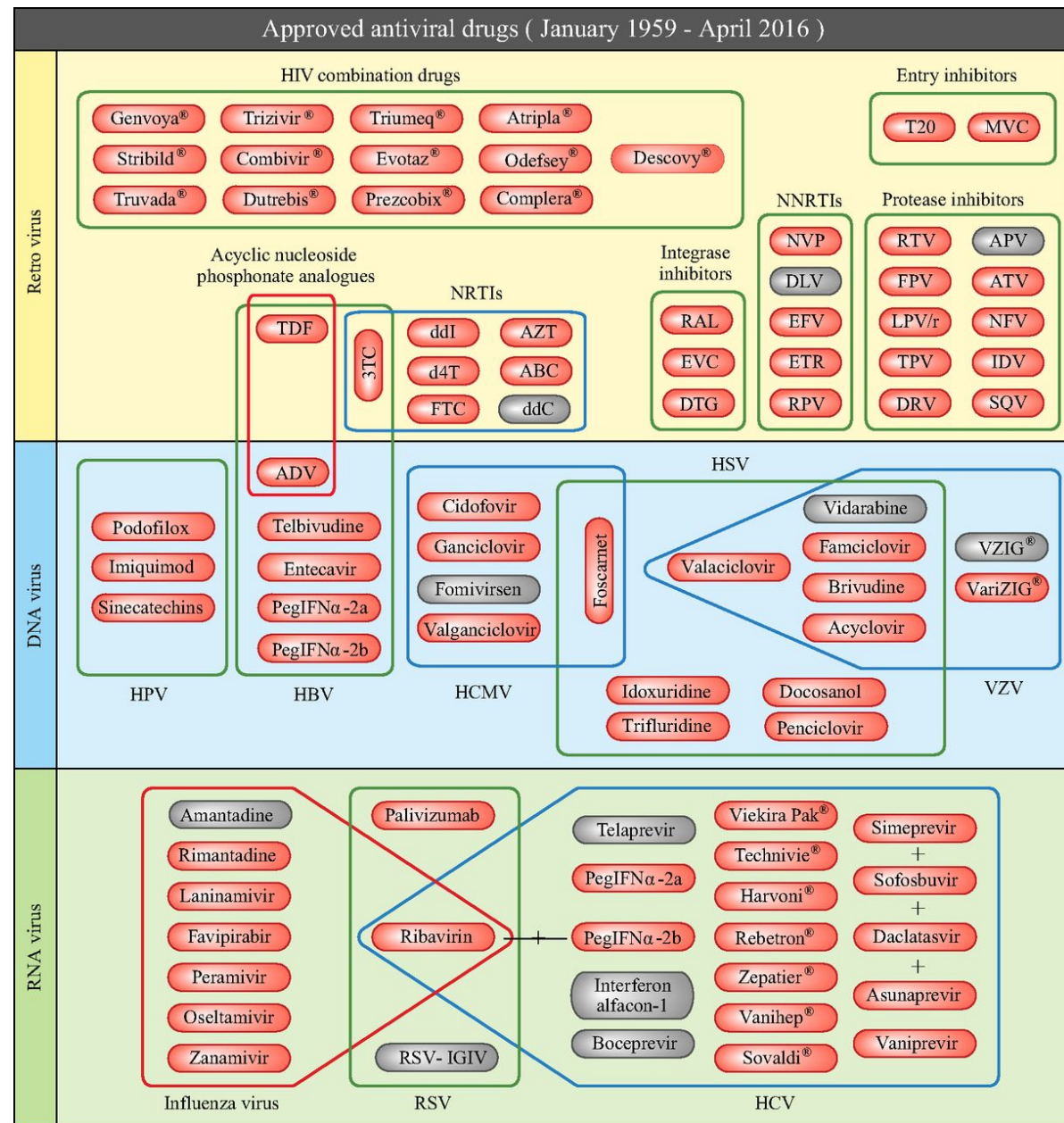
Virus family, morphology, and transmission of HIV, HBV, HCV, HSV, HCMV, HPV, RSV, VZV, and influenza virus.

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



Clinical Microbiology Reviews

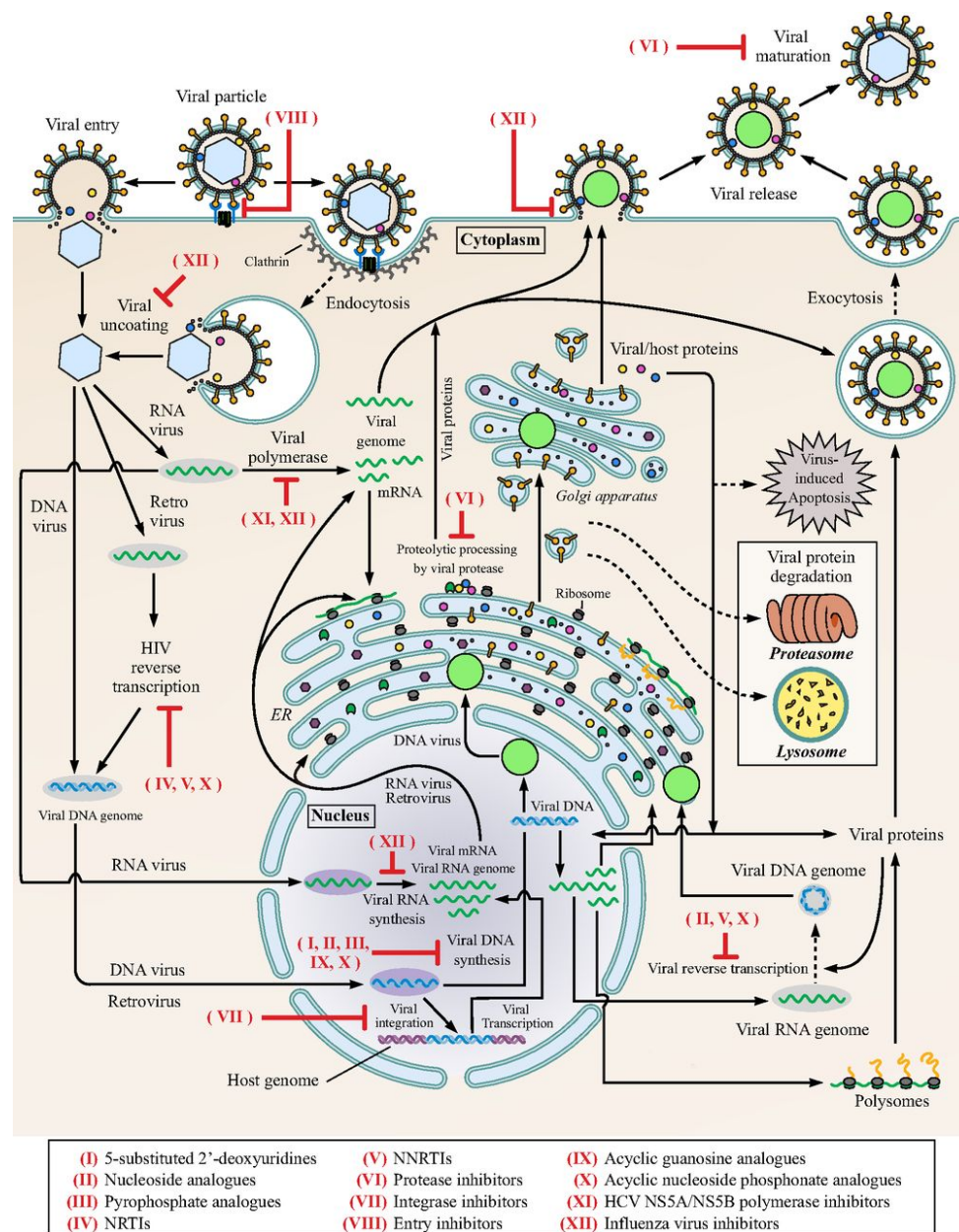
Antiviral drug groups for the treatment of 9 infectious diseases.



ik De Clercq, and Guangdi Li Clin. Microbiol. Rev. 16;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



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epidemiologic Notes and Reports

***pneumocystis* Pneumonia --- Los Angeles**

During the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

Patient 1: A previously healthy 33-year-old man with a history of lymphomas, leukopenia, and CMV viremia was treated with trimethoprim-sulfamethoxazole. He died of the presence of neoplasia.

Patient 2: A previously healthy 30-year-old man with documented seroconversion to CMV, leukopenia and mucosal candidiasis.

Patient 3: A 30-year-old man was treated for *P. carinii* pneumonia that responded to trimethoprim-sulfamethoxazole.



Persons using assistive technology might not be able to fully access information in this file. For assistance, please send e-mail to: mmwrq@cdc.gov. Type 508 Accommodation and the title of the report in the subject line of e-mail.

Current Trends Acquired Immune Deficiency Syndrome (AIDS): Precautions for Clinical and Laboratory Staffs

The etiology of the underlying immune deficiencies seen in AIDS cases is unknown. One hypothesis consistent with current observations is that a transmissible agent may be involved. If so, transmission of the agent would appear most commonly to require intimate, direct contact involving mucosal surfaces, such as sexual contact among homosexual males, or through parenteral spread, such as occurs among intravenous drug abusers and possibly hemophilia patients using Factor VIII products. Airborne spread and interpersonal spread through casual contact do not seem likely. These patterns resemble the distribution of disease and modes of spread of hepatitis B virus, and hepatitis B virus infections occur very frequently among AIDS cases.

There is presently no evidence of AIDS transmission to hospital personnel from contact with affected patients or clinical specimens. Because of concern about a possible transmissible agent, however, interim suggestions are appropriate to guide patient-care and laboratory personnel, including those whose work involves experimental animals. At present, it appears prudent for hospital personnel to use the same precautions when caring for patients with AIDS as those used for patients with hepatitis B virus infection, in which blood and body fluids likely to have been contaminated with blood are considered infective. Specifically, patient-care and laboratory personnel should take precautions to avoid direct contact of skin and mucous membranes with blood, blood products, excretions, secretions, and tissues of persons judged likely to have AIDS. The following precautions do not specifically address outpatient care, dental care, surgery, necropsy, or hemodialysis of AIDS patients. In general, procedures appropriate for patients known to be infected with hepatitis B virus are advised, and blood and organs of AIDS patients should not be donated.

Multiple options that work!

 **Aptivus** (Tipranavir)
The Basics | News | Research

 **Atripla**
(Efavirenz/Tenofovir/FTC)
[The Basics](#) | [News](#) | [Research](#)

Combivir (AZT/3TC)
The Basics | News | Research

Crixivan (Indinavir)
The Basics | News | Research

Edurant (Rilpivirine, TMC278)
The Basics | News | Research

Emtriva (Emtricitabine, FTC)
The Basics | News | Research

 **Epivir** (3TC, Lamivudine)
The Basics | News | Research

 Epzicom (Abacavir/3TC, Kivexa)

Fuzeon (Enfuvirtide, T-20)
The Basics | News | Research

Hivid (Zalcitabine, ddC)

 **Intelligence** (Etravirine, TMC125)
The Basics | News | Research

 **Invirase** (Saquinavir)
The Basics | News | Research

 **Isentress** (Raltegravir, MK-0518)
The Basics | Research

Kaletra (Lopinavir/Ritonavir)
The Basics | News | Research

Lexiva (Fosamprenavir, Telzir)
The Basics | Research

 **Norvir** (Ritonavir)
The Basics | News | Research

 Prezista (Darunavir, TMC114)
The Basics | News | Research

 **Rescriptor** (Delavirdine)
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Retrovir (Zidovudine, AZT)
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Reyataz (Atazanavir)
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Selzentry (Maraviroc, Celsentri)
The Basics | News | Research

 **Sustiva** (Efavirenz, Stocrin)
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Trizivir
(AZT/3TC/Abacavir)
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Truvada (Tenofovir/FTC)
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 **Videx** (Didanosine, ddI)
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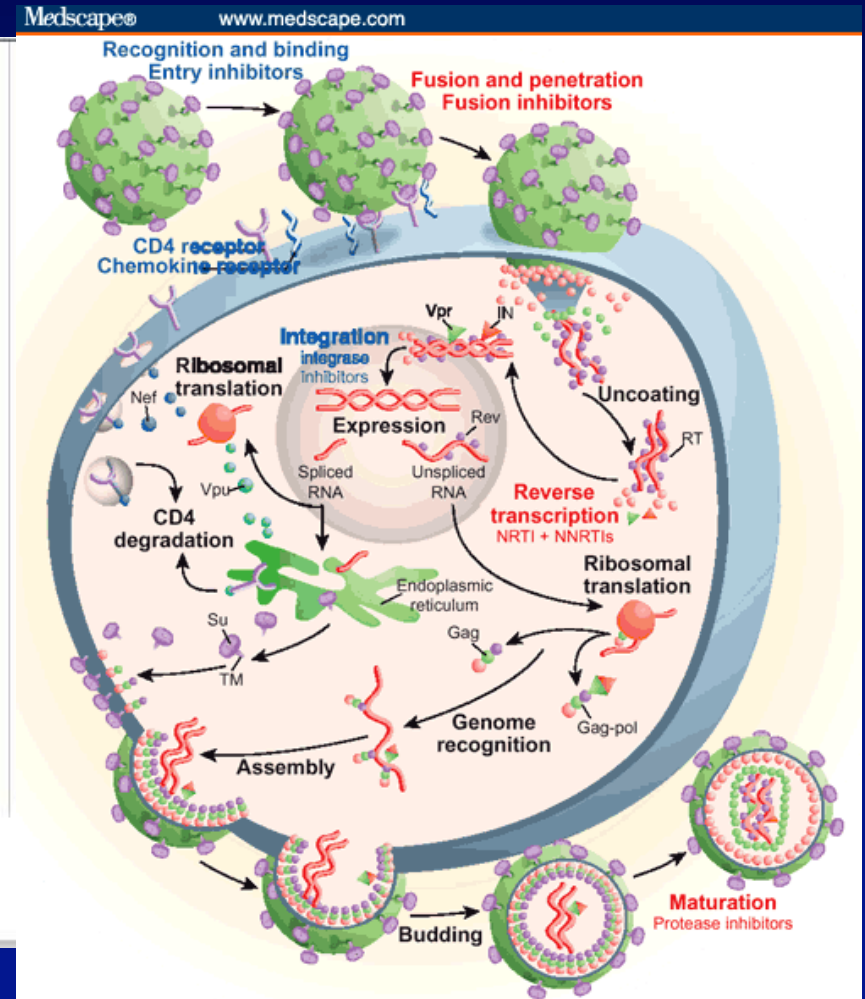
Viracept (Nelfinavir)
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Viramune (Nevirapine)
The Basics | News | Research

 **Viread** (Tenofovir)
The Basics | News | Research

 **Zerit** (Stavudine, d4T)
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Ziagen (Abacavir)
The Basics | News | Research



Source: Nat Med © 2003 Nature Publishing Group

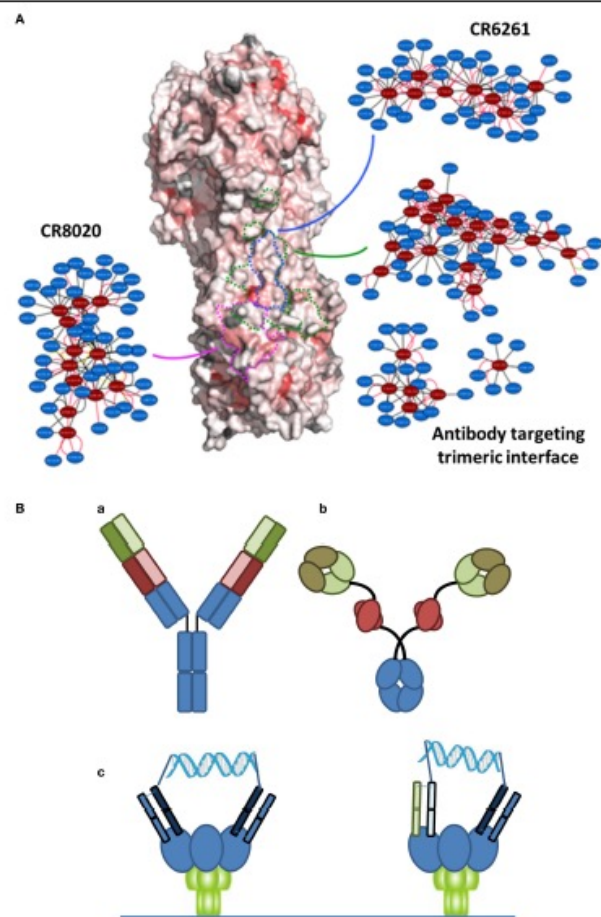


FIGURE 1 | (A) Network-view of bNAbs epitopes. HA trimer is represented in a solvent accessible surface format and colored based on normalized residue network scores. Coloring varies from white to red where white indicates poorly networked residues and red indicates highly networked residues. The three 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 PstI (red) targets the antibody to the cell surface of *Pseudomonas* enables engagement of a traditional Vh-Vl pentamer with the rarer PstV target. (c) Crosslinking of binding domains of variable and constant regions (Vh, CH1/VL, CL; Fab2), 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

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 Herbreteau, 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 ₀₋₄₈ (µg/mL×h)	AUC ₀₋₇₂ (µg/mL×h)	%AUC _{max}	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. AUC₀₋₂₄=AUC in steady state. AUC₀₋₄₈=AUC from administration to last observed concentration at time t. AUC₀₋₇₂=AUC area under the plasma concentration curve extrapolated to infinite time. CV=coefficient of variation. Nd=not determined.

Table 3: Pharmacokinetic data

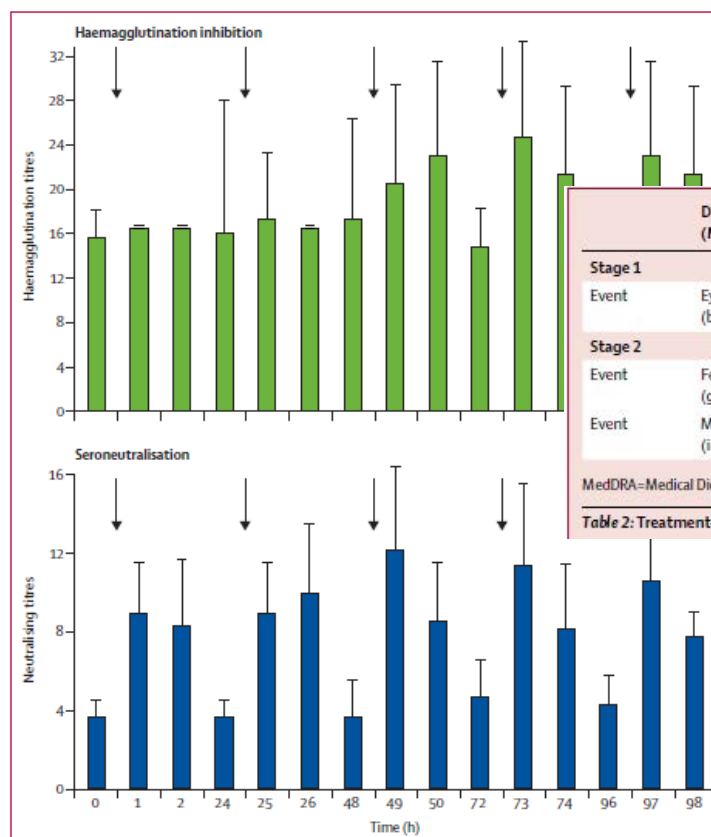


Figure 4: Haemagglutination inhibition and neutralising titres after five infusions of FBF001
Data are means (bars show SD). Titres measured in patients after five doses of FBF001 at 0 h, 24 h, 48 h, 72 h, and 96 h (arrows) in study phase 2.

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

Why do we have no licensed therapeutics for Nipah, SARS, MERS, Ebola, Dengue, Zika...

- Pre-clinical issues – biosafety, animal models
- Clinical trial issues – lack of patients, infrastructure
- Ethical and Economic issues – no market ☹

Observations on Vaccine Production Technologies and Factors Potentially Influencing Pandemic Influenza Vaccine Choices in Developing Countries

A discussion paper



Inequality is an issue

Reliance on a small number of developed country sources for pandemic vaccine and/or antigen is unlikely to remain an acceptable solution for most developing countries, particularly in view of the fact that the developed country industry is not currently in a position to offer sufficient quantities of antigen in a timely manner after the appearance of a pandemic strain.

Practically, the present situation of dependency, which is effectively unaltered by the WHO Pandemic Action Plan, means that the vast majority of developing countries will only receive significant quantities of vaccine after the needs of developed countries are met, which will likely be many months after the onset of a pandemic—months during which pandemic mortality may be severe.

As a result of the inequity, in the event of a pandemic, developing countries will suffer a disproportionate burden of serious disease and death, a problem that could be ameliorated by increased and equitably distributed global vaccine supplies, particularly in the developing world. These vaccine supply problems may be further exacerbated by non-health factors, in the form of export controls that may inhibit the ability of some countries to prepare for a pandemic because some kinds of technology transfer are unavailable to them.

Developing country leaders are likely to face question from their citizens if they remain vulnerable while the citizens of wealthy countries are vaccinated; this situation could become especially tense if a pandemic is severe enough to cause serious socioeconomic disruption.

<https://file.wikileaks.org/file/pandemic-vaccine-options-2009.pdf>

United States Senate
WASHINGTON, DC 20510

March 20, 2007

The Honorable Susan F. Schwab
United States Trade Representative
600 17th Street, Northwest
Washington, D.C. 20508

Dear Ambassador Schwab,

We write to express concern about plans of the Royal Thai Government to significantly expand its program of compulsory licensing of innovative U.S. pharmaceutical products.

In November 2006, the Thai Ministry of Public Health began to seek compulsory licenses for pharmaceutical products developed by U.S. companies. Recent actions by the Thai Ministry of Public Health demonstrate its intent to expand this compulsory licensing program to include nearly a dozen medications to treat high cholesterol and other conditions wholly unrelated to any urgent public health issue.

We strongly support WTO rules that recognize the rights of countries to consider actions, including compulsory licensing, to address urgent public health needs, such as those resulting from HIV/AIDS, tuberculosis, malaria and other pandemics. But we do not believe that WTO members intended those rules to be used to allow compulsory licenses on any medicine whatsoever as a matter of standard government policy, especially without any meaningful prior consultation with the patent holders.

Strong protection for intellectual property rights is critical for America's innovative economy. Thailand's actions appear to constitute a governmental policy to expropriate patents on all manner of innovative medicines not used to address urgent public health needs. That will harm the U.S. research-based industry that supports more than two million workers. Without a strong response by the U.S. government, we are concerned that respect for intellectual property rights worldwide will diminish.


We believe such policies could also have harmful consequences for patients. In bypassing the current legal suppliers of these products, Thailand is taking risks with both the safety and dependability of the drug supply. Moreover, Thailand's actions raise grave concerns about the investment climate in Thailand.


Access to novel therapeutics Is Patent protection important for science???

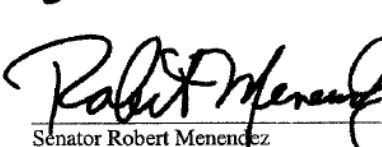
We ask you to encourage the Royal Thai Government to consult with our innovative companies to achieve a positive outcome, which ensures a continued focus on improving the health of Thai patients and preserves strong intellectual property protection.

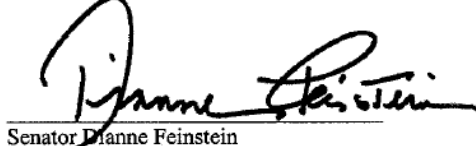
Thank you for your consideration of this important issue.

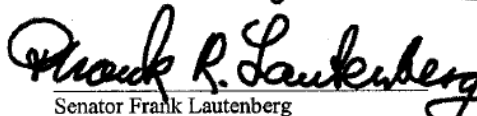
Sincerely,


Senator Joseph I. Lieberman


Senator Thomas R. Carper


Senator Robert Menendez


Senator Dianne Feinstein


Senator Frank Lautenberg

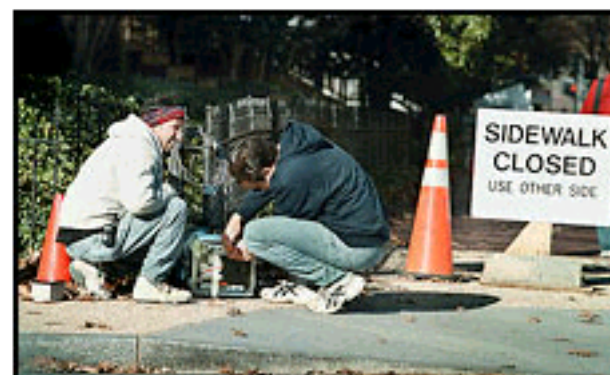
Capitol Hill Anthrax Matches Army's Stocks

5 Labs Can Trace Spores to Ft. Detrick

By Rick Weiss and Susan Schmidt
Washington Post Staff Writers
Sunday, December 16, 2001; Page A01

Genetic fingerprinting studies indicate that the anthrax spores mailed to Capitol Hill are identical to stocks of the deadly bacteria maintained by the U.S. Army since 1980, according to scientists familiar with the most recent tests.

Although many laboratories possess the Ames strain of anthrax involved in this fall's bioterrorist attacks, only five laboratories so far have been



Rich Magan, left, and Howard Schmidt of Lockheed Martin/REAC check the neighborhood near the Hart Office Building for chlorine dioxide gas to be introduced to kill anthrax in the structure. (Robert A. Reeder - The Washington Post)

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some
animals
are more
equal than
others!!....

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Bayer, U.S. Deal on Anthrax Drug

Faced with the possibility of compulsory licensing of its Cipro antibiotic (used as an anthrax drug) for whatever royalties the government would set, Bayer agreed to supply 100 million pills to the U.S. for almost half price.

By [Tom Jacobs](#) (TMF Tom9)
October 25, 2001

With big drug makers quaking in their patented boots, Germany-based drug maker **Bayer AG** (OTC: BAYZF) reached an agreement with the U.S. government for supplies of its Cipro anthrax antibiotic. Bayer will provide 100 million Cipro tabs for \$0.95 each, a little more than half the \$1.77 the government had reportedly been paying. This will give the federal government the ability to treat 12 million people for anthrax by January 2002, against 2 million now.

The deal follows Canada's decision to "break" Bayer's patent and buy from a generic drug makers, and its sudden reversal of that decision. Tommy Thompson, U.S. Secretary of Health and Human Services, had apparently been threatening Bayer with the same patent action in the United States. Bayer decided to negotiate at gunpoint.

Compulsory patent licensing

Technically, a government does not abrogate a patent holder's right to its invention. A patent granted today in the U.S. gives its holder the right to prevent anyone else from using the invention without a license for 20 years. If the patent holder grants a license, it's usually in exchange for an upfront payment, future royalties, or other benefits such as cross-licensing of another company's patents or an agreement not to challenge certain patents or applications. The latter two benefits aren't chump change, by the way. It's smart to avoid patent litigation, which is expensive and can throw a business into uncertainty.

But in recent years, some countries have passed laws allowing limited exceptions to the patent holder's absolute rights. These exceptions allow compulsory licensing, where a government requires the patent holder to license its invention to one or more selected entities at a royalty rate the government sets. In the U.S., compulsory licensing has mainly taken place through Federal Trade Commission (FTC) conditions for approval of drug company mergers, and

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Nipah Virus: A Recently Emergent Deadly Paramyxovirus

K. B. Chua,¹ W. J. Bellini,^{2*} P. A. Rota,² B. H. Harcourt,² A. Tamin,² S. K. Lam,¹ T. G. Ksiazek,² P. E. Rollin,² S. R. Zaki,² W.-J. Shieh,² C. S. Goldsmith,² D. J. Gubler,³ J. T. Roehrig,³ B. Eaton,⁴ A. R. Gould,⁴ J. Olson,² H. Field,⁵ P. Daniels,⁴ A. E. Ling,⁶ C. J. Peters,² L. J. Anderson,² B. W. J. Mahy²

A paramyxovirus virus termed Nipah virus has been identified as the etiologic agent of an outbreak of severe encephalitis in people with close contact exposure to pigs in Malaysia and Singapore. The outbreak was first noted in late September 1998 and by mid-June 1999, more than 265 encephalitis cases, including 105 deaths, had been reported in Malaysia, and 11 cases of encephalitis or respiratory illness with one death had been reported in Singapore. Electron microscopic, serologic, and genetic studies indicate that this virus belongs to the family *Paramyxoviridae* and is most closely related to the recently discovered Hendra virus. We suggest that these two viruses are representative of a new genus within the family *Paramyxoviridae*. Like Hendra virus, Nipah virus is unusual among the paramyxoviruses in its ability to infect and cause potentially fatal disease in a number of host species, including humans.

An outbreak of severe febrile encephalitis associated with human deaths was reported in peninsular Malaysia beginning in late September 1998. The outbreak was associated with respiratory illness in pigs and was initially attributed to Japanese encephalitis (JE) (1). JE is a mosquito-borne viral disease that is enzootic in the region, and pigs are among the amplifying vertebrate hosts (2). By February 1999, similar diseases in pigs and humans were recognized in other regions in Malaysia, in association with the movement of a large number of pigs from Ipoh southward into the new outbreak areas. In March 1999, a cluster of 11 cases of respiratory and encephalitis illnesses was noted in Singapore

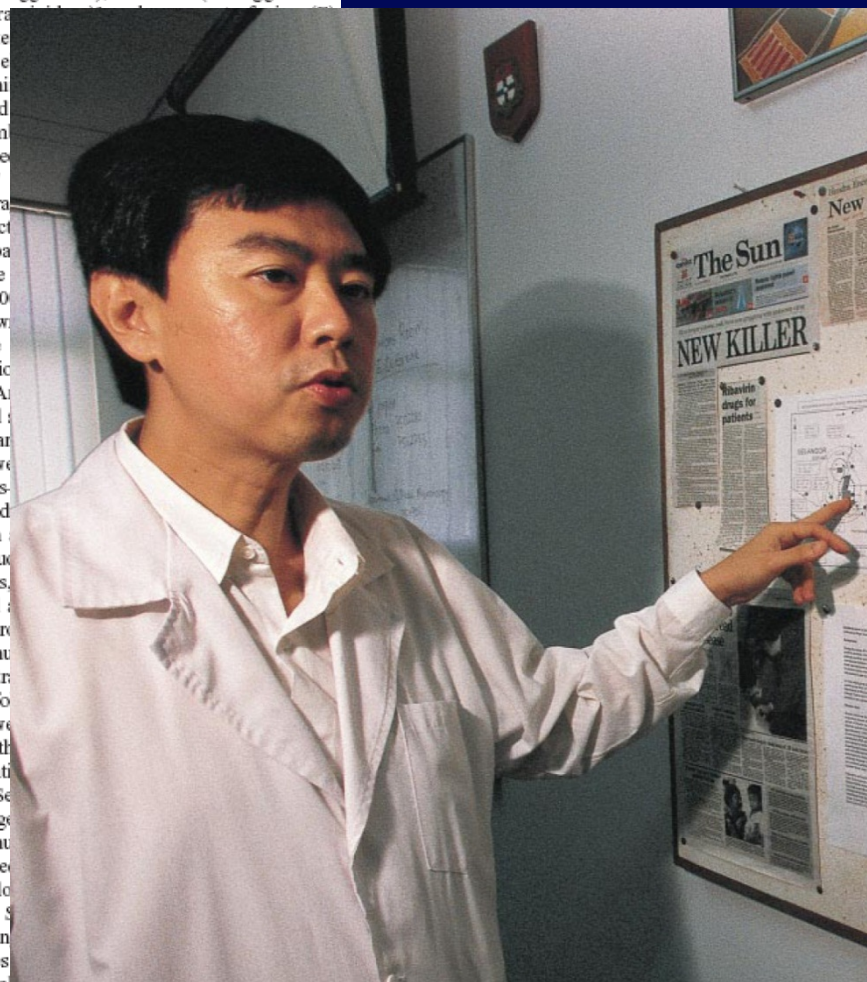
in abattoir workers who handled pigs from the outbreak regions in Malaysia. The outbreak in Singapore ended when the importation of pigs from Malaysia was prohibited, and the outbreak in Malaysia ceased when over 1 million pigs were culled from the outbreak area and immediately surrounding areas (3). A total of 265 cases of encephalitis, including 105 deaths, were associated with the outbreak in Malaysia.

Because some of the epidemiologic characteristics of the disease in humans were distinct from those of JE [most cases occurred in adult males who worked with pigs, very few case patients were young children, and neither mosquito control nor JE vaccination programs appeared to affect the course of the outbreak (4)], investigators in Malaysia expanded attempts to isolate an agent. In early March 1999, Vero cells inoculated with cerebrospinal fluid specimens from three fatal cases of encephalitis developed syncytia.

Electron microscopic (EM) studies of the virus, named Nipah virus (5), demonstrated features characteristic of a virus belonging to the family *Paramyxoviridae* (Fig. 1). This family of viruses typically possesses a single-stranded nonsegmented RNA genome of negative polarity that is fully encapsidated by protein. The helical

nucleocapsid structure is surrounded by a membrane derived from the plasma membrane from which the viruses bud. Virus particles vary in size from 120 to 500 nm. The paramyxovirus envelope contains two transmembrane glycoproteins, a cell receptor binding protein [G (glycoprotein), H (hemagglutinin), or HN (hemagglutinin/neuraminidase)] and a small surface protein (F). The virus is highly infectious, with a 50% tissue culture infective dose (TCID₅₀) of 0.07 TCID₅₀/g of tissue. The virus is highly infectious, with a 50% tissue culture infective dose (TCID₅₀) of 0.07 TCID₅₀/g of tissue. The virus is highly infectious, with a 50% tissue culture infective dose (TCID₅₀) of 0.07 TCID₅₀/g of tissue.

At the time of the outbreak, the virus was initially identified as a new paramyxovirus. The outbreak in Singapore ended when the importation of pigs from Malaysia was prohibited, and the outbreak in Malaysia ceased when over 1 million pigs were culled from the outbreak area and immediately surrounding areas (3). A total of 265 cases of encephalitis, including 105 deaths, were associated with the outbreak in Malaysia. Because some of the epidemiologic characteristics of the disease in humans were distinct from those of JE [most cases occurred in adult males who worked with pigs, very few case patients were young children, and neither mosquito control nor JE vaccination programs appeared to affect the course of the outbreak (4)], investigators in Malaysia expanded attempts to isolate an agent. In early March 1999, Vero cells inoculated with cerebrospinal fluid specimens from three fatal cases of encephalitis developed syncytia. Electron microscopic (EM) studies of the virus, named Nipah virus (5), demonstrated features characteristic of a virus belonging to the family *Paramyxoviridae* (Fig. 1). This family of viruses typically possesses a single-stranded nonsegmented RNA genome of negative polarity that is fully encapsidated by protein. The helical



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*To whom correspondence should be addressed.

Partnerships, Not Parachutists, for Zika Research

David L. Heymann, M.D., Joanne Liu, M.D., and Louis Lillywhite, M.B., B.Ch.

When the director-general of the World Health Organization (WHO) declared that the recently reported clusters of microcephaly and other neurologic disorders represent a Public Health Emergency of International Concern (PHEIC), she called for increased research into their cause, including the question of whether the Zika virus is the source of the problem.¹ The declaration provides an opportunity to step up the pace of research in order to find the answer to some important questions more quickly. It could not only facilitate the accumulation of knowledge about the relationship between the Zika virus and microcephaly, but also accelerate the study of newer technologies for mosquito control, which could have far-reaching effects on global health security beyond controlling Zika infections.

But to answer these research questions effectively and maximize their contribution to enhancing health security, we believe it is critical that research be conducted collaboratively. Building and strengthening public

health collaboration to the ulation ment tries health Yet not a and v recent some hone up to practi ratorie provid ing th place for de impro genera crisis many a play leged! portin their times permi which initiat netwo

These practices have been pejoratively labeled “parachute” research: fully equipped research teams from other countries arrive at the site where research is needed, conduct their research independently of others, and then leave. Parachute researchers reduce the effectiveness of emergency responses by neglecting to share their data with the public health teams from the affected country in which they’re working, while also missing an opportunity to enhance the capacity of host-country scientists, which could help prevent future outbreaks.

been included in the conference’s main program — reflects a new recognition that health is a critical aspect of human security



Theory aside, what happens when a virus emerges? The fear is real...

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Singapore reports 12th H1N1-related death

By Rekha | Posted: 21 August 2009 2004 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



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

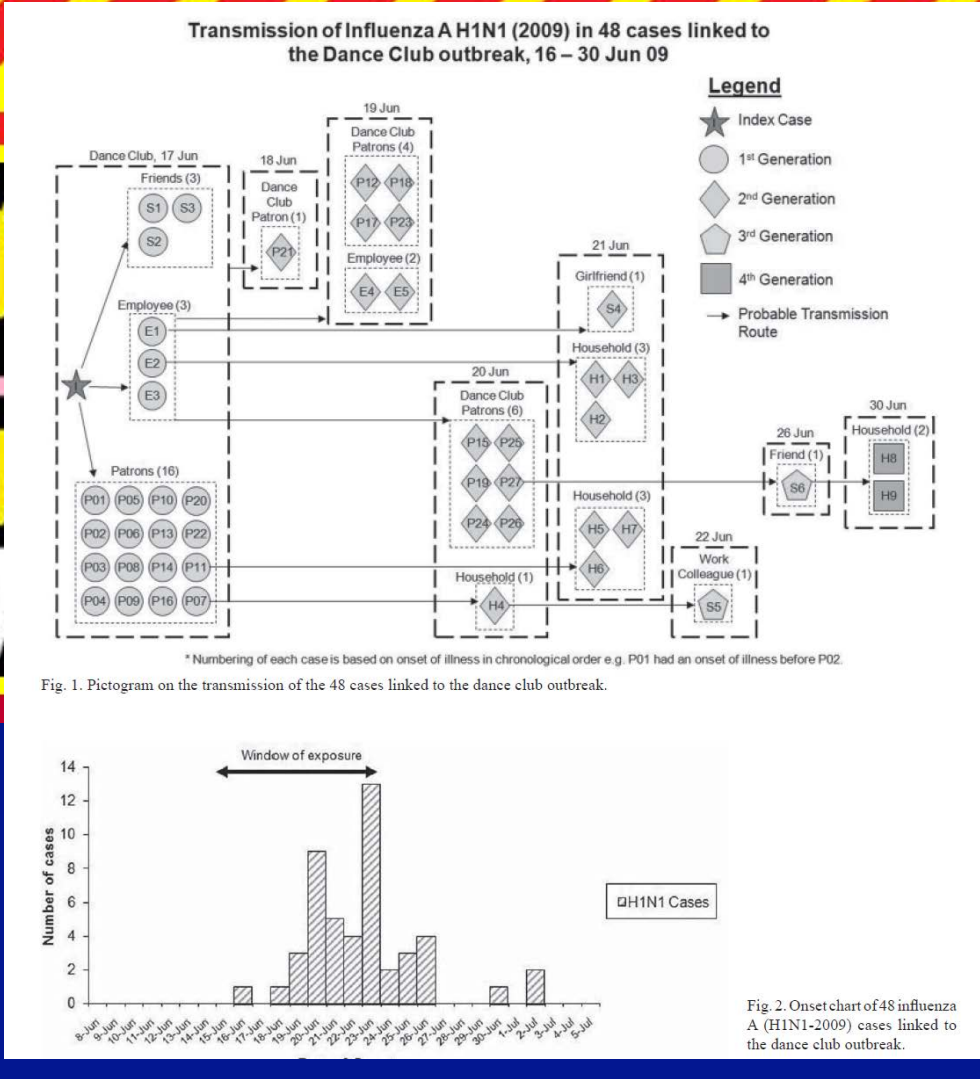
Pei Chan,¹*BSc (Hons)*, Hariharan Subramony,¹*MBBS*, Florence YL Lai,¹*MPhil*, Wee Siong Tien,¹*BSc (Life Sciences) (Hons)*, Hian Tan,¹*BSc (Life Sci) (Hons)*, Suhana Solhan,¹*BSc (Phar) (Hons)*, Hwi Kwang Han,¹*BEOHS*, Huay Foong,¹*BA*, Lyn James,¹*MBBS, MMed (PH), FAMS*, Peng Lim Ooi,¹*MSc, MPH, FAMS*

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



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**

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-

ease 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

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.

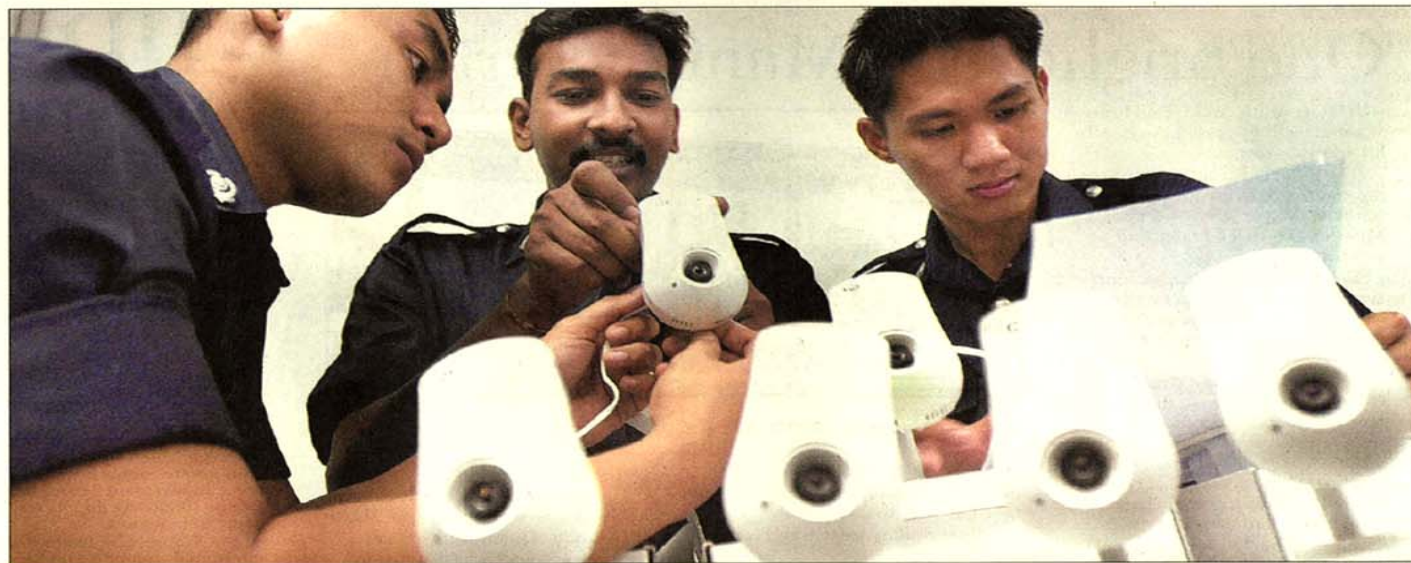
"But, to win this battle against Sars, we cannot afford any kinks in our armour," he added.

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

NAMING AND SHAMING IN PUBLIC

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

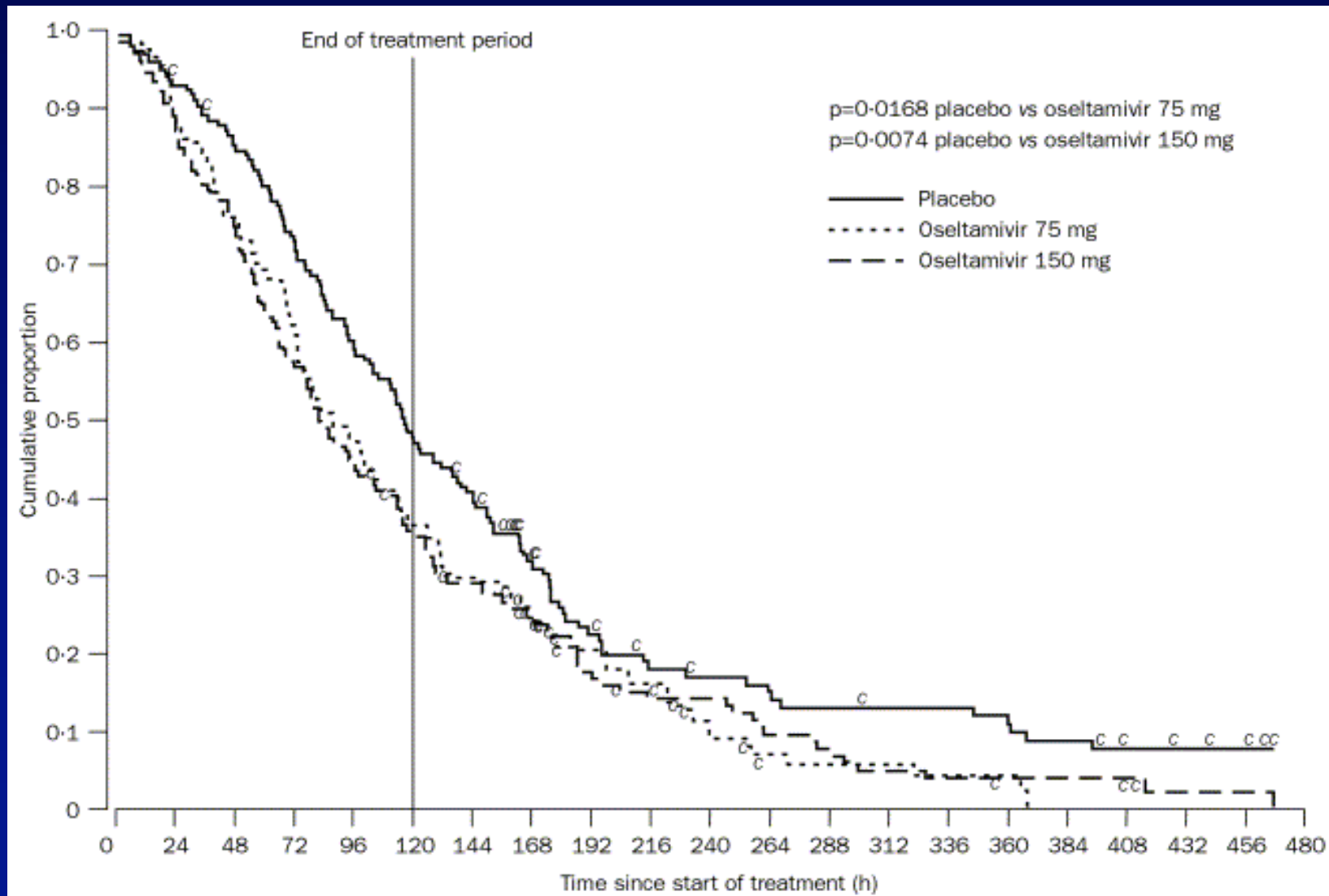
Kiang. "I think we should publish these names and shame them, because otherwise such Singaporeans will continue not to do what is necessary of them," he said, echoing a sentiment expressed by many Singaporeans who felt this was the only way to get irresponsible Sars-affected individuals to behave.



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

Oseltamivir vs Influenza



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

There was toxicity reported

Adverse Drug Reaction

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



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 period of intensive monitoring of adverse Japan or a combination of any of these possible. Additionally, many events such as convulsions, depressed levels of consciousness are complication encephalitis secondary to influenza making a direct to Tamiflu® administration very difficult.

Nonetheless, considering the rapid temporal relationship of adverse event to the use of oseltamivir, and cases which reported positive de-challenge (n=65) where there was rapid and full 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.

Ring
prophylaxis
worked
for
smallpox



The poster features a dark background with numerous orange, textured circles of varying sizes at the top, resembling virus particles. The text is in white and red, with the reward amount '\$1000' in large red font. The names of the disease in multiple languages are listed in a horizontal bar.

REWARD - RECOMPENSE
\$1000

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



The NEW ENGLAND
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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.

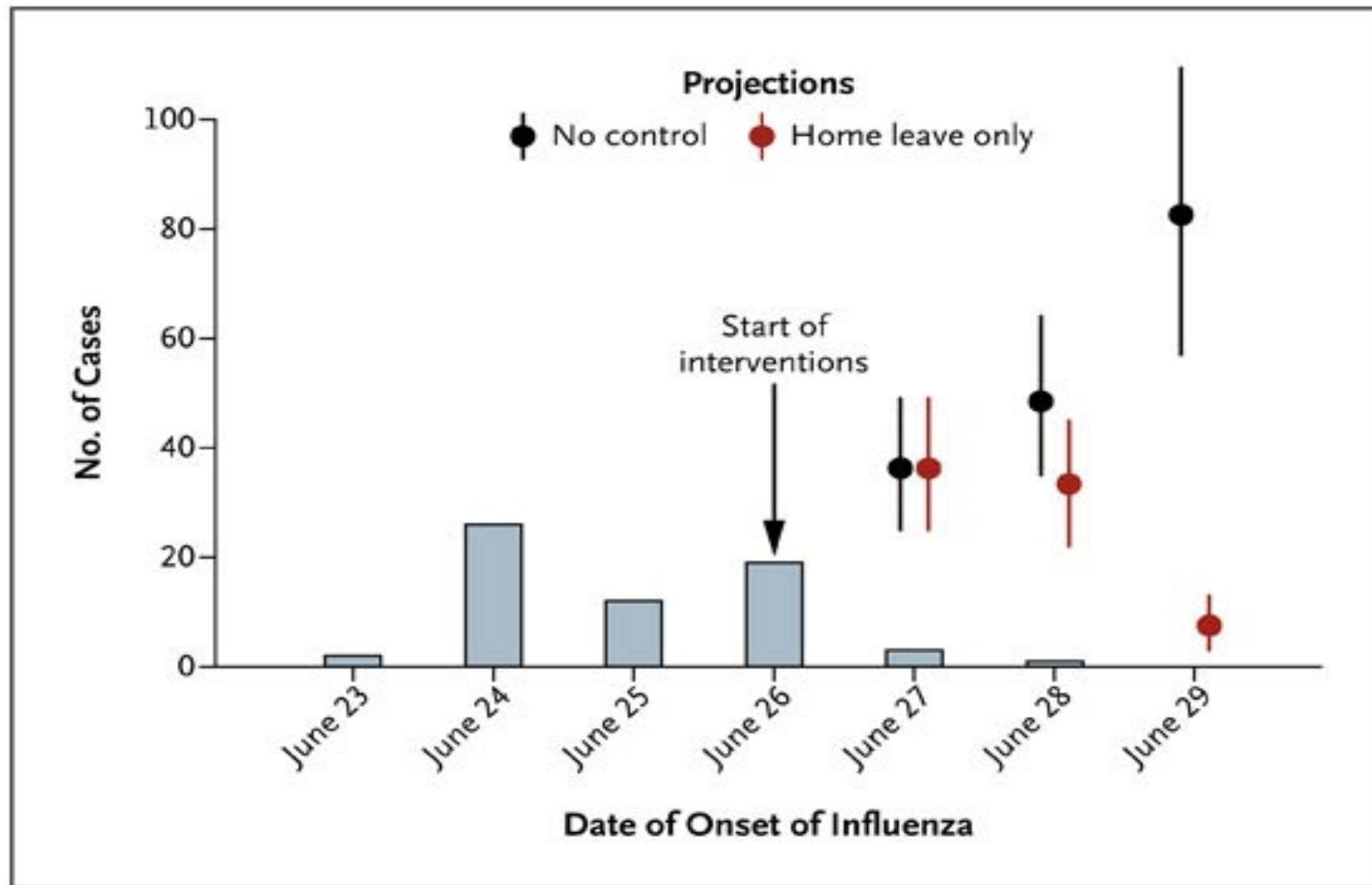
‡ The number of confirmed cases and symptomatic personnel who were not tested excludes 14 symptomatic personnel who could not remember the date of onset of their illness. The percentage of confirmed cases and symptomatic personnel who were not tested before intervention is based on the total number with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

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



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

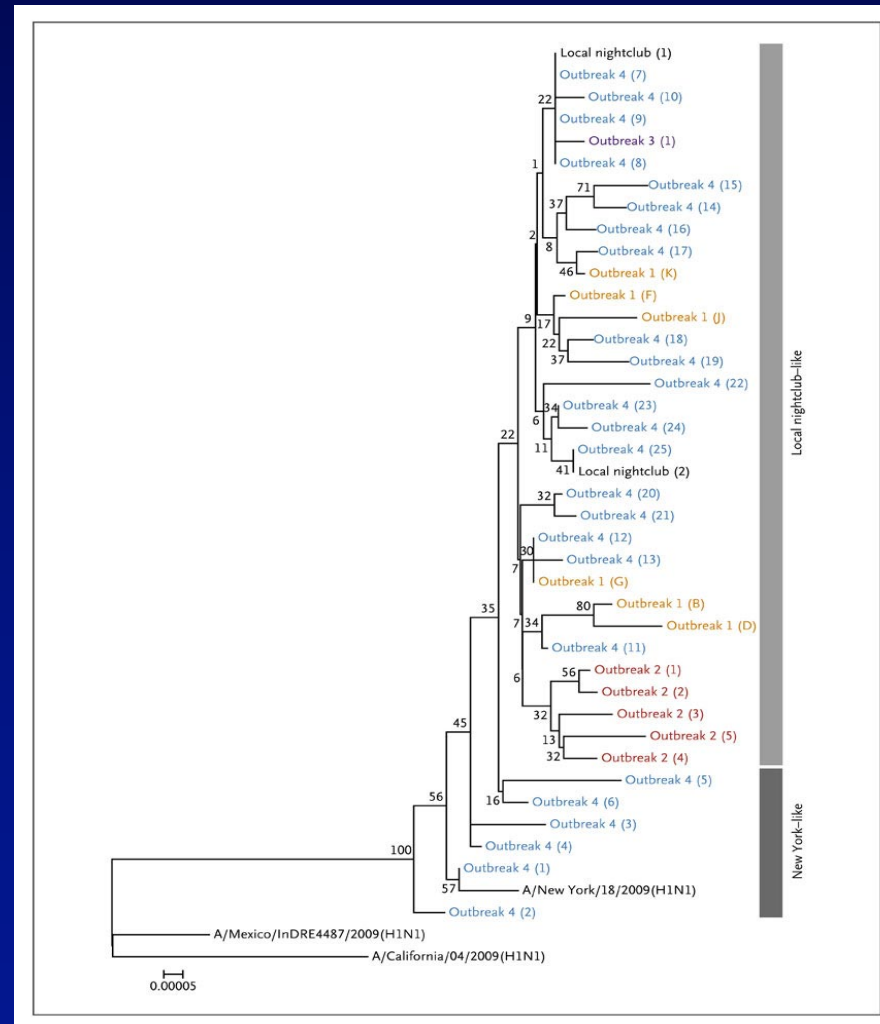


Lee VJ et al. *N Engl J Med* 2010;362:2166-2174



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



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



The NEW ENGLAND
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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



The NEW ENGLAND
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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



Zika virus and microcephaly: why is this situation a PHEIC?



When the Director-General of WHO declared, on Feb 1, 2016, that recently reported clusters of microcephaly and other neurological disorders are a Public Health Emergency of International Concern (PHEIC),¹ it was on the advice of an Emergency Committee of the International Health Regulations and of other experts whom she had previously consulted. We are the members of the Emergency Committee, and we were identified by the Director-General from rosters of experts that had been submitted by WHO Member States.

Our advice to declare a PHEIC was not made on the basis of what is currently known about Zika virus infection. During our discussions it became clear that infection with the Zika virus, unlike other arbovirus infections including dengue and chikungunya, causes a fairly mild disease with fever, malaise, and at times a maculopapular rash, conjunctivitis, or both.² Additional information from previous outbreaks suggested that about 20% of people infected with Zika virus develop these symptoms, and that the rest are asymptomatic.³ Fatality from Zika virus infection is thought to be rare.² Our advice to declare a PHEIC was rather made on the basis of what is not known about the clusters of microcephaly, Guillain-Barré syndrome, and possibly other neurological defects reported by country representatives from Brazil and retrospectively from French Polynesia that are associated in time and place with outbreaks of Zika infection.^{3,4}

The Emergency Committee meeting was convened rapidly by WHO. We were contacted by the Director-General 4 days before the Emergency Committee meeting, and by the time we met WHO had thoroughly prepared the meeting. At the start of the meeting, the WHO legal counsel provided three criteria to help the Emergency Committee decide whether the present situation was a PHEIC. A PHEIC must: (1) constitute a health risk to other countries through international spread; (2) potentially require a coordinated response because it is unexpected, serious, or unusual; and (3) have implications beyond the affected country that could require immediate action.

Representatives from four countries (Brazil, El Salvador, France, and the USA) that have had either outbreaks or importations of Zika virus, and a group of arbovirus specialists, took part in the meeting. Some

of them had been working for the past months with the WHO Regional Office in the Americas on the Zika virus outbreaks, and before that on those caused by the dengue and chikungunya viruses. During one country representative's account of Zika virus in French Polynesia, robust and convincing retrospective data were presented about an increase in neurological disorders during the period when there was an outbreak of Zika virus. Other presentations described current clusters of microcephaly and limited information about Zika virus identified in fetuses or infants, pointing out the temporal association with circulation of the Zika virus.

After these country presentations, and comments by the assembled arbovirologists, we were able to discern as a committee, and then agree unanimously in an initial poll, that the clusters of microcephaly and neurological disorders, and their possible association with the Zika virus, constituted a PHEIC. Upon further discussion, it became clear that there was no standard surveillance case definition for microcephaly. The first recommendation of the PHEIC was to call for standardised and enhanced surveillance of microcephaly in areas of known Zika virus transmission. Such surveillance is not only important in countries where there are current and recent outbreaks, but is also retrospectively relevant in African and Asian countries where outbreaks have been occurring since the Zika virus was first identified in 1947.^{5,6} Further, we felt that surveillance data should become available within months.

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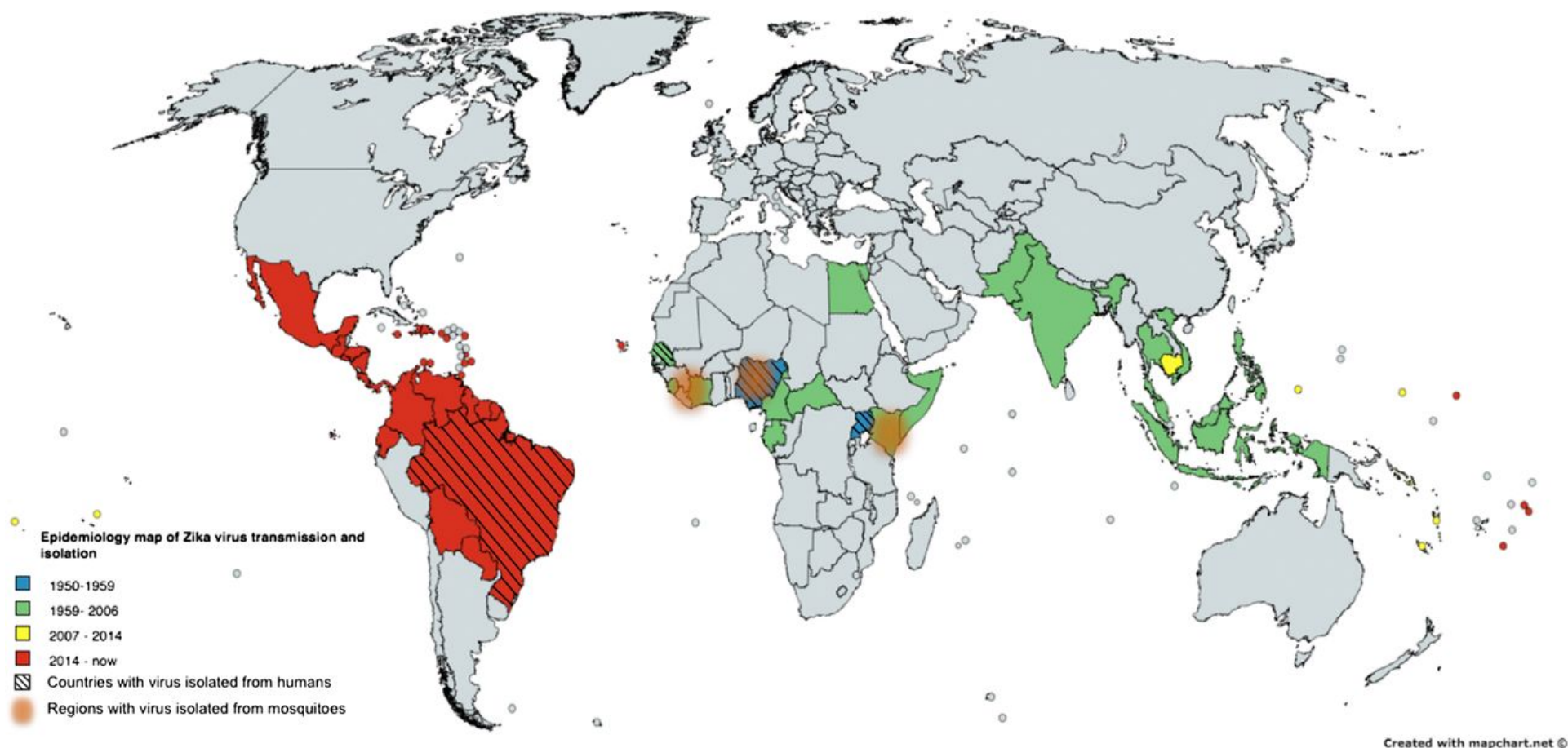


Since the Director-General declared the PHEIC on microcephaly and neurological disorders, many of us have had questions about how our recommendation relates to the PHEIC called by the Director-General for the 2014 Ebola outbreaks in west Africa based on the recommendation of a different Emergency Committee. The answer to us is clear. The Director-General declared the Ebola outbreaks a PHEIC because of what science knew about the Ebola virus from many years of research during outbreaks in the past, whereas she declared the current PHEIC because of what is not known about the current increase in reported clusters of microcephaly and other disorders, and how this might relate to concurrent Zika outbreaks.

We were told by the Director-General that she would convene us again within 3 months to reassess the situation, as required under the International Health Regulations. We are confident that virtual meetings will allow us to review global collective action and to learn from WHO about progress in understanding the present situation of microcephaly and neurological disorders and progress in implementation of the precautionary and preparatory measures related to Zika.

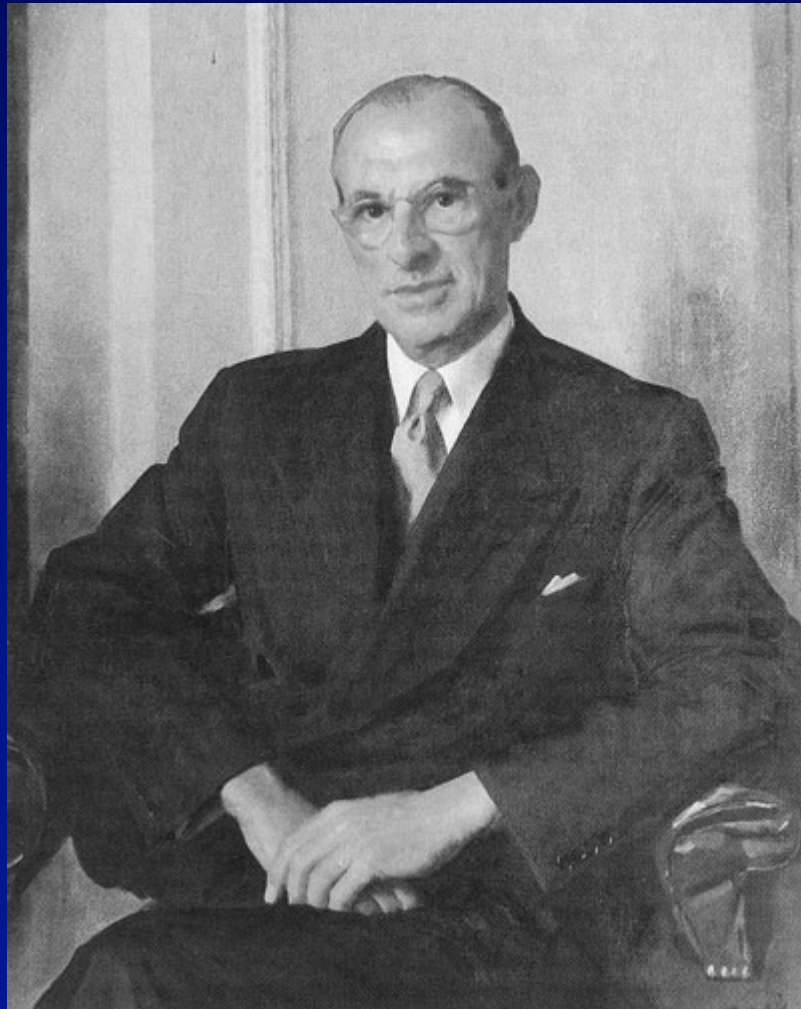
**David L Heymann, Abraham Hodgson, Amadou Alpha Sall, David O Freedman, J Erin Staples, Fernando Althabe, Kalpana Baruah, Ghazala Mahmud, Nyoman Kandun, Pedro F CVasconcelos, Silvia Bino, K U Menon*
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Epidemiologic map of Zika virus transmission and isolation.



Yin Mo, Alferez, Tambyah Br Med Bull 2016;bmb.lw023

Congenital Rubella



1. Replication of the virus in the throat for periods of 2–3 weeks
2. Viremia at high levels, particularly during the second week of infection, terminated by the appearance of antibodies
3. Clinically inapparent rubella virus infection in as many as a one-third of infected individuals
4. Correlation between the presence of serum antibodies and resistance to rubella virus infection
5. Viral infection of the placenta
6. Panembryonic infection of fetuses after viremic infections in their mothers
7. Confirmed rubella during the first trimester of pregnancy resulted in damage to 50%–90% of fetuses, with declining percentages through the second trimester [12, 13]
8. Cell death found in key organs of the fetus, together with inhibition of cellular mitosis and vascular endothelial damage
9. Excretion of virus at birth by babies with CRS, who continued to excrete virus for months, serving as vectors of transmission to others
10. Seronegativity in ~15% of American women of child-bearing age, with higher or lower percentages in other parts of the world, depending on social conditions and population density. Thus, in crowded urban areas, rubella virus infection was relatively continual in children, but women were usually immune, whereas in some island populations epidemics were sporadic, and a high proportion of women were susceptible.

Plotkin S CID 2006;43:S164-8

Infant HIV Infection through Week 1 (Periods 1 and 2 Combined) in All Mother–Infant Sets and According to Subgroup.

Table 2. Infant HIV Infection through Week 1 (Periods 1 and 2 Combined) in All Mother–Infant Sets and According to Subgroup.*

Subgroup	ZDV Alone	ZDV-Based ART	TDF-Based ART	Difference, ZDV-Based ART and TDF-Based ART vs. ZDV Alone	P Value for Interaction
	<i>no. of mother–infant sets/total no. (%)</i>			<i>percentage points (repeated CI)</i>	
All mother–infant sets	25/1386 (1.8)	7/1385 (0.5)	2/325 (0.6)	–1.3 (–2.1 to –0.4)	
Maternal gestational age at trial entry†					0.68
<34 wk	16/1229 (1.3)	6/1230 (0.5)	1/274 (0.4)	–0.8 (–1.6 to –0.1)	
≥34 wk	9/157 (5.7)	1/154 (0.6)	1/51 (2.0)	–4.8 (–8.9 to –0.6)	
Maternal CD4 count at trial entry					0.70
350–499 cells/mm ³	16/577 (2.8)	4/592 (0.7)	1/136 (0.7)	–2.1 (–3.7 to –0.5)	
≥500 cells/mm ³	9/809 (1.1)	3/793 (0.4)	1/189 (0.5)	–0.7 (–1.6 to 0.2)	
Maternal viral load at trial entry					0.22
<1000 copies/ml	0/299	1/253 (0.4)	0/57	0.3 (–0.4 to 1.0)	
≥1000 copies/ml	25/1083 (2.3)	6/1129 (0.5)	2/268 (0.7)	–1.7 (–2.8 to –0.7)	
Missing data	4	3	0		

* The analysis of infant HIV infection according to maternal gestational age at trial entry was a prespecified analysis; the other two subgroup analyses were post hoc analyses. CI denotes confidence interval, and HIV human immunodeficiency virus.

† Data on maternal gestational age at trial entry were missing for one woman in the group assigned to ZDV-based ART.

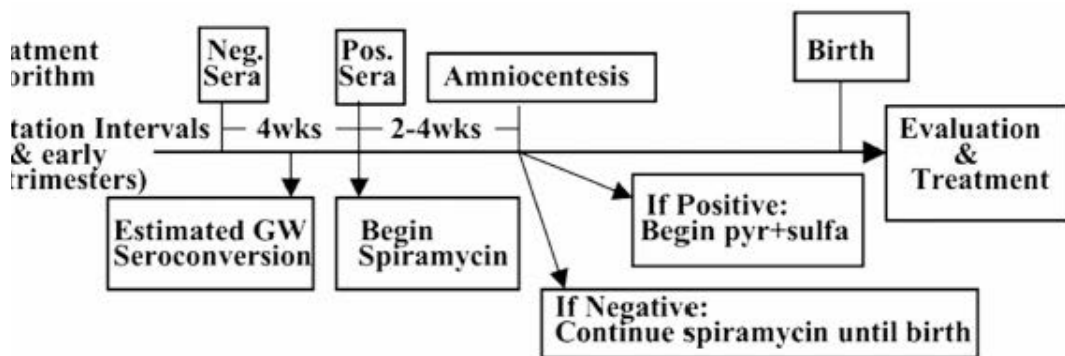


Fig. 8.
Parisian algorithm for diagnosis and treatment of congenital toxoplasmosis for whom there are data in Fig. 9. wk: weeks.

B: Findings at birth in 55 live infants born of 52 pregnancies with prenatal diagnosis of congenital toxoplasmosis

	n ^a	%
Subclinical infection	44/54	81
Multiple intracranial calcifications	5/54	9
Single intracranial calcification	2/54	4
Chorioretinitis scar	3/54	6
Abnormal lumbar puncture	1/54	2
Evidence of infection on inoculation of placenta	23/46	50
Positive cord blood IgM antibody	8/53	15

signs and symptoms in 210 infants with proven congenital infection (1949–1960). N: 300 (chorioretinitis: 76%; neurological disturbances: 51%; abnormal cranial volume: 21%; calcification: 32%) (data are adapted from Couvreur et al. 1984a, with permission).

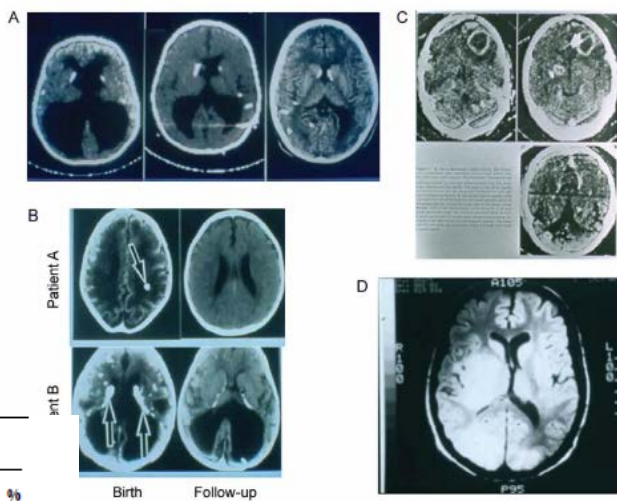


Fig. 2.
A: resolution of hydrocephalus and brain growth following treatment and shunt in child with congenital toxoplasmosis (Swisher et al. 1994, with permission); B: resolution or diminution of size of intracerebral calcifications during treatment for congenital toxoplasmosis in the first year of life. Cranial CT scans were obtained in the neonatal period and at one year of age. Each cranial CT scan was reviewed by the same study neuroradiologist. Calcification size and number were computed (Patel et al. 1996, with permission). Thirty two (82%) of 39 children had calcifications that diminished or resolved and seven (18%) had calcifications that remained the same size (C) and appearance of brain abscesses in a patient with a cardiac transplant (Ryning et al. 1979, with permission) (D) and a patient with toxoplasmic encephalitis who had

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Why prevent, diagnose and treat congenital toxoplasmosis?

Rima McLeod^{1,+}, Francois Kieffer², Mari Sautter¹, Tiffany Hosten¹, and Herve Pelloux³

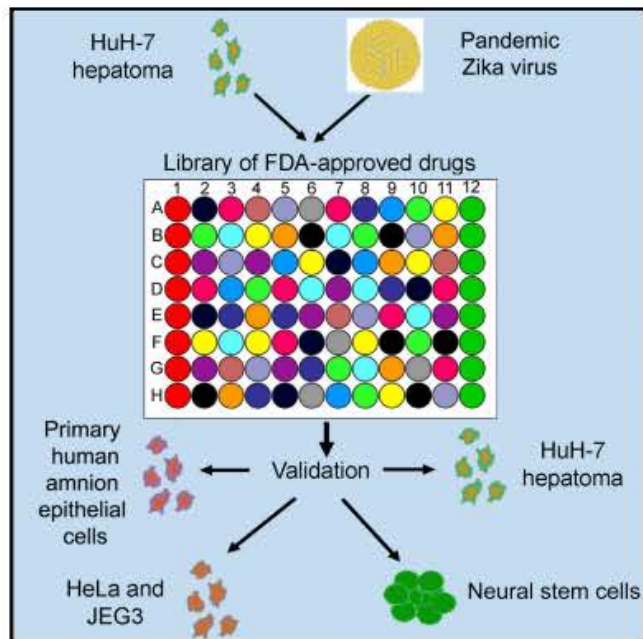
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Resource

Cell Host & Microbe

A Screen of FDA-Approved Drugs for Inhibitors of Zika Virus Infection

Graphical Abstract



Highlights

- 774 FDA-approved drugs screened for anti-Zika virus activity in a human hepatoma cell line
- Over 20 compounds showed anti-Zika virus activity
- Selected compounds validated in human neural stem cells and primary amnion cells

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In Brief

Currently there is no approved therapy to treat Zika virus (ZIKV) infection. Barrow et al. present a screen of FDA-approved drugs for anti-ZIKV activity in a hepatoma cell line. Selected compounds from the more than 20 identified candidates were validated in human neural stem cells and primary amnion cells.

SUNDAY, OCT 2, 2016 9:59 AM UTC

Zika vaccine trials have graduated from monkeys to humans, but still far off

A scientist explains that the vaccine is still in phase one out of three

ROBERT BEDNARCZYK, THE CONVERSATION



TOPICS: THE CONVERSATION, VACCINE, ZIKA, ZIKA VACCINE, ZIKA VIRUS, INNOVATION NEWS, TECHNOLOGY
NEWS, NEWS



In this photo provided by The National Institute of Allergy and Infectious Diseases shows a healthy volunteer receiving the NIAID Zika virus investigational DNA vaccine as part of an early-stage trial to test the vaccine's safety and immunogenicity. This is the first administration of this vaccine in a human. (The National Institute of Allergy and Infectious Diseases via AP) (Credit: AP)

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Data and image prepared by Dr Andrew J Tatem

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Severe Pediatric Adenovirus 7 Disease in Singapore Linked to Recent Outbreaks across Asia

Oon Tek Ng, Koh Cheng Thoon, Hui Ying Chua, Natalie Woon Hui Tan, Chia Yin Chong, Nancy Wen Sim Tee, Raymond Tzer Pin Lin, Lin Cui, Indumathi Venkatachalam, Paul Anantharajah Tambyah, Jonathan Chew, Raymond Kok Choon Fong, Helen May Lin Oh, Prabha Unny Krishnan, Vernon Jian Ming Lee, Boon Huan Tan, Sock Hoon Ng, Pei Jun Ting, Sebastian Maurer-Stroh, Vithiagarun Gunalan, Wei Xin Khong

During November 2012–July 2013, a marked increase in adenovirus type 7 (Ad7) infections associated with severe disease was documented among pediatric patients in Singapore. Phylogenetic analysis revealed close genetic link with severe Ad7 outbreaks in China, Taiwan, and other parts of Asia.

Recent reports have noted increased incidence of severe Ad7 disease in Asia: among the general population and pediatric inpatients in Taiwan; among persons in a military training camp in Shaanxi, China; and among those in a police training center in Kuala Lumpur, Malaysia (2–4). During January–June 2013, physicians in Singapore noted

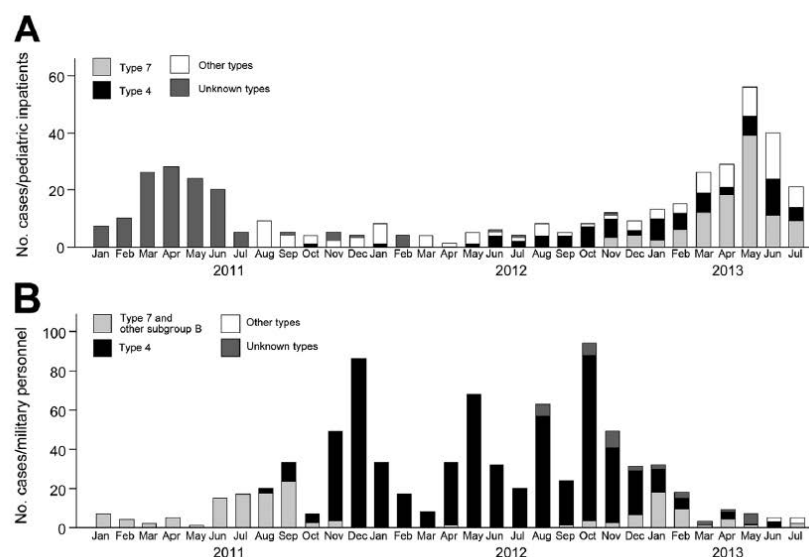


Figure 1. Number of adenovirus cases by month, January 2011–July 2013, Singapore. A) The first confirmed case of adenovirus type 7 was reported in November 2012 in KK Women's and Children's Hospital. The number of human adenovirus cases among the pediatric inpatient population increased and peaked in May 2013. B) A retrospective examination of the military surveillance data revealed the first appearance of adenovirus type 7 among military personnel in September 2012 and a small increase and decline over the next few months.

Therapeutic considerations for Emerging Viral Infections

- Capacity building in country
- Pre-approved interventional protocols
- Explore all therapeutic options
- Engage all communities especially those most affected



BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 20 1959

LARGE-SCALE USE OF SABIN TYPE 2 ATTENUATED POLIOVIRUS VACCINE IN SINGAPORE DURING A TYPE 1 POLIOMYELITIS EPIDEMIC

BY
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K. KANAGARATNAM, M.B., B.S., D.P.H. K. W. LEONG, M.B., B.S.

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From the Department of Bacteriology, University of Malaya, the Medical Departments, Singapore Government and Singapore City Council

In the latter half of 1958 Singapore experienced an epidemic outbreak of poliomyelitis due to the type 1 virus. Eleven weeks after the first case was reported the Minister of Health in the Singapore Government decided, after consultation, to make available the attenuated type 2 vaccine elaborated by Sabin (1957a, 1957b) for children between the ages of 3 months and 10 years. Dr. Sabin agreed to the release of this vaccine on condition that adequate laboratory control could be assured. The following communication gives the reasons for the selection of the type 2 vaccine, the experimental details, and the results of the campaign.

of 1951. The majority of cases were in children under the age of 2, and the general picture was that of an area in which poliomyelitis was endemic, but with periodic increases in the number of cases.

Paul (1958) drew attention to the fact that this endemic state of poliomyelitis was associated with a high infantile mortality rate, and if the infantile mortality rate fell below 60-80 per 1,000 live births a rise in the number of cases of poliomyelitis could be expected. The infantile mortality rates for Singapore since 1946 are shown in Table II.

This fall in the infantile mortality rate could presage a shift to the direction of increased activity of poliomyelitis and the possible appearance of cases in older

TABLE I.—Incidence of Poliomyelitis in Singapore Since 1946 up to Period of Epidemic



30 November – 3 December 2016

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