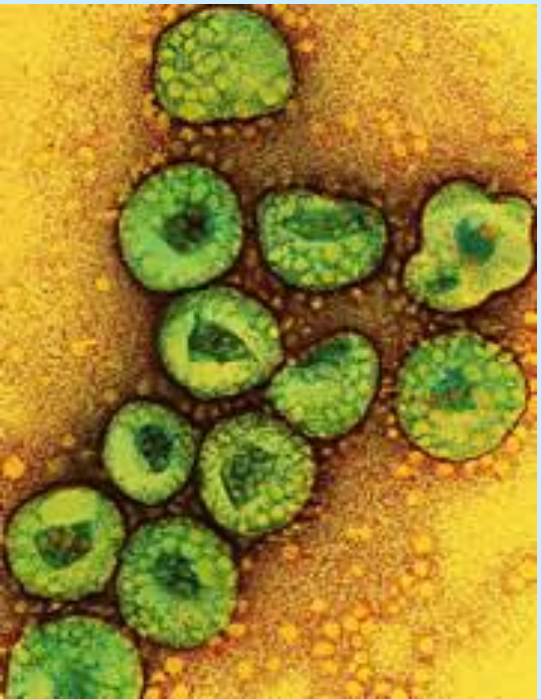
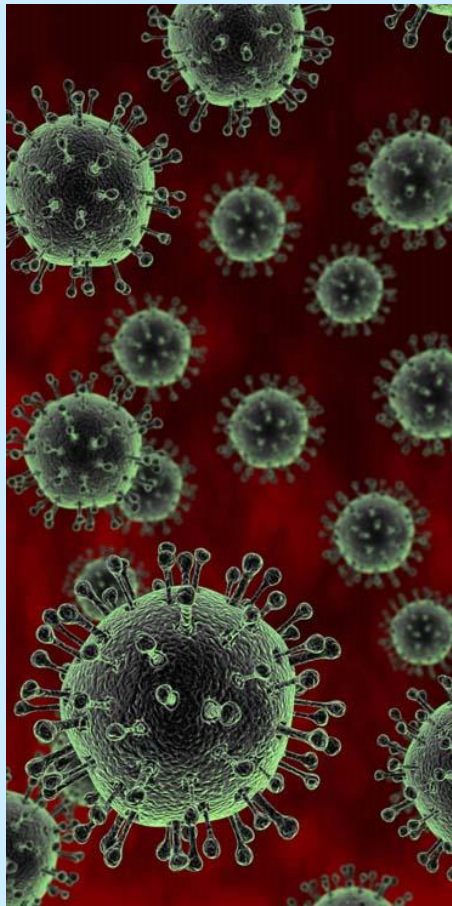
IS MERS, SARS AND BIRD FLU STILL A THREAT?

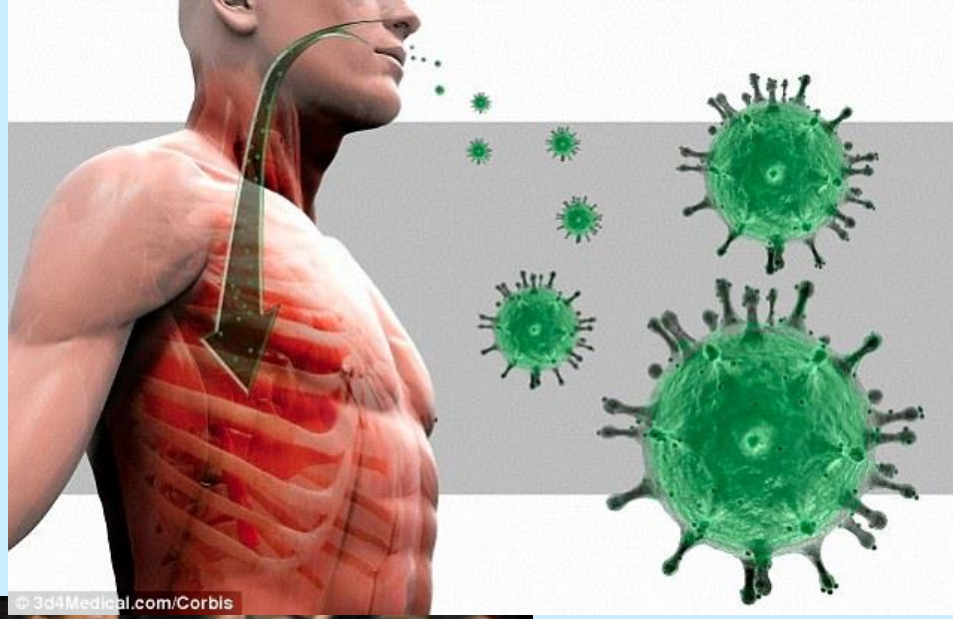
A trip down memory lane

Dr. Kim David, Dept. of Infectious Diseases,
Hvidovre Hospital, Denmark

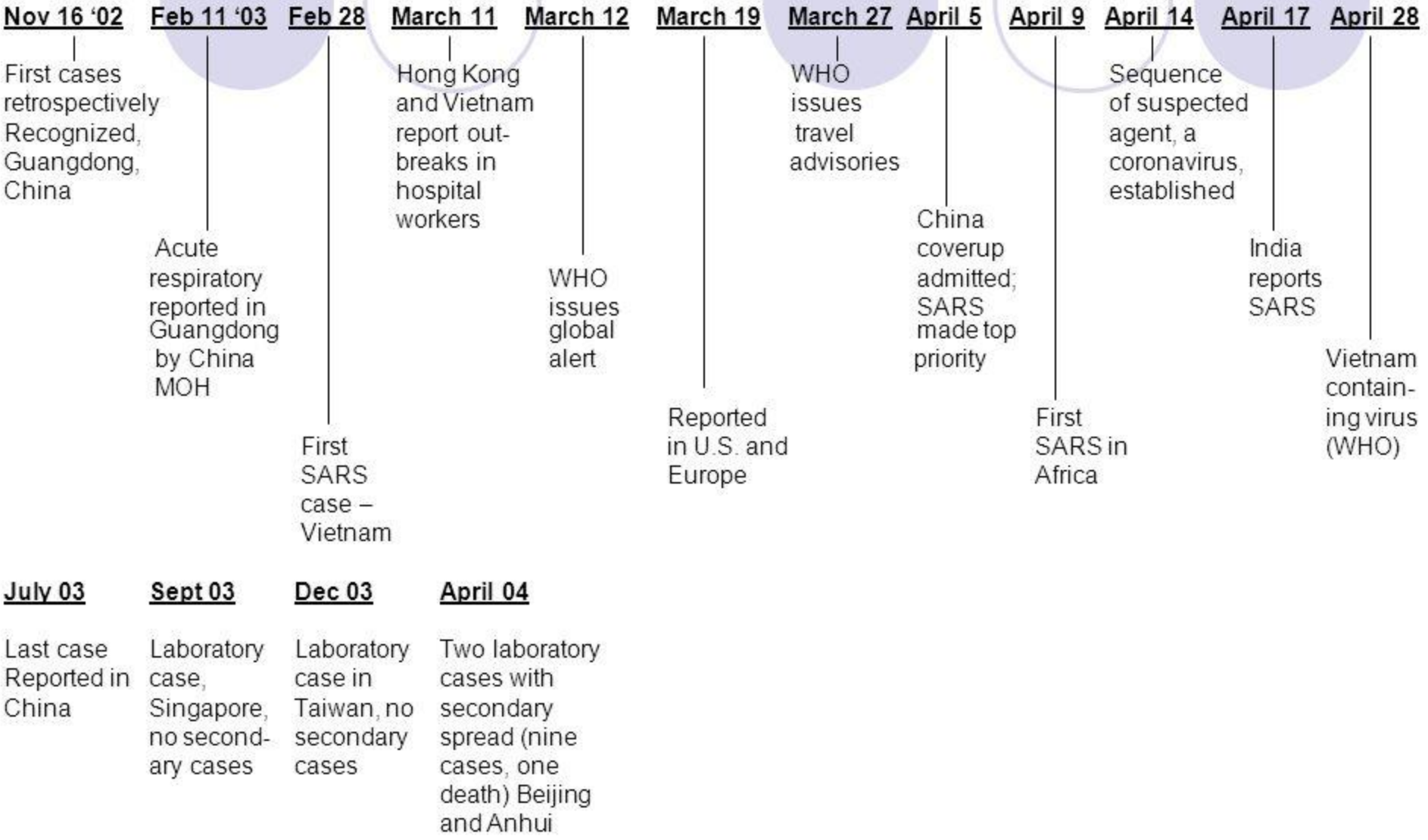




SARS-CoV presents much like flu symptoms, but can accelerate, compromising a person's breathing and lead to a deadly form of pneumonia. A worldwide outbreak in 2003 to 2004 infected 8,000 and killed 800 people



SARS Timeline



February 28, 2003

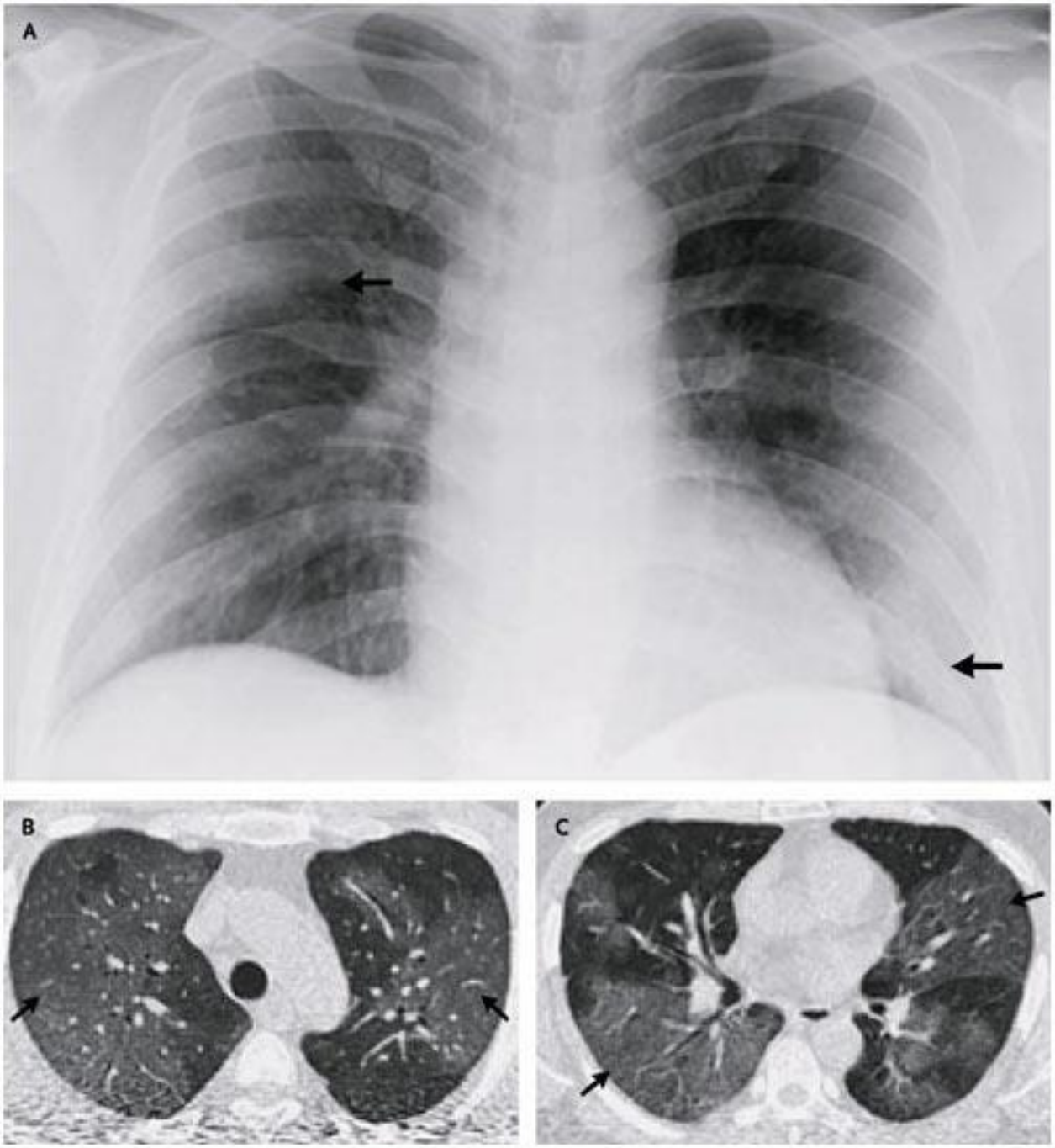
Dr Carlo Urbani, a WHO official based in Vietnam, is alarmed by these cases of atypical pneumonia in the French Hospital, where he has been asked to assist. He is concerned it might be avian influenza, and notifies the WHO Regional Office for the Western Pacific.

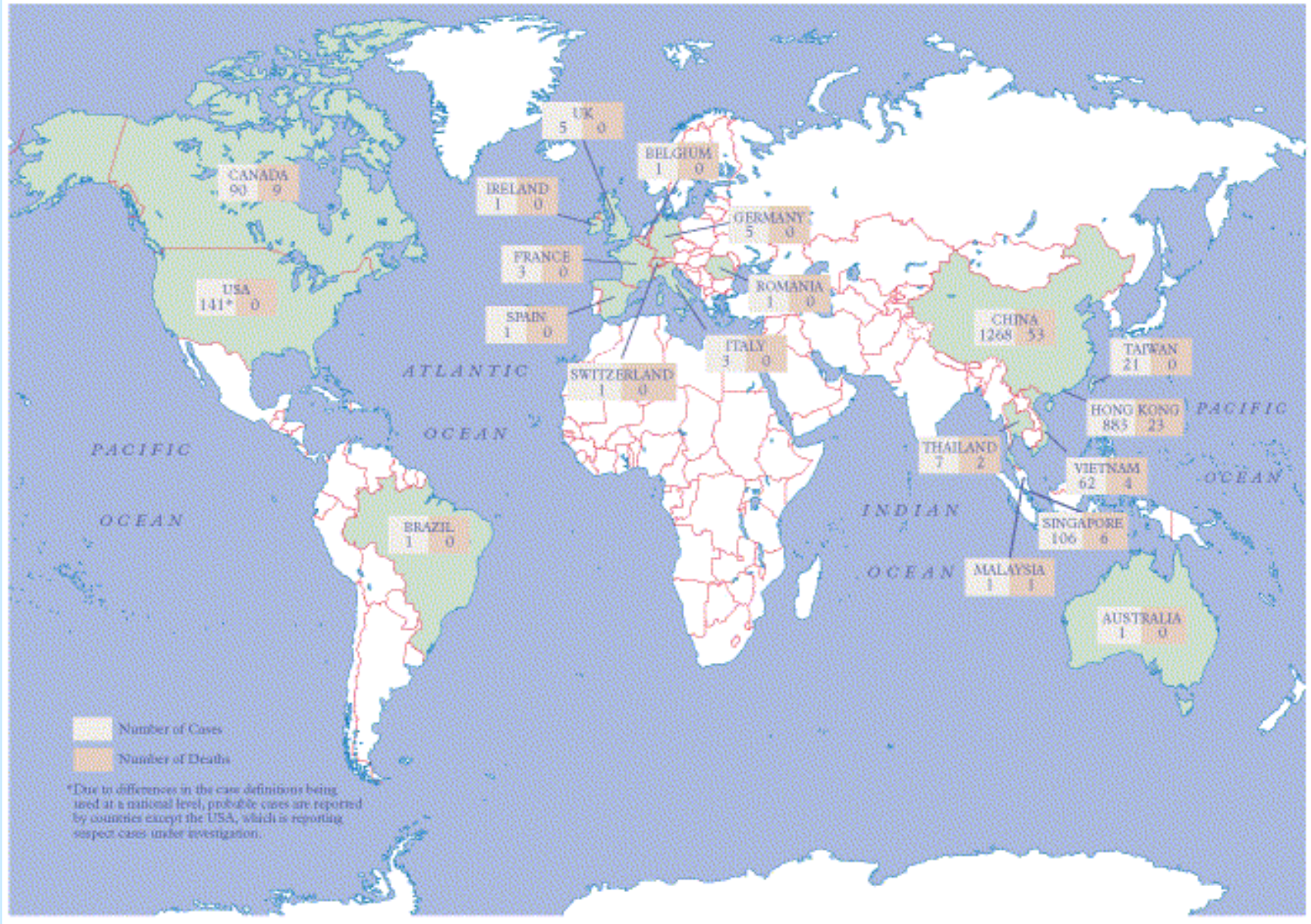
Dr Carlo Urbani was the former president of the Italian chapter of MSF and was one of the individuals who accepted the 1999 Nobel Peace prize on behalf of that organization

Dr Urbani died from SARS on 29 March 2003 at 11:45 AM, after 18 days of Intensive care.

A chest x-ray showing increased opacity in both lungs, indicative of pneumonia, in a patient with SARS. However, a totally non-specific x-ray.

An initial computed radiograph of the chest showed hazy opacities with a ground-glass appearance in the right upper and left lower lobes (Panel A, arrows). High-resolution computed tomographic (CT) scans of the chest (Panels B and C) revealed extensive, bilateral ground-glass opacities (arrows). The findings in this patient were similar to those seen in diffuse interstitial pneumonia and in early acute respiratory distress syndrome.





Worldwide deaths and reported cases of severe acute respiratory syndrome from Nov 1, 2002 to April 7, 2003

Suspect case of SARS

1. A person presenting after 1 November 2002[1] with history of:

- high fever (>38 °C)

AND

- cough or breathing difficulty

AND one or more of the following exposures during the 10 days prior to onset of symptoms:

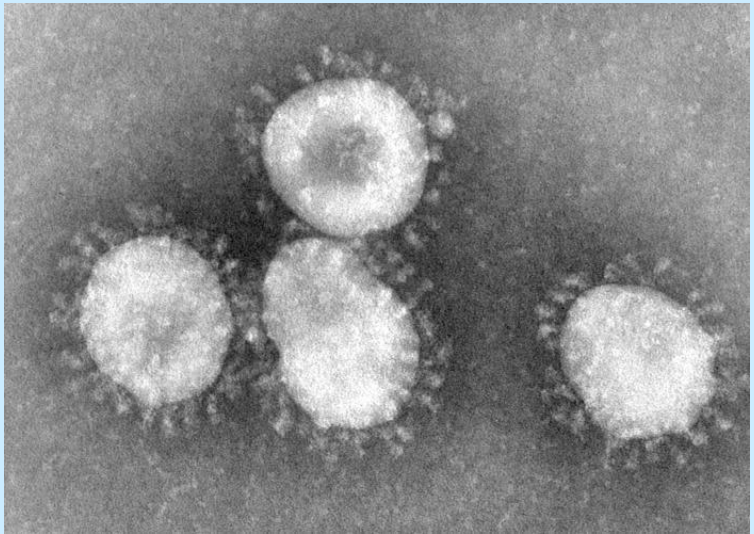
- **close contact[2]** with a person who is a suspect or probable case of SARS;
- history of travel, to an area with recent local transmission of SARS
- residing in an area with recent local transmission of SARS

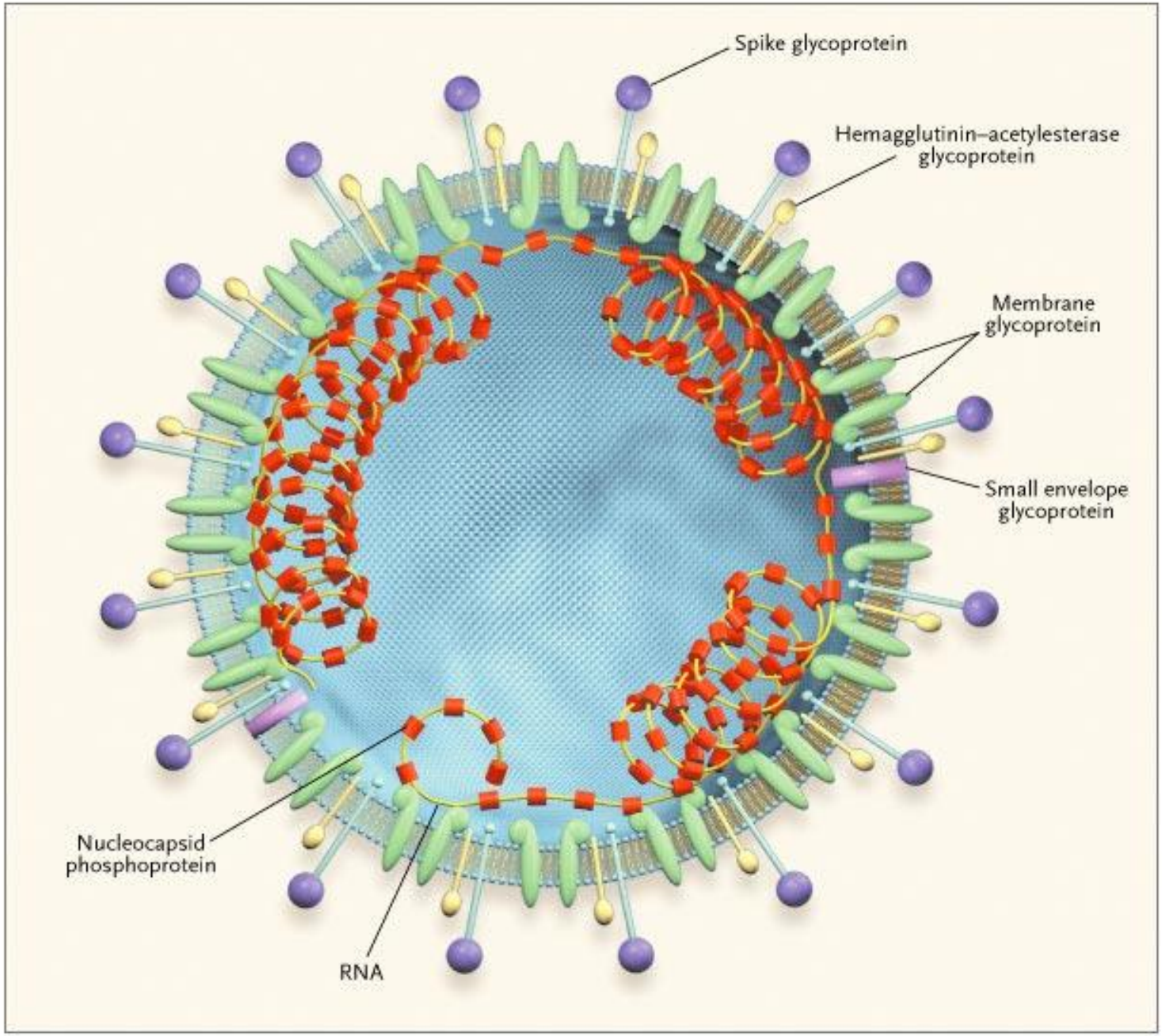
2. A person with an unexplained acute respiratory illness resulting in death after 1 November 2002,[1]but on whom no autopsy has been performed AND one or more of the following exposures during to 10 days prior to onset of symptoms:

- **close contact,[2]** with a person who is a suspect or probable case of SARS;
- history of travel to an area with recent local transmission of SARS
- residing in an area with recent local transmission of SARS

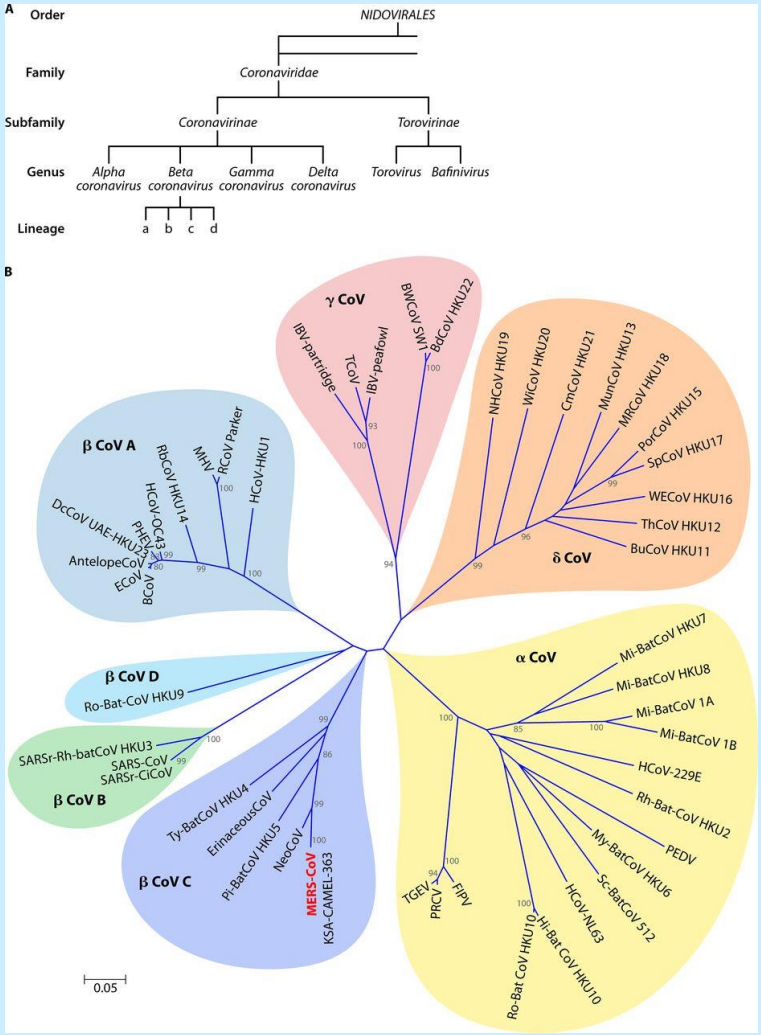
Coronaviruses were first described in the 1960s from the nasal cavities of patients with the common cold. The name "coronavirus" is derived from the Latin *corona*, meaning crown or halo, and refers to the characteristic appearance of virions under electron microscopy (E.M.) with a fringe of large, bulbous surface projections creating an image reminiscent of a royal crown or of the solar corona. Coronaviruses are pleomorph, single-stranded RNA vira of the size 80 to 160 nm in diameter.
The six coronaviruses that can infect people are: alpha coronaviruses 229E and NL63, and beta coronaviruses OC43, HKU1, SARS-CoV (the coronavirus that causes severe acute respiratory syndrome, or SARS), and MERS-CoV (the coronavirus that causes Middle East Respiratory Syndrome, or MERS).

Treatment of coronaviruses: No specific treatment available



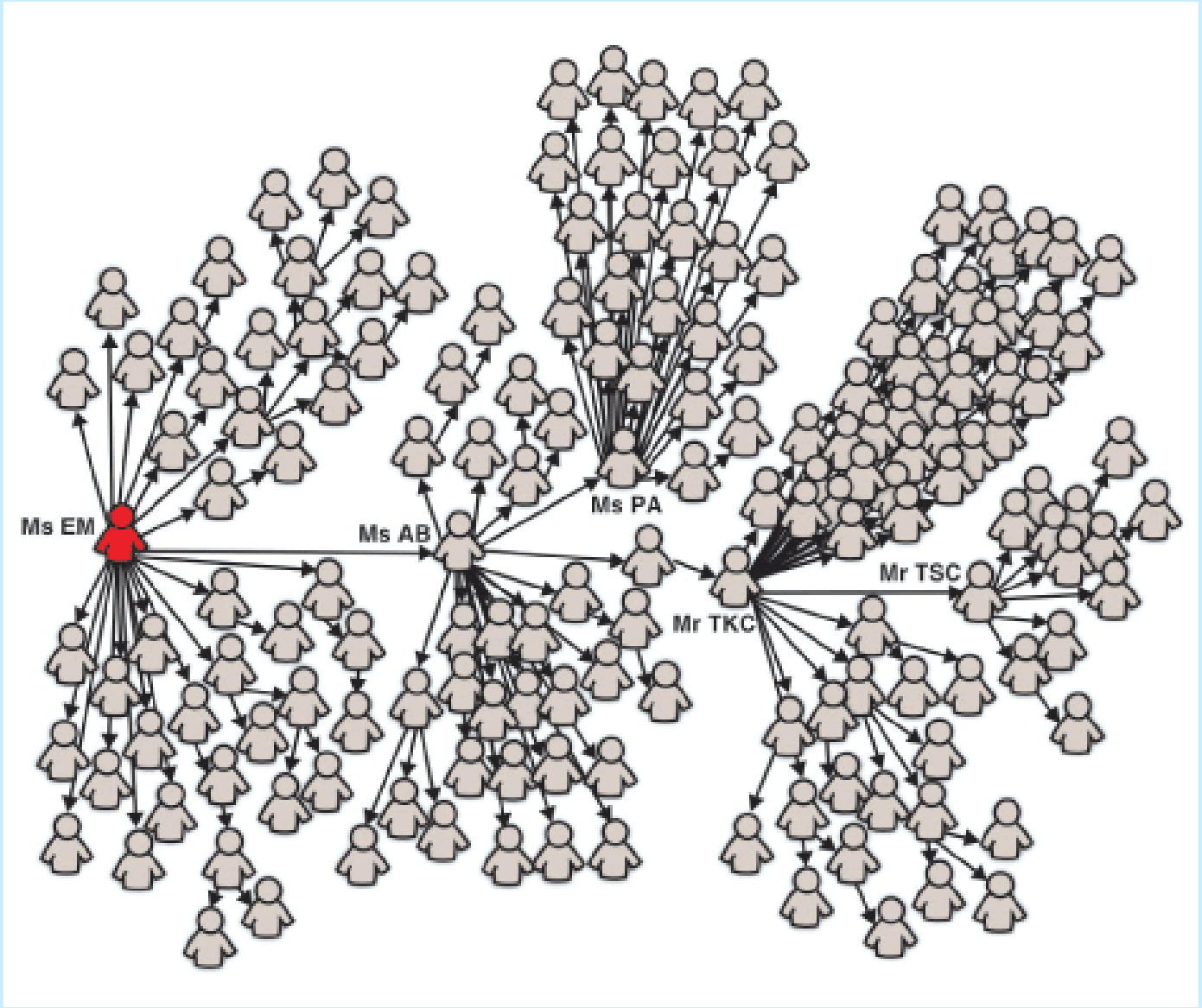

Spike glycoprotein
Hemagglutinin–acetylesterase glycoprotein
Membrane glycoprotein
Small envelope glycoprotein
Nucleocapsid phosphoprotein
RNA

(A) Taxonomy of Coronaviridae according to the International Committee on Taxonomy of Viruses.



Jasper F. W. Chan et al. Clin. Microbiol. Rev. 2015;28:465-522

Clinical Microbiology Reviews



This diagram detailing SARS transmission in Singapore shows the important role of “super-spreaders” in transmitting the disease. Five people caused more than half of the 205 cases there.

Pathogen	Single infections	Coinfections	Total
Rhinovirus	107	14	121
Coronaviruses	45	14	59
Influenza A and B	19	3	22
Respiratory syncytial virus	11	6	17
Parainfluenza	6	1	7
Chlamydia spp	3	0	3
Mycoplasma pneumoniae	1	0	1
Adenovirus	1	0	1
Total	193	38	231

BMJ 1997;315:1060–4

Feature	Coronavirus (n=42)	Influenza (n=19)	Rhinovirus (n=85)	Respiratory syncytial virus (n=11)	Unknown (n=134)	P value
Demography						
No (%) of men	15 (36)	10 (53)	33 (39)	7 (64)	67 (50)	NS
Median (range) age (years)	70.5 (60-87)	70 (65-89)	72 (61-88)	70 (62-86)	71 (61-86)	NS
Current smoker	3 (7; 0 to 15)	6 (32; 11 to 53)	11 (13; 6 to 20)	1 (9; 0 to 26)	21 (16; 10 to 22)	NS
Indication for influenza vaccine	25 (60; 45 to 75)	4 (21; 3 to 39)	50 (59; 49 to 70)	4 (36; 8 to 64)	67 (50; 42 to 59)	<0.05
Symptoms						
Upper respiratory:						
Rhinorrhoea	30 (71; 57 to 85)	12 (63; 41 to 85)	61 (72; 63 to 82)	9 (82; 59 to 100)	95 (71; 63 to 79)	NS
Sneezing	25 (60; 45 to 75)	6 (32; 11 to 53)	59 (69; 59 to 79)	9 (82; 59 to 100)	81 (60; 52 to 68)	<0.05
Sore throat	24 (57; 42 to 72)	11 (58; 36 to 80)	55 (65; 55 to 75)	9 (82; 59 to 100)	71 (53; 45 to 62)	NS
Dry cough	19 (45; 30 to 60)	10 (53; 31 to 75)	39 (46; 35 to 57)	3 (27; 1 to 53)	60 (45; 37 to 53)	NS
Nasal congestion	22 (52; 37 to 67)	9 (47; 25 to 69)	39 (46; 35 to 57)	8 (73; 47 to 99)	59 (44; 36 to 52)	NS
Hoarseness	19 (45; 30 to 60)	5 (26; 6 to 46)	35 (41; 31 to 52)	3 (27; 1 to 53)	53 (40; 32 to 48)	NS
Purulent nasal discharge	12 (29; 15 to 43)	6 (32; 11 to 53)	26 (31; 21 to 41)	6 (55; 26 to 84)	33 (25; 18 to 32)	NS
Any upper respiratory symptom	41 (98; 94 to 100)	19 (100)	83 (98; 95 to 100)	11 (100)	130 (97; 94 to 100)	NS
Lower respiratory:						
Purulent sputum	16 (38; 23 to 53)	13 (68; 47 to 89)	49 (58; 48 to 69)	8 (73; 47 to 99)	92 (69; 61 to 77)	<0.01
Wheeze	9 (21; 9 to 33)	8 (42; 20 to 64)	25 (29; 19 to 39)	7 (64; 36 to 92)	45 (34; 26 to 42)	NS
Pain on respiration	3 (7; 0 to 15)	3 (16; 0 to 32)	12 (14; 7 to 21)	0	11 (8; 3 to 13)	NS
Any lower respiratory symptom	18 (43; 28 to 58)	15 (79; 61 to 97)	54 (64; 54 to 74)	9 (82; 59 to 100)	93 (69; 61 to 77)	<0.02
Systemic:						
Headache	20 (48; 33 to 63)	13 (68; 47 to 89)	34 (40; 30 to 50)	6 (54; 25 to 84)	51 (38; 30 to 46)	NS
Feverishness	8 (19; 7 to 31)	9 (47; 25 to 69)	20 (24; 15 to 33)	3 (27; 1 to 53)	28 (21; 14 to 28)	NS
Sweating	4 (10; 1 to 19)	9 (47; 25 to 69)	14 (16; 8 to 24)	3 (27; 1 to 53)	24 (18; 12 to 25)	<0.01
Myalgia	10 (24; 11 to 37)	9 (47; 25 to 69)	11 (13; 6 to 20)	3 (27; 1 to 53)	29 (22; 15 to 29)	<0.05
Rigors	0	3 (16; 0 to 32)	2 (2; 0 to 5)	0	4 (3; 0 to 6)	<0.02
Any systemic symptom	26 (62; 47 to 77)	16 (84; 68 to 100)	48 (56; 45 to 67)	8 (73; 47 to 99)	72 (54; 46 to 62)	NS


Joint Symposium on
Atypical Pneumonia

Comparison of clinical and laboratory features between MERS and SARS patients

	MERS-CoV[7-10, 13, 29, 78, 81]	**SARS-CoV**[79, 114-118]
Date of first case report (place)	April 2012 (Zarqa, Jordan) June 2012 (Jeddah, KSA)	Nov 2002 (Guangdong, China)
Incubation period	Mean: 5.2 days(95%CI:1.9-14.7) Range: 2-13 days	Mean: 4.6 days (95%CI:3.8-5.8) Range: 2-14 days
Serial interval	7.6 days	8.4 days
Basic reproduction number	<1	2-3

Lancet. 2015 September 5; 386(9997): 995–1007.

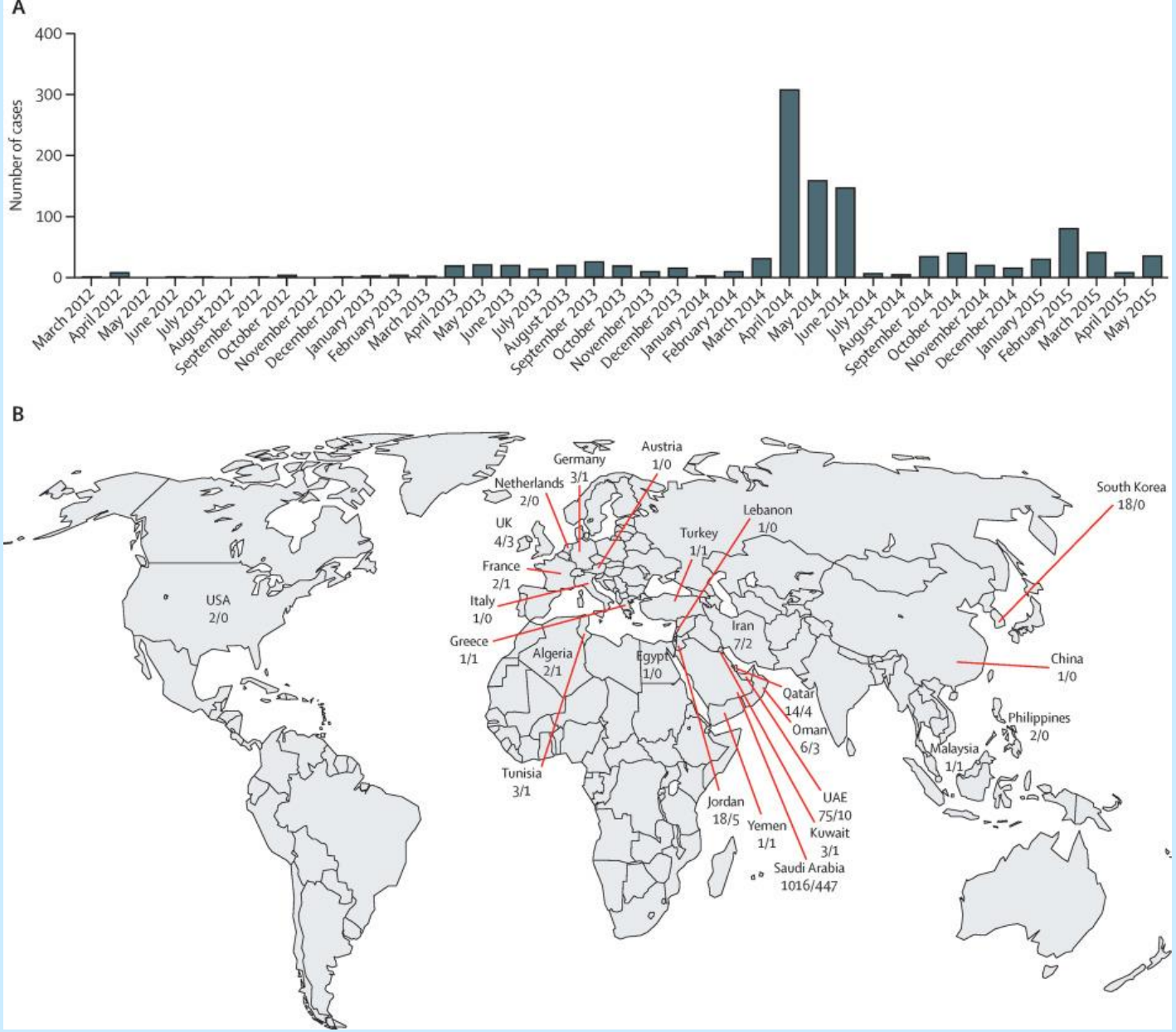
Age group		
Adults Children	Adults (98%) Children (2%)	Adults (93%) Children (5-7%)
Age (years): **Range, Median**	Range:1-94; Median: 50	Range: 1-91 Mean: 39.9
Gender (M,F)	M: 64.5%, F: 35.5%	M: 43%, F: 57%
Case fatality rate (CFR)-overall	40%	9.6%
CFR in patients with co-morbidities	13.3%	1-2%

Lancet. 2015 September 5; 386(9997): 995–1007.

Disease progression		
Time from onset to ventilatory support	Median 7 days	Mean 11 days
Time from onset to death	Median 11.5days	Mean 23.7days
Presenting symptoms		
Fever > 38C	98%	99-100%
Chills / rigors	87%	15-73%
Cough -dry -productive	83% 56% 44%	62-100% 29-75% 4-29%
Haemoptysis	17%	0-1%
Headache	11%	20-56%
Myalgia	32%	45-61%

Lancet. 2015 September 5; 386(9997): 995–1007.

Between 2012 and 21 July 2017, 2040 laboratory-confirmed cases of Middle East respiratory syndrome-coronavirus (MERS-CoV) infection were reported to WHO, 82% of whom were reported by the Kingdom of Saudi Arabia. In total, cases have been reported from 27 countries in the Middle East, North Africa, Europe, the United States of America, and Asia



Lancer Inf Dis: Volume 386, Issue 9997, 2015, 995–1007

Figure 1. Global MERS cases(A) Confirmed cases of MERS as of May 31, 2015, by date (n=1180). (B) Location of MERS deaths/cases, as of May 31, 2015 (n=1180). Shows countries in which patients were identified. Data from WHO14 and Promed Mail.15 MERS=Middle East ...

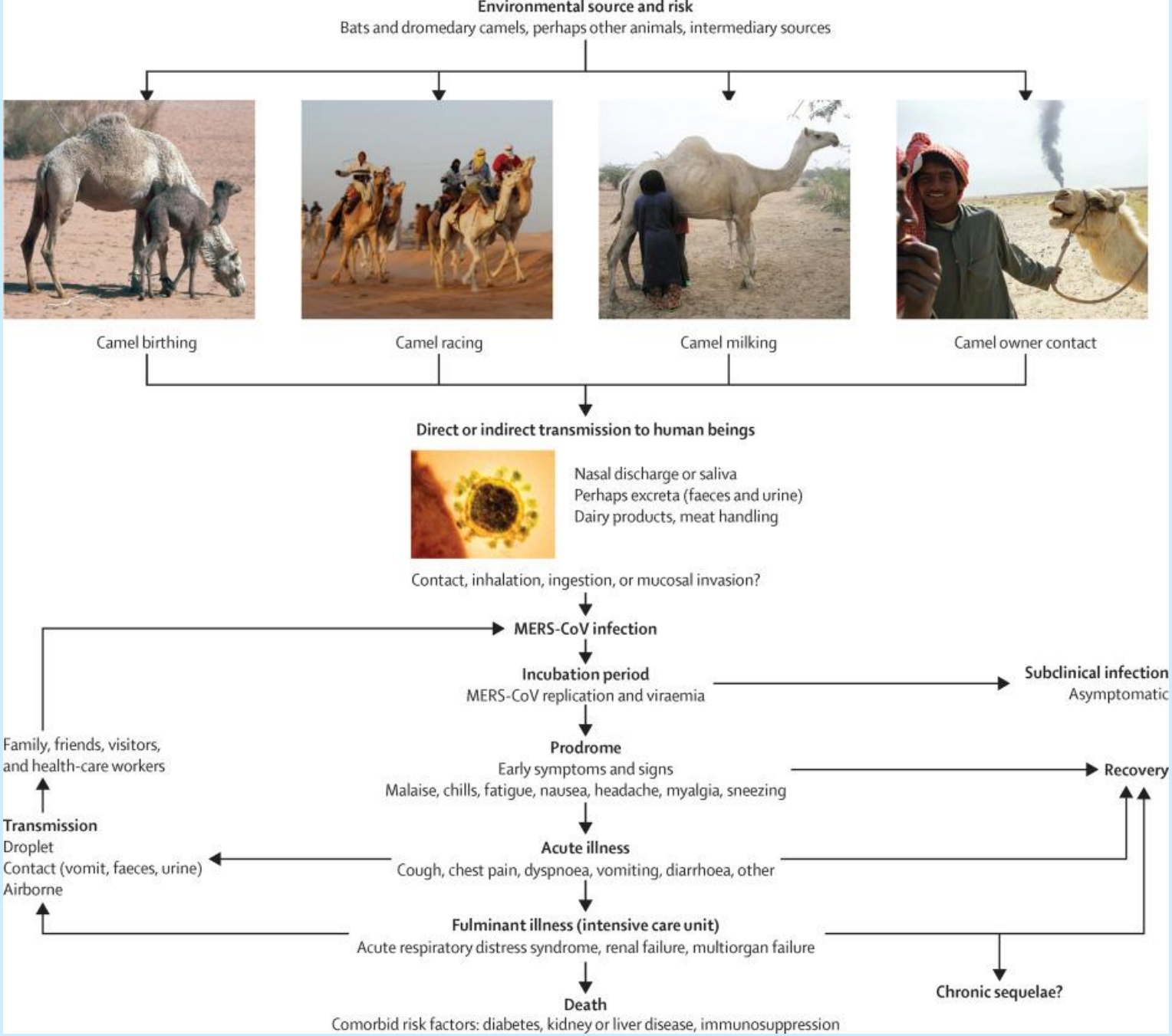


Figure 3. Ecology and transmission of MERS-CoVMERS-CoV might have originally spread from bats to camels and other, as yet unidentified, intermediate hosts. The virus has circulated in camel populations in Africa and the Arabian peninsula for at least 20 years....

Bird Flu

Where are we?

H5N1?, H7N9?+???

H5N1 avian influenza: Timeline of major events: WHO's homepage

human cases of avian flu:

1997

Bird flu virus H5N1 is isolated for the first time from a human patient in Hong Kong.

2003 **February** H5N1 sparks alarm with reappearance in Hong Kong.

H7N7 virus causes outbreak in chickens in The Netherlands

December South Korea has its first outbreak of avian flu in chickens, caused by H5N1.

2004

January Japan has the first outbreak of avian influenza (H5N1) since 1925.

January Vietnam's first human H5N1 cases

April Poultry workers have H7N3 avian flu

August Vietnam deaths from H5N1

September A mother who died after caring for her sick daughter is the first suspected case of person-to-person transmission of H5N1 avian flu in Thailand.

2005

January Rising numbers of cases in Vietnam and Thailand

February First report of a human bird flu case in Cambodia.

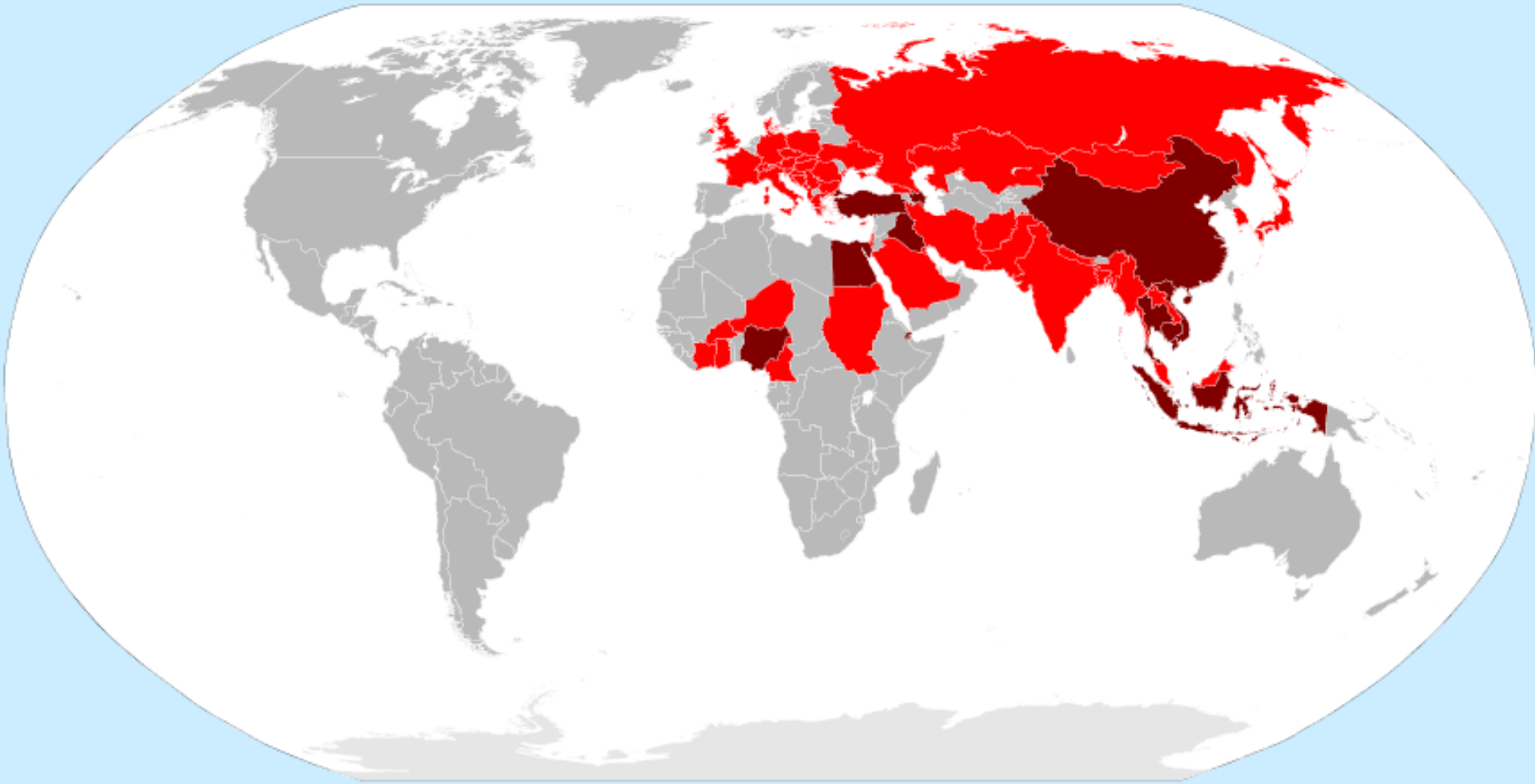
- Person to person transmission of H5N1

May Rumours of H5N1 deaths in China

- Rising numbers of cases in Vietnam, Cambodia and Thailand

Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2017

Country	2003-2009*		2010-2014**		2015		2016		2017		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Azerbaijan	8	5	0	0	0	0	0	0	0	0	8	5
Bangladesh	1	0	6	1	1	0	0	0	0	0	8	1
Cambodia	9	7	47	30	0	0	0	0	0	0	56	37
Canada	0	0	1	1	0	0	0	0	0	0	1	1
China	38	25	9	5	6	1	0	0	0	0	53	31
Djibouti	1	0	0	0	0	0	0	0	0	0	1	0
Egypt	90	27	120	50	136	39	10	3	3	1	359	120
Indonesia	162	134	35	31	2	2	0	0	0	0	199	167
Iraq	3	2	0	0	0	0	0	0	0	0	3	2
Lao People's Democratic Republic	2	2	0	0	0	0	0	0	0	0	2	2
Myanmar	1	0	0	0	0	0	0	0	0	0	1	0
Nigeria	1	1	0	0	0	0	0	0	0	0	1	1
Pakistan	3	1	0	0	0	0	0	0	0	0	3	1
Thailand	25	17	0	0	0	0	0	0	0	0	25	17
Turkey	12	4	0	0	0	0	0	0	0	0	12	4
Viet Nam	112	57	15	7	0	0	0	0	0	0	127	64
Total	**468**	**282**	**233**	**125**	**145**	**42**	**10**	**3**	**3**	**1**	**859**	**453**



Red: Countries with cases in birds
Black: Countries with human cases
Spread of Inf A/H5N1

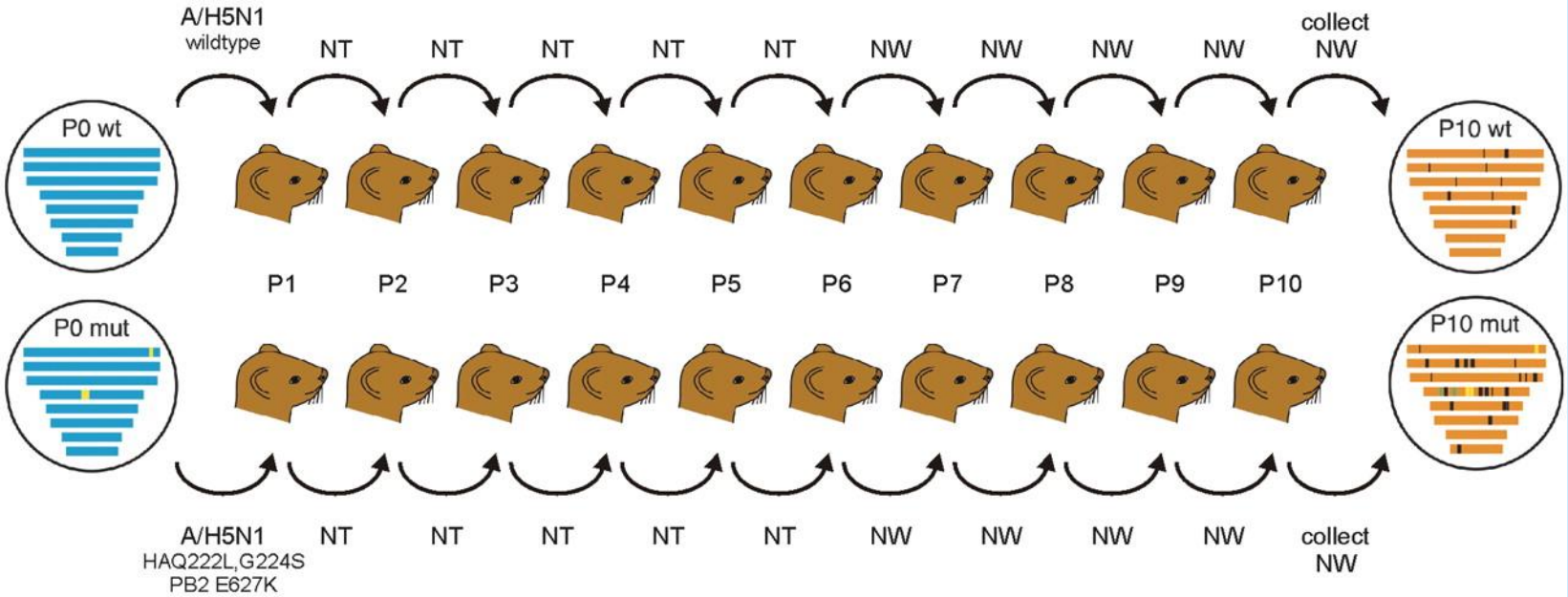
Airborne Transmission of Influenza A/H5N1 Virus Between Ferrets

Sander Herfst [1], Eefje J. A. Schrauwen [1], Martin Linster [1], Salin Chutinimitkul [1], Emmie de Wit [1,*], Vincent J. Munster [1,*],
Erin M. Sorrell [1], Theo M. Bestebroer [1], David F. Burke [2],
Derek J. Smith [1,2,3], Guus F. Rimmelzwaan [1], Albert D. M. E. Osterhaus [1], Ron A. M. Fouchier [1,†]
Science 22 Jun 2012:Vol. 336, Issue 6088, pp. 1534-1541

Abstract

Highly pathogenic avian influenza A/H5N1 virus can cause morbidity and mortality in humans but thus far has not acquired the ability to be transmitted by aerosol or respiratory droplet (“airborne transmission”) between humans. To address the concern that the virus could acquire this ability under natural conditions, we genetically modified A/H5N1 virus by site-directed mutagenesis and subsequent serial passage in ferrets. The genetically modified A/H5N1 virus acquired mutations during passage in ferrets, ultimately becoming airborne transmissible in ferrets. None of the recipient ferrets died after airborne infection with the mutant A/H5N1 viruses. Four amino acid substitutions in the host receptor-binding protein hemagglutinin, and one in the polymerase complex protein basic polymerase 2, were consistently present in airborne-transmitted viruses. The transmissible viruses were sensitive to the antiviral drug oseltamivir and reacted well with antisera raised against H5 influenza vaccine strains. Thus, avian A/H5N1 influenza viruses can acquire the capacity for airborne transmission between mammals without recombination in an intermediate host and therefore constitute a risk for human pandemic influenza.

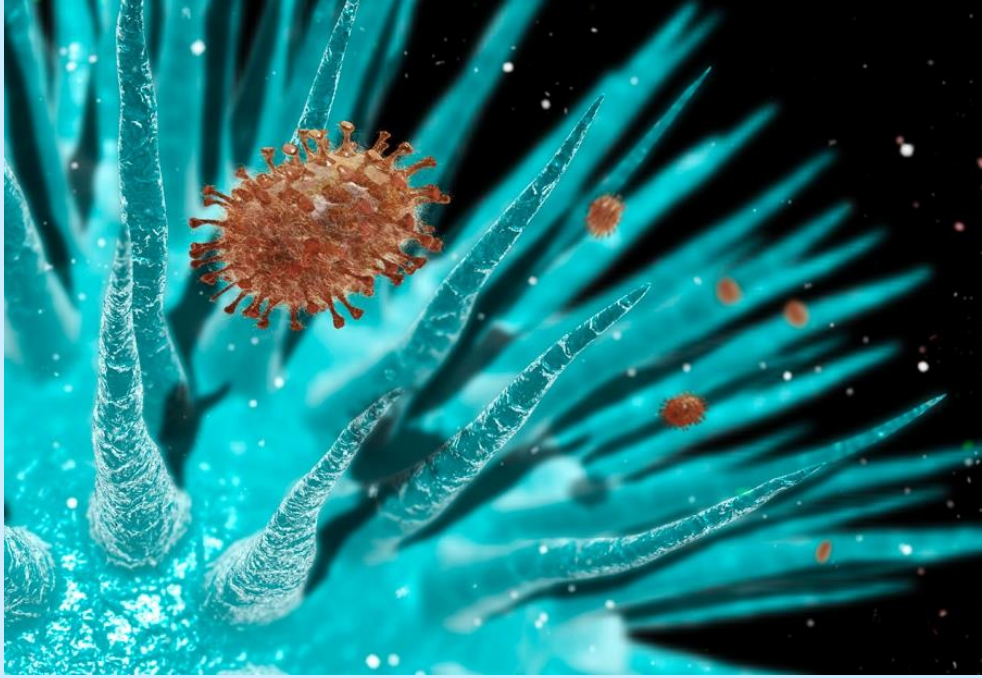
Fig. 2 Experiment 3, virus passaging in ferrets (P1 to P10, passages 1 to 10).



Sander Herfst et al. Science 2012;336:1534-1541

From march 2013 reports came of a new H7N9 bird flu virus spreading through China. A chinese study reminds us that a different avian influenza — H5N1 — still poses a pandemic threat.

A team of scientists in China has created hybrid viruses by mixing genes from H5N1 and the H1N1 strain behind the 2009 swine flu pandemic, and showed that some of the hybrids can spread through the air between guinea pigs. The results are published in *Science*[1].



Researchers have crossed two strains of avian flu virus to create one that can be transmitted through the air — and possibly settle on the cilia of lung cells as in this conceptual image.

WHO: H7N9 virus 'one of the most lethal so far‘ (CNN 2013)

Human infection with avian influenza A(H7N9) virus – China

Disease outbreak news

13 September 2017

On 18, 25 August and 4 September 2017, the National Health and Family Planning Commission of China (NHFPC) notified WHO of four additional laboratory-confirmed cases of human infection with avian influenza A(H7N9) virus in China.

To date, a total of 1562 laboratory-confirmed human infections with avian influenza A(H7N9) virus have been reported through IHR notification since early 2013. Around 40% case fatality rate.

Given the large numbers of HPAI A/H5N1 virus-infected hosts globally, the high viral mutation rate, and the apparent lack of detrimental effects on fitness of the mutations that confer airborne transmission, it may simply be a matter of chance and time before a human-to-human transmissible A/H5N1 virus emerges.