2019新冠狀病毒感染：實驗室診斷及臨床表現
2019-nCoV Infection: Clinical Manifestations & Diagnosis

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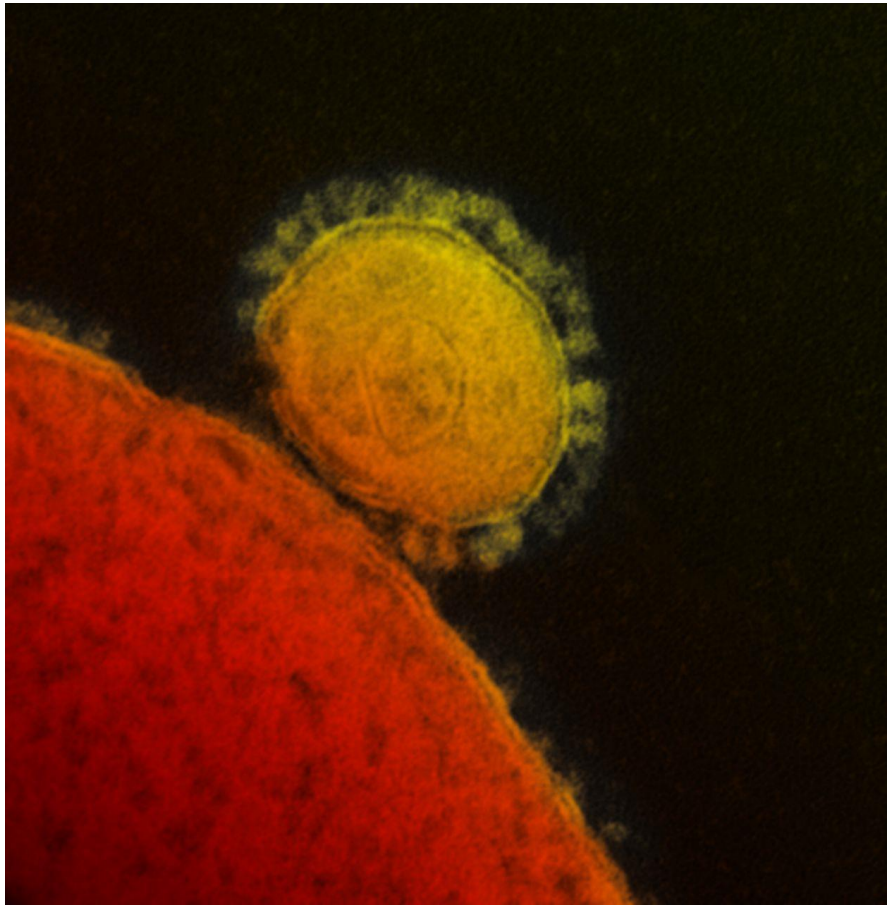
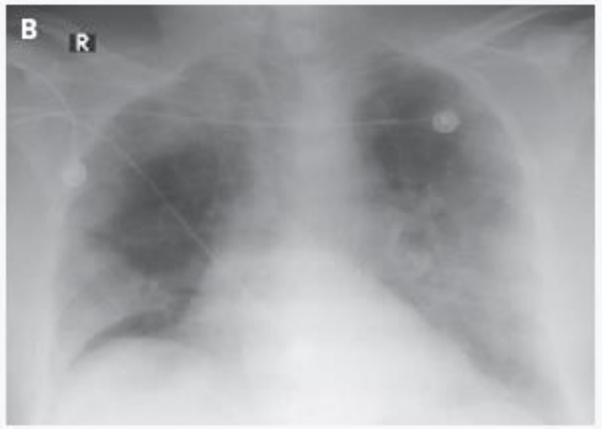
大綱

1. MERS-CoV infection
2. 冠狀病毒簡介
3. 2019-nCoV infection

Transmission of MERS-CoV



Milne-Price S. et al., Pathogens and Disease 2014



The world's first case of MERS-CoV infection with dramatic clinical presentation: Saudi Arabia (世界第一例)

- 60-year-old Saudi man on June 13 2012
- No significant past medical history, no smoking

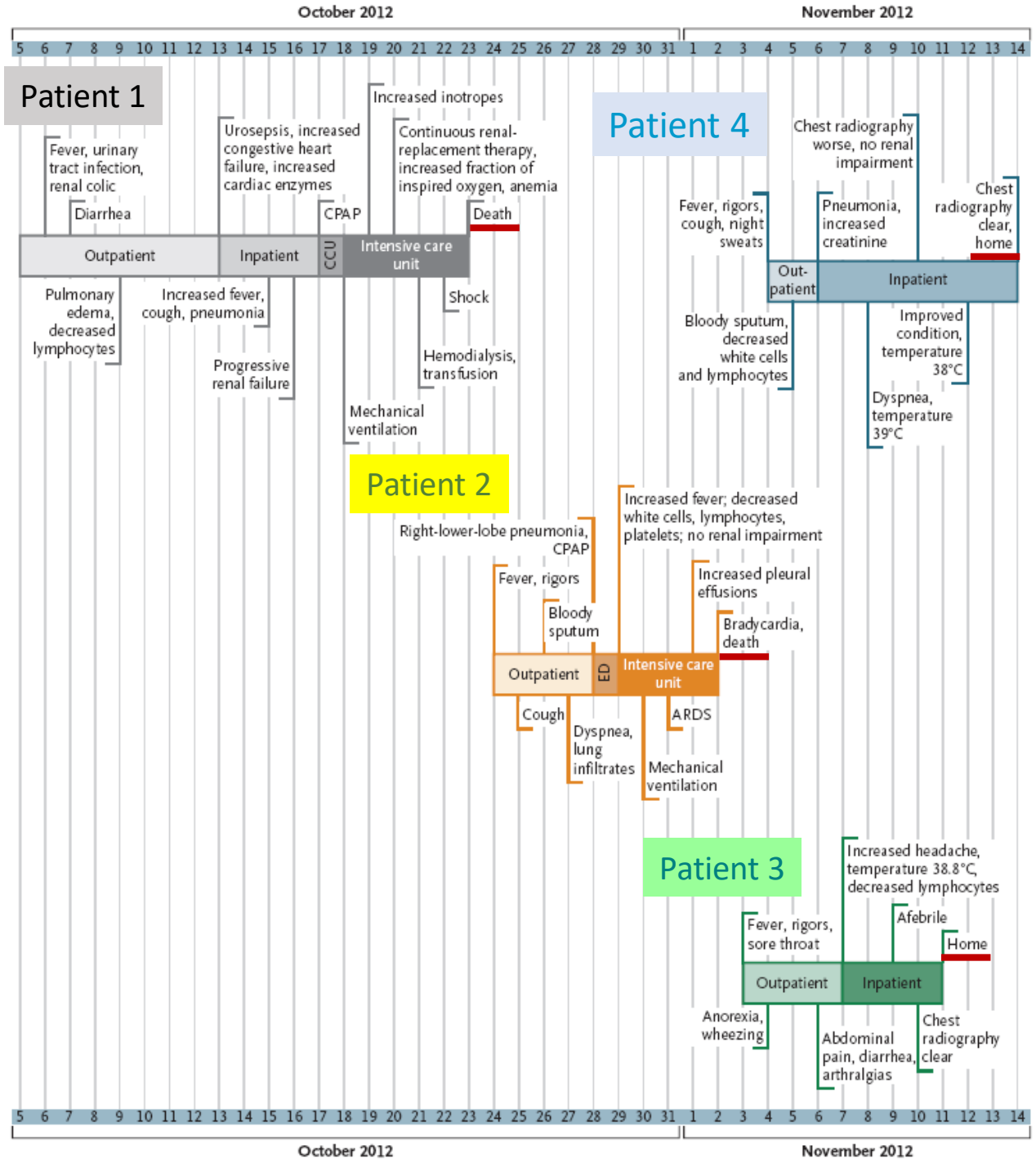
- 7-day history of fever, cough, expectoration, and shortness of breath

- Day 1: oseltamivir, levofloxacin, piperacillin-tazobactam
- Day 2: ICU,

Pneumonia and renal failure progressed

- Day 11: died

Zaki AM., et al., NEJM 2013



Potential for Person to person transmission

Family cluster of MERS-CoV

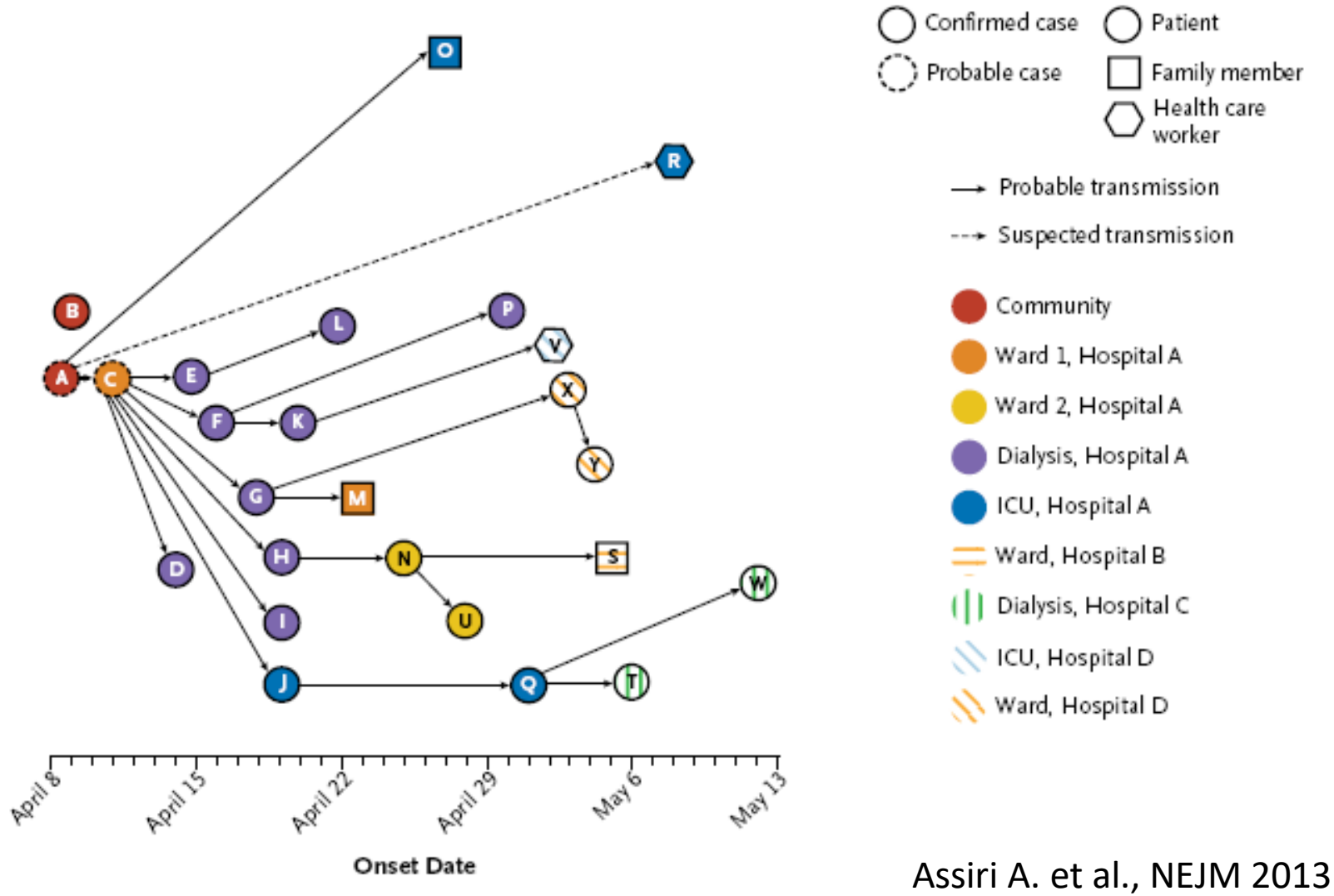
3 confirmed case (1, 2, 4) and
1 probable case (3)

- Patient 1: 70y, man
- Patient 2: 39y, son of 1
- Patient 3: 16y, son of 2, grandson of 1
- Patient 4: 31y, younger brother of 2, son of 1

Memish Z. et al., NEJM 2013

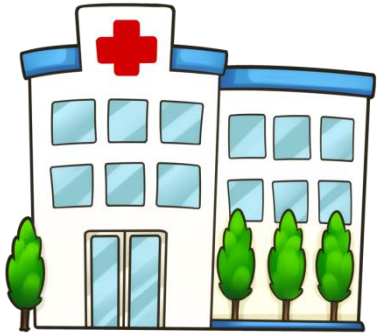
Potential for nosocomial outbreak

Hospital outbreak of MERS-CoV in the Middle East



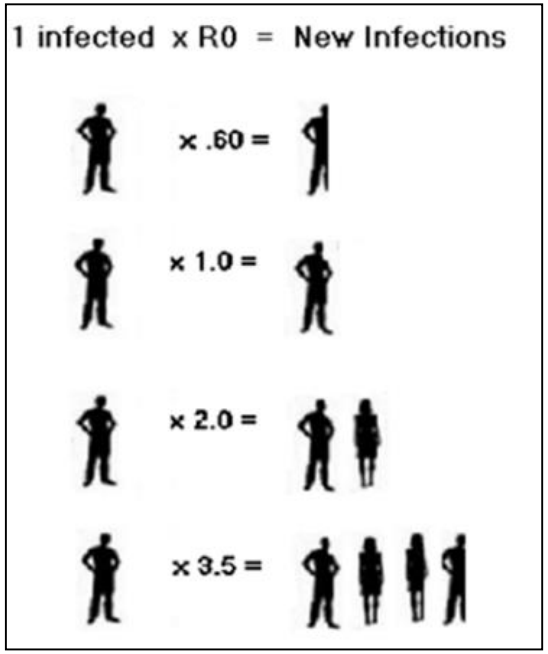
Assiri A. et al., NEJM 2013

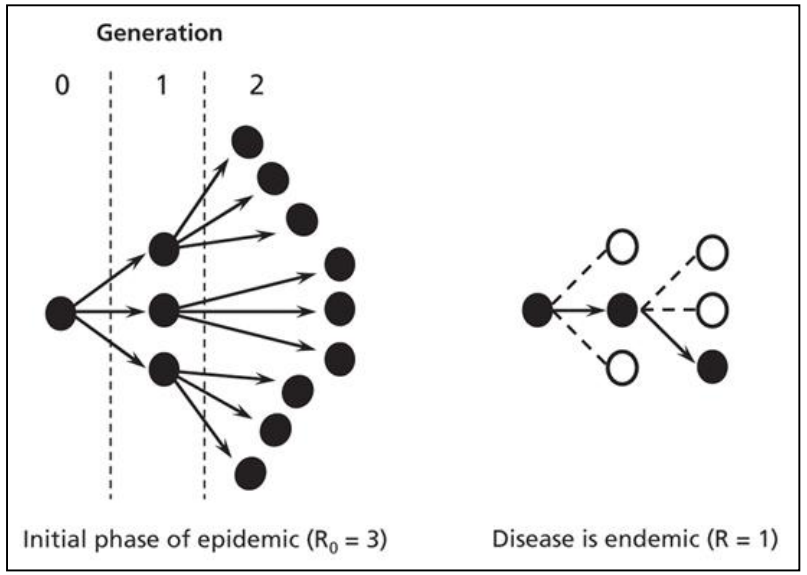
Lives of people and camels in Middle East



Potential for large scale outbreak or pandemic infection?

Transmissibility of MERS-CoV was considered to be low (R_0 less than 1).





Breban R. et al., Lancet. 2013:24;382:694-9
Cotton M. et al., MBio. 2014:18;5

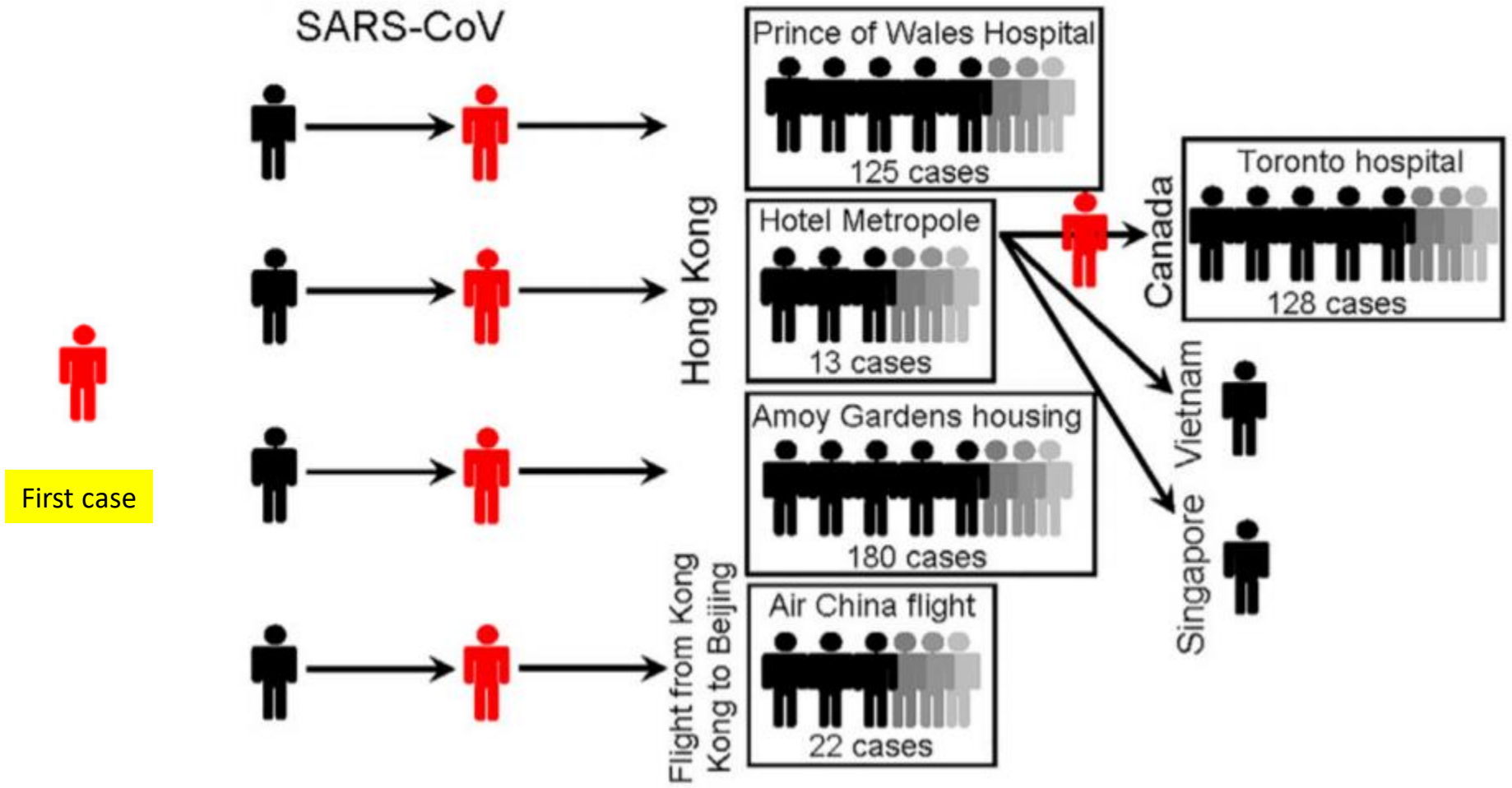
Countries reporting MERS-CoV infection as of 5 February 2015

- Egypt, Iran, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia (SAU), United Arab Emirates (UAE) and Yemen
- Algeria, and Tunisia
- Austria, France, Germany, Greece, Italy, the Netherlands, Turkey and UK
- Malaysia and Philippines
- USA

Experience from SARS:
Wide spread of SARS **before** the identification of the virus

Nov 2002

Feb-Mar 2003



Wong G., et al. Cell Host Microbe. 2015;18:398-401.

Science & Health

WHO: MERS Coronavirus Has Potential to Cause Pandemic

June 10, 2013 05:15 PM

Global Concern Grows About Deadly Middle East Respiratory Syndrome

GENEVA - The World Health Organization on Monday urged health workers around the world to be on the alert for symptoms of the deadly Middle East respiratory syndrome coronavirus (MERS), which has the potential to circle the globe and cause a pandemic.

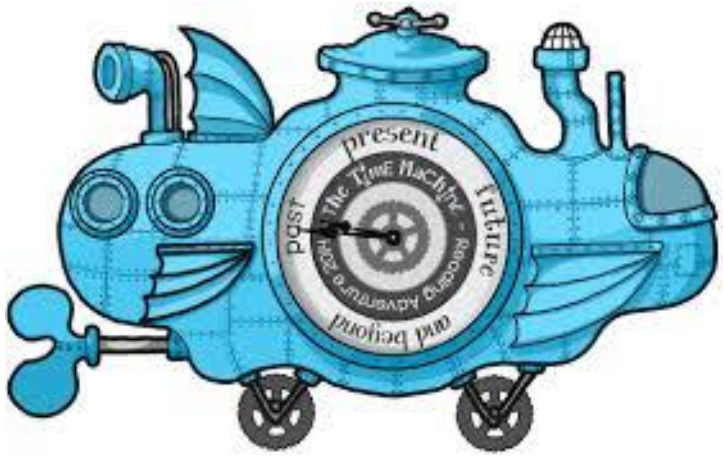
The United Nations agency, which issued new, long-awaited guidance to countries on influenza pandemics, said the world was also in the same "alert phase" for two human strains of bird flu - H5N1, which emerged a decade ago, and H7N9, first detected in China in March.

"We are trying to find out as much as we can and we are concerned about these (three) viruses," Andrew Harper, WHO special adviser for health security and environment, told a news briefing on its new scale for pandemic risk.

The interim guidance, to be finalized later this year, incorporates lessons from the 2009/2010 pandemic of H1N1 swine flu, which caused an estimated 200,000 deaths, roughly in line with annual seasonal flu.

Then, what happened in 2015 in Korea?
Why was it a big problem?

Back to 2015 when we did not know some “important” things that we know now



SMC diagnosed the first case of MERS in Korea

- May 4, 2015: a 68-yo Korean man returned to Korea from Middle East
- May 11: Developed fever and cough
- Treated for pneumonia at outside hospital (no MERS suspicion)

1.5 hr driving distance

- May 17: 1st visit to Samsung Medical Center ER with persistent Sx
- May 18: 2nd visit to SMC ER
  - Suspected for MERS-CoV infection on ID consultation (confirmed May 20)
  - Sx of pneumonia and travel hx to Bahrain and Qatar
    - Isolated the patient in a negative-pressure room
    - MERS-CoV PCR test sent to Korea CDC

Cho SY, Kang JM et al., Lancet. 2016;388:994-1001

- He returned to Korea from Middle East on May 4, 2015.
- He reported travelling "only" to Bahrain (18 April – May 2) and returned to Korea via Qatar (May 2–3) and denied travel hx to UAE or KSA.
- Later, he was found that he also traveled to the UAE (April 29–30) and KSA (May 1–2) during his stay in Bahrain.

Cho SY, Kang JM et al., Lancet. 2016;388:994-1001

Crowded ER at SMC

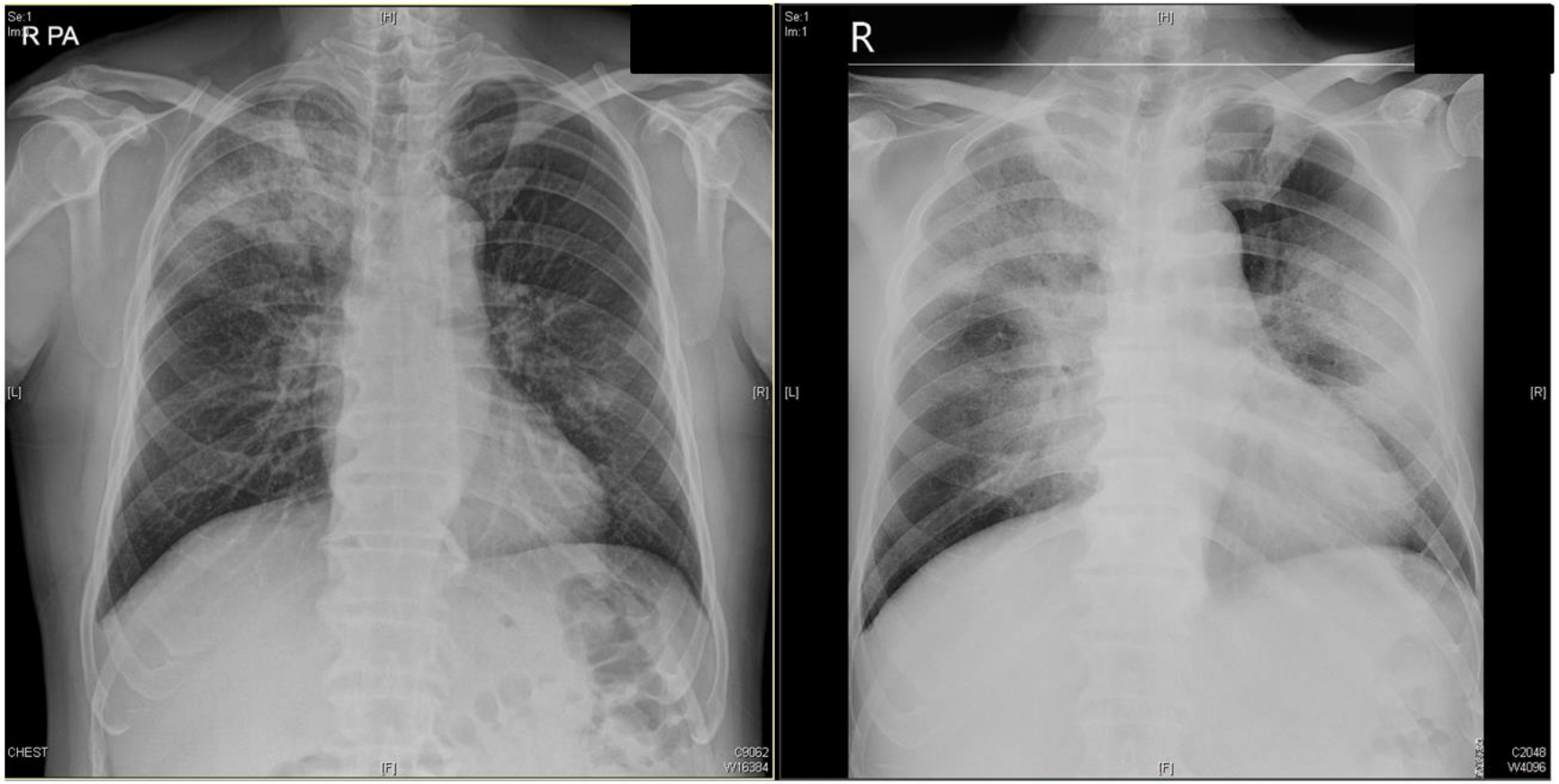
2014

Daily visit to ER	214
ER beds	56
Overcrowding index at ER	133.2% (4th highest in nation)
Hospital bed utilization	91.2%
Length of stay	7.7 d

The first patient (Patient A)

Symptom onset day 7

Symptom onset day 10



Transmitted MERS-CoV to 28 individuals before day 7

Osong Public Health Res Perspect 2015 6(4), 269e278

Cho SY et al., Lancet. 2016;388:994-1001

SMC diagnosed the first case of MERS in Korea

- May 20: confirmed as the first imported MERS case in Korea (PCR)

It was “9 days” from the first Sx onset, when the diagnosis was made at SMC.

Cho SY, Kang JM et al., Lancet. 2016;388:994-1001

Our challenge at that time

How to investigate the exposure and how to estimate who were in greater risk of infection based on the information available in 2015?

- $R_0<1$
- Defining close contact?
  - Applying our situation to the ones in the literature to define close contact
  - Within 2 meters how many hours? 1hr? 2 hrs?
  - Etc…

Our conclusion and request to Korean CDC at that time

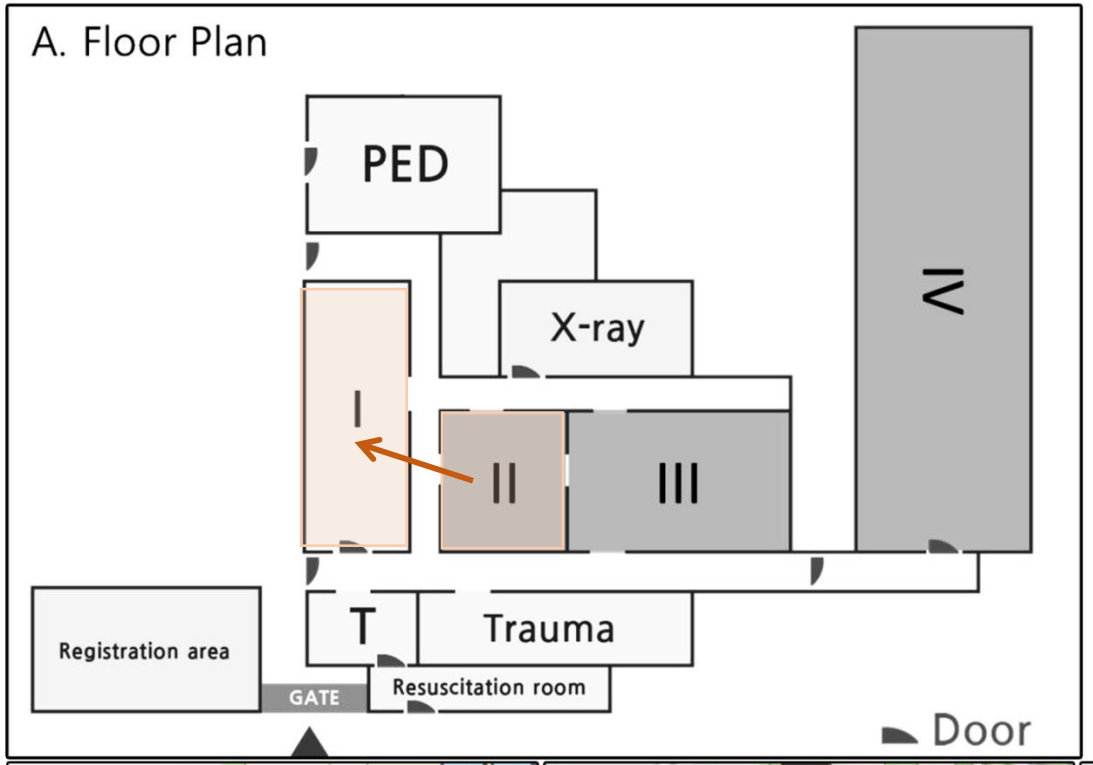
- **Phone conference with KCDC**
- MERS-CoV is a new virus.
- Still unknown facts and truth on MERS-CoV exist in the nature that should be scientifically confirmed.

-> Maximum precaution

-> A thorough and wide investigation

Until situation is confirmed safe!!!

ER Floor plan and patient location



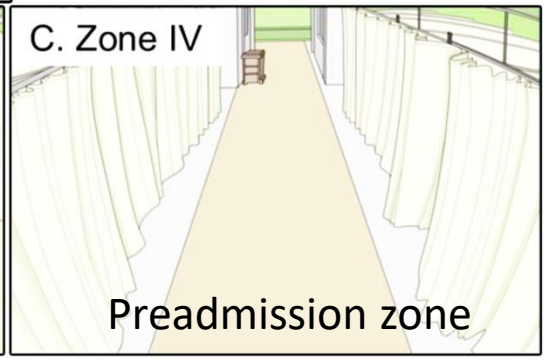
Information on location and duration of stay at each place were retrieved from EMR.

Duration of Stay at ER before isolation

Zone II (5/17): 4 hrs
Zone I (5/18): 5 hrs

Sitting area

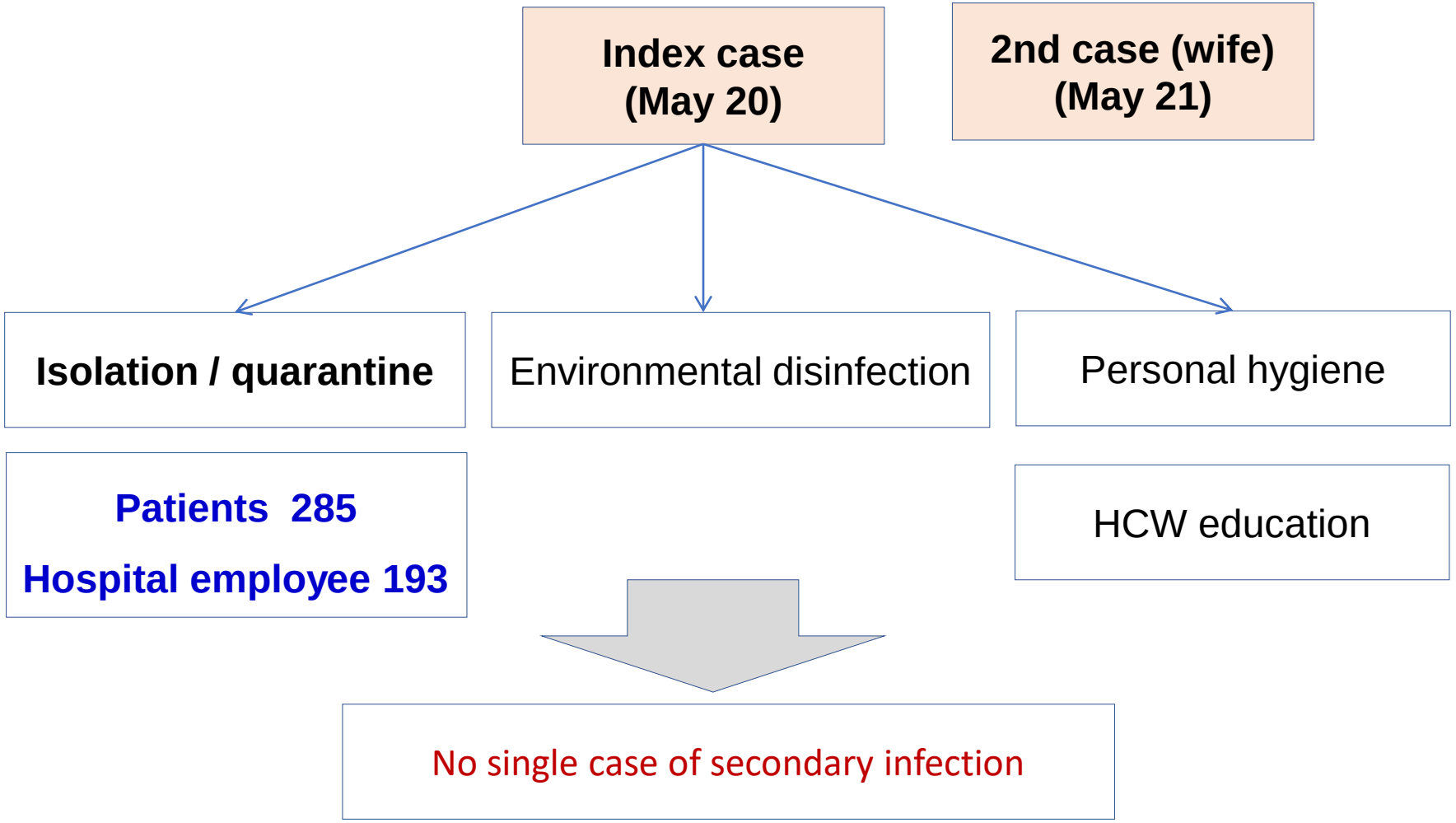
Serious patients



Cho SY, Kang JM et al., Lancet. 2016;388:994-1001

Exposure to the first case (patient A) at SMC

MERS Patient A in Korea: **68-yo Korean man**



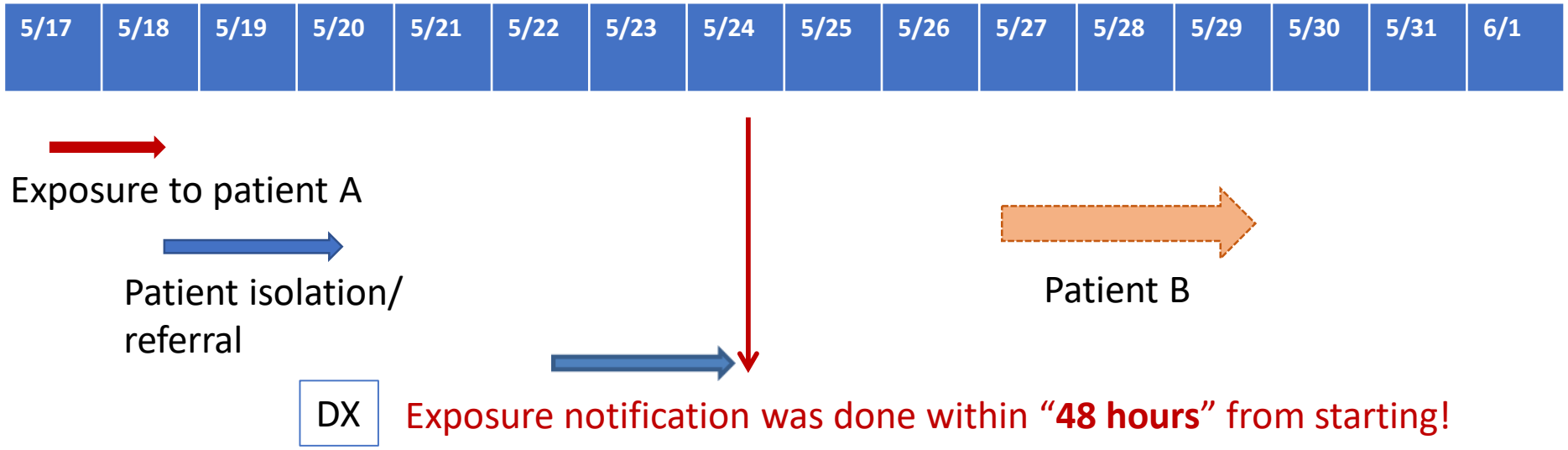
Cho SY, Kang JM et al., Lancet. 2016;388:994-1001

Clinical Course of MERS-CoV Infection

Exposure to Sx onset	2-14 days
Duration of fever	8 days (median)
Symptom onset to PCR (-)	17 days (median)
Chest X-ray infiltrates	80.8%
Mechanical ventilation required	24.5%
Symptom onset to MV	9 days (median)
Symptom onset to death	14 days (median)

Oh MD M al. Kotmo J Intern UM 2018 kjim.org/journal/view.php?doi=10.3904/kim.2018.031

Management after exposure to Patient A



We identified everybody who visited ER during his stay regardless of exposure degree.

- SMC MERS hotline, notification calls
- F/U calls for patients and family contacts
- Alert system with notification to physicians and reception desks for OPD visit, other planned tests (lab, radiology, day hospital, etc)

What's happening in Pyeongtaek St. Mary's Hospital?

First hospital where the 1st MERS patient was hospitalized.

KCDC

Close contact:

defined as a person who had physical contact with index case, or a person who stayed within a two-meter radius of a case for more than one hour in the same space

KCDC decided **16 medical staffs** were to be quarantined!

AND

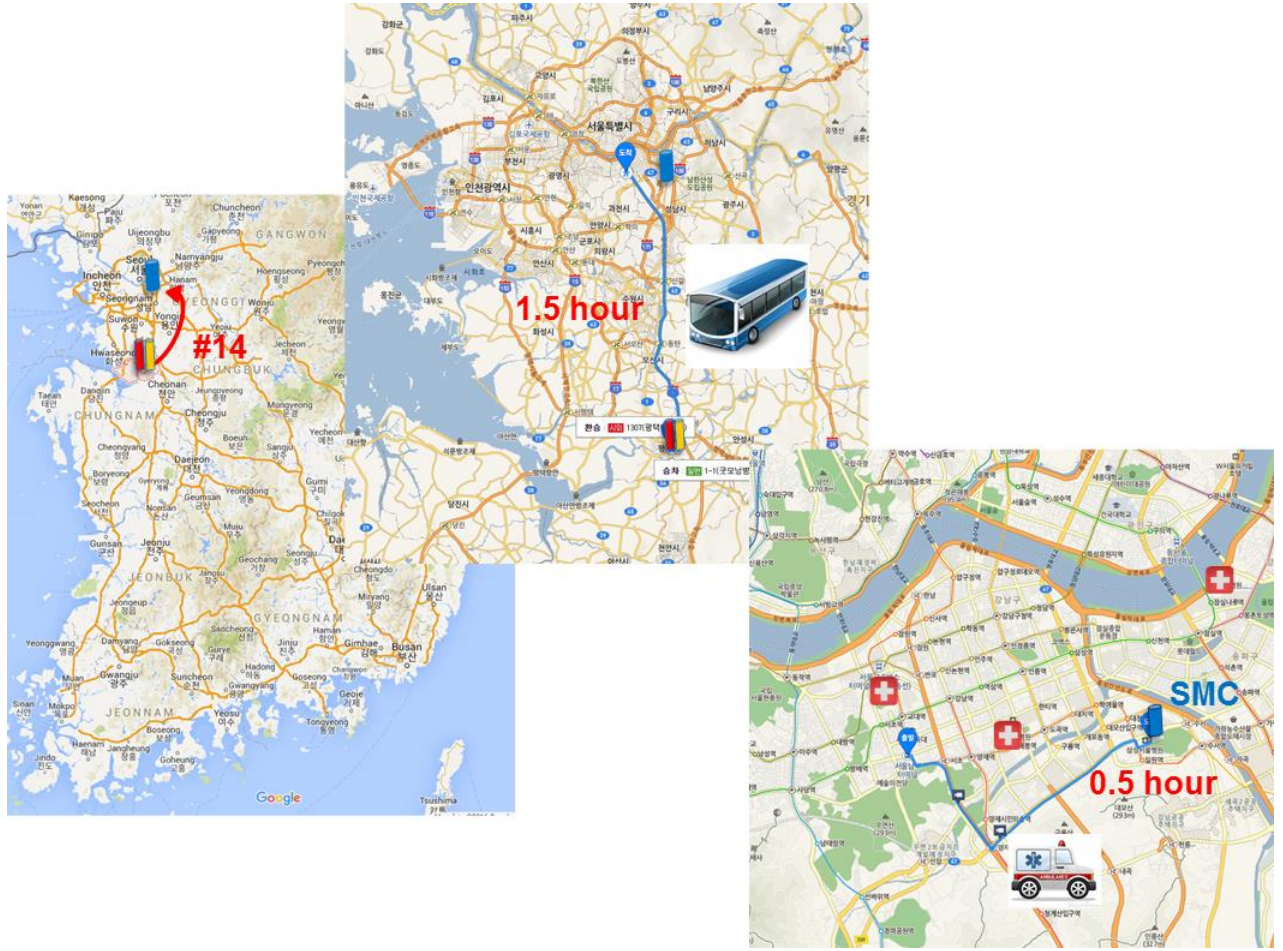
No other patients in the same ward who could have been exposed were investigated, notified or isolated. The rest of the patients were all discharged home without any follow-up plans.

Kim KM, et al. Epidemiol Health 2015;37

MERS outbreak at SMC by “Patient 14”

MERS Patient 14 in Korea : 35 y/o Korean gentleman

- May 27th, transferred from Pyungtaek Good-Morning Hospital to SMC ER because of pneumonia (Originated form Pyungtaek St. Mary’s Hospital)

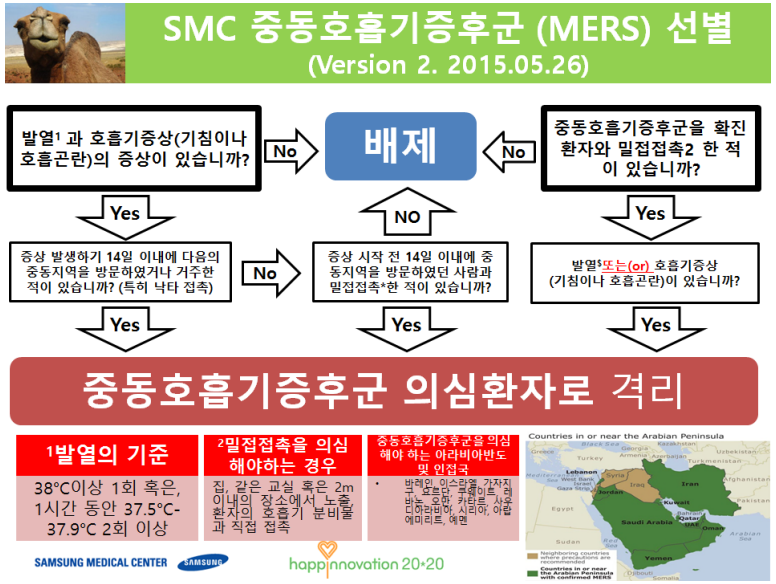


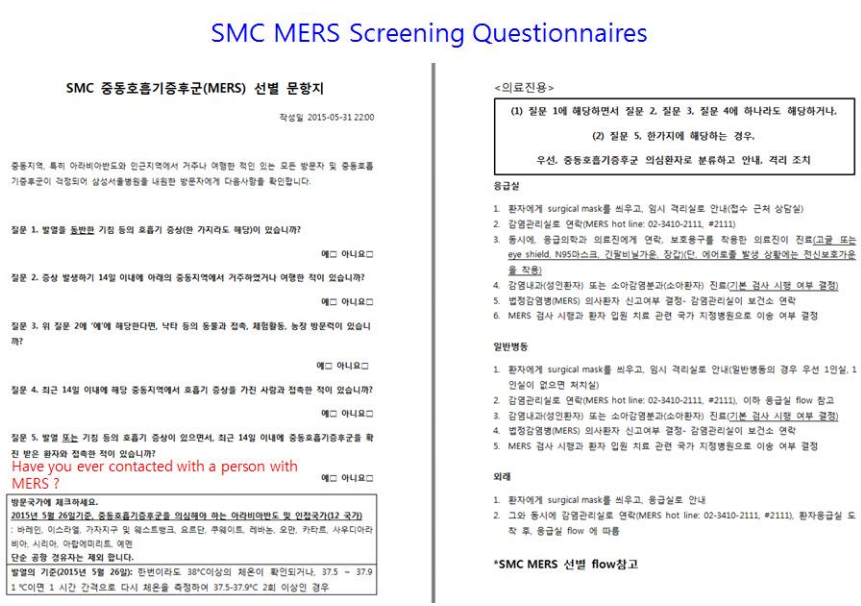
The New York Times June 17, 2015

- In South Korea, when a parent gets sick, it is widely considered a filial duty for the children to mobilize all connections to secure a bed in Samsung or....
- When that strategy fails, patients are often taken into the hospitals' emergency rooms, where they can wait for days for a bed in a general ward.

…….

Patient B passed SMC MERS Screening Questionnaires at ER arrival





No travel Hx to Middle East

No “known” hx of close “contact” with confirmed MERS-CoV patient

Cho SY et al., Lancet. 2016;388:994-1001

Patient B (14th MERS patient in Korea)

- A 35-year-old male without significant underlying disease
- May 15 - 17: Treated for community acquired pneumonia at the first hospital
  - At the **same ward** of the **same hospital** with Patient A

- May 20: Discharged from the first hospital
  - The same day when the 1st patient was diagnosed at 7 AM at SMC

- **May 21-** 25: Readmitted to the **same first hospital** because of fever

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- May 25
  - Moved to the second hospital because of worsening symptoms without being suspected as MERS patient despite the exposure and re-admission

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- May 27
  - Left the second hospital and came to our hospital (SMC, third hospital)
  - Without knowing his exposure to MERS-CoV

Cho SY, Kang JM et al., Lancet. 2016;388:994-1001

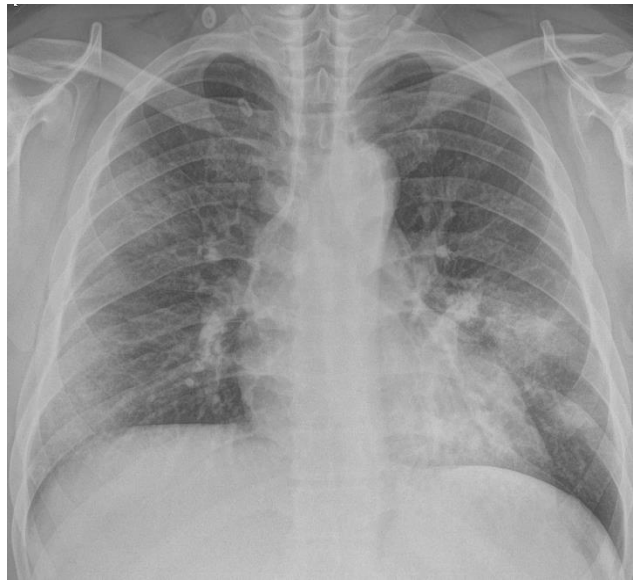
An MERS ER outbreak by "Patient B"

- May 27-29: **Antibiotic treatment in three ER locations** (zone II→ zone III → zone IV).
- May 29 (Friday night): 9 days of KCDC investigation from 1st patient dx
  - He received a call from the health authority for a possible exposure to MERS index case at previous hospital.
  - Immediate isolation
  - Moved to ICU and placed on mechanical ventilator
  - Traffic control and environmental sanitation in the ER
- May 30: Confirmed positive for MERS-CoV infection and transferred to the national medical center.

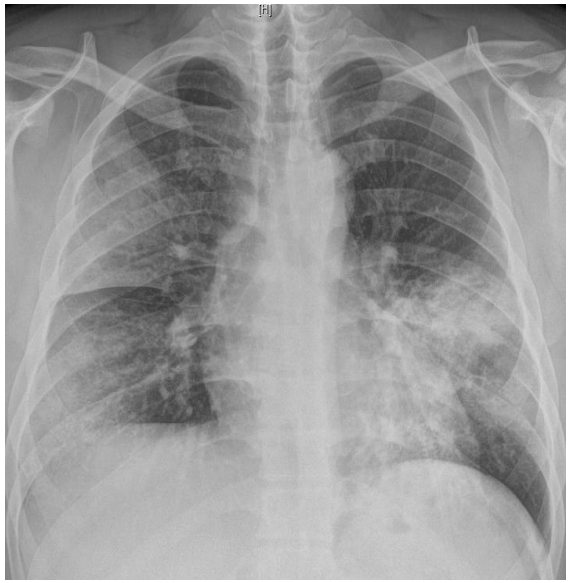
Cho SY, Kang JM et al., Lancet. 2016;388:994-1001

The patient B with severe symptoms

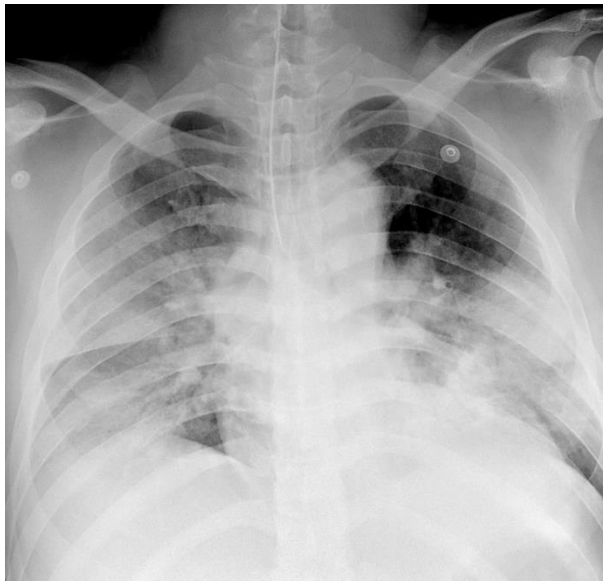
Symptom onset day 7
On arrival at ER (May 27)



In ER (May 29)



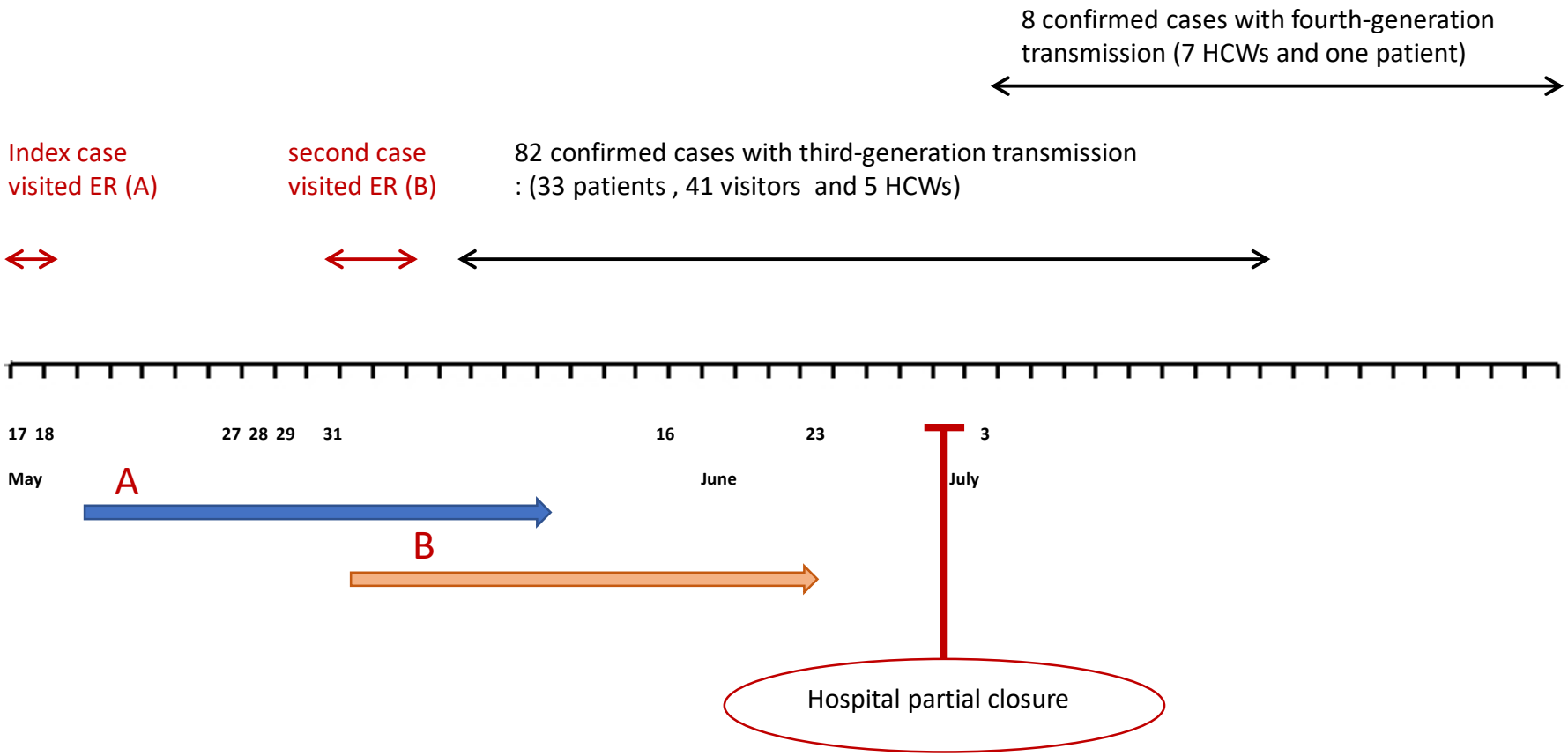
At ICU (May 30)



Transmitted MERS-CoV to 82 individuals in ER

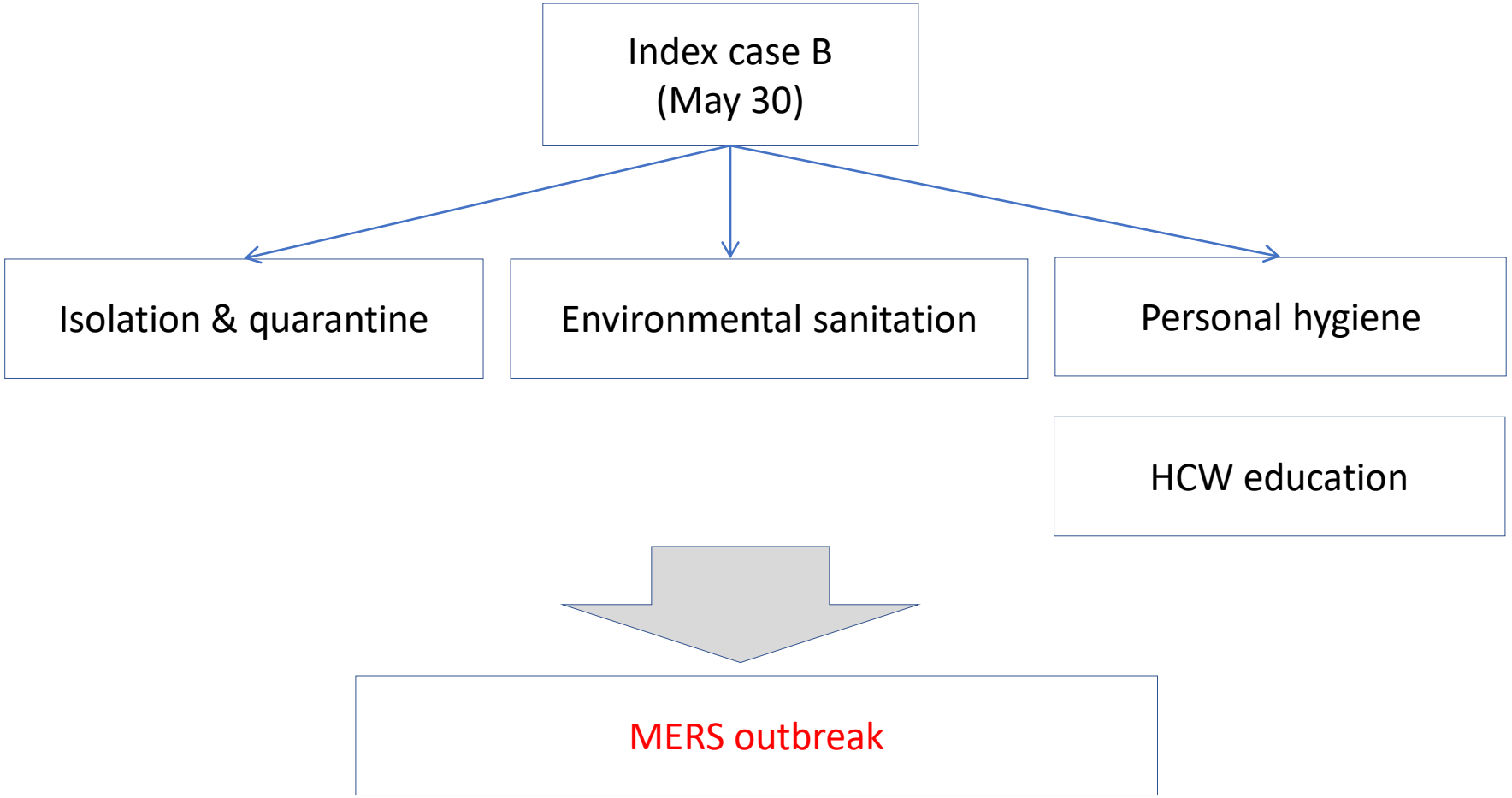
Cho SY et al., Lancet. 2016;388:994-1001

Timeline of what happened

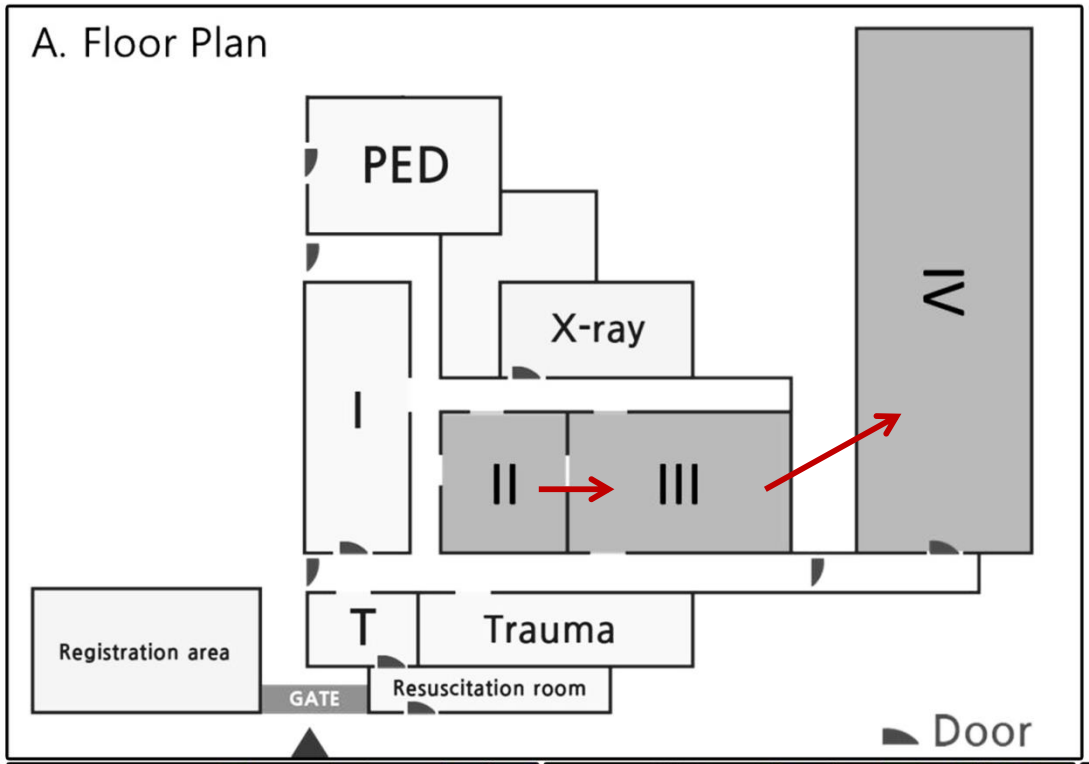


Cho SY, Kang JM et al., Lancet. 2016;388:994-1001

Patient B and MERS outbreak



ER Floor plan and patient B location

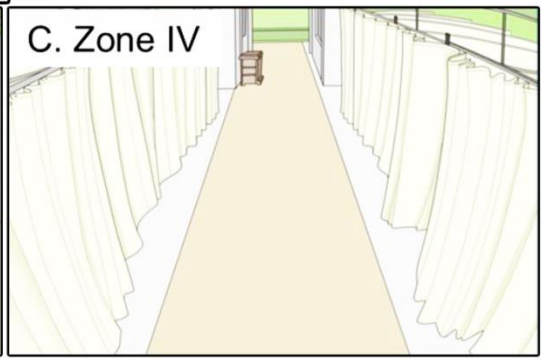


Information on location and duration of stay at each place were retrieved from EMR.

Zone II (5/27): 10 hrs
Zone III (5/27-28): 19 hrs
Zone IV (5/28-29): 25 hrs

Sitting area

Serious patients

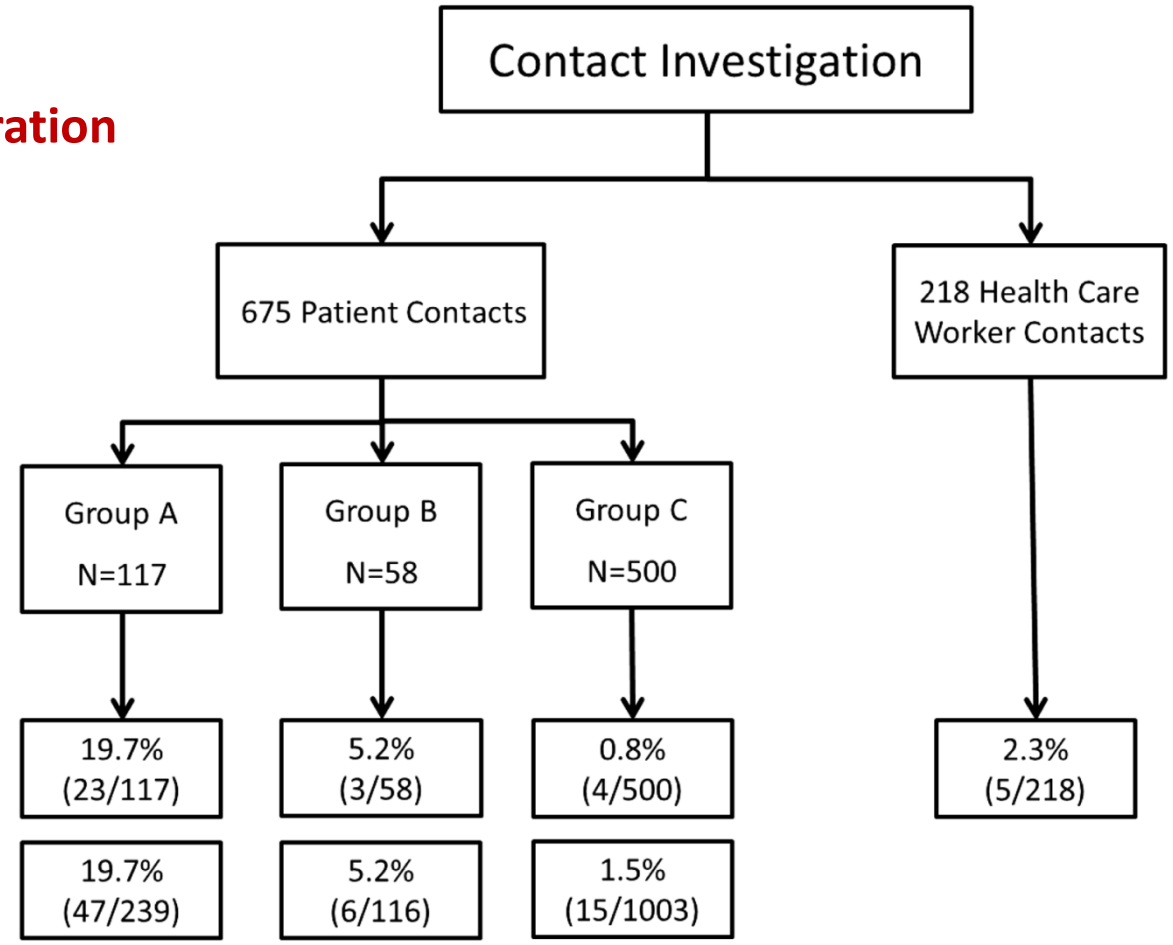


Preadmission zone

Cho SY, Kang JM et al., Lancet. 2016;388:994-1001

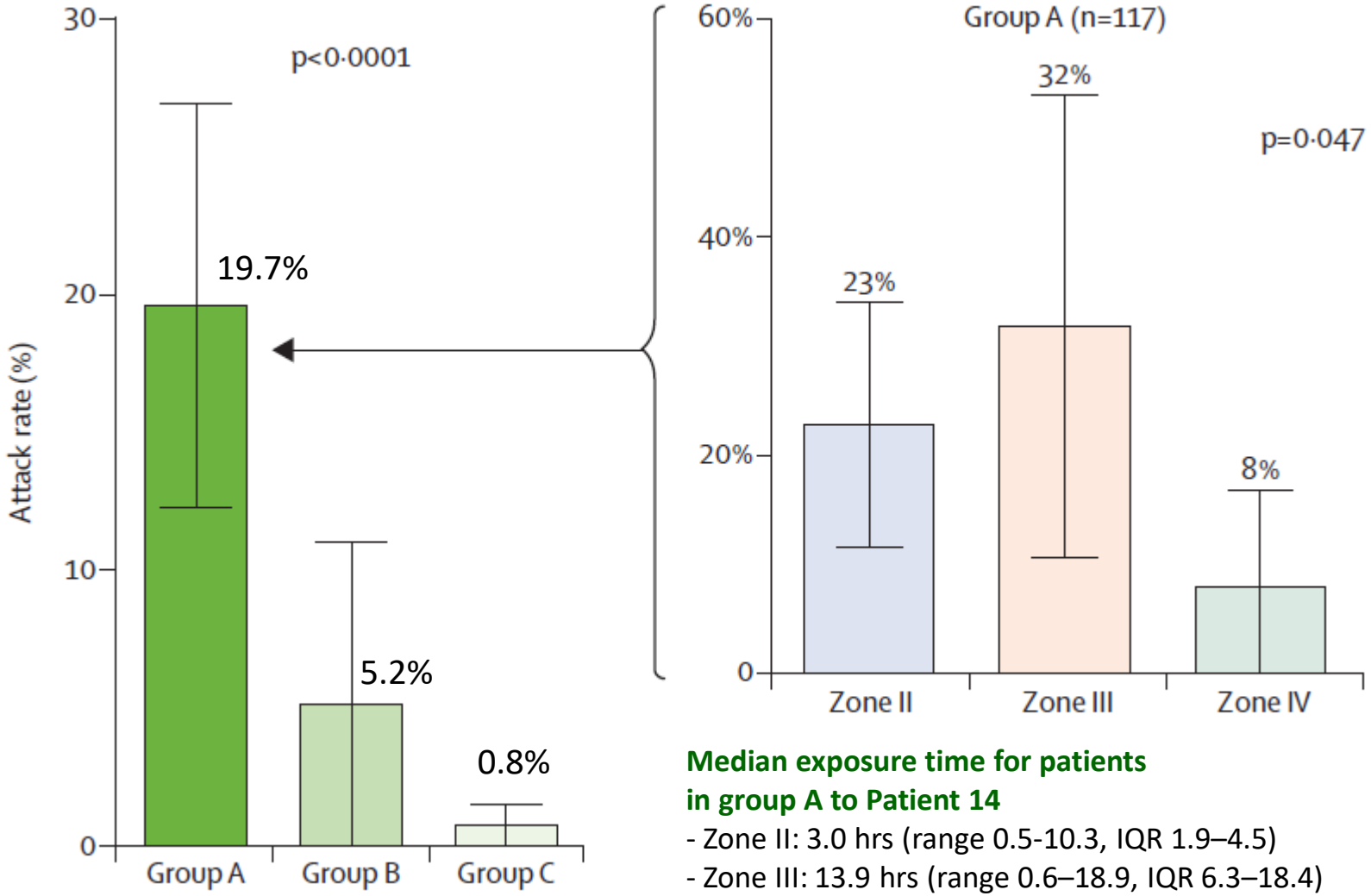
Contact investigation after the exposure to Patient B

A: same zone
B: overlap at registration or in radiology
C: different zones



Cho SY, Kang JM et al., Lancet. 2016;388:994-1001

Higher attack rates among patients who stayed in the same zones

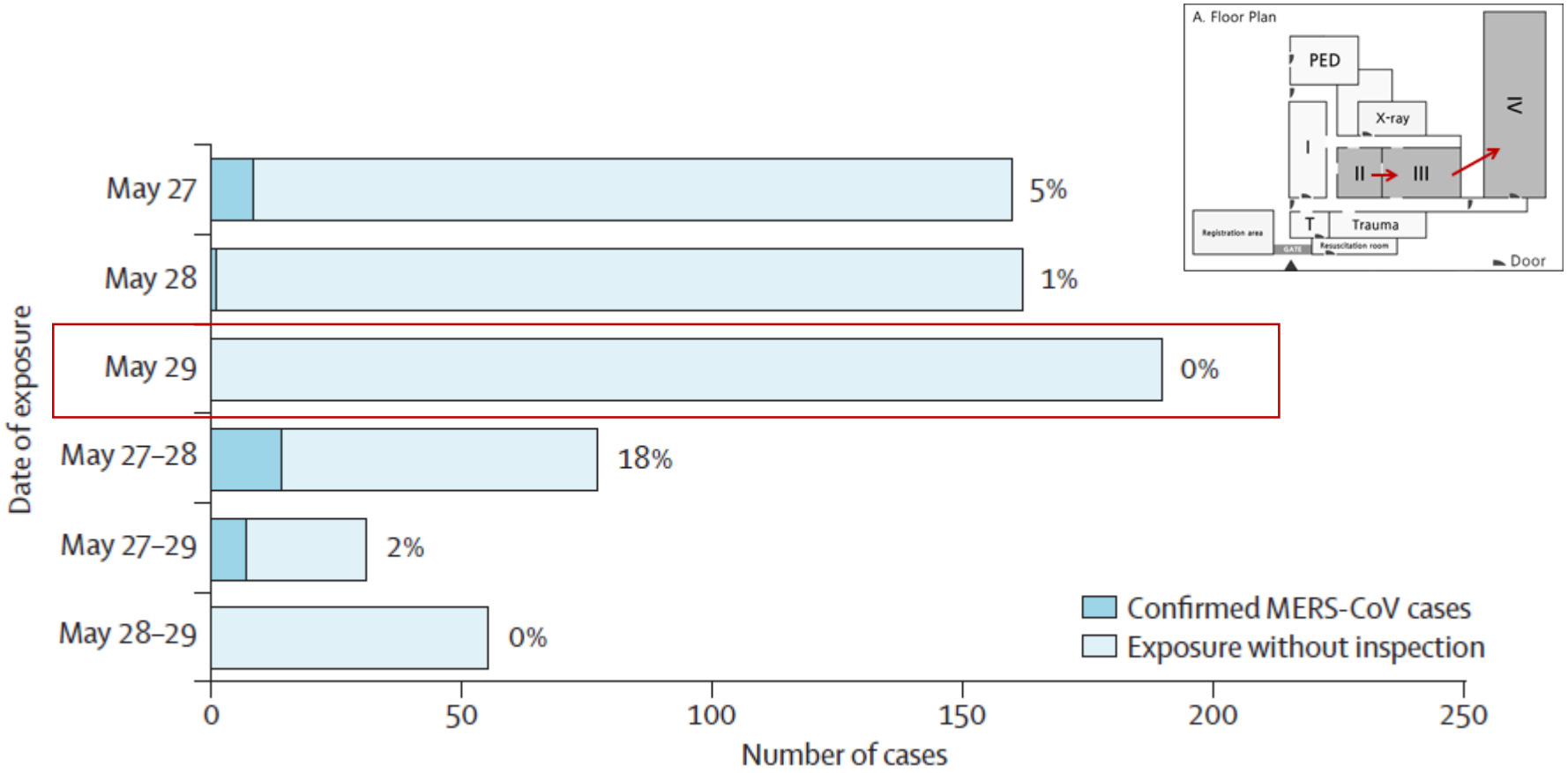


Median exposure time for patients in group A to Patient 14

- Zone II: 3.0 hrs (range 0.5-10.3, IQR 1.9–4.5)
- Zone III: 13.9 hrs (range 0.6–18.9, IQR 6.3–18.4)
- Zone IV: 17.4 hrs (range 0.2–23.2, IQR 9.2–21.4)

Cho SY, Kang JM et al., Lancet. 2016;388:994-1001

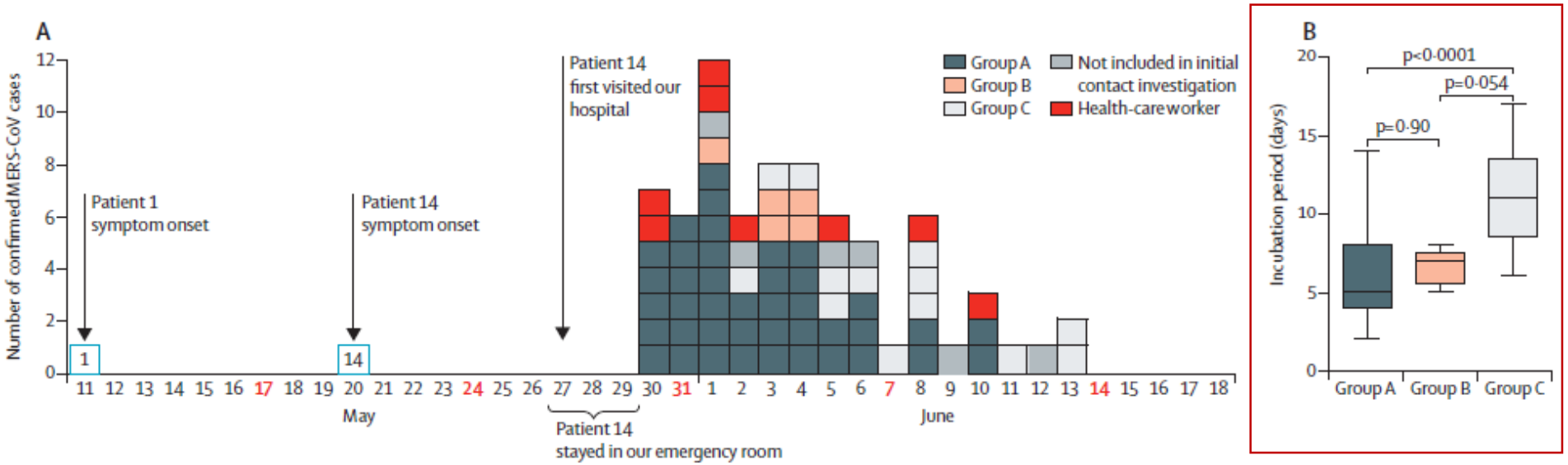
No confirmed cases among those exposed to only potentially contaminated environment



Cho SY, Kang JM et al., Lancet. 2016;388:994-1001

Epidemiologic curve: Close contacts had shorter incubation periods. 病毒量?

Median incubation period : 7 days
(range 2–17, IQR 5–10)



Incubation period can be longer than 14 days.

Cho SY, Kang JM et al., Lancet. 2016;388:994-1001

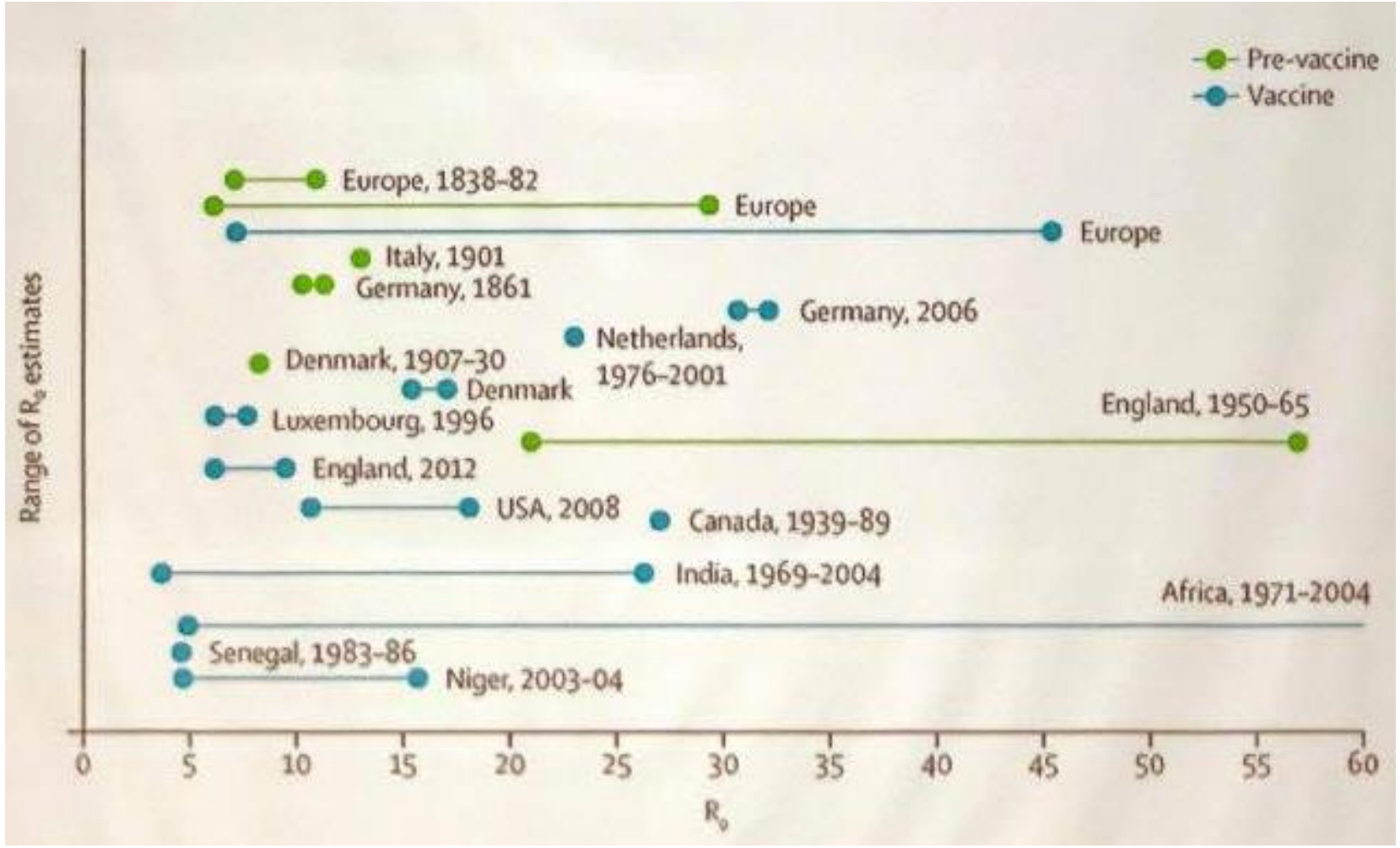
Basic Reproduction Number: R_0

- R_o is affected by 3 parameters
  - Transmission probability per contact
  - Duration of infectiousness
  - Number of contacts per unit time (contact rate)
- Contact rate is dependent on human social behavior, population density, organization, and seasonality
  - Community vs hospital
  - Kingdom Saudi Arabia vs Korea

R_o is not a biological constant of a pathogen

(Complexity of the basic reproduction number. EID 2019 Jan)

Many R_0s for Measles
What is Our Current R_0?



Lancet ID. R0 of Measles: a systematic review. July 27. 2017
https://doi.org/10.1016/s1473-3099(17)30307-9

New R_0 for MERS-CoV from Korean outbreak

Author	R_0
Hsieh YH	7.0 and 19.3.
Chang HJ	8.0977
Zhang XS., et al.	2.5 (95% CI, [1.7, 3.1]) 7.2 (95% CI, [5.3, 9.4])
Xia ZQ., et al.	4.422
Choi S., et al.	The first outbreak cluster in a hospital in Pyeongtaek: 4.04 Samsung Medical Center: 5.0

Peer J. 2015 Dec 17;3:e1505. doi: 10.7717/peerj.1505.
Influenza Other Respir Viruses. 2017 Sep;11(5):434-444.
J Hosp Infect. 2018 Jun;99(2):162-168.
Biomed Eng Online. 2017 Jun 13;16(1):79.
PLoS One. 2015 Dec 21;10(12):e0144778.

MERS again in Korea in 2018 , three years since 2015

World Health Organization | Western Pacific

Health topics | Our work | News | Emergencies

Home / Outbreaks and emergencies / MERS in the Republic of Korea

This time, there was no outbreak.

MERS in the Republic of Korea

Credit: Korea Centers for Disease Control and Prevention

On 8 September 2018, the Republic of Korea reported its first imported case of Middle East Respiratory Syndrome (MERS) since an outbreak in 2015. The case was a 61-year-old Korean man who had returned to the Republic of Korea on 7 September following a business trip to Kuwait.

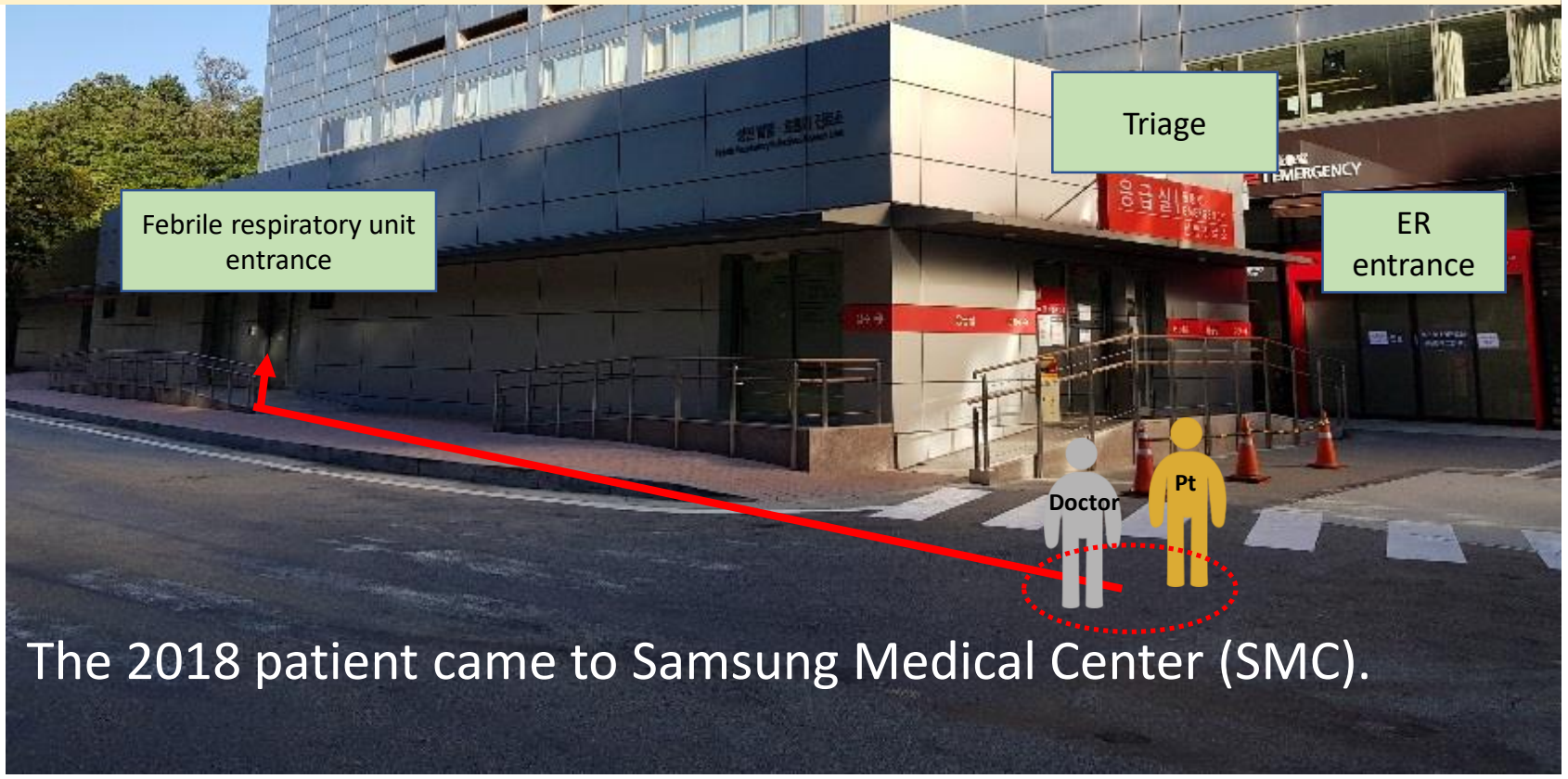
When the patient reported his symptoms and travel history to a doctor upon arriving home, MERS was immediately suspected. Measures were put in place before the patient arrived at the hospital to minimize contact with others. The Government immediately notified the World Health Organization (WHO), which supported the country to conduct investigations and share information internationally. The national public health emergency operations centre kicked into action to coordinate the response.

As a result, further spread of the disease within the Republic of Korea was prevented.

What was different?
2015 vs. 2018

Why was it different?
2015 vs. 2018

- **At SMC on September 7-8**
  - 19:15 Arrived at ER directly from the airport
  - 19:17 Placed in febrile respiratory isolation unit
  - 20:00 Chest x-ray in the unit
  - 21:05 Center for Infection Prevention and Control of SMC
  - 21:08 KCDC Call Center (telephone number 1339)
  - 21:34 Official report to KCDC with additional information
  - 00:01 Referred to nationally designated isolation unit
  - At around 1 am, the first test was positive and at 4 pm, the second test was confirmed positive. Only 4 HCWs were exposed with low risk.



The 2018 patient came to Samsung Medical Center (SMC).

Action after the exposure by the ministry of health and Korea CDC in 2018

- 21 individuals who had close contact with the patient:
  - family members, individuals who were seated near the patient during travel, flight attendants, close contacts while in Seoul and four health care workers
  - In quarantine at home
- 435 individuals, including the passengers on the flight, were passive surveillance.

http://www.who.int/csr/don/12-september-2018-mers-republic-of-korea/en/

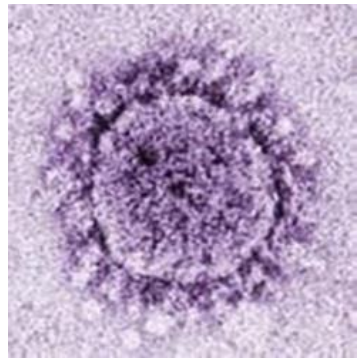
Hardware renovation: ER

New Triage

Every patient is screened for fever & respiratory symptoms before entering ER.

冠狀病毒（ Coronaviruses）

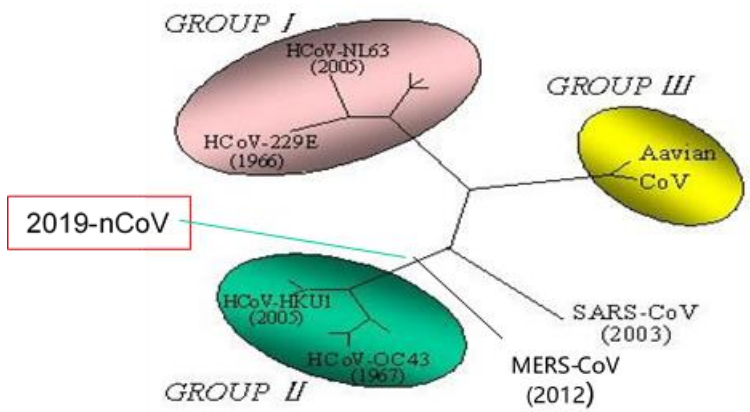
- 單股正鏈RNA病毒，巢病毒目（*Nidovirales*）冠狀病毒科（*Coronaviridae*）正冠狀病毒亞科（*Orthocoronavirinae*）。
- 分為α、β、γ和δ四個屬。
- 可以感染許多動物物種
  - 蝙蝠、狗、豬、老鼠、鳥、牛、鯨、馬、山羊、猴子等。
  - 人。
- 對熱敏感，56℃ 30 分鐘、乙醚、75%乙醇、含氯消毒劑、過氧乙酸和氯仿等脂溶劑均可有效滅活病毒。



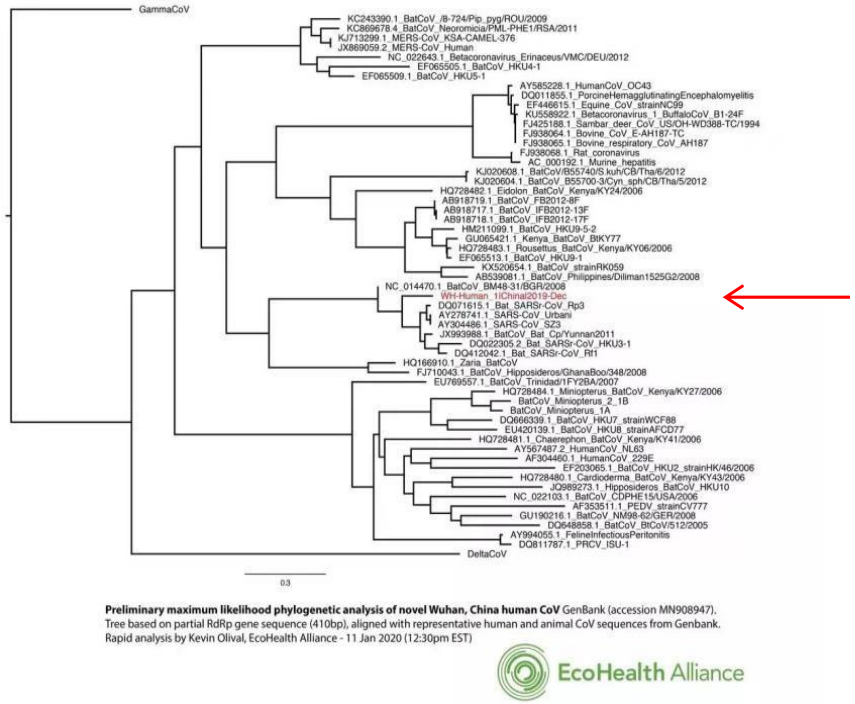
已知感染人的冠狀病毒有6種

- α屬：**229E、NL63**
- β屬：**OC43、HKU1、**

  MERSr-CoV、SARSr-C

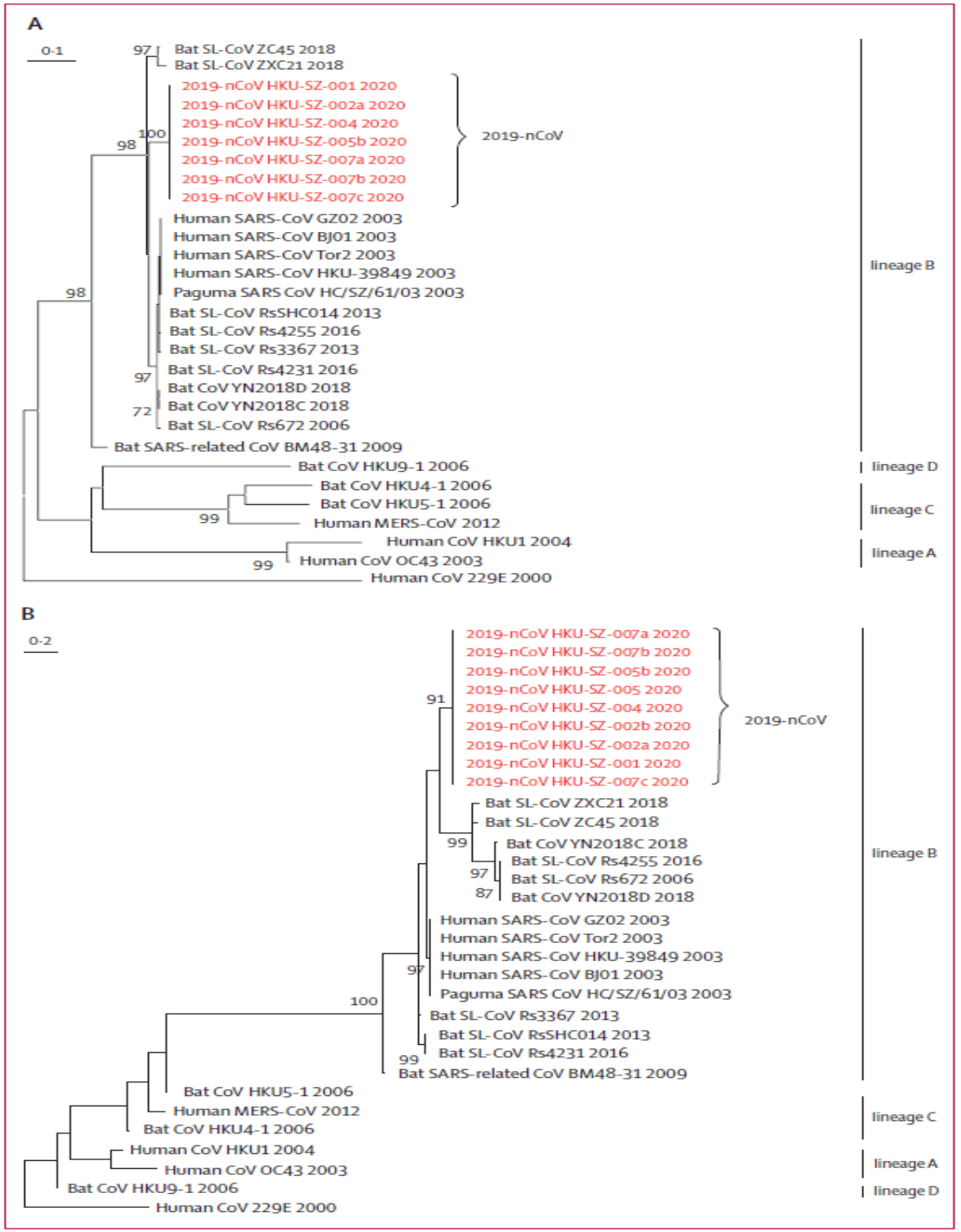


- **HKU1、 SARS-CoV 、MERS-CoV :可引起肺炎**
- **此次造成outbreak為一種新型冠狀病毒(β屬）（WHO命名為2019-nCoV）**



RdRp

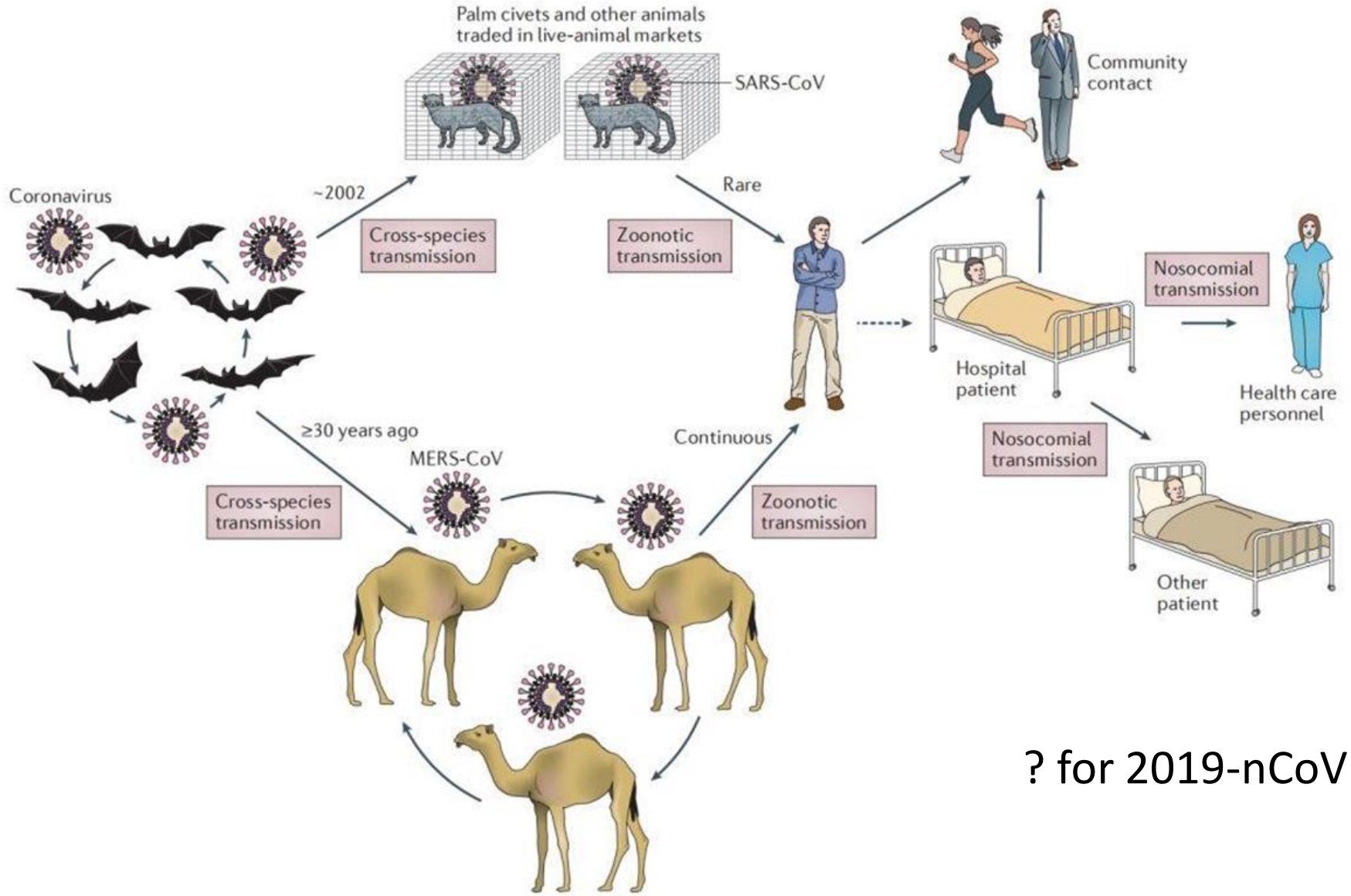
S glycoprotein



與SARS-CoV基因序列相似度較近但也只有80%，距離相當還遠 (人與猩猩相似度達98%)

Lancet Jan. 24, 2020

SARS和MERS的起源與傳播示意圖



? for 2019-nCoV

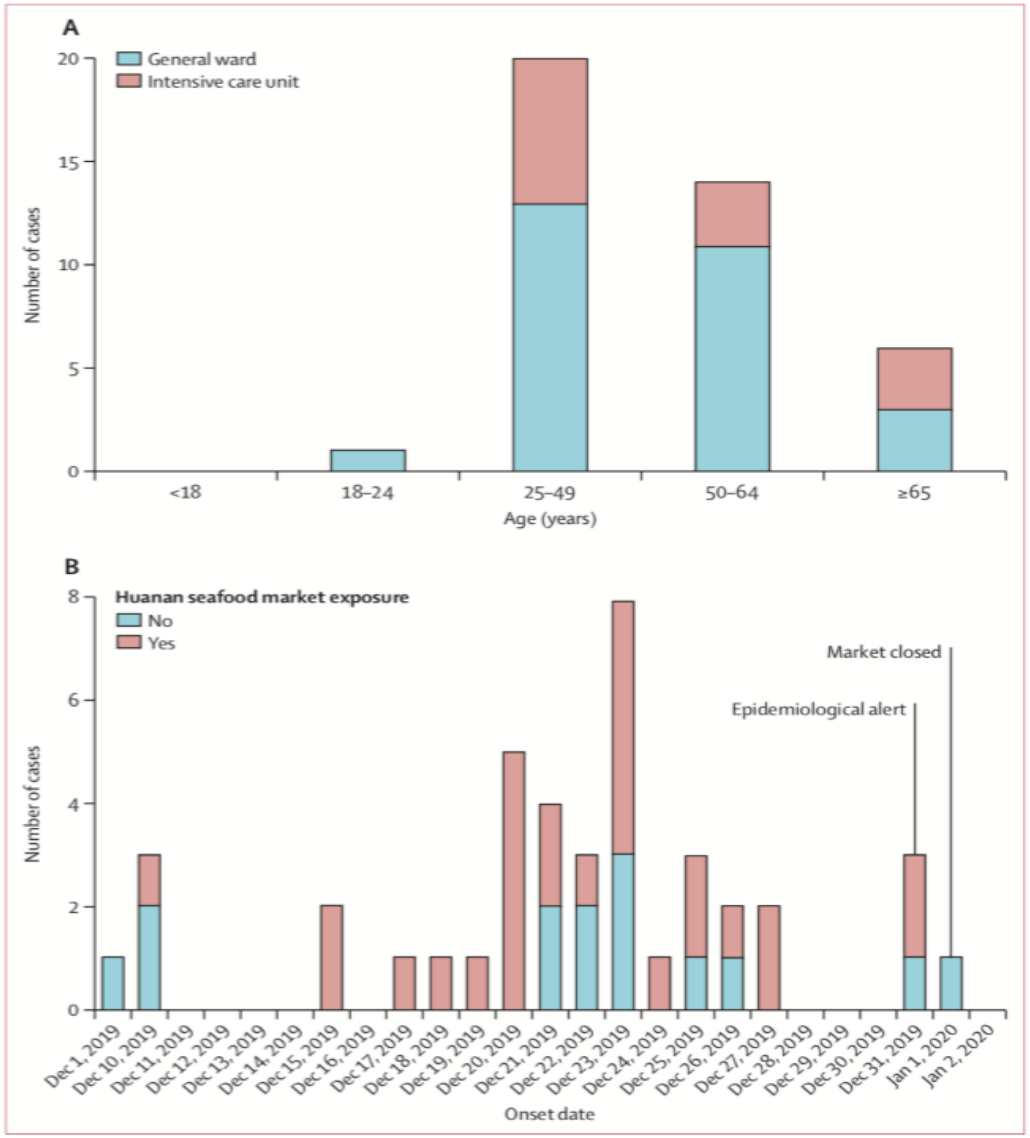


Figure 1: Date of illness onset and age distribution of patients with laboratory-confirmed 2019-nCoV infection

(A) Number of hospital admission by age group. (B) Distribution of symptom onset date for laboratory-confirmed cases. The Wuhan local health authority issued an epidemiological alert on Dec 30, 2019, and dosed the Huanan seafood market 2 days later.

1. 第一個個案沒有family cluster
   跟後來來的case也沒有流病學上相關
   海鮮市場的環境可能是來來源之一
   (病毒可在環境表面存活多久未知)

2. 這個流病圖是最初始、
   肺炎有嚴重到來來住院的41個病人。
   當時被診斷出的病人數還很少，
   其中應該有輕症沒被列入(診斷)進去的。
   也可能中間人傳人，只是尚未找出連結

Lancet Jan. 24 2020

	All patients (n=41)	ICU care (n=13)	No ICU care (n=28)	p value
Characteristics				
Age, years	49·0 (41·0–58·0)	49·0 (41·0–61·0)	49·0 (41·0–57·5)	0·60
Sex	..	..	..	0·24
Men	30 (73%)	11 (85%)	19 (68%)	..
Women	11 (27%)	2 (15%)	9 (32%)	..
Huanan seafood market exposure	27 (66%)	9 (69%)	18 (64%)	0·75
Current smoking	3 (7%)	0	3 (11%)	0·31
Any comorbidity	13 (32%)	5 (38%)	8 (29%)	0·53
Diabetes	8 (20%)	1 (8%)	7 (25%)	0·16
Hypertension	6 (15%)	2 (15%)	4 (14%)	0·93
Cardiovascular disease	6 (15%)	3 (23%)	3 (11%)	0·32
Chronic obstructive pulmonary disease	1 (2%)	1 (8%)	0	0·14
Malignancy	1 (2%)	0	1 (4%)	0·49
Chronic liver disease	1 (2%)	0	1 (4%)	0·68
Signs and symptoms				
Fever	40 (98%)	13 (100%)	27 (96%)	0·68
Highest temperature, °C	..	..	..	0·037
<37·3	1 (2%)	0	1 (4%)	..
37·3–38·0	8 (20%)	3 (23%)	5 (18%)	..
38·1–39·0	18 (44%)	7 (54%)	11 (39%)	..
>39·0	14 (34%)	3 (23%)	11 (39%)	..
Cough	31 (76%)	11 (85%)	20 (71%)	0·35
Myalgia or fatigue	18 (44%)	7 (54%)	11 (39%)	0·38
Sputum production	11/39 (28%)	5 (38%)	6/26 (23%)	0·32
Headache	3/38 (8%)	0	3/25 (12%)	0·10
Haemoptysis	2/39 (5%)	1 (8%)	1/26 (4%)	0·46
Diarrhoea	1/38 (3%)	0	1/25 (4%)	0·66
Dyspnoea	22/40 (55%)	12 (92%)	10/27 (37%)	0·0010
Days from illness onset to dyspnoea	8·0 (5·0–13·0)	8·0 (6·0–17·0)	6·5 (2·0–10·0)	0·22
Days from first admission to transfer	5·0 (1·0–8·0)	8·0 (5·0–14·0)	1·0 (1·0–6·5)	0·002
Systolic pressure, mm Hg	125·0 (119·0–135·0)	145·0 (123·0–167·0)	122·0 (118·5–129·5)	0·018
Respiratory rate >24 breaths per min	12 (29%)	8 (62%)	4 (14%)	0·0023

Data are median (IQR), n (%), or n/N (%), where N is the total number of patients with available data. p values comparing ICU care and no ICU care are from χ^2 test, Fisher's exact test, or Mann-Whitney U test. 2019-nCoV=2019 novel coronavirus. ICU=intensive care unit.

1. 此篇只有41位病人，且是較嚴重須住院的病人:
comorbidity (32%), symptoms/signs的分析, 以及mortality (15%) 的數字目前參考，尚無法定論。
隨著案例快速增加，都還在持續變動。

2. 有提到其他上呼吸道表現不很嚴重
腸胃道症狀也不明顯（但是GI症狀有後續研究報告）。

3. 看起來下呼吸道症狀
(dyspnea, chest pain)：
平均約在一週出現 (8 days, range 5-13 days)

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開始有dyspnea症狀後
重症者約1天快速進展至ARDS

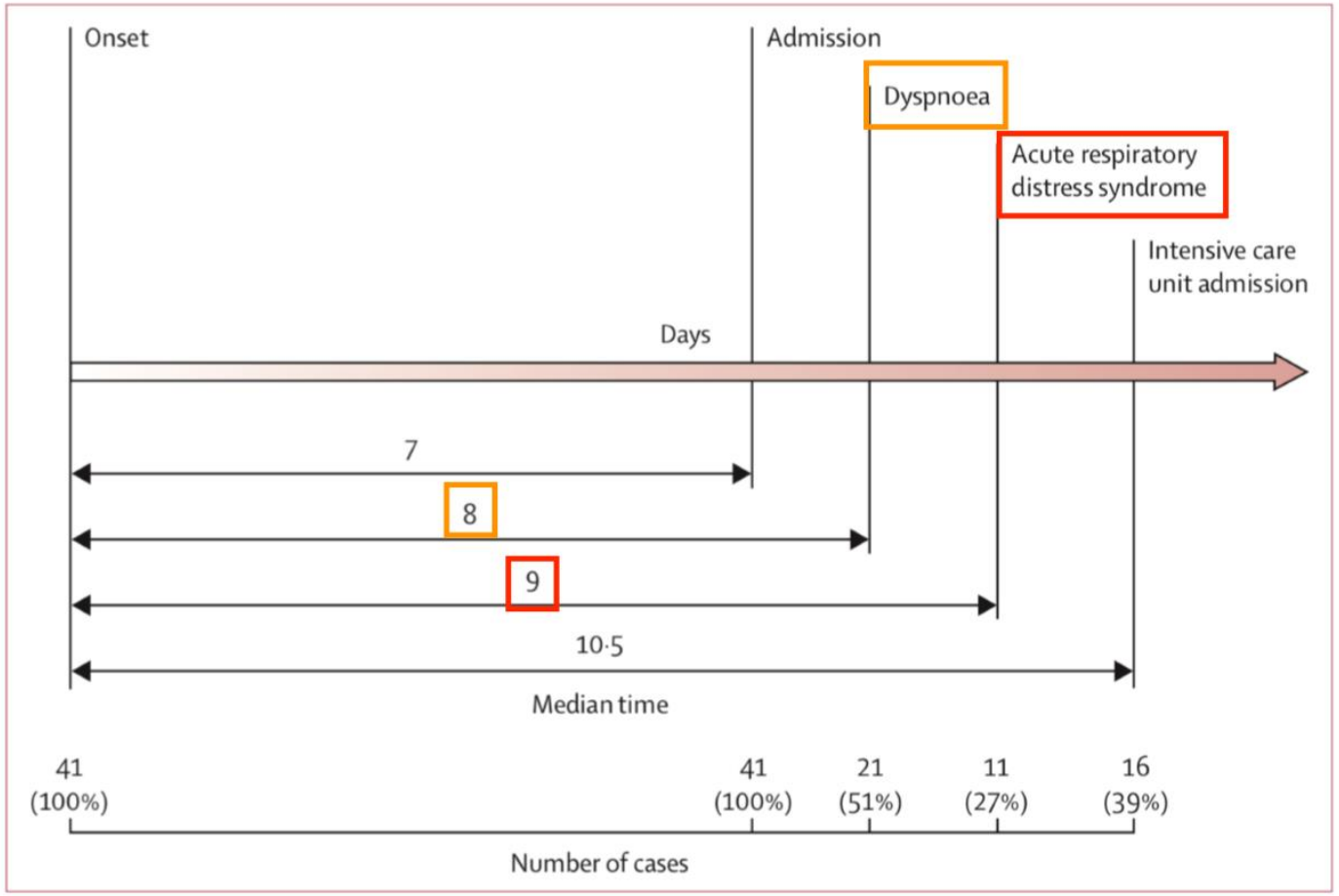

Figure 2: Timeline of 2019 –nCoV cases after onset of illness

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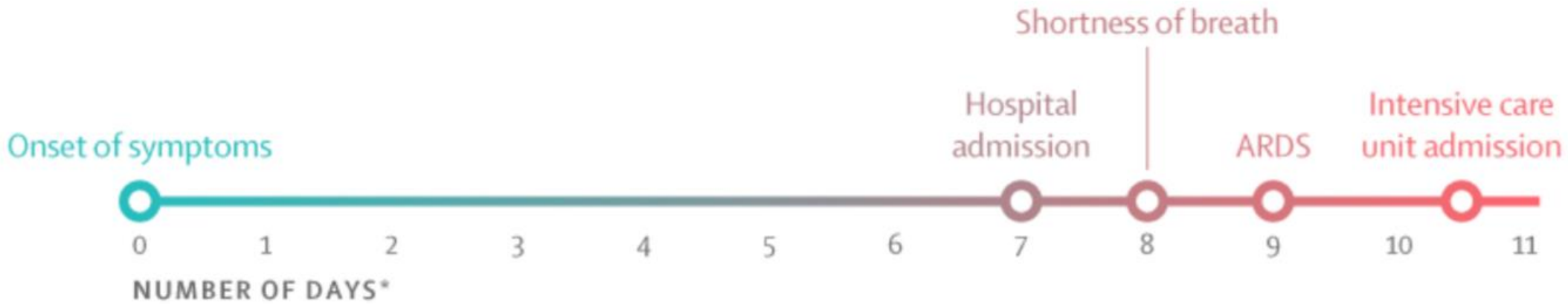
Timeline of coronavirus onset



ARDS=Acute respiratory disease syndrome

*Median time from onset of symptoms, including fever (in 98% of patients), cough (75%), myalgia or fatigue (44%), and others.

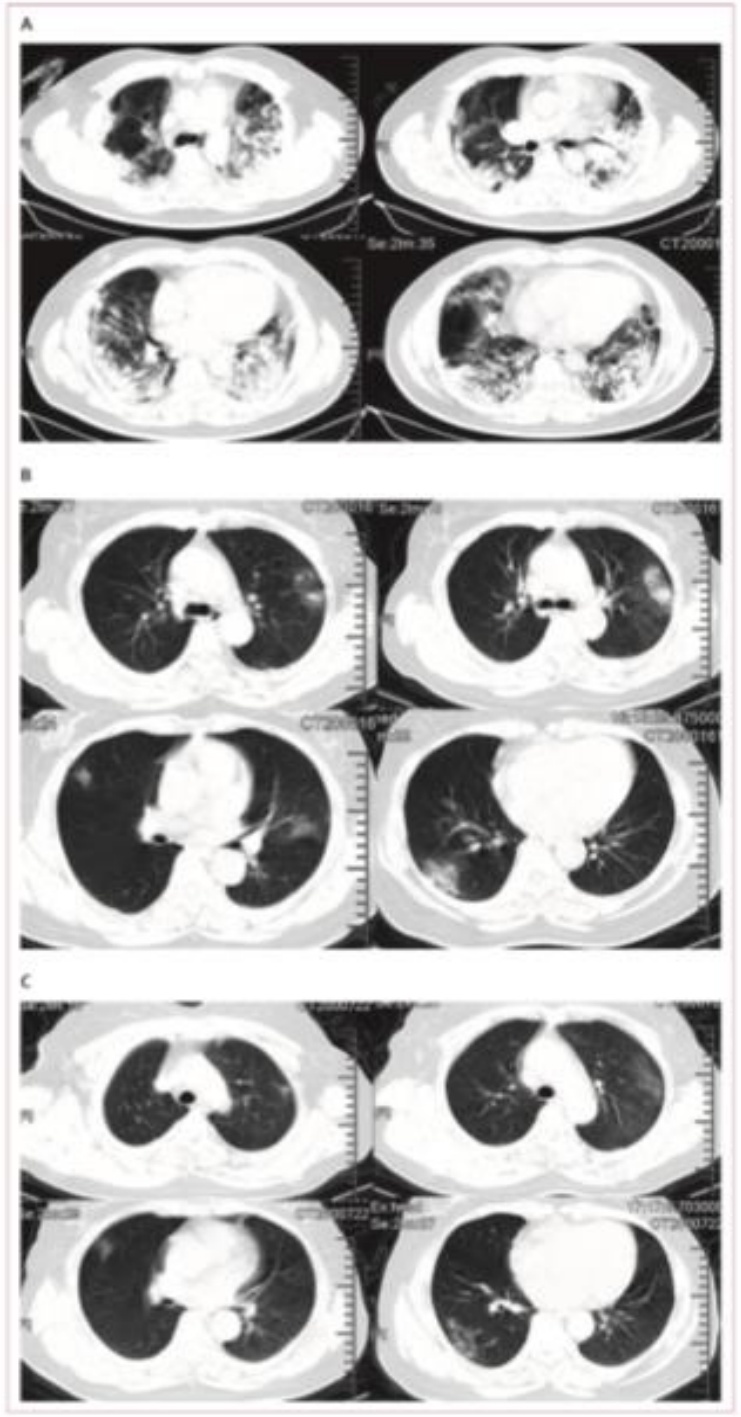
THE LANCET

Jan. 24 2020

Laboratory data 上：比較specific的可能是 lymphopenia，與重症有相關

（和大部分病毒感染同，初期主要以leukopenia表現）

	All patients (n=41)	ICU care (n=13)	No ICU care (n=28)	p value
White blood cell count, ×10⁹/L	6·2 (4·1–10·5)	11·3 (5·8–12·1)	5·7 (3·1–7·6)	0·011
<4	10/40 (25%)	1/13 (8%)	9/27 (33%)	0·041
4–10	18/40 (45%)	5/13 (38%)	13/27 (48%)	..
>10	12/40 (30%)	7/13 (54%)	5/27 (19%)	..
Neutrophil count, ×10⁹/L	5·0 (3·3–8·9)	10·6 (5·0–11·8)	4·4 (2·0–6·1)	0·00069
Lymphocyte count, ×10⁹/L	0·8 (0·6–1·1)	0·4 (0·2–0·8)	1·0 (0·7–1·1)	0·0041
<1·0	26/41 (63%)	11/13 (85%)	15/28 (54%)	0·045
≥1·0	15/41 (37%)	2/13 (15%)	13/28 (46%)	..
Haemoglobin, g/L	126·0 (118·0–140·0)	122·0 (111·0–128·0)	130·5 (120·0–140·0)	0·20
Platelet count, ×10⁹/L	164·5 (131·5–263·0)	196·0 (165·0–263·0)	149·0 (131·0–263·0)	0·45
<100	2/40 (5%)	1/13 (8%)	1/27 (4%)	0·45
≥100	38/40 (95%)	12/13 (92%)	26/27 (96%)	..



影像部分

1. **98%有雙側肺炎**
   一般肺炎，雙側involvement並不常見，是很重要的表現
   (常見的bilateral pneumonia: virus, PJP, *Legionella*)

2. 輕症住院病人(non-ICU)：
   以GGO和segmental consolidation為主
   一開始的CXR會容易被遺漏掉

3. 但此時病人若有**下呼吸道症狀(pleuritic pain, SOB)**，
   會是很重要的hints，或許可在有明確旅遊史(湖北)
   及有呼吸道症狀狀的病人，在CXR無明顯浸潤的狀況下
   ，考慮提早做CT

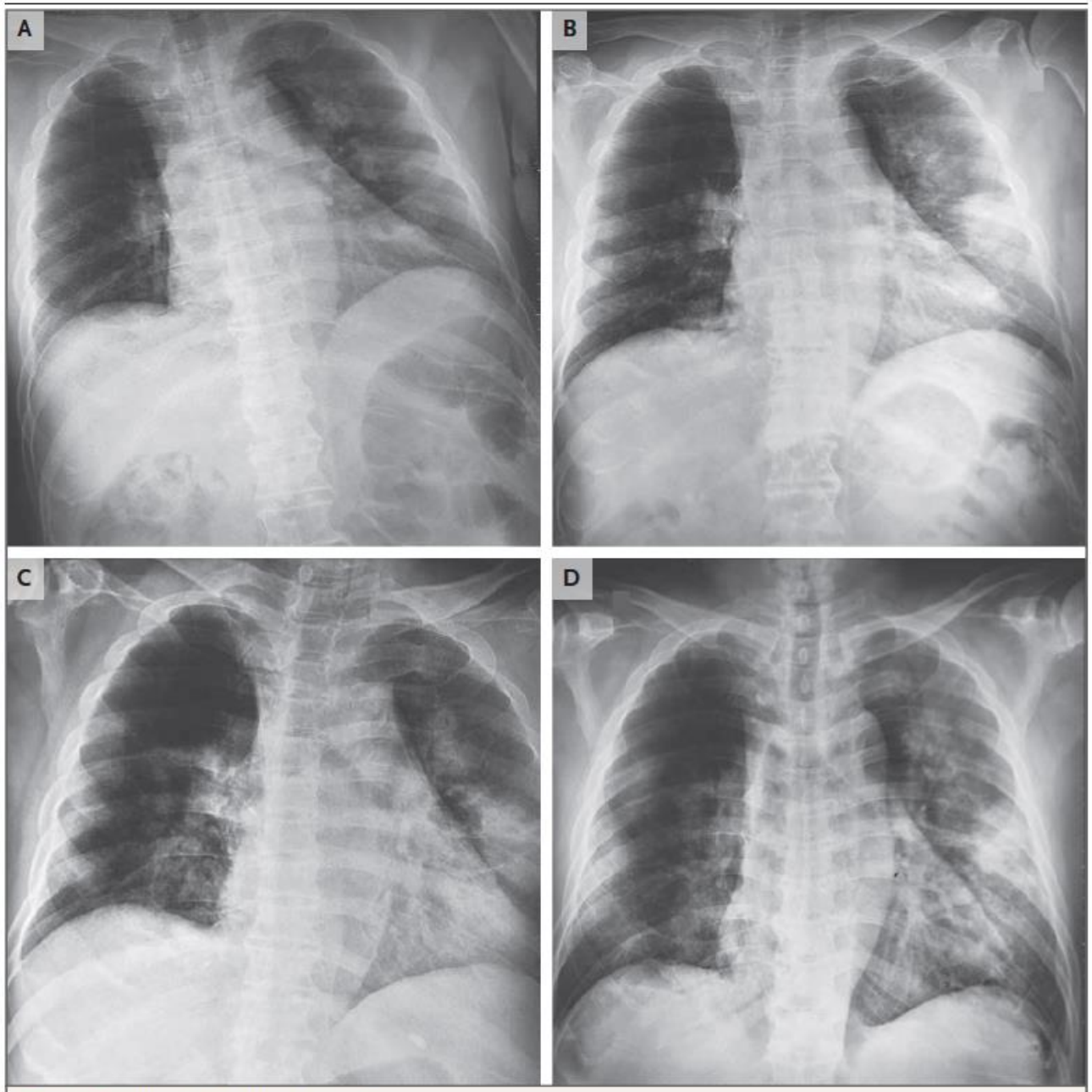
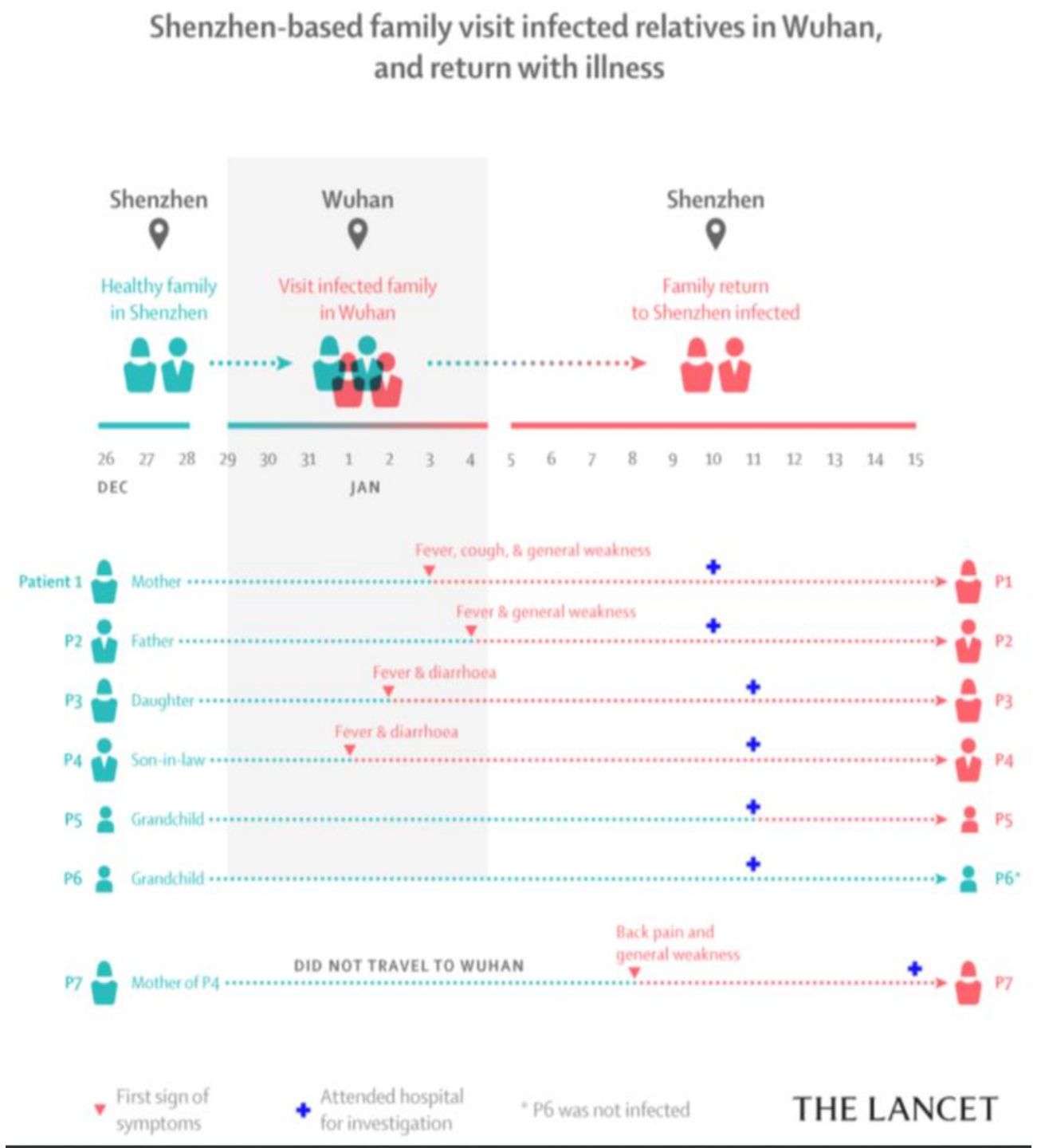


Figure 1. Radiographs of the Father's Chest.
Shown are chest radiographs obtained at admission (Panel A) and on day 3 (Panel B), day 5 (Panel C), and day 6 (Panel D) after admission.

Progression of CXR in a patient with 2019-nCoV infection

Jan. 28, 2020 NEJM



1. 從接觸到症狀出現
   約為3-7天
   (incubation time)

2. 一開始URI症狀可能不明顯：
   fever, weakness, diarrhea

3. 尤其是diarrhea。 在前一篇
   中的比例很低，作者還特別
   提出是跟MERS & SARS
   不同處，但是後續看來也許不一定

4. 下呼吸道症狀變明顯
   大約在5-10天

A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster

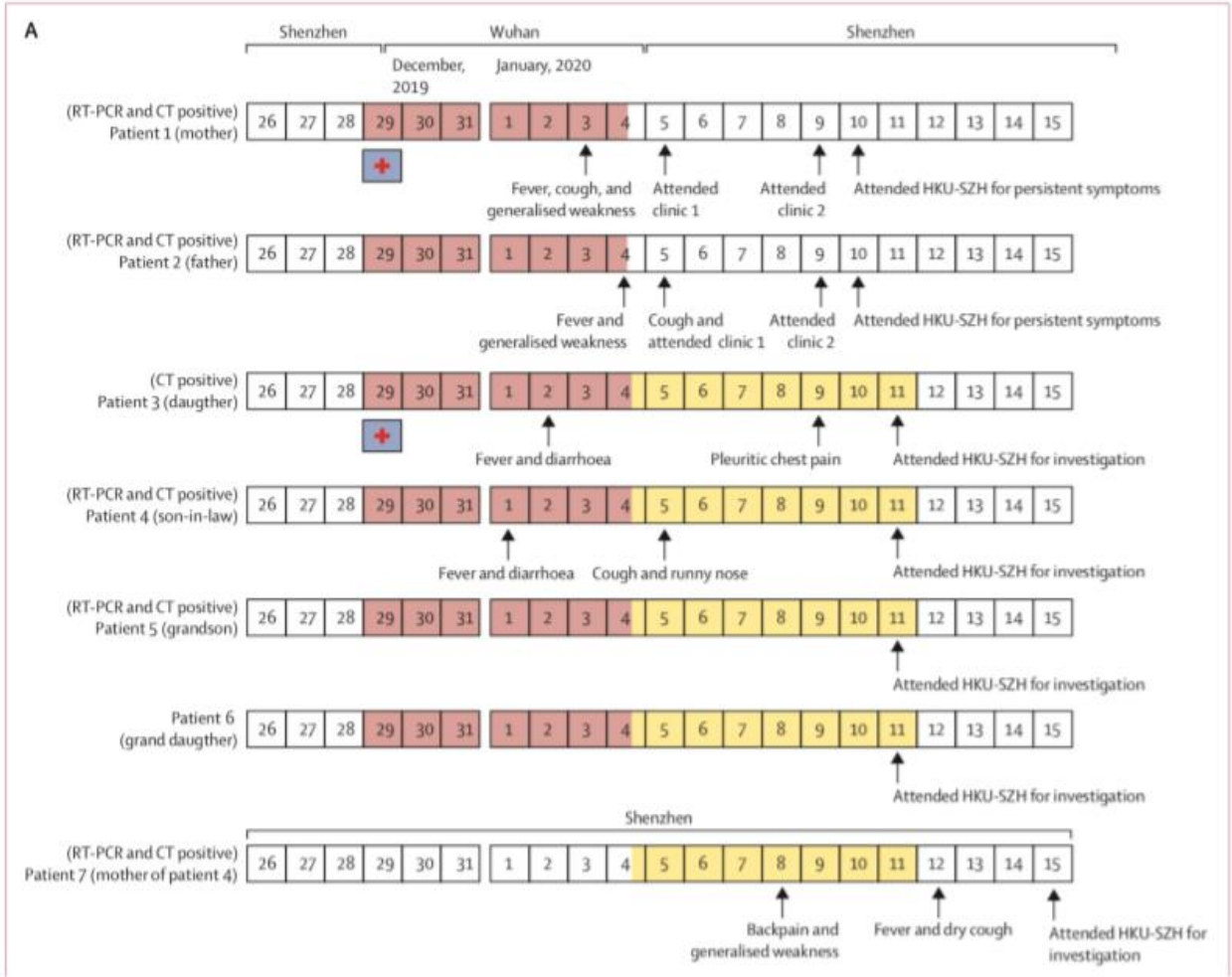
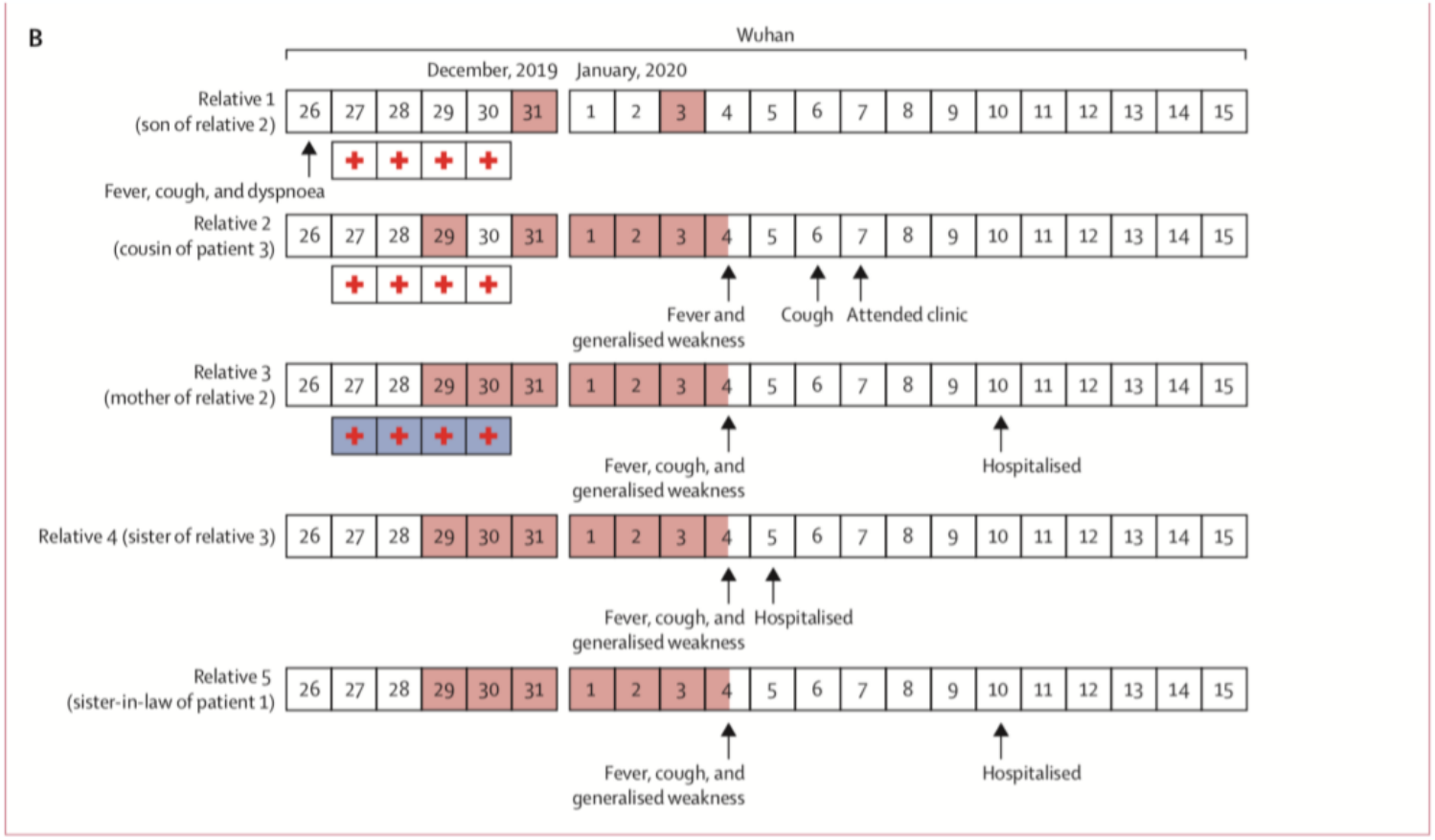


Figure 1: **Chronology of symptom onset of the Shenzhen family cluster and their contacts in Wuhan**
Dates filled in red are the dates on which patients 1–6 had close contacts with their relatives (relatives 1–5). Dates filled in yellow are the dates on which patients 3–6 stayed with patient 7. The boxes with an internal red cross are the dates on which patients 1 and 3 or relatives 1, 2, and 3 had stayed overnight (white boxes) at or had visited (blue boxes) the hospital in which relative 1 was admitted for febrile pneumonia. The information of relatives 1–5 was provided by patient 3. No virological data were available.

1. Incubation約3-7 days
2. 一開始的症狀多為weakness and diarrhea
3. 呼吸道症狀也有可能會接下來的1-4天後才出現
4. 下呼吸道症狀(chest pain, dyspnea)約9天出現（和上一篇的觀察類似）



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這是另外來探訪的親戚 ，Publish時**尚無確診**

有來過夜住宿的 

也有去醫院探訪的 

約在7天內陸續出現症狀

飛沫及環境的接觸應該還是主要的傳染來源

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 7
Interval between sample collection and symptom onset (days)	7	6	9	10	NA	7
Real-time RT-PCR (spike gene)	..	..	..	..	..	..
Nasopharyngeal swab	+(Ct 31)	+(Ct 27)	ND	+(Ct 31)	ND	+(Ct 27)
Throat swab	NA	NA	ND	ND	+(Ct 40)	+(Ct 33)
Sputum	NA	NA	NA	NA	+(Ct 27)	+(Ct 25)
Serum	ND	+(Ct 40)	NA	NA	ND	NA
Plasma	NA	NA	ND	ND	ND	ND
Urine	ND	ND	ND	ND	ND	NA
Stool	NA	NA	ND	ND	ND	ND

1. Throat swab檢出率沒有nasopharyngeal swab好 ？（有待商榷）
2. Patient 3: 皆無檢出，是用CT診斷
3. 在有限個案中，目前在stool、urine未檢出病毒

CT: Focal or multifocal ground glass opacities

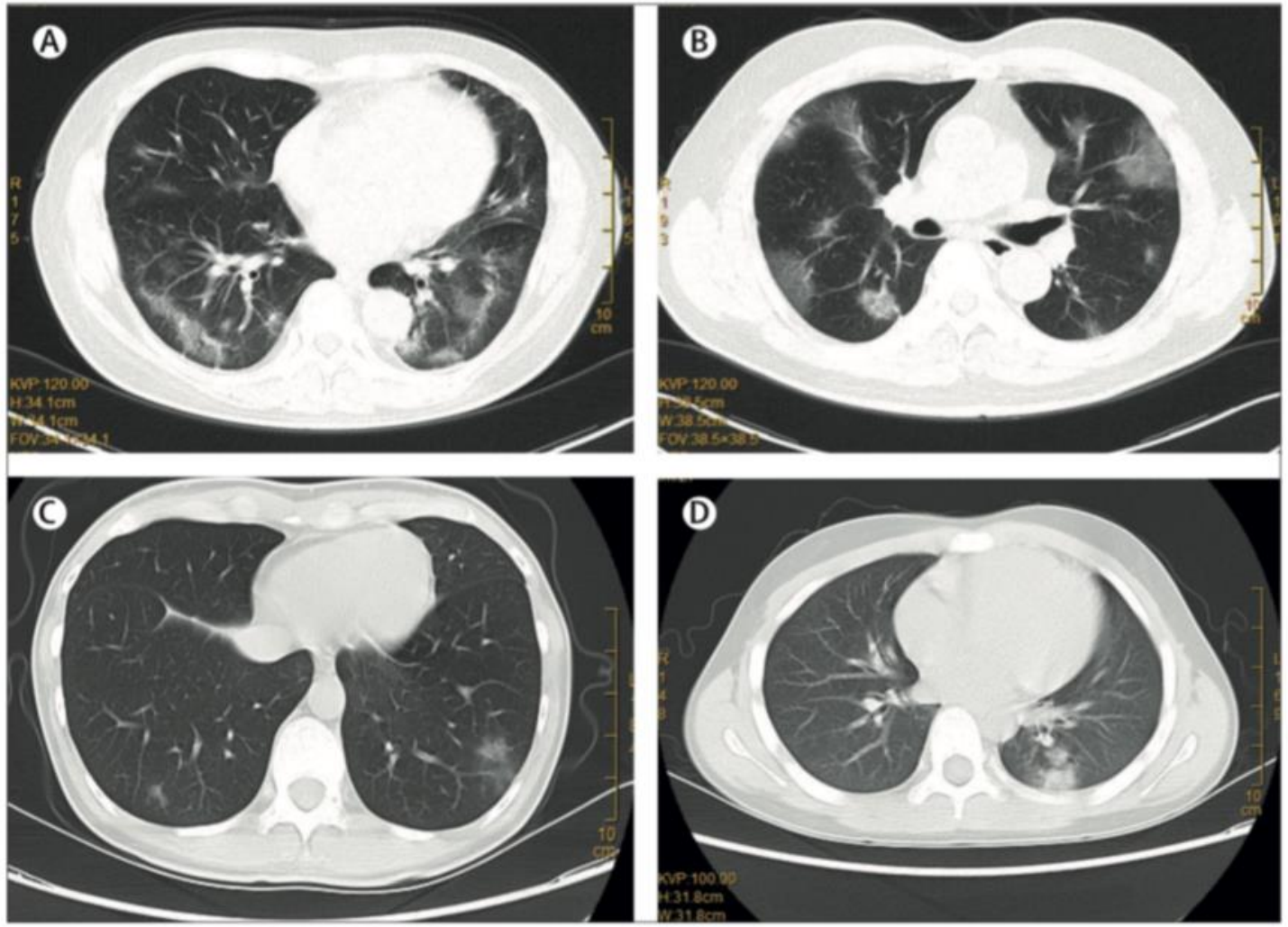


Figure 2: Representative images of the thoracic CT scans showing multifocal ground-glass changes in the lungs of patient 1 (A), patient 2 (B), patient 3 (C), and patient 5 (D)

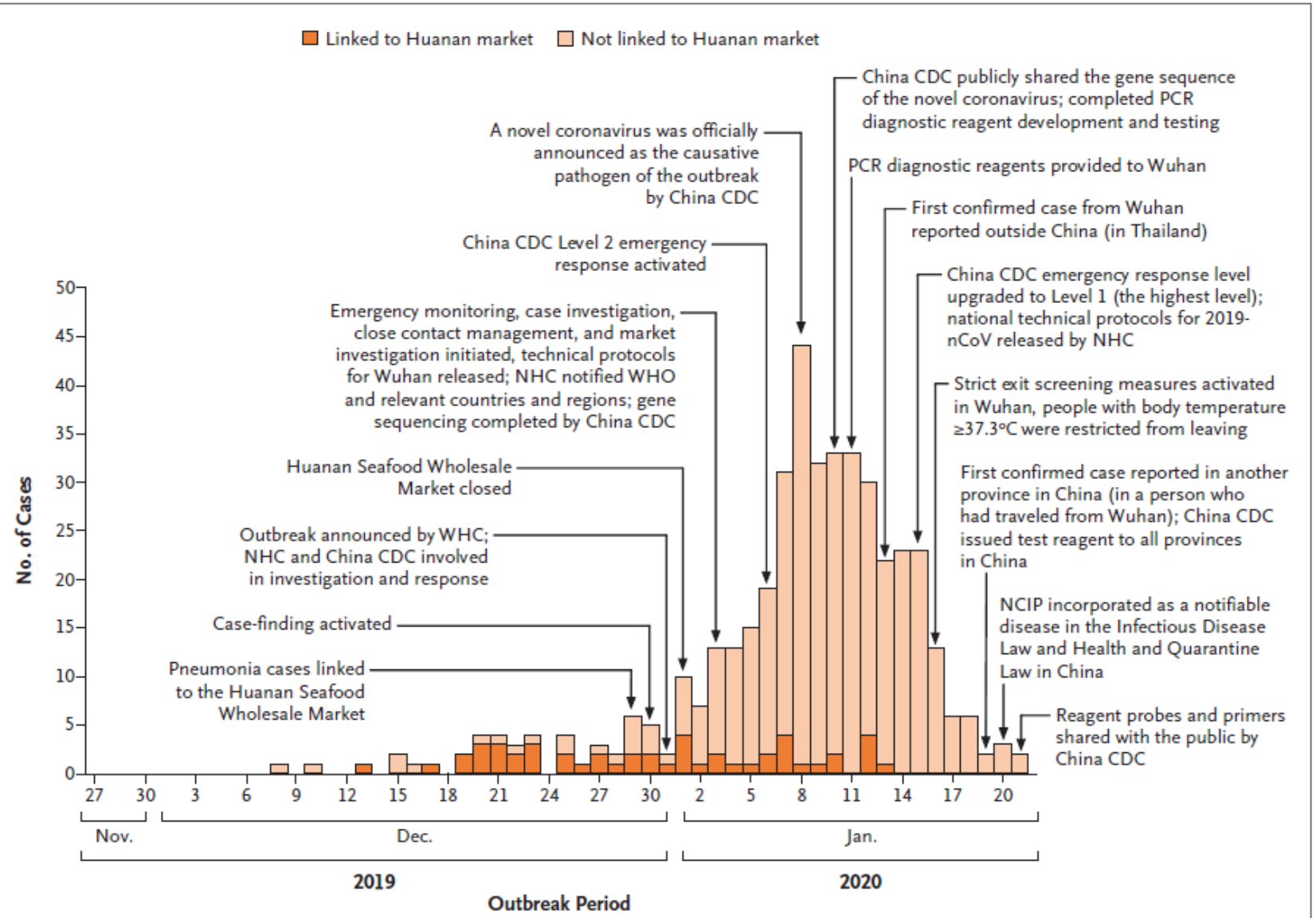


Figure 1. Onset of Illness among the First 425 Confirmed Cases of Novel Coronavirus (2019-nCoV)–Infected Pneumonia (NCIP) in Wuhan, China.

The decline in incidence after January 8 is likely to be due to delays in diagnosis and laboratory confirmation. China CDC denotes Chinese Center for Disease Control and Prevention, NHC National Health Commission of the People's Republic of China, PCR polymerase chain reaction, WHC Wuhan Health Commission, and WHO World Health Organization.

Jan. 30, 2020

The NEW ENGLAND JOURNAL of MEDICINE

Table 1. Characteristics of Patients with Novel Coronavirus–Infected Pneumonia in Wuhan as of January 22, 2020.*

Characteristic	Before January 1 (N=47)	January 1 –January 11 (N=248)	January 12 –January 22 (N=130)
Median age (range) — yr	56 (26–82)	60 (21–89)	61 (15–89)
Age group — no./total no. (%)			
<15 yr	0/47	0/248	0/130
15–44 yr	12/47 (26)	39/248 (16)	33/130 (25)
45–64 yr	24/47 (51)	106/248 (43)	49/130 (38)
≥65 yr	11/47 (23)	103/248 (42)	48/130 (37)
Male sex — no./total no. (%)	31/47 (66)	147/248 (59)	62/130 (48)
Exposure history — no./total no. (%)			
Wet market exposure	30/47 (64)	32/196 (16)	5/81 (6)
Huanan Seafood Wholesale Market	26/47 (55)	19/196 (10)	5/81 (6)
Other wet market but not Huanan Seafood Wholesale Market	4/47 (9)	13/196 (7)	0/81
Contact with another person with respiratory symptoms	14/47 (30)	30/196 (15)	21/83 (25)
No exposure to either market or person with respiratory symptoms	12/27 (26)	141/196 (72)	59/81 (73)
Health care worker — no./total no. (%)	0/47	7/248 (3)	8/122 (7)

* Reduced denominators indicate missing data. Percentages may not total 100 because of rounding.

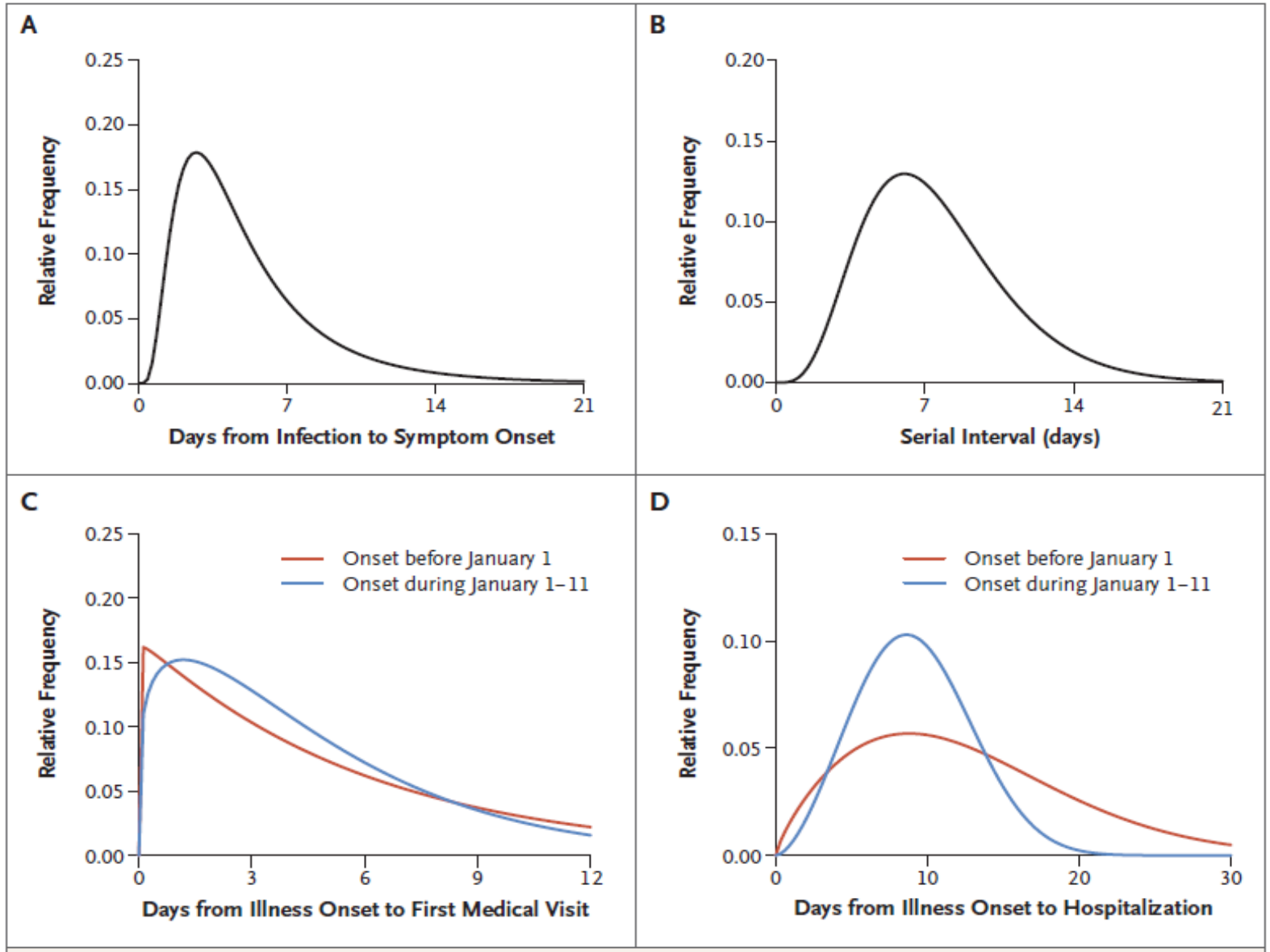
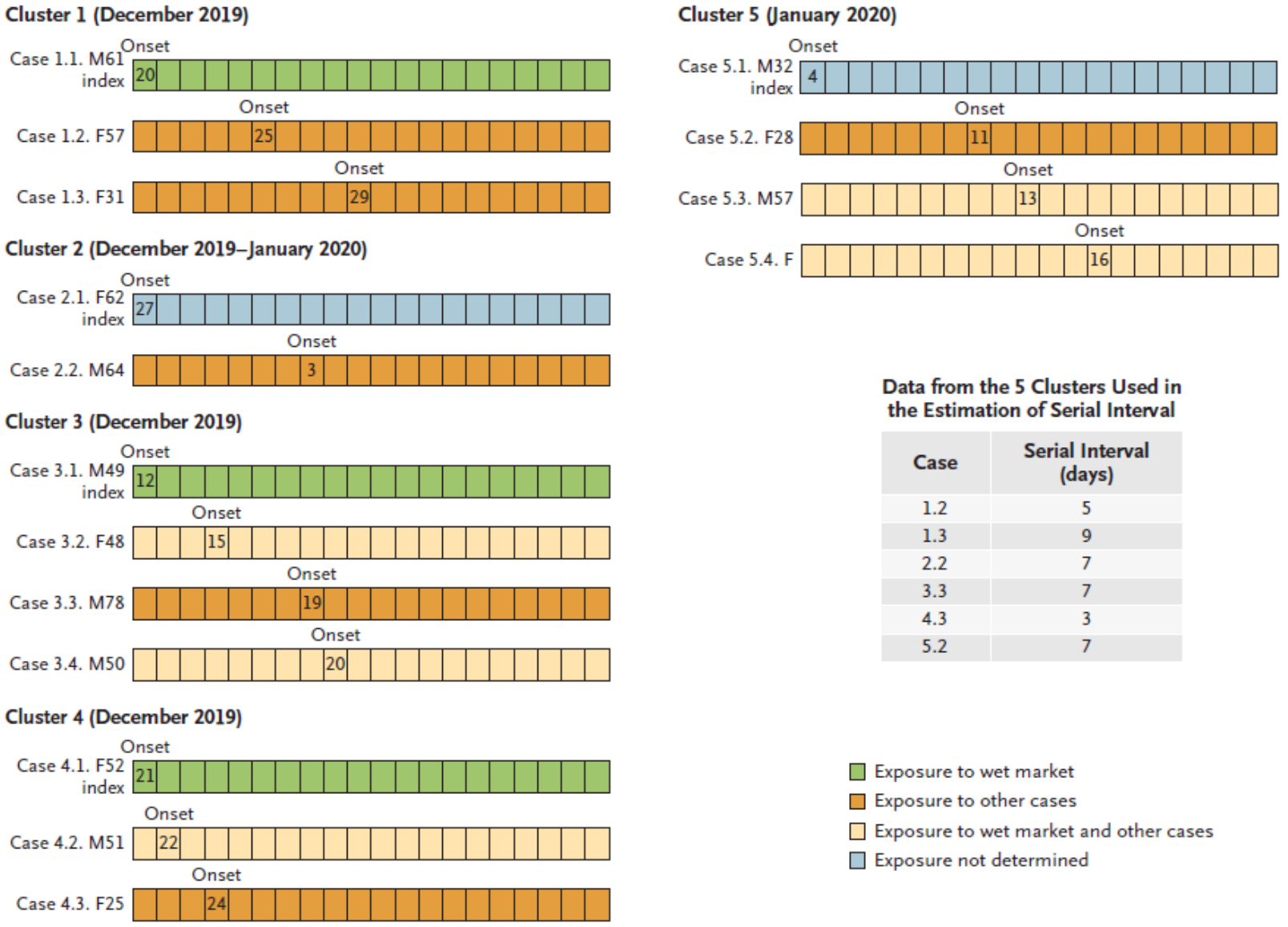


Figure 2. Key Time-to-Event Distributions.

The estimated incubation period distribution (i.e., the time from infection to illness onset) is shown in Panel A. The estimated serial interval distribution (i.e., the time from illness onset in successive cases in a transmission chain) is shown in Panel B. The estimated distributions of times from illness onset to first medical visit are shown in Panel C. The estimated distributions of times from illness onset to hospital admission are shown in Panel D.



Data from the 5 Clusters Used in the Estimation of Serial Interval

Case	Serial Interval (days)
1.2	5
1.3	9
2.2	7
3.3	7
4.3	3
5.2	7

Figure 3. Detailed Information on Exposures and Dates of Illness Onset in Five Clusters Including 16 Cases.

Numbers in boxes are calendar dates in December 2019 and January 2020. Data from the 5 secondary cases (patients who had clear exposure to only one index case and had no other potential source of infection) were used to estimate the serial interval distribution. The first four clusters were identified in Wuhan, and the fifth cluster was identified in Huanggang.

Key points:

•Main symptoms are fever, fatigue, and dry cough. Few patients have nasal congestion, runny nose, diarrhea and other symptoms. Severe cases develop dyspnea after one week, and severe cases progress rapidly to acute respiratory distress syndrome, septic shock, difficult-to-correct metabolic acidosis, and coagulopathy. It is worth noting that in the course of severe and critically ill patients, they can have only moderate to low fever, or even no fever.

•Some patients only show low fever, mild fatigue, etc., without pneumonia manifestations, mostly recovered after 1 week.

•Median age is 48 years, The age range is from 9 months to 96 years, and less than 0.6% of cases are under 15 years of age. Incubation period is 3 to 7 days, and the longest is no more than 14 days. Patients with underlying diseases and older age are more likely to develop severe illness and death.

•Current evidence suggests the main route of transmission of the virus is respiratory droplet and close contact transmission. The virus is highly contagious, with Interpersonal Communication Index (R0) between 2 and 3. There is no reliable evidence that the disease is contagious during the incubation period.

中国疾病预防控制中心
CHINESE CENTER FOR DISEASE CONTROL AND PREVENTION

Jan. 28, 2020

Comparison of clinical manifestations (SARS, MERS, 2019-nCoV)

	SARS-CoV 2002 (China)	MERS-CoV 2012 (Middle East)	MERS-CoV 2015 (Korea)	2019-nCoV (Wuhan, n=41)
Fever	99-100	98	81.7	98
Chills/rigors	15-73	87	NA	NA
Cough	62-100	83	56.9	76
Dry cough	29-75	56	NA	NA
Productive cough	4-29	44	39.8 (sputum)	28 (sputum production)
Hemoptysis	0-1	17	4.3	5
Headache	20-56	11	20.4	8
Myalgia	45-61	32	43	44 (myalgia or fatigue)
Malaise	31-45	38	NA	
Shortness of breath	40-42	72	41 (dyspnea)	55 (dyspnea)
Nausea	20-35	21	14	NA
Vomiting	20-35	21		
Diarrhea	20-25	26	19.4	3
Sore throat	13-25	14	9.1	NA
Rhinorrhea	2-24	6	1.6	NA
Decreased consciousness	NA	NA	5.4	NA

Hui D. et al., Curr Opin Pulm Med. 2014;20:233-241, Choi WS. et al., Infec Chemother. 2016;48:118-126; Huang C et al., Lancet 2020 Jan24

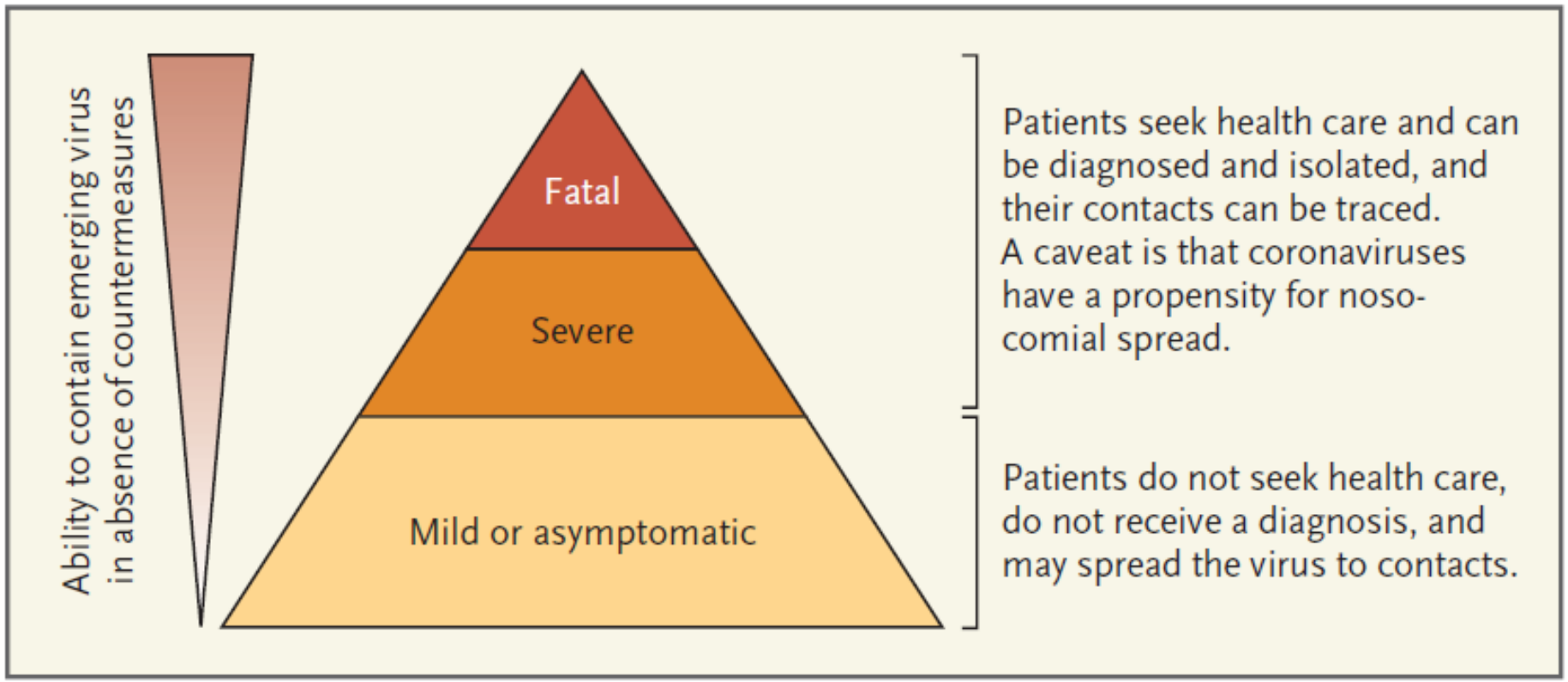


Figure 1. Surveillance Pyramid and Its Relation to Outbreak Containment.

The proportion of mild and asymptomatic cases versus severe and fatal cases is currently unknown for 2019-nCoV — a knowledge gap that hampers realistic assessment of the virus's epidemic potential and complicates the outbreak response.

Table 1. Pathogenicity and Transmissibility Characteristics of Recently Emerged Viruses in Relation to Outbreak Containment.

Virus	Case Fatality Rate (%)	Pandemic	Contained	Remarks
2019-nCoV	Unknown*	Unknown	No, efforts ongoing	
pH1N1	0.02–0.4	Yes	No, postpandemic circulation and establishment in human population	
H7N9	39	No	No, eradication efforts in poultry reservoir ongoing	
NL63	Unknown	Unknown	No, endemic in human population	
SARS-CoV	9.5	Yes	Yes, eradicated from intermediate animal reservoir	58% of cases result from nosocomial transmission
MERS-CoV	34.4	No	No, continuous circulation in animal reservoir and zoonotic spillover	70% of cases result from nosocomial transmission
Ebola virus (West Africa)	63	No	Yes	

* Number will most likely continue to change until all infected persons recover.

What did we learn from Korean MERS-CoV cases in 2015 and 2018 to face current 2019-nCoV outbreak (I)?

2015 MERS-CoV 1st case

- Index patient hide some travel information. Incomplete "TOCC" history taking
- 9 hours to isolate patient
- 2 days to get MERS-CoV PCR done (KCDC)
- 9 days to confirm MERS
- 9 days to reinvestigate the exposed individuals properly (KCDC)

2018 MERs-CoV 1st case

- Index patient reported all the information. TOCC important
- 2 minutes to isolate patient
- Less than 6 hours to get MERS-CoV PCR done (KCDC)
- Less than 12 hours to confirm MERS
- 1-2 days to investigate the whole thing and have appropriate action

What did we learn from Korean MERS-CoV cases in 2015 and 2018 to face current 2019-nCoV outbreak (II)?

2015 MERS-CoV exposure

- Lack of awareness
  - General public did not know MERS.
  - General physicians were not familiar with MERS and did not suspect MERS as initial diagnosis.
- Preparedness
  - Health care facility: limited preparedness
  - KCDC: delayed diagnosis and incomplete epidemiologic investigation
- Limited communication by KCDC and among health care facilities

2018 MERS-CoV exposure

- Increased awareness
  - Patient reported his visit to Middle East and symptoms
  - Physicians at all level are familiar with MERS.
- Preparedness
  - Health care facility: better equipped, isolation units, trained staff, protocol, drills
  - KCDC: clear case definition, rapid diagnosis and thorough epidemiologic investigation
- **Open and prompt communication by KCDC and media (public)**

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