Emerging infectious diseases: Coronavirus disease 2019 (COVID-19) as an example

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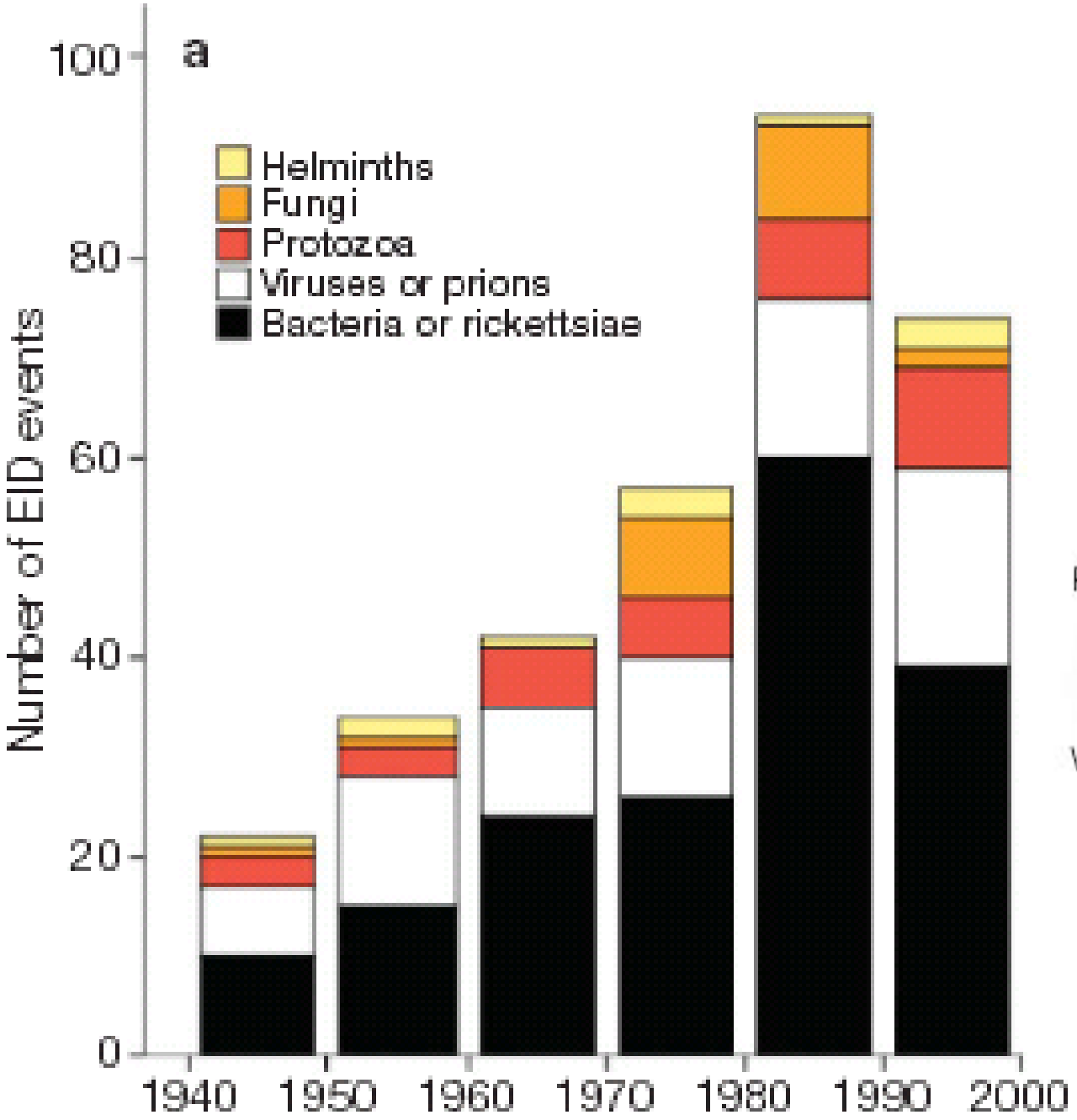
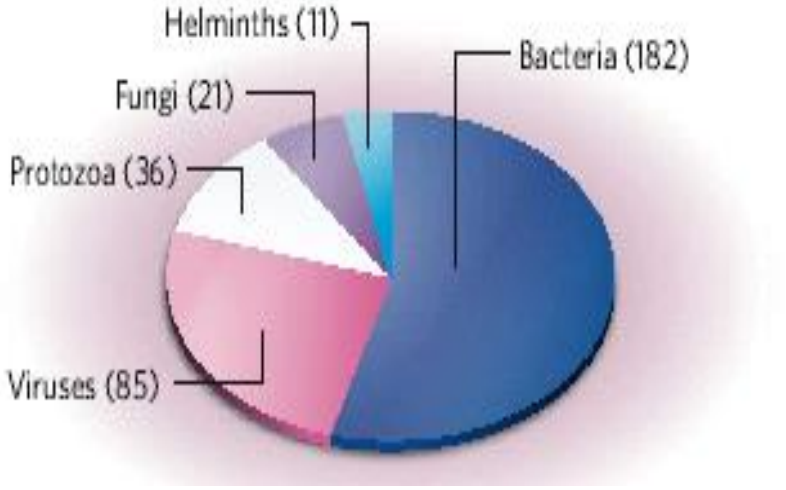
Emerging infectious diseases

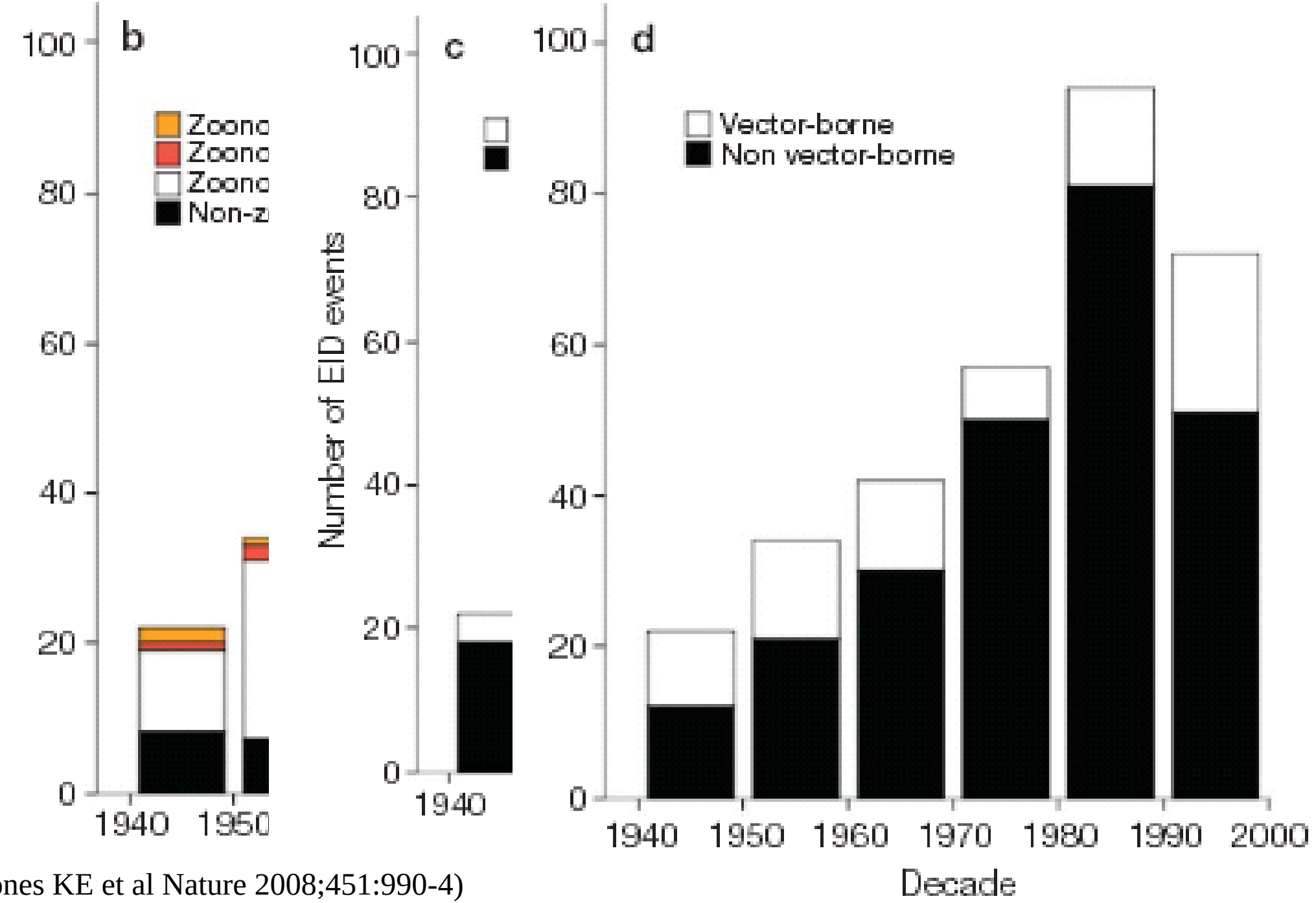
- Emerging infectious diseases are diseases
  - newly **recognized**,
  - newly **introduced**
  - newly **evolved**, or
  - that have recently and **rapidly changed in incidence or expansion** in geographical, host or vector range
- In 2008, a seminar listed **335 new human pathogens** discovered between 1940 and 2004
  - **60.3%** originated from (wild) **animal reservoirs** (zoonotic)
  - Approximately **20%** transmitted from animal reservoir hosts to humans by disease **vectors** (ticks, mosquitos, midges)

(Petersen E et al CMI 2018;24:369-75)



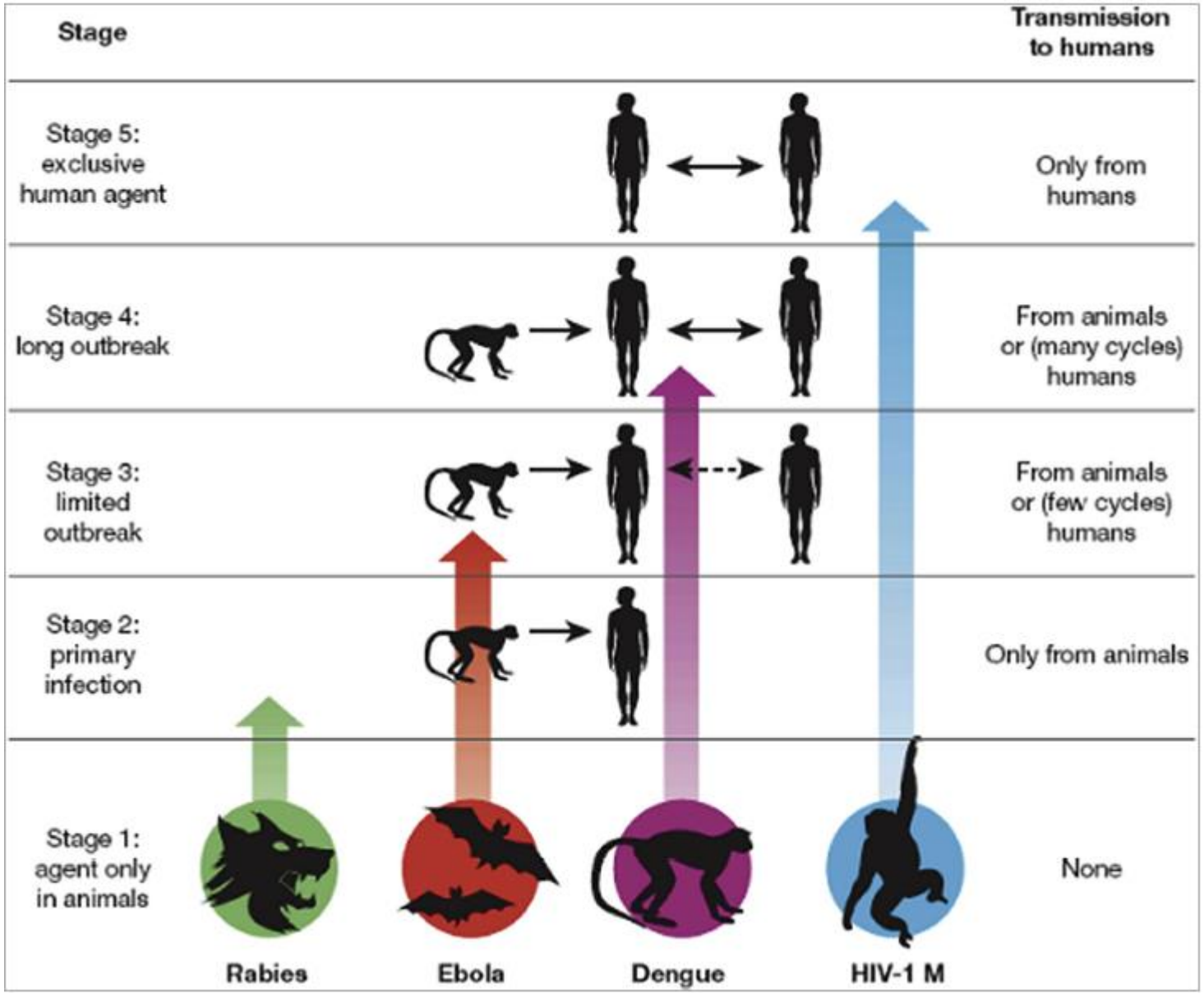


(Jones KE et al Nature 2008;451:990-4)



(Jones KE et al Nature 2008;451:990-4)

Illustration of five stages through which pathogens of animals evolve to cause diseases confined to humans.



(Petersen E et al CMI 2018;24:369-75)

One Health concept

- **One Health** recognizes that the **health of people** is connected to the **health of animals and the environment**
- The goal of One Health is to encourage the collaborative efforts of multiple disciplines-working locally, nationally, and globally-to achieve the best health for people, animals, and our environment

(Petersen E et al CMI 2018;24:369-75)

Emerging infections- an increasingly important topic: review by the Emerging Infections Task Force

- At least **four major drivers** of emergent infections:
  - increasing density of the human population;
  - stress from farmland expansion on the environment;
  - globalization of the food market and manufacturing;
  - environmental contamination
- The factors creating new opportunities for emerging infections include
  - **population growth**;
  - **spread in health care facilities**;
  - an **ageing population**;
  - **international travel**;
  - changing and expanding vector habitats

(Petersen E et al CMI 2018;24:369-75)

Emerging infections- an increasingly important topic: review by the Emerging Infections Task Force

Conclusions :

- Emerging infections are **unpredictable**
- The authors argue that
  - To discover new trends in infectious diseases, the clinicians have to **look for the unusual and unexpected and ensure proper diagnostics**
  - **Syndromic surveillance** must be **supported** by highly specialized laboratory services
- **Mathematical modeling** has **not** been able to predict outbreaks
- More emphasis on the **biology of evolution** is needed.
- EID **rarely** stands out **as unusual**, and the continuous pressure on health care budgets forces clinicians and laboratories to prioritize their diagnostic work-up to common and treatable conditions

(Petersen E et al CMI 2018;24:369-75)

全球新興傳染病永不止息

- 2002-2003 嚴重急性呼吸道症候群(SARS)

  全球8,096例，死亡774例

- 2009-2010 新型A型流感 (H1N1 Influenza A)

  全球1,311,522例，死亡14,142例(WHO)

  全球7-14億例(CIDRAP, U Minnesota)，15-57.5萬死亡(CDC)

- 2012-2020 中東呼吸症候群(MERS)

  全球2,533例，死亡871例

- 2013-2016 伊波拉出血熱(1976發現)

  西非大流行28637例，11,315死亡(WHO)

- 2019-2020 新冠病毒肺炎(COVID -19)

  全球35,789,350例，死亡 1,051,063例(迄2020-10-07)

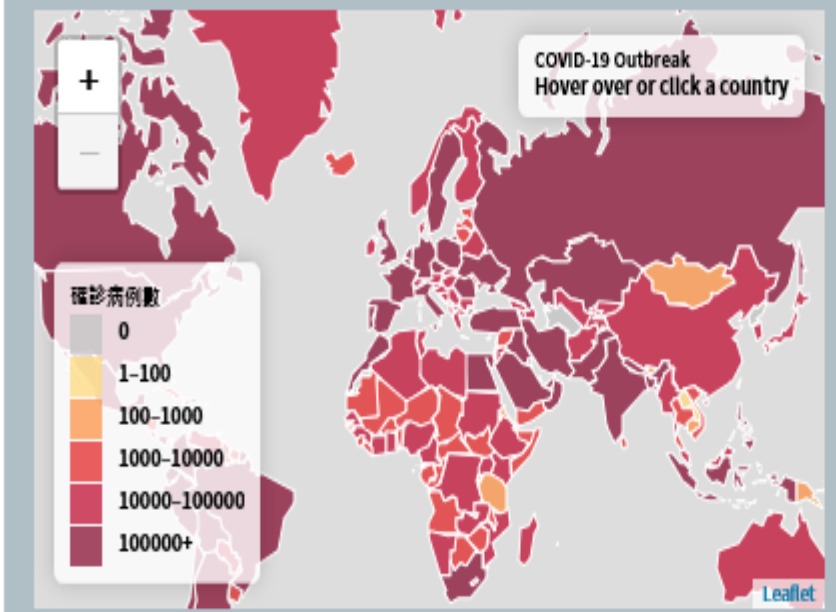
2011 發熱伴血小板減少綜合症（Severe Fever with Thrombocytopenia Syndrome, SFTS）首次由中國大陸報導，南韓及日本亦有確定病例，台灣2019亦首次出現病例


2019金門偏鄉教育
講座注意事項
李秉穎
醫乃方

Taxonomy of the Viruses

- Named as "2019-nCoV" (2019 novel coronavirus) by WHO initially
- "**the new coronavirus**", "**the Wuhan coronavirus**", or simply "**the coronavirus**“
- On **11 February** 2020, ICTV introduced the name severe acute respiratory syndrome coronavirus 2 **(SARS-CoV-2)**
- Earlier the same day, the WHO officially renamed the disease caused by the virus strain from 2019-nCoV acute respiratory disease to "coronavirus disease 2019" **(COVID-19)**
- **台灣稱”**嚴重特殊傳染性肺炎”（Severe Pneumonia with Novel Pathogens）

COVID-19 (武漢肺炎)

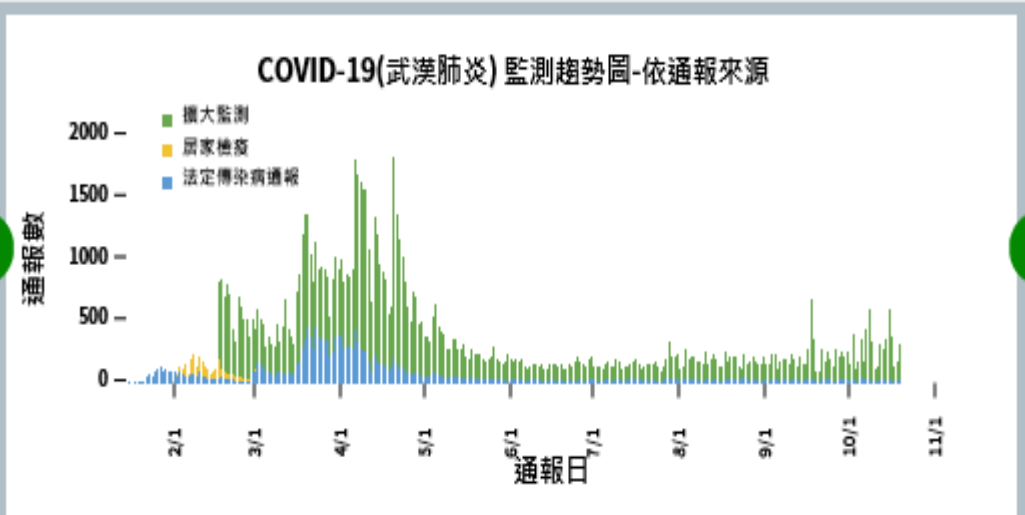


全球確定病例數	全球死亡病例數	全球致死率	國家/地區數
40,396,787	1,120,286	2.77%	188

更新時間：2020-10-20 09:20

	通報數	排除	確診	死亡	解除隔離
國內通報總計	99,367	98,102	540	7	493
昨日新增	316	209	5		

國內檢驗總計	累計件數
	213,696



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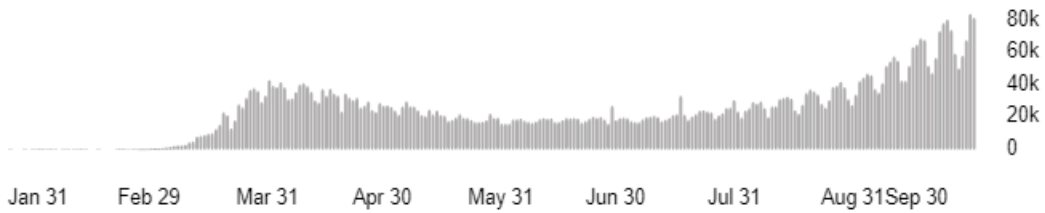
Global Situation

Daily | Weekly

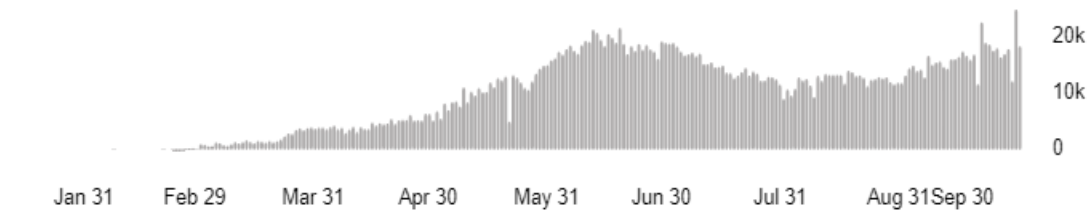
Europe

6,110,726
confirmed cases



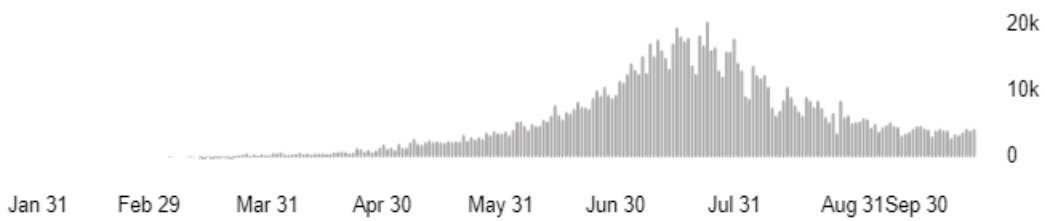
Eastern Mediterranean

2,448,756
confirmed cases



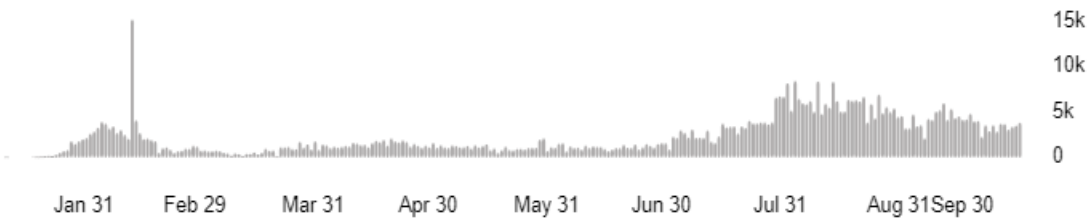
Africa

1,195,645
confirmed cases



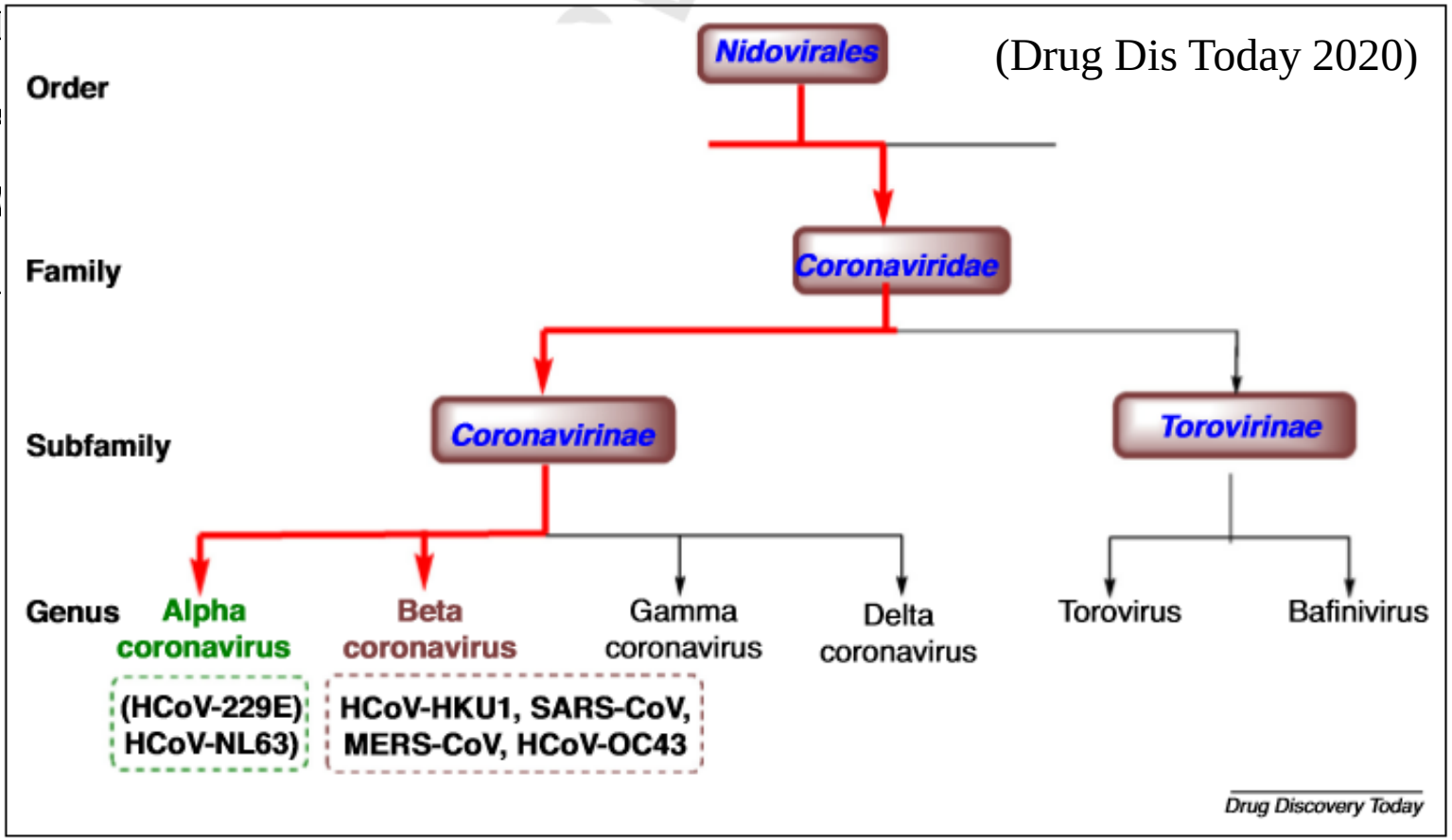
Western Pacific

621,915
confirmed cases



Virology of SARS-CoV-2

- Coronaviruses (CoV), first discovered in the 1960s, are a large family of viruses.
- Some coronavi
among animals,
- Rarely, animal
subsequently in
ole

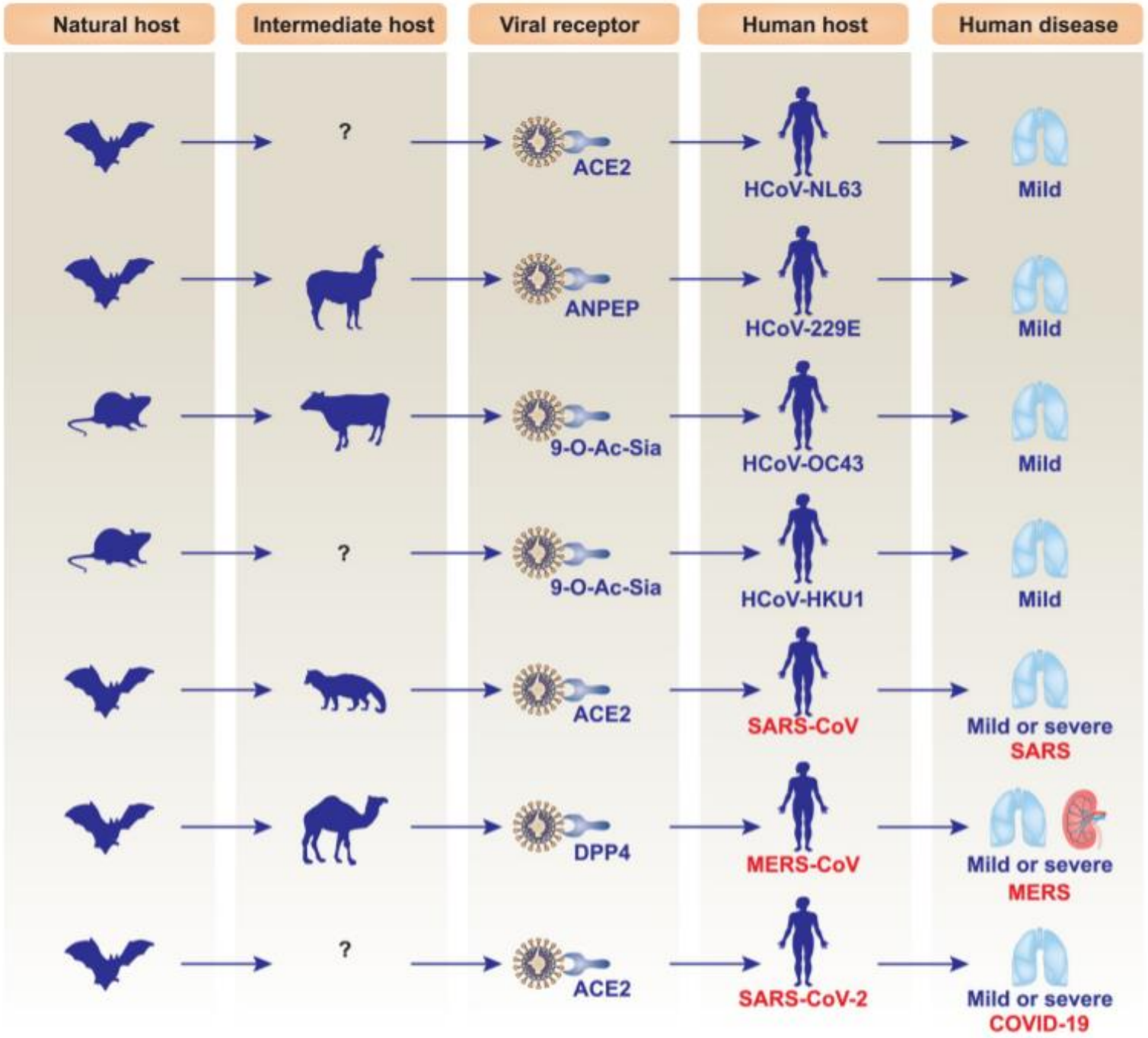


Virology of SARS-CoV-2

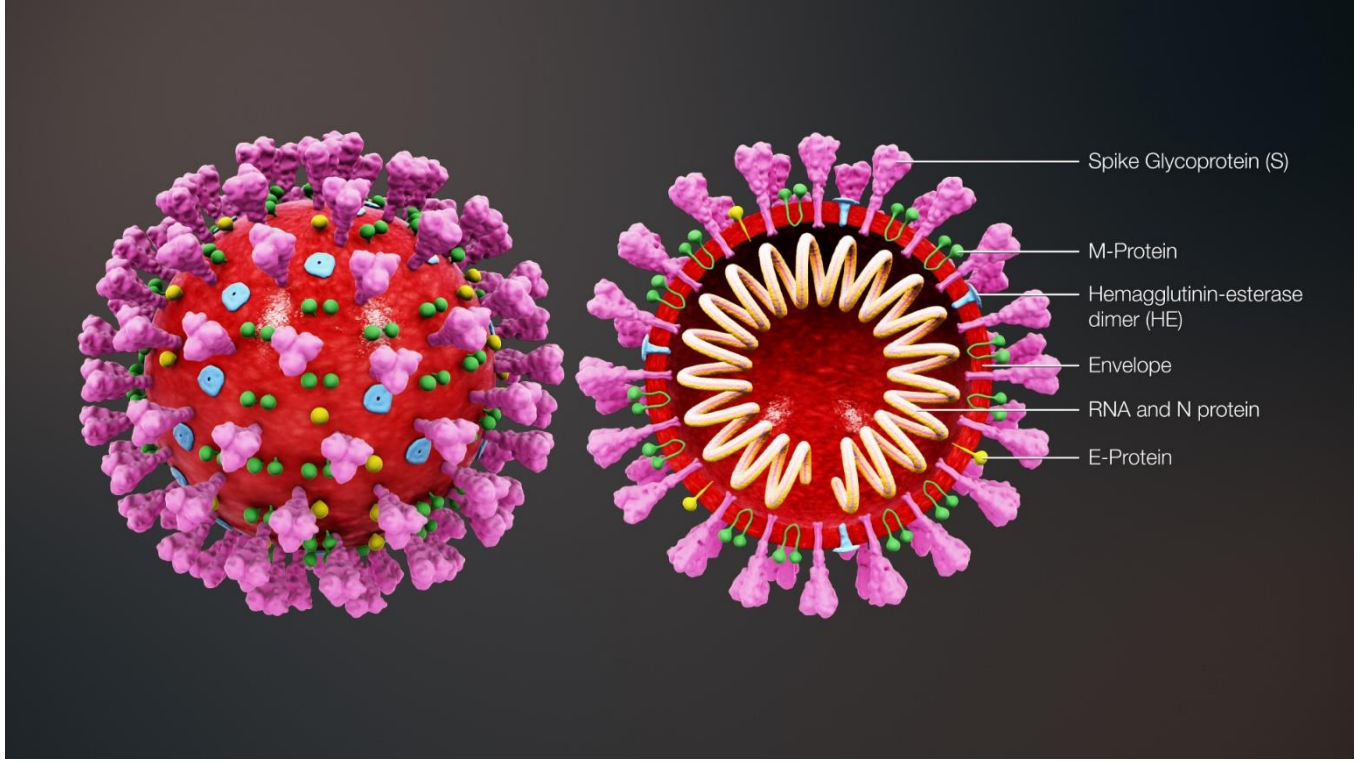
- A positive-sense single-stranded (+ssRNA) virus
- The seventh known coronavirus to infect people, after 229E (alpha-CoV), NL63 (alpha-CoV), OC43, HKU1, MERS-CoV, SARS-CoV
- A member of the subgenus Sarbecovirus (Beta-CoV lineage B)
- RNA sequence approximately **30,000 bases** in length
- Angiotensin converting enzyme 2 (ACE2) demonstrated as the receptor for 2019-nCoV

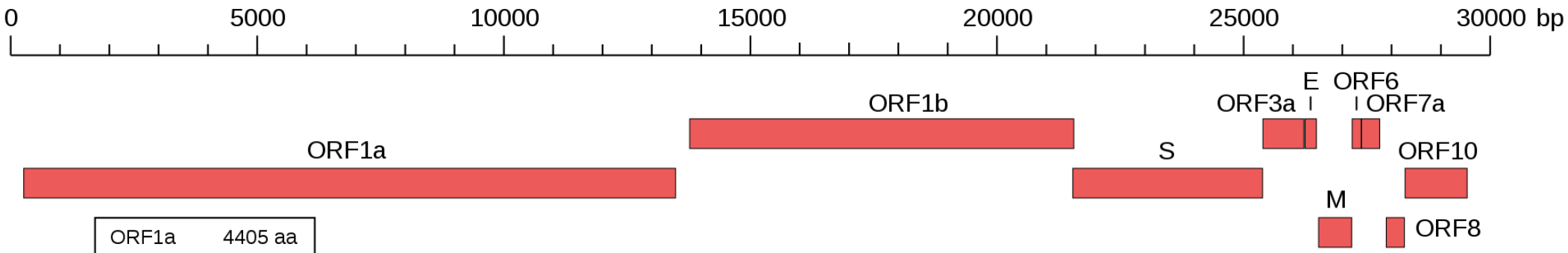
(Drug Dis Today 2020)

Hosts and consequences of human CoV infection



(Tang D et al PLoS Pathog 2020;16 (5): e1008536)





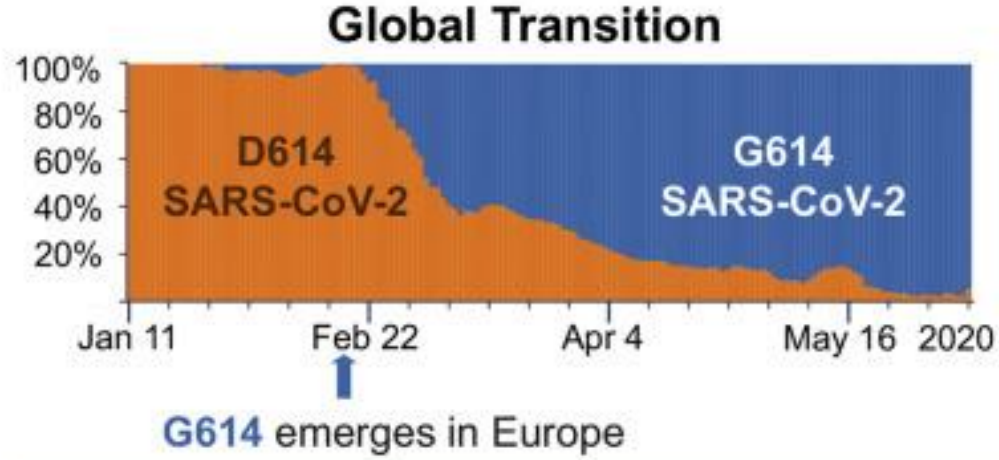
ORF1a	4405 aa
ORF1b	2595 aa
S	1282 aa
ORF3a	275 aa
E	75 aa
M	222 aa
ORF6	61 aa
ORF7a	121 aa
ORF8	121 aa
ORF10	419 aa

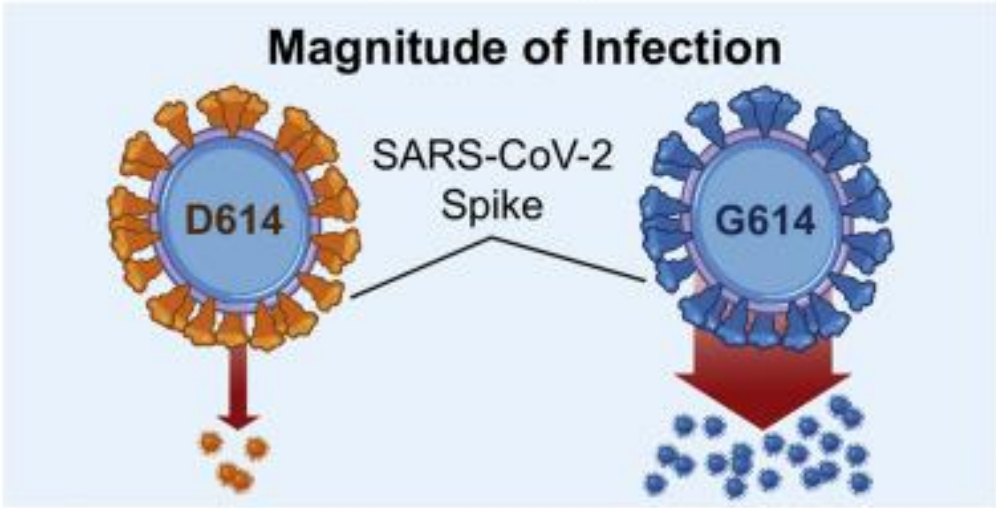
Wuhan-Hu-1 (GenBank MN908947)

Tracking changes in SARS-CoV-2 Spike: evidence that D614G increases infectivity of the COVID-19 virus

(Korber B et al. Cell 2020;182:812-27. e19)

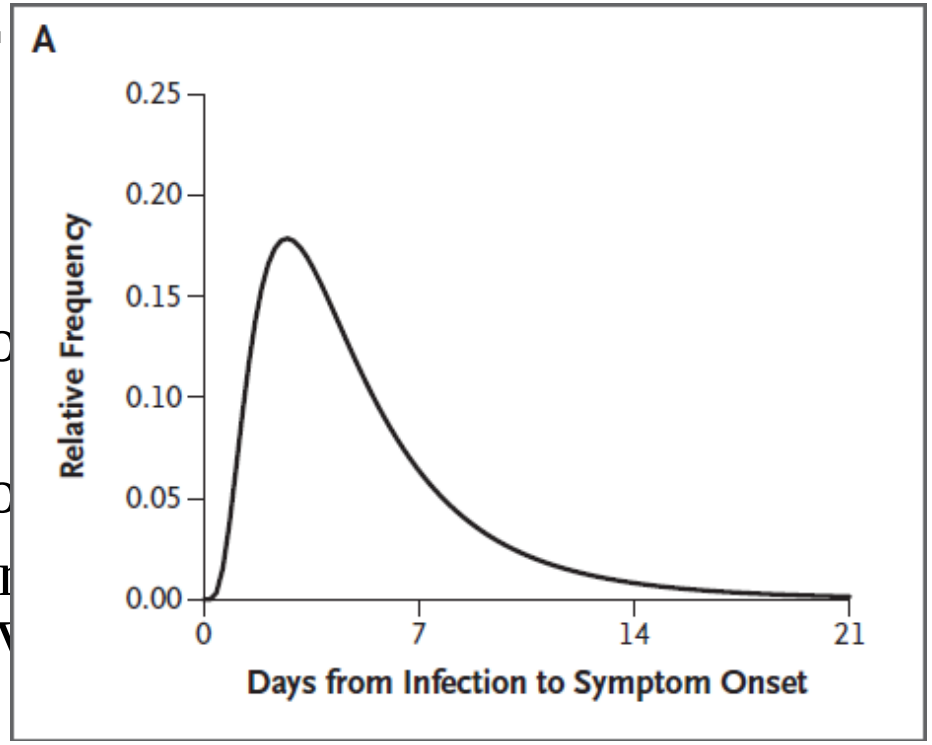
- A SARS-CoV-2 variant carrying the Spike protein amino acid change D614G has become the most prevalent form in the global pandemic
  - The G614 variant may have a fitness advantage
  - In infected individuals, **higher upper respiratory tract viral loads**, though **not with increased disease severity**





Incubation period of

- Incubation period
  - The time between infection and the onset o
  - Current estimates of the incubation period
    estimates will be refined as more data beco
  - Based on information from other coronavir
    SARS, the incubation period of 2019-nCo



- The mean incubation period **5.2 days** (95% CI, 4.1 to 7.0), with the 95th percentile of the distribution at **12.5 days** **(examined data on exposures among 10 confirmed cases)**

(Li Q et al NEJM 2020)

Incubation period of 2019 novel coronavirus (2019nCoV) infections among travelers from Wuhan, China, 20–28 January 2020 (Becker JA et al Euro Surveill. 2020;25(5):pii=2000062)

- Using the travel history and symptom onset of **88 confirmed cases** that were **detected outside Wuhan** in the early outbreak phase
  - Ages range from 2 to 72 years of age
  - 63 were Wuhan residents who travelled elsewhere and 25 were visitors who stayed in Wuhan for a limited time
  - By taking the date of symptom onset and travel history together, we inferred the possible incubation period for each of these cases
- Estimate the mean incubation period **6.4 days** (95% credible interval: 5.6–7.7), ranging from **2.1 to 11.1 days** (2.5th to 97.5th percentile).
- These values should help inform 2019-nCoV case definitions and appropriate quarantine durations

How is the virus that causes COVID most commonly transmitted between people? (WHO Q & A July 9, 2020)

- Current evidence suggests that COVID-19 spreads between people through **direct, indirect** (through contaminated objects or surfaces), or **close contact** with infected people via **mouth and nose secretions**
  - Include **saliva, respiratory secretions or secretion droplets**
  - People who are in close contact (within 1 metre) with an infected person can catch COVID-19 when those infectious droplets get into their mouth, nose or eyes
  - People with the virus may **leave infected droplets on objects and surfaces** such as tables, doorknobs and handrails; other people may become infected by touching these objects or surfaces, then touching their eyes, noses or mouths before cleaning their hands

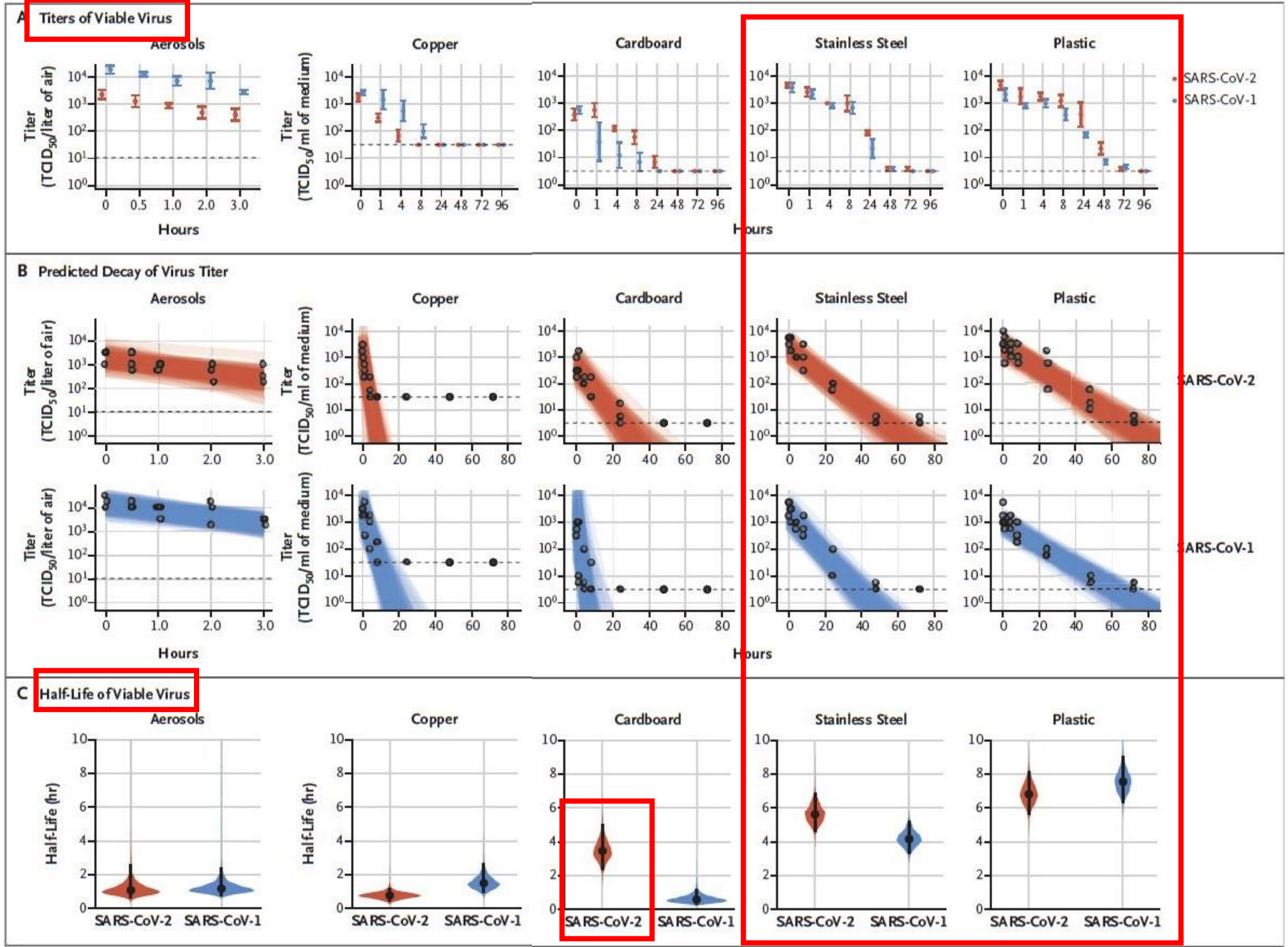
What do we know about aerosoal transmission?

(WHO Q & A July 9, 2020)

- Some medical procedures can produce very small droplets (called aerosolized **droplet nuclei or aerosols**) that are able to stay **suspended in the air** for longer periods of time
- When such medical procedures are conducted on people infected with COVID-19 in health facilities, these aerosols can contain the COVID-19 virus, may potentially be inhaled by others if they are not wearing appropriate personal protective equipment
- Reported outbreaks of COVID-19 in **some closed settings,** such as restaurants, nightclubs, places of worship or places of work where people may be **shouting, talking, or singing,** aerosol transmission cannot be ruled out

Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1 (van Doremalen N et al NEJM 2020)

- Aerosols (<5 µm) containing SARS-CoV-2 ($10^{5.25}$ 50% **tissue-culture infectious dose** [TCID50] per mL) or SARS-CoV-1 ($10^{6.75-7.00}$ TCID50 per mL) were generated with the use of a three-jet Collison nebulizer and fed into a Goldberg drum to **create an aerosolized environment**
  - The inoculum resulted in cycle-threshold values between 20 and 22, similar to those observed in samples obtained from the upper and lower respiratory tract in humans
- 10 experimental conditions involving two viruses (SARS-CoV-2 and SARS-CoV-1) in **five environmental conditions** (aerosols, plastic, stainless steel, copper, and card-board)
- All experimental measurements are reported as means across three replicates


A Titers of Viable Virus
Aerosols
Copper
Cardboard
Stainless Steel
Plastic
Titer (TCID50/liter of air)
Titer (TCID50/ml of medium)
Hours
SARS-CoV-2
SARS-CoV-1
B Predicted Decay of Virus Titer
C Half-Life of Viable Virus
Half-Life (hr)

Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1 (van Doremalen N et al NEJM 2020)

- Stability of SARS-CoV-2 was **similar** to that of SARS-CoV-1 **under the experimental circumstances** tested
- (**Differences** in the epidemiologic characteristics of these 2 viruses
  - High viral loads in the upper respiratory tract and the potential for persons infected with SARS-CoV-2 to shed and transmit the virus while asymptomatic)
- **Aerosol** and **fomite transmission** of SARS-CoV-2 is plausible, since the virus can remain viable and infectious in aerosols for hours and on surfaces up to days

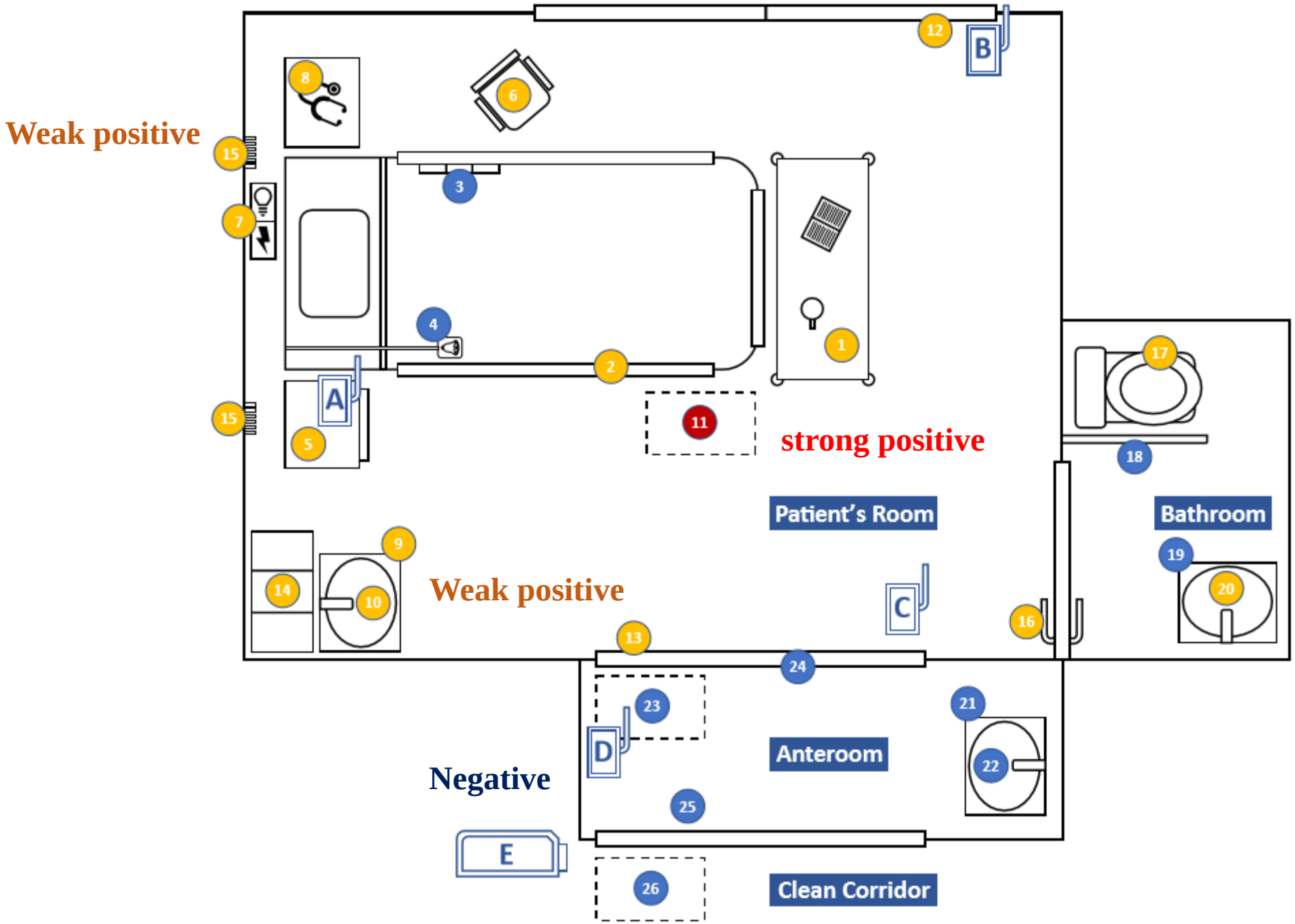
Air, surface environmental, and personal protective equipment contamination by SARS-CoV-2 from a symptomatic patient

(Ong SWX et al JAMA 2020)

Table 1. Sampling Time Points in Relation to Patient Illness and Clinical Cycle Threshold Values

Patient	Days of illness when samples were collected	Presence of symptoms during sampling	Symptoms	Disease severity[a]	Before/after routine cleaning	Cycle threshold value from clinical samples[b]
A	4, 10	Yes, both days	Cough, fever, shortness of breath	Moderate	After	31.31 (day 3); 35.33 (day 9)
B	8, 11	Yes on day 8; asymptomatic on day 11	Cough, fever, sputum production	Moderate	After	32.22 (day 8); not detected (day 11)
C	5	Yes	Cough	Mild	Before	25.69 (day 4)

- **After routine cleaning**, all samples were **negative**
- **Before routine cleaning**, **positive results** in **13 (87%) of 15** room sites (including air outlet fans) and 3 (60%) of 5 toilet sites
- Only 1 PPE swab, from the surface of **a shoe front**, was **positive**
- All **air samples** were **negative**


Weak positive
strong positive
Weak positive
Negative
Patient's Room
Bathroom
Anteroom
Clean Corridor
A
B
C
D
E
1
2
3
4
5
6
7
8
9
10
11
12
13
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25
26

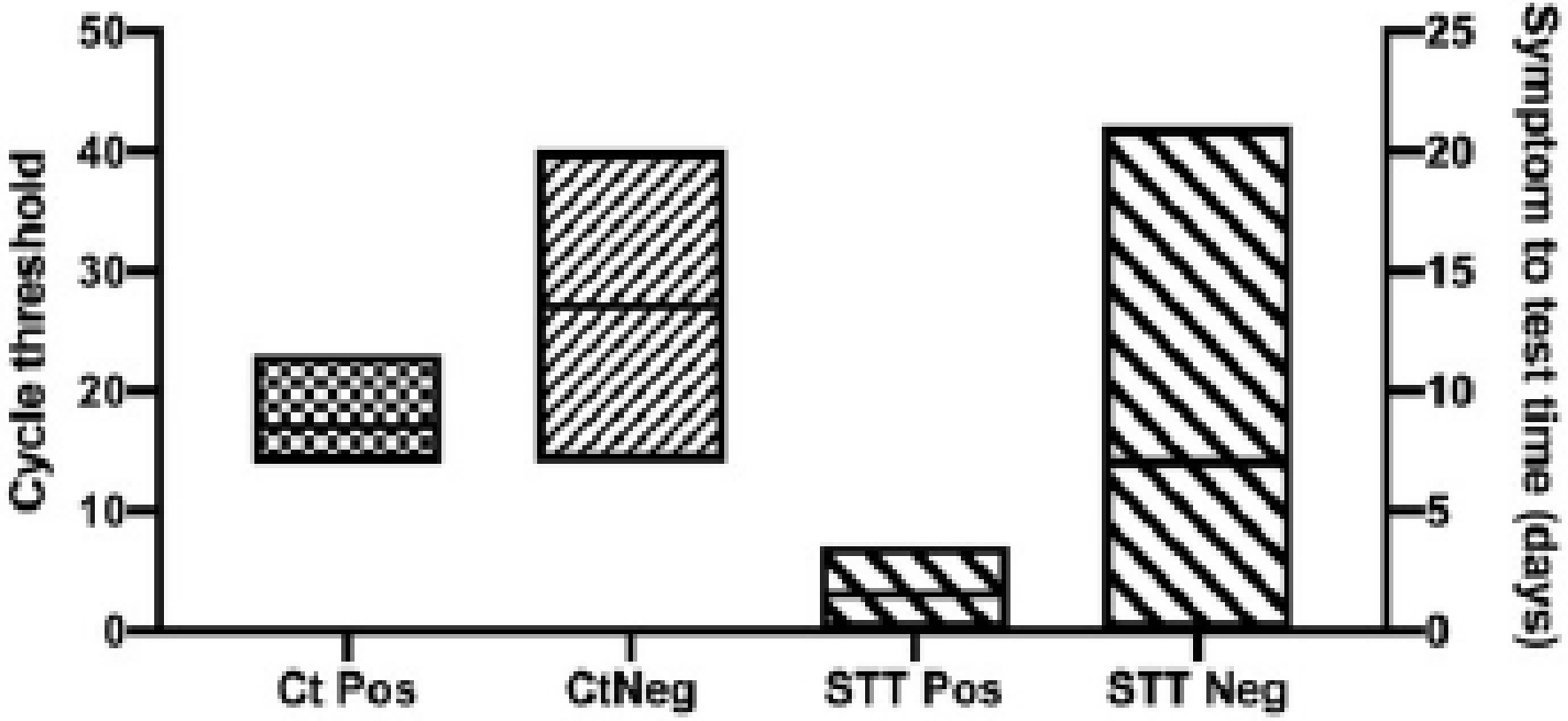
Transmission of SARS-CoV-2 (WHO Q & A)

- Understanding the time when infected patients may spread the virus to others is critical for control efforts
- Detailed medical information from people infected is needed to determine the **infectious period** of 2019-nCoV
- It may possible that people infected with 2019-nCoV **may be infectious before showing significant symptoms (pre-symptomatic)**
- However, based on currently available data, **the people who have symptoms** are causing the **majority** of virus spread

Predicting infectious SARS-CoV-2 from diagnostic samples (Bullard J et al CID 2020;online)

- Retrospective cross-sectional study, we took SARS-CoV-2 RT-PCR confirmed positive samples and determined their ability to infect Vero cell lines
- 90 RT-PCR SARS-CoV-2 positive samples were incubated on **Vero cells**
  - Twenty-six samples (**28.9%**) demonstrated **viral growth**
  - Median TCID50/ml was 1780 (282-8511).
  - There was **no growth** in samples with a **Ct > 24** or **symptom onset to test (STT) > 8 days**
  - Multivariate logistic regression using positive viral culture as a binary predictor variable, STT and Ct demonstrated an odds ratio for positive viral culture of 0.64 (95% CI 0.49-0.84, p<0.001) for every one unit increase in Ct
  - Area under the receiver operating characteristic curve for Ct vs. positive culture was OR 0.91 (95% CI 0.85-0.97, p<0.001), with 97% specificity obtained at a Ct of >24

Figure 2



- Positive SARS-CoV-2 culture samples had a **significantly lower Ct** when compared to culture negative samples (17 [16-18] vs 27 [22-33], $p<0.001$).
- **Symptom to test time** was also **significantly lower** in culture positive vs. culture negative samples (3 [2-4] vs. 7 [4-11], $p<0.001$)

Predicting infectious SARS-CoV-2 from diagnostic samples (Bullard J et al CID 2020;online)

Conclusions

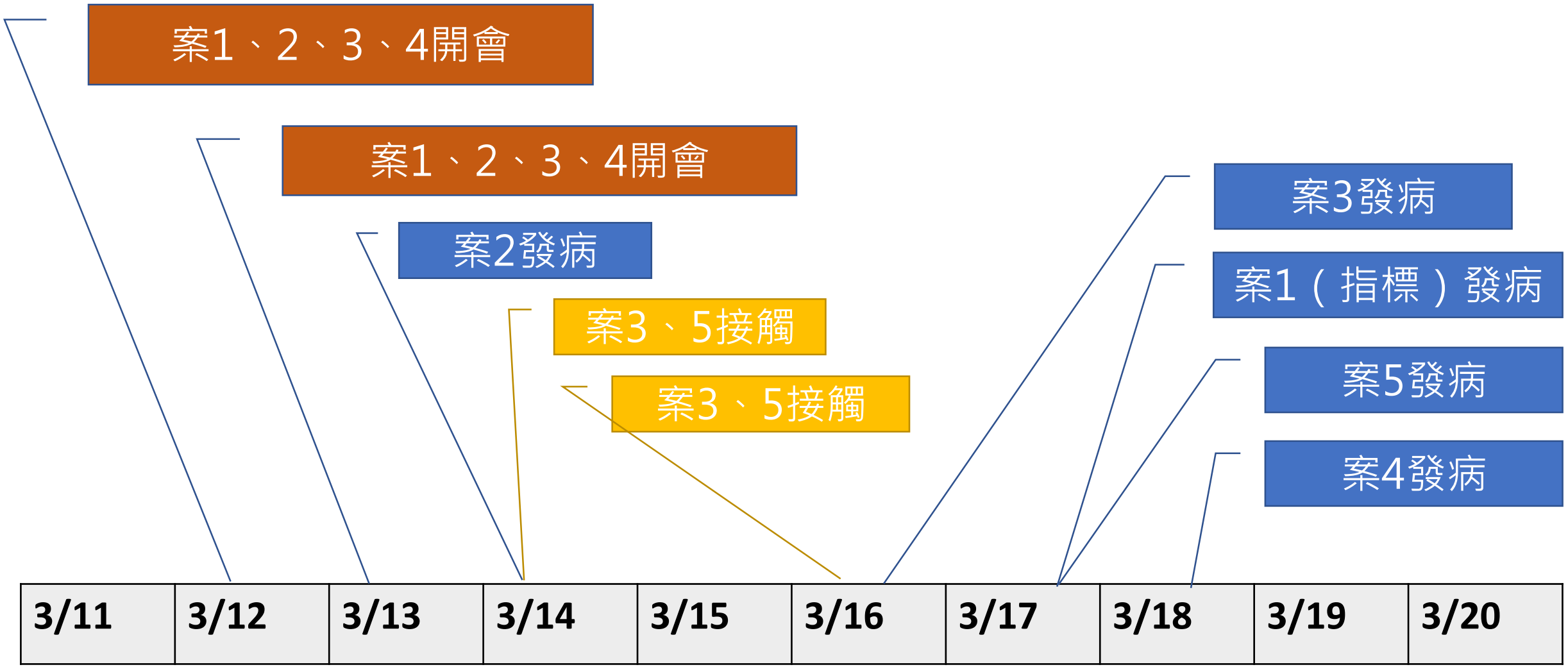
- SARS-CoV-2 **Vero cell infectivity** was **only observed for RT-PCR Ct < 24 and symptom onset to test < 8 days**
- Infectivity of patients with Ct >24 and duration of symptoms >8 days may be low

Presymptomatic Transmission of SARS-CoV-2 — Singapore, January 23–March 16, 2020

(Wei, et al. April 1, 2020 MMWR)

- 新加坡回顧1/23—3/16期間243名確診個案，發現有**七起2—5人的群聚事件**，可能有出現症狀前的疾病傳播
- 10/157 (6.4%)位本土個案是群聚的一部分
- 研究者追蹤個案暴露與發病的時間來判定是否有症狀前傳播，並且確認次波個案並沒有其他可能的來源
- 有四件可以確認暴露時間的群聚，其**傳播發生在症狀出現前1—3天**
- 結論與先前其他文章類似，COVID-19出現症狀前就可以傳播，因此在追蹤接觸者時應強烈考慮追蹤個案出現症狀前一段時間的接觸者，以涵蓋發病前可能傳播的時間

臺北區5人群聚（案1（指標）3/11自美國回來）




The facility is a 4-story building
Yhu-Cherng Huang
(Taiwan)
2020
TAIPEI
TAIWAN
September 4-6, 2020

Clinical manifestations of SARS-CoV-2 infection

- **Asymptomatic infection**
- Mild respiratory diseases
- Moderate-severe respiratory diseases:
  - Pneumonia, requiring oxygen supplementation
- Critical diseases
  - Respiratory failure
  - Acute respiratory distress syndrome (ARDS)
  - Multiple organs failure
- **Extrapulmonary manifestations**
- Sequelae

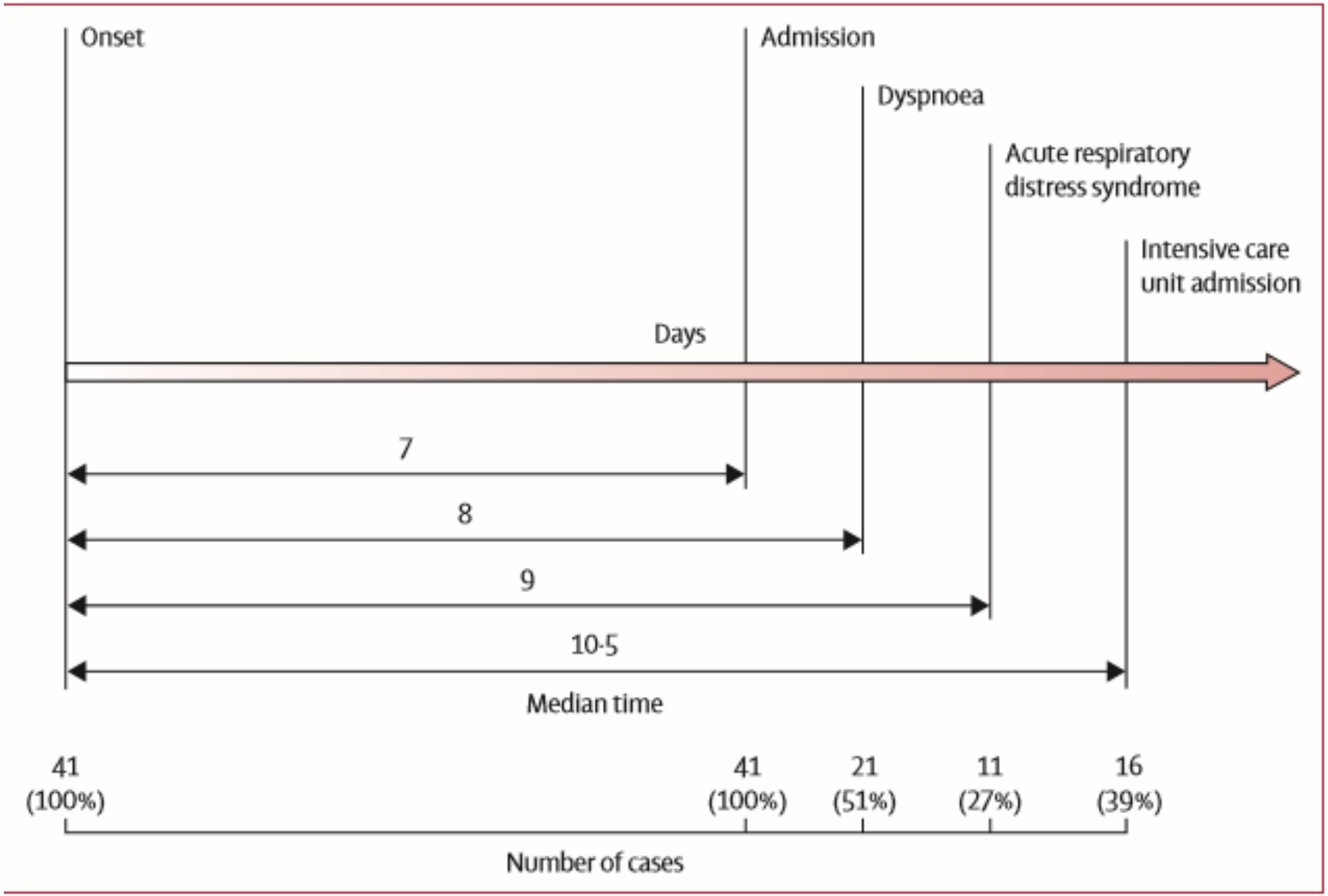


Figure 2: **Timeline of 2019-nCoV cases after onset of illness**

(Huang C et al Lancet 2020; 395: 497–506)

Characteristics of and Important Lessons From COVID-19 Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention

(Wu Z et al 2020 JAMA)

Box. Key Findings From the Chinese Center for Disease Control and Prevention Report

72 314 Cases (as of February 11, 2020)
- Confirmed cases: 44 672 (62%)
- Suspected cases: 16 186 (22%)
- Diagnosed cases: 10 567 (15%)
- Asymptomatic cases: 889 (1%)

Age distribution (N = 44 672)
- ≥80 years: 3% (1408 cases)
- 30-79 years: 87% (38 680 cases)
- 20-29 years: 8% (3619 cases)
- 10-19 years: 1% (549 cases)
- <10 years: 1% (416 cases)

Spectrum of disease (N = 44 415)
- Mild: 81% (36 160 cases)
- Severe: 14% (6168 cases)
- Critical: 5% (2087 cases)

Case-fatality rate
- 2.3% (1023 of 44 672 confirmed cases)
- 14.8% in patients aged ≥80 years (208 of 1408)
- 8.0% in patients aged 70-79 years (312 of 3918)
- 49.0% in critical cases (1023 of 2087)

Health care personnel infected
- 3.8% (1716 of 44 672)
- 63% in Wuhan (1080 of 1716)
- 14.8% cases classified as severe or critical (247 of 1668)
- 5 deaths

Coronavirus Disease 2019 Case Surveillance — United States, January 22–May 30, 2020 (Stokes EK et al MMWR 2020;69:759-65)

- Through May, 30, 2020,
  - **COVID-19 pandemic resulted in 5,817,385 reported cases and 362,705 deaths worldwide**
  - 1,761,503 aggregated reported cases and 103,700 deaths in the United States
- Cumulative incidence, 403.6 cases per 100,000 persons,
  - similar among males (401.1) and females (406.0)
  - highest among persons aged ≥80 years (902.0)
- Among 287,320 (22%) cases with sufficient data on underlying health conditions
  - cardiovascular disease (32%), diabetes (30%), and chronic lung disease (18%)
- Overall, 184,673 (**14%**) patients were **hospitalized**, 29,837 (**2%**) admitted to an intensive care unit (**ICU**), and 71,116 (**5%**) **died**

TABLE 1. Reported laboratory-confirmed COVID-19 cases and estimated cumulative incidence,* by sex† and age group — United States, January 22–May 30, 2020

	Males		Females		Total	
Age group (yrs)	No. (%)	Cumulative incidence*	No. (%)	Cumulative incidence*	No. (%)	Cumulative incidence*
0–9	10,743 (1.7)	52.5	9,715 (1.4)	49.7	20,458 (1.5)	51.1
10–19	24,302 (3.8)	113.4	24,943 (3.7)	121.4	49,245 (3.7)	117.3
20–29	85,913 (13.3)	370.0	96,556 (14.3)	434.6	182,469 (13.8)	401.6
30–39	108,319 (16.8)	492.8	106,530 (15.8)	490.5	214,849 (16.3)	491.6
40–49	109,745 (17.0)	547.0	109,394 (16.2)	536.2	219,139 (16.6)	541.6
50–59	119,152 (18.4)	568.8	116,622 (17.3)	533.0	235,774 (17.9)	550.5
60–69	93,596 (14.5)	526.9	85,411 (12.7)	434.6	179,007 (13.6)	478.4
70–79	53,194 (8.2)	513.7	52,058 (7.7)	422.7	105,252 (8.0)	464.2
≥80	41,394 (6.4)	842.0	72,901 (10.8)	940.0	114,295 (8.7)	902.0
All ages	**646,358 (100.0)**	**401.1**	**674,130 (100.0)**	**406.0**	**1,320,488 (100.0)**	**403.6**

Abbreviation: COVID-19 = coronavirus disease 2019.
* Per 100,000 population.
† The analytic dataset excludes cases reported through case surveillance that were missing information on sex (n = 19,918) or age (n = 2,379).

Incidence rate increased with age

(Stokes EK et al MMWR 2020;69:759-65)

Coronavirus Disease 2019 Case Surveillance — United States, January 22–May 30, 2020 (Stokes EK et al MMWR 2020;69:759-65)

- Symptom status (symptomatic versus asymptomatic) was reported for 616,541 (47%) cases
  - among these, **22,007 (4%) asymptomatic**
- Among 373,883 (28%) cases with data on individual symptoms,
  - **70%** noted **fever, cough, or shortness of breath**
  - 36% reported **muscle aches**, 34% reported **headache**
- Overall, 31,191 (**8%**) persons reported **loss of smell or taste**
- **Hospitalizations six times higher** among patients with a reported underlying condition (45.4% versus 7.6%)
- **Deaths 12 times higher** among patients with reported underlying conditions (19.5% versus 1.6%)

Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series (Bradley BT et al Lancet 2020;396:320-32)

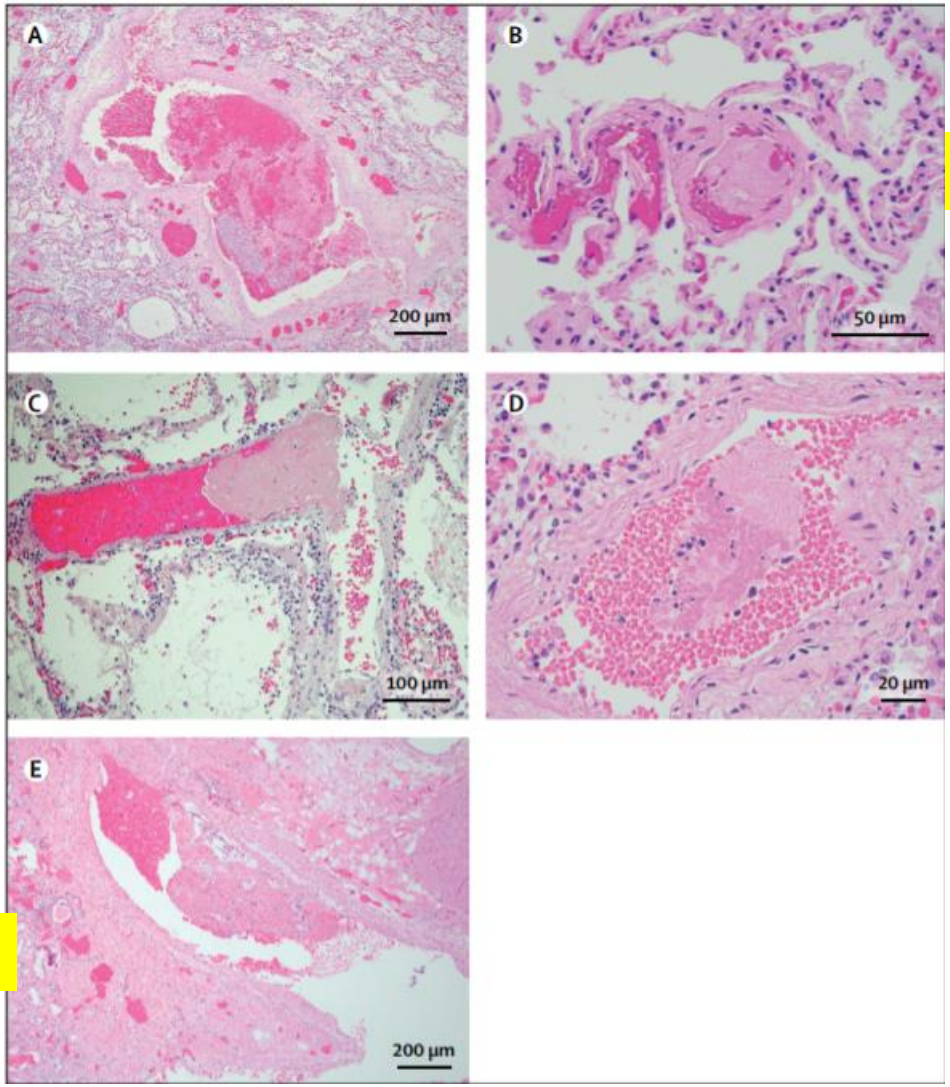
- Post-mortem examinations done on **14 people**
  - Median age **73·5 years** (range 42–84; IQR 67·5–77·25).
  - All patients had **clinically significant comorbidities**, the most common being hypertension, chronic kidney disease, obstructive sleep apnea, and metabolic disease including diabetes and obesity
- Major **pulmonary** finding **diffuse alveolar damage** in the acute or organizing phases, with **five patients** showing **focal pulmonary microthrombi**
- **Coronavirus**-like particles detected in the **respiratory system, kidney, and gastrointestinal tract**
- **Lymphocytic myocarditis** was observed in **one patient** with viral RNA detected in the tissue

Coagulopathy of fatal COVID-19 infections

Small vessel thrombus

Pulmonary microthrombus

Renal vein organizing thrombus

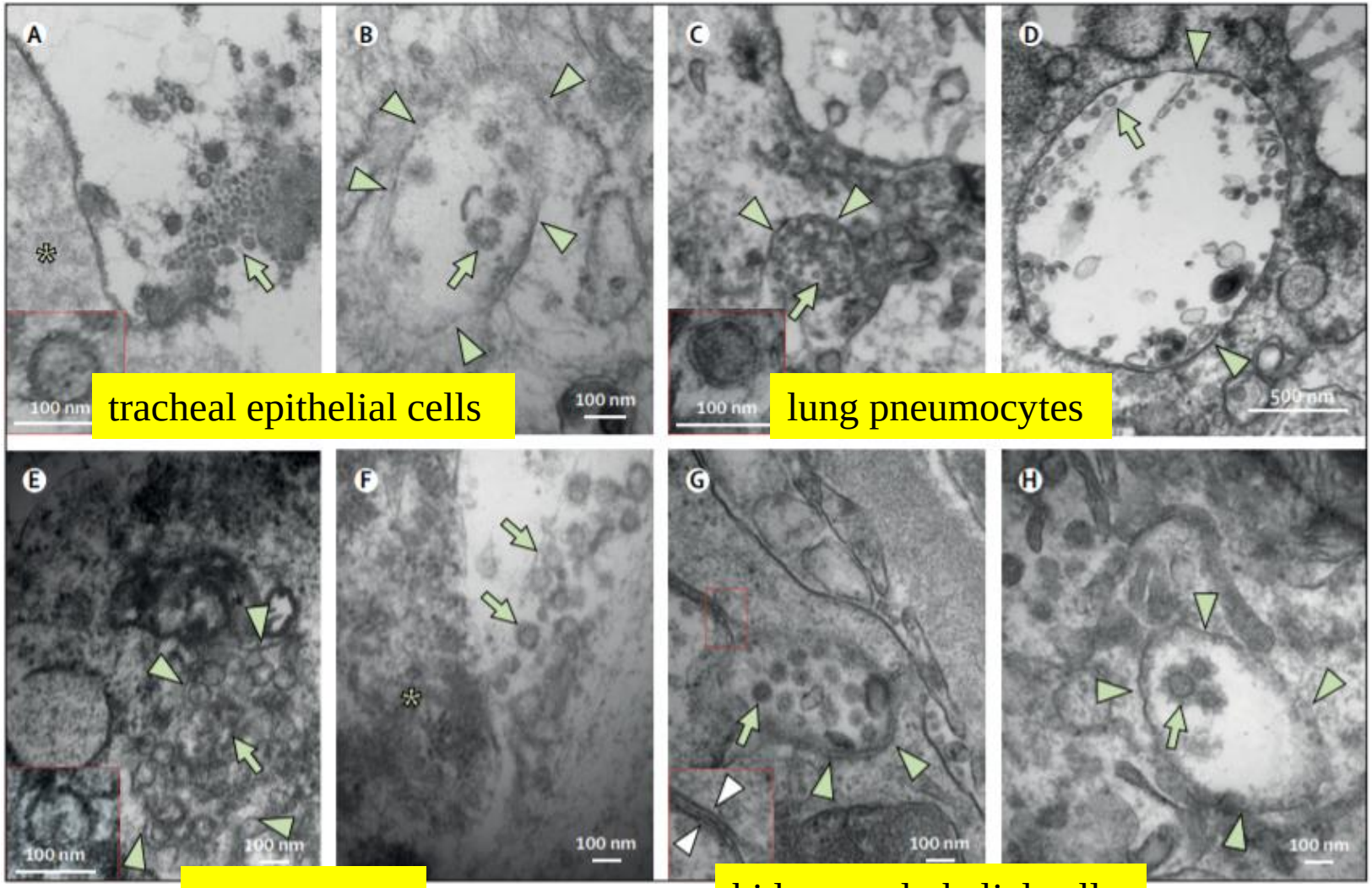


Pulmonary microthrombus

Pulmonary microthrombus

(Bradley BT et al Lancet 2020;396:320-32)

Ultrastructural features in fatal COVID-19 infections



(Bradley BT et al Lancet 2020;396:320-32)

Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series (Bradley BT et al Lancet 2020;396:320-32)

Conclusions

- The **primary pathology** observed in this cohort was **diffuse alveolar damage**, with **virus** located in the **pneumocytes and tracheal epithelium**
- **Microthrombi**, where observed, were **scarce** and endotheliitis was not identified
- Broad **tropism** for SARS-CoV-2 with coronavirus-like particles identified in the **pulmonary system, kidneys**, and **gastrointestinal tract**
- Although other **non-pulmonary organs** showed susceptibility to infection, their contribution to the pathogenesis of SARS-CoV-2 infection **requires further examination**

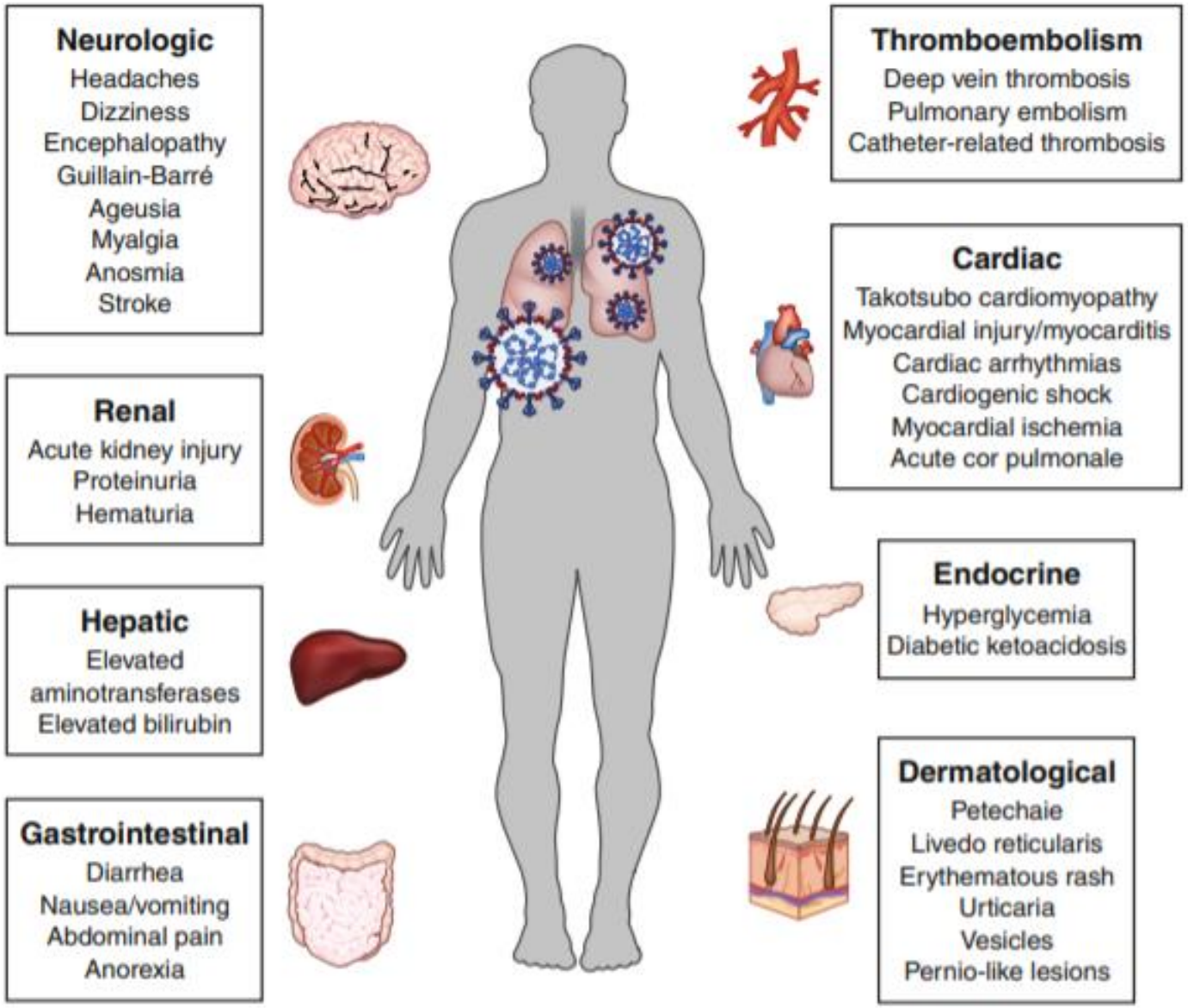
Extrapulmonary manifestations of COVID-19

(Gupta A et al Nat Med 2020;26:1017-32)

- While SARS-CoV-2 is known to cause substantial pulmonary disease, including pneumonia and acute respiratory distress syndrome (ARDS), clinicians have observed **many extrapulmonary manifestations** of COVID-19
  - Hematologic, cardiovascular, renal, gastrointestinal and hepatobiliary, endocrinologic, neurologic, ophthalmologic, and dermatologic systems
- **ACE2**, the entry receptor for the causative coronavirus SARS-CoV-2, is expressed in **multiple extrapulmonary tissues**

Other respiratory viruses, such as influenza virus, adenovirus etc., also have many extrapulmonary manifestations

Extrapulmonary manifestations of COVID-19



(Gupta A et al Nat Med 2020;26:1017-32)

Outcomes of **Maternal-Newborn Dyads** After Maternal SARS-CoV-2

(Verma S et al Pediatrics 2020; online)

- A multicenter, observational, descriptive cohort study collecting data from charts of maternal-newborn dyads that delivered at **four major New York City** metropolitan area hospitals between **March 1 and May 10**, 2020 with maternal SARS-CoV-2 infection
- A total of **149 mothers** with SARS-CoV-2 infection and **149 newborns** analyzed (3 sets of twins; **3 stillbirths**)
  - **40%** of these **mothers** were **asymptomatic**
  - Approximately **15%** of symptomatic mothers required some form of **respiratory support** and **8%** required **intubation**
  - Eighteen **newborns (12%) admitted to ICU**
  - 15 (**10%**) were born **preterm**, and five (3%) required mechanical ventilation.
  - **Symptomatic mothers** had more **premature deliveries** (16% vs 3%, P= 0.02) and **their newborns** were more likely to require **intensive care** (19% vs. 2%, P=0.001) than asymptomatic mothers
  - One newborn tested positive for SARS-CoV-2, considered a case of **horizontal postnatal transmission**

Outcomes of Maternal-Newborn Dyads After Maternal SARS-CoV-2

(Verma S et al Pediatrics 2020; online)

Conclusion:

- No distinct evidence of vertical transmission from mothers with SARS-CoV-2 to their newborns
- Observe **perinatal morbidities** among both mothers and newborns
- **Symptomatic mothers** more likely to experience **premature delivery** and their newborns to require intensive care

ARTICLE

https://doi.org/10.1038/s41467-020-17436-6 OPEN

Transplacental transmission of SARS-CoV-2 infection

Alexandre J. Vivanti[1,8], Christelle Vauloup-Fellous[2,8], Sophie Prevot[3], Veronique Zupan[4], Cecile Suffee[5], Jeremy Do Cao[6], Alexandra Benachi[1] & Daniele De Luca[4,7]✉

(NATURE COMMUNICATIONS | (2020) 11:3572 | https://doi.org/10.1038/s41467-020-17436-6)

SARS-CoV-2 outbreak is the first pandemic of the century. SARS-CoV-2 infection is transmitted through droplets; other transmission routes are hypothesized but not confirmed. So far, it is unclear whether and how SARS-CoV-2 can be transmitted from the mother to the fetus. We demonstrate the transplacental transmission of SARS-CoV-2 in a neonate born to a mother infected in the last trimester and presenting with neurological compromise. The transmission is confirmed by comprehensive virological and pathological investigations. In detail, SARS-CoV-2 causes: (1) maternal viremia, (2) placental infection demonstrated by immunohistochemistry and very high viral load; placental inflammation, as shown by histological examination and immunohistochemistry, and (3) neonatal viremia following placental infection. The neonate is studied clinically, through imaging, and followed up. The neonate presented with neurological manifestations, similar to those described in adult patients.

COVID-19 in children (Gupta A et al Nat Med 2020;26:1017-32)

- In a review of 72,314 patients with COVID-19 reported by the Chinese CDC, **less than 1%** of the patients were **younger than 10 years of age**
- In two retrospective studies from **China**, of >1,000 pediatric patients
  - The majority of the patients had mild or moderate disease,
  - **Only 1.8% required ICU admission**, **two deaths**
- A large group of **North American** pediatric ICUs, 38% of 48 critically ill children required invasive ventilation, with an in-hospital mortality rate of **4.2%**
- **Multisystem inflammation syndrome** in children
  - A person < 21 years of age presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (two or more) organ involvement in the setting of current or recent infection with SARS-CoV-2

Children and COVID-19: 9/24/20
Summary of State-Level Data Provided in this Report

Detail and links to state/local data sources provided in Appendix

Cumulative Number of Child COVID-19 Cases*

- 624,890 total child COVID-19 cases reported, and children represented 10.5% (624,890/5,965,268) of all cases
- Overall rate: 829 cases per 100,000 children in the population

Change in Child COVID-19 Cases, 9/10/20 – 9/24/20

Appendix Table 1: Case Data Available on 9/24/20

Summary data across the 49 states, NYC, DC, PR, and GU that provided age distribution of reported COVID-19 cases*

Child population, 2019	Cumulative total cases (all ages)	Cumulative child cases	Cumulative percent children of total cases	Cases per 100,000 children
75,423,548	5,965,268	624,890	10.5%	828.5

An outbreak of sev epicentre of the SA cohort study

Lucio Verdoni, Angelo Mazza, Annalisa Gerva

Summary

Background The Bergamo provinc coronavirus 2 (SARS-CoV-2) epidem the past month we recorded an outb with Kawasaki-like disease diagnose

Methods All patients diagnosed with to symptomatic presentation before like presentations were managed a Kawasaki disease shock syndrome activation syndrome (MAS) by the previous infection was sought by rev and by serological qualitative test de

Findings Group 1 comprised 19 patie and Feb 17, 2020. Group 2 included Feb 18 and April 20, 2020; eight of incidence (group 1 *vs* group 2, 0·3 v six of ten), KDSS (zero of 19 *vs* five ((three of 19 *vs* eight of ten; all p<0·0

Interpretation In the past month we after the SARS-CoV-2 epidemic beg rate of cardiac involvement, and feat severe form of Kawasaki disease. A SARS-CoV-2 epidemic.

JAMA | Original Investigation

Clinical Characteristics of 58 (Multisystem Syndrome Temp

Elizabeth Whittaker, MD; Alasdair Bamford, MD; Julia Kenny Padmanabhan Ramnarayan, MD; Alain Fraisse, MD; Owen M Michael Carter, MD; Adriana Tremoulet, MD; Chisato Shimizu for the PIMS-TS Study Group and EUCLIDS and PERFORM C

IMPORTANCE In communities with high rates of c emerged of children with an unusual syndrome o

OBJECTIVES To describe the clinical and laborator who met criteria for the pediatric inflammatory m with severe acute respiratory syndrome coronavi these characteristics with other pediatric inflamm

DESIGN, SETTING, AND PARTICIPANTS Case series admitted between March 23 and May 16, 2020, w of inflammation meeting published definitions fo May 22, 2020. Clinical and laboratory characteris review, and were compared with clinical characte (KD) (n = 1132), KD shock syndrome (n = 45), and been admitted to hospitals in Europe and the US

EXPOSURES Signs and symptoms and laboratory definitional criteria for PIMS-TS from the UK, the

MAIN OUTCOMES AND MEASURES Clinical, laborat meeting definitional criteria for PIMS-TS, and com pediatric inflammatory disorders.

RESULTS Fifty-eight children (median age, 9 years [[34%]) were identified who met the criteria for PIM chain reaction tests were positive in 15 of 58 patien were positive in 40 of 46 (87%). In total, 45 of 58 p prior SARS-CoV-2 infection. All children presented including vomiting (26/58 [45%]), abdominal pain Rash was present in 30 of 58 (52%), and conjunctiv Laboratory evaluation was consistent with marked (229 mg/L [IQR, 156-338], assessed in 58 of 58) an in 53 of 58). Of the 58 children, 29 developed shoc dysfunction) and required inotropic support and flu received mechanical ventilation); 13 met the Americ had fever and inflammation without features of sh coronary artery dilatation or aneurysm. Comparison syndrome showed differences in clinical and labora age, 9 years [IQR, 5.7-14] vs 2.7 years [IQR, 1.4-4.7] greater elevation of inflammatory markers such as 156-338] vs 67 mg/L [IQR, 40-150 mg/L] and 193

CONCLUSIONS AND RELEVANCE In this case series PIMS-TS, there was a wide spectrum of presenting ranging from fever and inflammation to myocardia artery aneurysms. The comparison with patients w insights into this syndrome, and suggests this diso inflammatory entities.

JAMA. 2020;324(3):259-269. doi:10.1001/jama.2020.1036 Published online June 8, 2020. Corrected on June 30, 2020

Circulation

ORIGINAL RESEARCH

Acute Heart Inflammatory Context of G

Edit

BACKGROUND: Cardiac injury adults with coronavirus disease syndrome coronavirus 2 (SARS- minimally symptomatic. We re with acute heart failure potent and the multisystem inflammat US Centers for Disease Control

METHODS: Over a 2-month p pandemic in France and Switze biological, therapeutic, and ea admitted to pediatric intensive shock, left ventricular dysfunct

RESULTS: Thirty-five children v Median age at admission was were present in 28%, includin symptoms were prominent. Le in one-third; 80% required ino extracorporeal membrane oxyg suggestive of cytokine storm (i macrophage activation (D-dime (B-type natriuretic peptide) was patients (88%) tested positive chain reaction of nasopharyng intravenous immunoglobulin, one-third. Left ventricular funct discharged from the intensive treated with extracorporeal me weaned.

CONCLUSIONS: Children may decompensation caused by sev infection (multisystem inflamm with immunoglobulin appears ventricular systolic function.

Circulation. 2020;142:429–436. DOI: 10.1161/CI

Multisystem Inflammatory Syndrome in Children in New York State

Elizabeth M. Dufort, M.D., Emilia H. Koumans, M.D., M.P.H., Eric J. Chow, M.D., M.P.H., Elizabeth M. Rosenthal, M.P.H., Alison Muse, M.P.H., Jemma Rowlands, M.P.H., Meredith A. Barranco, M.P.H., Angela M. Maxted, D.V.M., Ph.D., Eli S. Rosenberg, Ph.D., Delia Easton, Ph.D., Tomoko Udo, Ph.D., Jessica Kumar, D.O., Wendy Pulver, M.S., Lou Smith, M.D., Brad Hutton, M.P.H., Debra Blog, M.D., M.P.H., and Howard Zucker, M.D., for the New York State and Centers for Disease Control and Prevention Multisystem Inflammatory Syndrome in Children Investigation Team*

ABSTRACT

BACKGROUND

A multisystem inflammatory syndrome in children (MIS-C) is associated with coronavirus disease 2019. The New York State Department of Health (NYSDOH) established active, statewide surveillance to describe hospitalized patients with the syndrome.

METHODS

Hospitals in New York State reported cases of Kawasaki's disease, toxic shock syndrome, myocarditis, and potential MIS-C in hospitalized patients younger than 21 years of age and sent medical records to the NYSDOH. We carried out descriptive analyses that summarized the clinical presentation, complications, and outcomes of patients who met the NYSDOH case definition for MIS-C between March 1 and May 10, 2020.

RESULTS

As of May 10, 2020, a total of 191 potential cases were reported to the NYSDOH. Of 95 patients with confirmed MIS-C (laboratory-confirmed acute or recent severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection) and 4 with suspected MIS-C (met clinical and epidemiologic criteria), 53 (54%) were male; 31 of 78 (40%) were black, and 31 of 85 (36%) were Hispanic. A total of 31 patients (31%) were 0 to 5 years of age, 42 (42%) were 6 to 12 years of age, and 26 (26%) were 13 to 20 years of age. All presented with subjective fever or chills; 97% had tachycardia, 80% had gastrointestinal symptoms, 60% had rash, 56% had conjunctival injection, and 27% had mucosal changes. Elevated levels of C-reactive protein, D-dimer, and troponin were found in 100%, 91%, and 71% of the patients, respectively; 62% received vasopressor support, 53% had evidence of myocarditis, 80% were admitted to an intensive care unit, and 2 died. The median length of hospital stay was 6 days.

CONCLUSIONS

The emergence of multisystem inflammatory syndrome in children in New York State coincided with widespread SARS-CoV-2 transmission; this hyperinflammatory syndrome with dermatologic, mucocutaneous, and gastrointestinal manifestations was associated with cardiac dysfunction.

From the New York State Department of Health, Albany (E.M.D., A.M., J.R., A.M.M., D.E., J.K., W.P., L.S., B.H., D.B., H.Z.); the Centers for Disease Control and Prevention (CDC) COVID-19 Response (E.H.K., E.J.C.) and the Epidemic Intelligence Service, Center for Surveillance, Epidemiology, and Laboratory Services (E.J.C.), CDC, Atlanta; and the University at Albany School of Public Health, State University of New York, Rensselaer (E.M.R., M.A.B., E.S.R., T.U.). Address reprint requests to Dr. Dufort at the New York State Department of Health, Empire State Plaza, Corning Tower, Rm. 503, Albany, NY 12237, or at elizabeth.dufort@health.ny.gov.

*The members of the investigation team are listed in the Supplementary Appendix, available at NEJM.org.

Drs. Dufort, Koumans, and Chow, Ms. Rosenthal, and Ms. Muse contributed equally to this article.

This article was published on June 29, 2020, at NEJM.org.

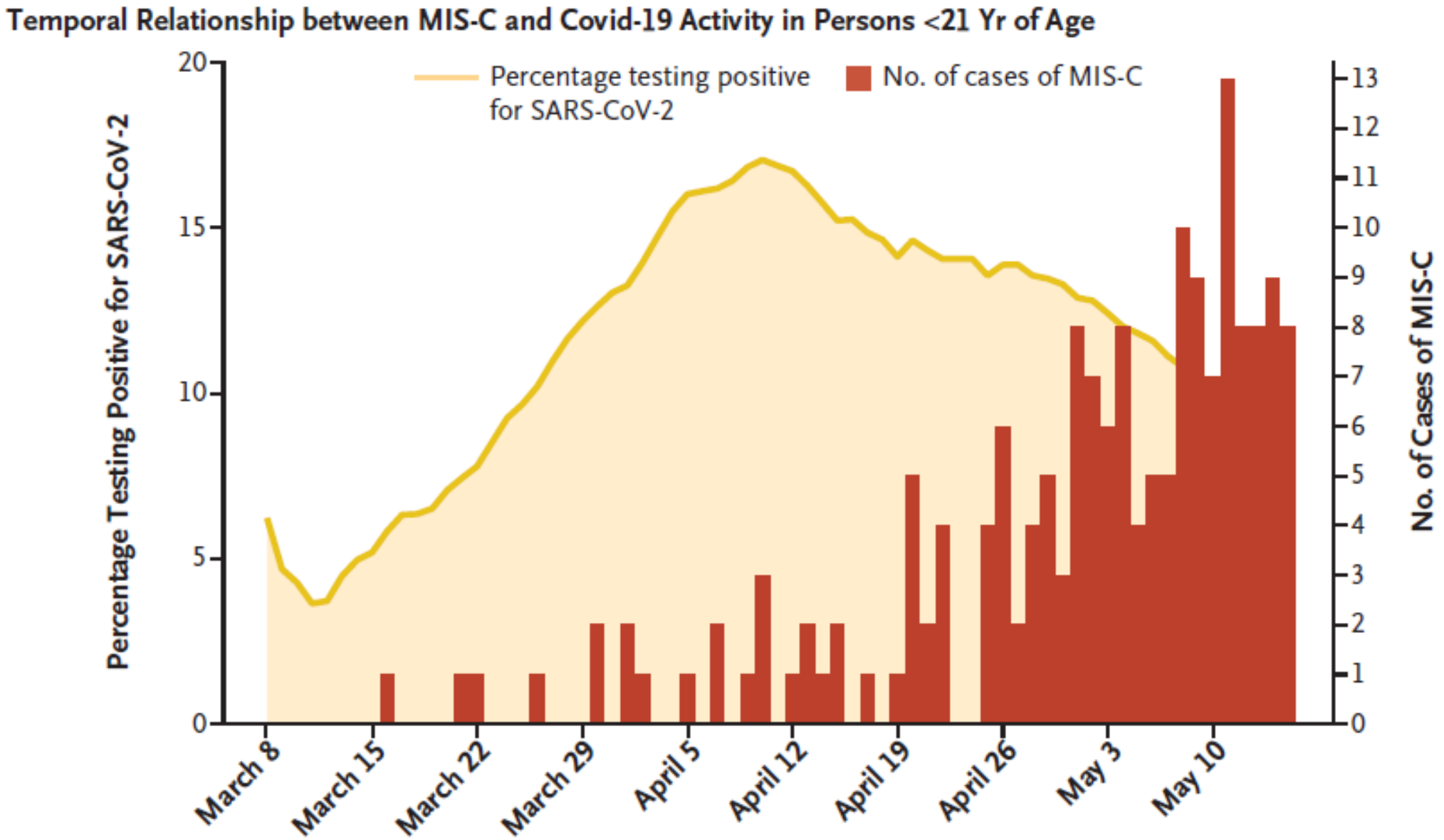
N Engl J Med 2020;383:347-58.
DOI: 10.1056/NEJMoa2021756

Multisystem Inflammatory Syndrome in U.S. Children and Adolescents (Feldstein LR et al NEJM 2020;383:334-46)

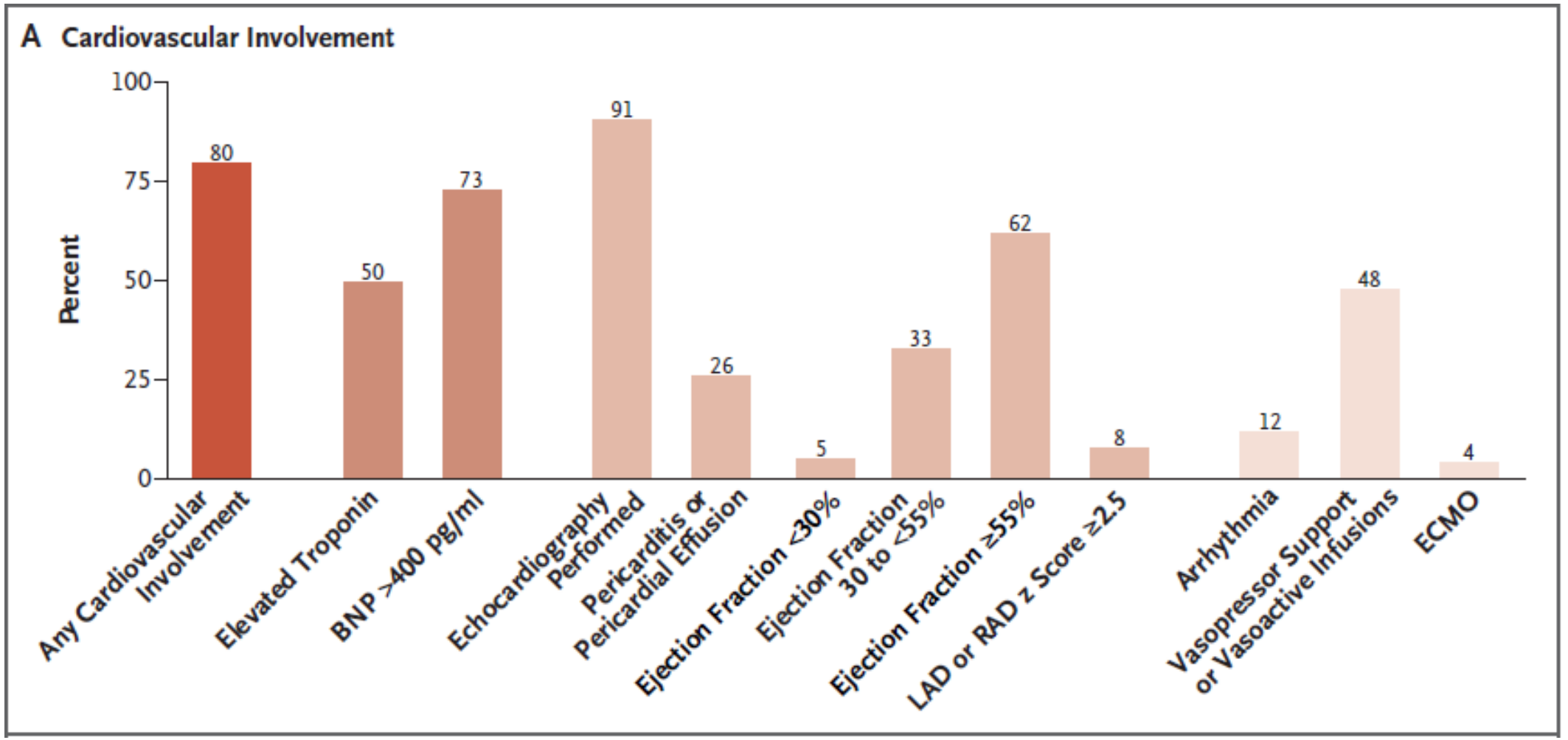
- Conducted **targeted surveillance** for multisystem inflammatory syndrome in children (MIS-C) from **March 15 to May 20**, 2020, in pediatric health centers across the U.S.
- The case definition included **six criteria**
  - Serious illness leading to **hospitalization**,
  - An age of **less than 21 years**,
  - **Fever** that lasted for **at least 24 hours**,
  - Laboratory evidence of **inflammation**,
  - **Multisystem organ** involvement,
  - Evidence of **infection with SARS-CoV-2** based on RT-PCR, antibody testing, or exposure to persons with Covid-19 **in the past month**

Multisystem Inflammatory Syndrome in U.S. Children and Adolescents (Feldstein LR et al NEJM 2020;383:334-46)

- **186 patients** with MIS-C **in 26 states**
- Median age **8.3 years**, 115 patients (**62%**) **male**, 135 (**73%**) **previously healthy**, 131 (70%) positive for SARS-CoV-2 by RT-PCR or antibody testing
- 164 (88%) hospitalized after April 16, 2020
- Organ-system involvement included **G-I system** in 171 patients (92%), **cardiovascular** in 149 (80%), **hematologic** in 142 (76%), **mucocutaneous** in 137 (74%), and **respiratory** in 131 (70%)
- Median duration of hospitalization 7 days (interquartile range, 4 to 10)
- 148 patients (**80%**) received **intensive care**, 37 (20%) received mechanical ventilation, 90 (**48%**) received **vasoactive support**, and 4 (**2%**) **died**



(Feldstein LR et al NEJM 2020;383:334-46)



(Feldstein LR et al NEJM 2020;383:334-46)

Multisystem Inflammatory Syndrome in U.S. Children and Adolescents (Feldstein LR et al NEJM 2020;383:334-46)

- **Coronary artery aneurysms** (z scores ≥2.5) were documented in 15 patients (**8%**), and **Kawasaki's disease–like** features were documented in 74 (**40%**)
- Most patients (171 [**92%**]) had **elevations in at least four bio-markers** indicating inflammation
- The use of immunomodulating therapies was common
  - **Intravenous immune globulin** used in 144 (**77%**),
  - Glucocorticoids in 91 (49%),
  - Interleukin-6 or 1RA inhibitors in 38 (20%)

Conclusions

- Multisystem inflammatory syndrome in children associated with SARS-CoV-2 led to serious and life-threatening illness in previously healthy children and adolescents

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
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October 2, 2020

Case Series of Multisystem Inflammatory Syndrome in Adults Associated with SARS-CoV-2 Infection — United Kingdom and United States, March–August 2020

Sapna Bamrah Morris, MD[1]; Noah G. Schwartz, MD[1,2]; Pragna Patel, MD[1]; Lilian Abbo, MD[3]; Laura Beauchamps, MD[3]; Shuba Balan, MD[3]; Ellen H. Lee, MD[4]; Rachel Paneth-Pollak, MD[4]; Anita Geevarughese, MD[4]; Maura K. Lash, MPH[4]; Marie S. Dorsinville, MPH[4]; Vennus Ballen, MD[4]; Daniel P. Eiras, MD[4]; Christopher Newton-Cheh, MD[5,6]; Emer Smith, MPH[7,8]; Sara Robinson, MPH[7]; Patricia Stogsdill, MD[9]; Sarah Lim, MBBCh[10]; Sharon E. Fox, MD, PhD[11,12]; Gillian Richardson, MPH[13]; Julie Hand, MSPH[13]; Nora T. Oliver, MD[14]; Aaron Kofman, MD[15]; Bobbi Bryant, MPH[1,16]; Zachary Ende, PhD[1,16]; Deblina Datta, MD[1]; Ermias Belay, MD[1]; Shana Godfred-Cato, DO[1]

Prevalence of **Asymptomatic** SARS-CoV-2 Infection

A Narrative Review (Oran DP & Topol EJ. Ann Intern Med 2020; doi:10.7326/M20-3012)

Table. Summary of SARS-CoV-2 Testing Studies

Cohort	Tested, *n*	SARS-CoV-2 Positive, *n* (%)	Positive but Asymptomatic, *n* (%)	Notes*
Iceland residents (6)	13 080	100 (0.8)	43 (43.0)	R
Vo', Italy, residents (7)	5155	102 (2.0)	43 (42.2)	R, L
Diamond Princess cruise ship passengers and crew (8)	3711	712 (19.2)	331 (46.5)	–
Boston homeless shelter occupants (9)	408	147 (36.0)	129 (87.8)	–
New York City obstetric patients (11)	214	33 (15.4)	29 (87.9)	L
U.S.S. *Theodore Roosevelt* aircraft carrier crew (12)	4954	856 (17.3)	~500 (58.4)	E
Japanese citizens evacuated from Wuhan, China (2)	565	13 (2.3)	4 (30.8)	L
Greek citizens evacuated from the United Kingdom, Spain, and Turkey (14)†	783	40 (5.1)	35 (87.5)	L
Charles de Gaulle aircraft carrier crew (13)	1760	1046 (59.4)	~500 (47.8)	E
Los Angeles homeless shelter occupants (10)	178	43 (24.2)	27 (62.8)	–
King County, Washington, nursing facility residents (15)	76	48 (63.2)	3 (6.3)	L
Arkansas, North Carolina, Ohio, and Virginia inmates (16)	4693	3277 (69.8)	3146 (96.0)	–
New Jersey university and hospital employees (17)	829	41 (4.9)	27 (65.9)	–
Indiana residents (18)	4611	78 (1.7)	35 (44.8)	R
Argentine cruise ship passengers and crew (19)	217	128 (59.0)	104 (81.3)	–
San Francisco residents (29)	4160	74 (1.8)	39 (52.7)	–

E = estimated from incomplete source data; L = longitudinal data collected; R = representative sample.
* A dash indicates that the study did not have a representative sample, collected no longitudinal data, and did not require estimation of missing data.
† Clarified via e-mail communication with coauthor.

Prevalence of Asymptomatic SARS-CoV-2 Infection

A Narrative Review (Oran DP & Topol EJ. Ann Intern Med 2020; doi:10.7326/M20-3012)

- Approximately **40% to 45%** of those infected with SARS-CoV-2 will remain **asymptomatic**
  - Suggests that the virus might have greater potential than previously estimated to spread silently and deeply through human populations
- Asymptomatic persons **can transmit** SARS-CoV-2 to others for an extended period, perhaps longer than 14 days
- The **absence** of COVID-19 **symptoms** in persons infected with SARS-CoV-2 might **not necessarily imply an absence of harm**
  - More research is needed to determine the significance of subclinical lung changes visible on computed tomography scans
- The focus of testing programs for SARS-CoV-2 should be substantially broadened to include persons who do not have symptoms of COVID-19

Humoral Immune Response to SARS-CoV-2 in Iceland

(Gudbjartsson DF et al NEJM 2020; Sep 1, doi: 10.1056/NEJMoa2026116)

- Measured antibodies in serum samples from **30,576 persons** in Iceland, using six assays (including two pan-Ig assays), determined that the appropriate measure of seropositivity was a positive result with both pan-Ig assays
  - pan-immunoglobulin (pan-Ig: IgM, IgG, and IgA) antibodies against the **nucleoprotein (N)** (Roche)
  - pan-Ig antibodies against the receptor binding domain (**RBD**) in the S1 subunit of the spike protein (pan-Ig anti–S1-RBD) (Wantai);
  - **IgM and IgG** antibodies against **N** (IgM anti-N and IgG anti-N) (EDI/Eagle);
  - **IgG and IgA** against the **S1 subunit** of the **spike protein** (IgG anti-S1 and IgA anti-S1) (Euroimmun)
- Of the 1797 persons who had recovered from **SARS-CoV-2 infection**,
  - 1107 of the 1215 who were tested (**91.1%**) were **seropositive**;
  - antiviral **antibody titers** assayed by two pan-Ig assays **increased** during 2 months after diagnosis by qPCR and **remained on a plateau** for the remainder of the study
- Of 4222 **quarantined persons**, **2.3%** were seropositive
- Of 23452 persons with **unknown exposure**, **0.3%** were positive

Table 1. Prevalence of SARS-CoV-2 Antibodies by Sample Collection as Measured by Two Pan-Ig Antibody Assays.*

Sample Collection	No. of Persons Tested	Both Pan-Ig Antibody Assays Positive		Either Pan-Ig Antibody Assay Positive	
		No. of Persons	Frequency % (95% CI)	No. of Persons	Frequency % (95% CI)
2017	472	0	0.0 (0.0–0.4)	1	0.2 (0.0–0.9)
Early 2020	470	0	0.0 (0.0–0.4)	4	0.9 (0.3–2.0)
Health care†	18,609	39	0.2 (0.2–0.3)	119	0.6 (0.5–0.8)
Reykjavik†	4,843	21	0.4 (0.3–0.6)	38	0.8 (0.6–1.1)
Vestmannaeyjar†	663	3	0.5 (0.1–1.2)	7	1.1 (0.5–2.0)
Quarantine	4,222	97	2.3 (1.9–2.8)	131	3.1 (2.6–3.7)
Hospitalized	48	45	93.8 (84.6–98.4)	47	97.9 (91.1–99.9)
Recovered	1,215	1,107	91.1 (89.4–92.6)	1,156	95.1 (93.8–96.3)

* The pan-Ig antibodies are anti-N and anti–S1-RBD. The latest available sample was used.
† Sampling restricted to persons who had not tested qPCR-positive and who had not been quarantined.

(Gudbjartsson DF et al NEJM 2020; Sep 1, doi: 10.1056/NEJMoa2026116)

Humoral Immune Response to SARS-CoV-2 in Iceland

(Gudbjartsson DF et al NEJM 2020; Sep 1, doi: 10.1056/NEJMoa2026116)

- Estimate that
  - **0.9%** of Icelanders were **infected with SARS-CoV-2**
  - the infection was **fatal in 0.3%**
  - **56%** of all SARS-CoV-2 infections in Iceland had been **diagnosed with qPCR**,
  - **14%** had occurred in **quarantined persons** who had **not been tested with qPCR** (or who had not received a positive result, if tested),
  - **30%** had occurred in persons **outside quarantine** and **not tested with qPCR**

Conclusions

- Results indicate that antiviral **antibodies against SARS-CoV-2 did not decline within 4 months after diagnosis**
- Estimate that the **risk of death** from infection was **0.3%**, **44%** of **persons infected** with SARS-CoV-2 in Iceland were **not diagnosed by qPCR**

Screening or not (廣篩與否)

- 目的
  - 找出”漏網之魚“
  - 避免”廣泛散播””造成失控”
- “沒有感染源的社區個案”
  - ”造成失控”的緣由

- **零漏接 VS. 零失分**

Clinical manifestations of SARS-CoV-2 infection

- **Asymptomatic infection**
  - 40-45%
- Mild respiratory diseases
  - 81%
  - 45-49%
- Moderate-severe respiratory diseases
  - 14%
  - 7.7-8.4%
    - Pneumonia, requiring oxygen supplementation
- Critical diseases
  - 5%
  - 2.8-3.0%
    - Respiratory failure
    - Acute respiratory distress syndrome (ARDS)
    - Multiple organs failure
- **Extrapulmonary manifestations**
- Sequelae

Genomewide Association Study of Severe Covid-19 with Respiratory Failure

RESULTS

We detected cross-replicating associations with rs11385942 at locus 3p21.31 and with rs657152 at locus 9q34.2, which were significant at the genomewide level ($P<5\times10^{-8}$) in the meta-analysis of the two case–control panels (odds ratio, 1.77; 95% confidence interval [CI], 1.48 to 2.11; $P=1.15\times10^{-10}$; and odds ratio, 1.32; 95% CI, 1.20 to 1.47; $P=4.95\times10^{-8}$, respectively). At locus 3p21.31, the association signal spanned the genes *SLC6A20*, *LZTFL1*, *CCR9*, *FYCO1*, *CXCR6* and *XCR1*. The association signal at locus 9q34.2 coincided with the *ABO* blood group locus; in this cohort, a blood-group–specific analysis showed a higher risk in blood group A than in other blood groups (odds ratio, 1.45; 95% CI, 1.20 to 1.75; $P=1.48\times10^{-4}$) and a protective effect in blood group O as compared with other blood groups (odds ratio, 0.65; 95% CI, 0.53 to 0.79; $P=1.06\times10^{-5}$).

CONCLUSIONS

We identified a 3p21.31 gene cluster as a genetic susceptibility locus in patients with Covid-19 with respiratory failure and confirmed a potential involvement of the ABO blood-group system. (Funded by Stein Erik Hagen and others.)

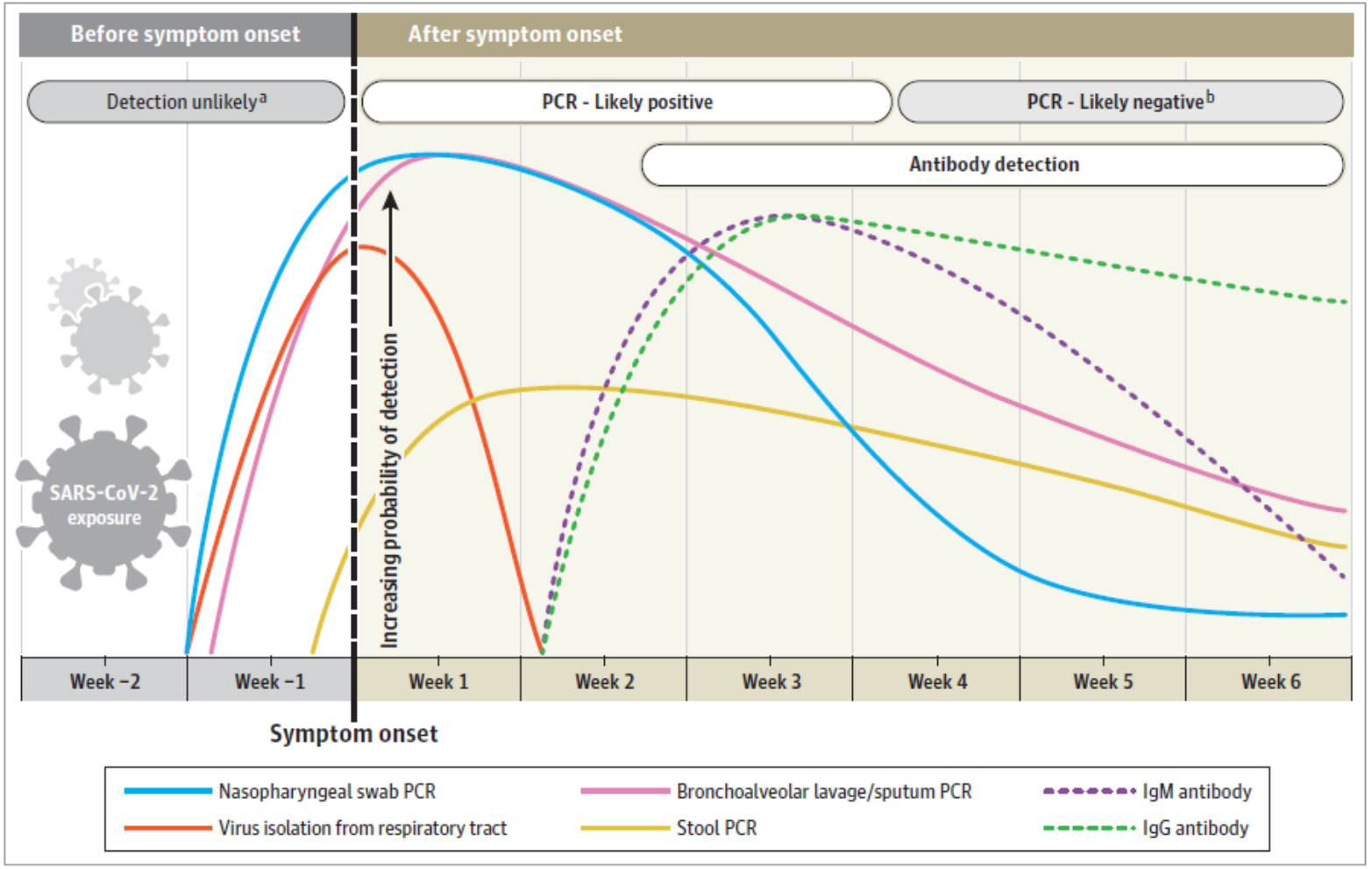
(NEJM 2020;383: 1522-34)

Diagnosis of SARS-CoV-2 infection

- **Clinical diagnosis**
  - Symptoms & signs, lab data, image studies
- **Epidemiologic diagnosis**
  - Seasonality, local epidemics
  - Travel, Occupation, Cluster, Contact
- **Laboratory diagnosis**
  - **PCR-based**
  - Virus culture
  - Serology: not timely

Interpreting Diagnostic Tests for SARS-CoV-2 (Sethuraman N et al JAMA 2020;May 6)

Figure. Estimated Variation Over Time in Diagnostic Tests for Detection of SARS-CoV-2 Infection Relative to Symptom Onset



Estimated time intervals and rates of viral detection are based on data from several published reports. Because of variability in values among studies, estimated time intervals should be considered approximations and the probability of detection of SARS-CoV-2 infection is presented qualitatively. SARS-CoV-2 indicates severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction.

[a] Detection only occurs if patients are followed up proactively from the time of exposure.

[b] More likely to register a negative than a positive result by PCR of a nasopharyngeal swab.

Laboratory Diagnosis of COVID-19: Current Issues and Challenges (Tang YW et al JCM 2020;58 (6):e00512-20)

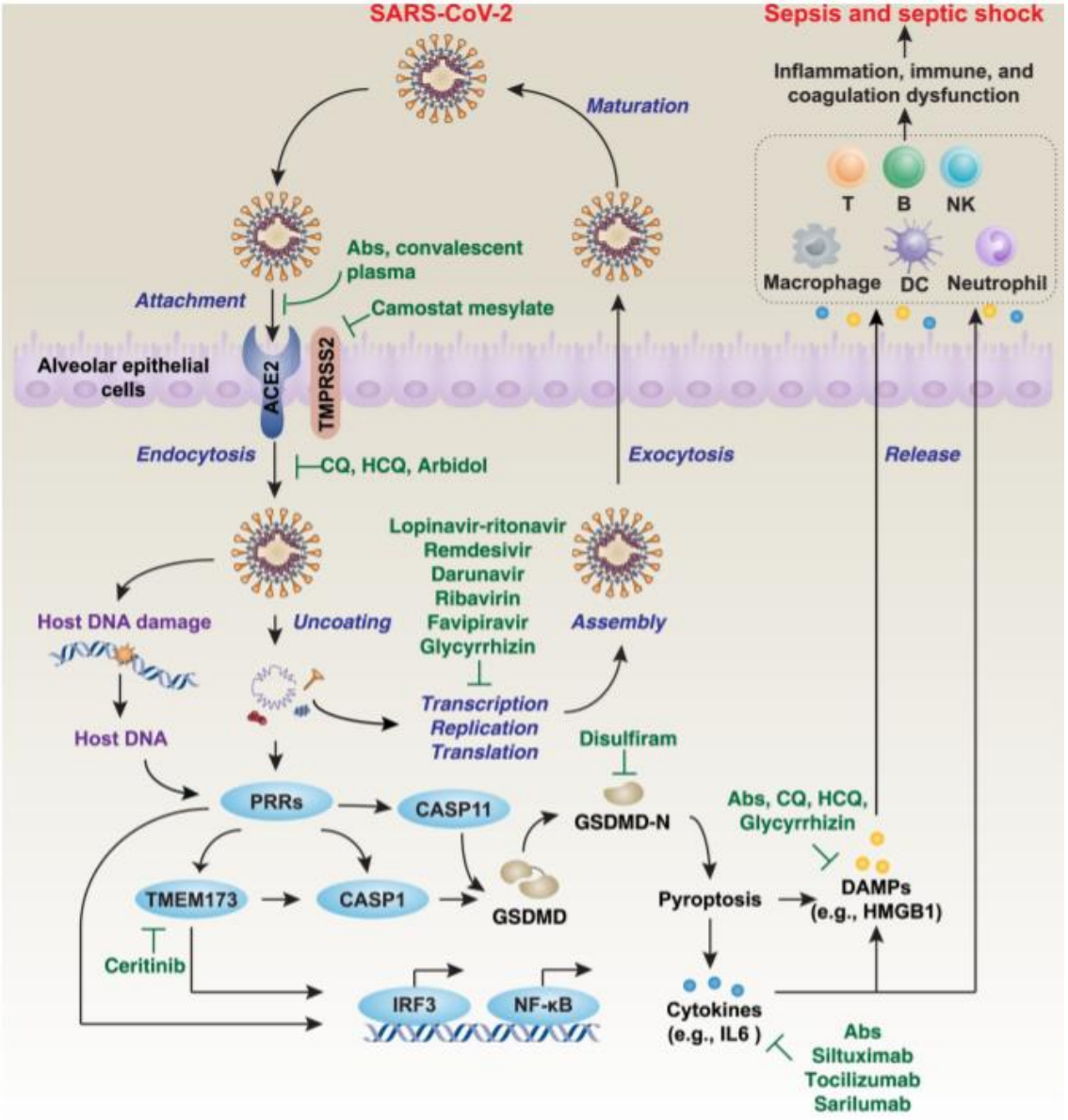
- In the **pre-analytical stage**, collecting the proper respiratory tract specimen at the **right time from the right anatomic site** is essential for a prompt and accurate molecular diagnosis of COVID-19
- In the **analytic stage**, **real-time RT-PCR** assays remain the molecular test of choice, while **antibody-based techniques** are being introduced as supplemental tools
- In the **post-analytical stage**, testing results should be **carefully interpreted** using both molecular and serological findings
- Finally, random-access, integrated devices available at the **point of care** with scalable capacities will facilitate the rapid and accurate diagnosis and monitoring of SARS-CoV-2 infections

SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients (Zou L et al NEJM 2020)

- Monitored SARS-CoV-2 viral loads in upper respiratory specimens obtained from 18 patients (9 men and 9 women; median age, 59 years; range, 26 to 76) in Zhuhai, Guangdong, China
- A total of 72 nasal swabs (sampled from the mid-turbinate and nasopharynx) and 72 throat swabs were analyzed
- Higher viral loads detected soon after symptom onset, with higher viral loads detected in the nose than in the throat
- **Viral load** detected in the asymptomatic patient was similar to that in the symptomatic patients
- How SARS-CoV-2 viral load correlates with culturable virus needs to be determined

Management of COVID-19

- Symptomatic treatment
- Supportive care
- Antiviral agents
  - Remdesivir
  - Others
- Adjunctive therapy
  - Antibody administration
    - Convalescent plasma
    - Synthetized antibody: polyclonal , momoclonal
  - Immunomodulation
    - IVIG
    - Steroid
  - Cytokine inhibitors



(Tang D et al PLoS Pathog 2020;16 (5): e1008536)

ıe effectively inhibit the
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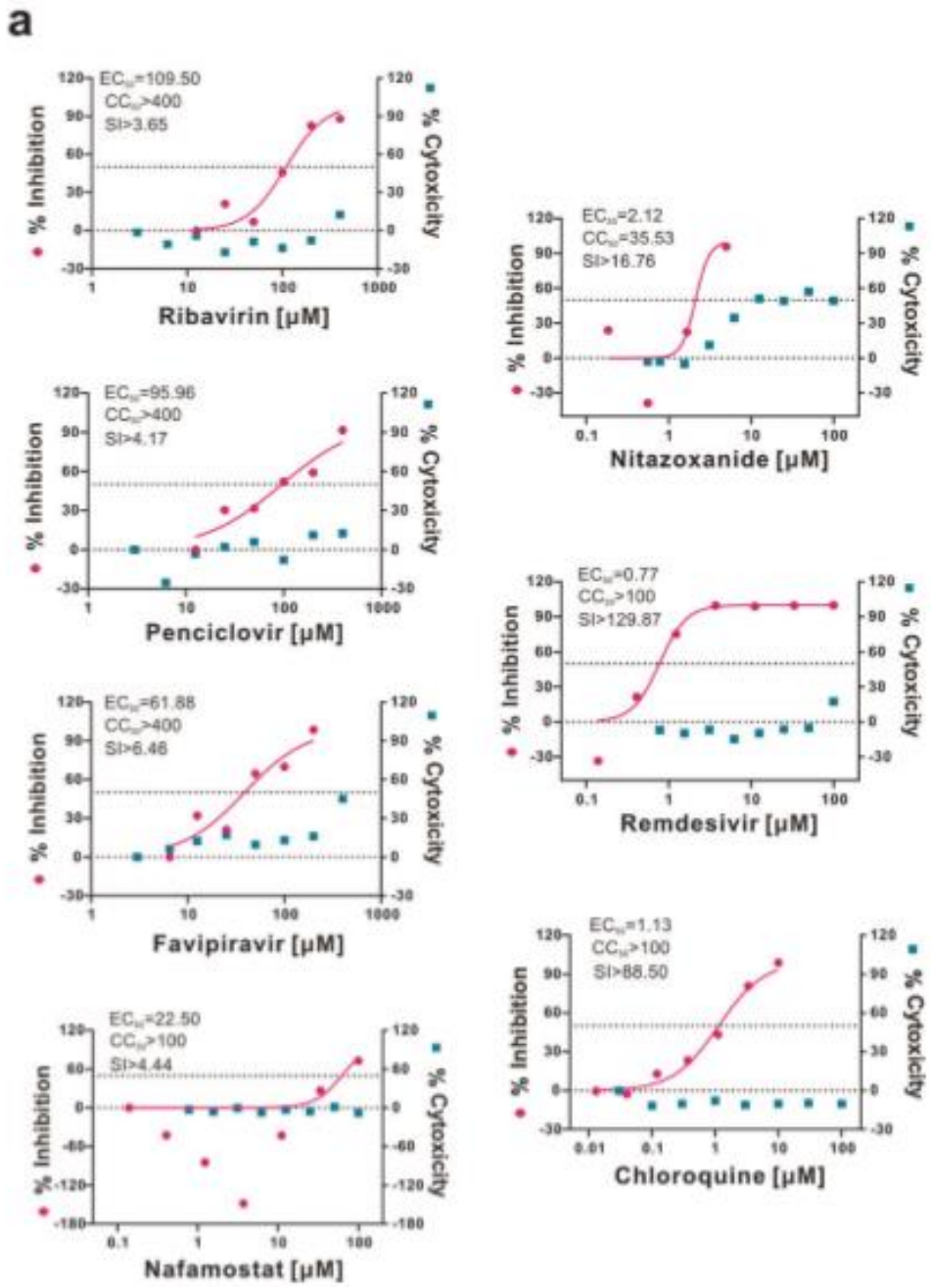
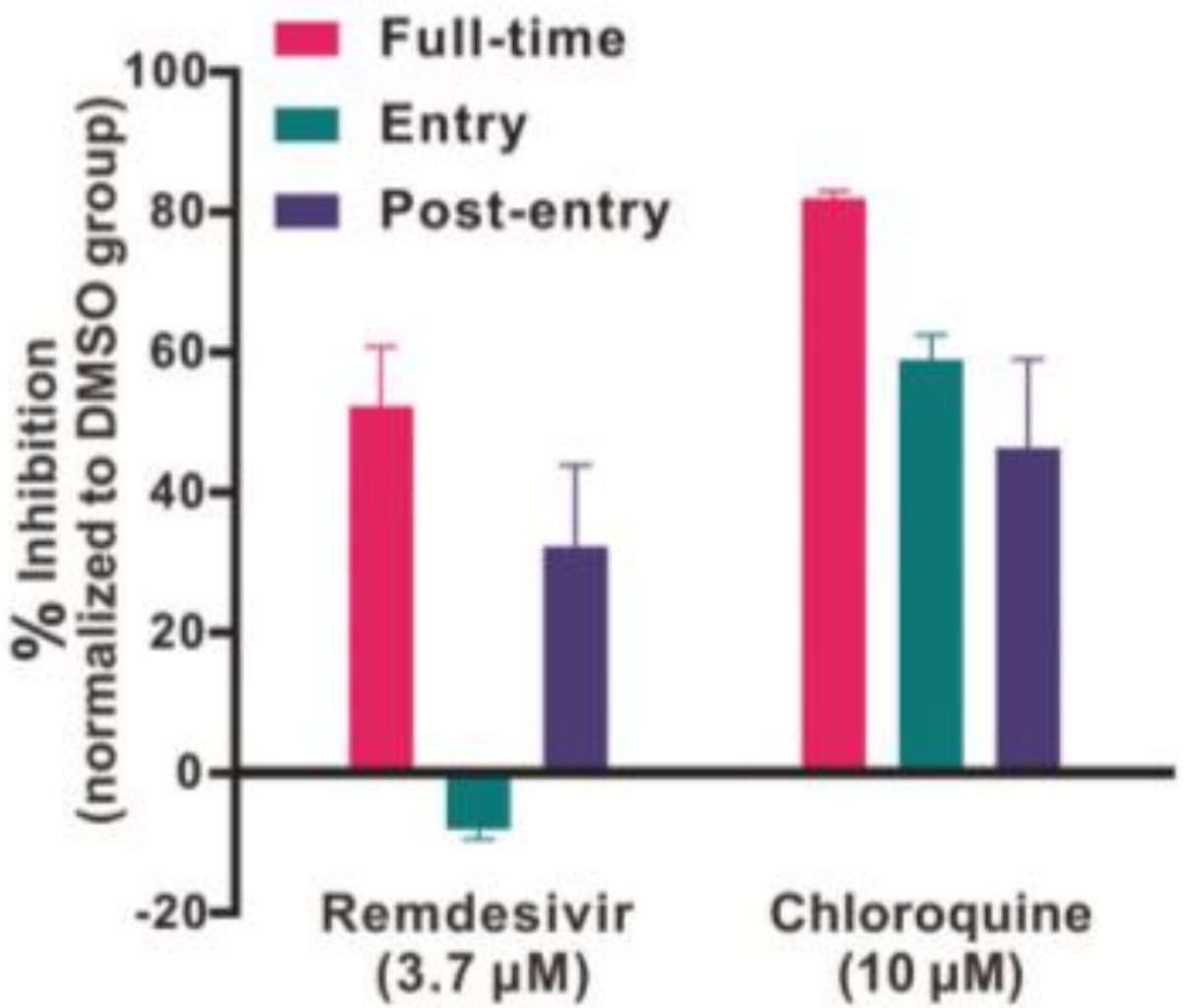




Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro (Cell Res 2020)

- **Remdesivir and chloroquine** highly effective in the control of 2019-nCoV infection in vitro
- Since these compounds have been used in human patients with a safety track record and shown to be effective against various ailments, we suggest that they should be assessed in human patients suffering from the novel coronavirus disease.

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19 (Boulware DR et al NEJM 2020; May online)

- A double-blind, randomized, placebo-controlled trial across the United States and parts of Canada testing hydroxychloroquine as postexposure prophylaxis
- Enrolled adults who had **household or occupational exposure** to someone with confirmed Covid-19 at a **distance of less than 6 ft for more than 10 minutes** while wearing **neither a face mask nor an eye shield** (**high-risk exposure**) or while wearing a face mask but no eye shield (moderate-risk exposure)
- **Within 4 days after exposure**, randomly assigned participants to receive either placebo or hydroxychloroquine (800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 additional days)
- The primary outcome the **incidence of either laboratory-confirmed Covid-19 or illness compatible with Covid-19 within 14 days**

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19 (Boulware DR et al NEJM 2020; May online)

- Enrolled 821 asymptomatic participants
- Overall, **87.6%** of the participants (719 of 821) reported a **high-risk exposure** to a confirmed Covid-19 contact
- Incidence of **new illness** compatible with Covid-19 **not differ significantly** between participants receiving hydroxychloroquine (49 of 414 [**11.8%**]) and those receiving placebo (58 of 407 [**14.3%**])
  - the absolute difference −2.4 percentage points (95% confidence interval, −7.0 to 2.2; P = 0.35)
- **Side effects** more common with hydroxychloroquine than with placebo (**40.1%** vs. **16.8%**), but no serious adverse reactions were reported

Table 2. Outcomes of Hydroxychloroquine Therapy for Postexposure Prophylaxis against Covid-19.*

Outcome	Hydroxychloroquine (N=414)	Placebo (N=407)	P Value
	number (percent)		
Confirmed or probable Covid-19	49 (11.8)	58 (14.3)	0.35
Laboratory-confirmed diagnosis	11 (2.7)	9 (2.2)	0.82
Symptoms compatible with Covid-19	48 (11.6)	55 (13.5)	0.46
All new symptoms	57 (13.8)	59 (14.5)	0.84
Any hospitalization	1 (0.2)	1 (0.2)	0.99
Death	0	0	—

* Symptoms were adjudicated by four infectious disease physicians, who were unaware of the trial-group assignments, in accordance with U.S. Council of State and Territorial Epidemiologists case definition of probable Covid-19 after an epidemiologic link with a close contact.[15] (Descriptions of the symptom complex are provided in the Supplementary Appendix.) The median number of new symptoms reported in the hydroxychloroquine group was 4 (interquartile range, 2 to 6), as compared with 3 (interquartile range, 2 to 5) in the placebo group.

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19 (Boulware DR et al NEJM 2020; May online)

Conclusions

- After high-risk or moderate-risk exposure to Covid-19, **hydroxychloroquine** did **not prevent illness** compatible with Covid-19 or confirmed infection when used as **postexposure prophylaxis within 4 days after exposure**

Remdesivir for the Treatment of Covid-19 — Preliminary Report (Beigel AJ et al NEJM 2020; May online)

- A double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults **hospitalized** with Covid-19 with **evidence of lower respiratory tract involvement**
- Patients were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to **10 days**
- The **primary outcome the time to recovery**, defined by either discharge from the hospital or hospitalization for infection control purposes only

Remdesivir for the Treatment of Covid-19 — Preliminary Report (Beigel AJ et al NEJM 2020; May online)

- A total of 1063 patients underwent randomization
- The **data and safety monitoring board** recommended **early unblinding** of the results on the basis of **findings from an analysis** that showed **shortened time to recovery in the remdesivir group**
- Preliminary results from the 1059 patients (538, remdesivir; 521, placebo) indicated that those who received remdesivir had a median recovery time of **11 days** (95% [CI], 9 to 12), as compared with **15 days** (95% CI, 13 to 19) in those who received placebo (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; P<0.001)
- Kaplan-Meier estimates of **mortality** by 14 days, **7.1%** with remdesivir and **11.9%** with placebo (**hazard ratio for death, 0.70**; 95% CI, 0.47 to 1.04)
- Serious adverse events reported for 114 of the 541 patients in the remdesivir group (21.1%) and 141 of the 522 patients in the placebo group (27.0%)

Remdesivir for the Treatment of Covid-19 — Preliminary Report (Beigel AJ et al NEJM 2020; May online)

Conclusions

- Remdesivir was superior to placebo in **shortening the time to recovery** in adults hospitalized with Covid-19 and evidence of lower respiratory tract infection

Effect of Dexamethasone in Hospitalized Patients with COVID-19 — Preliminary Report (RECOVERY Collaborative Group NEJM 2020)

- A **randomized, controlled**, **open-label**, adaptive, platform trial comparing a range of possible treatments with usual care in patients hospitalized with COVID-19
- Preliminary results for the comparison of **dexamethasone 6 mg** given once daily for **up to ten days** vs. usual care alone
- The primary outcome was **28-day mortality**
- **2104 patients** randomly allocated to receive **dexamethasone** were compared with 4321 patients concurrently allocated to usual care
- Overall, 454 (**21.6%**) patients allocated **dexamethasone** and 1065 (**24.6%**) patients allocated usual care **died within 28 days** (age adjusted rate ratio [RR] 0.83; 95% CI: 0.74 to 0.92; P<0.001)

Effect of Dexamethasone in Hospitalized Patients with COVID-19 — Preliminary Report (RECOVERY Collaborative Group NEJM 2020)

- The proportional and absolute mortality rate reductions varied significantly depending on level of **respiratory support** at randomization (test for trend p<0.001)
- Dexamethasone **reduced deaths**
  - by **one-third** in patients receiving **invasive mechanical ventilation** (29.0% vs. 40.7%, RR 0.65 [95% CI 0.51 to 0.82]; p<0.001)
  - by **one-fifth** in patients receiving **oxygen** without invasive mechanical ventilation (21.5% vs. 25.0%, RR 0.80 [95% CI 0.70 to 0.92]; p=0.002)
- But dexamethasone did not reduce mortality in patients not receiving respiratory support at randomization (17.0% vs. 13.2%, RR 1.22 [95% CI 0.93 to 1.61]; p=0.14)
- **Conclusions**:
  - In patients hospitalized with COVID-19, dexamethasone **reduced 28-day mortality** among those **receiving invasive mechanical ventilation or oxygen at randomization**, but not among patients not receiving respiratory support

台灣新型冠狀病毒（SARS-CoV-2）感染臨床處置暫行指引第八版

針對 SARS-CoV-2 之抗病毒與其他治療

- 根據最新隨機對照臨床試驗結果，若經主治醫師評估藥物治療的效益與風險，並充 分告知後，可考慮對嚴重肺炎以上程度（未使用吸氧治療下的 SpO2≦94%、需使用吸氧 治療、機械式呼吸器或 ECMO）之確診個案給予下列藥物治療。
  - Remdesivir
    - 成人劑量：200mg IVD D1，100mg IVD D2-10
    - 孩童劑量：5mg/kg IVD D1，2.5mg/kg IVD D2-10
    - 治療時已使用呼吸器或 ECMO 之病人療程最長 10 天，未使用者為 5 天，可視 臨床狀況延長至 10 天
  - Dexamethasone
    - 成人劑量：dexamethasone 6mg 每日一次，靜脈注射或口服，至多使用十天
    - 孕婦劑量：prednisolone 40mg 口服每日一次，或 hydrocortisone 80mg 靜脈注 射每日兩次，至多使用十天

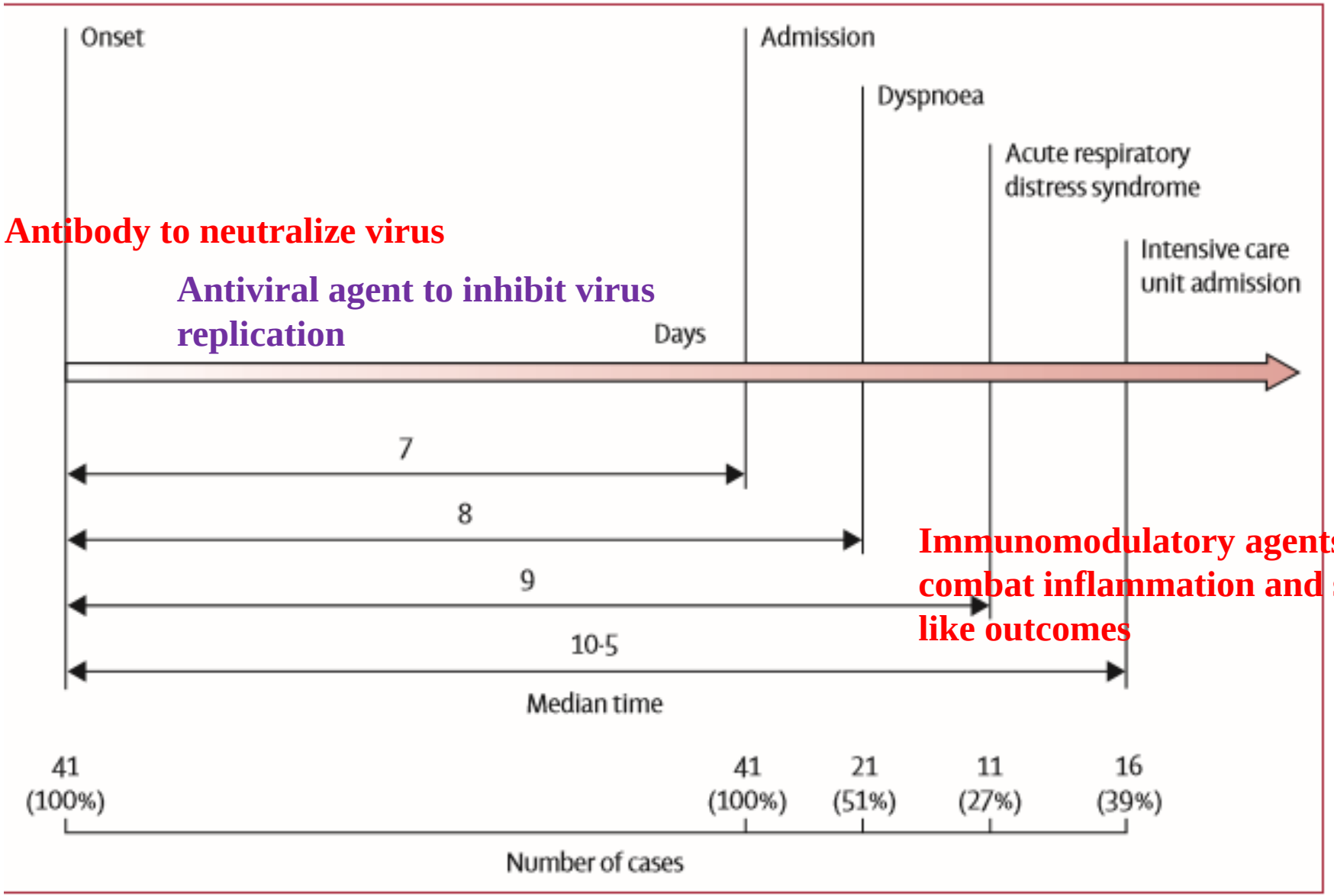


Figure 2: **Timeline of 2019-nCoV cases after onset of illness**

(Huang C et al Lancet 2020; 395: 497–506)

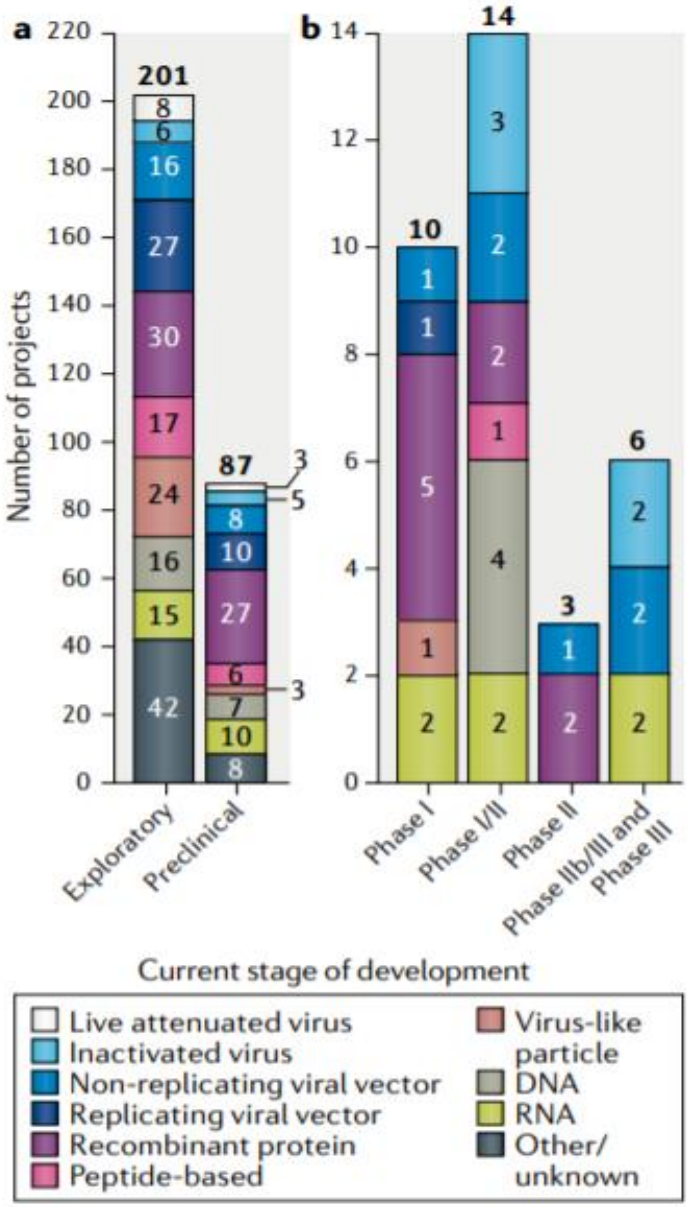
Evolution of the COVID-19 **vaccine** development landscape

(Le TT et al Nat Rev Drug Dis 2020;19:667-8)

- As of 3 September 2020, the global COVID-19 vaccine R&D landscape includes **321 vaccine candidates**
- **33 vaccine candidates** are in **clinical trials**, with plans to enroll more than 280,000 participants from at least 470 sites in 34 different countries

Evolution of the COVID-19 vaccine development landscape

(Le TT et al Nat Rev Drug Dis 2020;19:667-8)



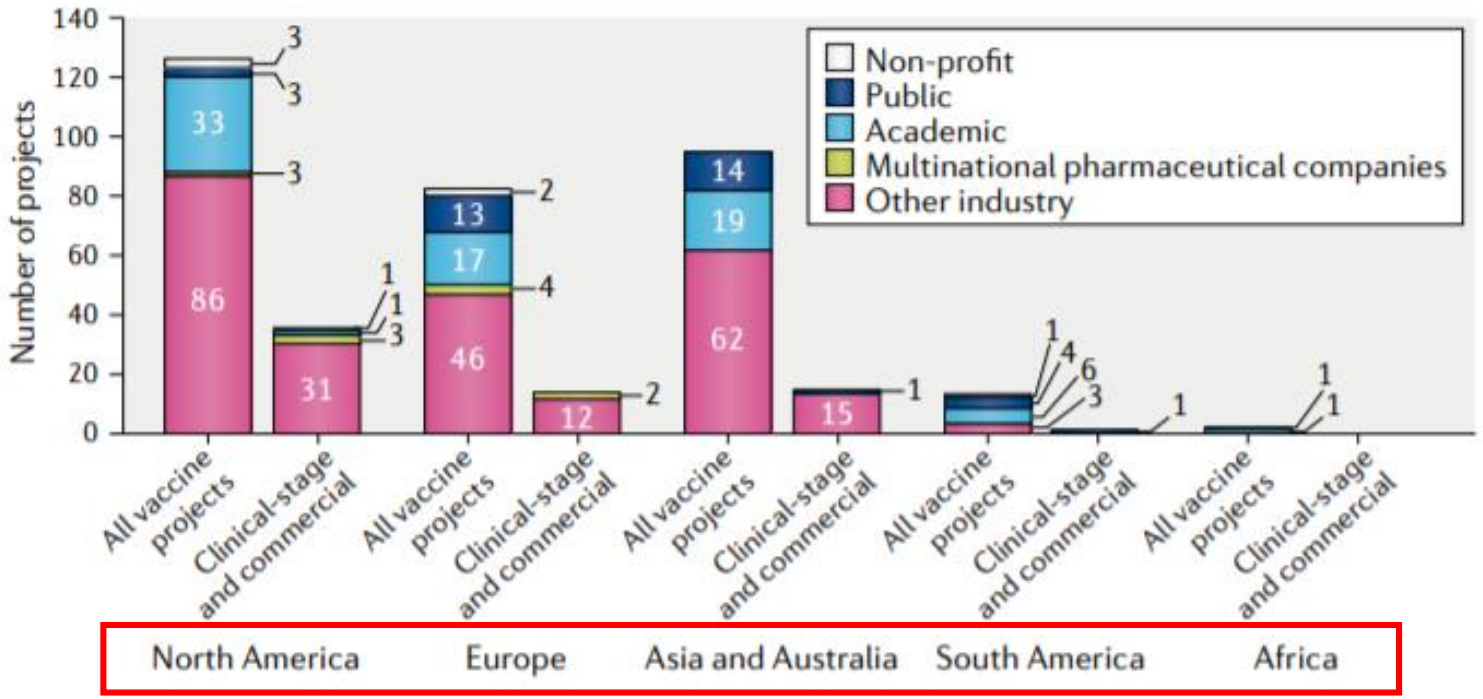
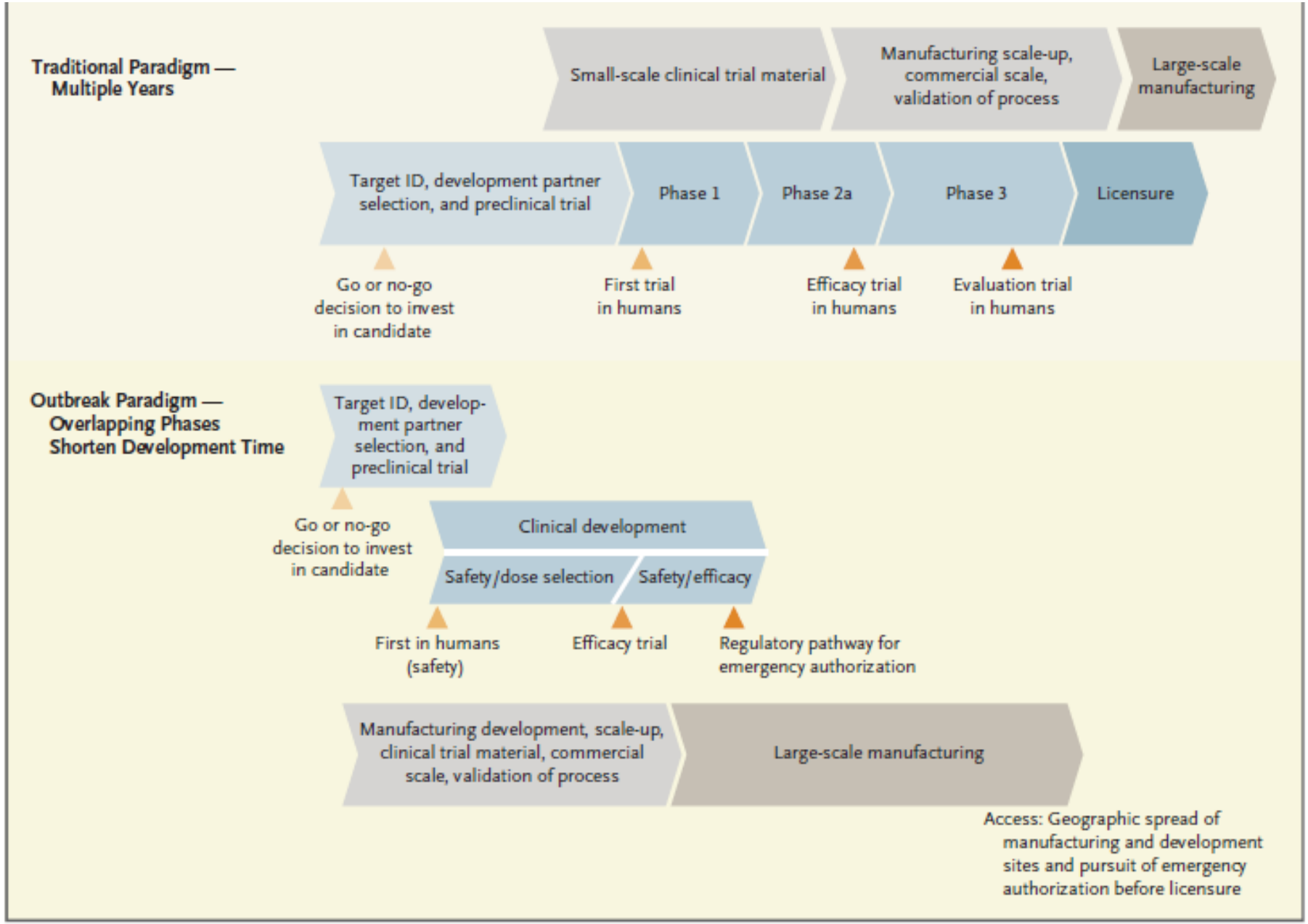


Fig. 2 | **Profile of COVID-19 vaccine developers by type and geographical location.** The 'other industry' category includes companies other than those in the 'multinational pharmaceutical company' category, which are defined as having revenues of more than US$10 billion per year. For partnerships, the location is that of the lead developer. See Supplementary Box 1 for details of the data set and analysis.



Difference between Traditional Vaccine Development and Development Using a Pandemic Paradigm.

(Lurie N et al NEJM 2020;382:1969-73)

Vaccine Platforms, Their Attributes, and the Status of Vaccine Candidates.*

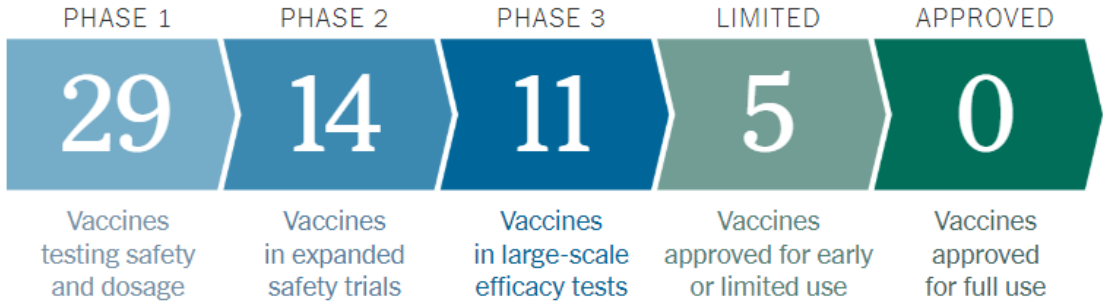
Technology	Attributes				Candidates in Preclinical Development	Candidates in Human Trials
	Single Dose	Licensed Platform	Speed	Current Scale		
DNA	No	No	Fast	Medium	Takis/Applied DNA Sciences/Evvivax Zydus Cadila	Inovio Pharmaceuticals, Phase 1 (NCT04336410)
Inactivated	No	Yes	Medium	Medium to high		Sinovac, Phase 1 (NCT04352608) Inactivated Beijing Institute of Biological Sciences/ Wuhan Institute of Biological Sciences, Phase 1 (ChiCTR2000031809)
Live attenuated	Yes	Yes	Slow	High	Codagenix/Serum Institute of India	
Nonreplicating vector	Yes	No	Medium	High	GeoVax/BravoVax Janssen Pharmaceutical Companies Altimmune Greffex Vaxart ExpreS2ion	CanSino Biologics, Phases 1 and 2 (ChiCTR2000030906 and ChiCTR2000031781) University of Oxford/ AstraZeneca, Phase 1/2 (NCT04324606) Shenzhen Geno-Immune Medical Institute, Phase 1/2 (NCT04276896)
Protein subunit	No	Yes	Medium to fast	High	WRAIR/U.S. Army Medical Research Institute of Infectious Diseases Clover Biopharmaceuticals Inc/GSK Vaxil Bio AJ Vaccines Genrex/EpiVax/University of Georgia Sanofi Pasteur Novavax Heat Biologics/University of Miami University of Queensland/GSK/ Baylor College of Medicine iBio/CC-Pharming	
Replicating viral vector	Yes	Yes	Medium	High	Zydus Cadila Institut Pasteur/Themis Tonix Pharma/Southern Research	
RNA	No	No	Fast	Low to medium	Fudan University/Shanghai JiaoTong University/RNACure Biopharma China CDC/Tongji University/Stermina Arcturus/Duke-NUS Imperial College London Curevac	Moderna/NIAID (NCT04283461) BioNTech/Pfizer, Phase 1/2 (NCT04368728)
Uncertain					University of Pittsburgh University of Saskatchewan ImmunoPrecise MIGAL Galilee Research Institute Doherty Institute Tulane University	

* Attributes refer to general attributes of the platform, and assessments are not intended as inferences about a particular candidate. NIAID denotes National Institute of Allergy and Infectious Diseases, and WRAIR Walter Reed Army Institute of Research.

(Lurie N et al NEJM 2020;382:1969-73)

Coronavirus Vaccine Tracker

By Jonathan Corum, Sui-Lee Wee and Carl Zimmer Updated October 3, 2020



Vaccines typically require years of research and testing before reaching the clinic, but scientists are racing to produce a safe and effective coronavirus vaccine by next year. Researchers are testing **44 vaccines** in clinical trials on humans, and at least 91 preclinical vaccines are under active investigation in animals.

PRECLINICAL TESTING : Scientists test a new vaccine on cells and then give it to **animals** such as mice or monkeys to see if it produces an immune response. We have confirmed 91 preclinical vaccines in active development.

PHASE 1 SAFETY TRIALS : Scientists give the vaccine to a **small number of people** to test safety and dosage as well as to confirm that it stimulates the immune system.

PHASE 2 EXPANDED TRIALS : Scientists give the vaccine to **hundreds of people** split into groups, such as children and the elderly, to see if the vaccine acts differently in them. These trials further test the vaccine's safety and ability to stimulate the immune system.

PHASE 3 EFFICACY TRIALS : Scientists give the vaccine to **thousands of people** and wait to see how many become infected, compared with volunteers who received a placebo. These trials can determine if the vaccine protects against the coronavirus. In June, the F.D.A. said that a coronavirus vaccine would have to protect at least 50% of vaccinated people to be considered effective. In addition, Phase 3 trials are large enough to reveal evidence of relatively rare side effects that might be missed in earlier studies.

EARLY OR LIMITED APPROVAL : China and Russia have approved vaccines without waiting for the results of Phase 3 trials. Experts say the rushed process has serious risks.

APPROVAL : Regulators in each country review the trial results and decide whether to approve the vaccine or not. During a pandemic, a vaccine may receive emergency use authorization before getting formal approval. Once a vaccine is licensed, researchers continue to monitor people who receive it to make sure it's safe and effective.

COMBINED PHASES : One way to accelerate vaccine development is to combine phases. Some coronavirus vaccines are now in Phase 1/2 trials, for example, in which they are tested for the first time on hundreds of people. (Note that our tracker would count a combined Phase 1/2 trial as both Phase 1 and Phase 2.)

PHASE 1

高端疫苗生物製劑股份有限公司
MEDIGEN VACCINE BIOLOGICS CORP

DYNAVAX
INNOVATING IMMUNOLOGY

Taiwan-based vaccine maker **Medigen** is making a vaccine made of a combination of spike proteins and an adjuvant from **Dynavax**. They have registered a Phase 1 trial set to start in September.

Updated Aug. 31

PHASE 1

Taiwan-based vaccine manufacturer **Adimmune** got permission to launch a Phase 1 trial on August 20. The vaccine contains the RBD section of the virus's spike protein.

Updated Aug. 20


Thank you for your attention!!