

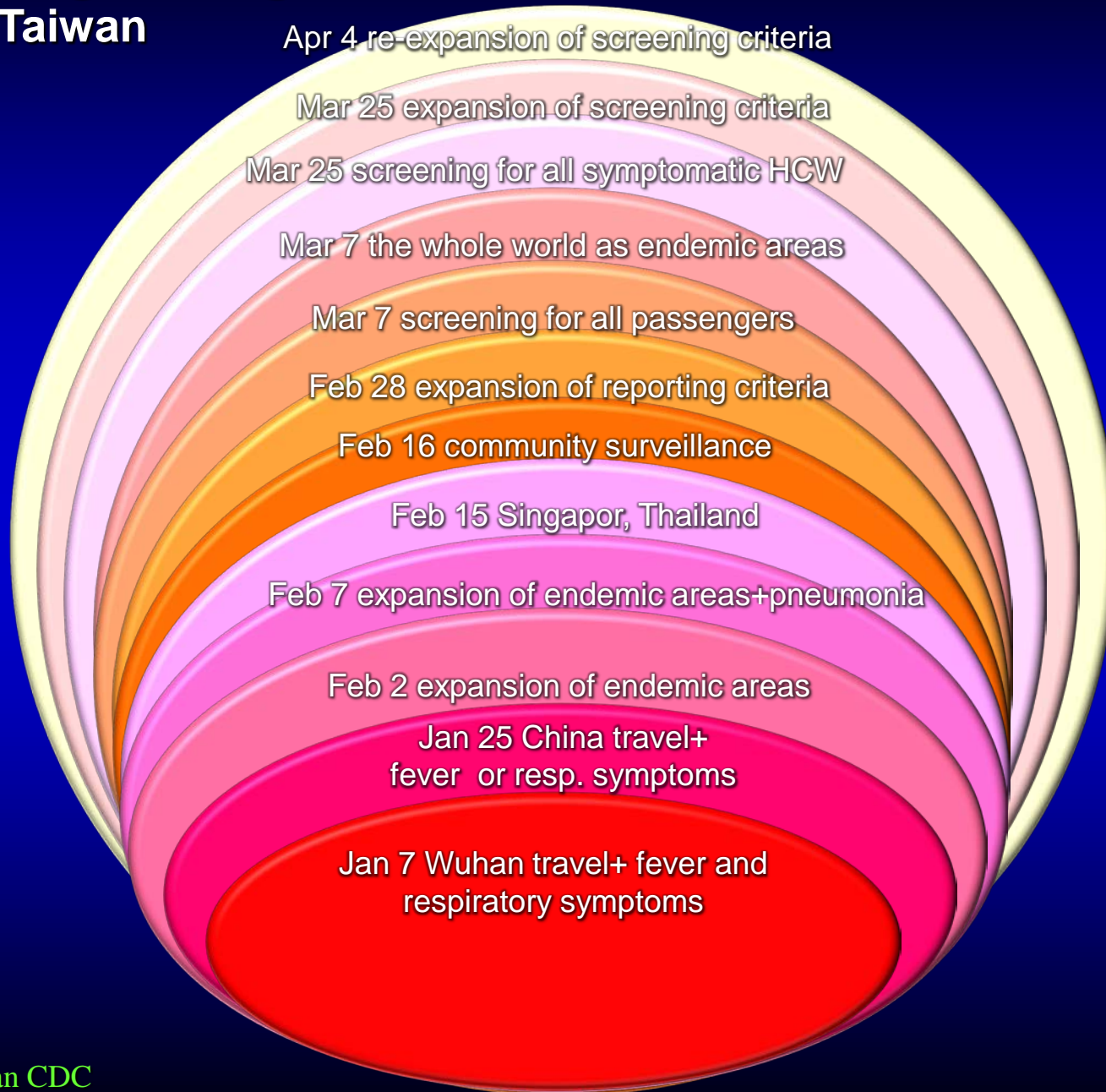
新冠病毒  
的  
預防與疫苗

李秉穎

台大兒童醫院

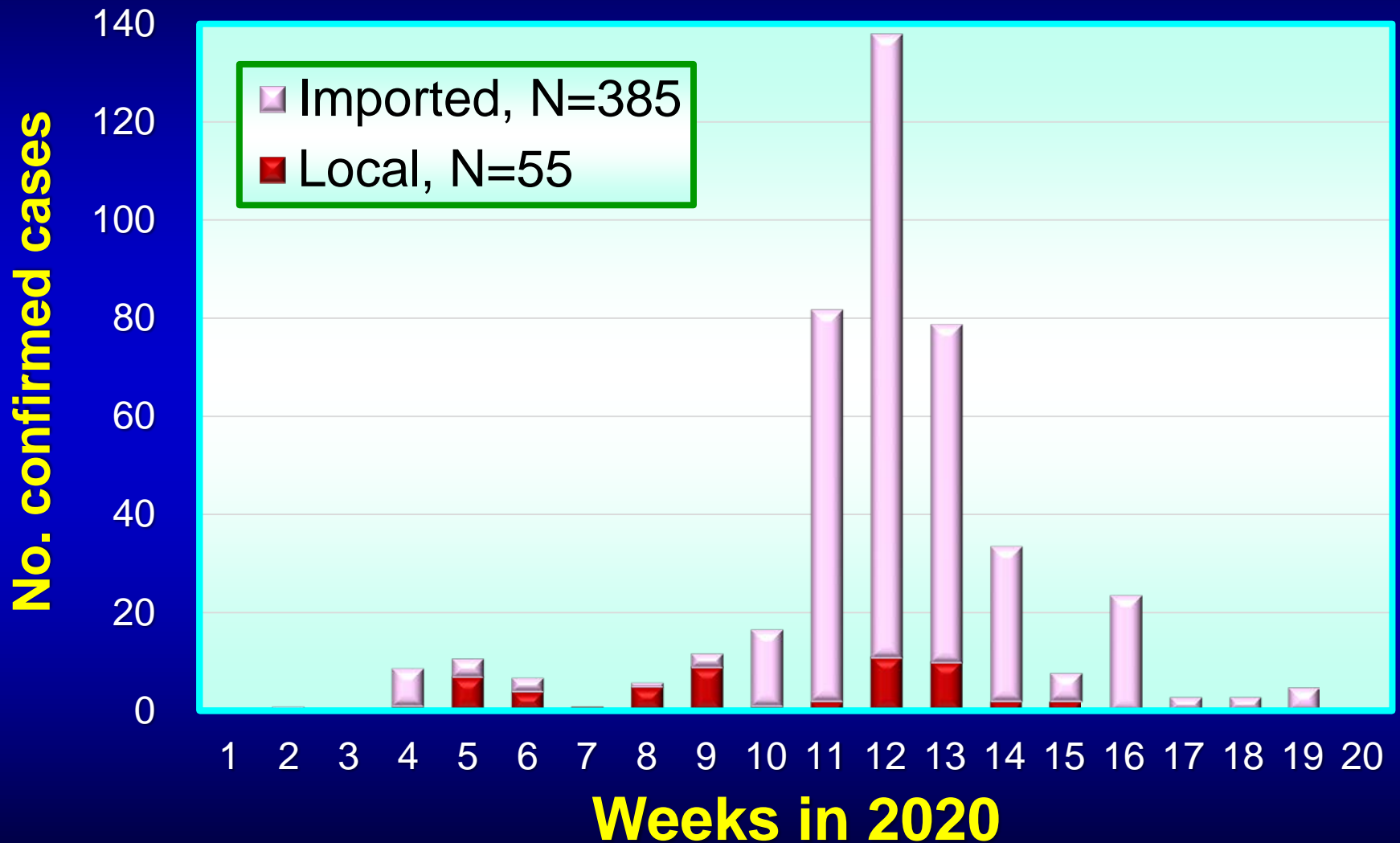
# Evolving strategies for the control of COVID-19

2020, Taiwan



# Confirmed cases of COVID-19 in Taiwan

N=440, Taiwan CDC, as of May 11, 2020



# Community-acquired COVID-19 without identifiable source of infection

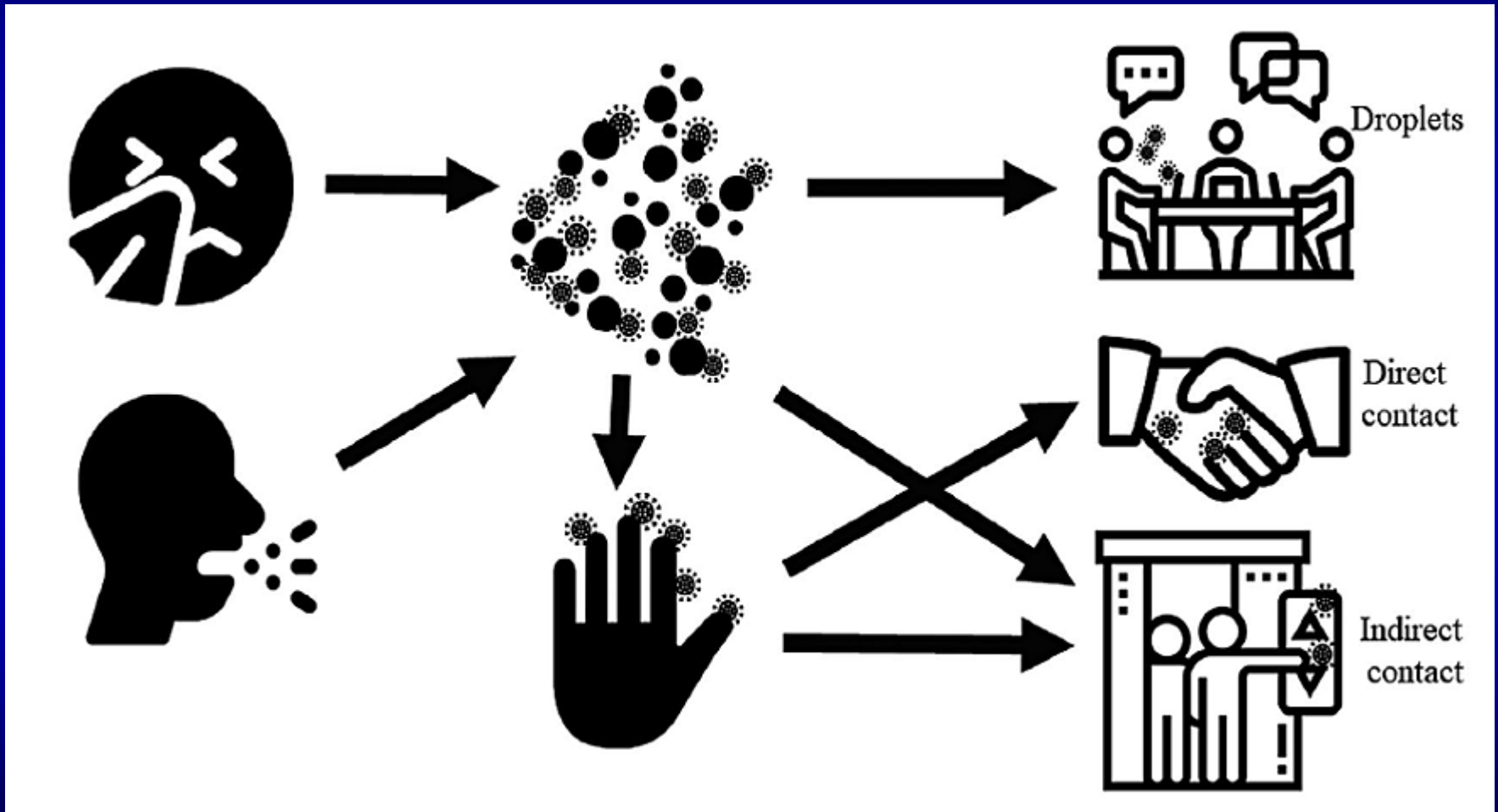
N=10, 2020, Taiwan

- Case 24, 67 yrs, ♀ → 2 family members → 0
- Case 27, 80+ yrs, ♂ → 5 family members → 0
- Case 34, 50+ yrs, ♀ → 8 nosocomial infections → 0
- Case 100, 20+ yrs, ♀ → 0
- Case 134, 30+ yrs, ♀ → 0
- Case 156, 20+ yrs, ♀ → 0
- Case 268, 50 yrs, ♂ → 0
- Case 332, 22 yrs, ♂ → 1 roommate
- Case 336, 50+ yrs, ♀ → 0
- Case 379, 30+ yrs, ♀ → 0

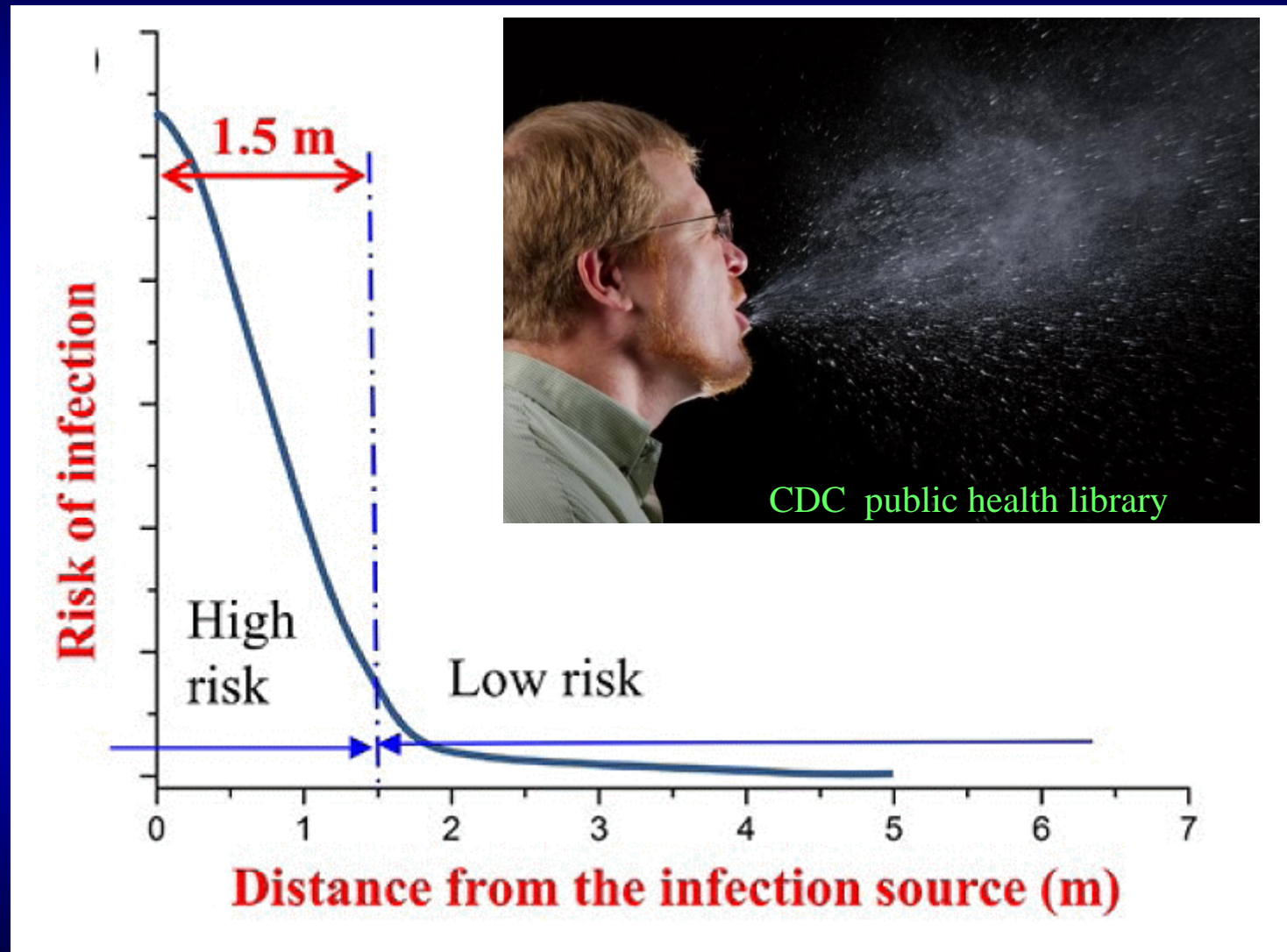
Secondary infection: 16



# Transmission routes of COVID-19



# Droplet transmission



CDC public health library

# Recommendation on medical mask




JAMA, Apr 21, 2020

- Used only by individuals **who have symptoms of respiratory infection.**
- Should also be worn by **health care workers**, by individuals who are taking care of or are in close contact with people who have respiratory infections, or otherwise as directed by a doctor.
- **Should not be worn by healthy individuals.**

Face masks should only be used by

- ☑ Individuals with symptoms of respiratory infection such as coughing, sneezing, and sometimes fever
- ☑ Health care workers
- ☑ Persons taking care of or in close contact with someone with a respiratory infection

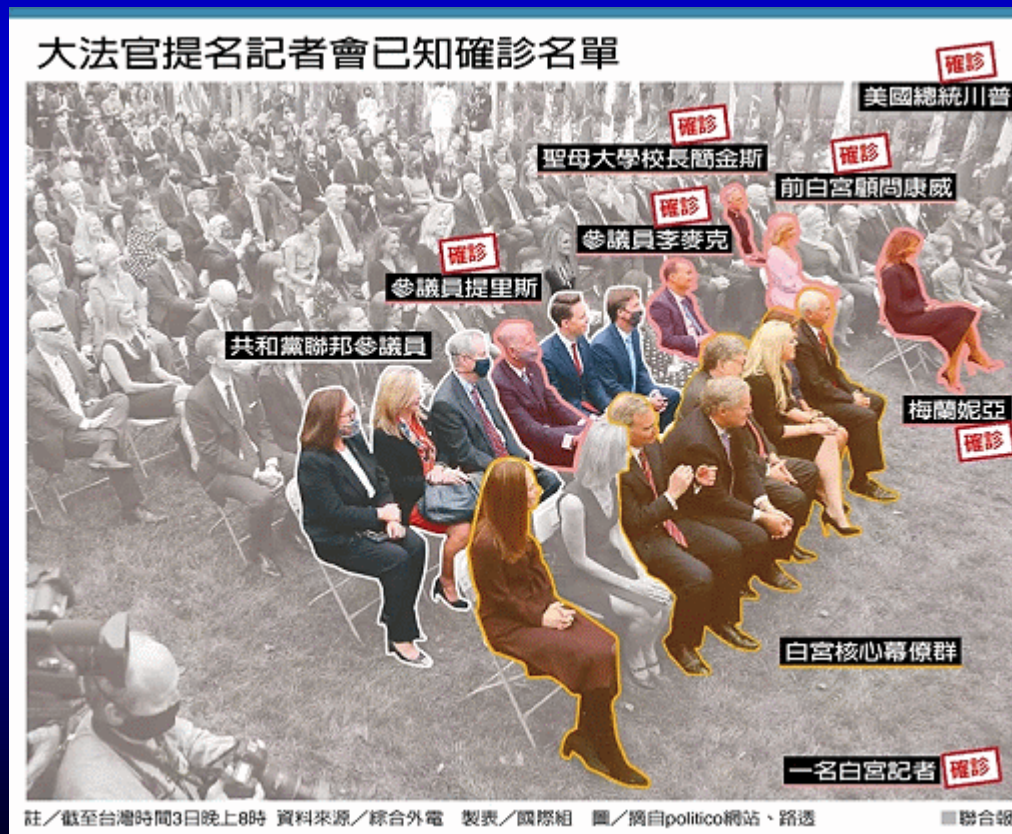
How do I use a face mask?

- 1 Wash hands for at least 20 seconds prior to putting on a face mask. 
- 2 Place face mask over nose and mouth. Ensure a tight seal with no gaps and secure elastics or straps. 
- 3 Avoid touching the front of the face mask. If you do, wash hands for at least 20 seconds.
- 4 Remove the face mask without touching the front. Discard in a closed bin. 
- 5 Wash hands again for at least 20 seconds.



# 川普住院辦公 大法官提名記者會爆群聚感染 聯合報，2020.10.4

- 川普伉儷和貼身幕僚希克斯相繼宣布確診新冠肺炎迄今，至少有十一位曾與他們密切接觸的人士採檢，也驗出陽性反應。「今日美國報」報導，川普九月廿六日宣布提名巴瑞特為聯邦最高法院大法官的場合上，確診十一人中，至少有六人出席。



# 社交距離建議

2020，美國疾病管制  
及預防中心

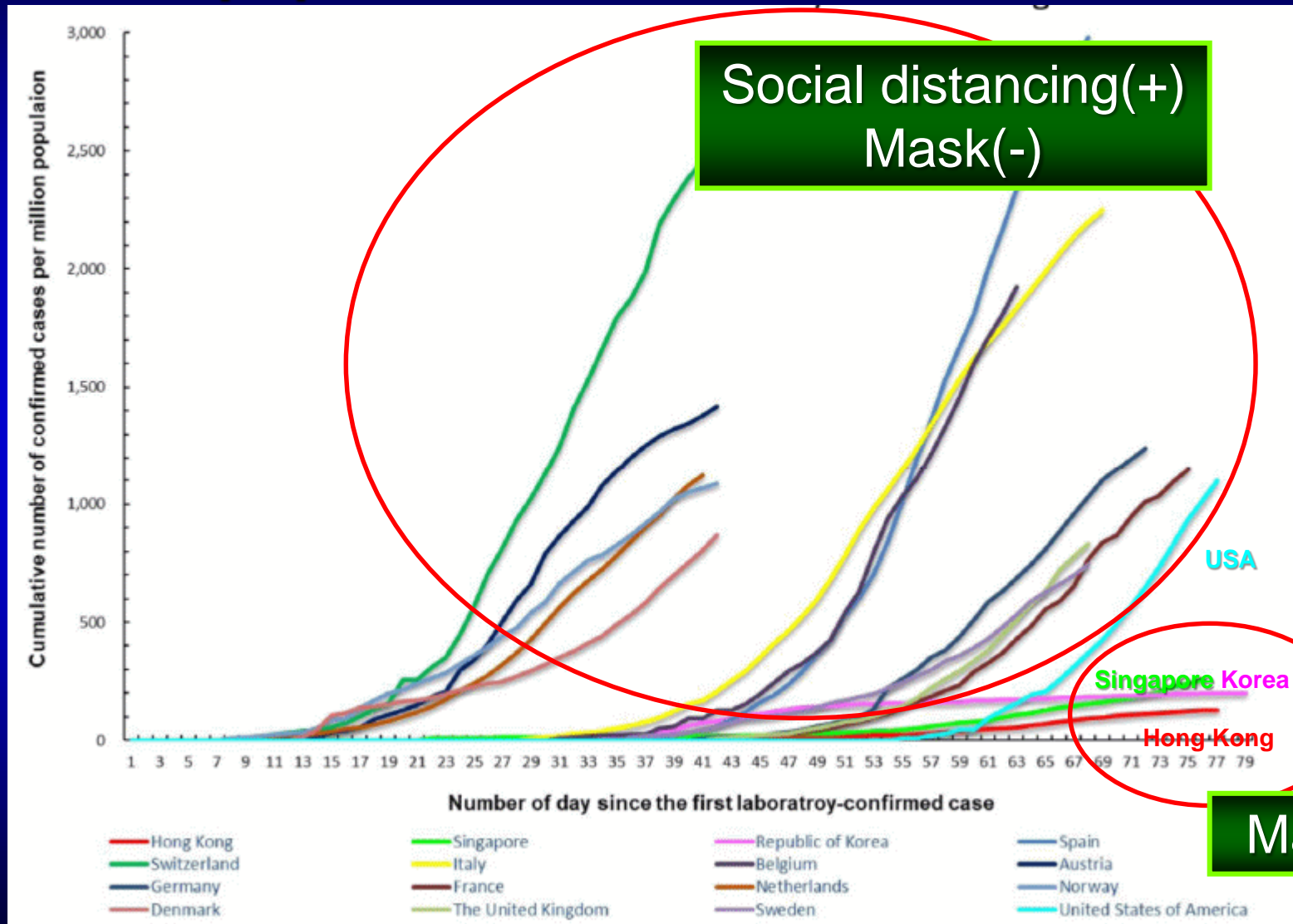


- **社交距離 (物理距離):**

- 無論戶內或戶外，與非同居者**保持6英尺 (大約兩個手臂長度)距離**

- **要訣：**出門前知道相關規定、選擇交通方式、出外減少接觸、選擇安全社交活動、聚會保持距離、活動時保持距離

# Cumulative number of confirmed COVID-19 per million population 2020



Social distancing(+)  
Mask(-)

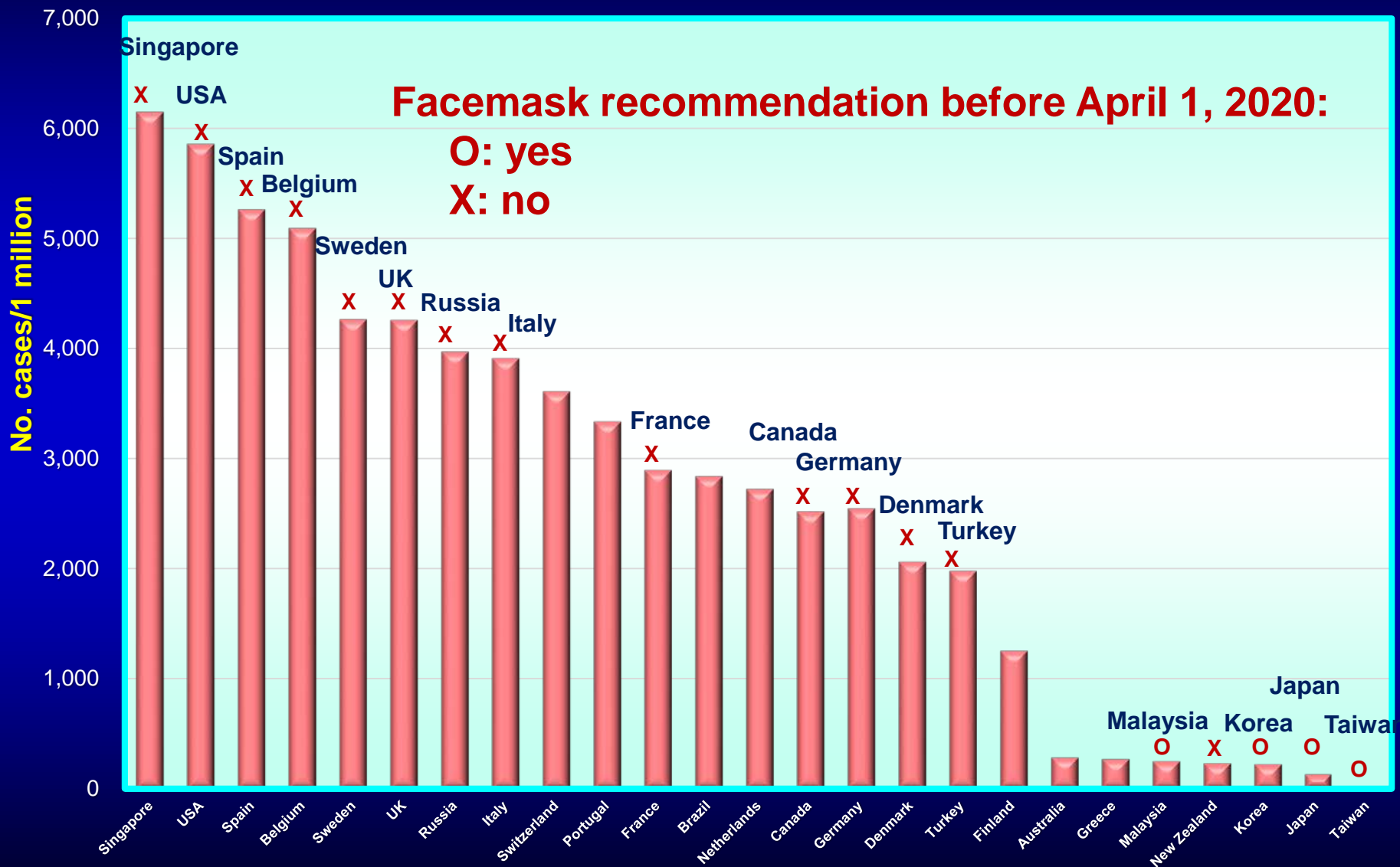
Mask(+)





# Incidence of COVID-19

As of June 6, 2020, Taiwan CDC



# 預防冠狀病毒感染：SARS, MERS, COVID-19

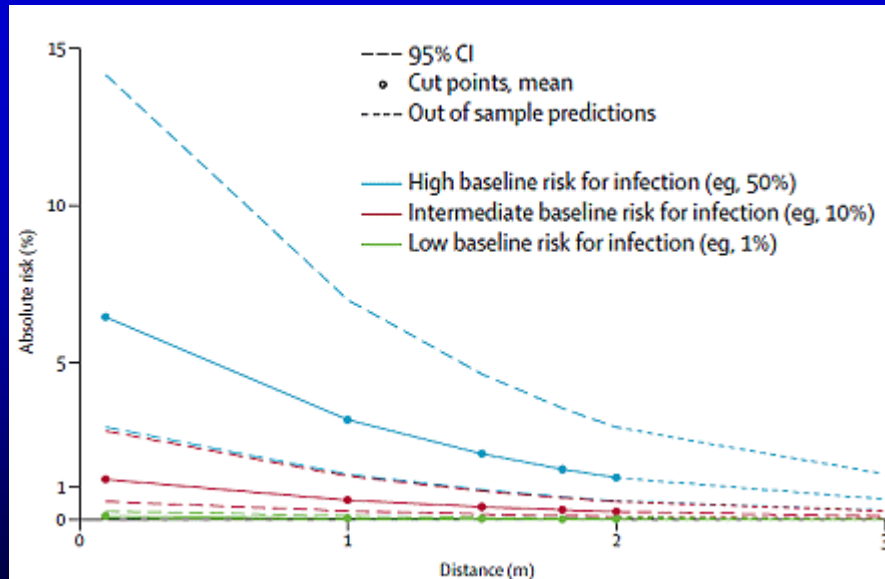
N=172，綜合分析，2020，WHO

- 感染率：

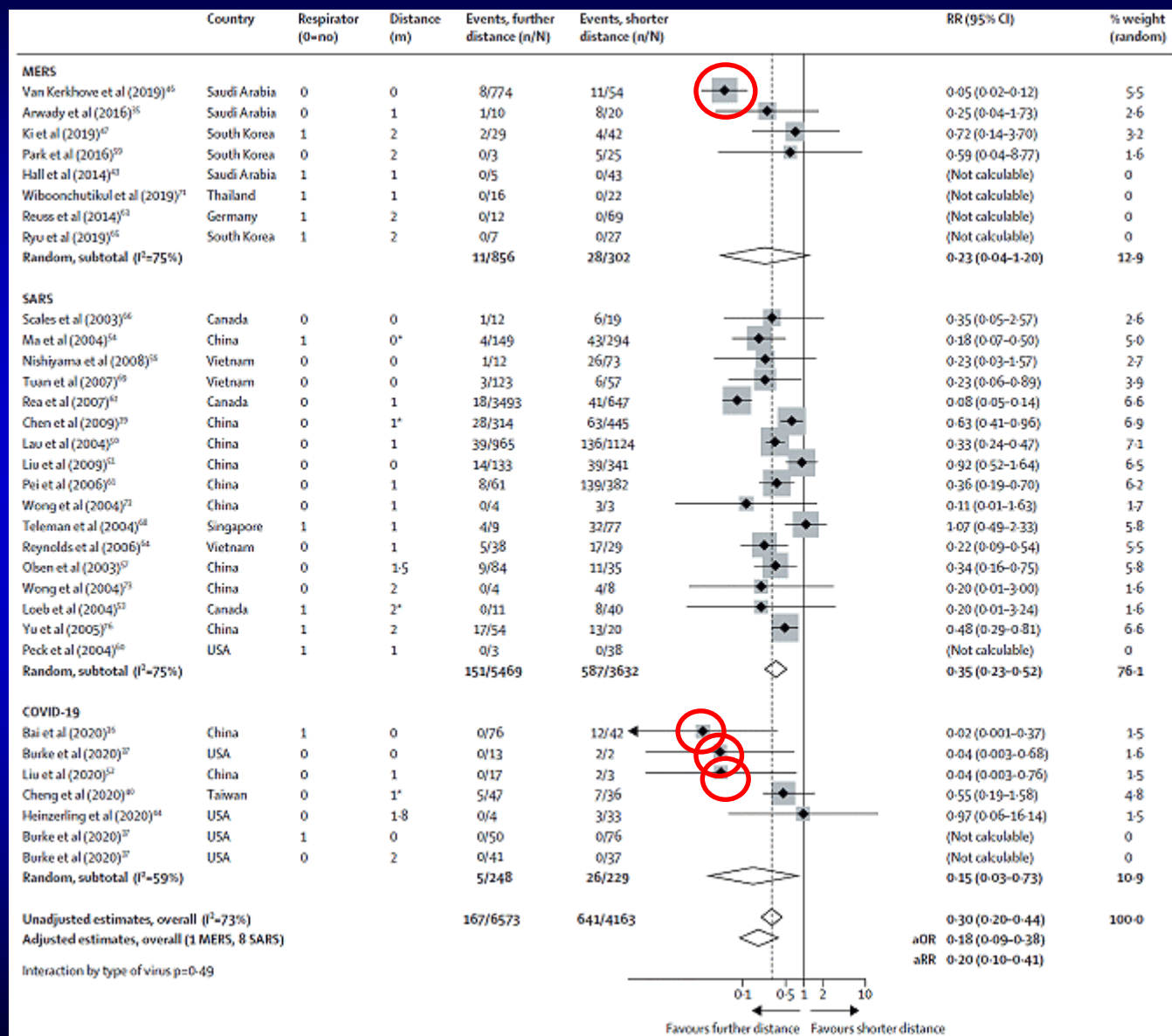
- 保持距離 > 1公尺：↓82%

- 口罩：↓85%

- 護目設備：↓72%



# 新冠病毒傳染預防的綜合分析 2020



# 社交距離有效的參考文獻

- MERS，沙烏地阿拉伯，2015：**居住同一房間**女性醫護人員為危險因素
- COVID-19，中國，2020：護理師在未完好防護的「**非典型**」**新冠病房**比較容易罹病
- COVID-19，美國，2020：9位確診者的404位密切接觸者追蹤，發現2例密切接觸者得到感染，均為確診者的**配偶**
- COVID-19，中國，2020：26個群聚感染，其中**家庭群聚感染**為重要因素之一。

# SARS Transmission, Risk Factors, and Prevention in Hong Kong 2004

Factors	Case <sup>b</sup>	Control <sup>c</sup>	Matched univariate OR (95% CI)	Matched multivariate OR (95% CI)	p value <sup>d</sup>
% visited mainland China (reference=no)	12.7	6.5	2.09 (1.33 to 3.27) <sup>e</sup>	1.95 (1.11 to 3.42)	0.020
% visited PWH (reference=no)	3.6	0.5	8.27 (2.32 to 29.49) <sup>e</sup>	7.07 (1.62 to 30.75)	0.009
% visited other hospitals/clinics (reference=no)	40.7	17.0	3.36 (2.49 to 4.54)	3.70 (2.54 to 5.39)	<0.001
% visited Amoy Gardens (reference=no)	15.5	2.0	9.10 (4.87 to 17.00) <sup>e</sup>	7.63 (3.77 to 15.43)	<0.001
% visited crowded places frequently (reference=occasionally/seldom/no)	21.9	20.8	1.07 (0.76 to 1.50) NS	-	-
% contacted someone with fever or influenza (reference=no)	9.0	6.4	1.42 (0.87 to 2.32) NS	-	-
% social contact with someone who visited a patient in a hospital (reference=no)	8.2	5.2	1.66 (0.96 to 2.85) NS	-	-
% social contact with medical personnel (reference=no)	7.6	8.6	0.87 (0.52 to 1.44) NS	-	-
% had a SARS case in the housing estate (reference=no)	6.6	8.5	0.76 (0.44 to 1.31) NS	-	-
% disinfected the living quarters thoroughly (reference=no)	46.6	74.5	0.30 (0.23 to 0.39) <sup>e</sup>	0.41 (0.29 to 0.58)	<0.001
Wore a mask in public places frequently (reference=occasionally/seldom/no)	27.9	58.7	0.27 (0.20 to 0.37) <sup>e</sup>	0.36 (0.25 to 0.52)	<0.001
Washed hands 11 or more times per day (reference=1-10 times/day)	18.4	33.7	0.44 (0.31 to 0.63) <sup>e</sup>	0.58 (0.38 to 0.87)	0.008

<sup>a</sup>N.S., not significant; OR, odds ratio; CI, confidence interval; PWH, Prince of Wales Hospital; -, not used by the multivariate analyses. The reference time period was the 10 days before the date of the patient's onset of fever.

<sup>b</sup>n = 330.

<sup>c</sup>n = 660.

<sup>d</sup>p values for multivariate OR.

<sup>e</sup>p < 0.005.

# SARS transmission, risk factors, and prevention in Hong Kong 2004

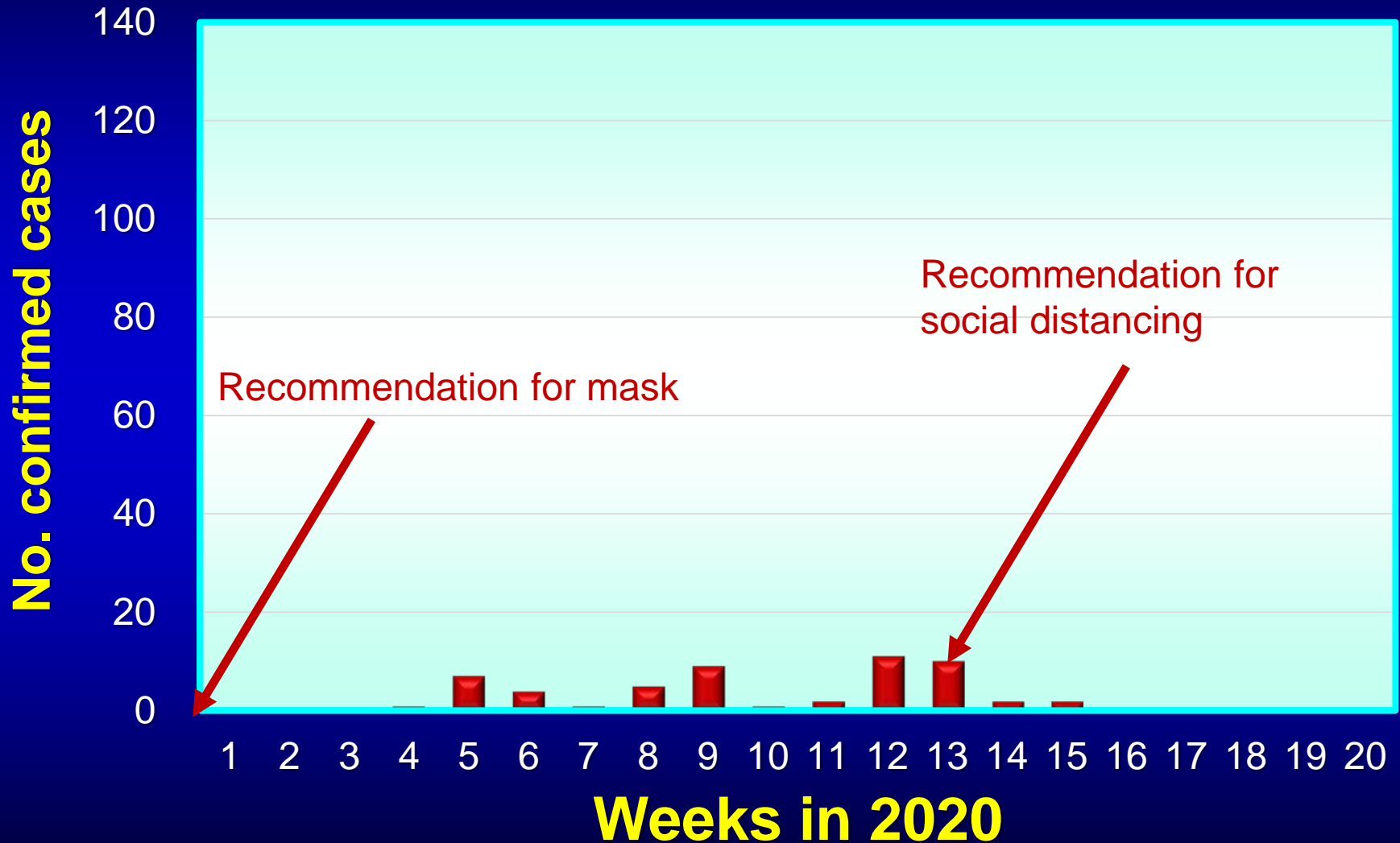
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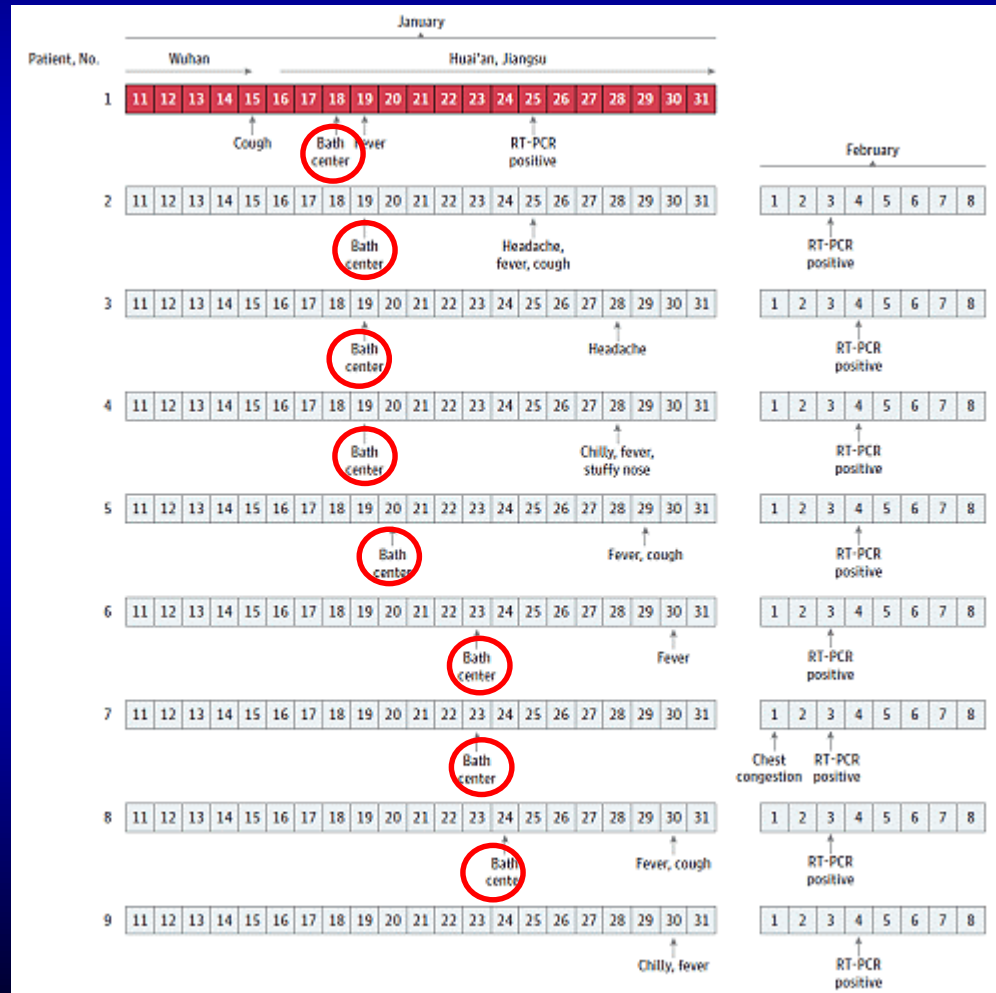
# Locally transmitted cases of COVID-19 in Taiwan

N=55, Taiwan CDC, as of May 11, 2020



# A patient with COVID-19 transmit the virus to 8 users in a public bath in different days

## Jiangsu, China, 2020



# Transmission route for respiratory syncytial virus

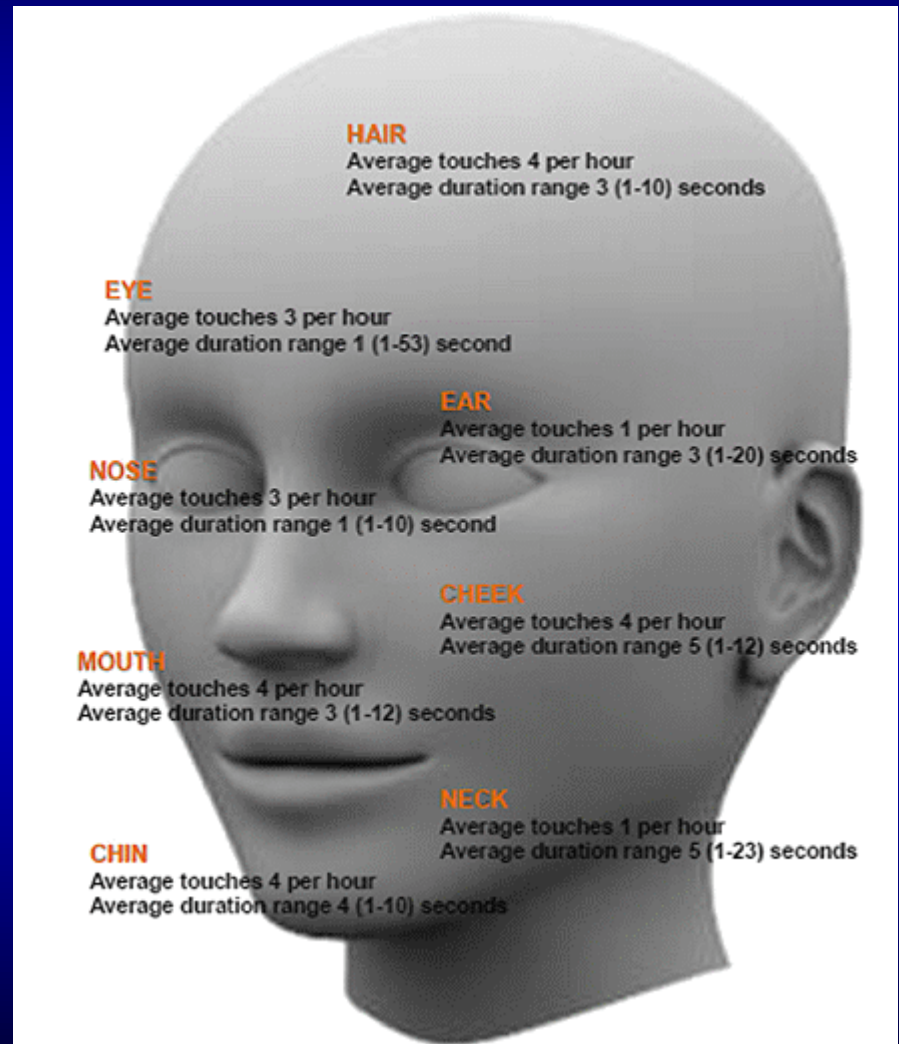
**Nose > Eyes > Mouth**

Inoculation route	Dose (Log <sub>10</sub> TCID <sub>50</sub> )	No. of subjects:				
		Inoculated	Shedding RSV	With seroresponse		
				CF <sup>a</sup>	NT <sup>b</sup>	ELISA <sup>c</sup>
Nose	5.2	4	3	2	3	3
	3.2	4	1	1	1	1
	2.2	4	0	0	0	0
Eyes	5.2	4	3	0	2	3
	3.2	4	1	0	0	0
	2.2	4	0	0	0	0
Mouth	5.2	8	1 <sup>d</sup>	1	1	1

# 醫學生上課時觸摸臉部頻率

N=26，澳洲，2015

- 平均每小時觸摸臉部23次，其中44%接觸黏膜
- 眼睛：3/小時
- 鼻部：3/小時
- 嘴部：4/小時



# Cost-effectiveness of preventive strategies against VOCID-19

Effect

Economic loss

High

Low

Face mask

Hand cleaning

Don't touch  
eye/nose/mouth

Environ. sanitation

Social distancing

Low

High



# 劍橋大學研究：新冠出現3種變異！亞歐美 3洲病毒株皆不同！ Heho健康網，2020.4.16



美國、澳洲地區：流行**A**類型病毒

東亞(含武漢)地區：流行**B**類型病毒

歐洲地區：流行**C**類型病毒



# 腸病毒71型的基因型演變 台灣，1998-2005

- 基因型變化  
不影響抗體  
中和力

Sera	Virus	
	Genogroup B <sup>a</sup>	Genogroup C <sup>b</sup>
Anti-genogroup B <sup>c</sup>		
B1	>1024	1024
B2	>1024	1024
B3	>1024	>1024
B4	>1024	512
B5	>1024	1024
B6	>1024	512
B7	>1024	>1024
Anti-genogroup C <sup>d</sup>		
C1	>1024	1024
C2	>1024	1024
C3	>1024	1024
C4	>1024	512
C5	>1024	1024
C6	>1024	1024
Non-EV71 antisera		
EV6 no. 1	64	64
EV6 no. 2	128	128
CB5	<8	<8
CA16	<8	<8
HSV-1	<8	<8

# Coronavirus immunity has no evidence; second infection still possible says WHO

Medical Daily, Apr 26, 2020 By Susmita Pathak

- “There is currently **no evidence** that people who have recovered from COVID-19 and have **antibodies** are protected from a second infection,” WHO wrote in the statement, clearing all doubts.
- There are some of them with considerably low levels of neutralizing antibodies in the blood, which indicate that the immunity of the cells may not be enough for recovery.

# Dr. Anthony Fauci says there's a chance coronavirus vaccine may not provide immunity for very long June 3, 2020, CNBC

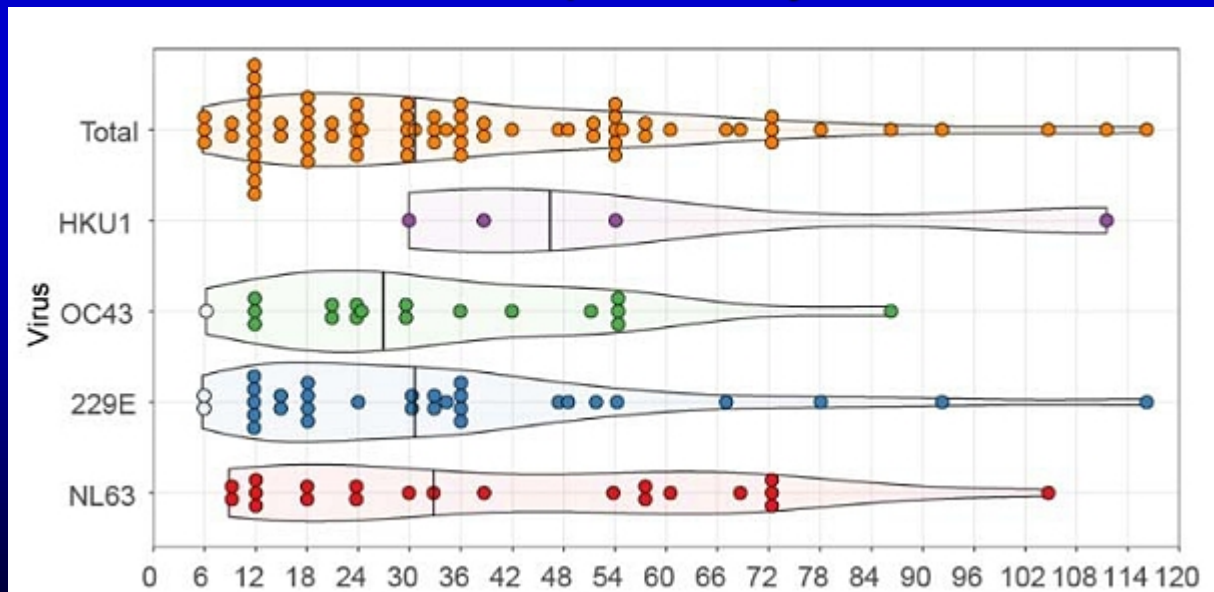


- If Covid-19 acts like other coronaviruses, **“it likely isn’t going to be a long duration of immunity,”** Fauci, director of the National Institute of Allergy and Infectious Diseases, told JAMA Editor Howard Bauchner.
- “When you look at the history of coronaviruses, the common coronaviruses that cause the common cold, the reports in the literature are **that the durability of immunity that’s protective ranges from three to six months to almost always less than a year,**” he said. “That’s not a lot of durability and protection.”

# Short duration of protection and frequent reinfection of coronaviruses

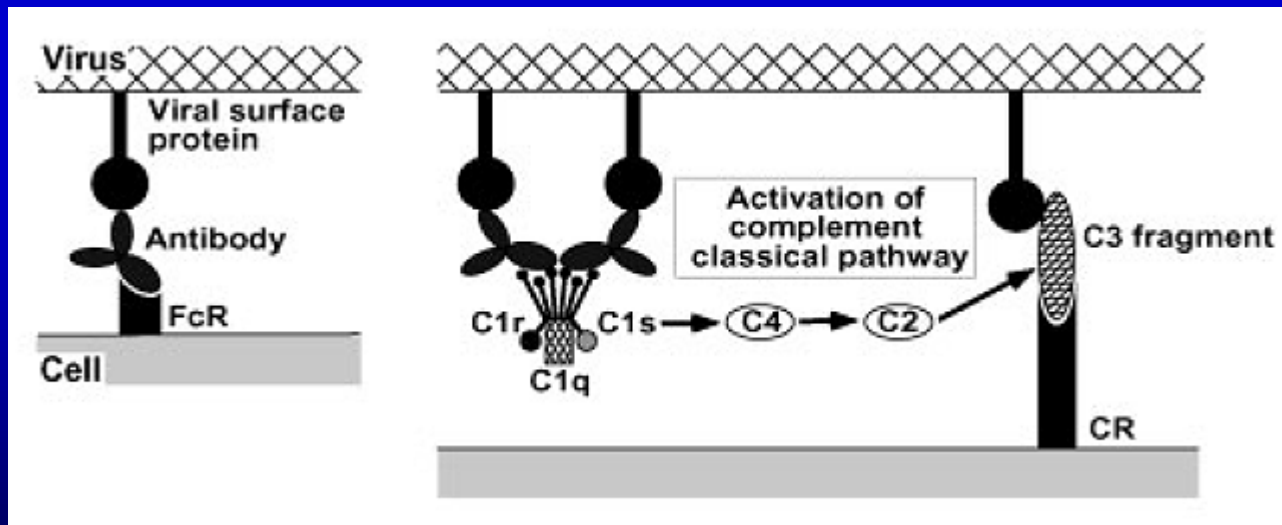
N=10, 1985-2020, The Netherlands

- Infection: **1.4-fold increase** in antibody levels
- HCoV-NL63: 15.3/100 person-years
- HCoV-229E: 20.1/100 person-years
- HCoV-OC43: 16.4/100 person-years
- HCoV-HKU1: 6.3/100 person-years



# Antibody-dependent enhancement Flaviviruses

- Hawkes RA, **1964**: the infectivities of **Murray Valley encephalitis virus, West Nile virus and Japanese encephalitis virus** were enhanced in the presence of chicken antisera when assayed on chick embryo fibroblast cells, but not on swine kidney cells.
- Halstead SB, 1977: **dengue virus**
- Halstead SB, 1980: dengue hemorrhagic fever in Thailand



FcR: immune cells

Complement receptor: more widely distributed among different cells



# Enhanced respiratory syncytial virus disease by inactivated RSV vaccine

- Formalin inactivated vaccine against RSV, **1966**, USA:
  - **Seronegative children** before vaccination: increase in the **frequency and severity of RSV LRTI**
  - **Hospitalization** ↑: vaccine vs. control = 80% vs. 5%
  - 2 vaccinated toddler **died** of severe RSV infection.
- RSV vaccines encoding **antigens not processed in the cytoplasm** → nonprotective antibody response → lack of affinity maturation in B cells → potentiating Th2-mediated



# Live attenuated dengue vaccine

Sanofi Pasteur, N=22177+11089, 2015

- Pooled rates of efficacy for **symptomatic dengue** during the first 25 months: 60.3% (95% CI, 55.7 to 64.5)
  - < 9 years: 44.6% (95% CI, 31.6 to 55.0)
  - ≥ 9 years: 65.6% (95% CI, 60.7 to 69.9)
- Pooled relative risks of **hospitalization**: 0.84 (95%CI, 0.56 to 1.24)
  - **< 9 yrs: 1.58** (95% CI, 0.83 to 3.02)
  - ≥ 9 yrs: 0.50 (95% CI, 0.29 to 0.86)

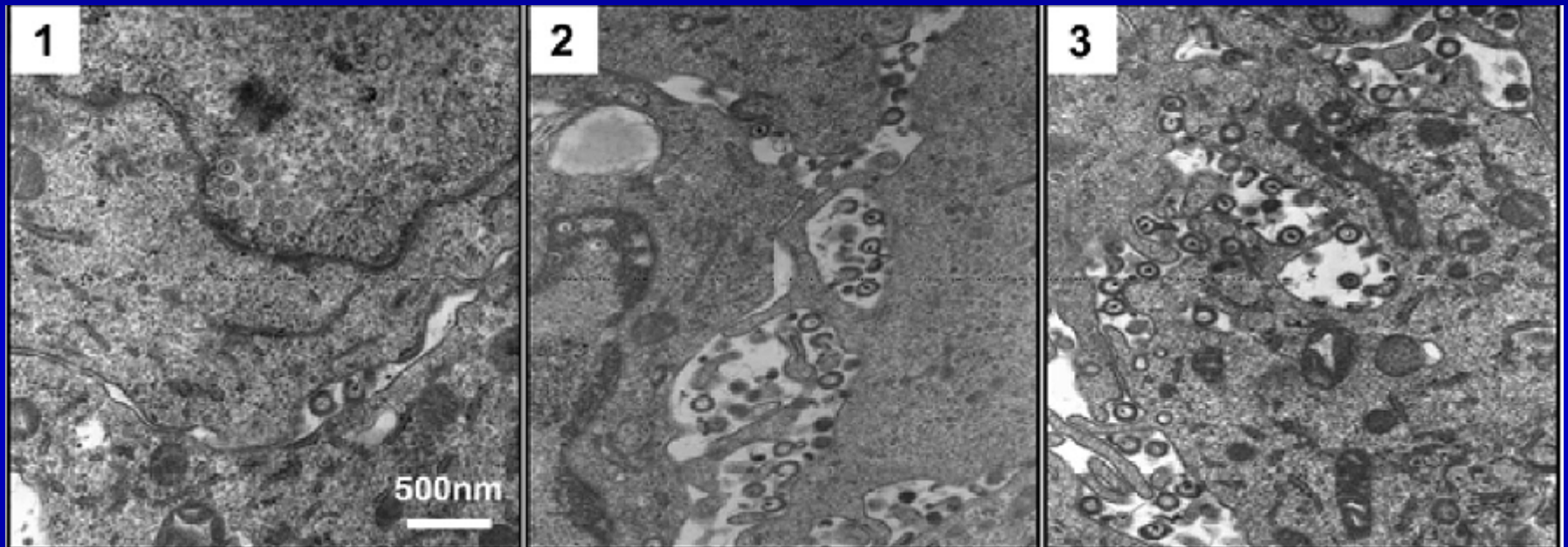
# Antibody-dependent enhancement of SARS

2014, Kaohsiung Medical University, Taiwan

Anti-sera 10-fold dilution

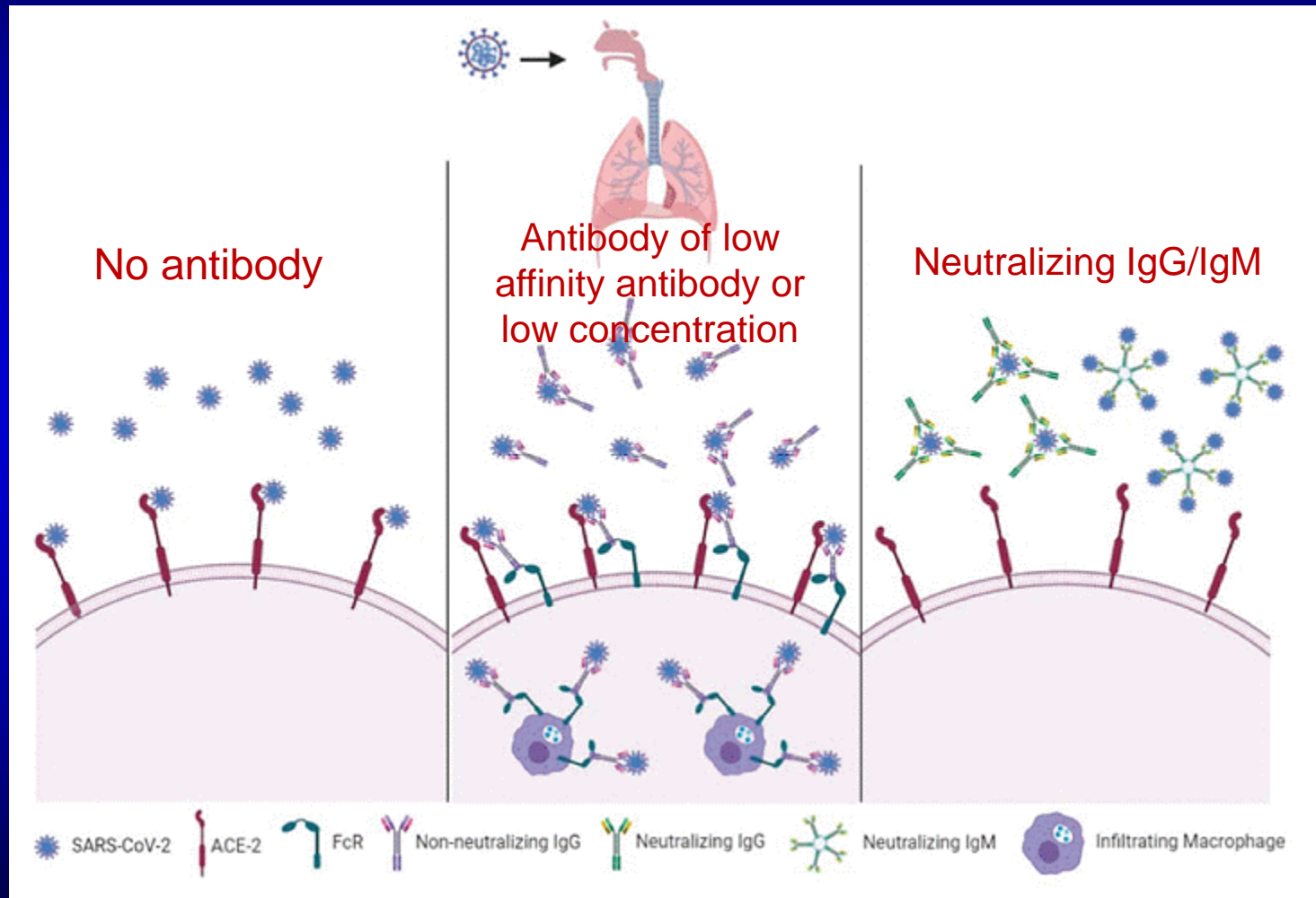
Control sera 10-fold dilution

Anti-sera 1000-fold dilution

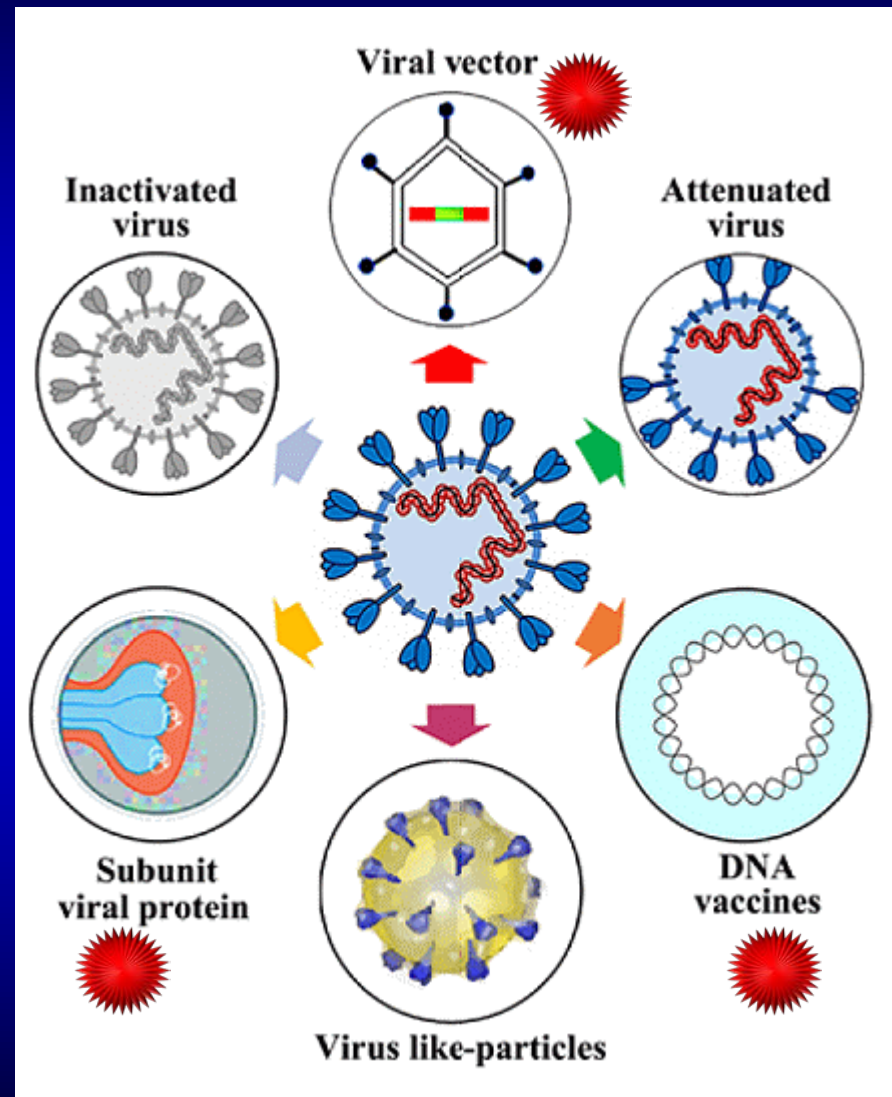


SARS-CoV viral particles were observed in HL-CZ cells treated with more diluted anti-sera against SARS-CoV (2000-fold dilution) (Fig. 2C-3) compared to those treated with less diluted anti-sera (10-fold) (Fig. 2C-1) and less diluted normal control sera (10-fold) (Fig. 2C-2).

# Susceptibility of the elderly to SARS-CoV-2 infection and ADE

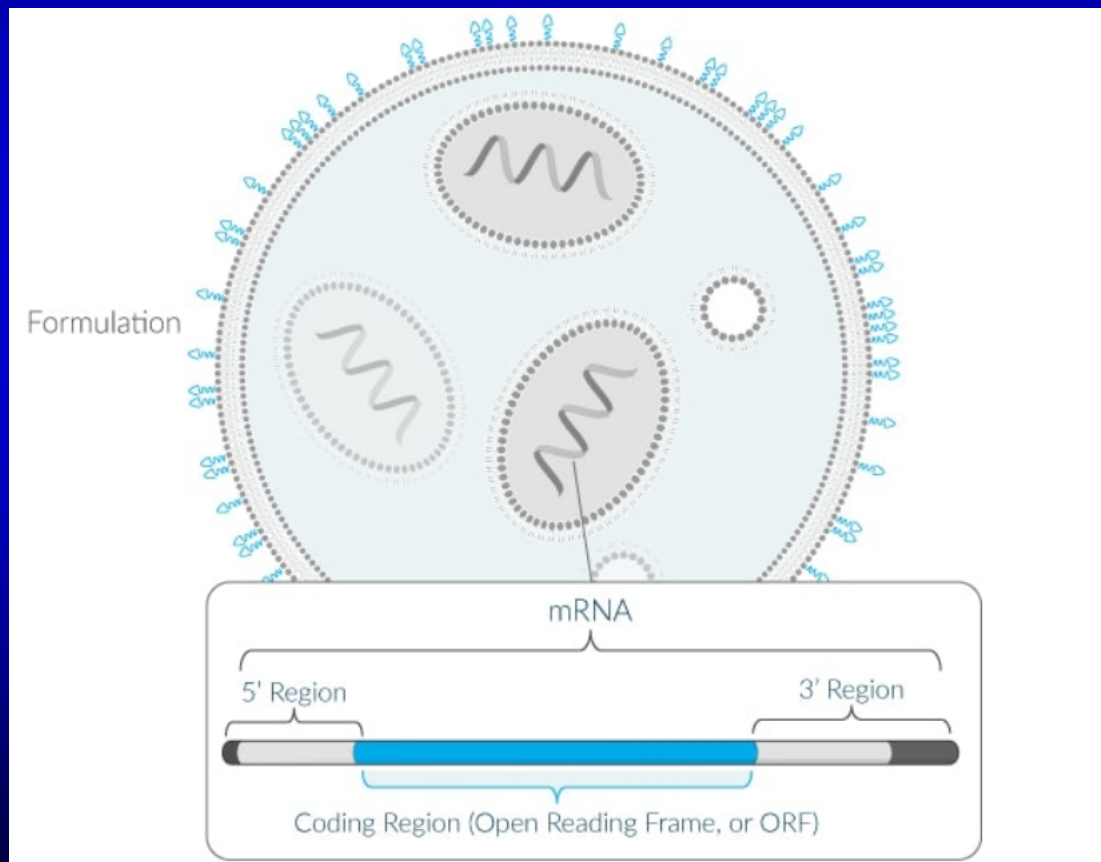


# Strategy types for COVID- 19 vaccine development



# Moderna, Inc. (Cambridge, MA, USA) : mRNA

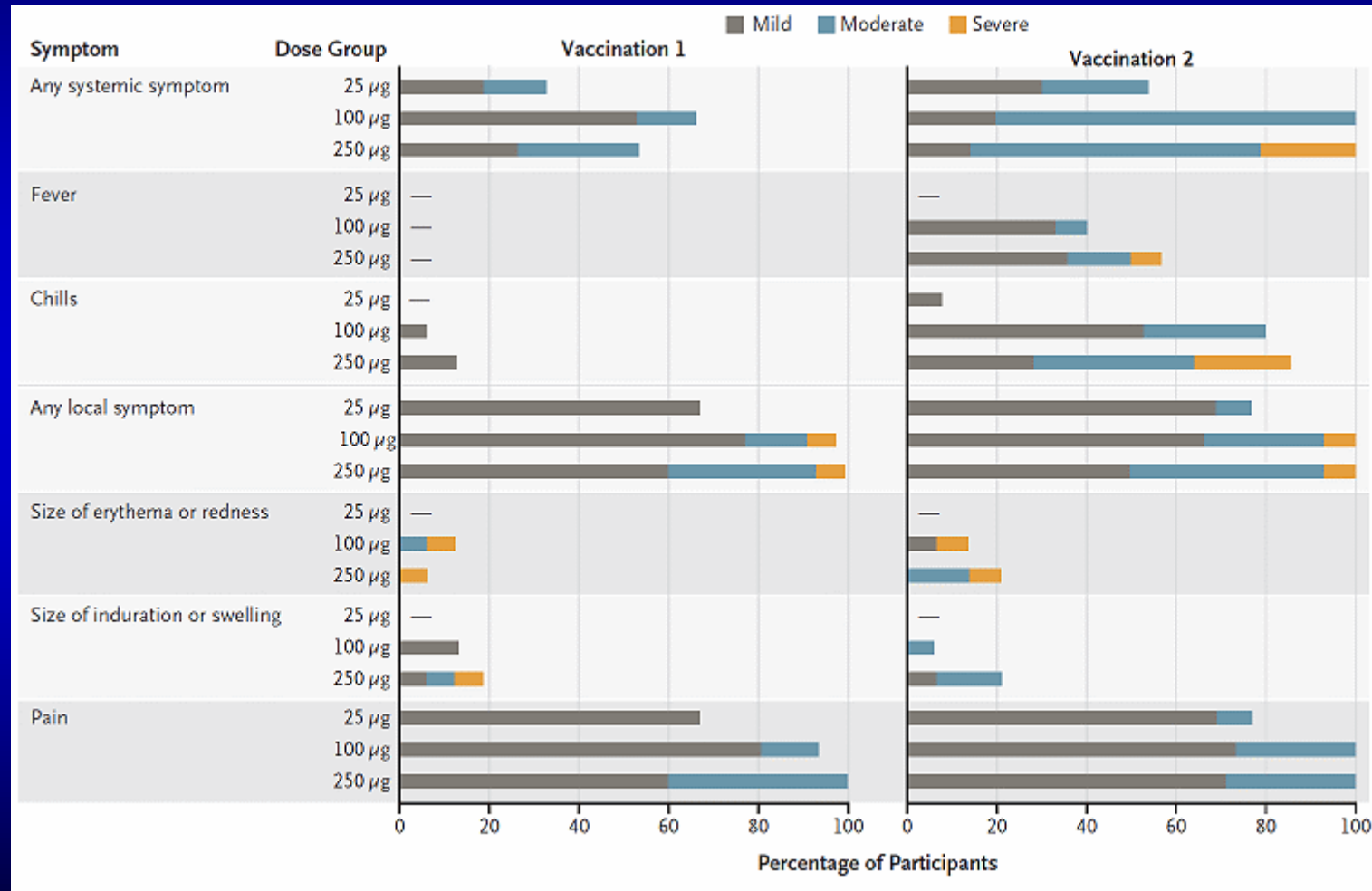
- 設計簡單，快速生產
- 致免性較差，沒有上市疫苗





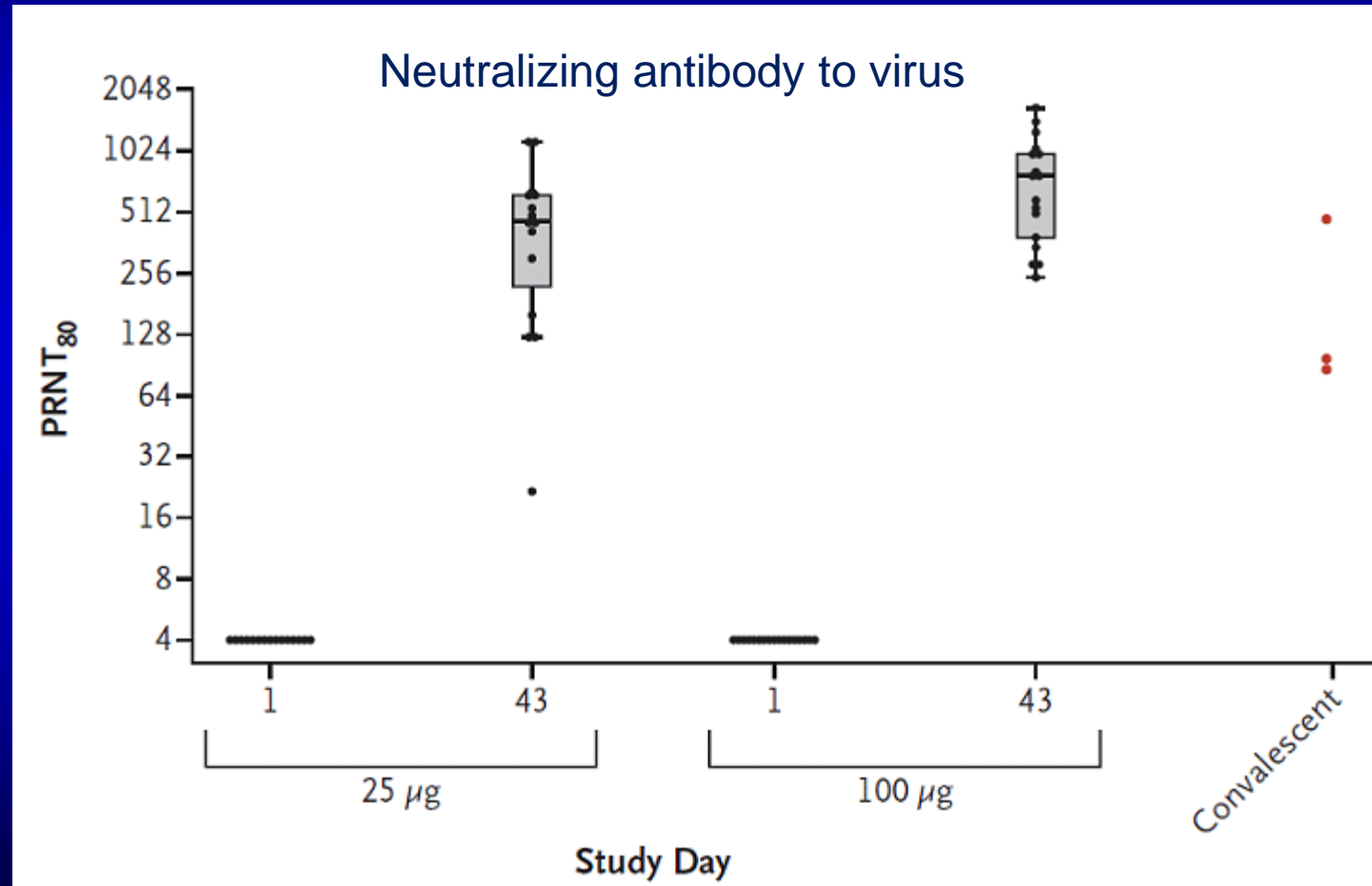
# mRNA vaccine: stabilized prefusion SARS-CoV-2 spike protein trimer, S2P (Moderna, Inc.)

2 doses, N=45, 18-55 yrs, 2020, USA



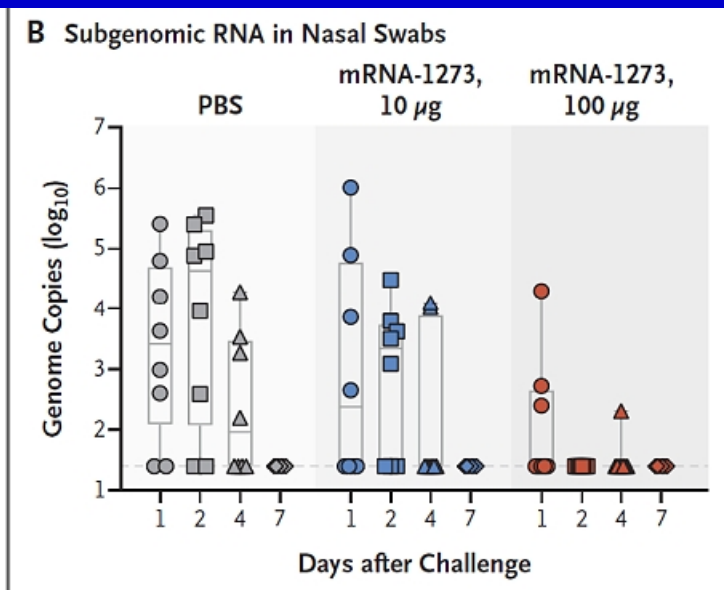
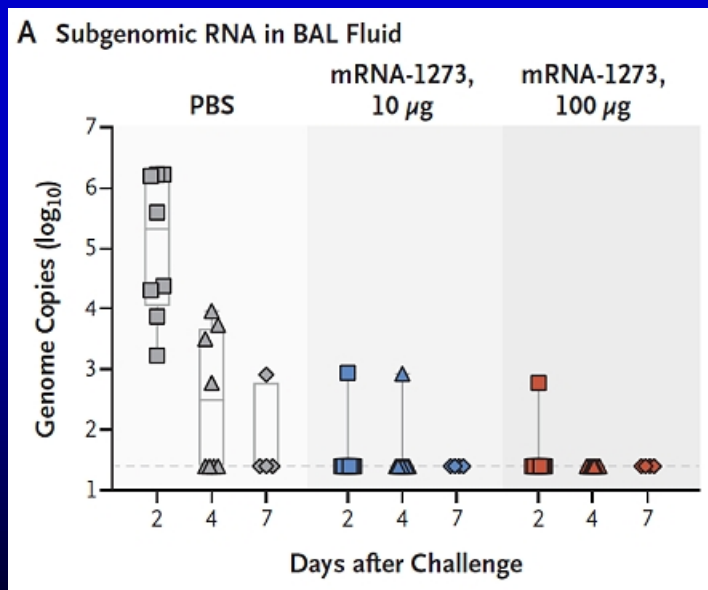
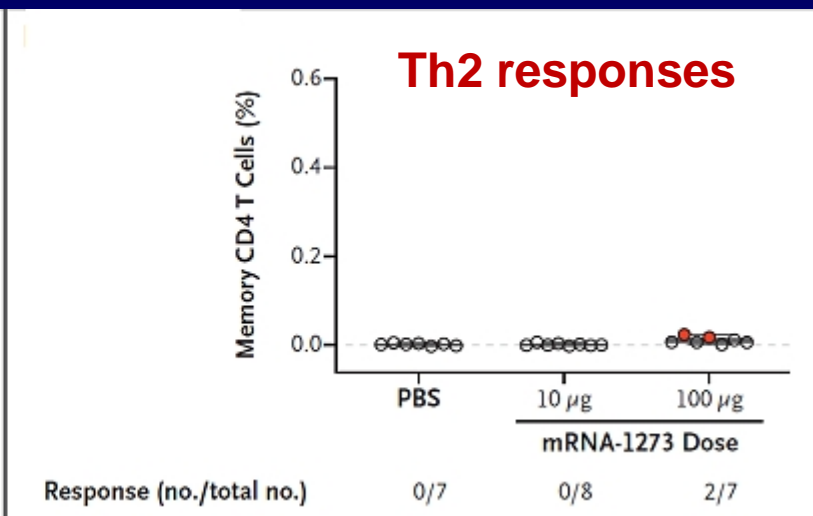
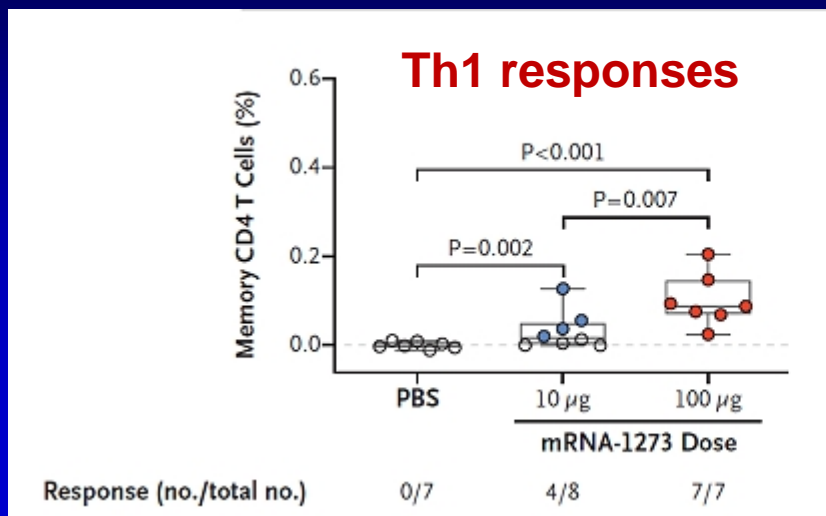
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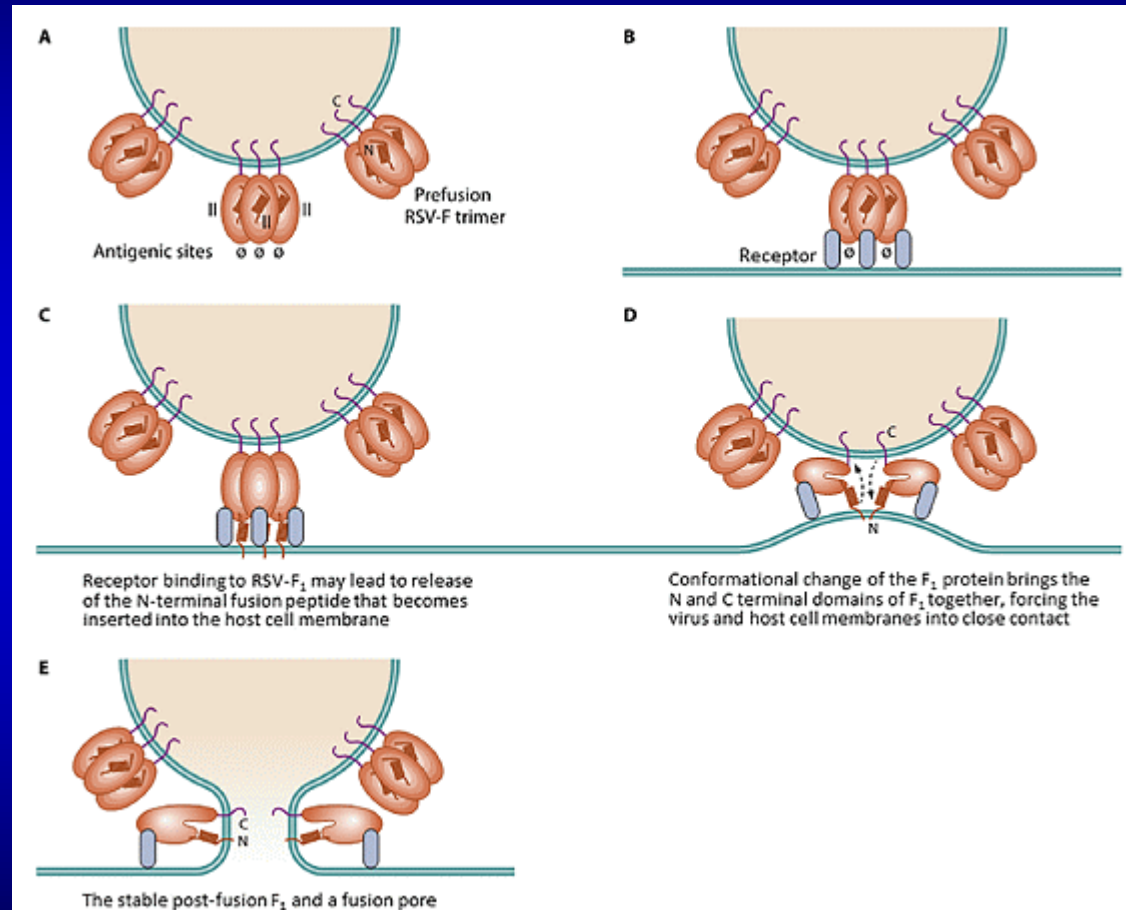
# mRNA vaccine (Moderna, Inc.)

## Rhesus macaques challenge test, 2020, USA



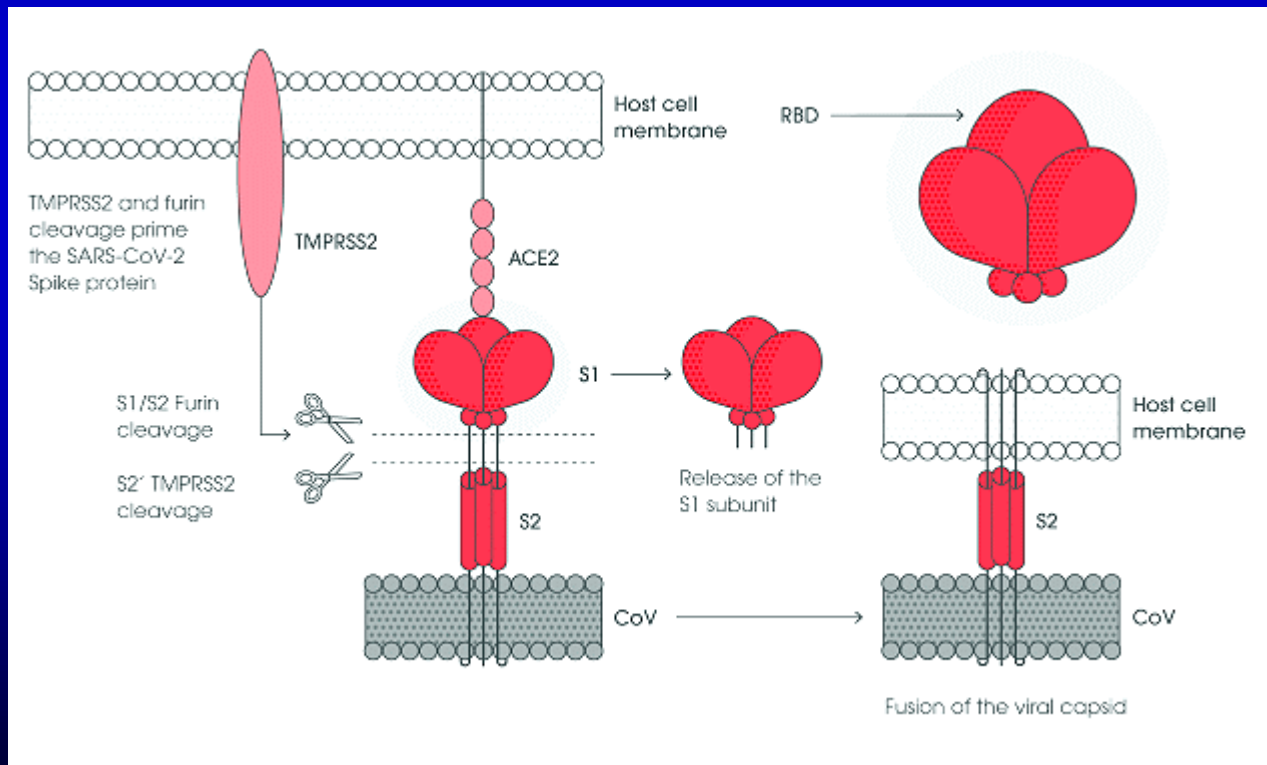
# Conformational change of F protein of respiratory syncytial virus

- Prefusion: metastable state
- Postfusion: stable state
- **Neutralizing antibody activity: prefusion >> postfusion**



# Structural and functional mechanism of SARS-CoV-2 cell entry Abcam

- S protein
  - **S1**: receptor-binding domain
  - S2: mediates the fusion of the viral and host cell membranes



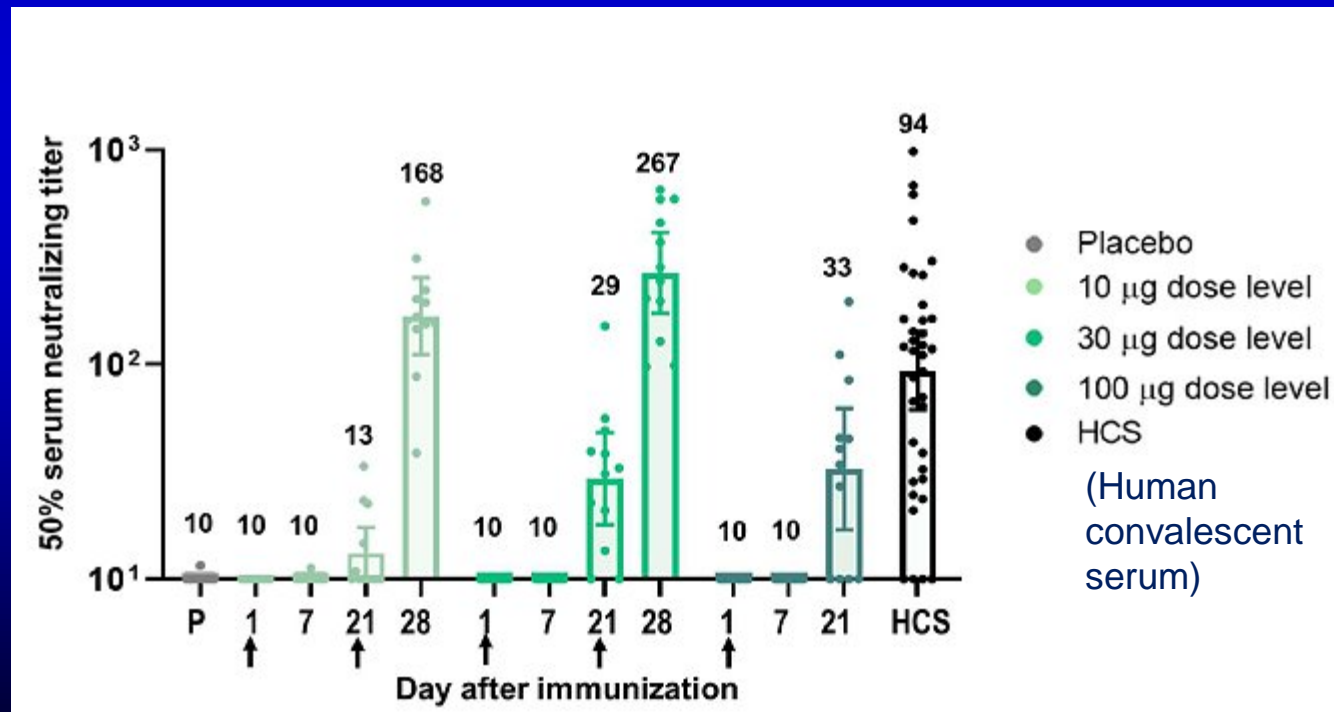


# COVID-19 RNA vaccine candidate (BNT162b1)

N=45, 2 doses, 18~55 years, Pfizer

- **Modified RNA (modRNA):**

- Encodes the receptor binding domain (**RBD**) of the SARS-CoV-2 spike protein
- Formulated in lipid nanoparticles

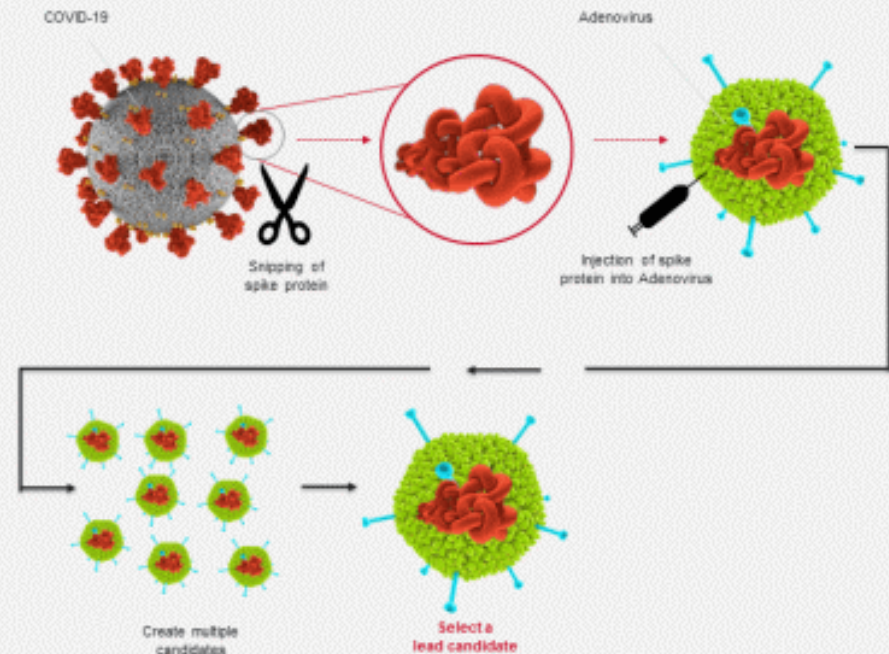


# Johnson & Johnson: adenovirus vector

## Designing a vaccine

January – March 2020

- **January 2020:** SARS-CoV-2 sequence available
- Vaccine design commences
- SARS-CoV-2 spike protein inserted into Ad26 vector
- Multiple vaccine candidates constructed
- **March 2020:** Validated with pre-clinical testing to identify lead candidate



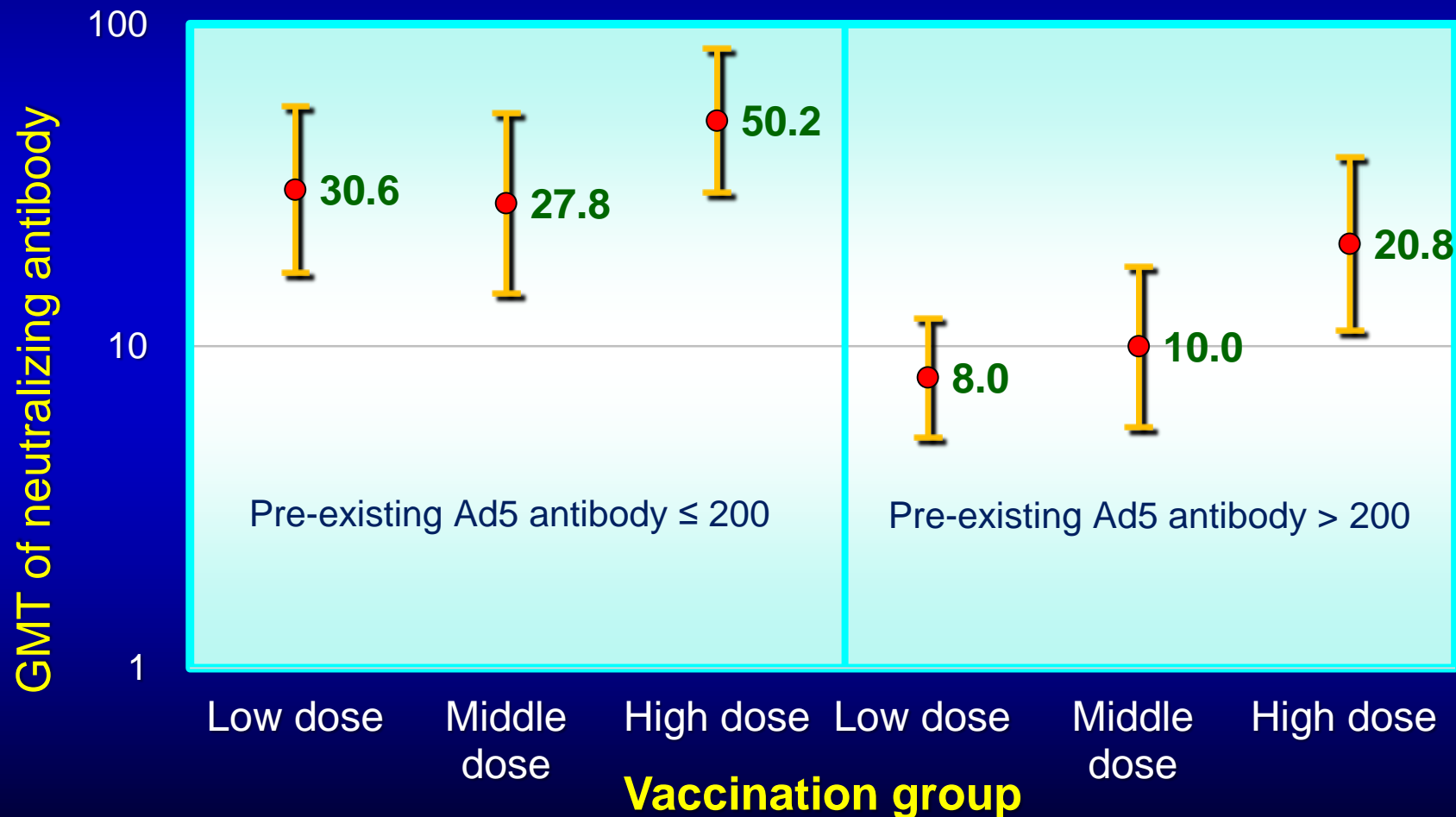
Johnson & Johnson

18

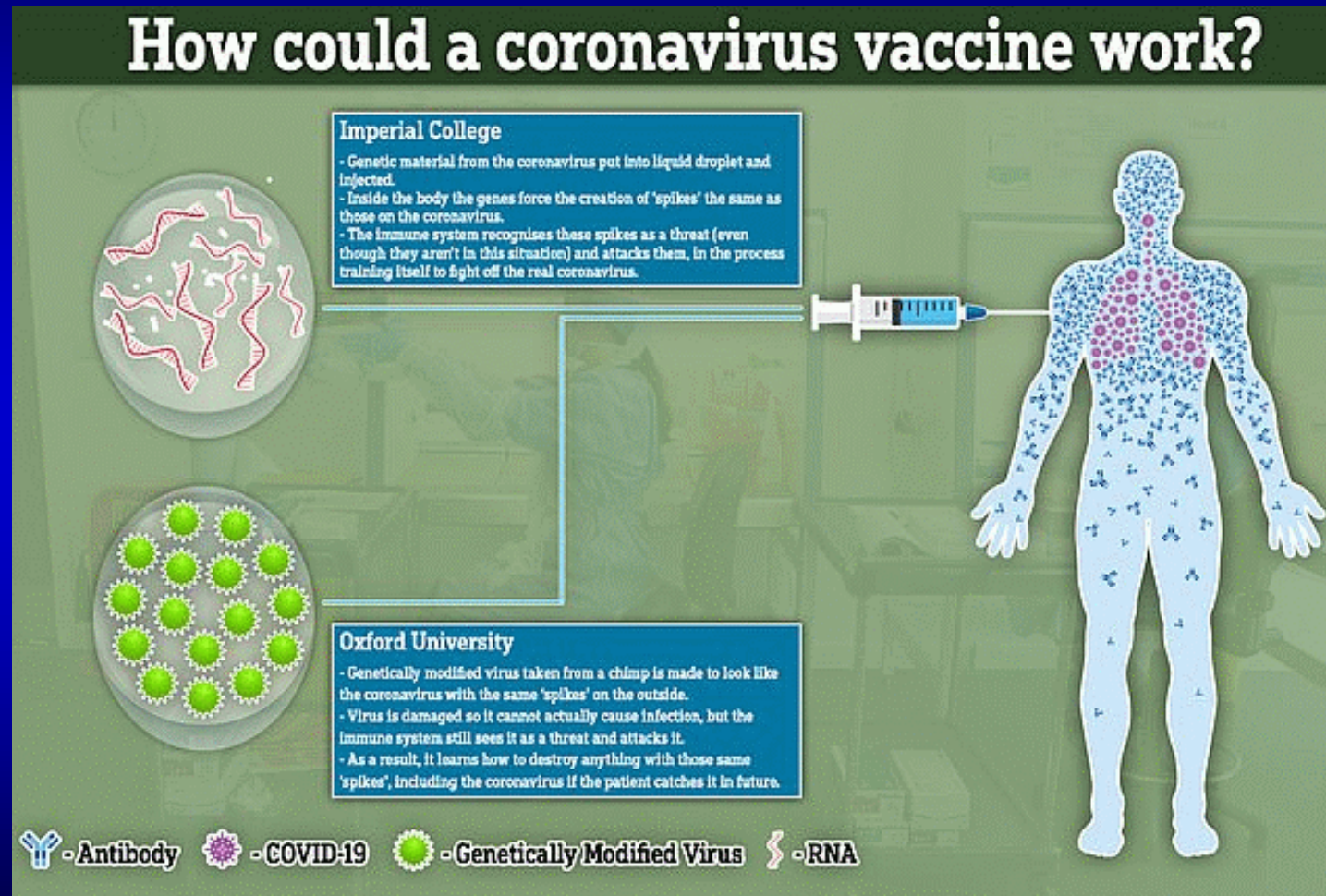
# Recombinant adenovirus type-5 (Ad5) vectored vaccine expressing the spike glycoprotein

One dose, N=195, 18-60 yrs, 2020, China

Neutralizing antibodies to live SARS-CoV-2



# AstraZeneca: adenovirus vector AZD1222 SARS-CoV-2 vaccine





# 台灣的新型冠狀病毒候選疫苗

組織	疫苗製造平台	抗原標的	人體臨床試驗
AdImmune	Insect cell	Recombinant spike protein	Aug. 2020
Medigen/US NIH	CHO cell (CDMO)	Recombinant spike protein (S-2P)	Sep. 2020
UBI Asia	Synthetic peptide/recombinant protein	RBD or rS1	Unknown
NHRI/Enimmune	Synthetic DNA	S DNA	Dec 2020



# 疫苗保護效力的判定

- **已知保護性免疫反應臨界值**：B型肝炎表面抗體  $\geq 10$  mIU/mL
- **對照研究**：疫苗組與對照組暴露病原後，發病率減少的比率
- **人類挑戰試驗 (human challenge trial)**：受試者故意接受病原暴露
- **免疫橋接 (immune bridging)**：參考類似疫苗的免疫反應資料

# COVID-19疫苗接種對象優先順序草案

預防接種諮詢小組，2020.7.6

順序	族群	估計人數(萬)
1	醫事人員	33.2
2	中央及地方政府防疫人員(含機場CIQS人員)	14
3	維持社會運作之必要人員	9
4	安養、養護、日間照顧、社福等長期照護機構受照顧者、照顧者及工作人員、居服員、社工人員	15.8
5	軍人	20
6	65歲以上長者	348.5
7	19-64歲具有易導致嚴重疾病之高風險疾病者	384
8	罕見疾病及重大傷病	3.5
9	50-64歲成人	530

# Thanks....



New Zealand