HKU Med
LKS Faculty of Medicine
Department of Medicine
香港大學內科學系

Primer on Infectious Diseases with Public Importance

Update on COVID-19 & Vaccines Development

傳染病攻略–溫故與知新

2019冠狀病毒：新知一覽

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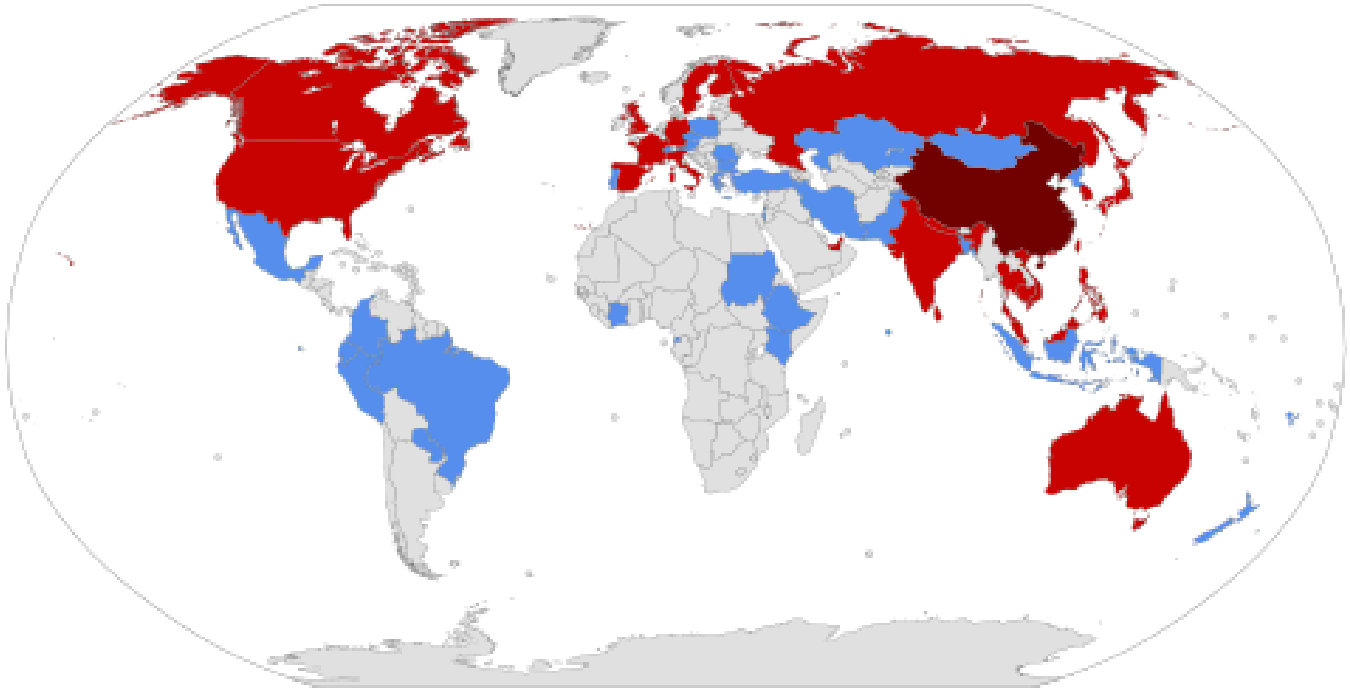
披露聲明

- Received honoraria from Pfizer, Roche, MSD, Abbvie, Ferring, Gilead and Chong Lap

1 Introduction 簡介

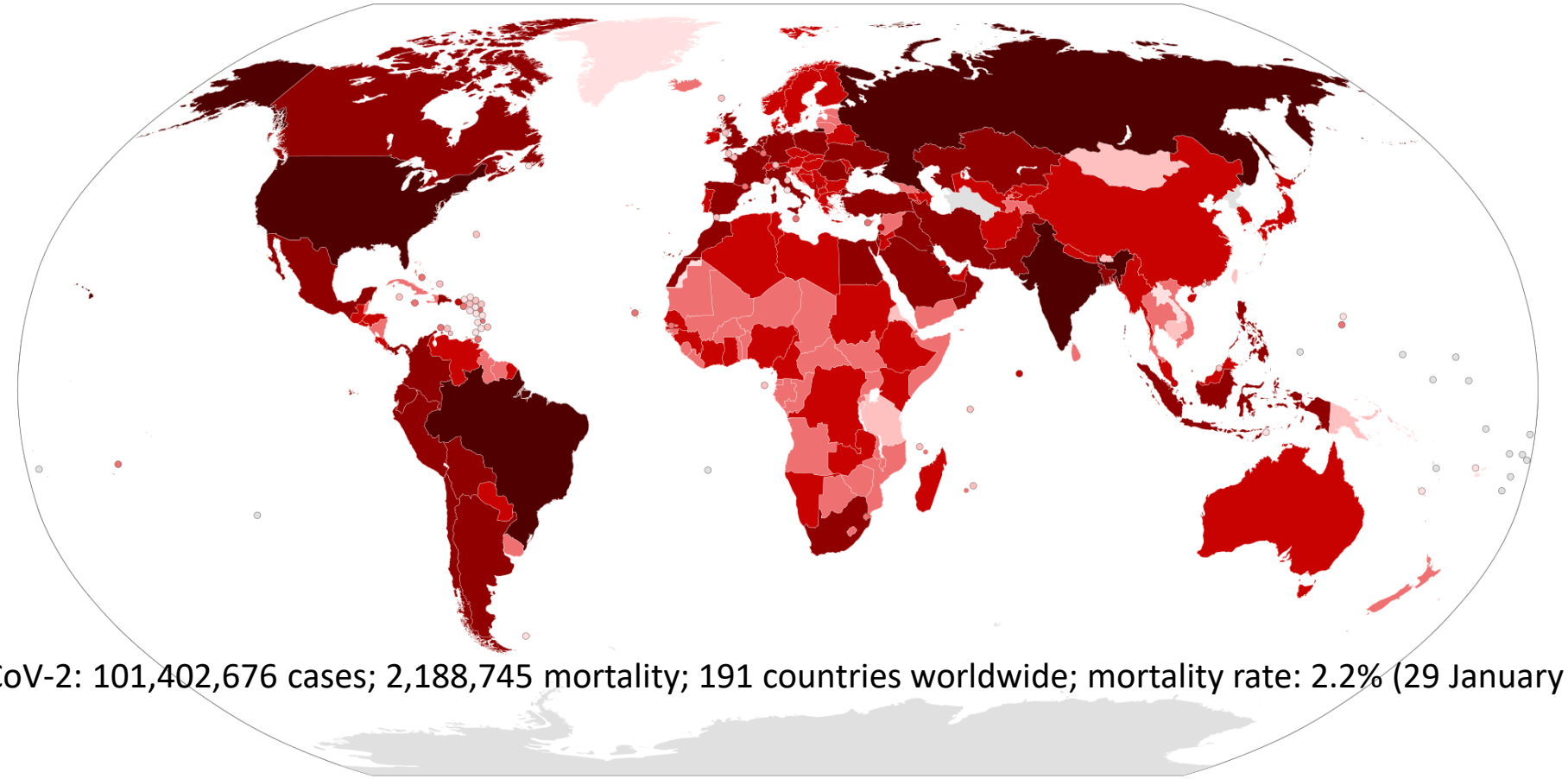
COVID-19 Pandemic: 5 March 2020
2019冠狀病毒全球大流行: 2020年3月5日



COVID-19: 218,584 cases; 8938 mortality; 157 countries worldwide; mortality rate: 4.1% 5 March 2020)

https://en.wikipedia.org/wiki/2019_novel_coronavirus_(2019-nCoV)
https://www.chp.gov.hk/files/pdf/statistics_of_the_cases_novel_coronavirus_infection_en.pdf

2019冠狀病毒爆發：2021年1月29日



SARS-CoV-2: 101,402,676 cases; 2,188,745 mortality; 191 countries worldwide; mortality rate: 2.2% (29 January 2021)

https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200507covid-19-sitrep-128.pdf?sfvrsn=44cc8ed8_2
https://en.wikipedia.org/wiki/2019_novel_coronavirus_(2019-nCoV)
https://www.chp.gov.hk/files/pdf/statistics_of_the_cases_novel_coronavirus_infection_en.pdf

2019冠狀病毒全球大流行: 變化

5 March 2020

2019–20 coronavirus pandemic by country and territory [show all]

Location[a]	Cases[b]	Deaths	Deaths per 10 million capita	Recoveries [c]	Ref.
157	218,584	8,938		85,711	
China (mainland)[d]	80,928	3,245	23	70,420	[33]
Italy[e]	35,713	2,978	492	4,025	[36]
Iran	17,361	1,135	140	5,710	[33]
Spain	14,769	638	137	1,081	[37]
Germany	12,327	28	3	105	[38]
United States[f]	9,452	150	5	106	[33][39]
France[g]	9,134	264	39	602	[40]
South Korea	8,565	91	18	1,947	[41]
Switzerland[h]	2,772	21		15	[42]
United Kingdom[i]	2,626	104	16	65	[43][44]
Netherlands[j][k]	2,059	58		–	[33][46]
Austria	1,646	4		9	[33][47]
Norway[l]	1,590	6		1	[33][48]
Belgium	1,486	14		31	[33]
Sweden[m]	1,231	10		15	[33][49]
Denmark[n]	1,117	4		–	[50][51]
Japan	899	29	2	191	[33][52]
Malaysia	790	2		60	[53][54]
Canada	727	9	3	11	[55]
Diamond Princess[o]	712	7		527	[52]
Portugal	642	2		3	[33][56]
Australia	596	6	2	43	[33]
Brazil	529	4		2	[33][57]
Czech Republic	522	0		3	[33][58]
Qatar	452	0		4	[33][59]
Israel	433	0	0	11	[33][60]
Greece	418	5		14	[61][33]
Ireland	366	2		5	[33][62]
Finland	359	0	0	10	[33][63]
Singapore	313	0	0	117	[64][65]
Pakistan	307	1		2	[33][66]
Poland	287	5		1	[67]

29 January 2021

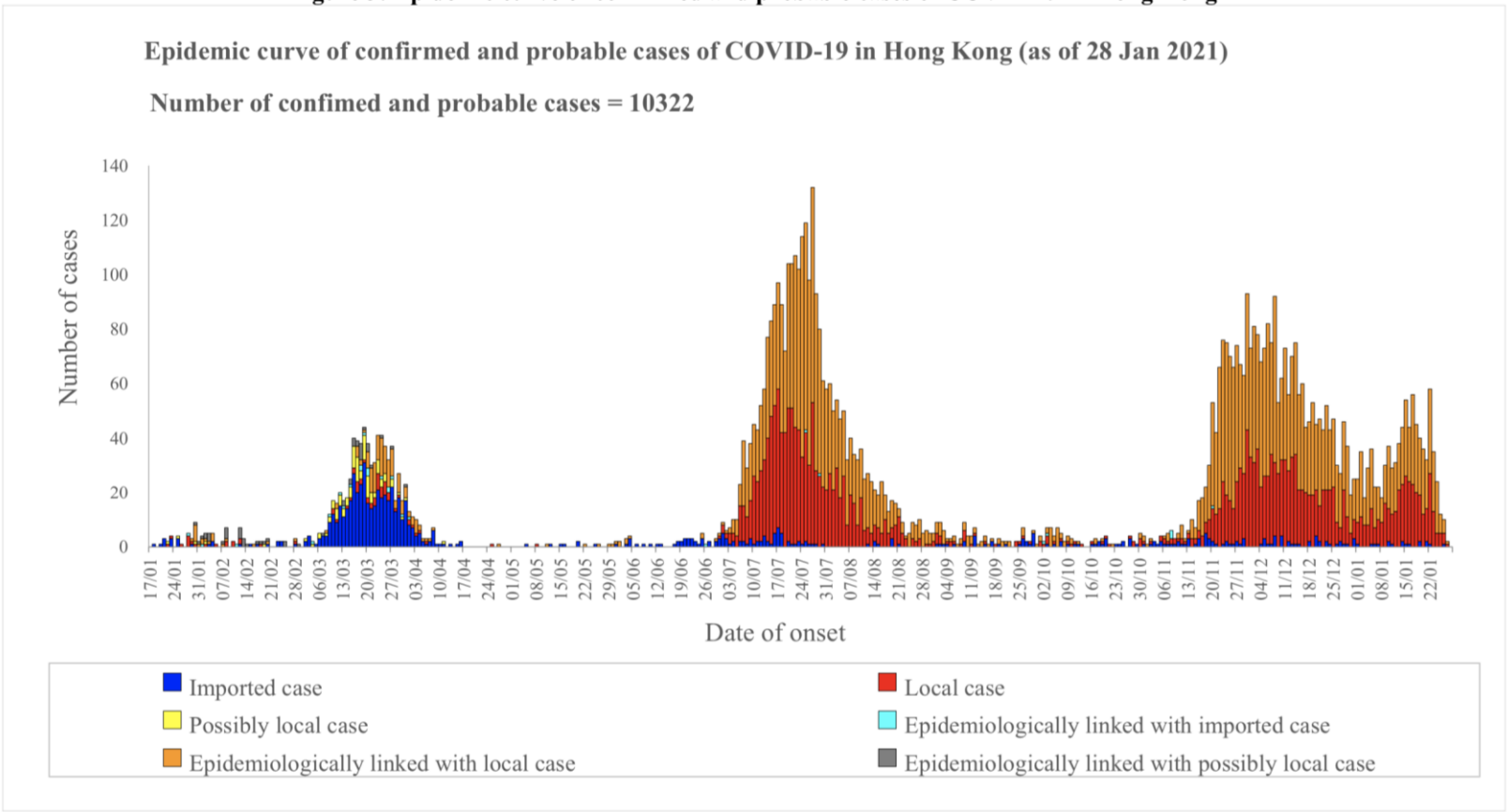
COVID-19 pandemic by location [show all]

Location[a]	Cases[b]	Deaths[c]	Recov.[d]	Ref.
World[e]	101,402,676	2,188,745	55,993,156	[4]
United States[f]	26,027,106	437,743	11,166,500	[16]
India	10,701,193	153,847	10,373,606	[17]
Brazil	9,060,786	221,676	7,923,794	[18][19]
Russia[g]	3,793,810	71,651	3,229,258	[20]
United Kingdom[h]	3,743,734	103,126	No data	[22]
France[i]	3,130,629	74,800	No data	[23][24]
Spain[j]	2,670,102	57,291	No data	[25]
Italy	2,515,507	87,381	1,953,509	[26]
Turkey[k]	2,457,118	25,605	2,340,216	[30]
Germany[l]	2,194,545	56,219	1,882,926	[32][31]
Colombia	2,067,575	52,913	1,894,384	[33]
Argentina[m]	1,905,505	47,601	1,693,131	[35]
Mexico	1,825,519	155,145	1,376,073	[36]
Poland	1,496,665	36,443	1,250,892	[37]
South Africa	1,437,798	43,105	1,272,197	[38][39]
Iran	1,398,841	57,736	1,189,975	[40]
Ukraine[n]	1,206,412	22,351	992,031	[41][42]
Peru	1,119,685	40,484	1,033,357	[43][44]
Indonesia	1,037,993	29,331	842,122	[45]
Netherlands[o]	966,252	13,816	No data	[47][48]
Czech Republic	964,660	15,944	851,400	[49]
Canada[p]	766,103	19,664	689,419	[52]
Romania	721,513	18,105	666,001	[53][54]
Chile[q]	714,143	18,174	670,336	[58]
Belgium[r]	699,662	20,933	No data	[60][61]
Portugal	685,383	11,608	493,699	[62][63]

https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200507covid-19-sitrep-128.pdf?sfvrsn=44cc8ed8_2
https://en.wikipedia.org/wiki/2019_novel_coronavirus_(2019-nCoV)

香港最新状況

Figure 3: Epidemic curve of confirmed and probable cases of COVID-19 in Hong Kong



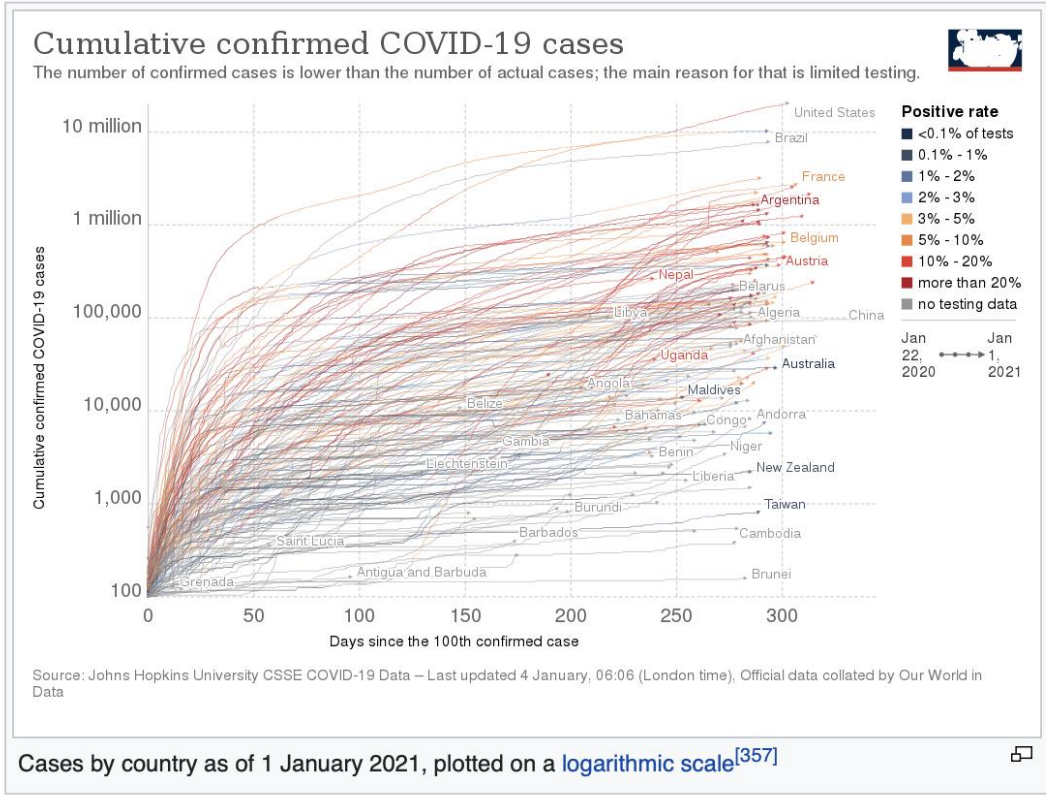
D614G mutation
Spike protein
More transmissible

3rd wave: elderly

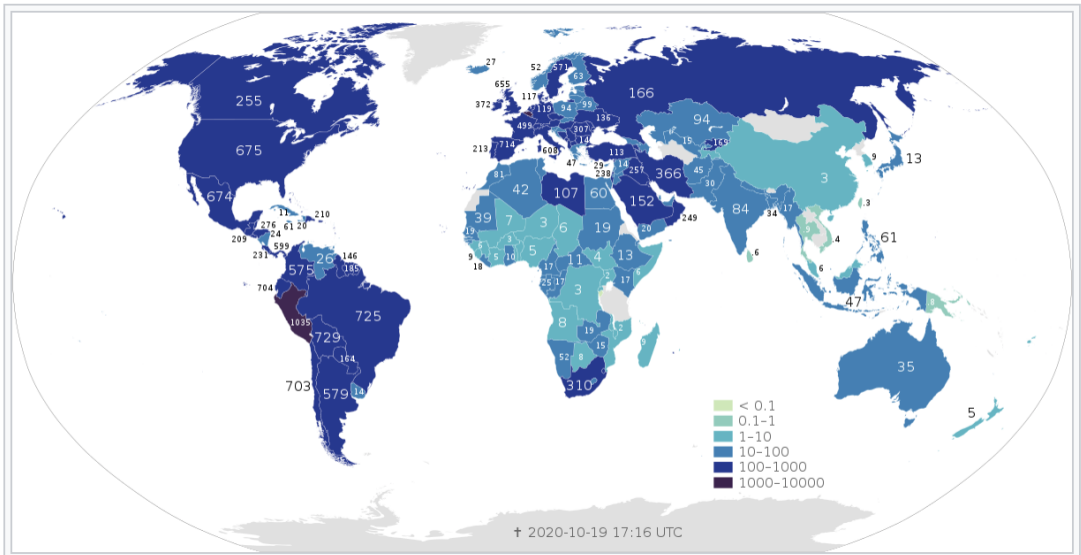
4th wave commenced
Latin dancing cluster
Nepalese clade
Community clusters

https://chp-dashboard.geodata.gov.hk/covid-19/en.html

2019冠狀病毒爆發：2021年1月1日



Cases by country as of 1 January 2021, plotted on a logarithmic scale[357]



Total confirmed deaths per million of COVID-19 by country and territory:

- 1000+ deaths per million inhabitants
- 100–1000 deaths per million inhabitants
- 10–100 deaths per million inhabitants
- 1–10 deaths per million inhabitants
- 0.1–1 deaths per million inhabitants
- 0.01–0.1 deaths per million inhabitants
- No deaths or no data

https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200507covid-19-sitrep-128.pdf?sfvrsn=44cc8ed8_2
https://en.wikipedia.org/wiki/2019_novel_coronavirus_(2019-nCoV)

香港 vs. 紐約

- Hong Kong population: 7.5 million in 1104 km^2; 3rd densely populated in the world
- NYC population: 8.3 million in 784 km^2

- Hong Kong Covid-19: 9075 cases; 154 deaths (mortality rate 1.7%); ICU occupancy <50%
- NYC Covid-19: 711000 cases; 34,552 deaths; (mortality rate 4.9%); ICU occupancy 100%

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https://www1.nyc.gov/site/doh/covid/covid-19-data.page
https://chp-dashboard.geodata.gov.hk/covid-19/en.html
Celum C et al. NEJM 2020; DOI:10.1056

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Dying in a Leadership Vacuum

The Editors

Covid-19 has created a crisis throughout the world. This crisis has produced a test of leadership. With no good options to combat a novel pathogen, countries were forced to make hard choices about how to respond. Here in the United States, our leaders have failed that test. They have taken a crisis and turned it into a tragedy.

The magnitude of this failure is astonishing. According to the Johns Hopkins Center for Systems Science and Engineering,[1] the United States leads the world in Covid-19 cases and in deaths due to the disease, far exceeding the numbers in much larger countries, such as China. The death rate in this country is more than double that of Canada, exceeds that of Japan, a country with a vulnerable and elderly population, by a factor of almost 50, and even dwarfs the rates in lower-middle-income countries, such as Vietnam, by a factor of almost 2000. Covid-19 is an overwhelming challenge, and many factors contribute to its severity. But the one we can control is how we behave. And in the United States we have consistently behaved poorly.

We know that we could have done better. China, faced with the first outbreak, chose strict quarantine and isolation after an initial delay. These measures were severe but effective, essentially eliminating transmission at the point where the outbreak began and reducing the death rate to a reported 3 per million, as compared with more than 500 per million in the United States. Countries that had far more exchange with China, such as Singapore and South Korea, began intensive testing early, along with aggressive contact tracing and appropriate isolation, and have had relatively small outbreaks. And New Zealand has used these same measures, together with its geographic advantages, to come close to eliminating the disease, something that has allowed that country to limit the time of closure and to largely reopen society to a prepandemic level. In general, not only have many democracies done better than the United States, but they have also outperformed us by orders of magnitude.

Why has the United States handled this pandemic so badly? We have failed at almost every step. We had ample warning, but when the disease first arrived, we were incapable of testing effectively and couldn't provide even the most basic personal protective equipment to health care workers and the general public. And we continue to be way behind the curve in testing. While the absolute numbers of tests have increased substantially, the more useful metric is the number of tests performed per infected person, a rate that puts us far down the international list, below such places as Kazakhstan, Zimbabwe, and Ethiopia, countries that cannot boast the biomedical infrastructure or the manufacturing capacity that we have.[2] Moreover, a lack of emphasis on developing capacity has meant that U.S. test results are often long delayed, rendering the results useless for disease control.

Although we tend to focus on technology, most of the interventions that have large effects are not complicated. The United States instituted quarantine and isolation measures late and inconsistently, often without any effort to enforce them, after the disease had spread substantially in many communities. Our rules on social distancing have in many places been lackadaisical

2

Virology 病毒學

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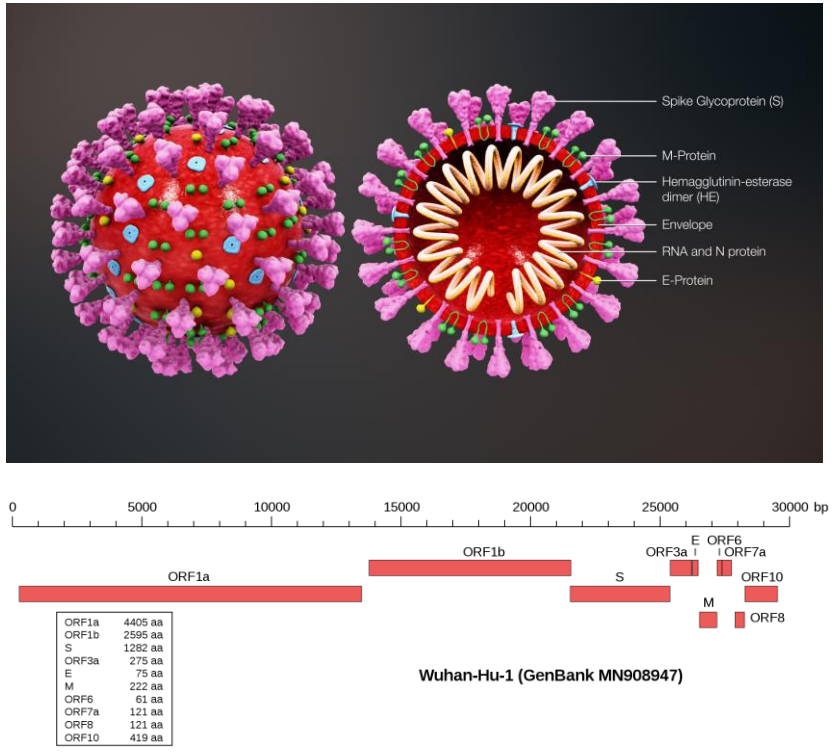
Virology 病毒學



Positive sense, single stranded RNA CoV, Beta-CoV lineage B

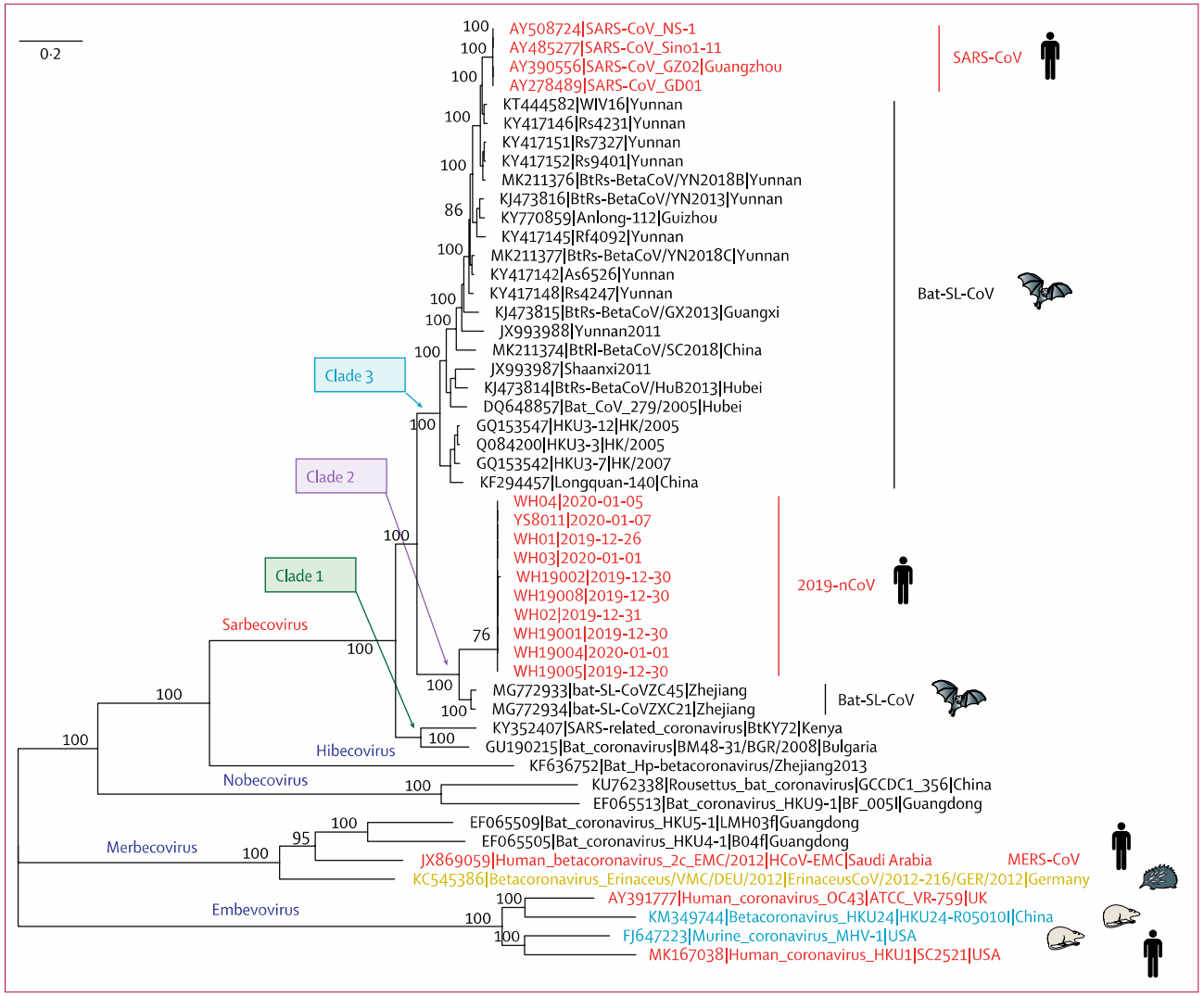


***Figure 3*: Phylogenetic analysis of full-length genomes of 2019-nCoV and representative viruses of the genus Betacoronavirus**
2019-nCoV=2019 novel coronavirus. MERS-CoV=Middle East respiratory syndrome coronavirus. SARS-CoV=severe acute respiratory syndrome coronavirus.

SARS-CoV 79.5%; bat CoV 96%

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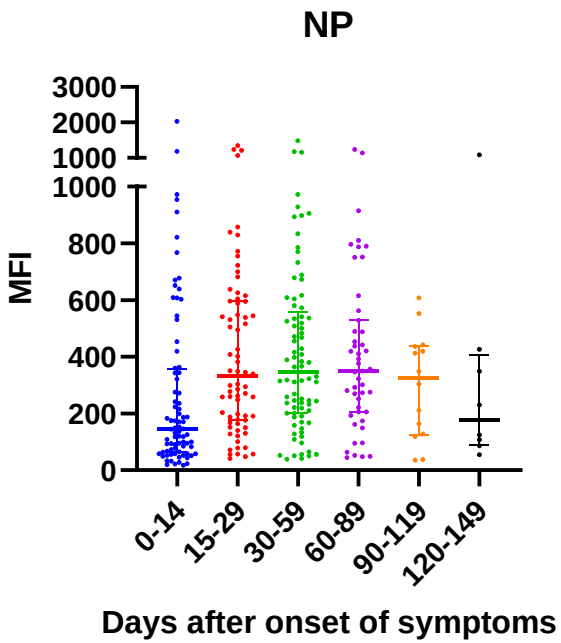
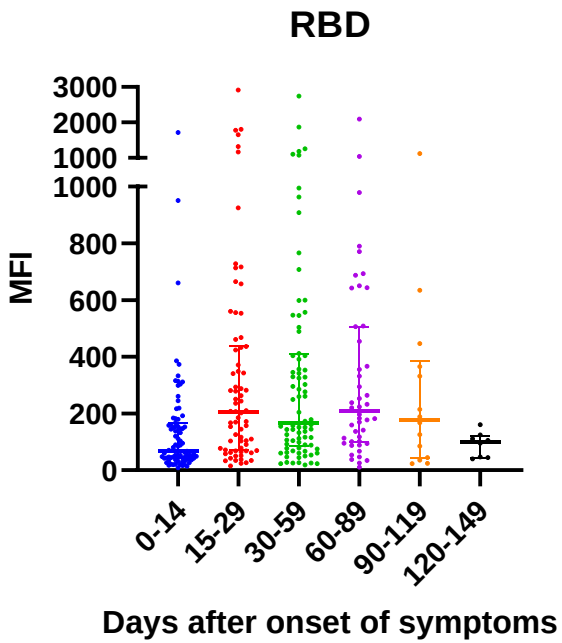
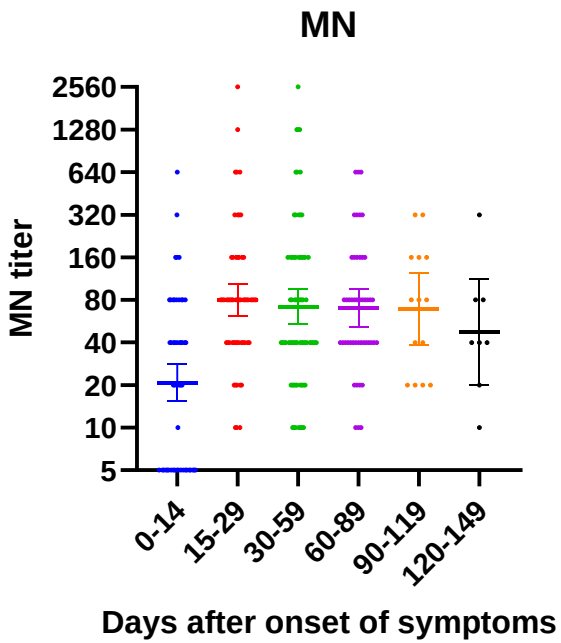
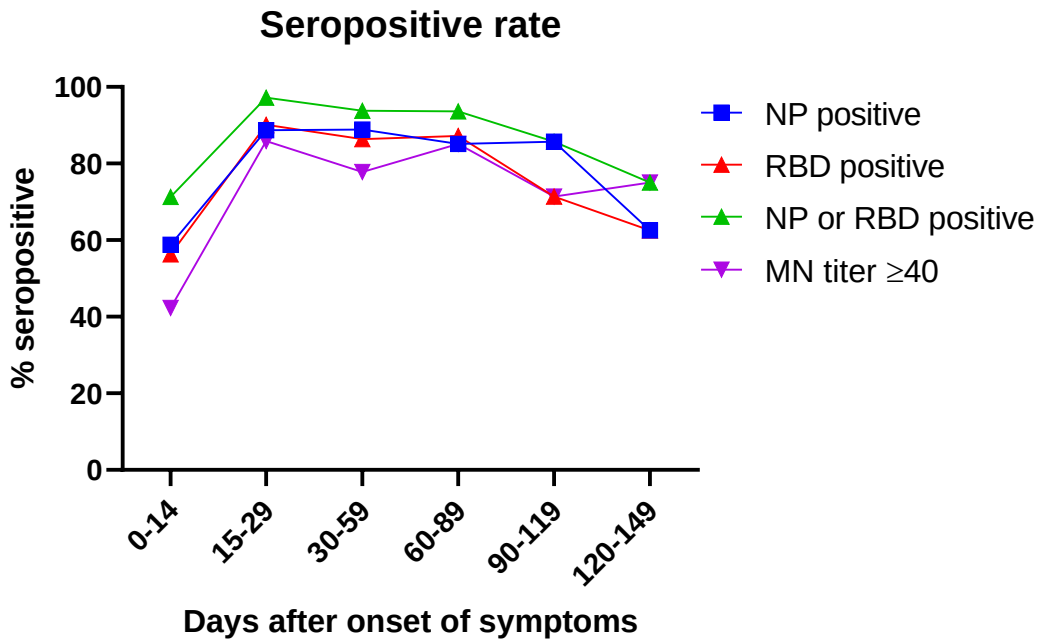
Lu R et al. Lancet 2020; 395:565-74
Chan JF et al. *Lancet* 2020. https://doi.org/10.1016/S0140-6736(20)30154-9





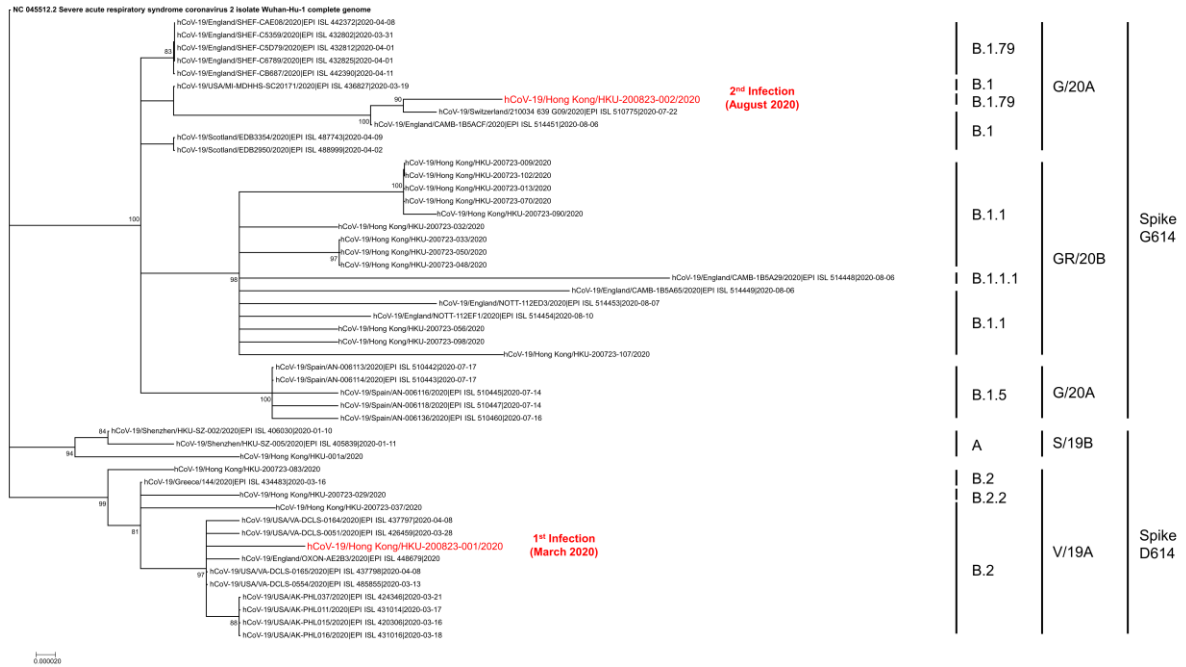


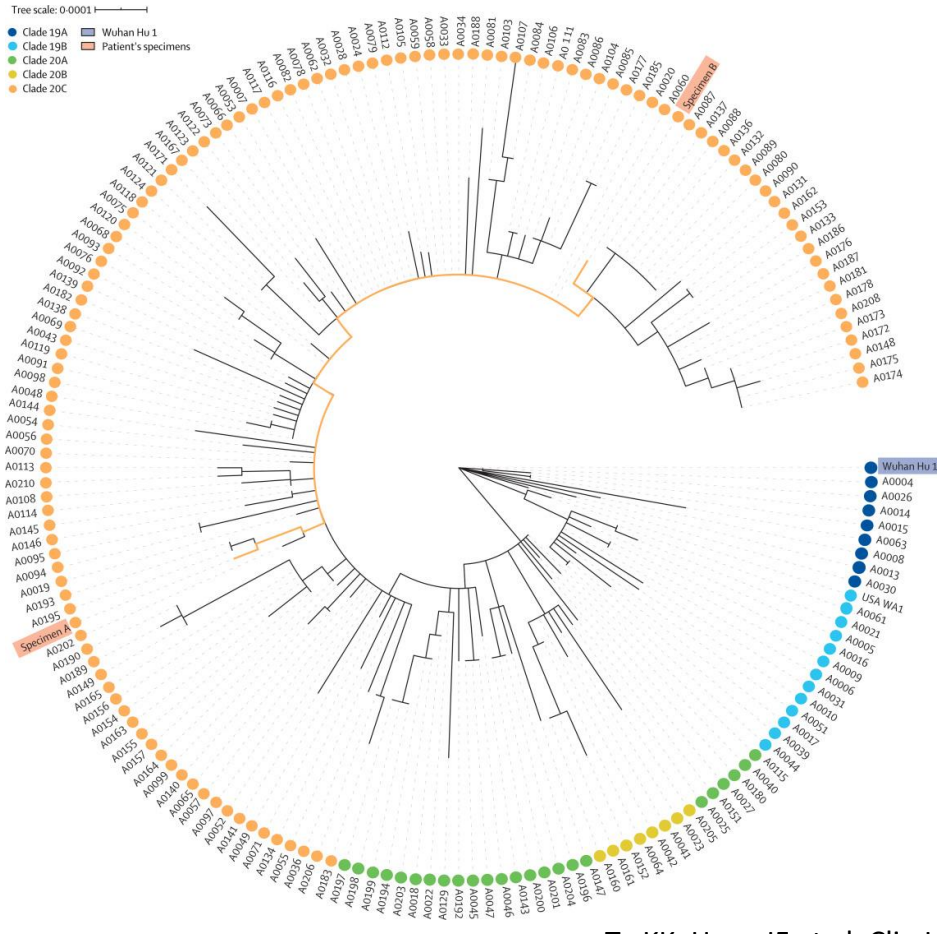
To KK, Hung IF unpublished data



To KK, Hung IF unpublished data

通過全基因組測序確認,
由不同進化分支/譜系SARS-CoV-2毒株導致2019冠狀病毒二次感染

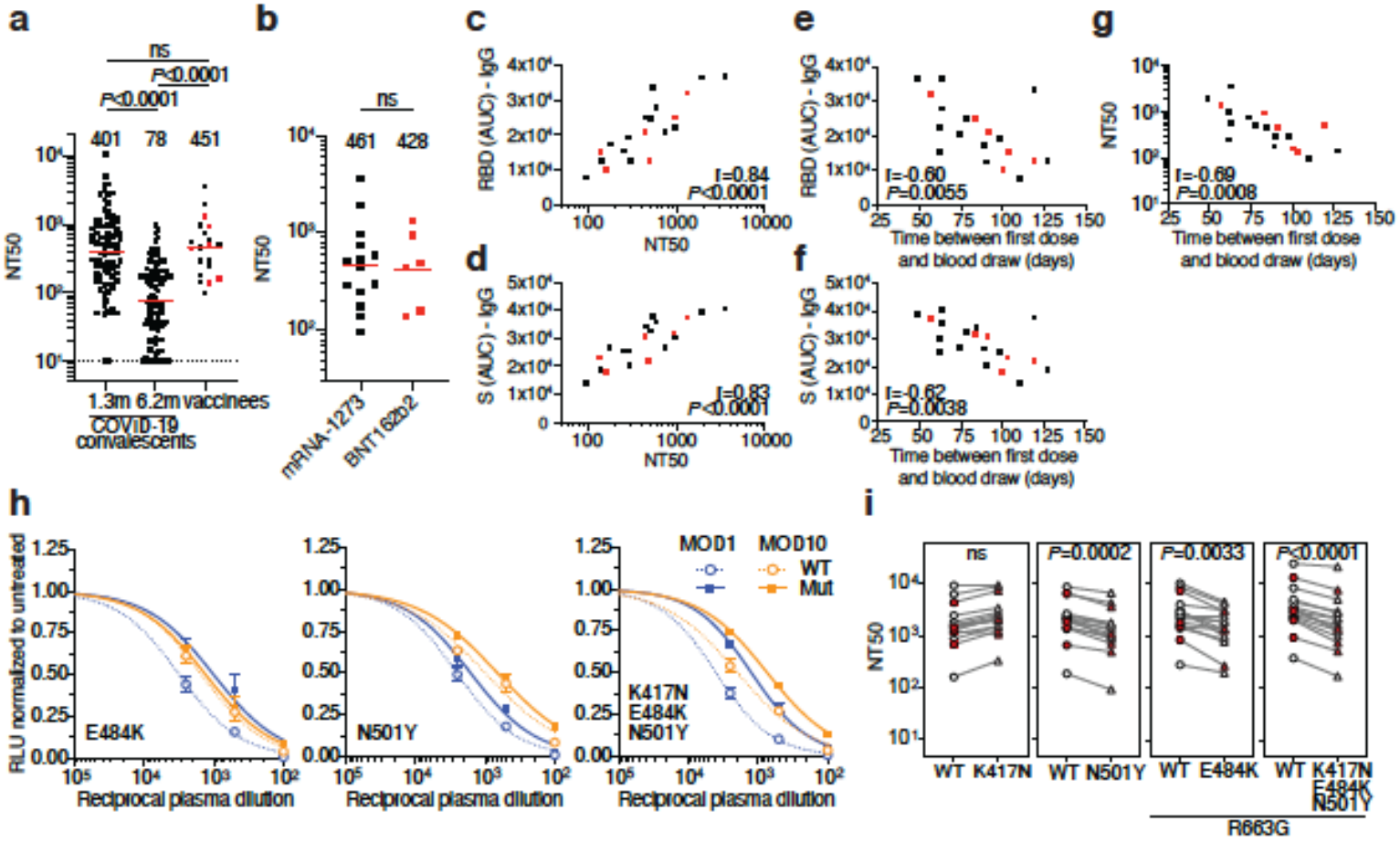


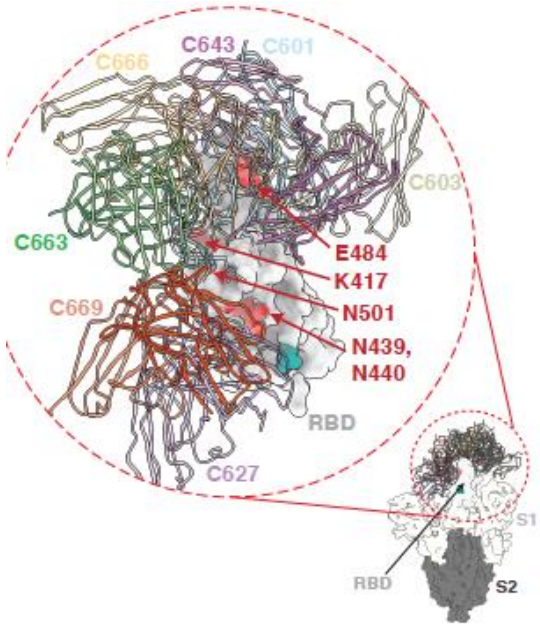


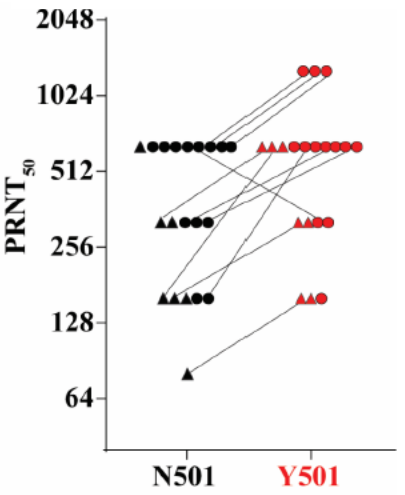
To KK, Hung IF et al. Clin Infect Dis 2020
Tillett RL et al. Lance Infect Dis 2020

N501Y + E484K and K417N mutations (RBD)

刺突蛋白RBD區域突變 (受體結合區) 英國&南非演化分支







Xie X et al. bioRxiv 2021
Wang Z et al. bioRxiv 2021

3

Infection Control & Diagnostics
感染控制及診斷

Infection Control Measures 感染控制措施

The world this week

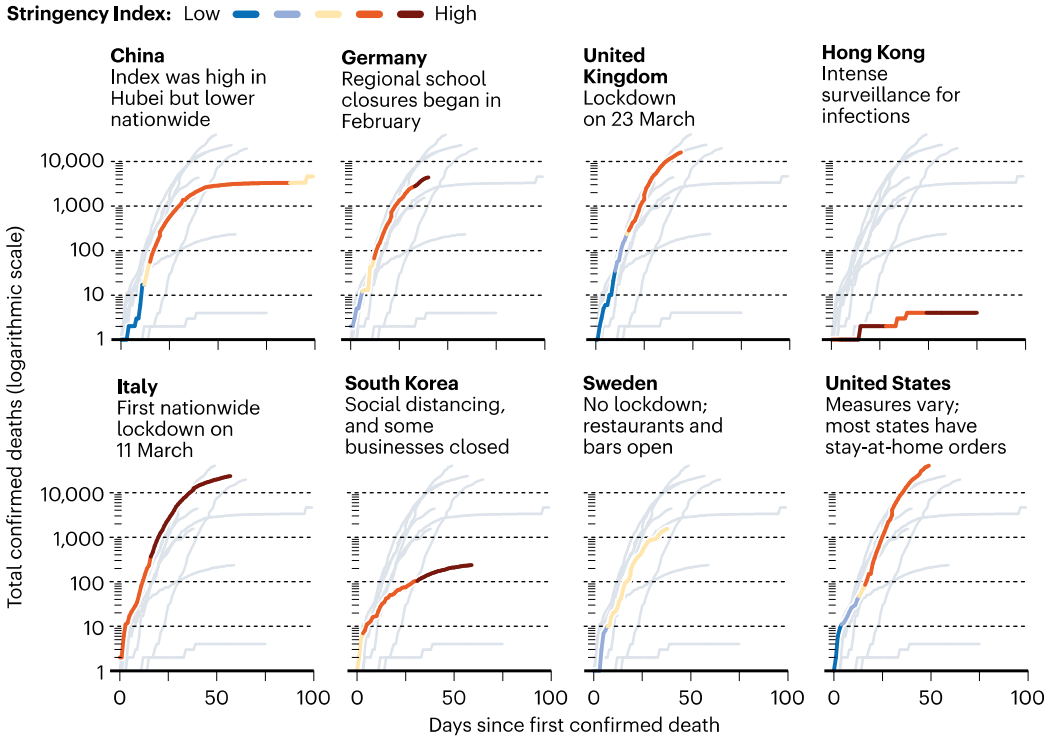
News in focus

Lockdown in Italy: scientists are working out what effects specific measures, such as social distancing, have in slowing the spread of COVID-19.

WHOSE CORONAVIRUS STRATEGY WORKED BEST? SCIENTISTS HUNT MOST EFFECTIVE POLICIES

PANDEMIC PROTECTIONS

Researchers have created a 'stringency index' that describes the overall severity of a country's response to the coronavirus outbreak and allows responses to be compared. The index takes into account seven control measures, such as school closures and restrictions on people's movements.

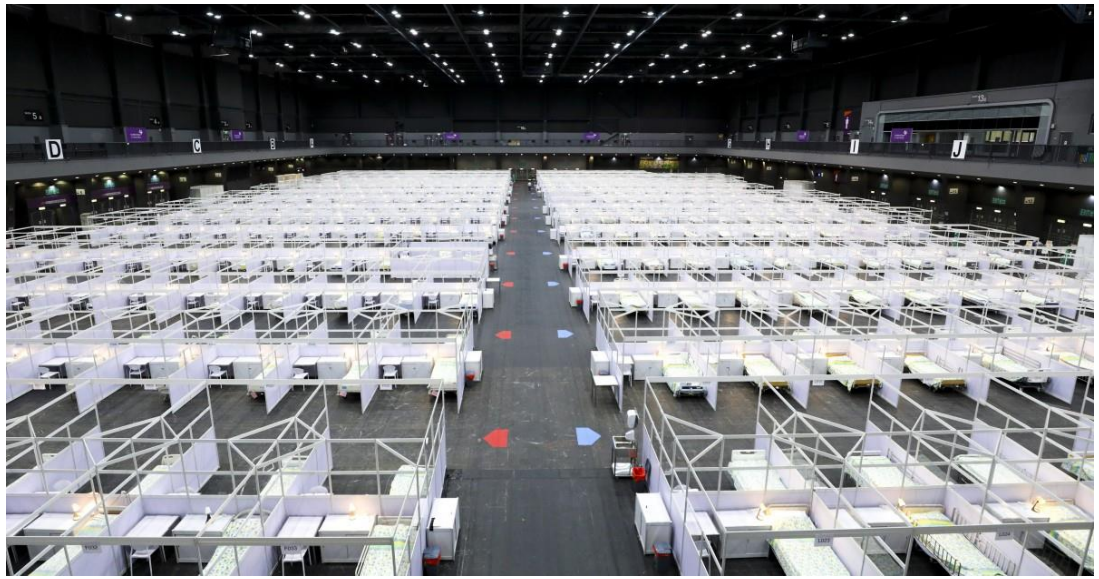


Confirmed deaths undercount true COVID-19 mortality. Stringency index developed by the Oxford COVID-19 Government Response Tracker. Data downloaded on 21 April; countries vary in day of most recent data update.

https://www.nature.com/articles/d41586-020-01248-1

感染控制措施

- Universal face masks with good compliance
- Social distancing
- Border control and screening
- Easily accessible diagnostic testing
- Contact tracing
- Home quarantine
- Centralized quarantine
- Hospitalization for confirmed
- Negative pressure isolation rooms: moderate and severe cases
- Asia World Expo Community Hospital for mild cases



https://www.nature.com/articles/d41586-020-01248-1
Chan JF, et al. Clin Infect Dis 2020;71:2139-2149

診斷

Current infection

RT-PCR

- Targeting RNA-dependent RNA polymerase (RdRp)
- Spike (S)
- Nucleocapsid (N)

Samples

- Nasopharyngeal swab
- Deep throat saliva
- Throat swab
- Sputum
- Stool

Recent past infection

- Serology
- IgG/ IgM
- Neutralizing antibody

http://videocwp.ha.org.hk/wmv/deep%20throat%20saliva%20v2.mp4

唾液 vs. 鼻咽拭子

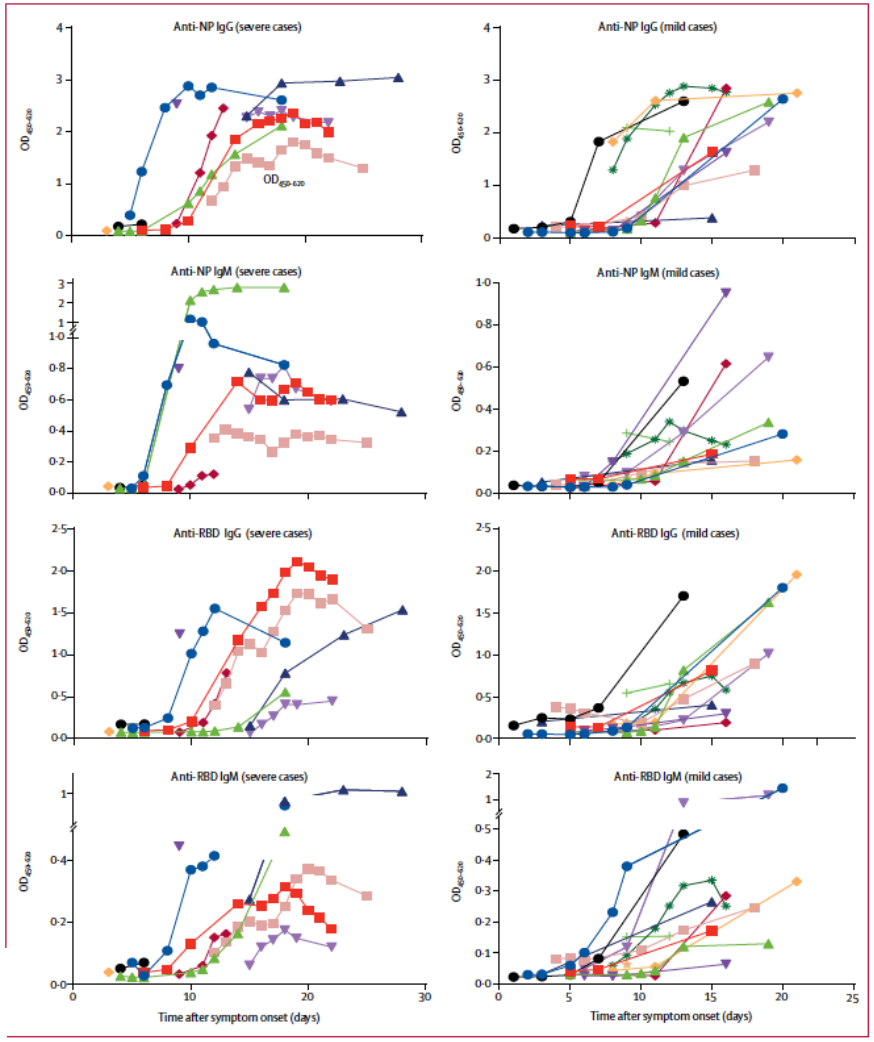


Figure 4: Temporal profiles of serum IgM and IgG against NP and spike protein RBD, as ascertained by EIA
Each line represents an individual patient. NP=nucleoprotein. RBD=receptor-binding domain. $OD_{450-620}$=optical density at 450–620 nm.

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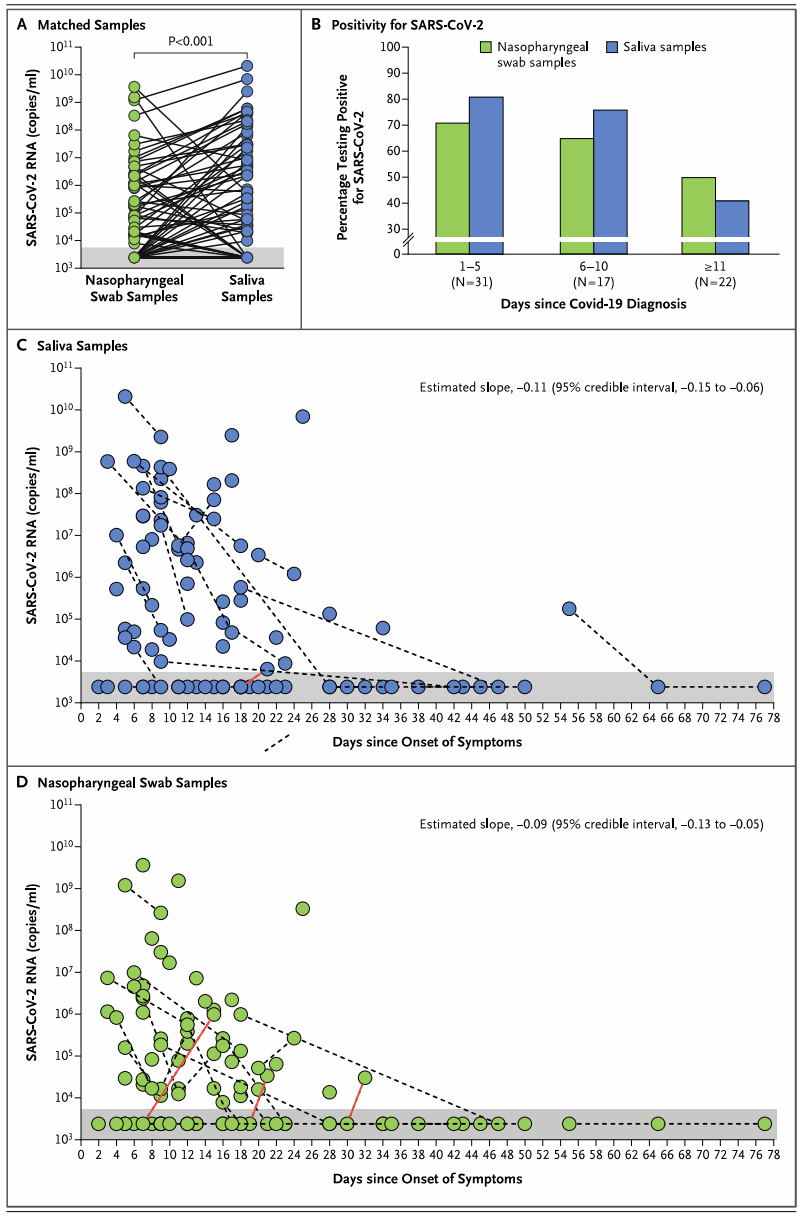


Higher mean log copies/mL in saliva 5.58 (5.09-6.07) vs. NPS 4.93 (4.53-5.33)

Higher % positive up to 10 days after diagnosis in saliva than NPS
Day 1 to 5: 81% vs. 71%
Day 6 to 10: 75% vs. 67%

Less variation for saliva viral load
More NPS sampling variation

Negates need for direct interaction between patients and HCW,

Alleviates PPE and swabs demand

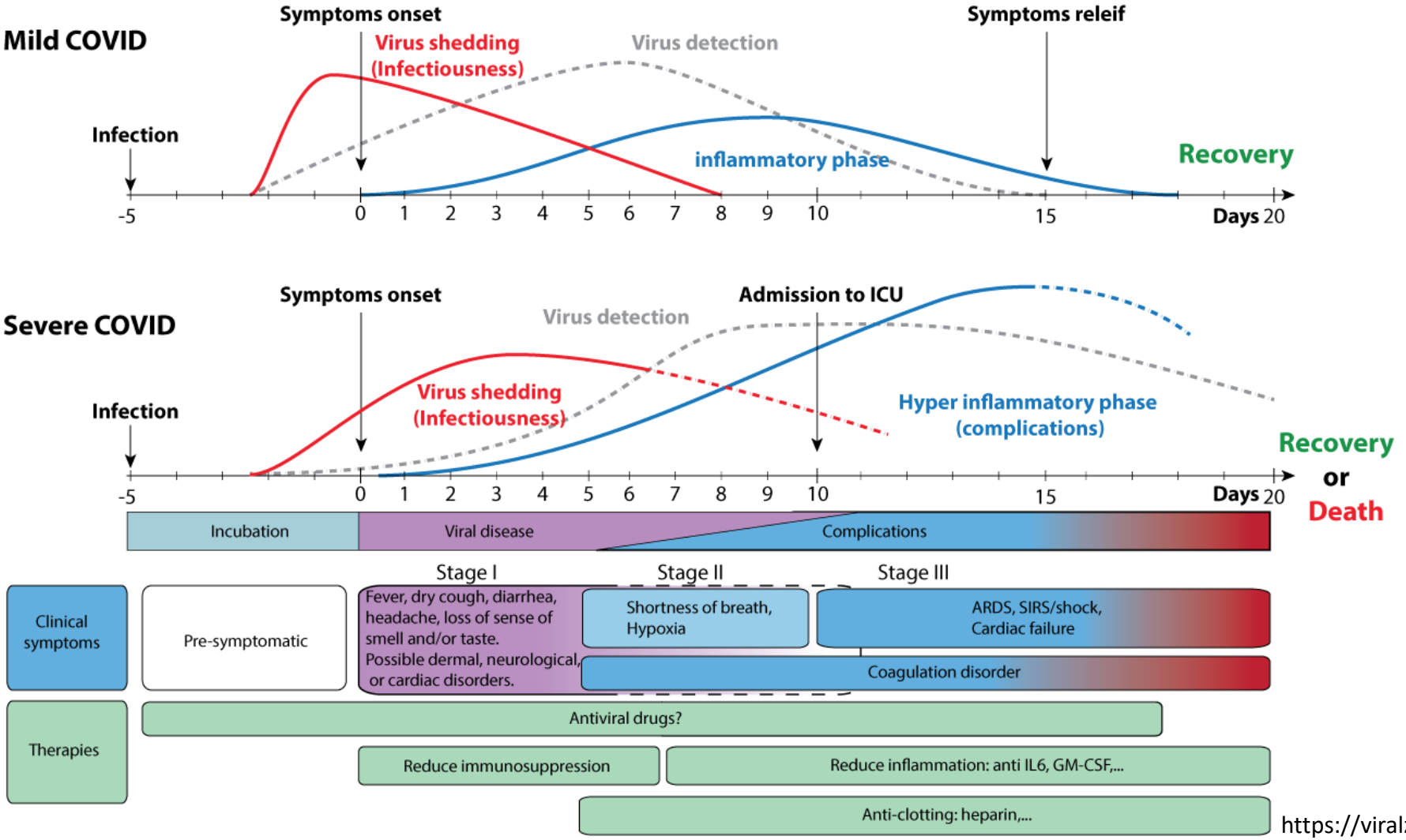
To KK et al. Lancet Infect Dis 2020;20:565-74
Wyllie AL, et al. NEJM 2020;383:1283-86

4

Clinical Characteristics
臨床特徵

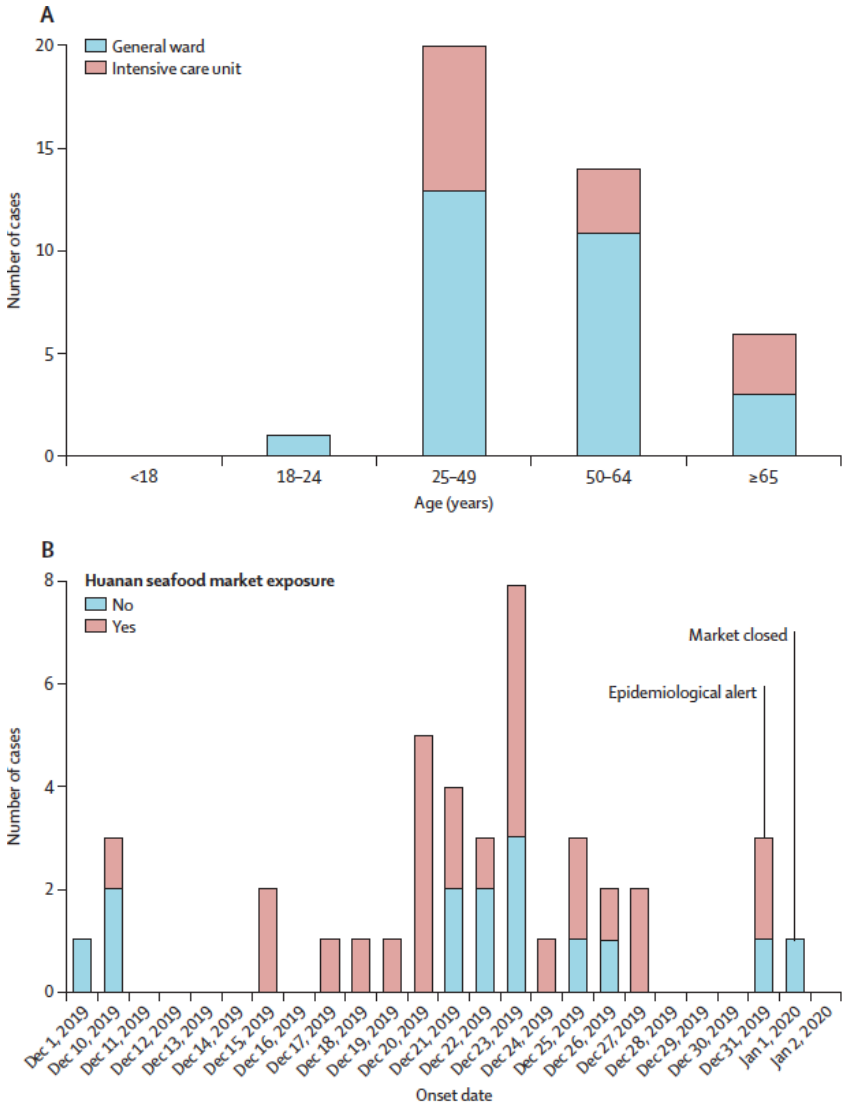
Covid-19 Disease Pathogenesis Models

2019冠狀病毒發病機制



https://viralzone.expasy.org/9116

高危群組



	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)	0·0023
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

Guan W, N Zhong et al. NEJM DOI:10.1056

Huang C et al. Lancet 2020; S0140-6736

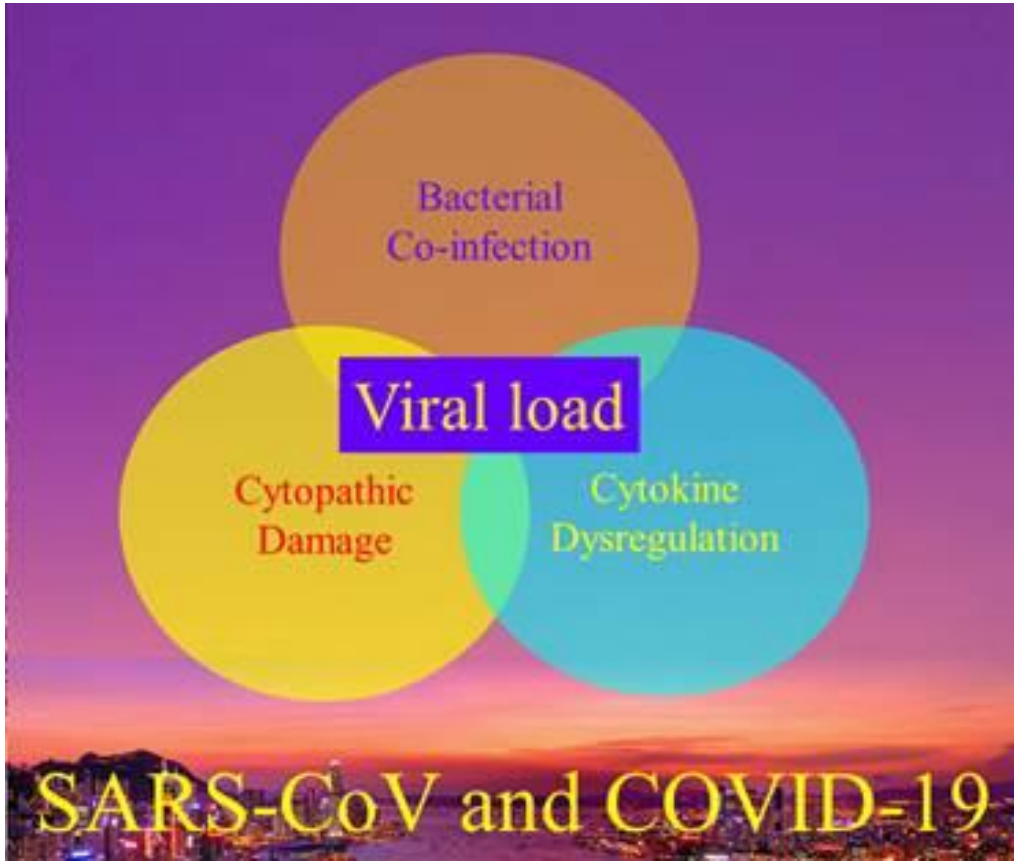
HKU Med
LKS Faculty of Medicine
Department of Medicine
香港大學內科學系

5

Antivirals and Immunomodulators
抗病毒及免疫調節藥物

Principles of Antiviral Treatments
抗病毒治療之原理

- Early commencement of antiviral Combination therapy
  - Increase spectrum of activity
  - Increase potency
  - Reduce resistance emergence
- Rapid suppression of viral load
- Prevent subsequent complications
- Reduce viral shedding



Courtesy of Dr. KY Lai

重新利用舊有已核准或上市藥物之篩選

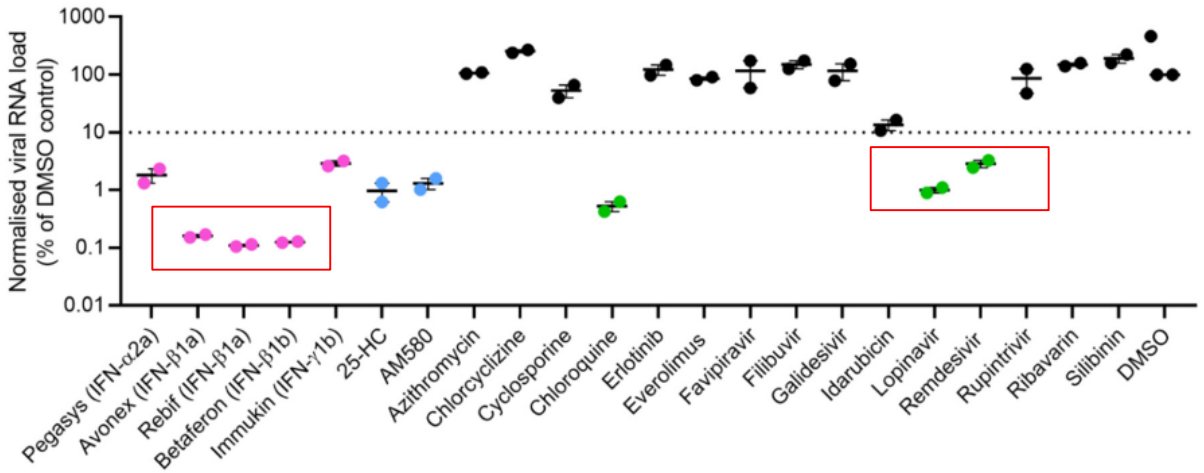


Table 2. Antiviral activities and cytotoxicities of the anti-SARS-CoV-2 antiviral agents identified in the primary screening.

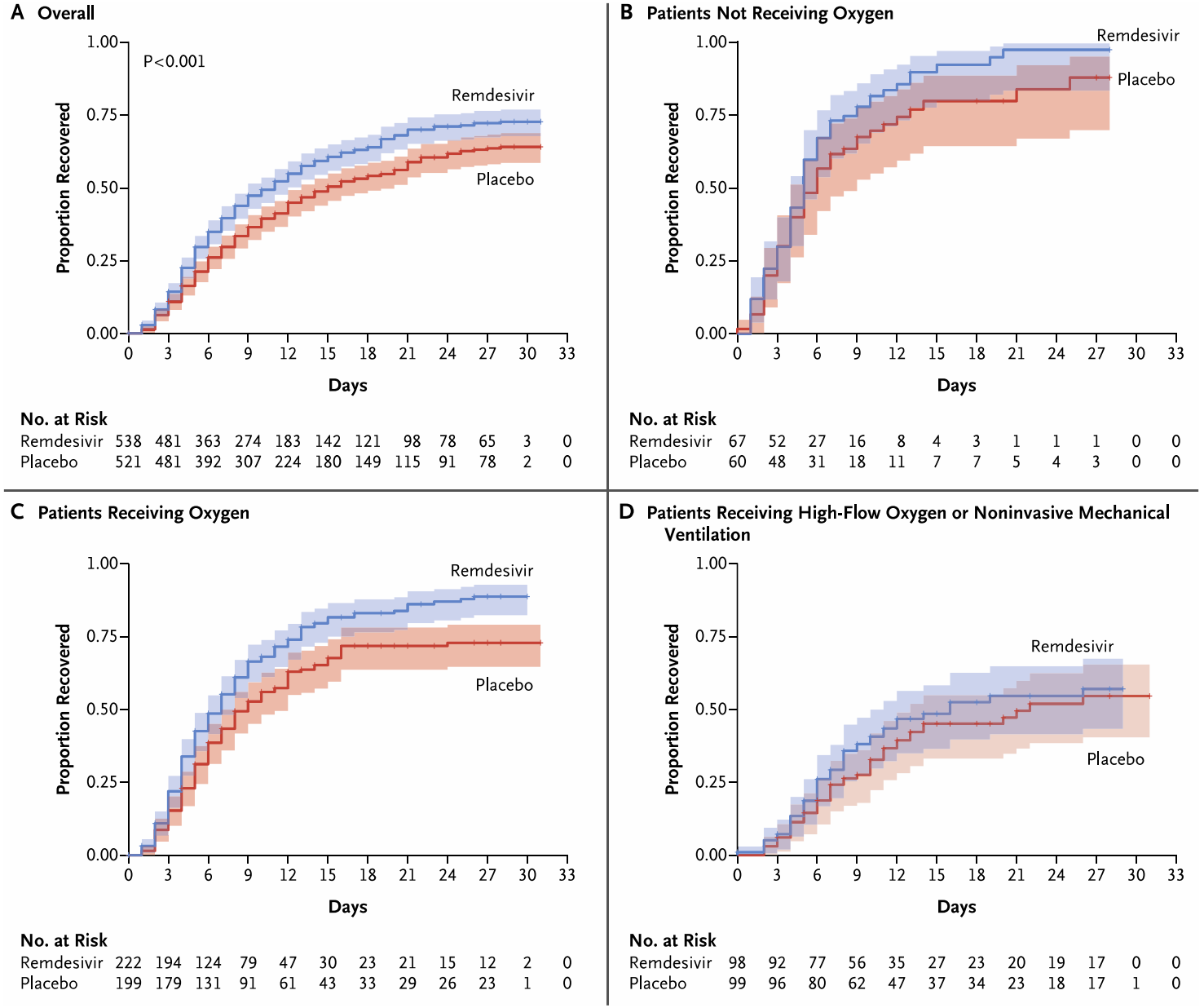
Antiviral Agent	CC_{50} (CellTiterGlo®) [a]	EC_{50} (Plaque Reduction Assay)	Select Index (CC_{50}/EC_{50})
Pegasys (pegylated IFN-α2a)	>50,000 IU/mL	1068.0 IU/mL	>46.8
Avonex (IFN-β1a)	>50,000 IU/mL	109.6 IU/mL	>456.2
Rebif (IFN-β1a)	>50,000 IU/mL	70.8 IU/mL	>706.2
Betaferon (IFN-β1b)	>50,000 IU/mL	31.2 IU/mL	>1602.6
Immukin (IFN-γ1b)	>50,000 IU/mL	142.2 IU/mL	>351.6
25-hydroxycholesterol	>50 μM	4.2 μM	>11.9
AM580	126 μM	7.6 μM	16.6
Lopinavir	102 μM	11.6 μM	8.8
Remdesivir	>100 μM	1.04 μM	96.2

HKU Med

Yuan S et al. Viruses 2020;628;doi:10.3390

瑞德西韋

Clinical recovery: 11 days vs 15 days
HR 1.32; 95% CI 1.12-1.55; p<0.001



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Beigel JH, et al NEJM 2020; doi;10.1056

地塞米松針對2019冠狀病毒住院患者

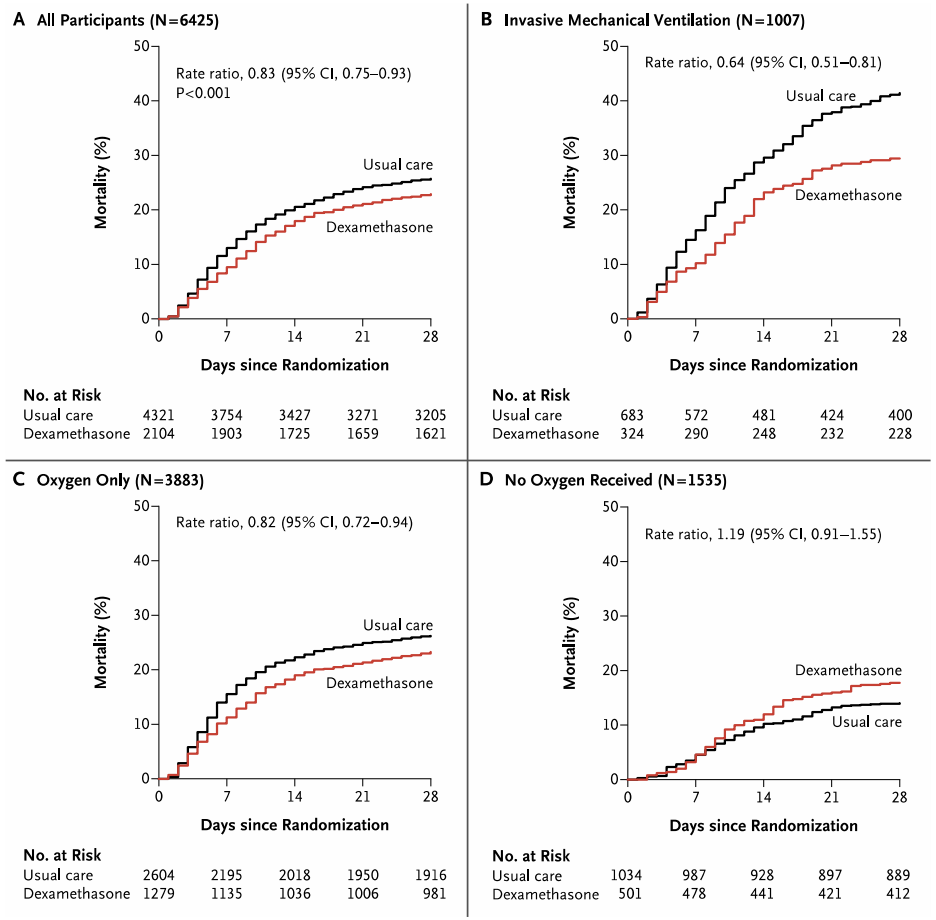


Table 2. Primary and Secondary Outcomes.

Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
	no./total no. of patients (%)		
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
Invasive mechanical ventilation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)

The RECOVERY Collaborative Group NEJM 2020; DOI:10.1056

2019冠狀病毒抗病毒藥物療效評價—世界衛生組織臨床測試結果

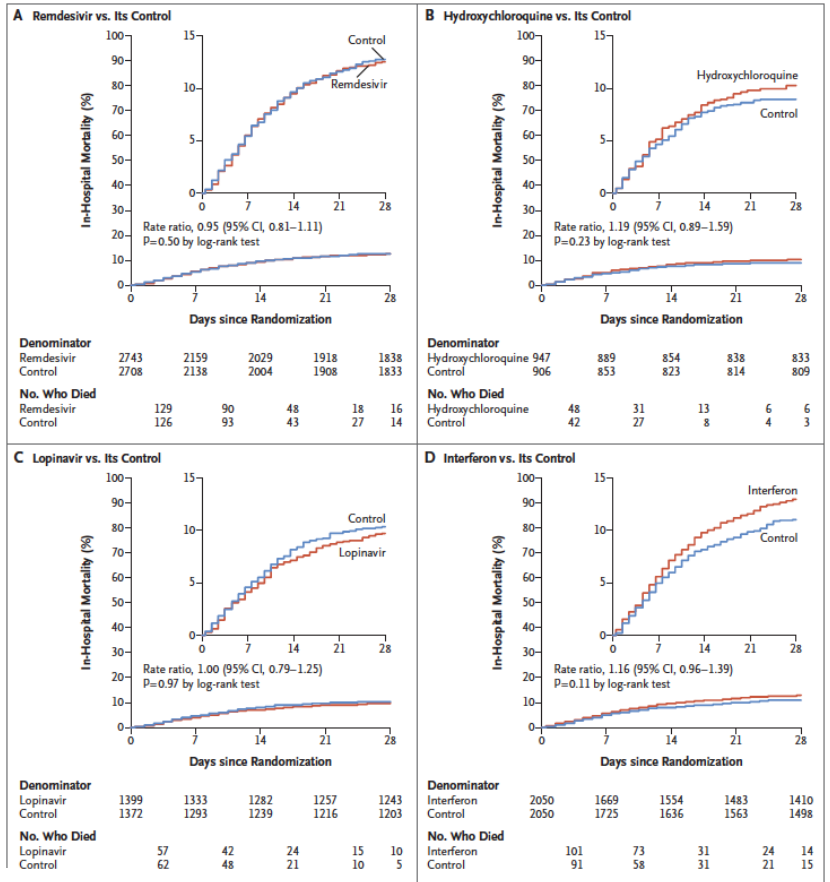
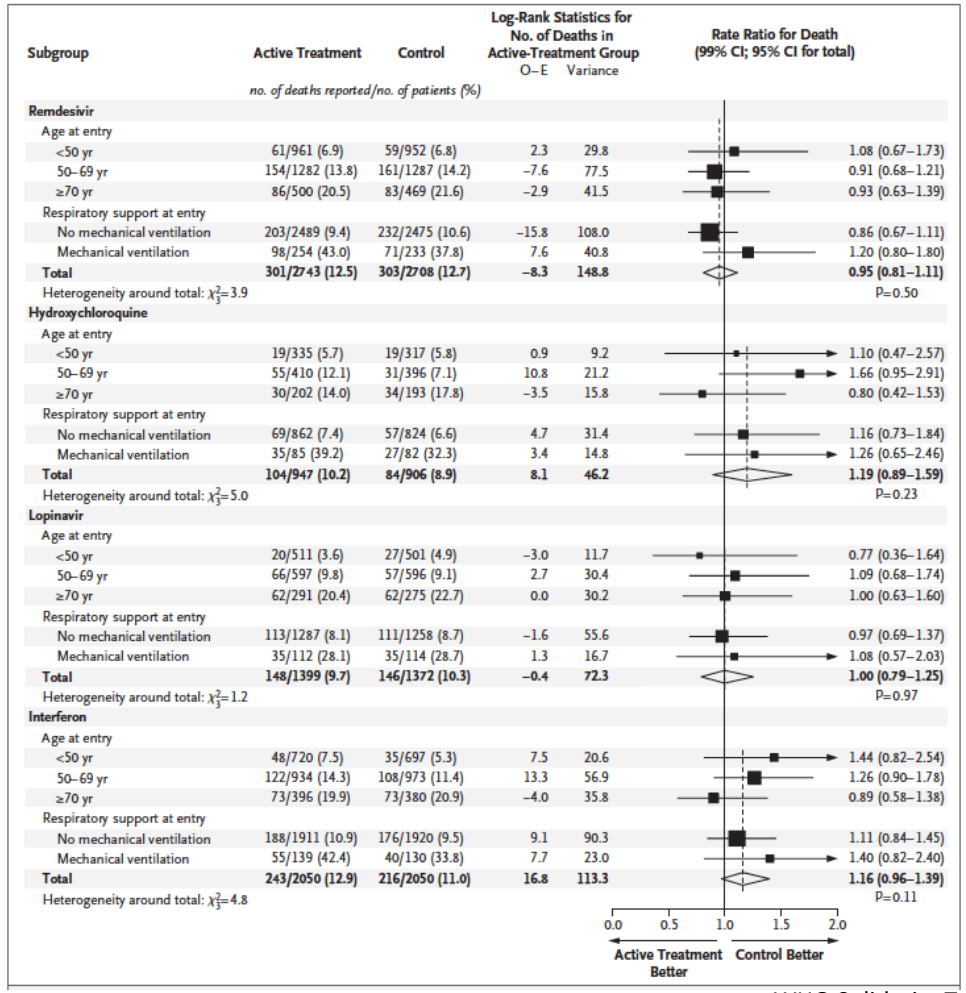


Figure 2. Effects of Remdesivir, Hydroxychloroquine, Lopinavir, and Interferon on In-Hospital Mortality.

Shown are Kaplan–Meier graphs of in-hospital mortality at any time (the primary outcome), comparing each treatment with its control without standardization for any initial patient characteristics. Insets show the same data on an expanded y axis. The rate ratios for death were standardized for age and for ventilation status at entry. Denominators for the few events on day 0, but not thereafter, include patients with no follow-up. Numbers of deaths are by week, and then deaths after day 28. CI denotes confidence interval.

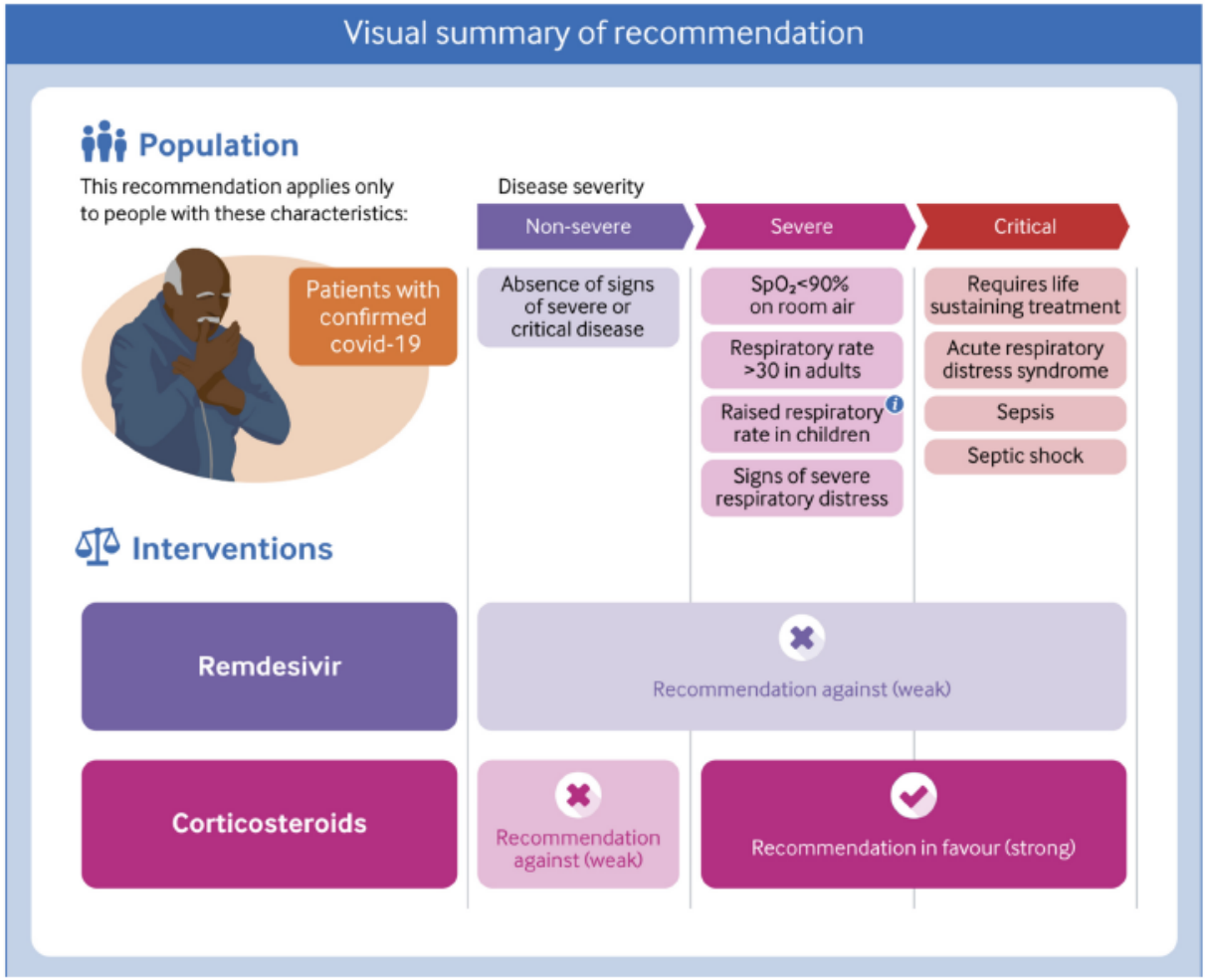


Subgroup	Active Treatment	Control	Log-Rank Statistics for No. of Deaths in Active-Treatment Group O–E	Variance	Rate Ratio for Death (99% CI; 95% CI for total)
	no. of deaths reported/no. of patients (%)				
Remdesivir					
Age at entry					
<50 yr	61/961 (6.9)	59/952 (6.8)	2.3	29.8	1.08 (0.67–1.73)
50–69 yr	154/1282 (13.8)	161/1287 (14.2)	−7.6	77.5	0.91 (0.68–1.21)
≥70 yr	86/500 (20.5)	83/469 (21.6)	−2.9	41.5	0.93 (0.63–1.39)
Respiratory support at entry					
No mechanical ventilation	203/2489 (9.4)	232/2475 (10.6)	−15.8	108.0	0.86 (0.67–1.11)
Mechanical ventilation	98/254 (43.0)	71/233 (37.8)	7.6	40.8	1.20 (0.80–1.80)
Total	**301/2743 (12.5)**	**303/2708 (12.7)**	**−8.3**	**148.8**	**0.95 (0.81–1.11)**
Heterogeneity around total: χ^2_3=3.9					P=0.50
Hydroxychloroquine					
Age at entry					
<50 yr	19/335 (5.7)	19/317 (5.8)	0.9	9.2	1.10 (0.47–2.57)
50–69 yr	55/410 (12.1)	31/396 (7.1)	10.8	21.2	1.66 (0.95–2.91)
≥70 yr	30/202 (14.0)	34/193 (17.8)	−3.5	15.8	0.80 (0.42–1.53)
Respiratory support at entry					
No mechanical ventilation	69/862 (7.4)	57/824 (6.6)	4.7	31.4	1.16 (0.73–1.84)
Mechanical ventilation	35/85 (39.2)	27/82 (32.3)	3.4	14.8	1.26 (0.65–2.46)
Total	**104/947 (10.2)**	**84/906 (8.9)**	**8.1**	**46.2**	**1.19 (0.89–1.59)**
Heterogeneity around total: χ^2_3=5.0					P=0.23
Lopinavir					
Age at entry					
<50 yr	20/511 (3.6)	27/501 (4.9)	−3.0	11.7	0.77 (0.36–1.64)
50–69 yr	66/597 (9.8)	57/596 (9.1)	2.7	30.4	1.09 (0.68–1.74)
≥70 yr	62/291 (20.4)	62/275 (22.7)	0.0	30.2	1.00 (0.63–1.60)
Respiratory support at entry					
No mechanical ventilation	113/1287 (8.1)	111/1258 (8.7)	−1.6	55.6	0.97 (0.69–1.37)
Mechanical ventilation	35/112 (28.1)	35/114 (28.7)	1.3	16.7	1.08 (0.57–2.03)
Total	**148/1399 (9.7)**	**146/1372 (10.3)**	**−0.4**	**72.3**	**1.00 (0.79–1.25)**
Heterogeneity around total: χ^2_3=1.2					P=0.97
Interferon					
Age at entry					
<50 yr	48/720 (7.5)	35/697 (5.3)	7.5	20.6	1.44 (0.82–2.54)
50–69 yr	122/934 (14.3)	108/973 (11.4)	13.3	56.9	1.26 (0.90–1.78)
≥70 yr	73/396 (19.9)	73/380 (20.9)	−4.0	35.8	0.89 (0.58–1.38)
Respiratory support at entry					
No mechanical ventilation	188/1911 (10.9)	176/1920 (9.5)	9.1	90.3	1.11 (0.84–1.45)
Mechanical ventilation	55/139 (42.4)	40/130 (33.8)	7.7	23.0	1.40 (0.82–2.40)
Total	**243/2050 (12.9)**	**216/2050 (11.0)**	**16.8**	**113.3**	**1.16 (0.96–1.39)**
Heterogeneity around total: χ^2_3=4.8					P=0.11

Limitations:
1. Heterogeneity of each countries (ICU support)
2. No data on symptoms onset days (late presenters)
3. No virological data, biochemical and inflammatory markers

WHO Solidarity Trial Consortium NEJM 2020; DOI:10.1056

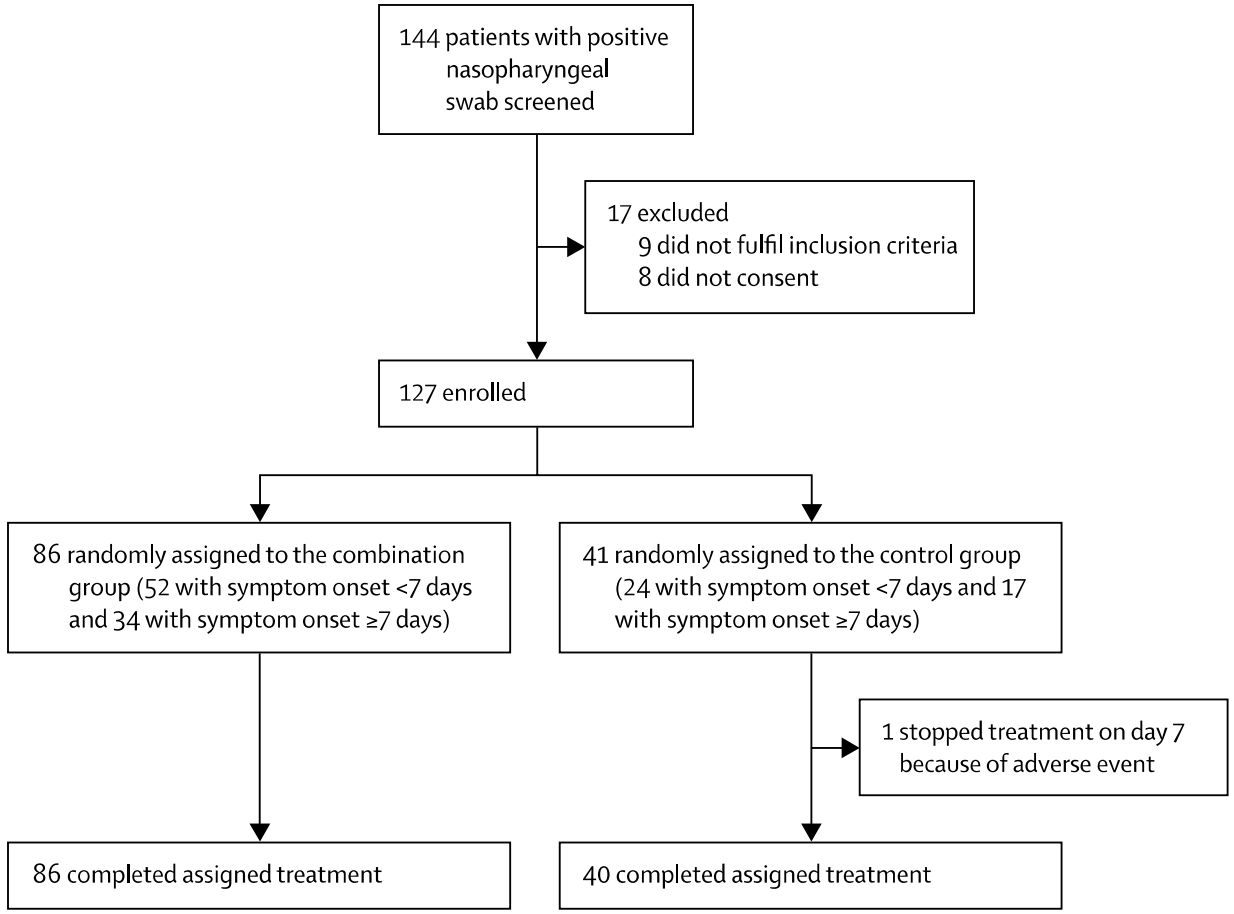
世衛組織對於2019冠狀病毒現行藥物指引



Rochwerg B et al. BMJ 2020;370:m3379

干擾素β-1b + 洛匹那韋/利托那韋 + 利巴韋林

- **IFN beta-1b 8MU alternate day x 3 doses + lopinavir-ritonavir 400/100mg bd + ribavirin 400mg bd vs. lopinavir/ ritonavir 400mg bd for 14 days**
- **Time from symptom onset to treatment for triple therapy within combo group: Median 4 days (3-6)**
- **Median number of IFN beta-1b received: 2 doses**



Hung IF et al. Lancet 2020:doi.org/10.1016/PII

干擾素β-1b + 洛匹那韋/利托那韋 + 利巴韋林

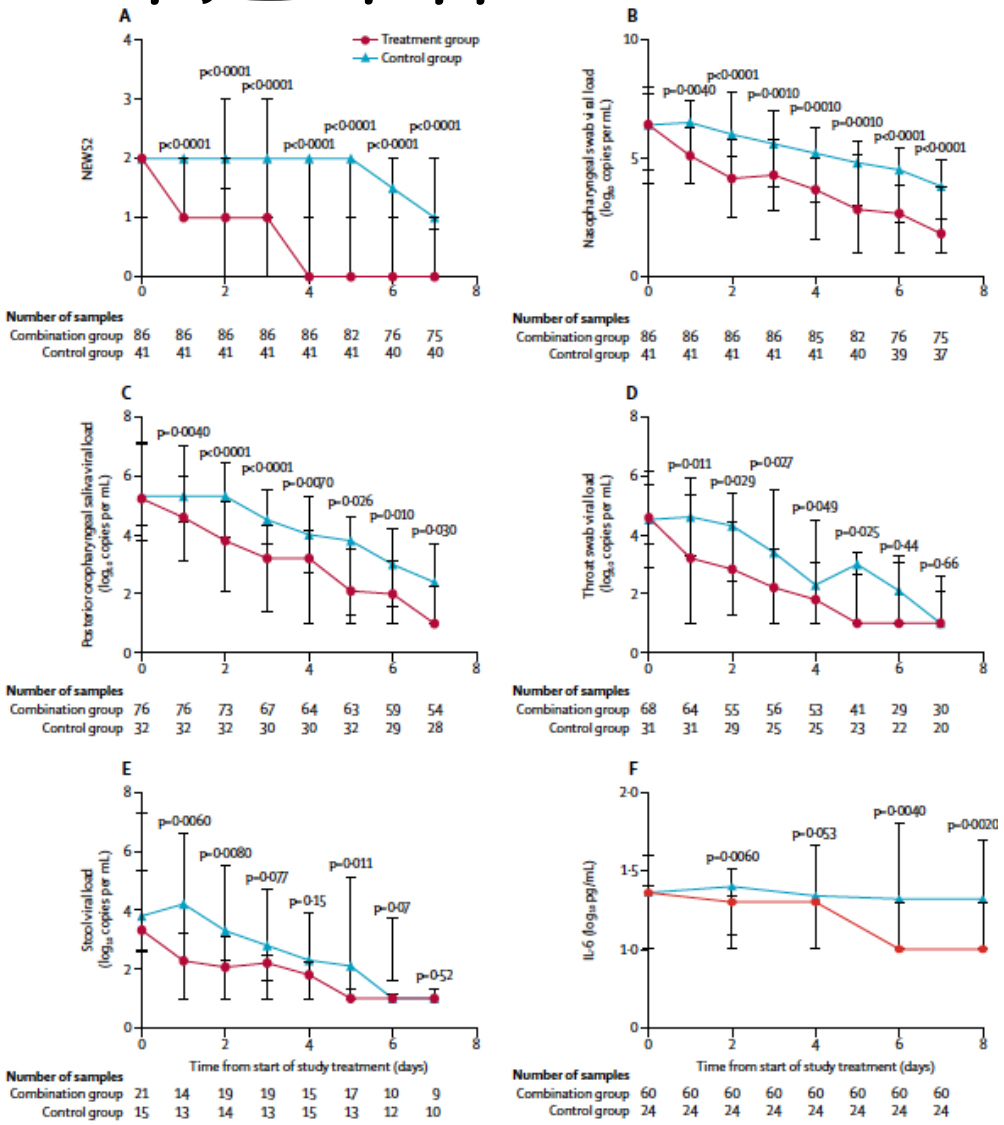
Primary outcome:
Combo group significantly shorter
median time from start of treatment
to negative NPS: 7 (5-11) vs. 12 (8-15) days

HR: 4.37 [95% CI 1.86-10.24} p=0.0010

No significant nsp5 mutations
were identified in serial NPS

Few GI side effects and self-limiting

Conclusion:
IFN beta-1b based triple therapy is
safe and superior to lopinavir-ritonavir
alone



Hung IF et al. Lancet 2020:doi.org/10.1016/PII

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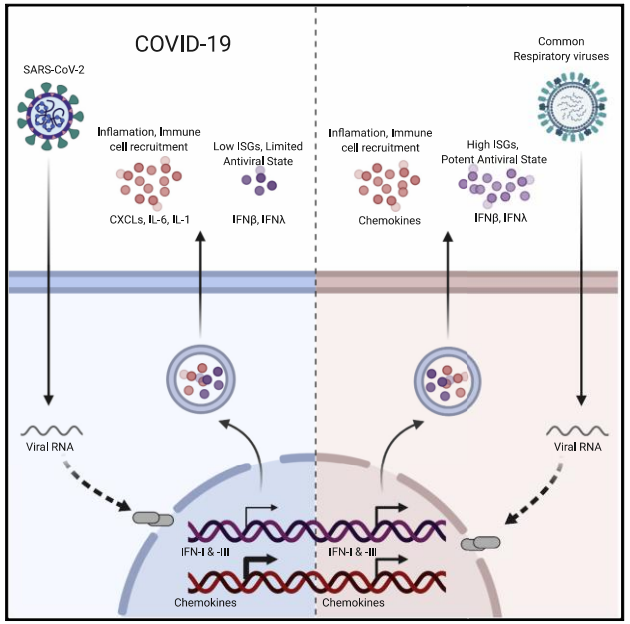
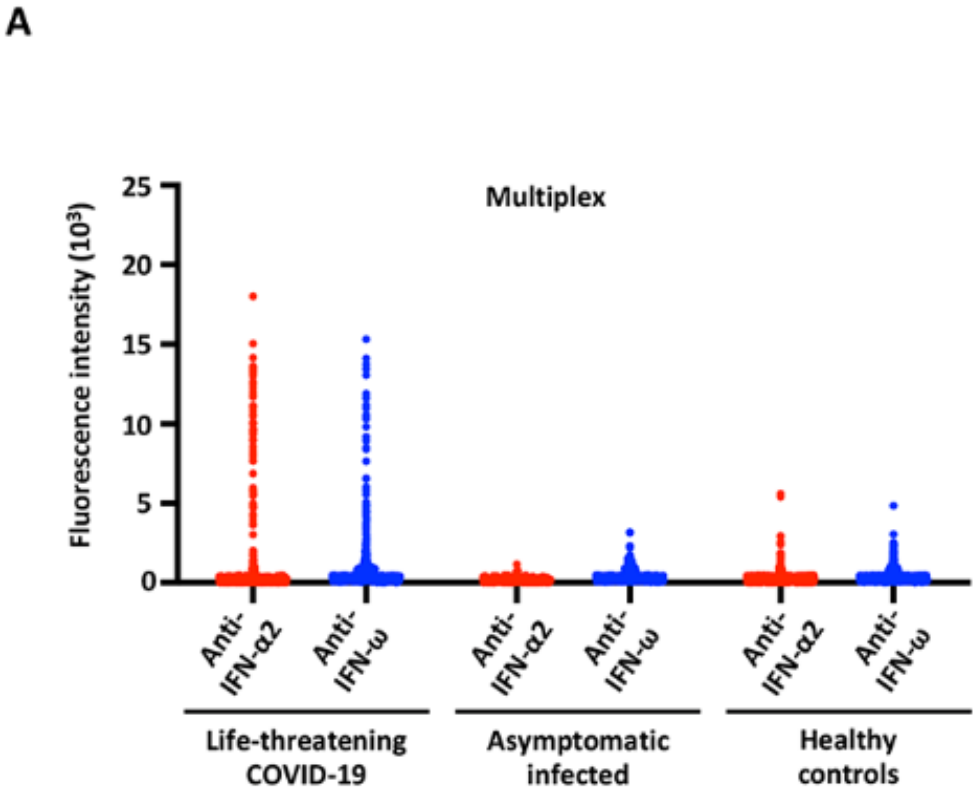
針對2019冠狀病毒的干擾素相關藥物



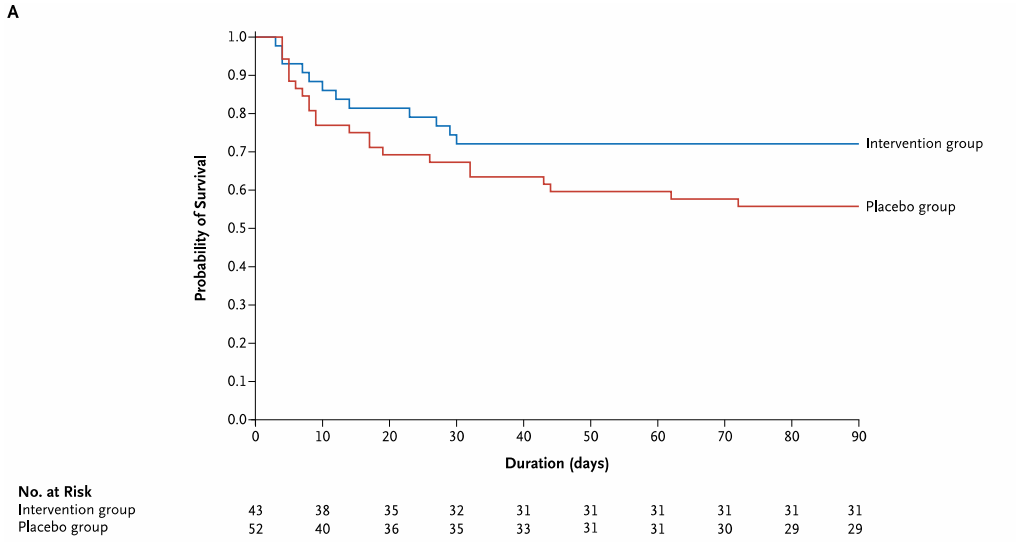
Highlights

- SARS-CoV-2 infection induces low IFN-I and -III levels with a moderate ISG response
- Strong chemokine expression is consistent across *in vitro*, *ex vivo*, and *in vivo* models
- Low innate antiviral defenses and high pro-inflammatory cues contribute to COVID-19



Blanco-Melo D, et al. Cell 2020;181:1036-45
Bastard P et al. Science 2020;eabd4585

針對中東呼吸綜合症的 干擾素β-1b & 洛匹那韋/利托那韋



95 patients enrolled

Time to enrollment from symptoms onset:
7 days vs 7.5days

7 doses of IFN beta-1b given

28-day Mortality: 23% vs 33%
ICU stay: 28% vs 42%
Hospital Stay 30% vs 44%

Median days to viral load clearance:
17 (9-25) vs 20 (10-33) days

Arabi YM et al. NEJM 2020;DOI:10.1056

2019冠狀病毒康復者恢復血漿

EAP to EUA transition

All program forms must be completed and submitted by November 30, 11:59 CST. Any uncompleted work will be submitted to the central IRB as a potential non-compliance.

Due to the overwhelming volume of program inquiries, it may take longer to receive a response. We appreciate your patience as we work through our communications backlog.

The US COVID Plasma Team is currently focused on collecting missing information and verifying the accuracy of information for each patient enrolled in the EAP.

Top priorities

1. Ensuring information on the patient is accurate
2. Ensuring physician information is accurate

Complete data is vital

We will improve the accuracy of patient data by:

- Pursuing delinquent reporting by physicians
- Obtaining missing medical history information

Historical EAP program participation

November 29, 2020

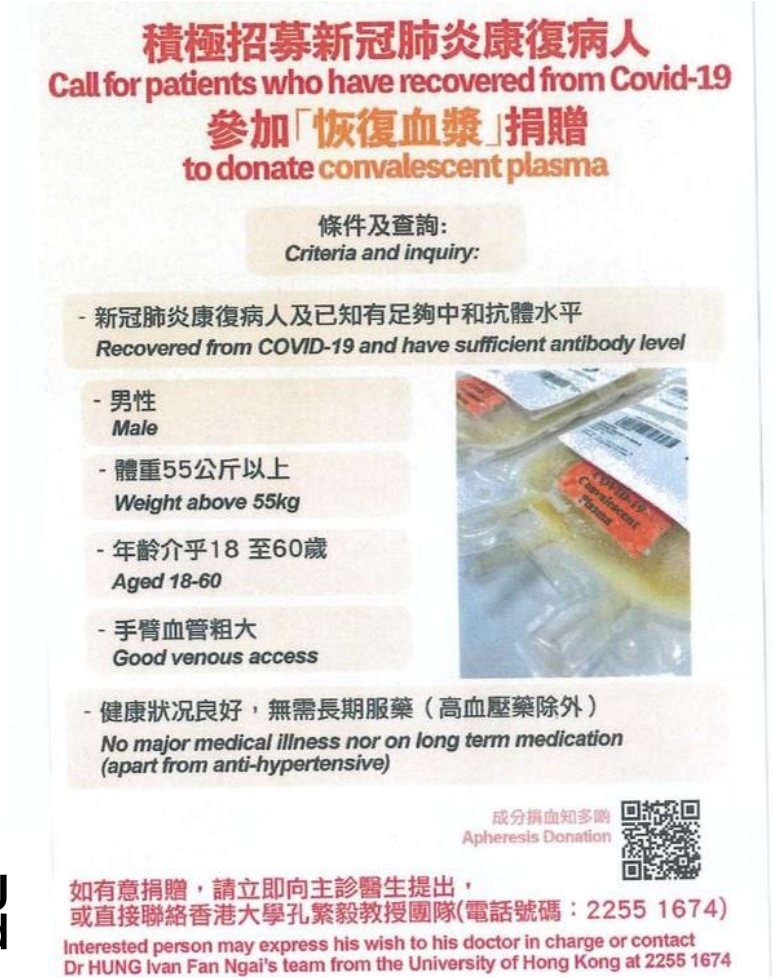
2,731
Sites

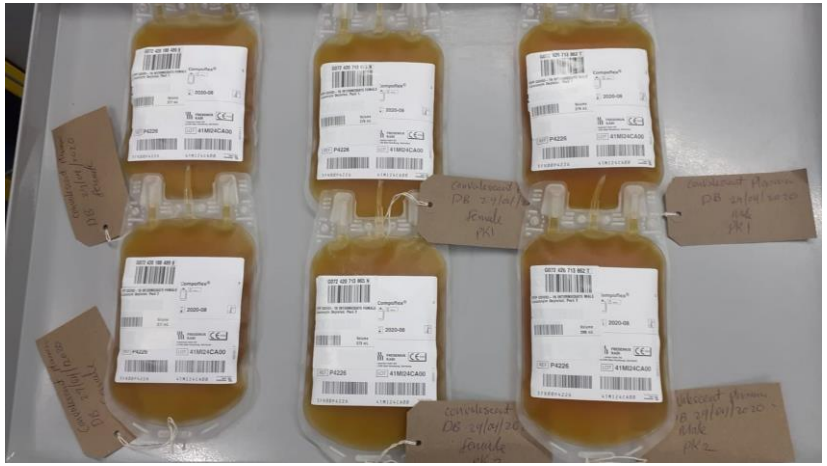
12,747
Physicians

105,742
Patients

92,283
Infused

香港 恢復血漿 捐贈計劃





HK Red Cross 2020

早期高滴定量恢復血漿治療
可降低2019冠狀病毒老年患者病情惡化風險

Table 2. Trial End Points in the Intention-to-Treat Population.*

End Point	Convalescent Plasma (N=80)	Placebo (N=80)	Relative Risk (95% CI)
	no./total no. (%)		
Primary end point: severe respiratory disease	13/80 (16)	25/80 (31)	0.52 (0.29–0.94)
Secondary end points			
Life-threatening respiratory disease	4/80 (5)	10/80 (12)	0.40 (0.13–1.22)
Oxygen supplementation at an F_{IO_2} of 100%	4/80 (5)	6/80 (8)	0.67 (0.20–2.27)
Noninvasive ventilation	1/80 (1)	6/80 (8)	0.17 (0.02–1.35)
Admission to intensive care unit	2/80 (2)	6/80 (8)	0.33 (0.07–1.60)
Mechanical ventilation	2/80 (2)	4/80 (5)	0.50 (0.09–2.65)
Critical systemic illness	5/80 (6)	6/80 (8)	0.83 (0.27–2.62)
Acute respiratory failure	2/80 (2)	5/80 (6)	0.40 (0.08–2.00)
Shock	2/80 (2)	1/80 (1)	2.00 (0.19–21.6)
Multiple organ dysfunction syndrome	3/80 (4)	5/80 (6)	0.60 (0.15–2.43)
Death from Covid-19	2/80 (2)	4/80 (5)	0.50 (0.09–2.65)
Life-threatening respiratory disease, critical systemic illness, or death, alone or in combination	7/80 (9)	12/80 (15)	0.58 (0.24–1.41)

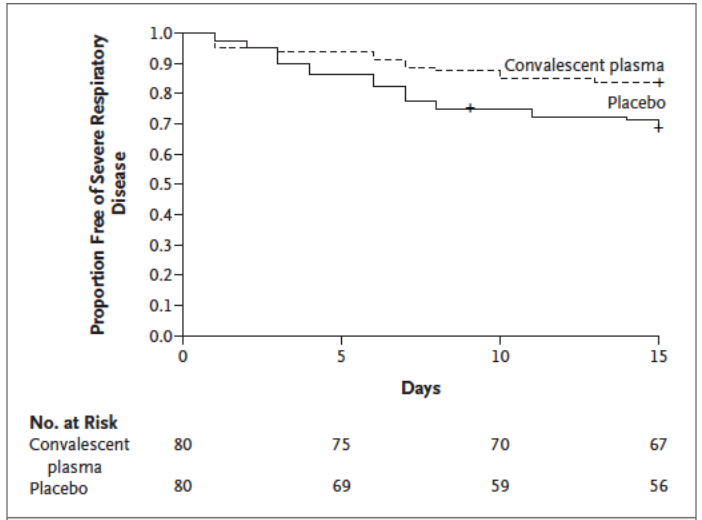


Figure 1. Time to the Development of Severe Respiratory Disease Due to Coronavirus Disease 2019, According to Trial Group in the Intention-to-Treat Analysis.

Shown are Kaplan–Meier estimates of the time from the intervention (administration of convalescent plasma or placebo) to the development of severe respiratory disease. The tick marks on the curves represent the interquartile range in the Kaplan–Meier time-to-event analysis in the convalescent plasma and placebo groups.

Libster R et al. NEJM 2021

雙抗體雞尾酒藥物

- Two monoclonal Ab: REGN10933 and REGN10987
- Derived from humanized mice and human convalescent plasma
- Ab against SARS-CoV-2 spike protein
- Two Ab to prevent rapid mutational escape
- RECOVERY trial

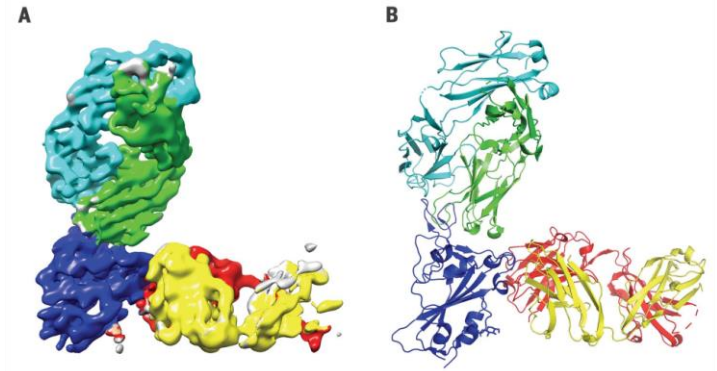
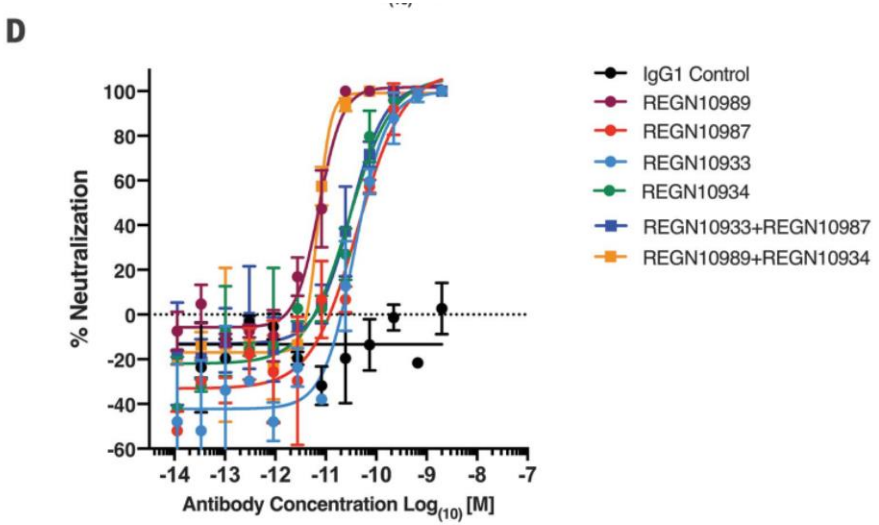


Fig. 4. Complex of REGN10933 and REGN10987 with the SARS-CoV-2 RBD. (A) 3.9-Å cryo-EM map of the REGN10933-RBD-REGN10987 complex, colored according to the chains in the refined model (B). RBD is colored dark blue; REGN10933 heavy and light chains are green and cyan, respectively; and REGN10987 heavy and light chains are yellow and red, respectively.



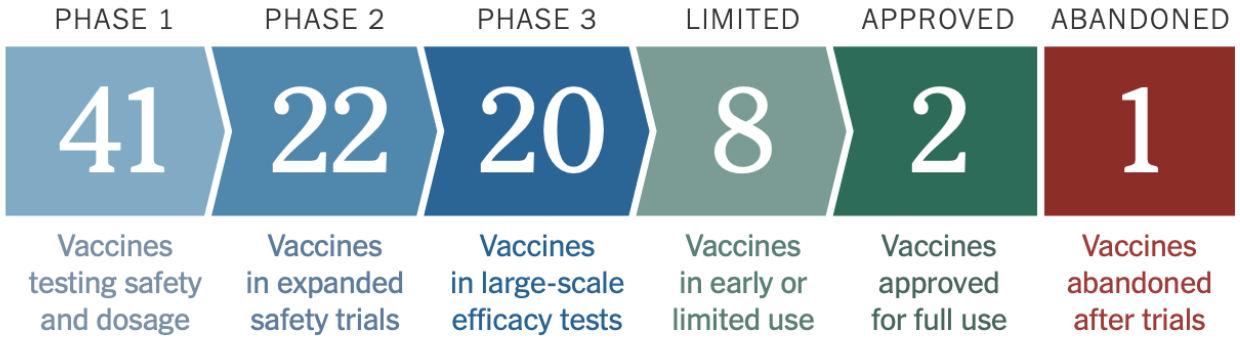
Hansen J et al. Science 369;1010-1014
Baum A et al. Science 369;1014-1018

6

Vaccines 疫苗

Coronavirus Vaccine Tracker

By Carl Zimmer, Jonathan Corum and Sui-Lee Wee Updated Jan. 14, 2021



Vaccines typically require years of research and testing before reaching the clinic, but in 2020, scientists embarked on a race to produce safe and effective coronavirus vaccines in record time. Researchers are currently testing **68 vaccines** in clinical trials on humans, and 20 have reached the final stages of testing. At least 90 preclinical vaccines are under active investigation in animals.

New York Times 18 Jan 2021

Leading vaccines

Developer	How It Works	Phase	Status
Pfizer-BioNTech	mRNA	2 3	Approved in Saudi Arabia and other countries. Emergency use in U.S., E.U., other countries.
Moderna	mRNA	3	Emergency use in U.S., E.U., other countries.
Gamaleya	Ad26, Ad5	3	Early use in Russia. Emergency use in Belarus, other countries.
Oxford-AstraZeneca	ChAdOx1	2 3	Emergency use in Britain, India, other countries.
CanSino	Ad5	3	Limited use in China.
Johnson & Johnson	Ad26	3	
Vector Institute	Protein	3	Early use in Russia.
Novavax	Protein	3	
Sinopharm	Inactivated	3	Approved in China, U.A.E., Bahrain. Emergency use in Egypt.
Sinovac	Inactivated	3	Limited use in China, Indonesia.
Sinopharm-Wuhan	Inactivated	3	Limited use in China, U.A.E.
Bharat Biotech	Inactivated	3	Emergency use in India.

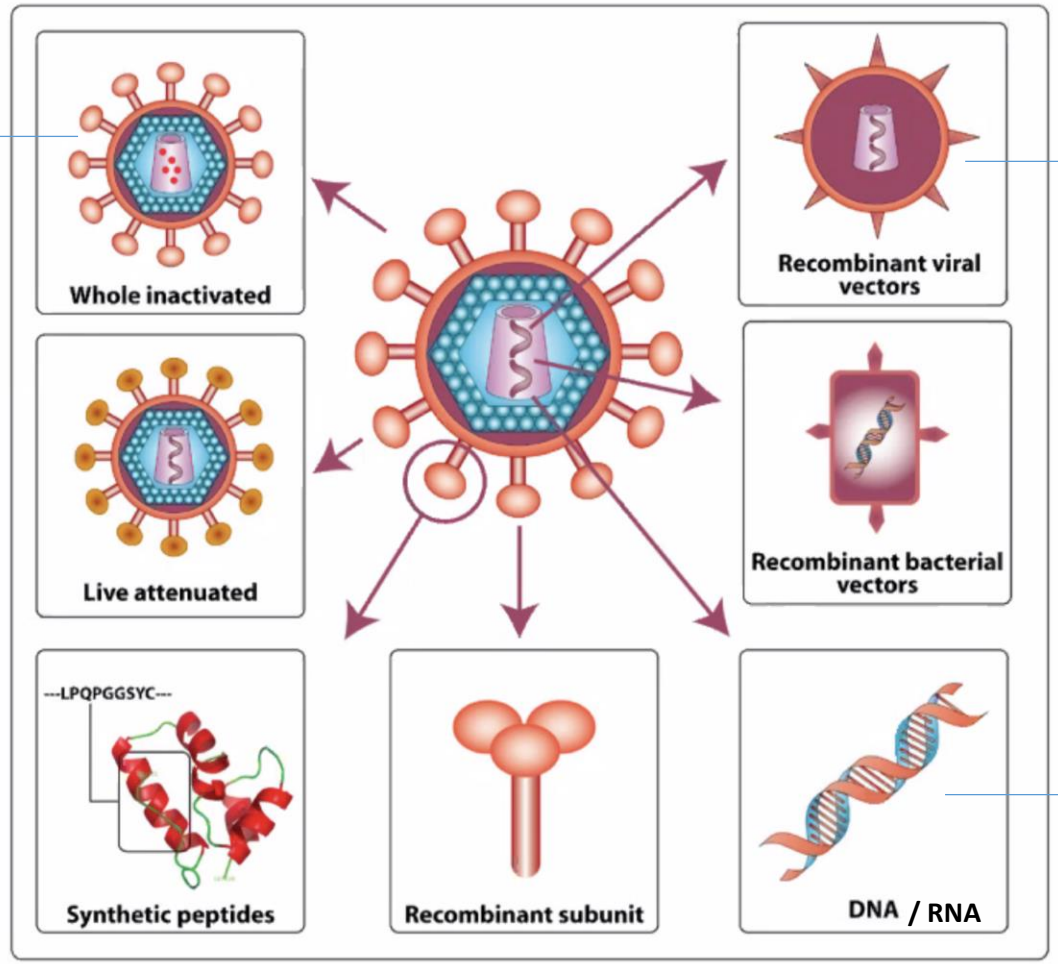
New York Times 18 Jan 2021

Vaccine Platforms 疫苗技術平台

Whole Inactivated Vaccine

Sinovac/ Sinopharm
2 doses IM

Pending phase III results



Adenovirus Vector Vaccine

AstraZeneca – ChAdOx1
2 doses IM; Phase 3: overall 70% efficacy
Johnson & Johnson – Ad26
1 or 2 doses IM
Sputnik– V Ad25 and Ad5
2 doses IM
CanSino – Ad5
1 or 2 doses IM

Apart from AstraZeneca; all pending Phase III results

mRNA Vaccine

Pfizer – BNT162/ Tozinameran BNT162b2
Pre-fusion S protein in lipid nanoparticle
2 doses IM (30 mcg), - 75ºC storage
Phase III 95% efficacy; 7 days after 2nd dose
NA 1:361 after boost
Robust CD4+ and CD8+ stimulation

Moderna – mRNA – 1273
2 doses IM (100 mcg), - 20ºC storage
94% efficacy; Phase III results published
NA 1:654 after boost

Matrix-M Spike Protein Nanoparticle Vaccine

Novavax
NVX CoV2373 spike protein + Matrix-M adjuvant; 2 x doses IM
NA 1:128 prime; 1:3906 boost
Phase III preliminary results:
Efficacy 89.3% overall
86% vs UK mutants; 60% vs SA mutants
95.6% against original strain

Courtesy of Prof G Poland
Polack FP et al NEJM 2020; 10.1056

理想疫苗

- Stable at room temperature
- Easy mass administration
- Induces robust immunity after a single dose
- Prevention of infection
- Prevention of symptomatic disease
- Prevention of complications
- Prevention of transmission

3款疫苗比較

明報製圖

表1：香港特區政府預先採購之疫苗

疫苗	Tozinameran BNT162b2 復星醫藥/德國藥廠BioNTech	AZD1222 阿斯利康(AstraZeneca)/牛津大學	CoronaVac 科興控股(香港)有限公司
技術平台	mRNA(經基因改造過的棘突蛋白核酸段)	不能複製的黑猩猩腺病毒(ChAdOx1)載體，插入新型冠狀病毒基因(含全段棘突蛋白基因)	滅活全病毒SARS-CoV-2
給藥方案 (Dosing regimen)	兩劑相隔21日， 0.3mL含30μg， 肌肉注射	標準劑量：5×10^{10}病毒顆粒(0.5mL)； 低劑量：2.5×10^{10}病毒顆粒 (0.22或0.5mL，視乎不同批次)； 肌肉注射，兩劑相隔28日	0.5mL含3μg， 肌肉注射， 兩劑相隔14 / 28日
佐劑	脂質納米粒	無	氫氧化鋁

表2：疫苗成分及技術平台

成分	脂肪(含聚乙二醇(polyethylene glycol)、膽固醇等)、氯化鉀、磷酸二氫鉀、氯化鈉、磷酸氫二鈉、蔗糖等化學物	未有資料	未有資料
誘發免疫原 (immunogens)	棘突蛋白基因核酸段、 脂質納米粒等	棘突蛋白、腺病毒載體蛋白、 細胞培養剩餘物等	新型冠狀病毒蛋白、 細胞培養剩餘物等
技術平台往績	首次應用	伊波拉疫苗(cAd3-EBO)	甲型肝炎疫苗、小兒麻痺疫苗
科學理論優點	易於製造及量產；誘發良好的中和抗體、細胞介導免疫反應及細胞毒性T淋巴細胞免疫反應	誘發良好的中和抗體、細胞介導免疫反應及細胞毒性T淋巴細胞免疫反應	誘發良好的中和抗體反應
科學理論缺點	必須以極低溫(-70°C)儲存以保持其效力；物流運輸需具冷凍設施，以免中斷冷藏鏈	最佳劑量仍未清楚	傾向Th2免疫反應

表3：3款疫苗第三期臨牀研究保護效力之比較

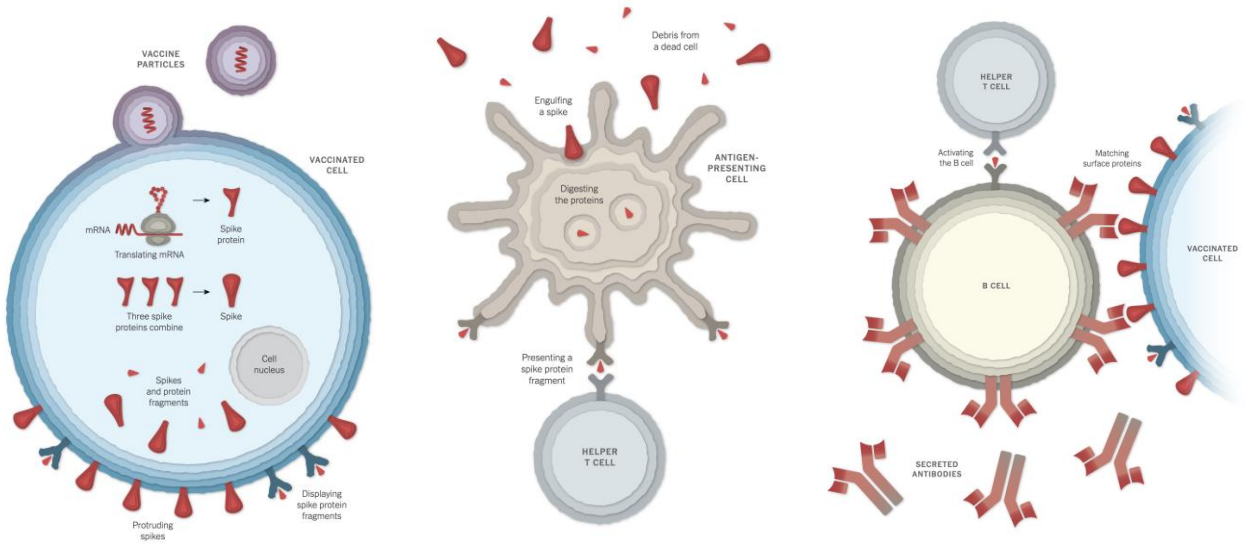
臨牀保護效力 (Clinical efficacy)	**95.0%**(第二劑後7日計算，**N=17,411**)	**70.4%**(兩劑，不論劑量；第二劑後最少14日計算，**N=5,807**)； **90.0%**(第一劑低劑量， 第二劑標準劑量，**N=1,367**)	第三期臨牀研究結果 仍未正式於國際醫學期刊刊登
臨牀保護效力 (以年齡層； Efficacy according to age group)	95.6%(16至55歲，N=9,897)； 93.7%(>55歲，N=7,500)； 94.7%(>65歲，N=3,848)； 100.0%(>75歲，N=774)	未有資料	未有資料

表4：3款疫苗第三期臨牀研究安全數據之比較

副作用發生率 (Incidence of side effects)	疫苗與相關生物製品諮詢委員會(Vaccines and Related Biological Products Advisory Committee)12月10日會議之數據(數據基於美國食品藥品管理局文件)： 84.1%注射部位反應； 62.9%疲倦；55.1%頭痛； 38.3%肌肉痛；31.9%發冷； 23.6%關節痛；**14.2%發燒**	第一/二期臨牀研究數據(標準劑量，不論有或無服撲熱息痛(paracetamol))： 83%注射部位觸痛(tenderness)； 70%疲倦；68%頭痛； 67%注射部位觸痛； 61%不適；60%肌肉痛； 56%發冷；31%關節痛； 25%惡心(nausea)； 25%注射部位發熱；**18%發燒**	第二期臨牀研究數據： 注射時間表為0/14日(3μg)： 23.3%注射部位反應； 5.0%腹瀉；3.3%疲倦； **3.3%發燒**；2.5%肌肉痛 注射時間表為0/28日(3μg)： 10.0%注射部位反應； 8.3%疲倦；**3.3%發燒**； 2.5%頭痛；1.7%肌肉痛
嚴重副作用	未有報告 (近期英國有報道指醫護注射後出現過敏反應， 疑似是對PEG過敏)	第三期臨牀研究報告了 2宗橫貫性脊髓炎 (1宗原因不明，另一宗本身有隱性多發性硬化症；共12,021人參與安全研究，病發率為0.017%)	未有報告 (巴西第三期臨牀研究曾有自殺個案，未證實與疫苗有關)

Ming Pao 2020

輝瑞/BioNTech（mRNA核酸疫苗）



疫苗	Tozinameran BNT162b2 復星醫藥/德國藥廠BioNTech
技術平台	mRNA(經基因改造過的棘突蛋白核酸段)
給藥方案 (Dosing regimen)	兩劑相隔21日， 0.3mL含30μg， 肌肉注射
佐劑	脂質納米粒
表2：疫苗成分及技術平台	
成分	脂肪(含聚乙二醇(polyethylene glycol)、膽固醇等)、氯化鉀、磷酸二氫鉀、氯化鈉、磷酸氫二鈉、蔗糖等化學物
誘發免疫原 (immunogens)	棘突蛋白基因核酸段、脂質納米粒等
技術平台往績	首次應用
科學理論優點	易於製造及量產；誘發良好的中和抗體、細胞介導免疫反應及細胞毒性T淋巴細胞免疫反應
科學理論缺點	必須以極低溫-70°C儲存以保持其效力；物流運輸需具冷凍設施，以免中斷冷藏鏈
表3：3款疫苗第三期臨牀研究保護效力之比較	
臨牀保護效力 (Clinical efficacy)	**95.0%**(第二劑後7日計算，**N=17,411**)
臨牀保護效力 (以年齡層； Efficacy according to age group)	95.6%(16至55歲，N=9,897)； 93.7%(>55歲，N=7,500)； 94.7%(>65歲，N=3,848)； 100.0%(>75歲，N=774)
表4：3款疫苗第三期臨牀研究安全數據之比較	
副作用發生率 (Incidence of side effects)	疫苗與相關生物製品諮詢委員會(Vaccines and Related Biological Products Advisory Committee)12月10日會議之數據(數據基於美國食品藥品管理局文件)： 84.1%注射部位反應； 62.9%疲倦；55.1%頭痛； 38.3%肌肉痛；31.9%發冷； 23.6%關節痛；**14.2%發燒**
嚴重副作用	未有報告 (近期英國有報道指醫護注射後出現過敏反應， 疑似是對PEG過敏)

Vaccine name: Comirnaty (also known as tozinameran/ BNT162b2)

mRNA vaccine (spike protein)
2 doses, 3 weeks apart
Muscle injection
Freezer storage -70C

Efficacy 95%
New vaccine platform
Excellent neutralizing Ab, T cells response (CD4 and CD8)

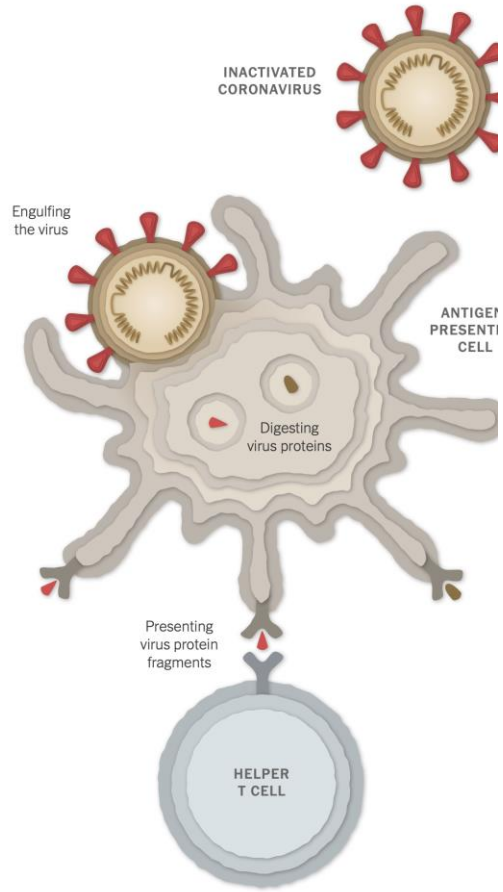
Little difference in Protection of ethnicity
Good antibody response in elderly, DM and obesity

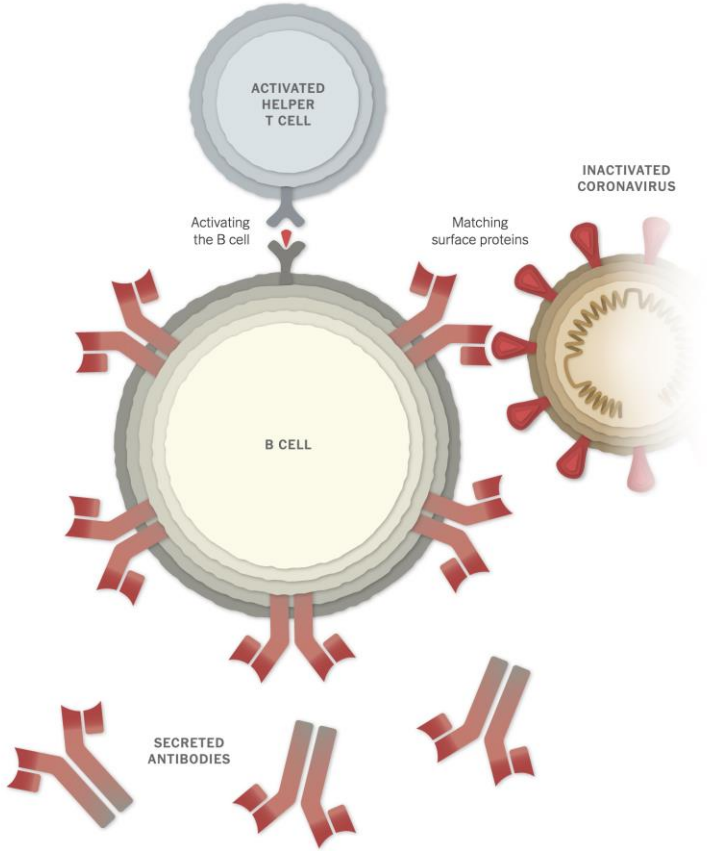
No serious adverse effects: short lived fatigue (62.9%), headache (55.1%), myalgia (38.3%), fever (14.2%)

33 elderly home residents >75 years died after BNT 162b2
Norwegian Medicines Agency and German Government to provide details for the panel

New York Times 3 Jan 2021
Ming Pao 2020

科興 滅活疫苗





疫苗	CoronaVac 科興控股(香港)有限公司
技術平台	滅活全病毒SARS-CoV-2
給藥方案 (Dosing regimen)	0.5mL含3μg，肌肉注射，兩劑相隔14 / 28日
佐劑	氫氧化鋁
表2：疫苗成分及	
成分	未有資料
誘發免疫原 (immunogens)	新型冠狀病毒蛋白、細胞培養剩餘物等
技術平台往績	甲型肝炎疫苗、小兒麻痺疫苗
科學理論優點	誘發良好的中和抗體反應
科學理論缺點	傾向Th2免疫反應
表3：3款疫苗第三	
臨牀保護效力 (Clinical efficacy)	第三期臨牀研究結果仍未正式於國際醫學期刊刊登
臨牀保護效力 (以年齡層；Efficacy according to age group)	未有資料
表4：3款疫苗第三	
副作用發生率 (Incidence of side effects)	第二期臨牀研究數據： 注射時間表為0/14日(3μg)： 23.3%注射部位反應； 5.0%腹瀉；3.3%疲倦； **3.3%發燒**；2.5%肌肉痛 注射時間表為0/28日(3μg)： 10.0%注射部位反應； 8.3%疲倦；**3.3%發燒**； 2.5%頭痛；1.7%肌肉痛
嚴重副作用	未有報告 (巴西第三期臨牀研究曾有自殺個案，未證實與疫苗有關)

Vaccine name: CoronaVac

Inactivated whole cell vaccine
2 doses, 2-4 weeks apart
Muscle injection
4C storage

Efficacy >50%
Coventional vaccine platform (HAV and polio)
Good neutralizing Ab

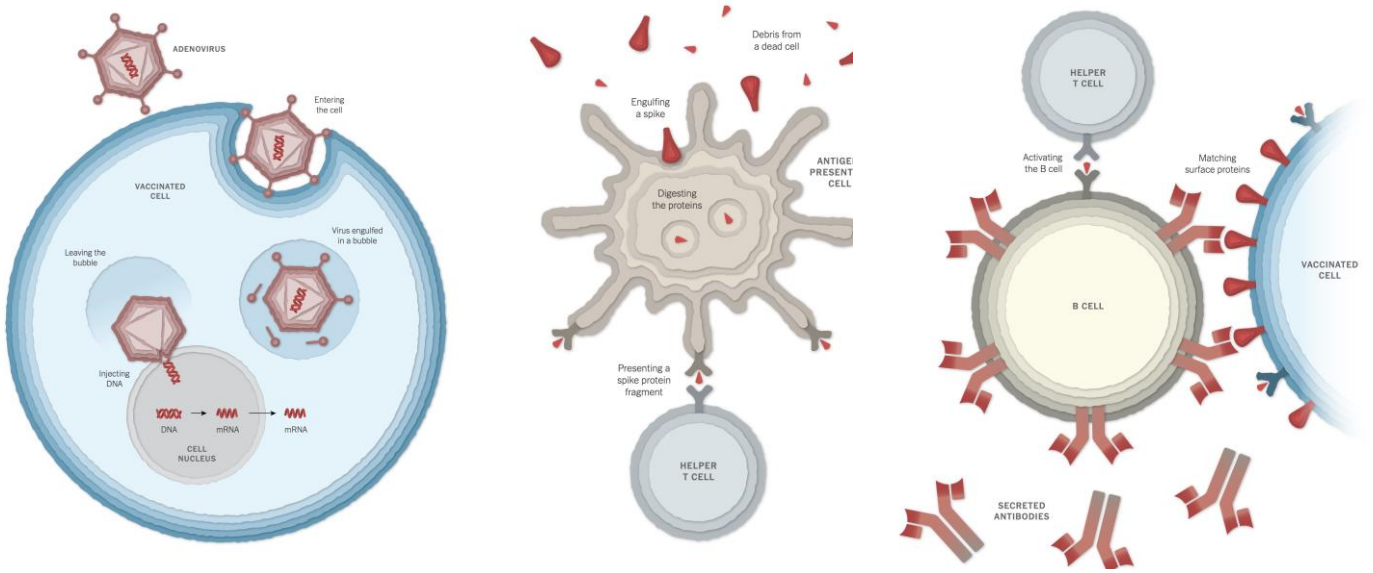
Pending Phase 3 results this month (trial in Brazil, Turkey and Indonesia)
Phase 1/2 published in the Lancet: 97% 3ug; 100% 6ug
No data in the elderly or immunocompromised groups

No serious adverse effects; overall very safe: short lived fatigue (3.3%), headache (2.5%), myalgia (1.7%), fever (3.3%)

Vaccination launched in Jiaxing for HCWs and high-risks

New York Times 3 Jan 2021
Ming Pao 2020

阿斯利康 / 牛津大學病毒載體疫苗



疫苗	AZD1222 阿斯利康(AstraZeneca)/牛津大學
技術平台	不能複製的黑猩猩腺病毒(ChAdOx1)載體，插入新型冠狀病毒基因(含全段棘突蛋白基因)
給藥方案 (Dosing regimen)	標準劑量：5×10^{10}病毒顆粒(0.5mL)；低劑量：2.5×10^{10}病毒顆粒(0.22或0.5mL，視乎不同批次)；肌肉注射，兩劑相隔28日
佐劑	無
表2：疫苗成分及	
成分	未有資料
誘發免疫原 (immunogens)	棘突蛋白、腺病毒載體蛋白、細胞培養剩餘物等
技術平台往績	伊波拉疫苗(cAd3-EBO)
科學理論優點	誘發良好的中和抗體、細胞介導免疫反應及細胞毒性T淋巴細胞免疫反應
科學理論缺點	最佳劑量仍未清楚
表3：3款疫苗第三	
臨牀保護效力 (Clinical efficacy)	**70.4%**(兩劑，不論劑量；第二劑後最少14日計算，**N=5,807**)；**90.0%**(第一劑低劑量，第二劑標準劑量，**N=1,367**)
臨牀保護效力 (以年齡層；Efficacy according to age group)	未有資料
表4：3款疫苗第三	
副作用發生率 (Incidence of side effects)	第一/二期臨牀研究數據(標準劑量，不論有或無服撲熱息痛(paracetamol))：83%注射部位觸痛(tenderness)；70%疲倦；68%頭痛；67%注射部位觸痛；61%不適；60%肌肉痛；56%發冷；31%關節痛；25%惡心(nausea)；25%注射部位發熱；**18%發燒**
嚴重副作用	第三期臨牀研究報告了2宗橫貫性脊髓炎(1宗原因不明，另一宗本身有隱性多發性硬化症；共12,021人參與安全研究，病發率為0.017%)

Vaccine name: ADZ1222

ChAdOx1 Adenovirus Vector vaccine
2 doses, 4 weeks apart
Muscle injection
4C storage for 6 months

Efficacy up to 90%
Good neutralizing Ab

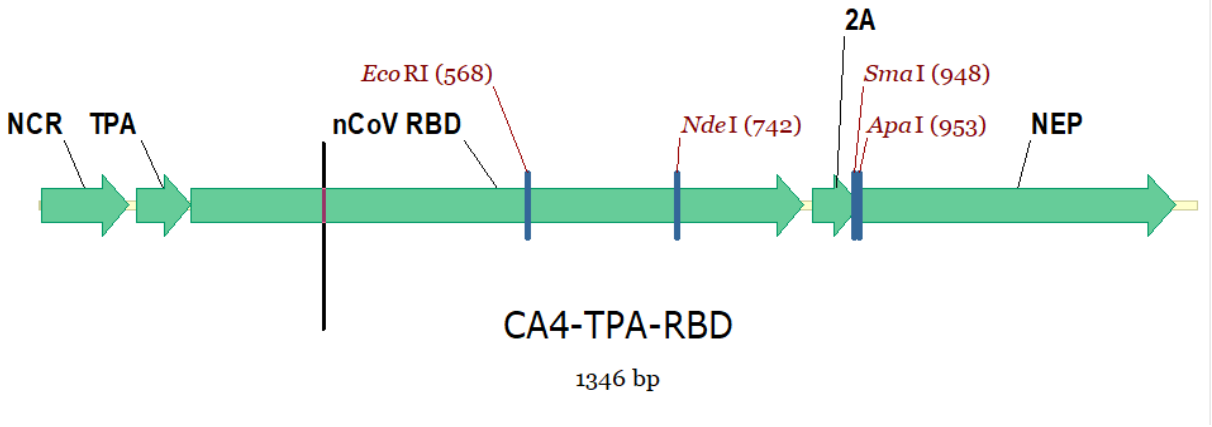
Phase 3 interim results published in the Lancet
Overall 70.4%; standard dose x 2 62.1%; half dose then standard dose 90%
Good efficacy in the elderly (>70)

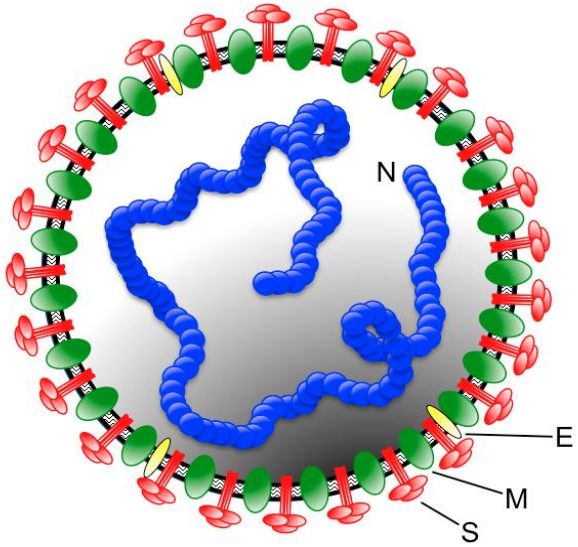
No serious adverse effects; overall very safe: short lived fatigue (70%), headache (68%), myalgia (60%), fever (18%)

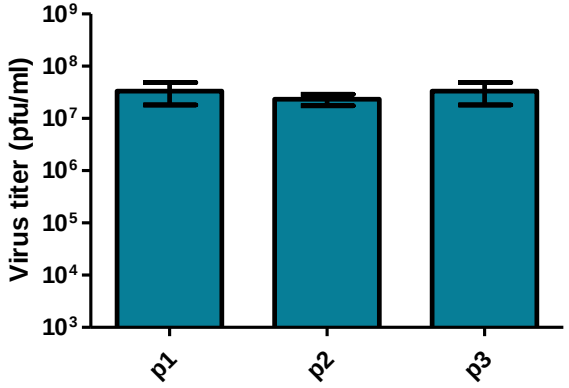
Two volunteer developed transverse myelitis (rare)

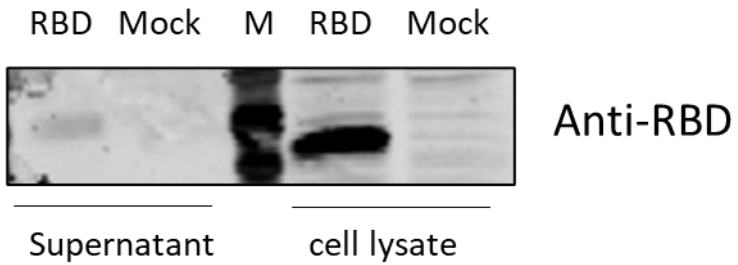
New York Times 3 Jan 2021
Ming Pao 2020

香港大學 噴鼻式流感病毒載體2019冠狀病毒疫苗

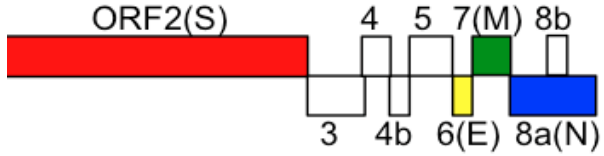








Anti-RBD



Courtesy of Prof H Chen

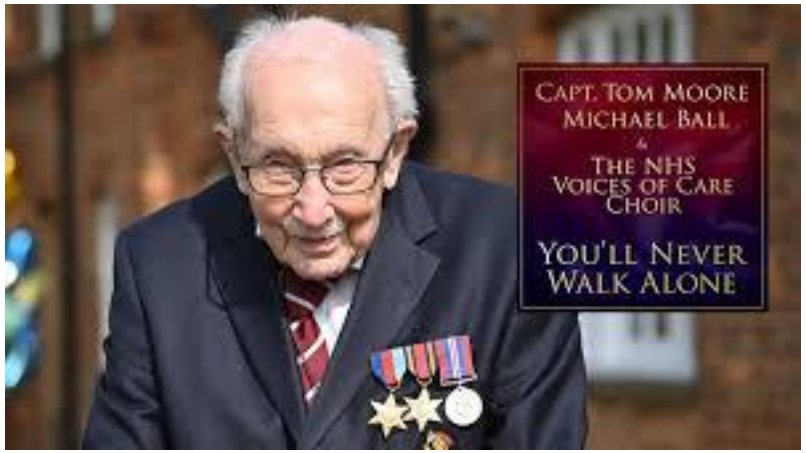
評估噴鼻式流感病毒載體2019冠狀病毒疫苗的安全性及免疫原性於健康成年人之第一期隨機雙盲安慰劑對照組劑量增量與擴展臨床測試

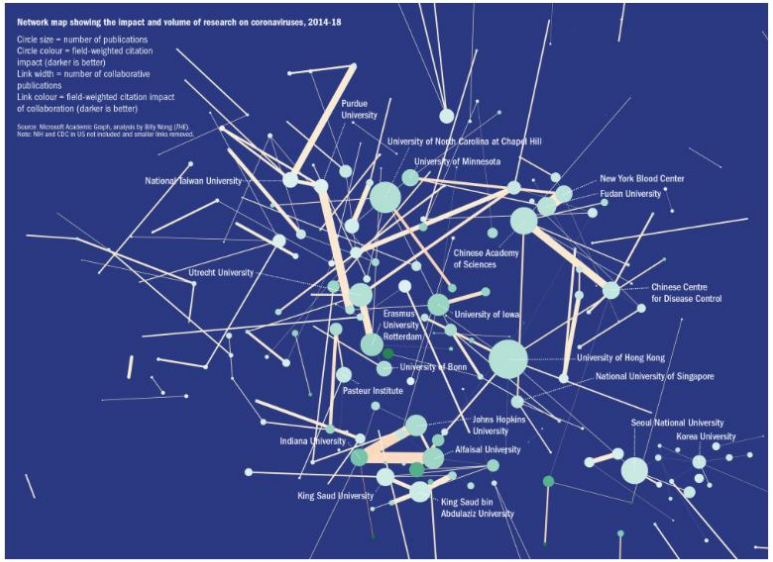
- Phase 1 clinical trial to commence 2/2021
- Supported by FHB, HKSAR and CEPi
- Induce local IgA mucosal immunity
- Healthy subjects
- Age 18-55
- 100 subjects

7

Conclusions 總結

You'll Never Walk Alone!





Acknowledgement

Gratitude to:

- Isolation wards medical and nursing colleagues all HA hospitals
- A&E and other departments
- DH/ CHP colleagues
- HA, HKU, DH laboratory colleagues

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- Dr. Tom Chung
- Dr. Anthony Tam
- Dr. Jenny Lo
- Dr. WL Law
- Dr. MY Chu
- Dr Veronica Chan
- Dr Alwin Yeung
- Dr. Rodney Lee
- Dr. KH Chan
- Dr. Li Xin
- Dr. Derek Hung
- Dr. Kelvin Chiu
- Dr Raymond Liu
- Dr Owen Tsang
- Dr. Albert Lie
- Prof CS Lau
- Dr WM Chan
- Dr WW Yan
- Dr HP Shum
- Dr. WS Leung
- Dr. Jacky Chan
- Dr. Jasper Chan
- Dr. Kelvin To
- Dr. Vincent Cheng
- Dr. Johnny Chan
- Dr. David Lung
- Dr. Kitty Fung
- Dr TL Que

Pneumonia is Preventable by Vaccinations
預防肺炎 由疫苗做起

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Division of Infectious Diseases, University Department of Medicine;

Honorary Clinical Tutor, Department of Microbiology, HKU

HKU Public Lecture Series

6th February 2021

Pneumonia: definitions
肺炎的定義

- Infection of lung parenchyma with the following features:
  - Respiratory symptoms: shortness of breath, cough with sputum, chest pain
  - Systemic symptoms: fever, malaise
  - Radiological features: infiltrates on chest X-ray or computed tomography
- Reasonable exclusion of the followings:
  - Pulmonary oedema
  - Haemorrhage
  - Infarct
  - Malignancy
  - Fibrosis
  - Others e.g. protein

Pneumonia: imaging
肺炎的影像

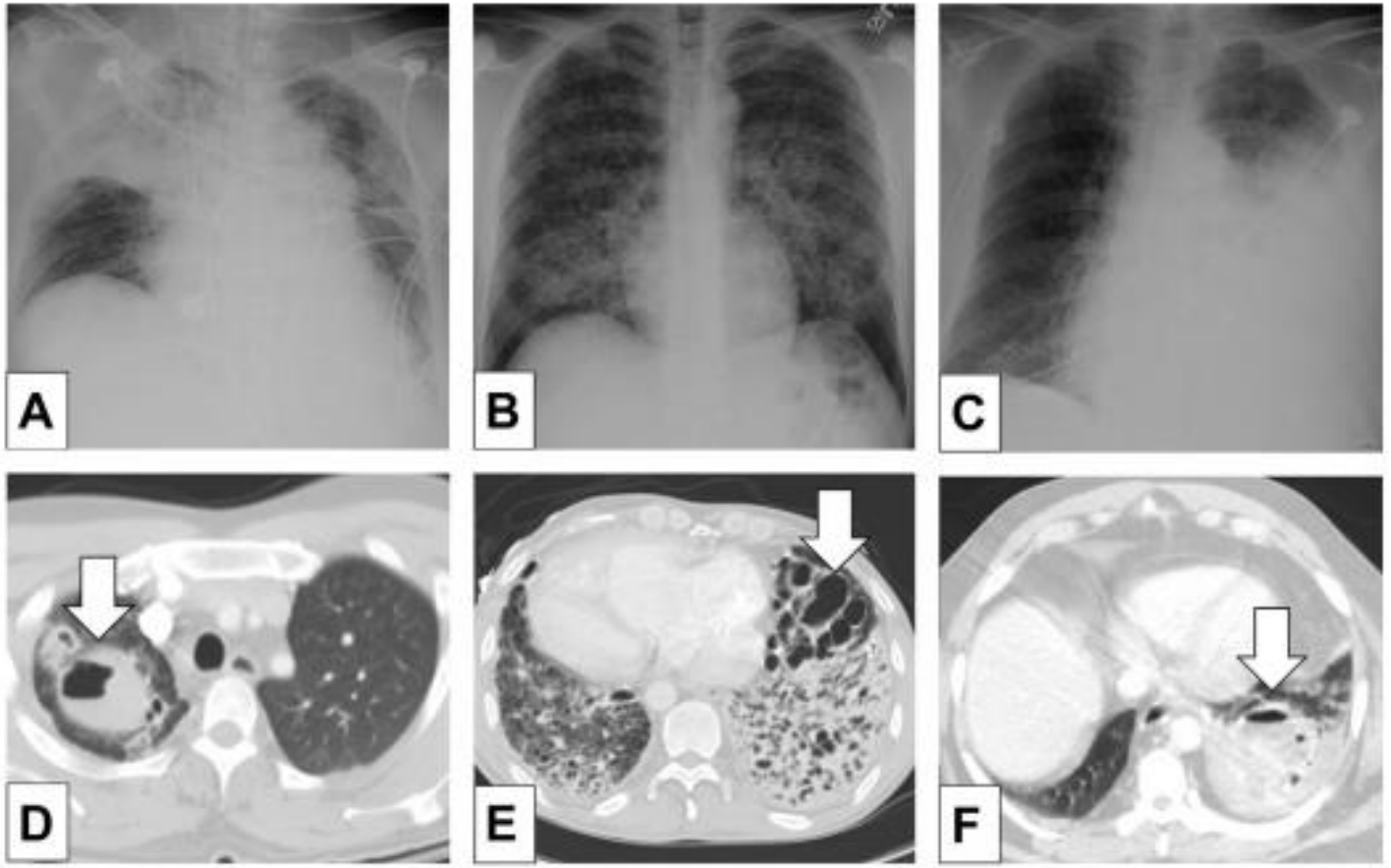


Fig. 1. Variations in radiographic appearance of pneumonia. (*A*) Lobar consolidation of the right upper lobe. (*B*) Bilateral interstitial infiltrates. (*C*) Large left parapneumonic pleural effusion. (*D*) Right upper lobe cavitary lesions (*white arrow*). (*E*) Diffuse bronchiectasis involving primarily the anterior left lower lobe (*white arrow*). (*F*) Pulmonary abscess with air fluid level in the posterior left lower lobe (*white arrow*).

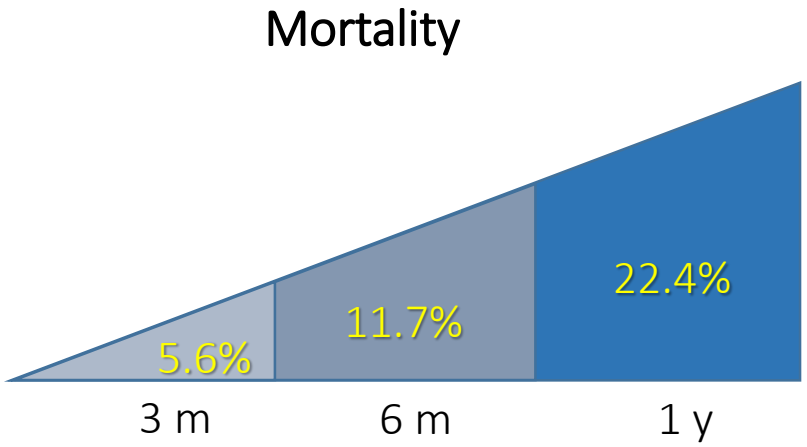
Lanks CW et al. *Med Clin N Am* 2019; **103**:487-501.

Important causes of pneumonia
常見的肺炎成因

Bacteria/Mycobacteria 細菌 /分支桿菌	Virus 病毒	Fungi 真菌
• *Streptococcus pneumoniae* • *Haemophilus influenzae* • *Staphylococcus aureus* • *Streptococcus pyogenes* • *Klebsiella pneumoniae* • *Pseudomonas aeruginosa* • *Legionella pneumophila* • *Mycoplasma pneumoniae* • *Chlamydophila pneumoniae* • *Mycobacterium tuberculosis*	• Influenza viruses • Adenovirus • Pandemic coronarviruses (SARS-CoV, MERS-CoV2, SARS-CoV-2)	• *Pneumocystis jiroveci* • *Cryptococcus neoformans* • *Aspergillus* species • *Talaromyces marneffei* and other dimorphic fungi

CAP Exerts a High Burden of Morbidity and Mortality on Older Adults
肺炎增加長者的死亡風險

Hong Kong
2010
N=488
≥65 years



Readmission

Within 1 year of discharge
32.0%

Ma HM et al. *Intern Med J*. 2013;**43**:1201-1205.

CAP Exerts a High Burden of Morbidity and Mortality on Older Adults
肺炎增加年老病人的死亡風險

Variable	Death, *n* (%)	Univariate		Multivariate			
				Model 1		Model 2	
		Hazard ratio (95% confidence interval), *P*-value†					
Age (years)							
65–74	16 (17.4)	1 (Reference)		1 (Reference)		1 (Reference)	
75–84	42 (21.3)	1.23 (0.69–2.19)	0.48	1.09 (0.60–1.96)	0.78	0.94 (0.52–1.70)	0.84
≥85	38 (27.3)	1.65 (0.92–2.96)	0.09	1.02 (0.53–1.94)	0.96	1.01 (0.52–1.94)	0.98
Male sex	65 (26.1)	**1.60** (1.04–2.45)	**0.03**	**1.78** (1.13–2.81)	**0.01**	**1.60** (1.01–2.53)	**0.05**
Nursing home residence	25 (28.4)	1.47 (0.93–2.31)	0.10	0.85 (0.51–1.41)	0.47	0.79 (0.47–1.34)	0.39
Mid-arm circumference (cm)							
≤21.0	45 (42.9)	**6.14** (2.89–13.03)	**<0.01**	**6.62** (3.00–14.62)	**<0.01**	**3.79** (1.68–8.56)	**<0.01**
21.1–23.0	22 (20.2)	**2.49** (1.11–5.59)	**0.03**	**2.60** (1.14–5.94)	**0.03**	1.80 (0.78–4.15)	0.17
23.1–26.0	21 (17.5)	2.12 (0.94–4.78)	0.07	2.05 (0.90–4.68)	0.09	1.63 (0.71–3.72)	0.25
≥26.1	8 (8.5)	1 (Reference)		1 (Reference)		1 (Reference)	
Charlson's Comorbidity Index							
0	5 (6.7)	1 (Reference)		1 (Reference)		1 (Reference)	
1	32 (23.4)	**3.87** (1.51–9.93)	**0.01**	2.75 (0.98–7.22)	0.06	1.69 (0.64–4.48)	0.29
2	27 (25.5)	**4.22** (1.63–10.96)	**<0.01**	2.72 (0.96–7.58)	0.06	1.84 (0.67–5.08)	0.24
≥3	32 (29.1)	**4.93** (1.92–12.66)	**<0.01**	**3.21** (1.10–9.33)	**0.03**	2.15 (0.75–6.22)	0.16
Clinical Frailty Scale							
Robust (1–3)	26 (12.8)	1 (Reference)		1 (Reference)		1 (Reference)	
Pre-frail (4)	12 (20.3)	1.73 (0.87–3.43)	0.12	1.34 (0.63–2.86)	0.45	1.64 (0.77–3.51)	0.20
Frail (5–7)	58 (34.9)	**3.18** (2.00–5.05)	**<0.01**	**2.19** (1.21–3.97)	**0.01**	**2.09** (1.14–3.81)	**0.02**
Readmission for CAP	68/137 (49.6)	**6.48** (4.17–10.08)	**<0.01**	NA		**4.47** (2.80–7.14)	**<0.01**

†Statistically significant values are in bold. CAP, community-acquired pneumonia.

Ma HM et al. *Intern Med J*. 2013;**43**:1201-1205.

Cause of Death	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
1. Malignant neoplasms (ICD10: C00-C97)	11406	11658	11510	11791	12310	12093	12316	12456	12839	13076	13241	13336	13589	13803	14316	14209	14354	14594	14871
2. Pneumonia (ICD10: J12-J18)	3026	3194	3877	3676	4291	4201	4978	5486	5312	5814	6211	6960	6830	7502	8004	8292	8032	8437	9271
3. Diseases of heart (ICD10: I00-I09, I11, I13, I20-I51)	4703	4969	5311	5866	5868	5619	6372	6777	6414	6636	6334	6283	5834	6405	6190	6201	6138	6088	6096
4. Cerebrovascular diseases (ICD10: I60-I69)	3130	3218	3462	3416	3434	3302	3513	3691	3443	3423	3339	3276	3252	3336	3259	3224	3124	3016	2970
5. External causes of morbidity and mortality† (ICD10: V01-Y89)	1844	2068	2044	2243	2150	1961	1854	1766	1938	1864	1567	1655	1860	1834	1993	1813	1697	1871	1848
6. Nephritis, nephrotic syndrome and nephrosis	1053	1055	1184	1182	1261	1287	1347	1419	1448	1493	1545	1629	1589	1684	1655	1706	1659	1622	1667

Available from: https://www.chp.gov.hk/en/statistics/data/10/27/380.html#. Last accessed on 30th January 2021

Important causes of pneumonia
常見的肺炎成因

Bacteria/Mycobacteria 細菌 /分支桿菌	Virus 病毒	Fungi 真菌
• *Streptococcus pneumoniae* • *Haemophilus influenzae* • *Staphylococcus aureus* • *Streptococcus pyogenes* • *Klebsiella pneumoniae* • *Pseudomonas aeruginosa* • *Legionella pneumophila* • *Mycoplasma pneumoniae* • *Chlamydophila pneumoniae* • *Mycobacterium tuberculosis*	• Influenza viruses • Adenovirus • Pandemic coronarviruses (SARS-CoV, MERS-CoV2, SARS-CoV-2)	• *Pneumocystis jiroveci* • *Cryptococcus neoformans* • *Aspergillus* species • *Talaromyces marneffei* and other dimorphic fungi

Streptococcus pneumoniae (S. pneumoniae/pneumococcus) 肺炎鏈球菌

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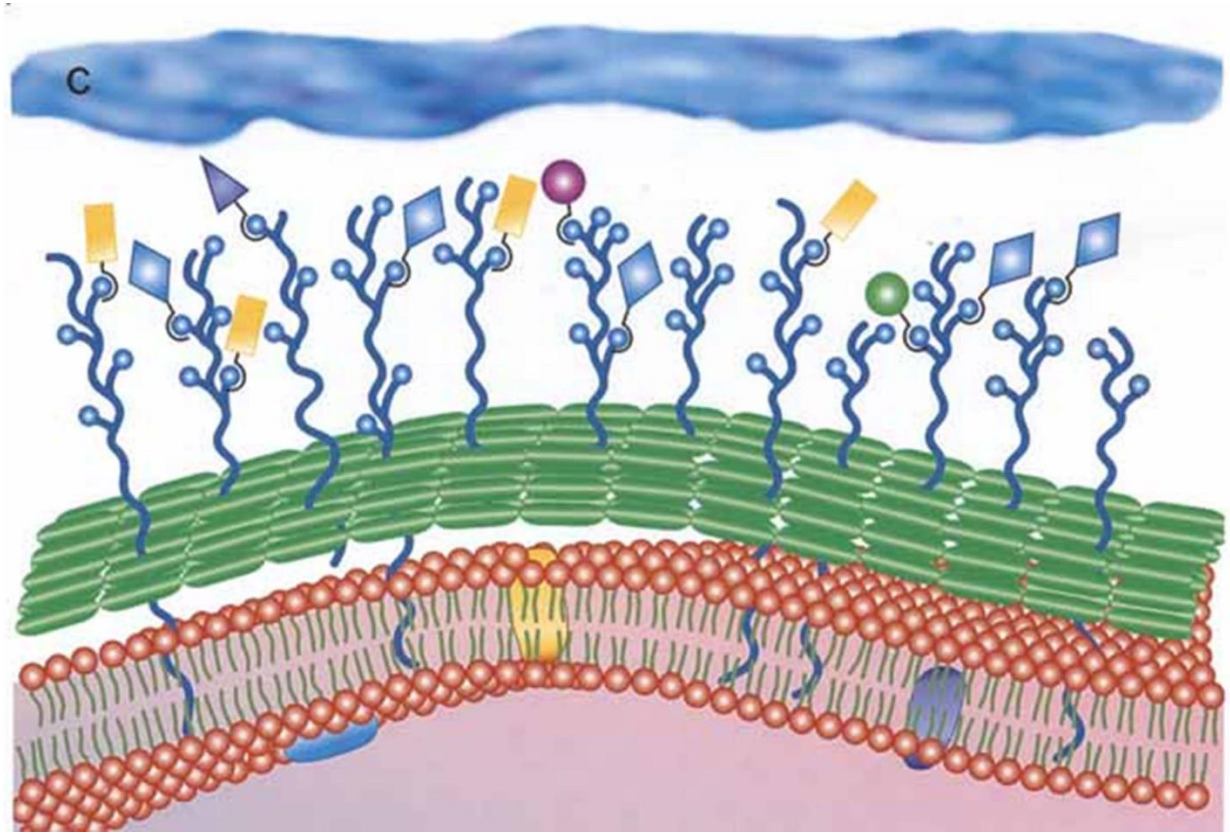
S. pneumoniae overview
肺炎鏈球菌總覽

- Gram positive diplococci with polysaccharide capsules
  - Define their serotypes, virulence factors and vaccine targets
- Bacteria first isolated by Pasteur in 1881
- Polysaccharide capsules isolated in 1916-17
- 92 serotypes described by 2011
  - <30 serotypes accounting for >90% bacterial isolates



US CDC. Epidemiology & Prevention of vaccine-preventable diseases. Available from: https://www.cdc.gov/vaccines/pubs/pinkbook/pneumo.html. Last accessed on 30th January 2021.
Loughran AJ et al. *Microbiol Spectrum* 2018; **7**(2):GPP3-0004-2018.

侵入性肺炎鏈球菌病

Defined as isolation of *S. pneumoniae* from a normally sterile site (blood, CSF)

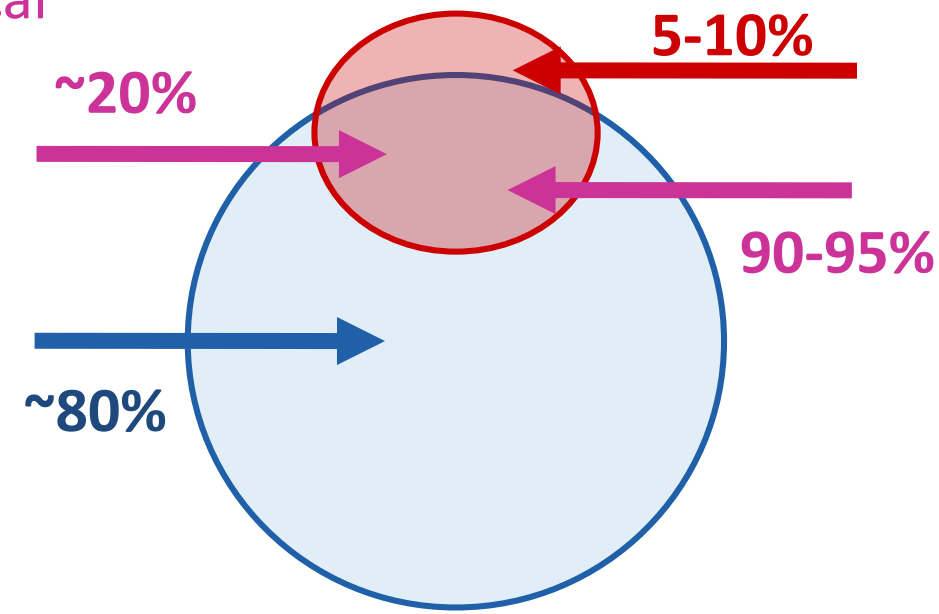
Invasive pneumococcal diseases

Bacteraemic pneumococcal Pneumonia

菌血型肺炎

Non-bacteraemic pneumococcal Pneumonia

非菌血型肺炎



Meningitis, pleuritis, arthritis

腦膜炎，胸膜炎，關節炎

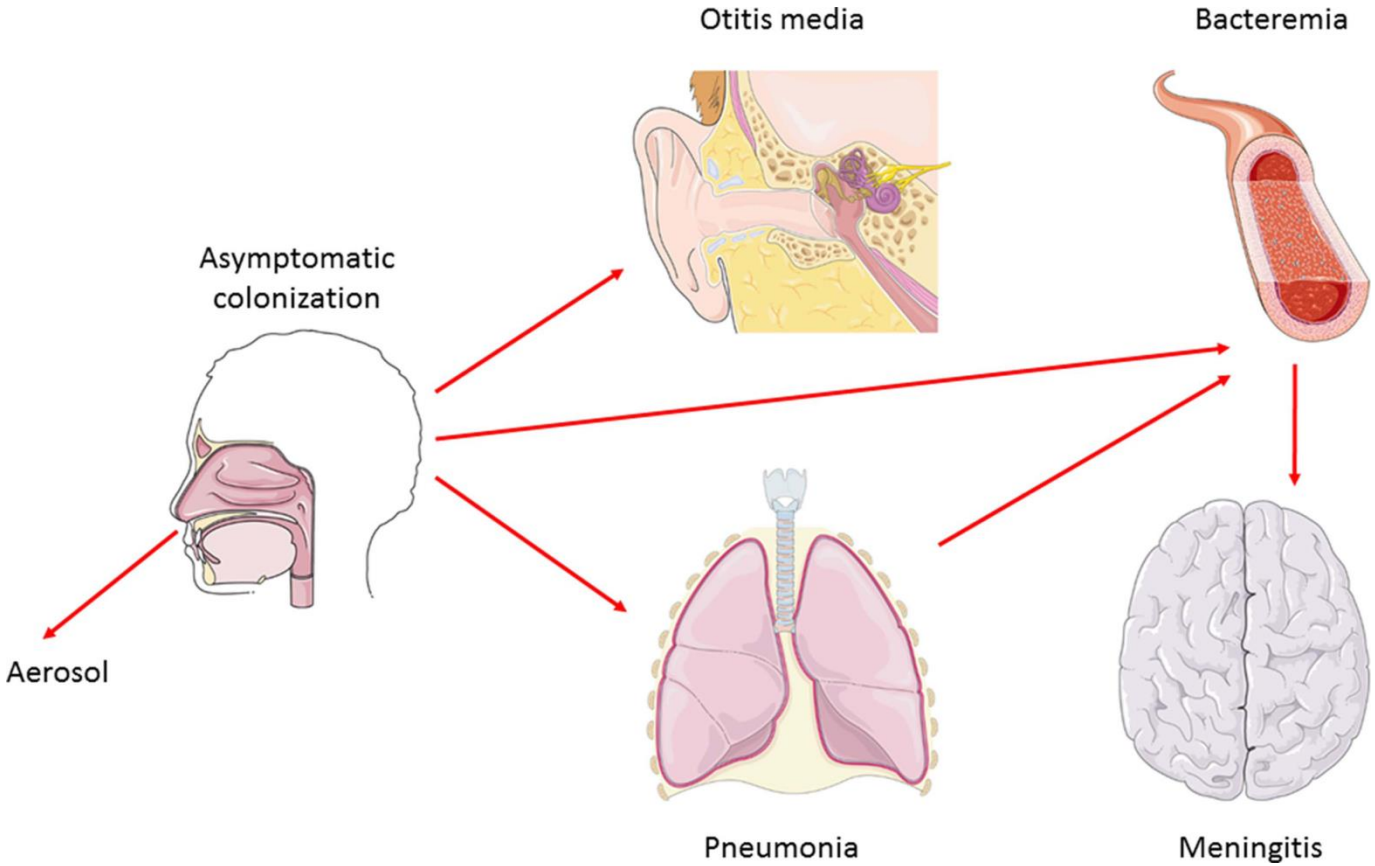
Bacteraemic pneumococcal pneumonia

菌血型肺炎

Pneumococcal pneumonia

Lynch JP III et al. *Semin Respir Crit Care Med* 2009; **30**:210-38.

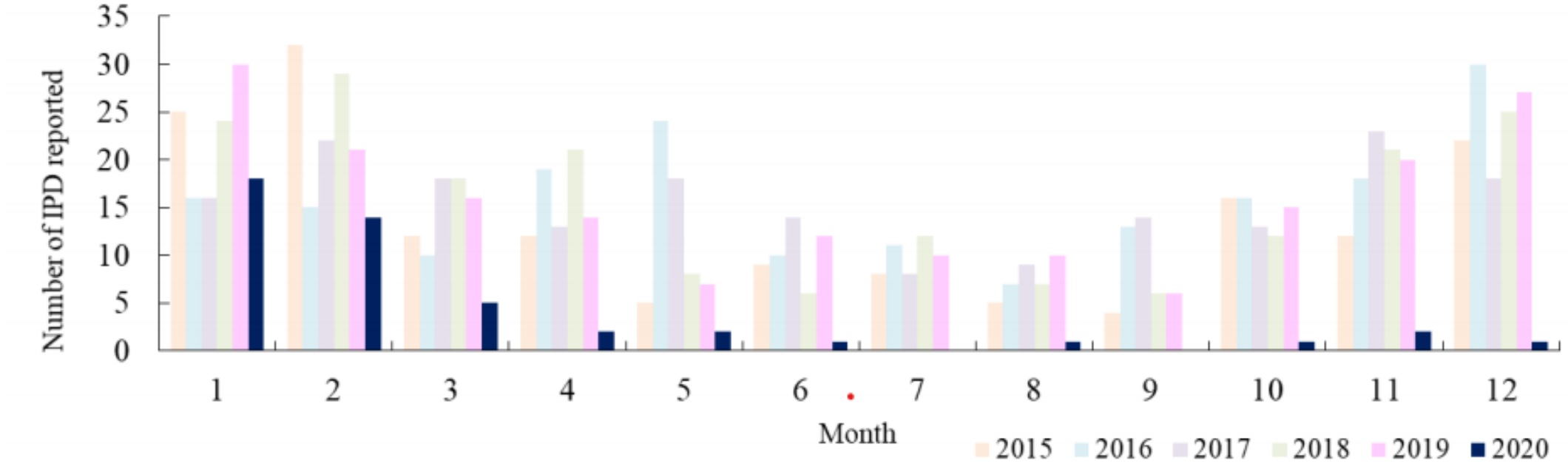
S. pneumoniae: pathogenesis
肺炎鏈球菌病的原理



- Nasopharyngeal carriage of the bacteria is required for transmission of bacteria and for IPD
- Clinical illness appears when the bacteria spread to tissues outside the nasopharynx
  - Local spread: pneumonia, otitis media, sinusitis
  - Spread to the bloodstream: bacteraemia and further dissemination (especially meninigitis)

Loughran AJ et al. *Microbiol Spectrum* 2018; **7**(2):GPP3-0004-2018.

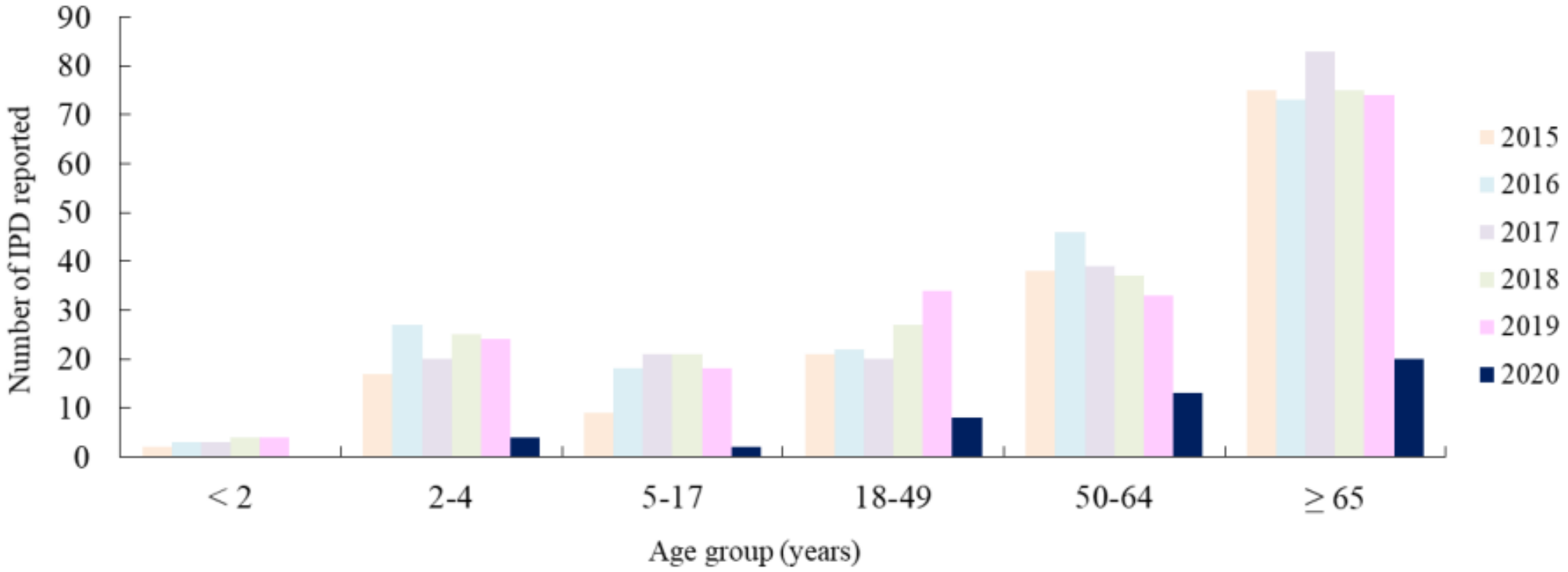
IPD in HK: Updated epidemiology
侵入性肺炎鏈球菌病的流行病學



- Consistent seasonal trend with more cases in the winter months

Centre for Health Protection, DH, HKSARG. Report on IPD. Available from: https://www.chp.gov.hk/files/pdf/ipd_202012.pdf. Last accessed on 30th January 2021

IPD in HK: Updated epidemiology
侵入性肺炎鏈球菌病的流行病學



- Overall annual incidence of IPD: 1.7 to 2.9 per 100,000 population
- Annual incidence of IPD for aged >65 years: 7.7 per 100,000 population

Hung IF et al. *Int J Infect Dis*. 2013;**17**:e364-373.
Centre for Health Protection, DH, HKSARG. Report on IPD. Available from: https://www.chp.gov.hk/files/pdf/ipd_202012.pdf. Last accessed on 30th January 2021.

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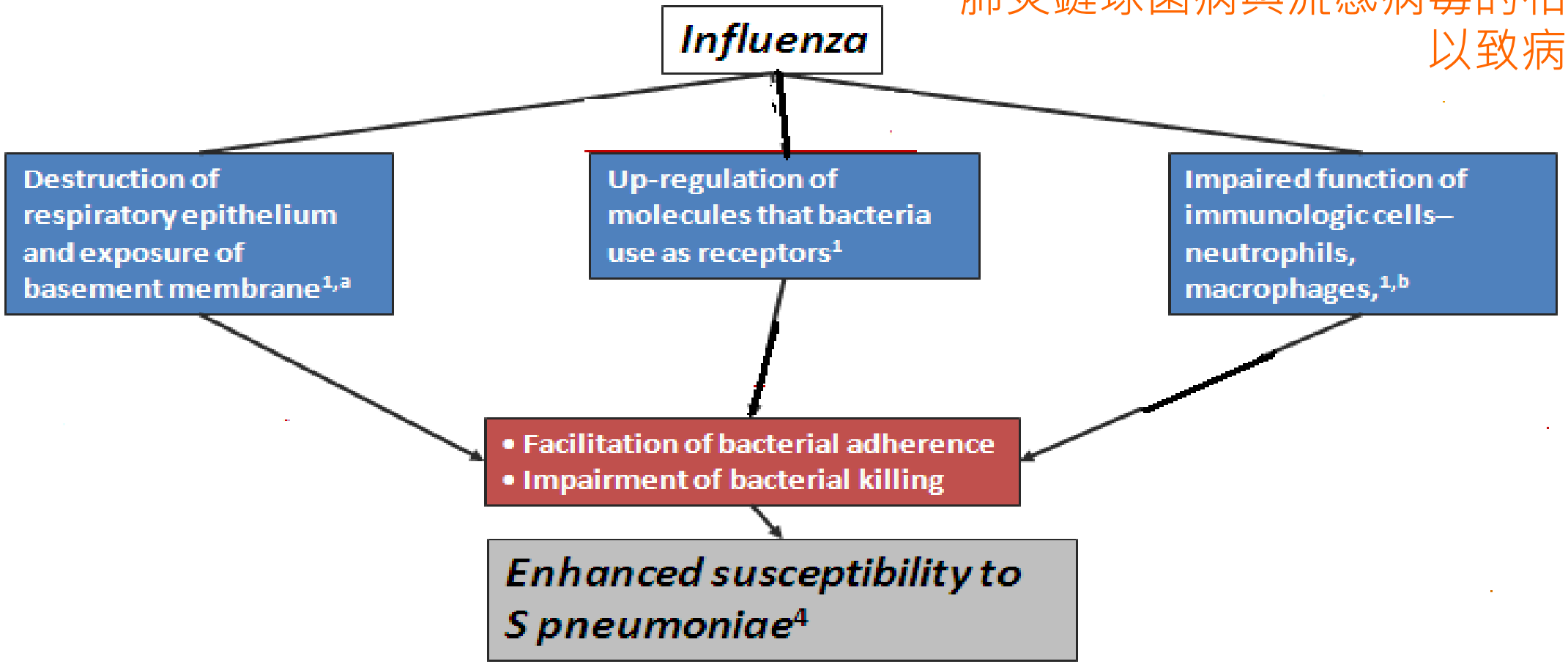
Age is not the only risk factor
年齡不是唯一的高危因素

Co-exisiting health conditions 慢性病	• Chronic heart, lung, kidney and liver diseases 慢性心，肺，肝，腎疾病 • Diabetes mellitus 糖尿病 • Cerebrospinal fluid leaks 腦脊髓液滲漏 • Presence of cochlear implant 人工耳蝸 • Primary immunodeficiencies 先天免疫力缺乏症 • HIV infection 後天免疫力病毒感染 • Anatomical or functional asplenia 脾臟功能缺乏 • Malignancy 癌症 • Solid organ or stem cell transplantation 器官或幹細胞移植 • Autoimmune diseases 自身免疫性疾病
Risky behaviours 高危生活習慣	• Smoking 抽煙 • Alcoholism 嗜酒
Environmental factors 環境因素	• Resident of institutions 長期院舍住客 • Recent respiratory viral infections 近期呼吸病毒感染

Centers for Disease Control and Prevention (CDC). *MMWR Morb Mortal Wkly Rep.* 2010;**59**:1102-1106.
van Hoek AJ et al. *J Infect*. 2012;**65**:17-24.
Wotton CJ et al. *J Epidemiol Community Health*. 2012;**66**:1177-1181.
Klemets P et al. *BMC Infect Dis*. 2008;**8**:96.

Multiple mechanisms for synergism between influenza and pneumococcal infections
肺炎鏈球菌病與流感病毒的相互作用以致病情加劇



[a]eg, exposure of receptors for pneumococcus by neuraminidase may facilitate adherence[2]

[b]eg, down-regulation of a scavenger receptor on alveolar macrophages by interferon gamma may impair bacterial killing[3]

1. Alicino C, et al. *J Prev Med Hyg*. 2011;52(3):102-106.
2. Peltola VT, McCullers JA. *Pediatr Infect Dis J*. 2004;23 (suppl 1):S87-S97.
3. Sun K, Metzger DW. *Nat Med*. 2008;14:558-564.
4. Diavatopoulos DA, Short KR, Price JT, et al. *FASEB J*. 2010;24(6):1789-1798.

"Given the high burden of pneumococcal disease in children and adults, WHO considers the prevention of pneumococcal disease to be a high priority in both industrialized and developing countries."

無論在發達國家還是發展中國家，預防成年人和兒童感染肺炎鏈球菌都非常重要。

World Health Organization. *Wkly Epidemiol Rec*. 2012;**87**(14):129-144.

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Pneumococcal vaccinations: historical perspective
肺炎鏈球菌疫苗的歷史

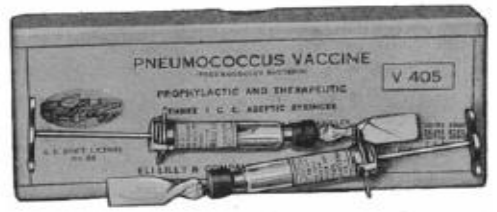
- Whole-cell heat killed pneumococcal vaccines in 1911
- Trials of pneumococcal polysaccharide vaccines (PPV) during WWII with successful prevention of pneumonia
- 2 hexavalent PPV first licensed in 1947; but low uptake rates as doctors preferred antibiotics then
- Progressive broadening of serotypes with the currently available 23-valent PPV (PPV23) licensed in 1983

Pneumococcus Vaccine, Prophylactic and Therapeutic (Pneumococcus Bacterin).

Used for the prophylaxis and treatment of pneumonia.

DOSAGE: Initial dose in treatment, 50 million. Subsequent doses, given at intervals of twenty-four hours, should be increased rapidly.

In case of epidemics of pneumonia, the advisability of preventive inoculations of the vaccine should be con-



sidered. Wright, after his extensive work among the natives of South Africa, decided that a dose of 1,000 million killed pneumococci was productive of the most satisfactory results, and that the incidence of pneumonia was materially reduced in the three months following inoculation. Lister's more recent work on both animals and man has established certain important facts as to the value of this method of preventing pneumonia. He recommends three subcutaneous injections at seven-day intervals consisting of 2,000 million killed pneumococci of the types against which immunization is desired.

The most recent work is that of Cecil and Austin at Camp Upton, New York. These workers vaccinated 12,510 men against Types I, II and III of the pneumococcus and arrived at the conclusion that prophylactic vaccination against these organisms is practical and apparently gives protection against the pneumonias produced by these types of the pneumococcus.

1,000 million killed pneumococci in each c. c.

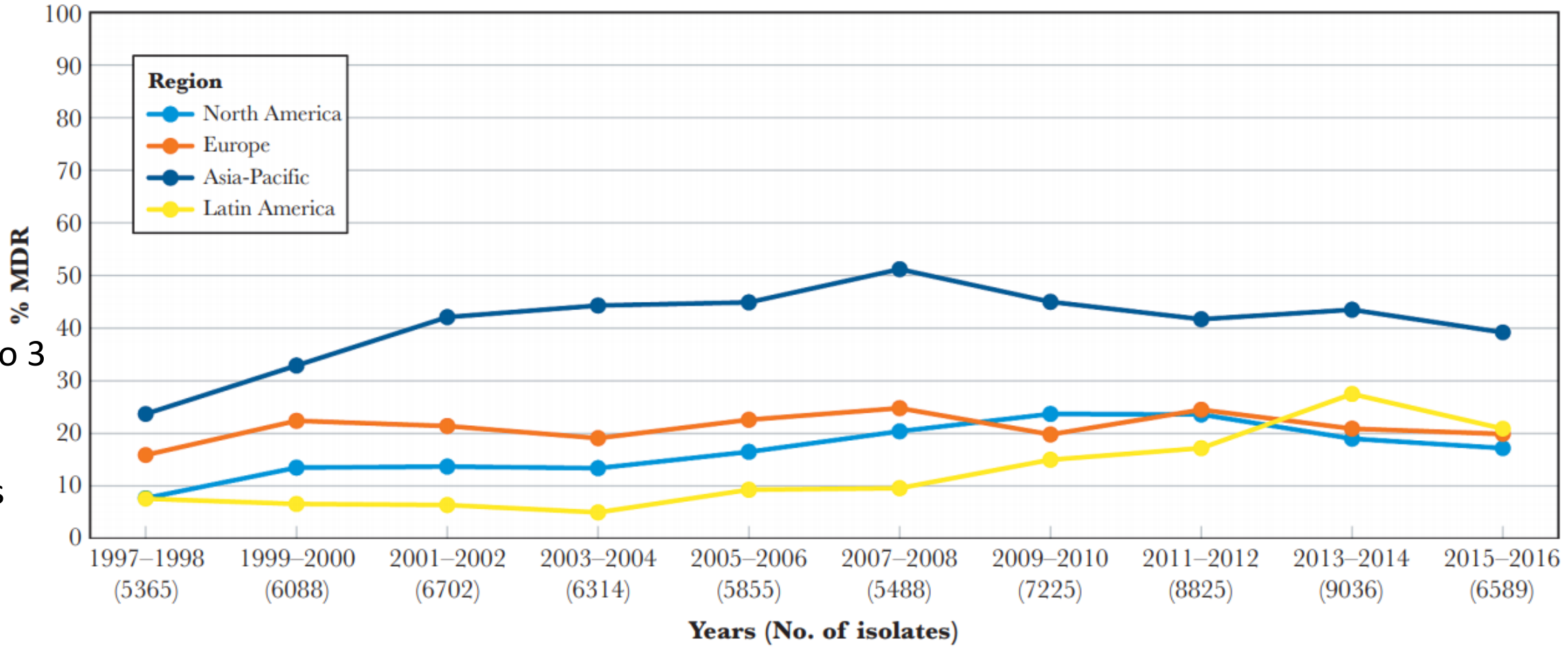
V 396	Two 1 c. c. ampoule vials.
V 398	One 5 c. c. ampoule vial.
V 399	One 20 c. c. vial.
V 401	One 1 c. c. aseptic syringe.
V 404	Three 1 c. c. ampoule vials, one each of 250, 500 and 1,000 million.
V 405	Three 1 c. c. aseptic syringes, one each of 250, 500 and 1,000 million.

FIG. 2. Pneumococcus vaccine, prophylactic and therapeutic (pneumococcus bacterin) packaging. '1000 million killed pneumococci in each c.c.,' likely Types I, II and III. Source: Hand Book of Pharmacy and Therapeutics. Eli Lilly and Company, Indianapolis, IN, USA, 1919:208.

Grabenstein JD. *Clin Microbiol Infect* 2012;**18**:15-24.

Antimicrobial resistance in *S. pneumoniae*
抗藥性肺炎鏈球菌

resistant to 3 or more classes of antibiotics



Sader HS et al. *Open Forum Infect Dis* 2019; **6**:S14-23.

多醣性疫苗

PPV23

Plain Polysaccharide Vaccine

Polysaccharide

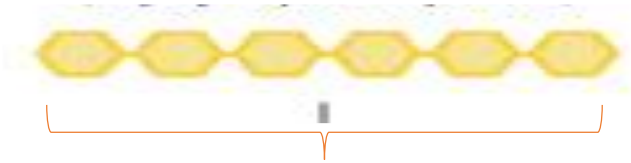
結合性疫苗

PCV13

Polysaccharide Conjugate Vaccine

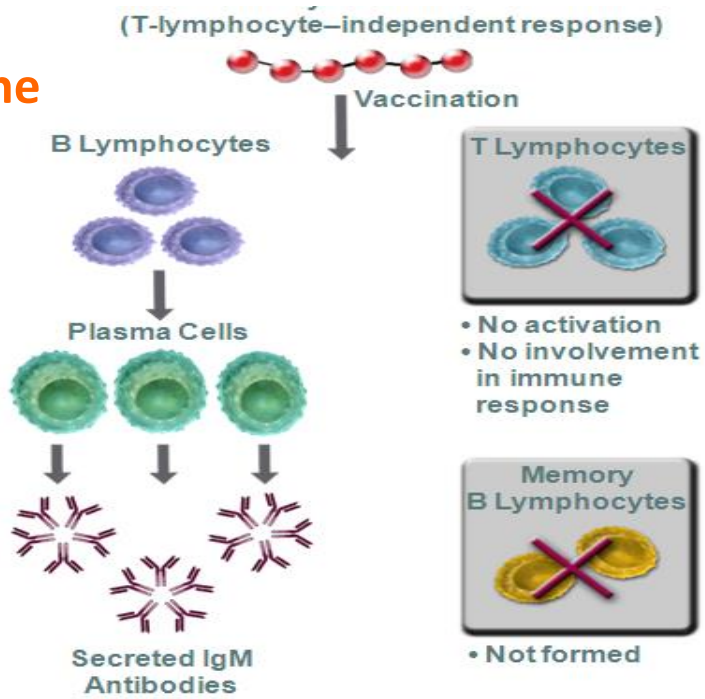
Polysaccharide + **Carrier protein**

PPV23



Polysaccharide

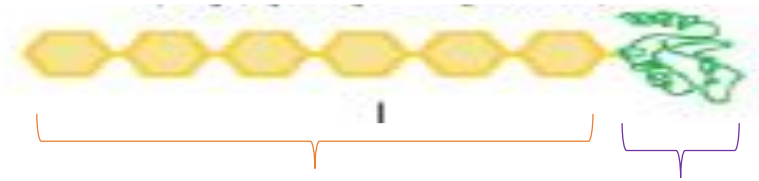
Plain Polysaccharide Vaccine



Weaker immune response
免疫力較弱

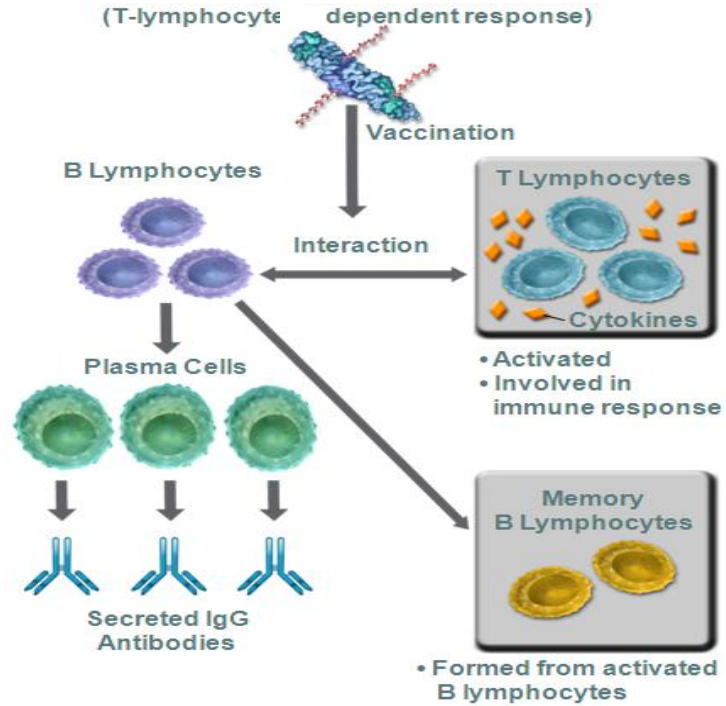
Poor memory
免疫記憶較短暫

PCV13



Polysaccharide + Carrier protein

Polysaccharide Conjugate Vaccine



Powerful immune response
免疫力較強大

Long term memory
免疫記憶較持久

Pollard AJ et al. *Nature Reviews Immunology*. 2009;**9:**213-220. CDC Pink Book. http://www.cdc.gov/vaccines/pubs/pinkbook/index.html

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Pneumococcal Serotypes in the 7-Valent, 10-Valent, and 13-Valent Pneumococcal Conjugate Vaccines[1]
各種疫苗所包涵的血清型

7-valent*	**Carrier: CRM_{197}**	**4**	**6B**	**9V**	**14**	**18C**	**19F**	**23F**						
10-valent†	***H influenzae* protein D, tetanus, and diphtheria toxoid**	**4**	**6B**	**9V**	**14**	**18C**	**19F**	**23F**	**1**	**5**	**7F**			
13-valent‡	**Carrier: CRM_{197}**	**4**	**6B**	**9V**	**14**	**18C**	**19F**	**23F**	**1**	**5**	**7F**	**3**	**6A**	**19A**

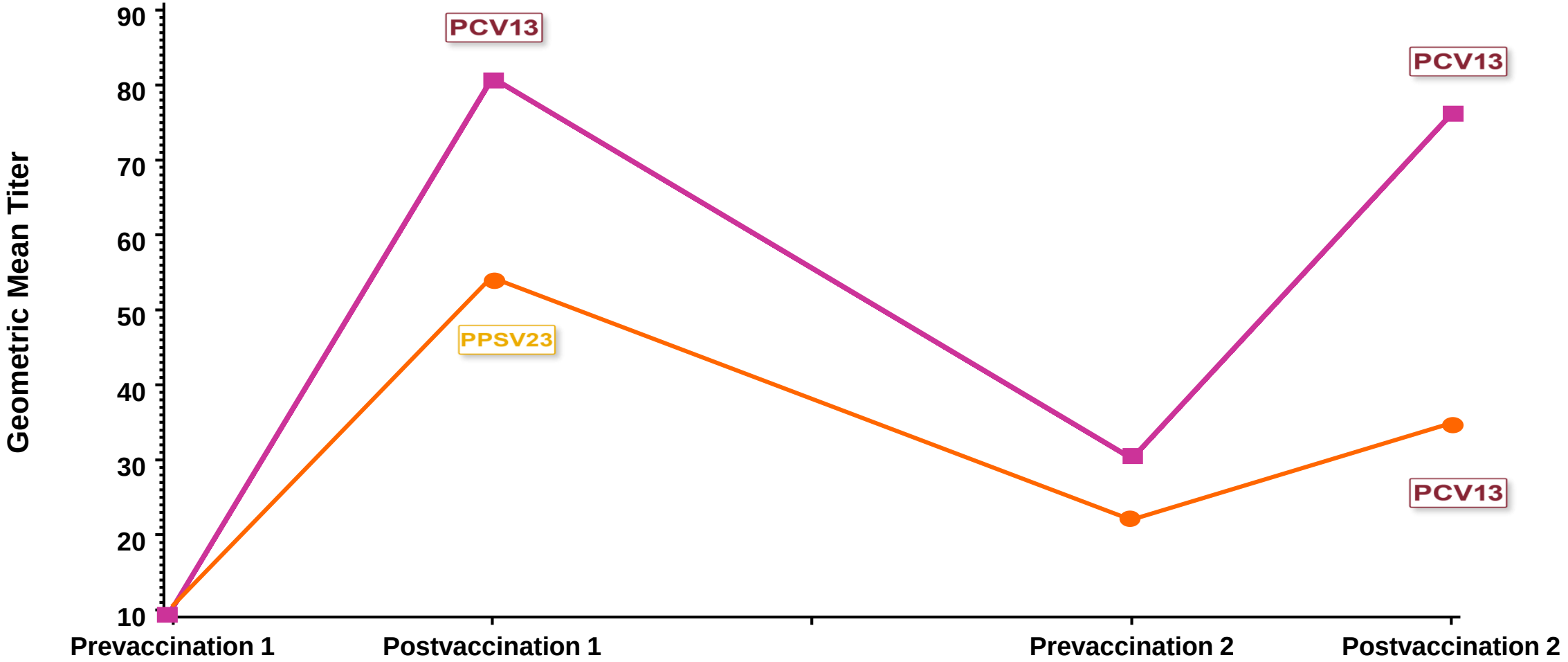
23-valent§	**1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F**

Adapted from Isaacman DJ, et al. *Int J Infect Dis*. 2010;14:e197-e209.

1. Isaacman DJ, et al. *Int J Infect Dis*. 2010;14:e197-e209. **2.** Prevenar [summary of product characteristics]. Kent, UK: Pfizer Limited. **3.** Synflorix [summary of product characteristics]. Belgium: GlaxoSmithKline Biologicals s.a. **4.** Prevenar 13 [summary of product characteristics]. Kent, UK: Pfizer Limited. **5.** Pneumovax® 23 [prescribing information]. Whitehouse Station, NJ: Merck & Co., Inc.

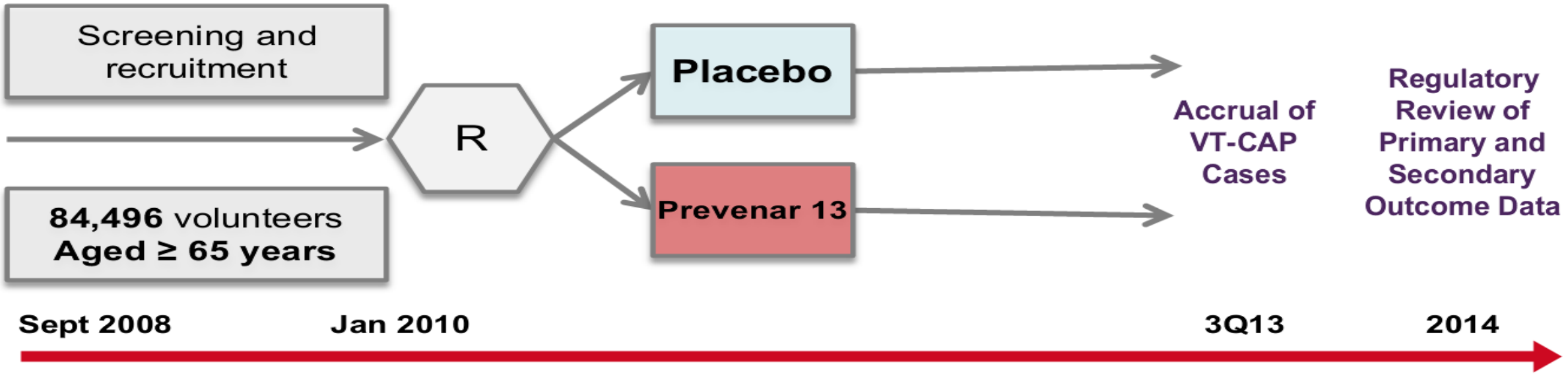
Immunogenicity and Safety of Sequential PCV13 in PPSV23-Exposed Adults ≥70 Years

OPA Antibody Response: Serotype 1



Jackson LA et al. *Vaccine*. 2013;**31**:3585-3593.

Community-Acquired Pneumonia Immunisation Trial in Adults (CAPiTA)

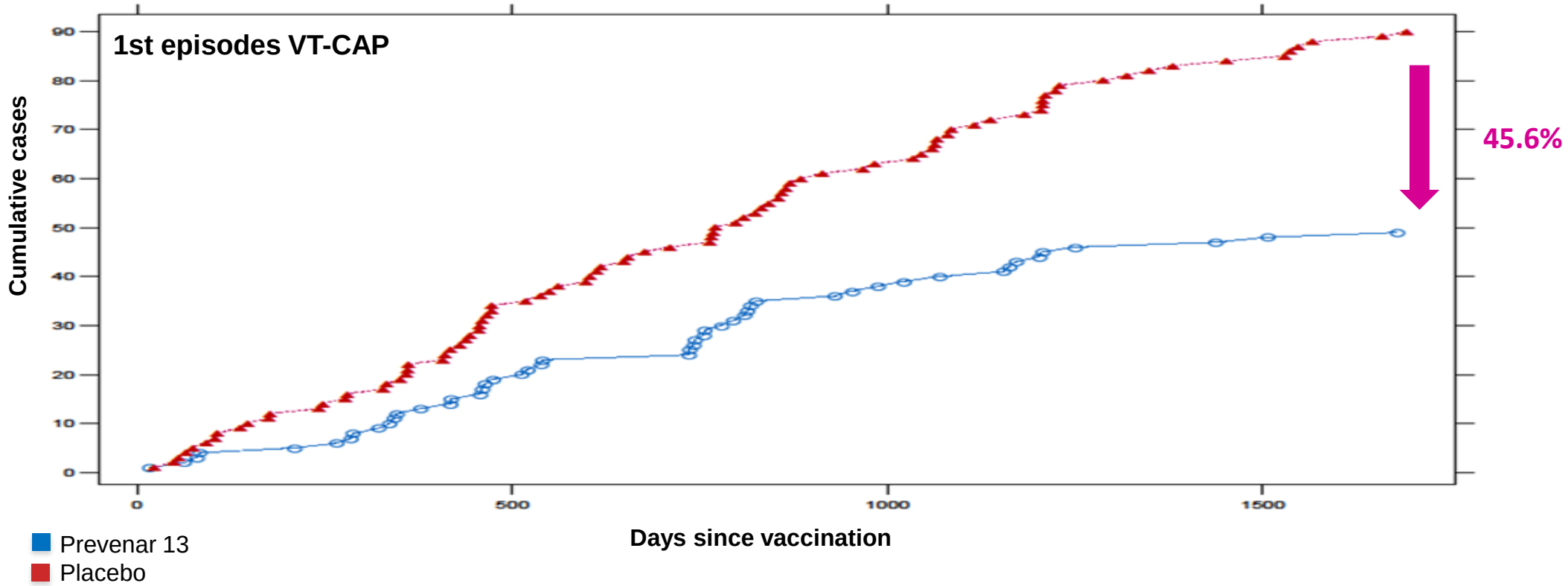


Bonten MJM et al. *N Eng J Med* 2015;**372**:1114-25.

CAP = Community acquired pneumonia社區感染的肺炎

VT-CAP=vaccine-type community-acquired pneumonia

VT = Vaccine type 疫苗包含的血清型



Mean duration of follow-up=3.97 years

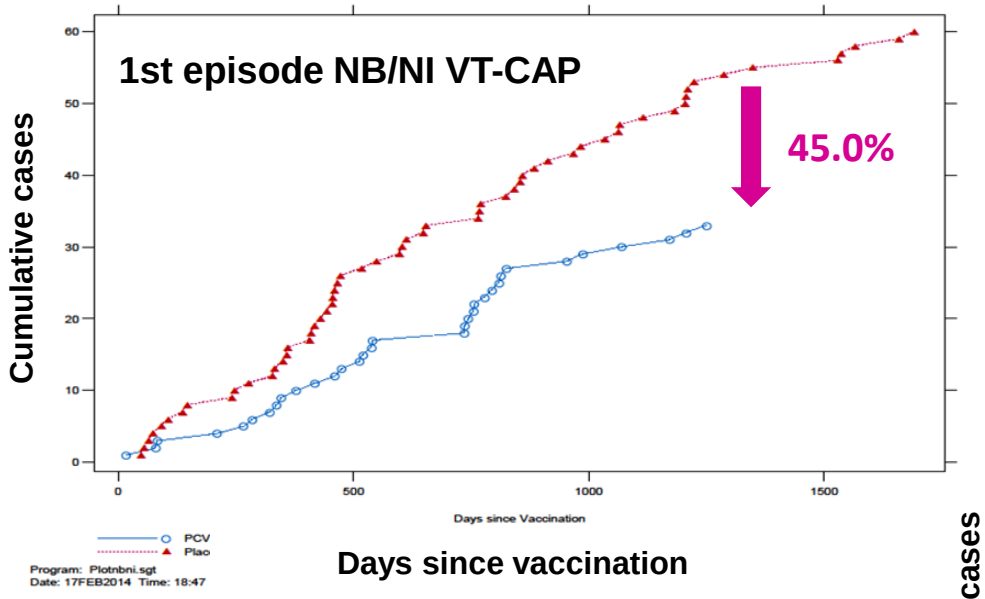
Bonten MJM et al. *N Eng J Med* 2015;**372**:1114-25.

NB/NI = non-bacteraemia/non-invasive非菌血型或侵入性

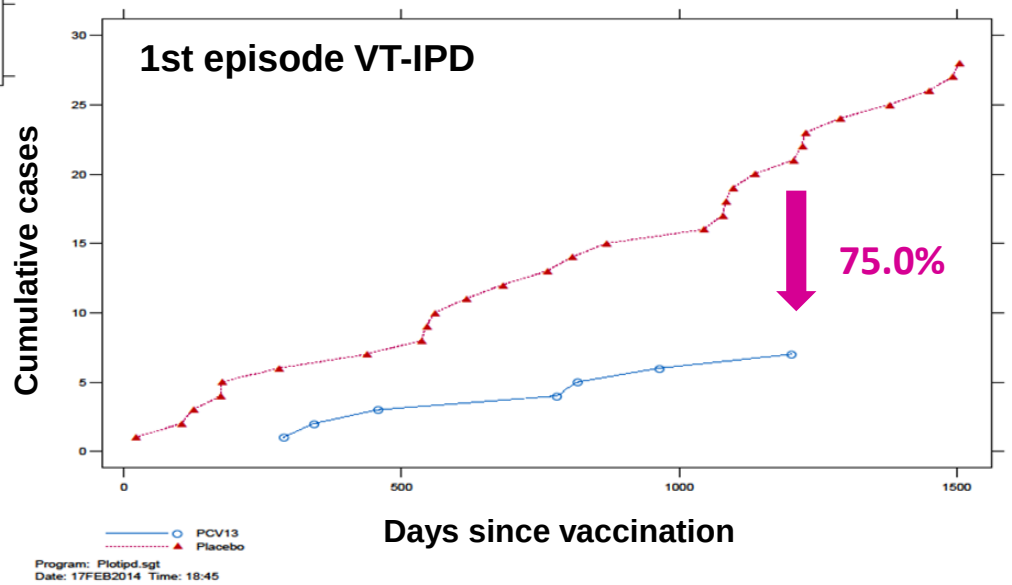
IPD = Invasive pneumococcal disease 侵入性肺炎鏈球菌病

CAP = Community acquired pneumonia社區感染的肺炎

VT = Vaccine type 疫苗包含的血清型

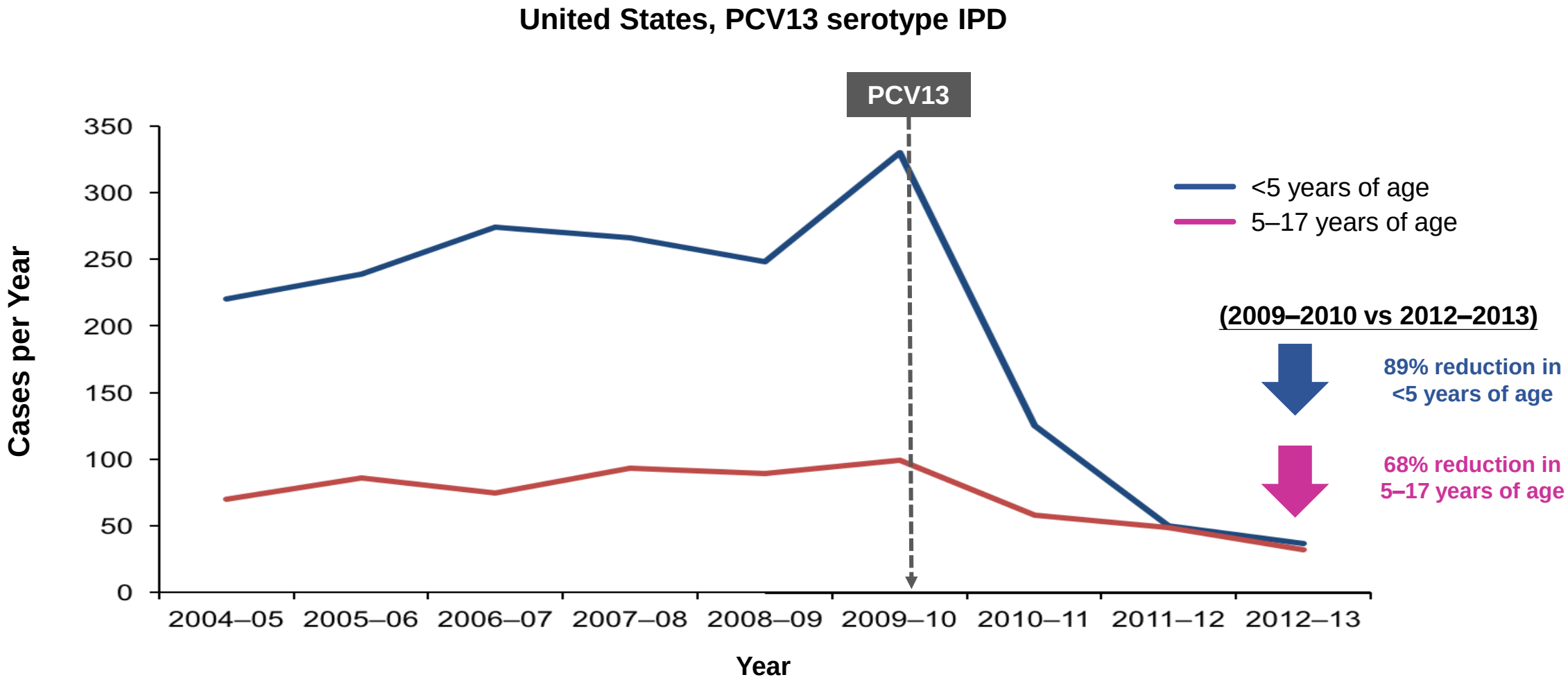


Mean duration of follow-up=3.97 years



Bonten MJM et al. *N Eng J Med* 2015;**372**:1114-25.

United States: IPD Cases Caused by the PCV13 Serotypes (plus 6C) in Children <18 Years of Age
13價結合性疫苗在兒童青少年的表現



Moore MR et al. *Lancet Infect Dis*. 2015;**15**(3):301-309.

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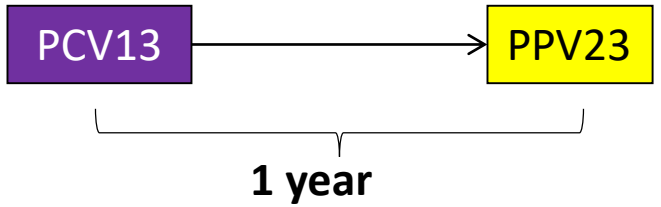
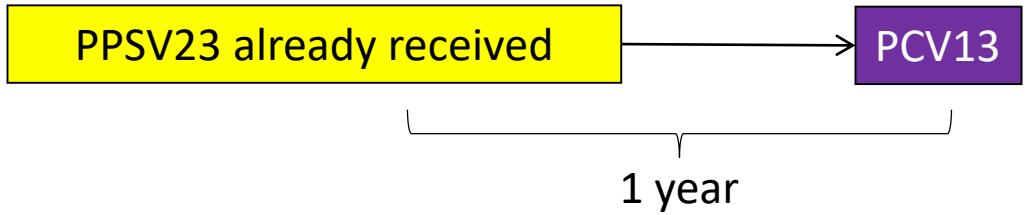
Pneumococcal vaccinations: Local recommendations (2016)
香港關於肺炎鏈球菌疫苗的指引

High-risk vaccine-naïve individuals aged ≥2 years



High-risk individuals aged ≥2 years who previously received PPSV23



Elders aged ≥ 65 years without high-risk conditions

PCV13 or PPV23

High-risk conditions:

- Chronic heart, lung, kidney and liver diseases 慢性心，肺，肝，腎疾病
- Diabetes mellitus 糖尿病
- Cerebrospinal fluid leaks 腦脊髓液滲漏
- Presence of cochlear implant 人工耳蝸
- Primary immunodeficiencies 先天免疫力缺乏症
- HIV infection 後天免疫力病毒感染
- Anatomical or functional asplenia 脾臟功能缺乏
- Malignancy 癌症
- Solid organ or stem cell transplantation 器官或幹細胞移植
- Autoimmune diseases 自身免疫性疾病

Centre for Health Protection. Updated recommendations on the use of pneumococcal vaccines for high-risk individuals. Available from: https://www.chp.gov.hk/files/pdf/updated_recommendations_on_the_use_of_pneumococcal_vaccines_amended_120116_clean_2.pdf. Last accessed 31st January 2021

Important causes of pneumonia
常見的肺炎成因

Bacteria/Mycobacteria 細菌 /分支桿菌	Virus 病毒	Fungi 真菌
• *Streptococcus pneumoniae* • *Haemophilus influenzae* • *Staphylococcus aureus* • *Streptococcus pyogenes* • *Klebsiella pneumoniae* • *Pseudomonas aeruginosa* • *Legionella pneumophila* • *Mycoplasma pneumoniae* • *Chlamydophila pneumoniae* • *Mycobacterium tuberculosis*	• Influenza viruses • Adenovirus • Pandemic coronarviruses (SARS-CoV, MERS-CoV2, SARS-CoV-2)	• *Pneumocystis jiroveci* • *Cryptococcus neoformans* • *Aspergillus* species • *Talaromyces marneffei* and other dimorphic fungi

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Influenza viruses
流行性感冒病毒

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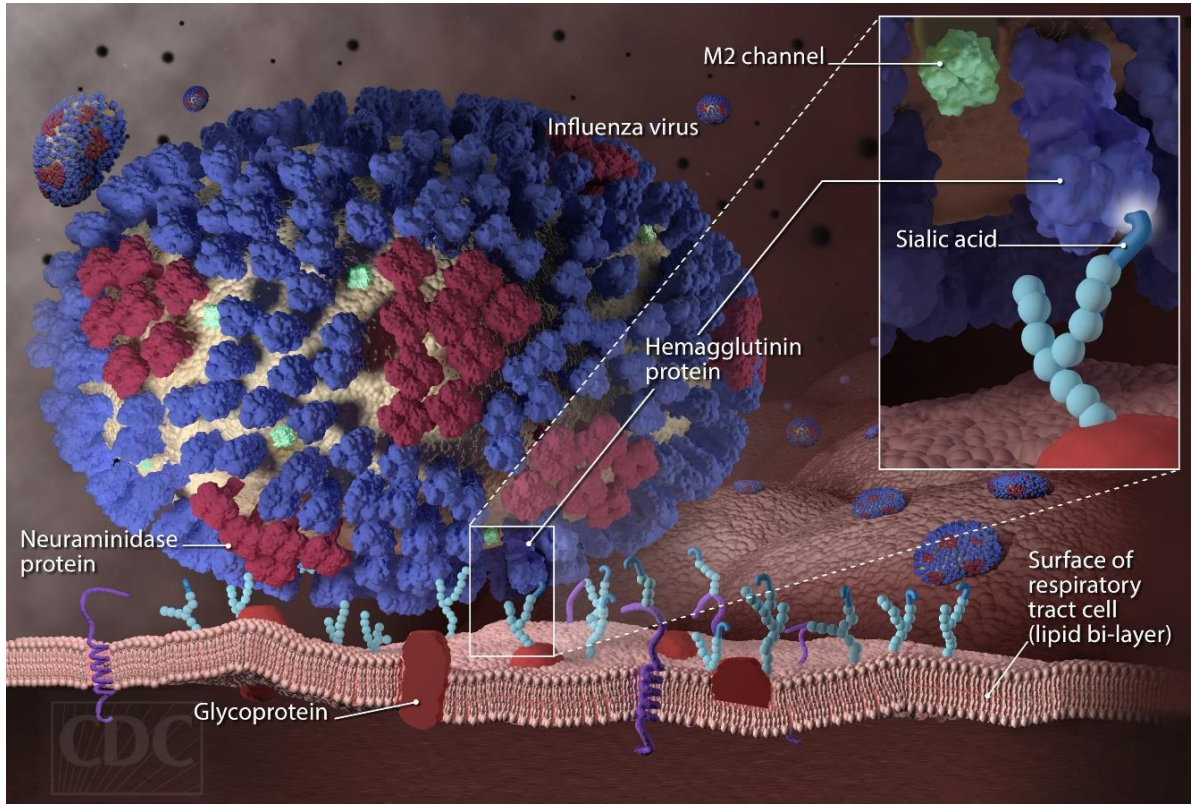
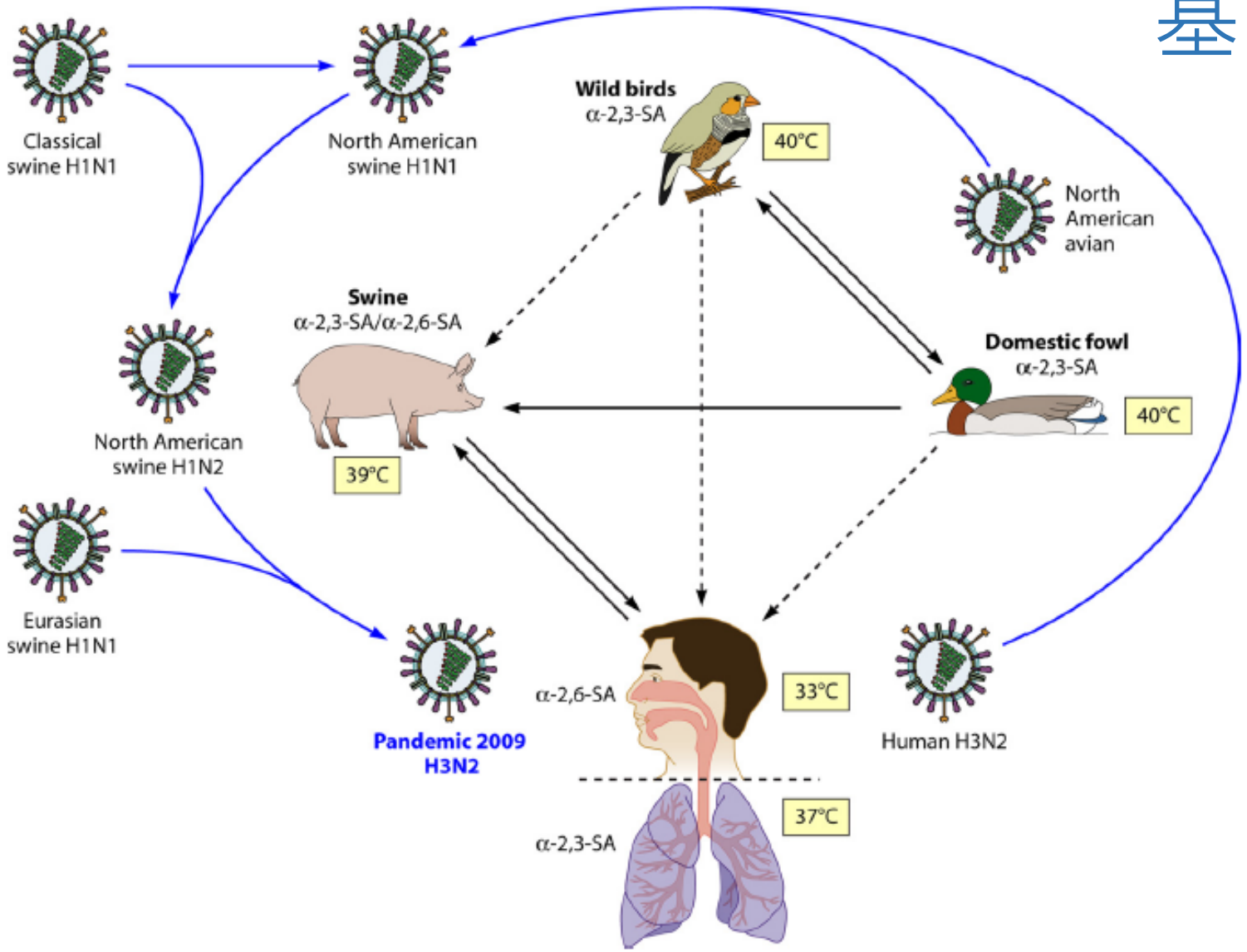
Influenza: overview
流行性感冒病毒總覽

- Human diseases mainly caused by influenza A and B viruses
- Range of manifestations:
  - Respiratory symptoms: cough, shortness of breath, runny nose
  - Systemic symptoms: fever, malaise, myalgia
- Can be severe and lethal for patients at extremes of ages or with chronic illnesses
- Threats:
  - Antigenic drift
  - Avian influenza (H5N1/H7N9)



Krammer F et al. *Nat Rev Dis Primers* 2018; **4**:3
https://www.cdc.gov/flu/images/influenza-virus-labels.jpg

Genetic Reassortment
基因洗牌效應



Cheng VCC et al. *Clin Microbiol Rev* 2012;**25**:223-63.

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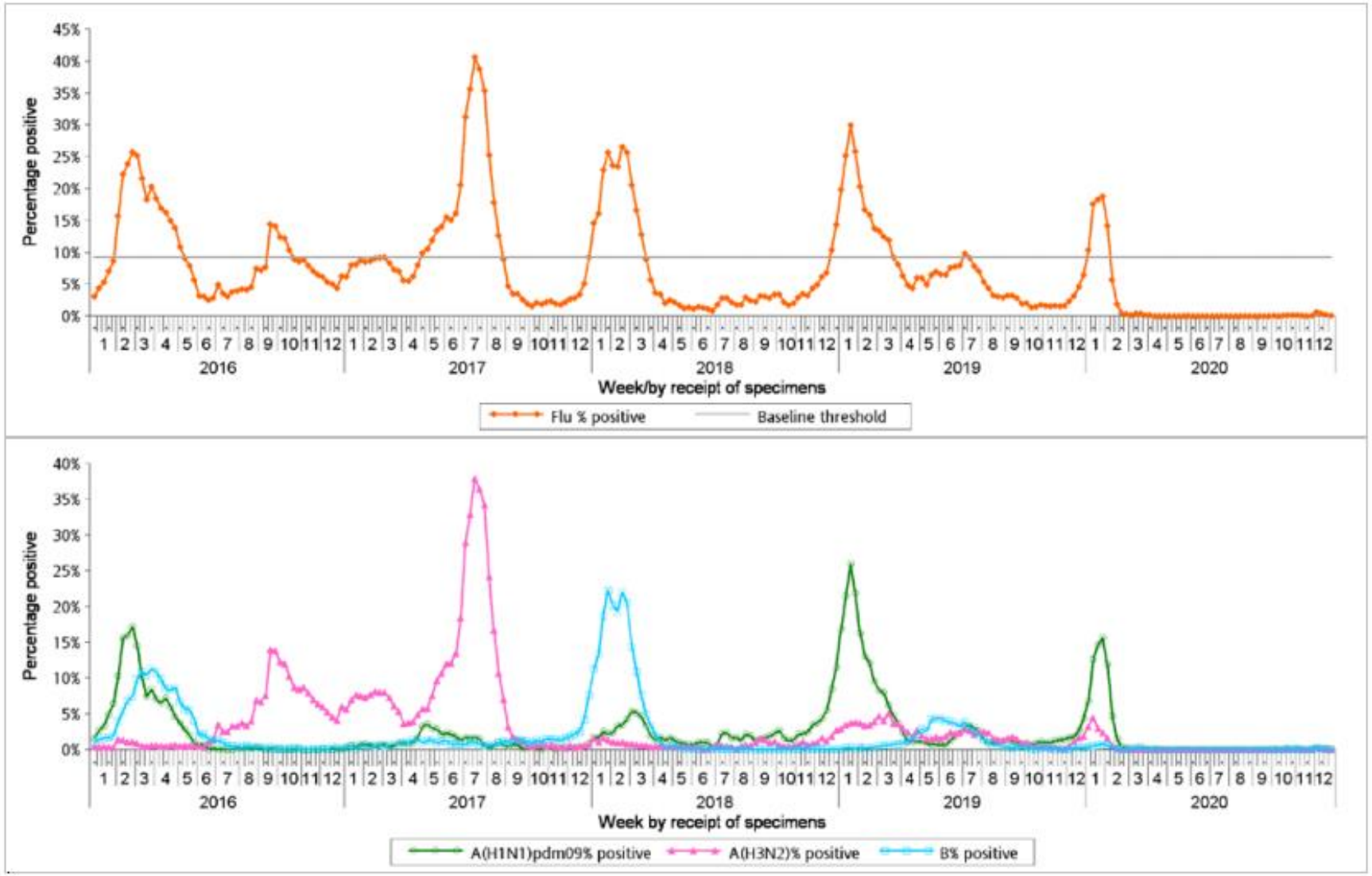
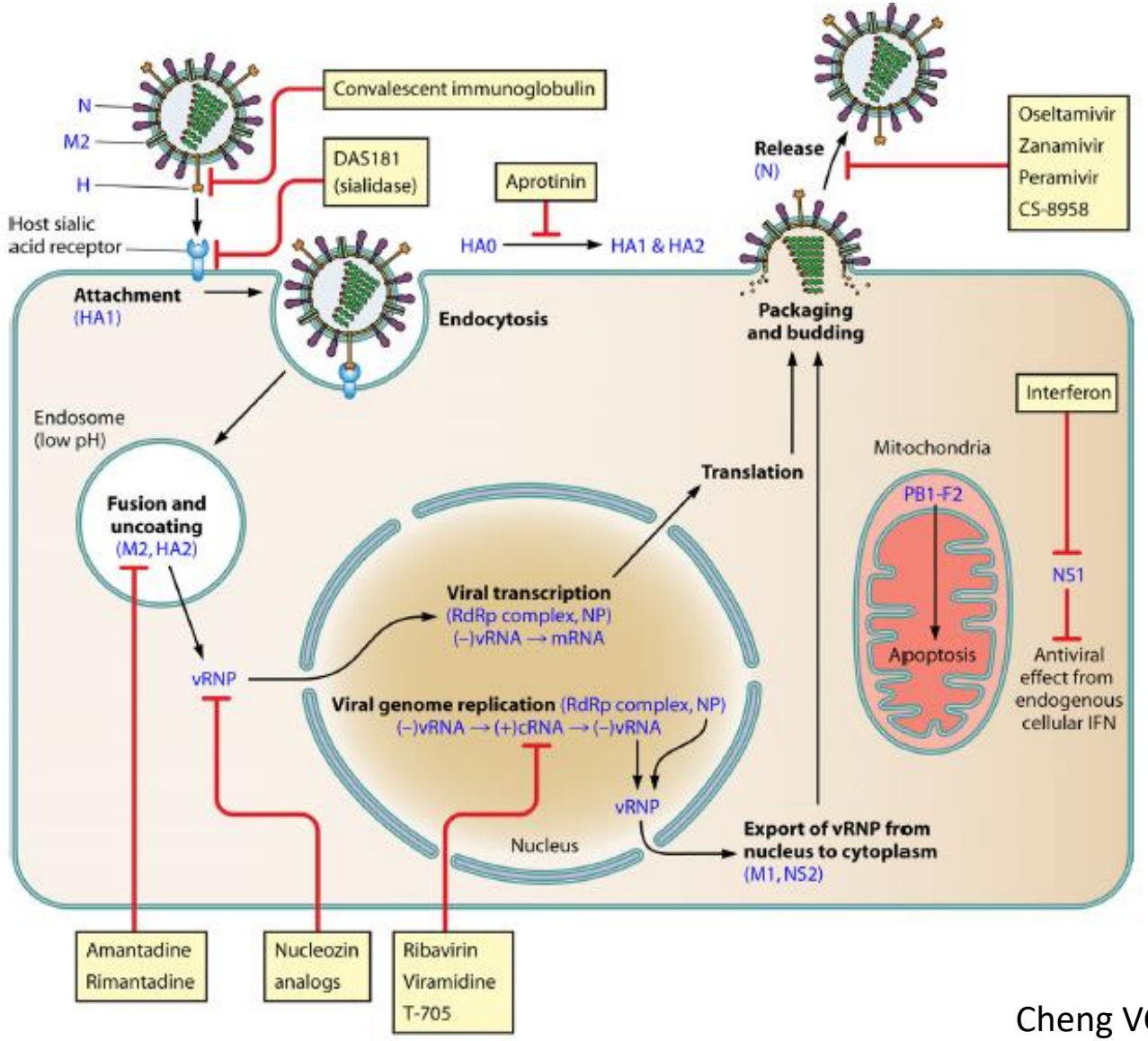
Influenza surveillance in HK
香港流感的流行病學監察



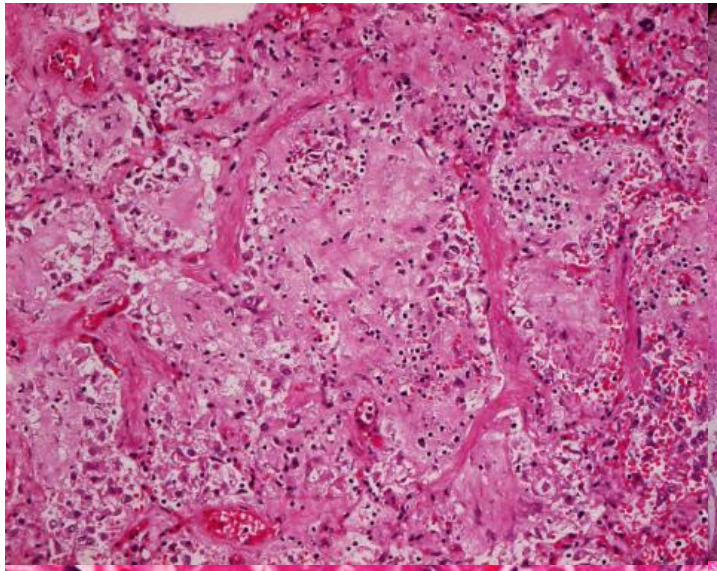
https://www.chp.gov.hk/files/pdf/fluexpress_week52_31_12_2020_eng.pdf. Accessed on 31st January 2021.

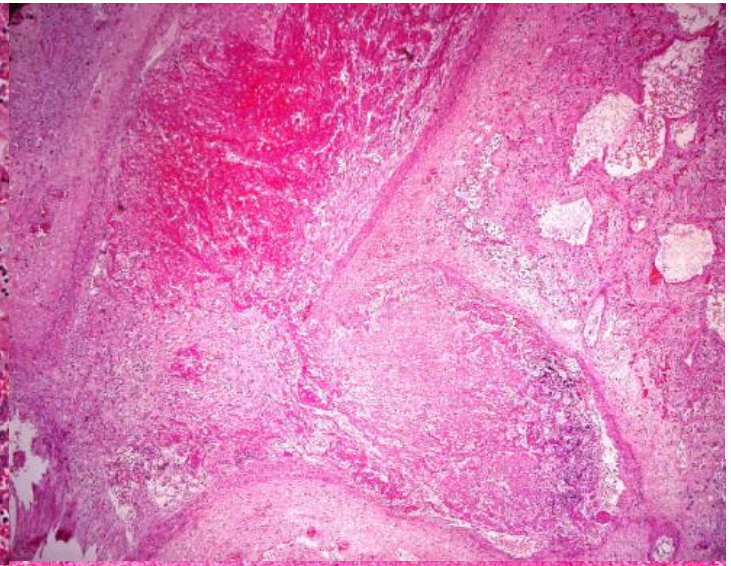
Antiviral targets
抗流感病毒藥物的原理



Cheng VCC et al. *Clin Microbiol Rev* 2012;**25**:223-63.

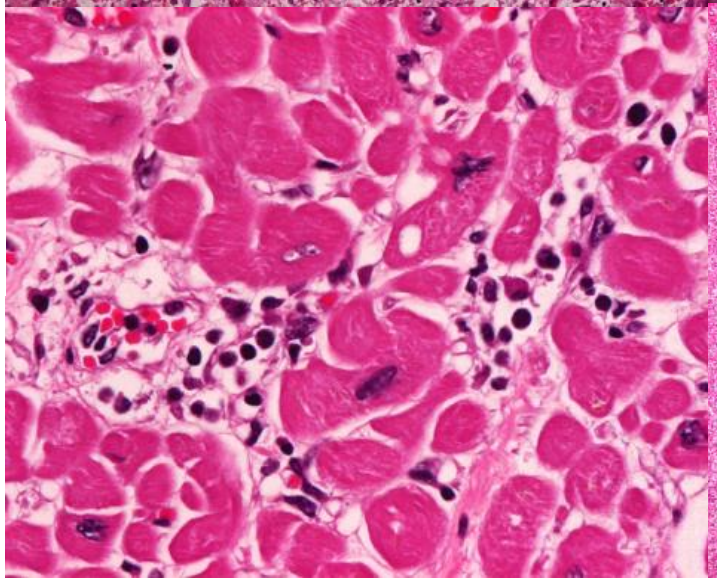
Diffuse alveolar damage
大範圍氣泡受損

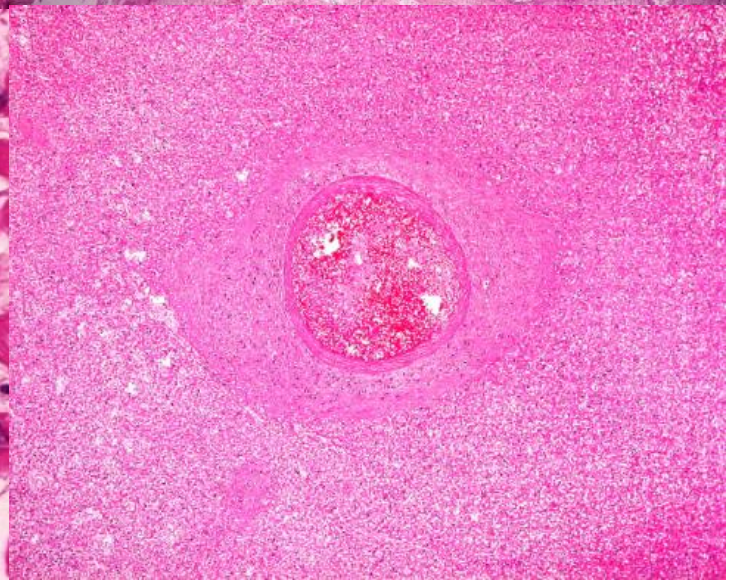




Pulmonary vascular thrombosis
肺部血管栓塞

Myocarditis
心肌發炎

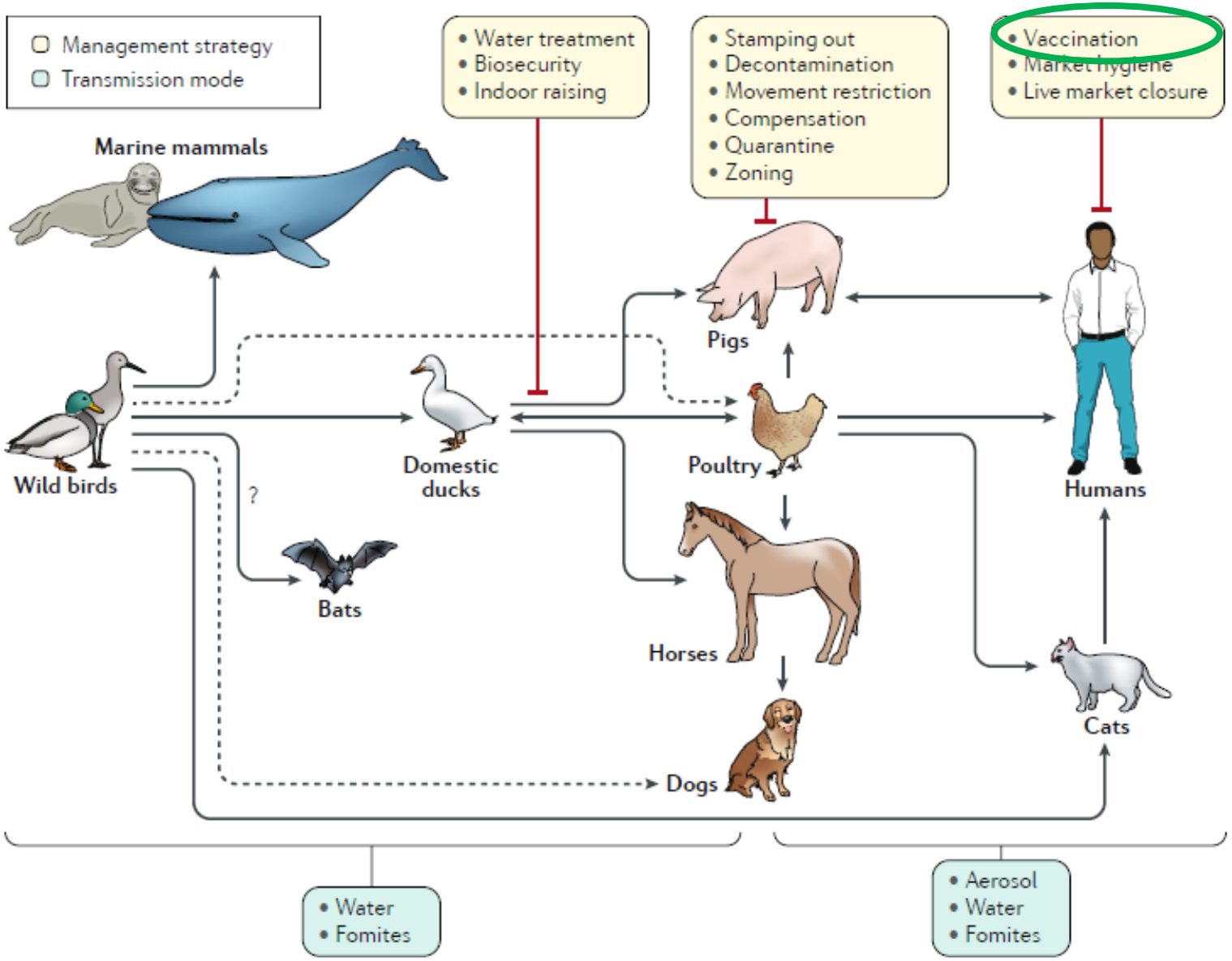




Thrombosis in splenic vessel
脾臟血管栓塞

Cheng VCC et al. *Clin Microbiol Rev* 2012;**25**:223-63.

Prevention
預防流感的方法



Krammer F et al. *Nat Rev Dis Primers* 2018; **4**:3

Vaccination strategies
增加流感疫苗效用的方法

- Types of seasonal influenza vaccine
- Target population
  - Old idea: direct protection
  - New idea: indirect protection
- Enhanced immunogenicity
  - Adjuvant seasonal influenza vaccine
  - High dose seasonal influenza vaccine
  - Intradermal seasonal influenza vaccine with TLR-7 agonist

Types of vaccines
流感疫苗的種類

Inactivated influenza vaccine (IIV) **滅活流感疫苗**	• Given intra-muscularly • Registered for individuals aged above 6 months • Currently quadrivalent: containing two strains each of influenza A (H1N1 and H3N2) and influenza B (Victoria lineage and Yamagata lineage) viruses
Live attenuated influenza vaccine (LAIV) **減活流感疫苗**	• Given intra-nasally • Registered for healthy non-pregnant individuals aged 2-49 • Contraindicated in patients with chronic illness or immunocompromised states, or care-takers of transplant recipients
Recombinant vaccine **基因重組疫苗**	• Egg-free vaccine • Licensed for adults aged 18 and above • Shorter shelf life of 9 months from production dates • Not available in HK

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Target population
流感疫苗的目標群組

Old idea: direct protection

- Immunize the elderly
- High risk population: immunosuppressed, chronic illness, obese, pregnant women
- Stop them getting sick and dying

直接保護

- 為長者及其他高危一族注射疫苗
- 減低發病或死亡

New idea: indirect protection

- Immunize children universally
- Block transmission of influenza
- Protect not only those at high risk but also larger low risk group
- Herd immunity

間接保護

- 為兒童注射
- 防止傳播甚至達到群體免疫

Clustered Randomized Study on indirect protection

- Isolated Hutterite communities in Canada
- 947 children aged 3-15y in 50 communities
- 3.1% adults from the immunized children community vs. 7.6% from the unimmunized children community developed influenza confirmed by RT-PCR (herd immunity 61% effective)

Courtesy of A Finn; ADVAC 2017

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Adjuvant MF59 Influenza Vaccine
帶有額外蛋白的流感疫苗

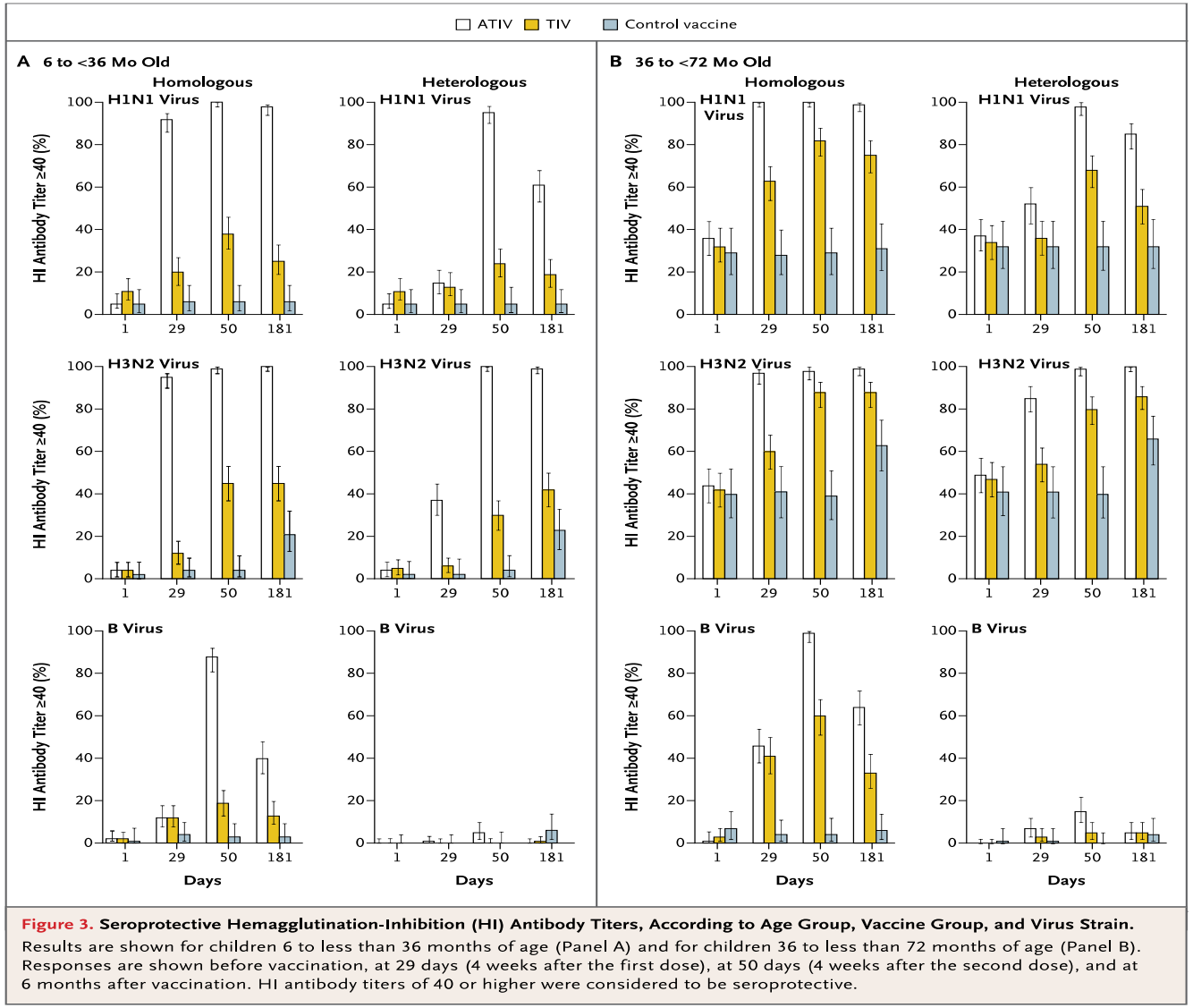

Figure 3. Seroprotective Hemagglutination-Inhibition (HI) Antibody Titers, According to Age Group, Vaccine Group, and Virus Strain.
Results are shown for children 6 to less than 36 months of age (Panel A) and for children 36 to less than 72 months of age (Panel B). Responses are shown before vaccination, at 29 days (4 weeks after the first dose), at 50 days (4 weeks after the second dose), and at 6 months after vaccination. HI antibody titers of 40 or higher were considered to be seroprotective.

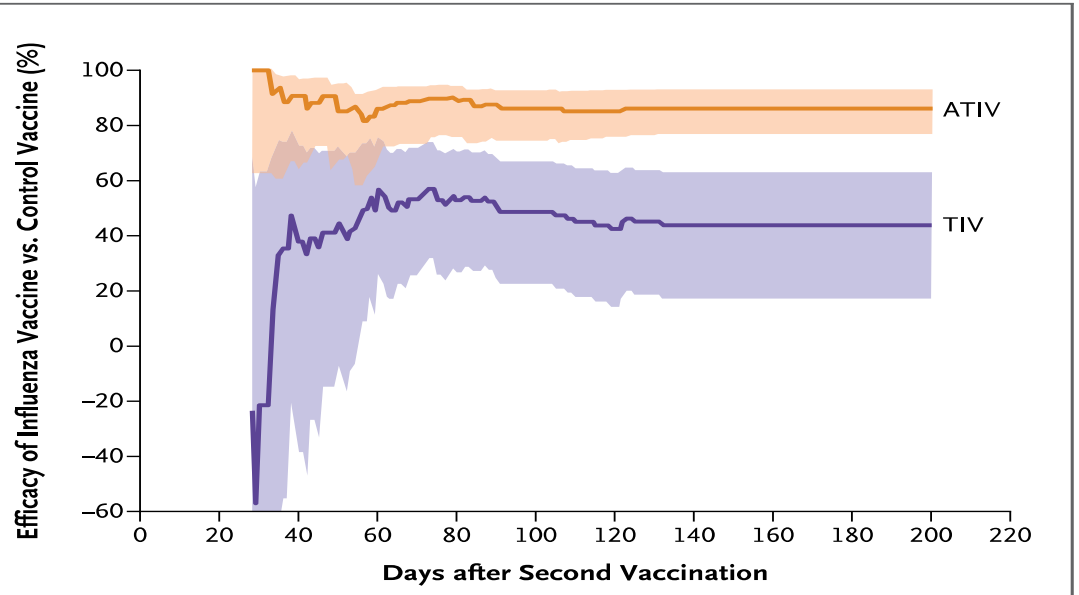

Figure 2. Efficacy of Influenza Vaccines versus Control Vaccine over Time.
The cumulative efficacy of ATIV and of TIV, as compared with control (non-influenza) vaccine, is shown. The data are for efficacy against all viral strains over time after the second dose of vaccine in children 6 to less than 72 months of age. Shaded areas represent 95% confidence intervals.

Versikari et al. *N Eng J Med* 2011;**365**:1406-16.

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High Dose Influenza Vaccine
高劑量流感疫苗

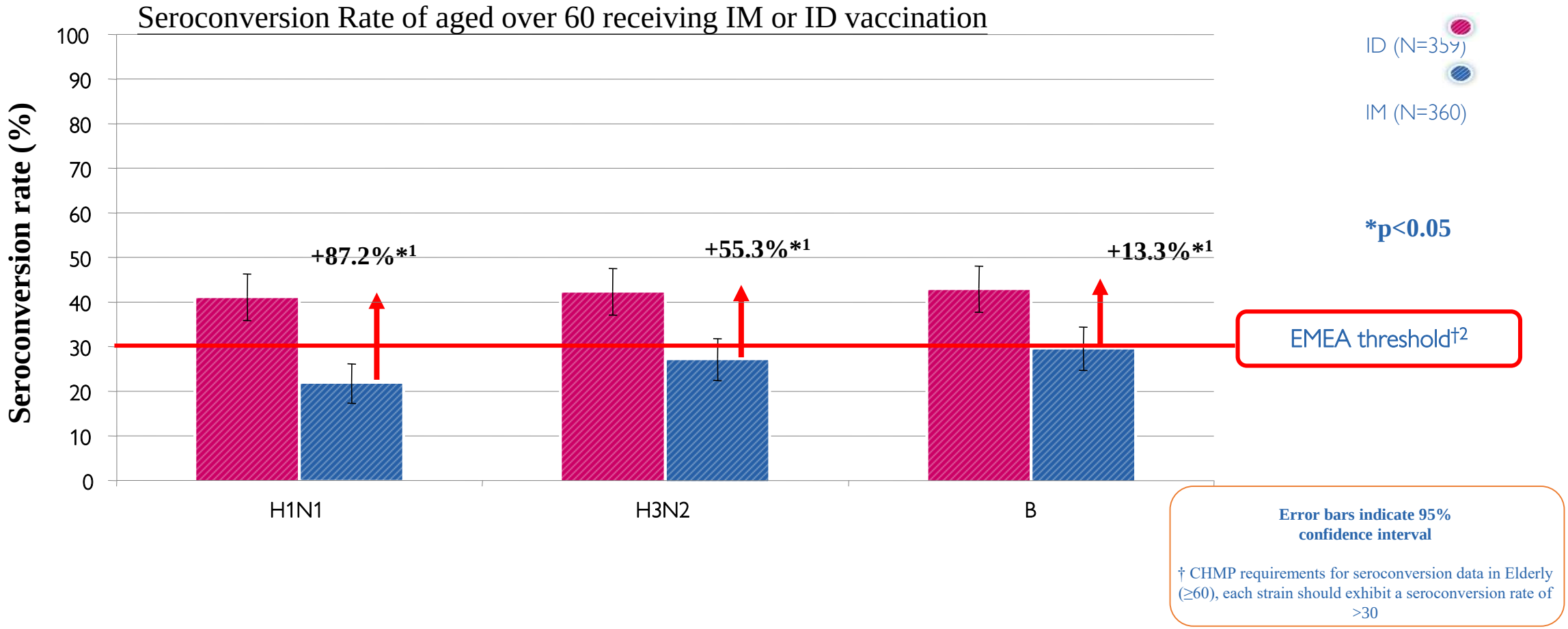
Table 4. Hemagglutination Inhibition Immunogenicity of High-Dose Vaccine and Standard-Dose Vaccine against Influenza Viral Types and Subtypes Contained in the Vaccine.*

Viral Type/ Subtype	Year 1			Year 2			Combined†		
	IIV3-HD (N=2375)	IIV3-SD (N=2382)	IIV3-HD vs. IIV3-SD	IIV3-HD (N=2879)	IIV3-SD (N=2872)	IIV3-HD vs. IIV3-SD	IIV3-HD (N=5254)	IIV3-SD (N=5254)	IIV3-HD vs. IIV3-SD
	geometric mean titer (95% CI‡)		*ratio of geometric mean titers (95% CI‡)*	*geometric mean titer (95% CI‡)*		*ratio of geometric mean titers (95% CI‡)*	*geometric mean titer (95% CI‡)*		*ratio of geometric mean titers (95% CI‡)*
A/H1N1	481.8 (457.7–507.1)	271.8 (257.4–287.1)	1.8 (1.6–1.9)	407.0 (390.2–424.4)	227.4 (216.8–238.5)	1.8 (1.7–1.9)	439.2 (425.1–453.8)	246.6 (237.9–255.6)	1.8 (1.7–1.9)
A/H3N2	685.5 (651.4–721.4)	349.8 (332.1–368.6)	2.0 (1.8–2.1)	460.0 (440.8–480.0)	252.8 (241.6–264.4)	1.8 (1.7–1.9)			
B	138.1 (132.2– 144.2)	97.6 (93.3–102.0)	1.4 (1.3–1.5)	98.2 (94.5–102.0)	61.8 (59.4–64.2)	1.6 (1.5–1.7)			
	% with seroprotection (95% CI§)		*percentage-point difference (95% CI¶)*	*% with seroprotection (95% CI§)*		*percentage-point difference (95% CI¶)*	*% with seroprotection (95% CI§)*		*percentage-point difference (95% CI¶)*
A/H1N1	98.1 (97.5–98.6)	94.2 (93.2–95.1)	3.9 (2.8–5.0)	98.8 (98.3–99.2)	93.3 (92.3–94.2)	5.5 (4.5–6.5)	98.5 (98.1–98.8)	93.7 (93.0–94.3)	4.8 (4.1–5.5)
A/H3N2	99.2 (98.7–99.5)	96.5 (95.6–97.2)	2.7 (1.9–3.5)	98.6 (98.2–99.0)	95.0 (94.2–95.8)	3.6 (2.7–4.5)			
B	91.6 (90.4–92.7)	83.9 (82.3–85.3)	7.7 (5.9–9.6)	86.2 (84.9–87.4)	72.8 (71.1–74.4)	13.4 (11.4–15.5)			

* The number of participants in the high-dose and standard-dose categories are those participants in the full analysis set and the immunogenicity subset who had at least one hemagglutination inhibition (HAI) assay result for the year. Seroprotection is defined as an HAI titer of at least 1:40.
† The type A (H1N1) virus used to make the 2012–2013 influenza vaccine was the same virus used to make the 2011–2012 vaccine, but the type A (H3N2) and type B viruses used to make the 2012–2013 influenza vaccine were different from those in the 2011–2012 influenza vaccine, so only the results from the type A (H1N1) strain can be combined.
‡ The geometric mean titer confidence intervals were calculated according to the t distribution and the assumption that log (HAI titer) follows a normal distribution.
§ The confidence intervals were calculated with the use of the Clopper–Pearson exact method.[15]
¶ The confidence intervals were calculated with the use of the Newcombe–Wilson score method.[16]

DiazGranados et al. *N Eng J Med* 2014;**371**:635-45

Seroncoversion Rate of Elderly receiving Intramuscular (IM) or Intradermal (ID) Vaccination
長者肌肉與皮下疫苗注射的抗體保護率



1. *Holland D, et al. J Infect Dis 2008; 198(5): 650–658; Hung IF et al Vaccine 2010*
2. *European Agency for the Evaluation of Medicinal Products. Note for guidance on harmonization of requirements for influenza vaccines. March 1997; CPMP/BWP/214/96*

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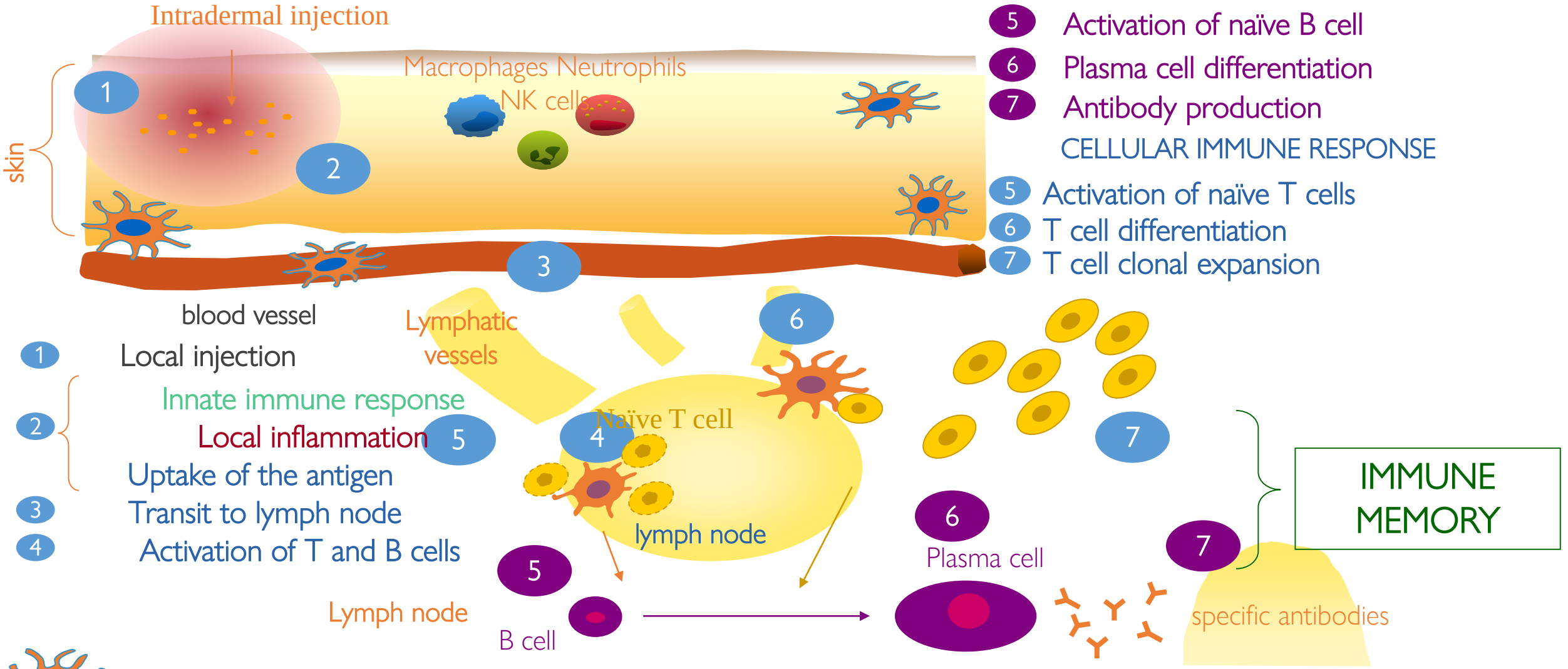
Immune Mechanisms after Intradermal Injection
皮下注射流感疫苗的免疫反應



HUMORAL IMMUNE RESPONSE

5 Activation of naïve B cell

6 Plasma cell differentiation

7 Antibody production

CELLULAR IMMUNE RESPONSE

5 Activation of naïve T cells

6 T cell differentiation

7 T cell clonal expansion

1 Local injection

2 Innate immune response
Local inflammation

Uptake of the antigen

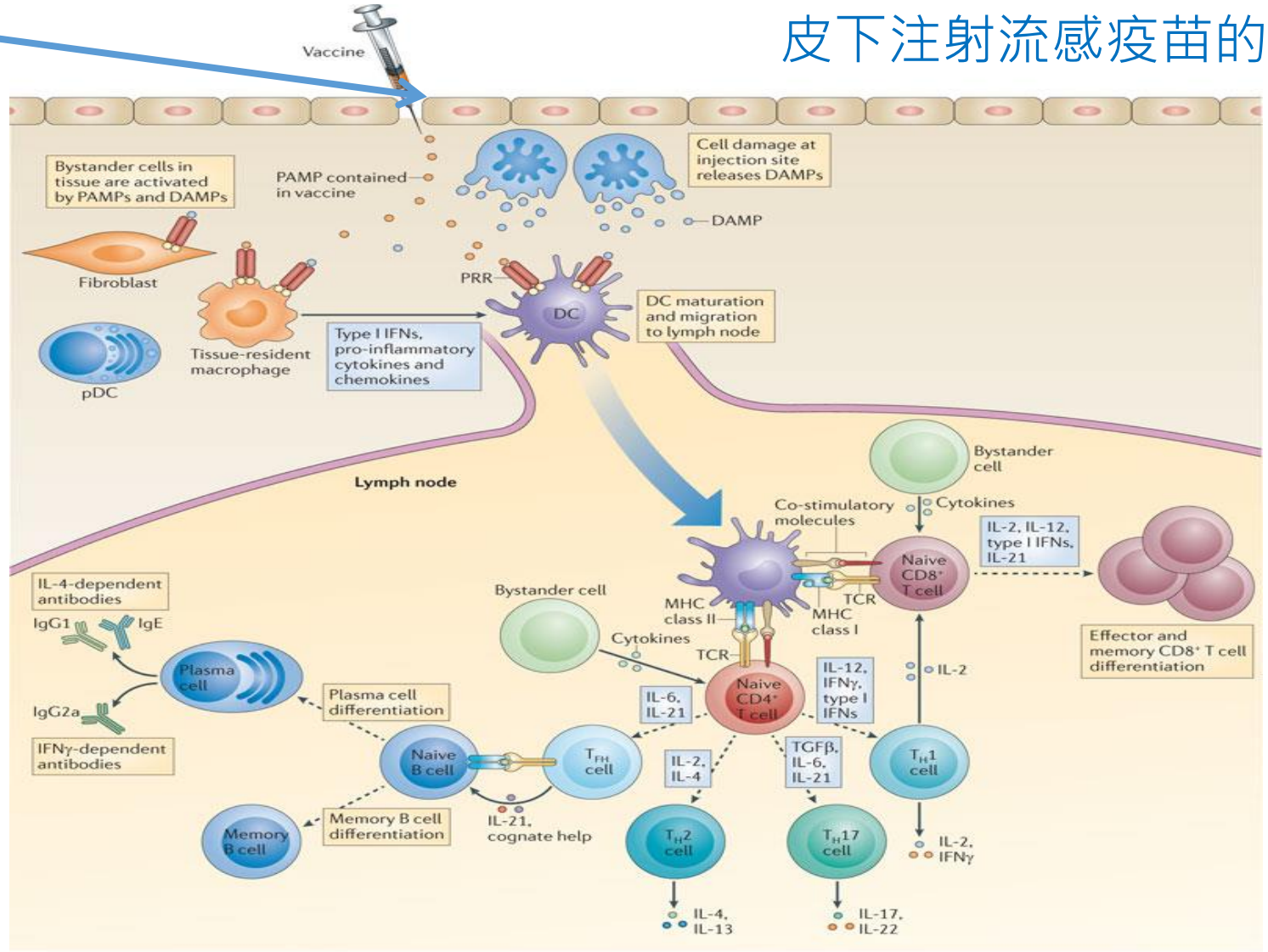
3 Transit to lymph node

4 Activation of T and B cells

Induction of Adaptive Immune Responses to Vaccines Through PRR-mediated Dendritic Cell Activation

皮下注射流感疫苗的免疫反應

1. Topical imiquimod 咪喹莫特 (TLR stimulation)
2. ID vaccination

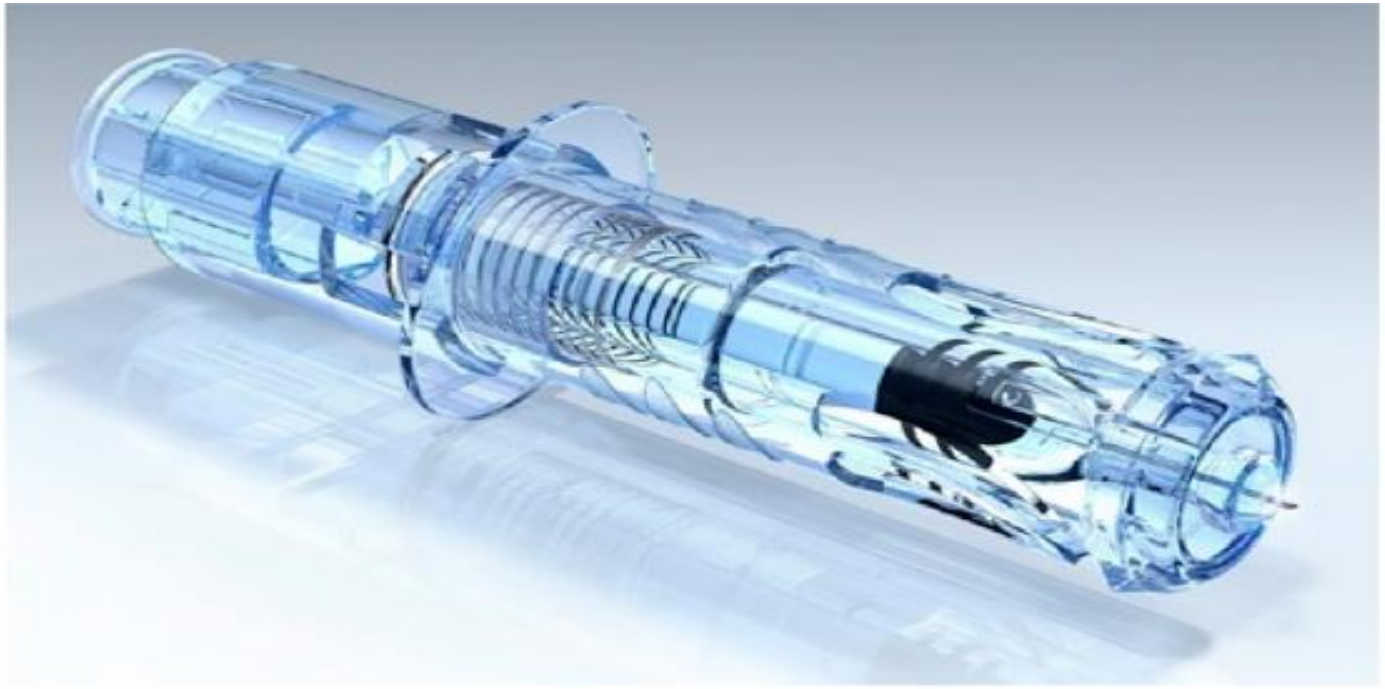


Desmet CJ et al. *Nature Reviews Immunology* 2012;**12**:479-91

Intradermal Devices
皮下注射流感疫苗的儀器

(a)

MicronJet Needle



(b)

Intanza Needle

http://www.nanopass.com

Coudeville L et al. Hum Vaccin 2010:841-8

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MAJOR ARTICLE

Immunogenicity of Intradermal Trivalent Influenza Vaccine With Topical Imiquimod: A Double Blind Randomized Controlled Trial

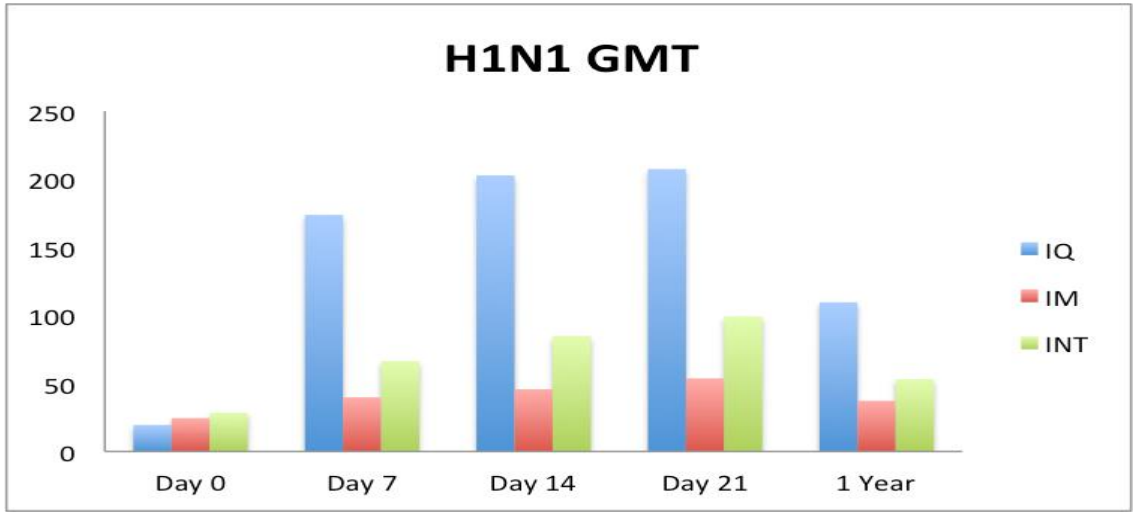
Ivan F. N. Hung,[1,2] Anna J. Zhang,[1] Kelvin K. W. To,[1] Jasper F. W. Chan,[1] Can Li,[1] Hou-Shun Zhu,[2] Patrick Li,[1] Clara Li,[1] Tuen-Ching Chan,[2] Vincent C. C. Cheng,[1] Kwok-Hung Chan,[1] and Kwok-Yung Yuen[1]

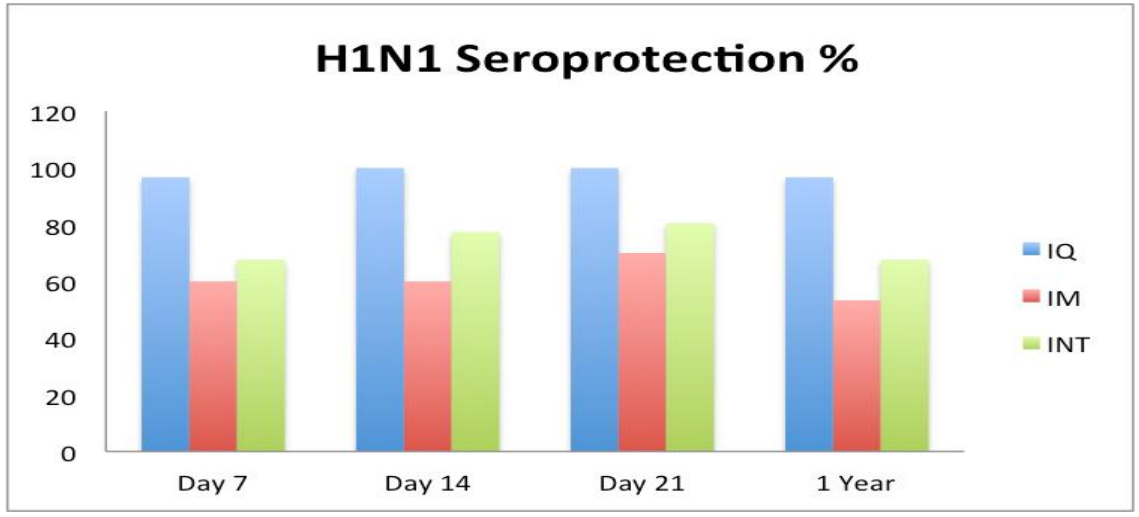
[1]State Key Laboratory for Emerging Infectious Diseases, Carol Yu's Centre for Infection and Division of Infectious Diseases, and [2]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong Special Administrative Region, China

Hung IF et al. *Clin Infect Dis* 2014;**59**:1246-55.

Table 2. Comparison of the Immunogenicity by Hemagglutination Inhibition Assay

Vaccine Antigens	Imiquimod Ointment + Intradermal Vaccine (n = 30)	Aqueous Cream + Intramuscular Vaccine (n = 30)	Aqueous Cream + Intradermal Vaccine (n = 31)	*P* Value
California (H1N1)				
GMT values (95% CI)				
Day 0	19.5 (14.7–25.9)	24.5 (18–33.5)	28.5 (19.1–42.4)	.26
Day 7	173.8 (109.4–276.1)	39.8 (28.4–55.8)	69.5 (44.1–109.6)	**<.001**
Day 14	202.8 (127.4–322.1)	45.7 (31.8–65.6)	84.9 (53.6–134.6)	**<.001**
Day 21	207.5 (127.6–337.3)	53.7 (36.9–78.2)	99.3 (63.2–155.6)	**<.001**
Year 1	109.6 (75.3–159.6)	37.2 (26.1–53)	53.2 (34.5–82)	**.001**
CPMP criteria				
Day 0				
Seroprotection (%)	30	36.7	38.7	.77
Day 7				
Seroconversion (%)	90	13.3	38.7	**<.001**
Seroprotection (%)	96.7	60	67.7	**.002**
GMT-fold increase value (95% CI)	16.8 (7.1–26.5)	1.9 (1.4–2.5)	3.4 (4.6–2.9)	**<.001**





Hung IF et al. *Clin Infect Dis* 2014;**59**:1246-55.

Table 3. Comparison of the Immunogenicity by Microneutralization Assay

Vaccine Antigens	Imiquimod Ointment + Intradermal Vaccine (n = 30)	Aqueous Cream + Intramuscular Vaccine (n = 30)	Aqueous Cream + Intradermal Vaccine (n = 31)	*P* Value
California (H1N1)				
GMT values (95% CI)				
Day 0	14.1 (10.7–18.6)	17 (11.7–24.5)	15.6 (11.4–21.4)	.72
Day 7	117.5 (67.9–203.2)	27.5 (18.4–41.3)	36.3 (22.8–58.3)	**<.001**
Day 14	141.2 (82.8–241)	33.1 (21.7–50.6)	63.5 (40–101.2)	**<.001**
Day 21	154.9 (90.6–264.9)	34.5 (22.6–55.6)	72.6 (46.5–113.8)	**<.001**
Year 1	63.1 (38.6–103)	24 (15.6–36.8)	25.5 (17.9–36.4)	**.002**
Perth (H3N2)				
GMT values (95% CI)				
Day 0	56.2 (35.2–89.7)	38.9 (24.5–61.8)	59.4 (35.2–100.2)	.40
Day 7	478.6 (302.7–756.8)	91.2 (53.6–155.2)	198.2 (117.2–335)	**<.001**
Day 14	575.4 (371.5–891.3)	112.2 (66.5–189.2)	302.7 (169.8–538.3)	**<.001**
Day 21	691.8 (444.6–1076.5)	141.3 (85.5–233.3)	345.9 (191.4–625.2)	**<.001**
Year 1	208.9 (135.8–321.4)	72.4 (43.2–121.6)	124.2 (77.3–199.5)	**.008**
Brisbane (B)				
GMT values (95% CI)				
Day 0	31.6 (20.8–48.1)	28.8 (20–41.5)	32.6 (22.3–47.8)	.90
Day 7	131.8 (87.9–197.7)	47.9 (32.7–70.1)	50.8 (36.1–71.8)	**<.001**
Day 14	169.8 (114.3–252.3)	52.5 (35–78.7)	63.5 (43.6–92.7)	**<.001**
Day 21	186.2 (122.7–282.4)	63.1 (41–97.1)	67.9 (46.2–100)	**<.001**
Year 1	72.4 (47.8–109.9)	44.7 (29.4–67.9)	46.6 (31.1–69.5)	.18

Hung IF et al. *Clin Infect Dis* 2014;**59**:1246-55.

Table 4. Clinical Efficacy (Hospitalization and Nasopharyngeal Aspirate Positivity for Influenza A after 1 Year Post-Vaccination)

Clinical Efficacy	Imiquimod Ointment + Intradermal Vaccine N (%) (n = 30)	Aqueous Cream + Intramuscular Vaccine (n = 30)	Aqueous Cream + Intradermal Vaccine (n = 31)	*P* Value
Number of patients hospitalized for pneumonia or influenza	3 (10)	11 (36.7)	11 (35.5)	**.03**
NPA sample positive for influenza A	1 (3.3)	8 (26.7)	7 (22.6)	**.04**

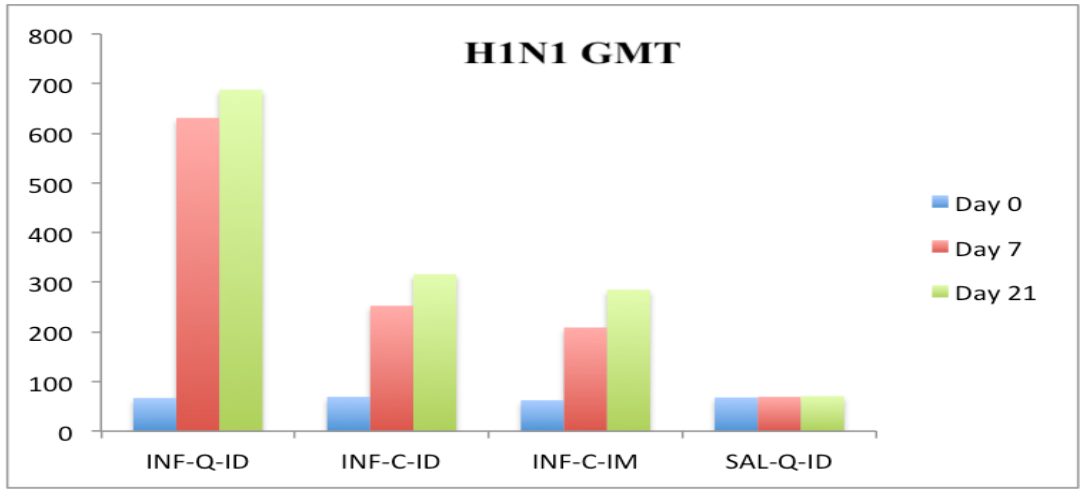
Hung IF et al. *Clin Infect Dis* 2014;**59**:1246-55.

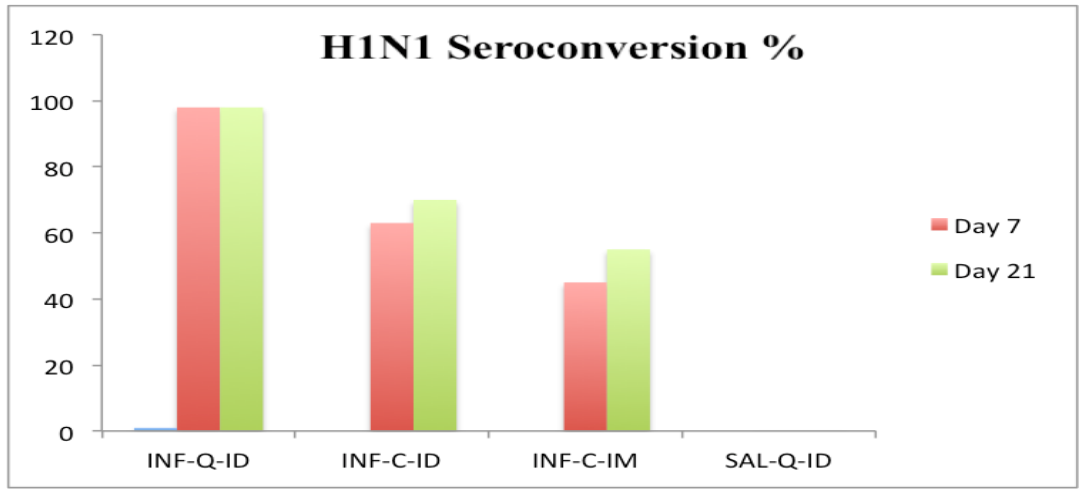
Topical imiquimod before intradermal trivalent influenza vaccine for protection against heterologous non-vaccine and antigenically drifted viruses: a single-centre, double-blind, randomised, controlled phase 2b/3 trial

Ivan Fan-Ngai Hung, Anna Jinxia Zhang, Kelvin Kai-Wang To, Jasper Fuk-Woo Chan, Patrick Li, Tin-Lun Wong, Ricky Zhang, Tuen-Ching Chan, Brian Chun-Yuan Chan, Harrison Ho Wai, Lok-Wun Chan, Hugo Pak-Yiu Fong, Raymond Kar-Ching Hui, Ka-Lun Kong, Arthur Chun-Fung Leung, Abe Ho-Ting Ngan, Louise Wing-Ki Tsang, Alex Pat-Chung Yeung, Geo Chi-Ngo Yiu, Wing Yung, Johnson Y-N Lau, Honglin Chen, Kwok-Hung Chan, Kwok-Yung Yuen

Hung IF et al. *Lancet Infect Dis* 2016;**16**:209-18

	INF-Q-ID (n=40)	INF-C-ID (n=40)	INF-C-IM (n=40)	SAL-Q-ID (n=40)	p value
A/California/H1N1					
GMT					
Day 0	66·8 (50·6–88·2)	69·2 (49·2–97·2)	62·3 (40·3–96·6)	68·0 (46·1–100·3)	0·979
Day 7	631·0 (441·4–902·0)	252·6 (181·0–352·6)	208·9 (141·9–307·6)	69·2 (47·4–101·0)	<0·0001
Day 21	687·9 (476·0–994·0)	316·2 (224·4–445·7)	285·1 (189–430·1)	70·8 (49·0–102·3)	<0·0001
CPMP criteria					
Day 0					
Seroprotection	35 (88%)	33 (83%)	28 (70%)	33 (83%)	0·379
Day 7					
Seroprotection	40 (100%)	38 (95%)	36 (90%)	34 (85%)	0·029
Seroconversion	39 (98%)	25 (63%)	18 (45%)	0	<0·0001
GMT fold increase	18 (9·9–26·2)	6·1 (3·7–8·4)	6·4 (3·6–9·1)	1·1 (1·0–1·1)	<0·0001
Day 21					
Seroprotection	40 (100%)	39 (98%)	37 (93%)	35 (88%)	0·074
Seroconversion	39 (98%)	28 (70%)	22 (55%)	0 (0%)	<0·0001
GMT fold increase	19·8 (11·4–28·3)	8·5 (4·6–12·4)	10·7 (4·0–17·4)	1·1 (1·0–1·2)	<0·0001





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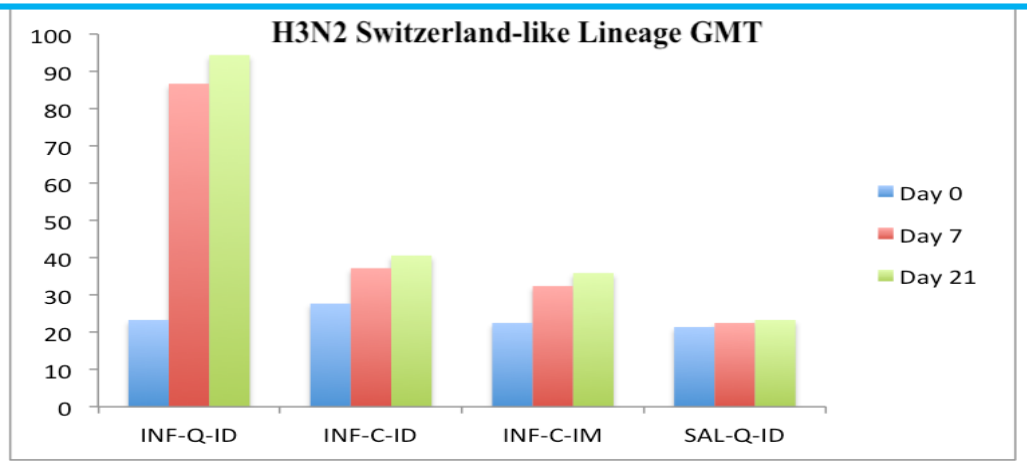
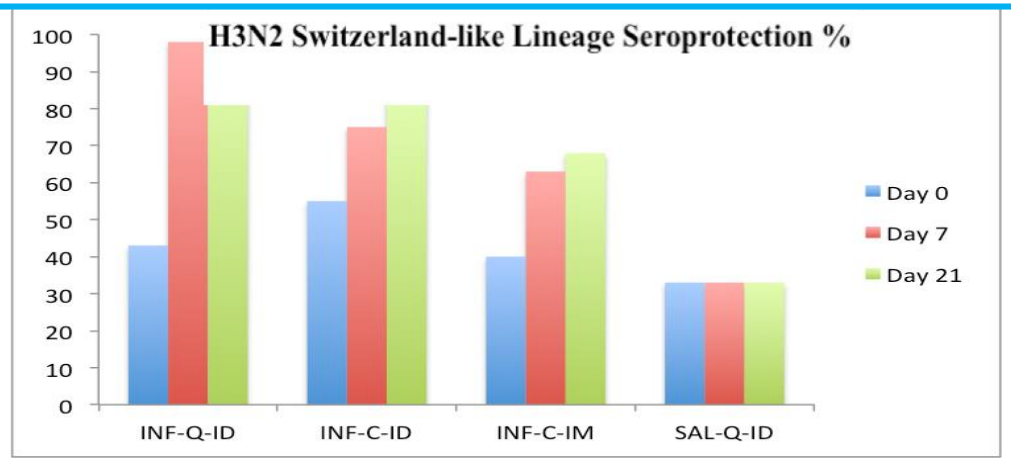
	INF-Q-ID (n=40)	INF-C-ID (n=40)	INF-C-IM (n=40)	SAL-Q-ID (n=40)	p value
A/HK/485197/14 (H3N2 Switzerland-like lineage)					
GMT					
Day 0	23·3 (18·2–29·9)	27·7 (23·3–33)	22·5 (17·7–28·6)	21·4 (18·2–25·2)	0·321
Day 7	86·7 (70·8–105·9)	37·2 (31·0–44·5)	32·4 (26·6–39·4)	22·5 (19·4–26·1)	<0·0001
Day 21	94·4 (76·0–117·2)	40·6 (34·0–48·3)	35·9 (29·6–43·5)	23·3 (20·3–26·7)	<0·0001
CPMP criteria					
Day 0					
Seroprotection	17 (43%)	22 (55%)	16 (40%)	13 (33%)	0·235
Day 7					
Seroprotection	39 (98%)	30 (75%)	25 (63%)	13 (33%)	<0·0001
Seroconversion	28 (70%)	3 (8%)	3 (8%)	0	<0·0001
GMT fold increase	4·8 (3·7–5·9)	1·5 (1·2–1·8)	1·7 (1·3–2·1)	1·1 (1–1·2)	<0·0001
Day 21					
Seroprotection	38 (95%)	33 (83%)	27 (68%)	13 (33%)	<0·0001
Seroconversion	28 (70%)	4 (10%)	4 (10%)	0	<0·0001
GMT fold increase value	5·2 (3·9–6·5)	1·7 (1·4–1·9)	1·8 (1·4–2·2)	1·2 (1·0–1·4)	<0·0001





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Prototype A/WSN/1933 (H1N1)					
GMT values					
Day 0	26·3 (20·7–33·4)	26·3 (19·8–35·0)	27·2 (20·3–36·6)	27·2 (21·1–35·1)	0·995
Day 7	86·6 (71·8–104·5)	38·5 (30·9–47·5)	34·1 (25·2–46·1)	27·2 (21·1–35·1)	<0·0001
Day 21	91·2 (77·1–107·8)	49 (39·1–61·3)	39·1 (28·9–52·9)	27·2 (21·1–35·1)	<0·0001
CPMP criteria					
Day 0					
Seroprotection	14 (35%)	17 (43%)	19 (48%)	18 (45%)	0·704
Day 7					
Seroprotection	40 (100%)	23 (58%)	22 (55%)	18 (45%)	<0·0001
Seroconversion	30 (75%)	4 (10%)	1 (3%)	0 (0%)	<0·0001
GMT fold increase value	5·8 (2·4–9·2)	1·7 (1·3–2·2)	1·3 (1·2–1·5)	1·0 (1·0–1·0)	<0·0001
Day 21	40 (100%)	29 (73%)	26 (65%)	18 (45%)	<0·0001
Seroprotection					
Seroconversion	29 (73%)	6 (15%)	2 (5%)	0 (0%)	<0·0001
GMT fold increase value	5·8 (2·4–9·2)	2·1 (1·3–2·9)	1·5 (1·3–1·7)	1·0 (1·0–1·0)	<0·0001
A/HK/408027/09 (prepandemic seasonal H1N1)					
GMT values					
Day 0	33·5 (25·3–44·4)	34·1 (25·4–45·7)	42·7 (31·4–58·0)	35·9 (25·8–49·9)	0·655
Day 7	83·7 (65·7–106·6)	56·2 (41·5–76·2)	56·2 (41·6–75·9)	39·8 (28·9–54·8)	0·005
Day 21	85·1 (67·4–107·2)	61·3 (45·1–83·3)	68 (50·3–92·0)	40·5 (29·5–55·7)	0·004
CPMP criteria					
Day 0					
Seroprotection	27 (68%)	26 (65%)	29 (73%)	23 (58%)	0·563
Day 7					
Seroprotection	39 (98%)	32 (80%)	33 (83%)	23 (58%)	<0·0001
Seroconversion	25 (63%)	6 (15%)	2 (5%)	1 (3%)	<0·0001
GMT fold increase value	3·6 (2·0–5·1)	1·9 (1·5–2·4)	1·4 (1·2–1·7)	1·1 (1·0–1·1)	<0·0001
Day 21					
Seroprotection	40 (100%)	32 (80%)	35 (88%)	24 (60%)	<0·0001
Seroconversion	26 (65%)	7 (18%)	6 (15%)	1 (3%)	<0·0001
GMT fold increase value	3·7 (2·1–5·2)	2·1 (1·6–2·5)	1·8 (1·5–2·1)	1·3 (0·9–1·6)	<0·0001

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	INF-Q-ID (n=40)	INF-C-ID (n=40)	INF-C-IM (n=40)	SAL-Q-ID (n=40)
Redness				
Grade 1	5 (13%)	3 (8%)	1 (3%)	1 (3%)
Grade 2	0	0	0	0
Swelling				
Grade 1	7 (18%)	5 (13%)	3 (8%)	2 (5%)
Grade 2	3 (8%)	3 (8%)	0 (0%)	1 (3%)
Pain				
Grade 1	4 (10%)	1 (3%)	2 (5%)	0
Grade 2	0	0	0	0
Fever	1 (3%)	1 (3%)	0	2 (5%)
Headache	0	0	0	1 (3%)
Malaise	2 (5%)	1 (3%)	1 (3%)	1 (3%)
Runny nose	2 (5%)	1 (3%)	1 (3%)	1 (3%)
Cough	2 (5%)	0	0	0
Sore throat	1 (3%)	0	1 (3%)	2 (5%)
Nausea	0	0	1 (3%)	0
Severe adverse events	0	0	0	0

Data are n (%). Fever was defined as body temperature ≥37·5°C. Redness and swelling were graded based on size: grade 1, <20 mm; grade 2, 20–50 mm; grade 3, >50 mm (none of the participants developed more than a grade 2 skin reaction). Pain was also graded: grade 1, pain on touch; and grade 2, pain when arm was moved. Severe adverse events were defined as any undesired event related to the vaccination resulting in death, life-threatening or disabling conditions, or which resulted in prolonged hospital admission INF-Q-ID=imiquimod cream + intradermal vaccine. INF-C-ID=aqueous cream + intradermal vaccine. INF-C-IM=aqueous cream + intramuscular vaccine. SAL-Q-ID=imiquimod cream + intradermal normal saline vaccine.

Table 4: **Adverse events**

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Priority groups for influenza vaccination (HK, 2020-2021)
香港優先接種流感疫苗的群組

- Pregnant women　懷孕婦女
- Residents of residential care homes 長期院舍住客
- Persons aged 50 and above 50歲以上人士
- Children aged 6 months – 11 years 6個月至11歲大的兒童
- Patients with chronic medical illnesses, including obesity 慢性病人（包括過度肥胖）
- Healthcare workers　醫護人員
- Poultry workers and pig farmers 家禽家畜從業員

https://www.chp.gov.hk/files/pdf/recommendations_on_siv_for_2020-21.pdf

Conclusion
總結

1. Pneumonia is a significant cause of morbidity and mortality 肺炎可以導致嚴重疾病甚至死亡

2. *Streptococcus pneumoniae* and influenza viruses, the leading bacterial and viral causes of pneumonia respectively, are preventable by vaccinations 肺炎鏈球菌與流感病毒分別是細菌與病毒中最常見的肺炎成因，而且兩種疾病都可以用疫苗有效預防

3. Prevention is better than treatment, which is not always effective especially when significant inflammation sets in 肺炎引起的發炎反應可以很強烈，而且併發症極多，所以預防勝於治療