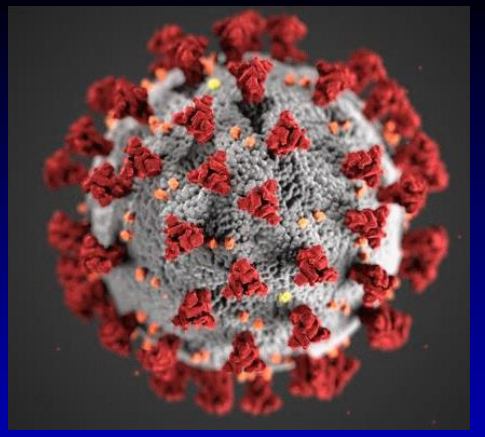
COVID-19疫苗研發現況及影響

李秉穎

台大兒童醫院

G.Q.

冠狀病毒
Coronavirus

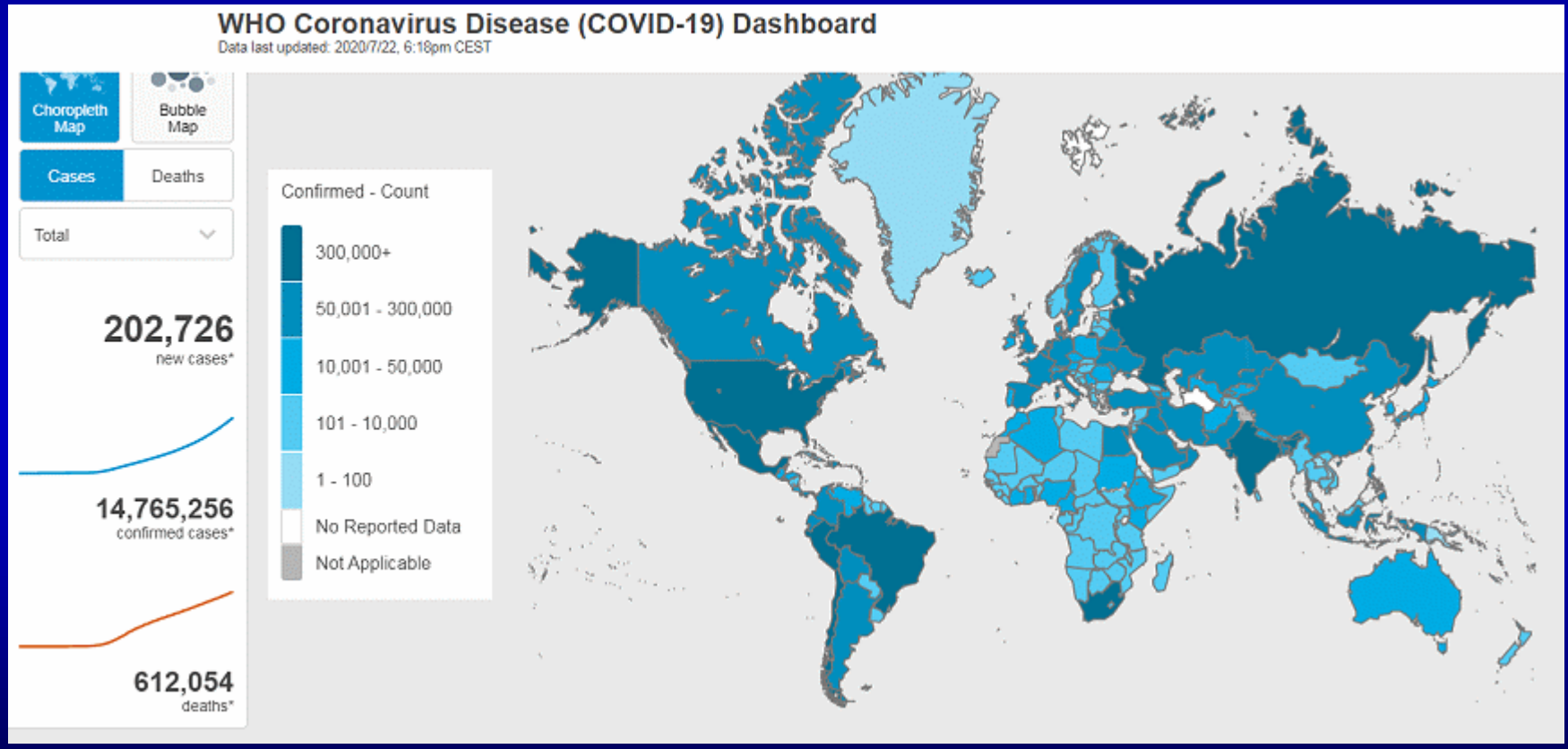


Public Health Image Library, CDC, USA

- 7種感染人類的冠狀病毒：
  - 一般感冒：HCoV-229E、HCoV-NL63、HCoV-HKU1、HCoV-OC43
  - 肺炎，高死亡率： SARS-CoV、MERS-CoV、SARS-CoV-2 (新型冠狀病毒)
    - SARS：蝙蝠 □ 果子狸 □ 人類`
    - MERS：蝙蝠 □ 駱駝 □ 人類
    - **新型冠狀病毒：蝙蝠 □ ???? □ 人類**

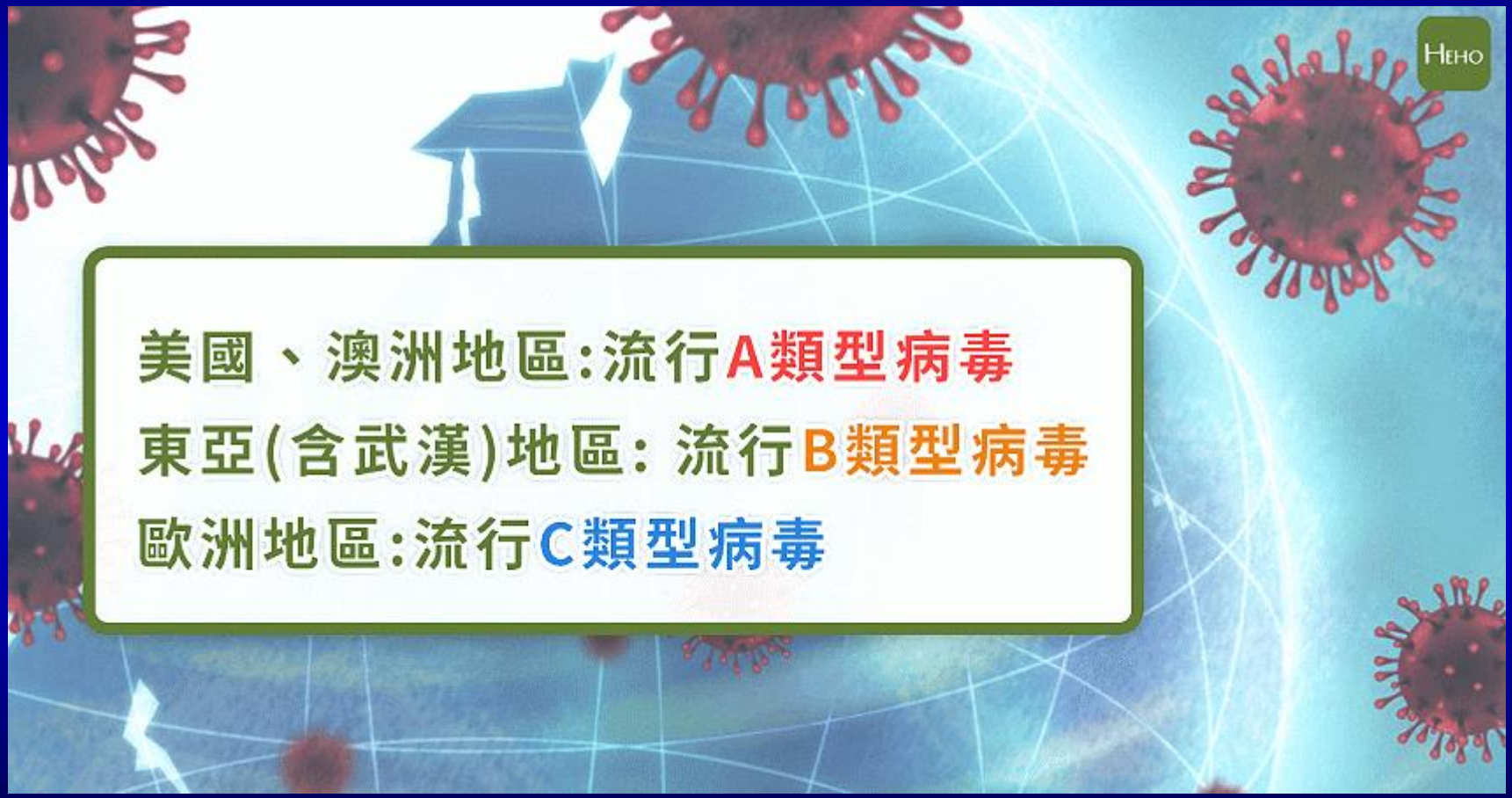
G.Q.

新型冠狀病毒全世界擴散
2020.7.22



G.Q. WHO website.

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



G.Q.

新冠病毒大幅變異！看懂爆發1個月後，症狀、重症、致死率差別多少 Heho健康網，2020.4.8

- 病毒不同，代表病毒在傳播的過程中已經開始突變。
- 最初的症狀80%都是發燒！但現在無症狀感染者越來越多
- 現在疫情在歐美重新爆發之後，**症狀越來越多改變**，甚至還出現了腹瀉，或是嗅覺、味覺失調的症狀。
- **重症、致死率也在提升**！而最一開始，根據中國武漢市的一家醫院、中國溫州的兩家醫院做出的患者分析，發現重症率大約徘徊在15%左右，而死亡率則是4%左右。

G.Q.

腸病毒71型的基因型演變
台灣，1998-2005

- Genogroups: VP1, VP4, 5'UTR
  - A: 1, B: 4, C: 4

TABLE III. Chronological Change of EV71 Subgenogroups in West Pacific Region (Modified From Cardosa et al. [2003] With Permission)

	1980	1986	1997	1998	1999	2000	2001	2002	2003	2004	2005
Singapore	—	—	B3, B4	B3,C1	B3	**B4**	B4	C1,B4	—	—	—
Sarawak	—	—	**B3**	C1	No EV71	**B4**, C1	No EV71	C1	C1, **B5**	No EV71	—
Thailand	—	—	—	—	—	—	—	C1	—	—	—
Taiwan	**B1**	**B1**	—	**C2**[a],B4	B4	**B4**	B4	B4	B4	C4	C4
Japan	—	—	B3, B4, C2	—	—	—	—	B4,C2	C4	C4	—
China	—	—	C3	C4	—	C4	C4	C4	C4	C4	—
Korea	—	—	—	—		**C3**	No EV71	No EV71	—	—	—
Perth	—	—	—	—	**B3, C2**[a]	C1	No EV71	No EV71	—	—	—

—, No data available. No EV71, no EV71 identified despite active surveillance.
Boldface typing indicates major subgenogroups causing large outbreaks.
[a]Severe neurological diseases were found in the outbreaks.

Lin KH. J Med Virol 2006;78(2):254.

G.Q.

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[a]	Genogroup C[b]
Anti-genogroup B[c]		
B1	>1024	1024
B2	>1024	1024
B3	>1024	>1024
B4	>1024	512
B5	>1024	1024
B6	>1024	512
B7	>1024	>1024
Anti-genogroup C[d]		
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

Kung SH. Clin Microbiol Infect 2007; 13: 782–787

G.Q.

We shouldn’t worry when a virus mutates during disease outbreaks

Nathan D. Grubaugh, Yale University, 2020

- Our media streams and scientific communications flooded with trepidation and misrepresentation of mutations surrounding the outbreak of SARS-CoV-2.
- Mutation is a humdrum aspect of life for an RNA virus
- While this amazing capacity to mutate fuels the engine of evolutionary change, most mutations adversely impact some aspect of virus function and are removed by natural selection.
- **Mutations are not indicative of outlandish and devastating new viral characteristics.**

G.Q.

Grubaugh ND. Nat Microbiol 2020;18 : 1–2.

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.

G.Q. https://www.medicaldaily.com/coronavirus-immunity-has-no-evidence-second-infection-still-possible-says-who-452253

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."

G.Q. https://www.cnbc.com/2020/06/02/dr-anthony-fauci-says-theres-a-chance-coronavirus-vaccine-may-not-provide-immunity-for-very-long.html

陸研究：新冠抗體僅2到3個月有效 難防二次感染　2020.6.22，聯合新聞網

- 大陸研究指出，感染新冠病毒後患者體內的抗體水平，**兩到三個月後便開始下降**。這為新冠患者免疫二次感染的設想和尚在研發中的新冠疫苗應用前景蒙上陰影，但仍需進一步的研究才能有定論。
- 財新網報導，上述研究名為「新冠肺炎無症狀感染者的臨床及免疫學評估」（Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections），近日發布於「自然·醫學」期刊上，作者來自重慶醫科大學、重慶市疾控中心、重慶醫科大學第一附屬醫院、萬州市人民醫院、萬州市疾控中心和重慶醫科大學第二附屬醫院。

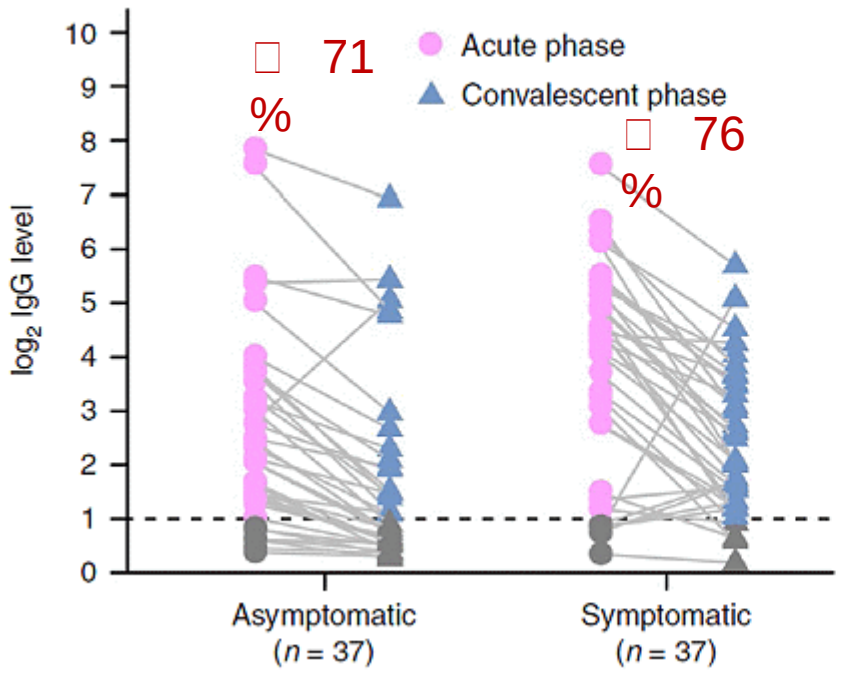
G.Q.

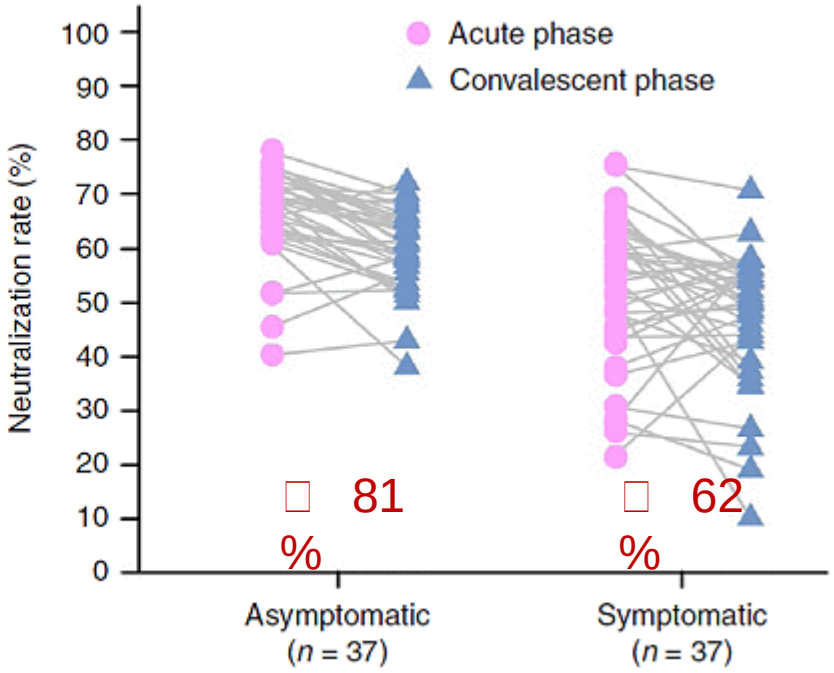
Antibody levels start to decrease within 2–3 months after infection

N=74, 2020, China

IgG (Magnetic chemiluminescence enzyme immunoassay)

Neutralizing antibody





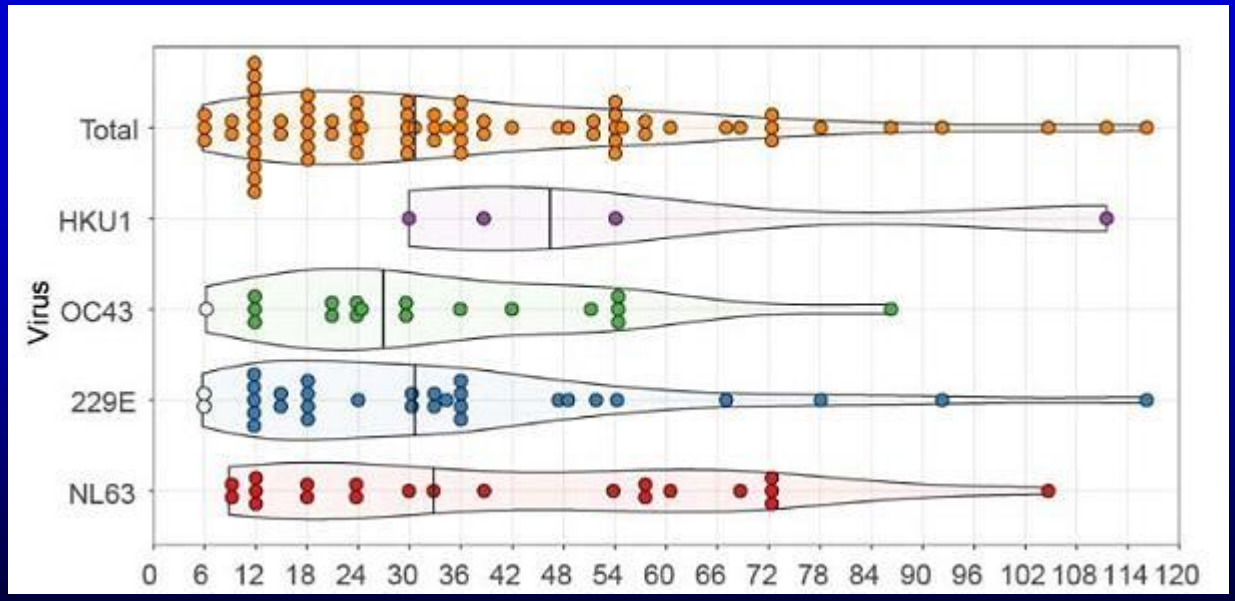
Convalescence: 8 weeks after discharge

G.Q. Long Q. Nat Med 2020; doi.org/10.1038/s41591-020-0965-6.

Short duration of protection and frequent reinfection of coronaviruses

N=10, 1985-2020, The Netherlands

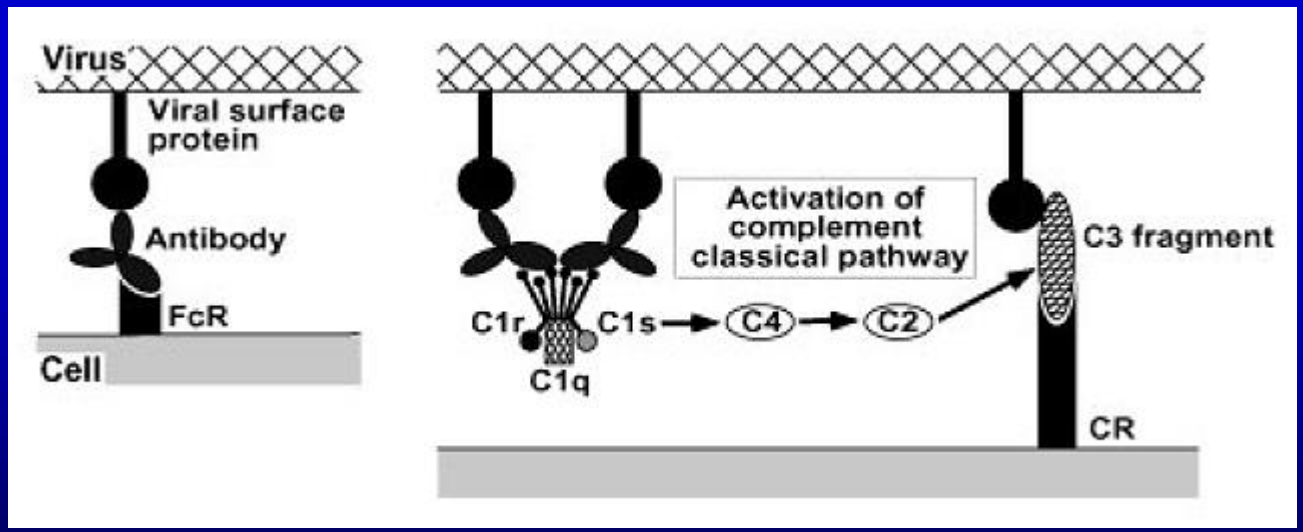
- Infection: **1.4-fold increase** in antibody levels
- HCoV-NL63: 15.3/100 person-years
- HCoV-229E: 20.1/100 person-years
- HCoV-OC43: 16.4/100 person-years
- HCoV-HKU1: 6.3/100 person-years



G.Q. Edridge AWD. medRxiv 2020; doi: https://doi.org/10.1101/2020.05.11.20086439.

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

G.Q.

Takada A. Rev Med Virol 2003; 13: 387–398.

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

G.Q.

Acosta PL. Clin Vaccine Immunol 2016; 23(3): 189–195.

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)

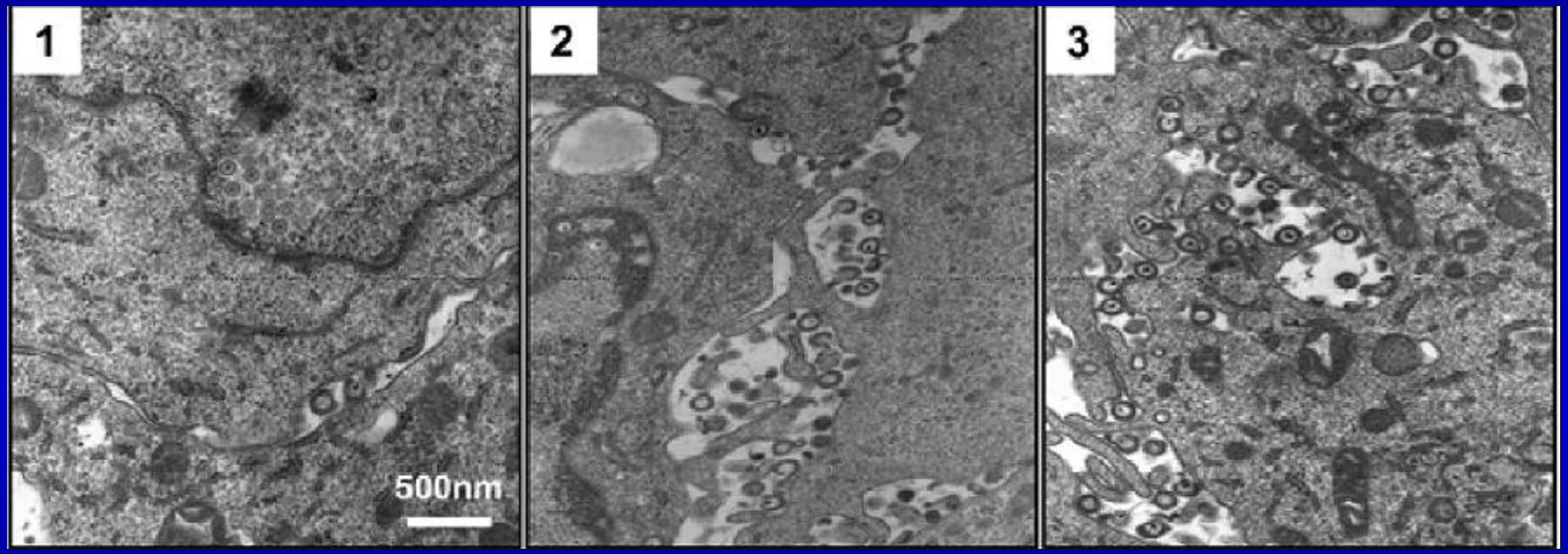
G.Q.

Hadinegoro SR. N Engl J Med 2015;373(13):1195-206.

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



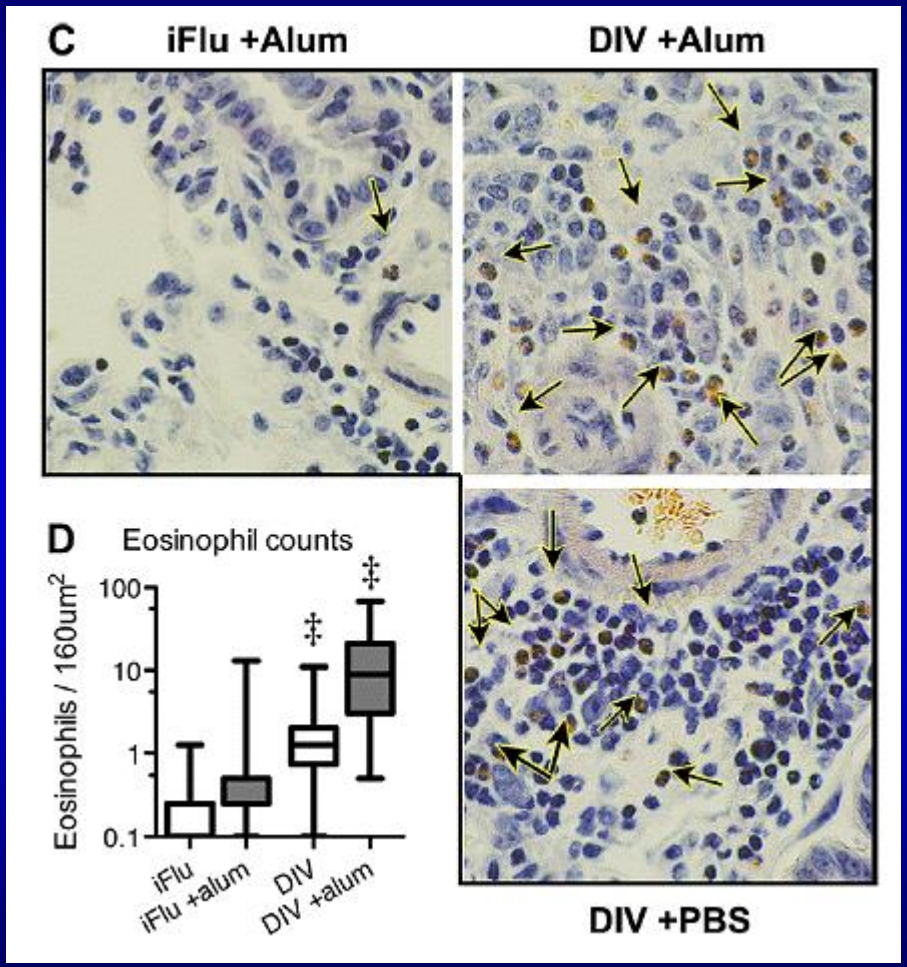
SARS-CoV viral particles were observed in HL-CZ cells treated with more diluted anti-sera against SARS-CoV (2000-fold dilution) (Fig. 2C-3) compared to those treated with less diluted anti-sera (10-fold) (Fig. 2C-1) and less diluted normal control sera (10-fold) (Fig. 2C-2).

G.Q.

Wang SF. Biochem Biophys Res Commun 2014; 451(2): 208–214.

Inactivated SARS vaccine: aged mice with life-threatening Th2 immunopathology 2011, USA

- Old mice:
  - Th2 immunopathology
  - **Poor protection**
- Young mice
  - Th2 immunopathology
  - **Good protection**



iFlu: nonspecific immunogen; DIV: double-inactivated SARS-CoV vaccine; Arrows: eosinophils

G.Q.

Bolles M. J. Virol 2011;85:12201.

COVID-19 vaccine design: the Janus face of immune enhancement


Janus, the two-headed Roman god of doors and beginnings.Credit: Science History Images/Alamy

- **Antibody- dependent enhancement**
  - 2008–2009 trivalent inactivated seasonal influenza vaccine: enhance disease during H1N1 pandemic flu?
  - **Dengue fever**
  - **Respiratory syncytial virus vaccine**, 1960's
- **Cellular immunopathology**
  - Experimental SARS-CoV vaccines in animals
    - Lung or liver: eosinophil infiltrations
    - **TH2- or TH17** type immune responses: directed to virus- induced expression of the SARS nucleocapsid (N) protein

G.Q.

Hotez PJ. Nat Rev Immunol 2020 : doi: 10.1038/s41577-020-0323-4.

Antibody-dependent enhancement
Other viruses

- ADE for entry into monocytes and macrophages in vitro:
  - Sindbis and Ross River viruses (*Togaviridae*), porcine reproductive and respiratory syndrome virus (*Arteriviridae*), foot-and-mouth disease virus and Coxsackievirus (*Picornaviridae*), feline infectious peritonitis virus (*Coronaviridae*), respiratory syncytial virus (*Paramyxoviridae*), rabies virus (*Rhabdoviridae*), Pichinde virus and Lassa fever virus (*Arenaviridae*), influenza A virus (*Orthomyxoviridae*), hantavirus (*Bunyaviridae*), equine infectious anaemia virus (*Retroviridae*), reovirus (*Reoviridae*), Aleutian mink disease parvovirus (*Parvoviridae*), polyomavirus (*Papovaviridae*), rabbitpox virus (*Poxviridae*), murine cytomegalovirus, Epstein-Barr virus and herpes simplex virus (*Herpesviridae*)

G.Q.

Takada A. Rev Med Virol 2003; 13: 387–398.

Antibody-dependent enhancement
Clinical significance

- **Controversial**
- **Antibodies: a mixture of neutralising, enhancing, and non-neutralising, non-enhancing antibodies**. Virus infectivity may be
  - Neutralised without complement
  - Neutralised in the presence of complement
  - Enhanced through FcR-dependent manner
  - (for FcR-bearing cells)
  - Enhanced through FcR-independent, complement-dependent
  - Enhanced by direct activation of viral proteins
  - Enhanced by suppression of antiviral pathways at the transcriptional level

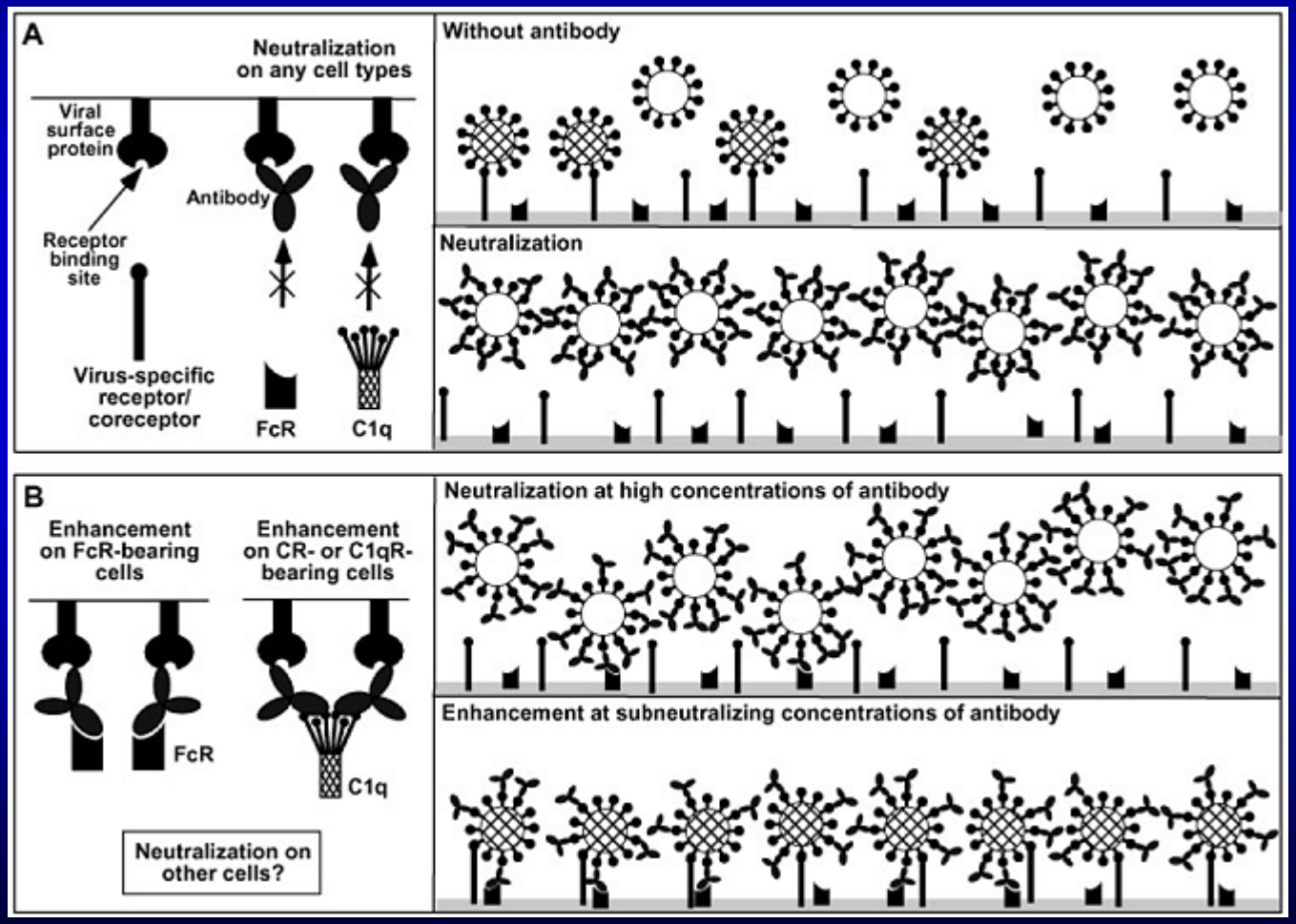
G.Q.

Takada A. Rev Med Virol 2003; 13: 387–398.

Antibody-dependent enhancement

Neutralizing or enhancing?

- **Enhancing antibody:** recognize non-neutralizing epitopes, suboptimal concentration, low affinity



G.Q.

Takada A. Rev Med Virol 2003; 13: 387–398.

Antibody-dependent enhancement
Vaccine development

- Antibody responses induced by subunit vaccines tend to be associated with severe disease by several retroviruses.
- **Induce strong cytotoxic T-lymphocyte responses** that avoid harmful antibody responses (Th1)
  - Plasmid DNA
  - Viral vector-based vaccines
  - Live attenuated vaccines
- **Abolish enhancing epitopes while maintaining neutralising epitopes**.

G.Q.

Takada A. Rev Med Virol 2003; 13: 387–398.

Assessment of risk of disease enhancement with COVID-19 vaccines

Consensus report for CEPI/BC March 12–13, 2020 meeting

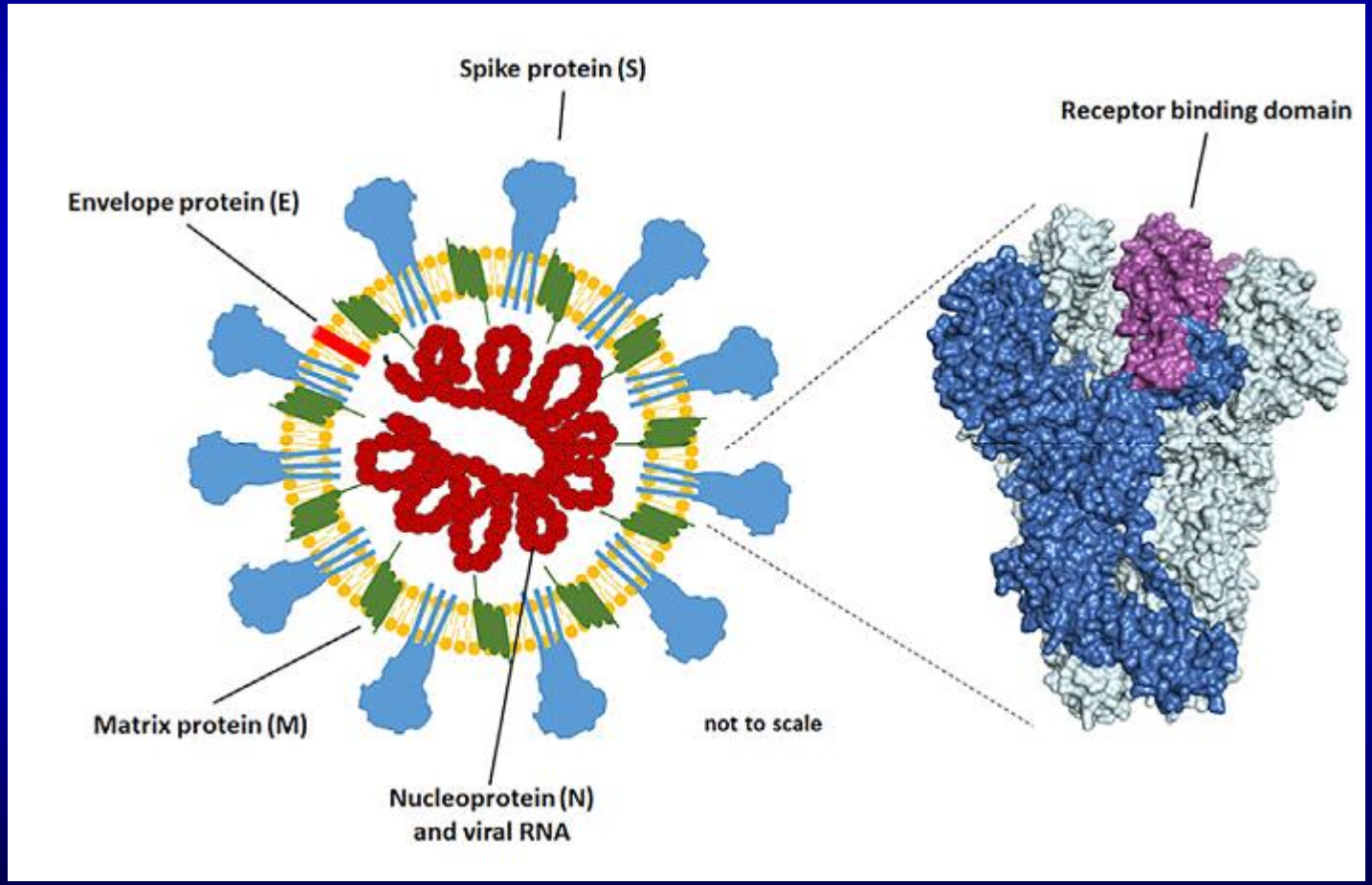
- **Animal data** to support clinical development could address:
  - **Neutralizing antibody responses, Th1 response.**
  - Post-vaccination challenge data from non-human primates: immunopathology
  - Animal studies should be considered before entering human Phase 1
- **Clinical trials**
  - Level of neutralizing antibodies. Relative ratio of binding to neutralizing antibodies
  - CD8 T cells and/or CD4 Th1 biased response
  - Demonstration of some disease enhancement with any candidate vaccine after viral challenge in animal models **should not necessarily represent a no-go signal**

G.Q.

Lambert PH. Vaccine. 2020; doi: 10.1016/j.vaccine.2020.05.064.

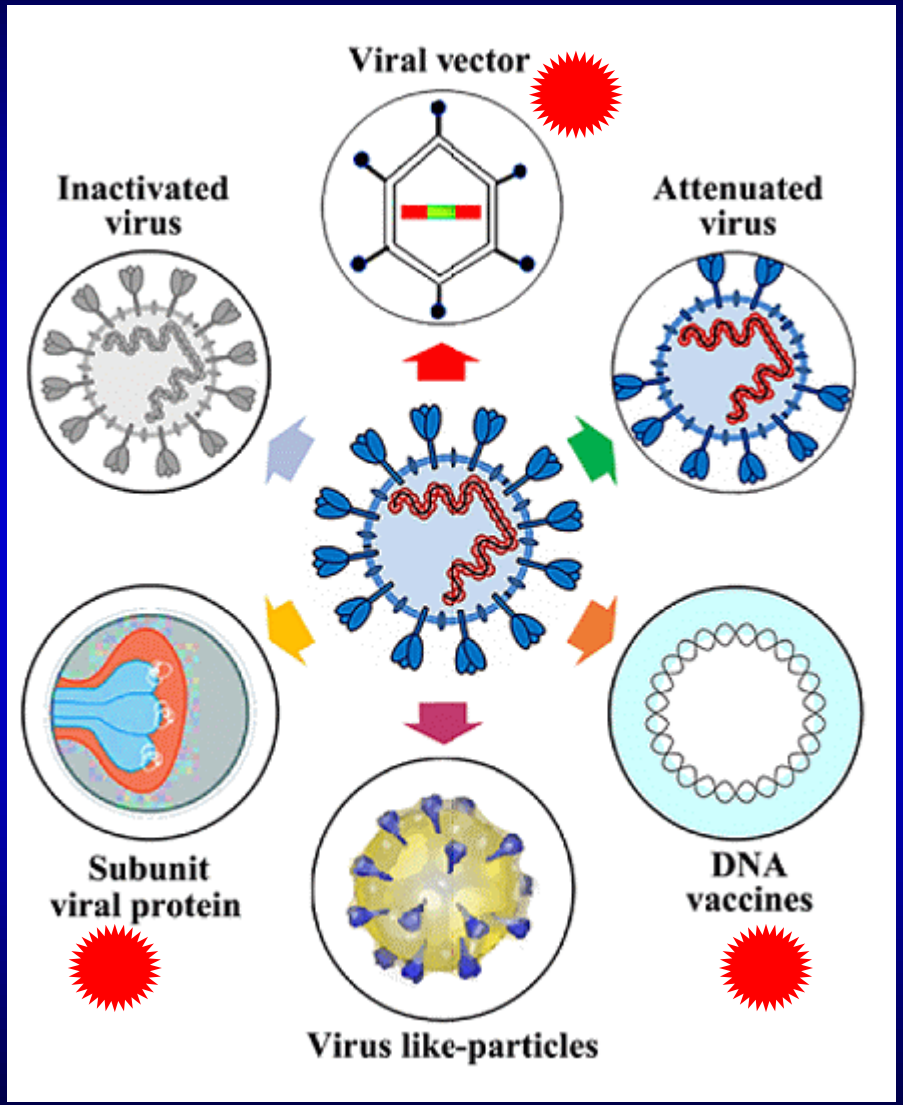
疫苗的研發

- Target antigen: S protein



Amanat F. Immunity 2020;52(4):583.

Strategy types for COVID- 19 vaccine development



G.Q.

Calina D. Int J Mol Med 2020; 46(1): 3.

新型冠狀病毒候選疫苗

23種已經開始臨床試驗，WHO，2020.6.15

Platform	Type of candidate vaccine	Developer	Coronavirus target	Current stage of clinical evaluation/regulatory status-Coronavirus candidate
Inactivated	Inactivated + alum	Sinovac	SARS-CoV2	Phase 3 NCT04456595 Phase 1/2 NCT04383574 NCT04352608
Non-Replicating Viral Vector	ChAdOx1-S	University of Oxford/AstraZeneca	SARS-CoV2	Phase 3 ISRCTN89951424 Phase2b/3 2020-001228-32 Phase 1/2 PACTR202006922165132 2020-001072-15
Non-Replicating Viral Vector	Adenovirus Type 5 Vector	CanSino Biological Inc./Beijing Institute of Biotechnology	SARS-CoV2	Phase 2 ChiCTR2000031781 Phase 1 ChiCTR2000030906
Protein Subunit	Adjuvanted recombinant protein (RBD-Dimer)	Anhui Zhifei Longcom Biopharmaceutical/ Institute of Microbiology, Chinese Academy of Sciences	SARS-CoV2	Phase 2 NCT04466085 Phase 1 NCT04445194
RNA	LNP-encapsulated mRNA	Moderna/NIAID	SARS-CoV2	Phase 3 (not yet recruiting) NCT04470427 Phase 2 NCT04405076 Phase 1 NCT04283461
DNA	DNA plasmid vaccine with electroporation	Inovio Pharmaceuticals/ International Vaccine Institute	SARS-CoV2	Phase 1/2 NCT04447781 NCT04336410
DNA	DNA plasmid vaccine + Adjuvant	Osaka University/ AnGes/ Takara Bio	SARS-CoV2	Phase 1/2 NCT04463472
DNA	DNA plasmid vaccine	Cadila Healthcare Limited	SARS-CoV2	Phase 1/2 CTRI/2020/07/026352 (not yet recruiting)
Inactivated	Inactivated	Wuhan Institute of Biological Products/Sinopharm	SARS-CoV2	Phase 1/2 ChiCTR2000031809
Inactivated	Inactivated	Beijing Institute of Biological Products/Sinopharm	SARS-CoV2	Phase 1/2 ChiCTR2000032459
Inactivated	Whole-Virion Inactivated	Bharat Biotech	SARS-CoV2	Phase 1/2 CTRI/2020/07/026300
Protein Subunit	Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine	Novavax	SARS-CoV2	Phase 1/2 NCT04368988
	adjuvanted with Matrix M			
RNA	3 LNP-mRNAs	BioNTech/Fosun Pharma/Pfizer	SARS-CoV2	Phase 1/2 2020-001038-36 NCT04368728
DNA	DNA Vaccine (GX-19)	Genexine Consortium	SARS-CoV2	Phase 1 NCT04445389
Inactivated	Inactivated	Institute of Medical Biology , Chinese Academy of Medical Sciences	SARS-CoV2	Phase 1 NCT04412538
Non-Replicating Viral Vector	Adeno-based	Gamaleya Research Institute	SARS-CoV2	Phase 1 NCT04436471 NCT04437875
Protein Subunit	Native like Trimeric subunit Spike Protein vaccine	Clover Biopharmaceuticals Inc./GSK/Dynavax	SARS-CoV2	Phase 1 NCT04405908
Protein Subunit	Recombinant spike protein with Advax™ adjuvant	Vaxine Pty Ltd/Medytox	SARS-CoV2	Phase 1 NCT04453852
Protein Subunit	Molecular clamp stabilized Spike protein with MF59 adjuvant	University of Queensland/CSL/Seqirus	SARS-CoV2	Phase 1 ACTRN12620000674932p
RNA	LNP-nCoVsaRNA	Imperial College London	SARS-CoV2	Phase 1 ISRCTN17072692
RNA	mRNA	Curevac	SARS-CoV2	Phase 1 NCT04449276
RNA	mRNA	People's Liberation Army (PLA) Academy of Military Sciences/Walvax Biotech.	SARS-CoV2	Phase 1 ChiCTR2000034112
VLP	Plant-derived VLP adjuvanted with GSK or Dynavax adjs.	Medicago Inc.	SARS-CoV2	Phase 1 NCT04450004

G.Q. WHO website.

新型冠狀病毒候選疫苗

140種未開始臨床試驗，WHO，2020.6.15

					BreastCA vaccine
Protein Subunit	S protein	AJ Vaccines	SARS-CoV2	Pre-Clinical	
Protein Subunit	II-Key peptide	Generex/EpiVax	SARS-CoV2	Pre-Clinical	Influenza, HIV, SARS-CoV
Protein Subunit	S protein	EpiVax/Univ. of Georgia	SARS-CoV2	Pre-Clinical	H7N9
Protein Subunit	Protein Subunit EPV-CoV-19	EpiVax	SARS-CoV2	Pre-Clinical	
Protein Subunit	S protein (baculovirus production)	Sanofi Pasteur/GSK	SARS-CoV2	Pre-Clinical	Influenza, SARS-CoV
Protein Subunit	gp-96 backbone	Heat Biologics/Univ. Of Miami	SARS-CoV2	Pre-Clinical	NSCLC, HIV, malaria, Zika
Protein Subunit	Peptide vaccine	FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo	SARS-CoV2	Pre-Clinical	Ebola
Protein Subunit	Subunit vaccine	FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo	SARS-CoV2	Pre-Clinical	
Protein Subunit	S1 or RBD protein	Baylor College of Medicine	SARS-CoV2	Pre-Clinical	SARS
Protein Subunit	Subunit protein, plant produced	iBio/CC-Pharming	SARS-CoV2	Pre-Clinical	
Protein Subunit	Recombinant protein, nanoparticles (based on S-protein and other epitopes)	Saint-Petersburg scientific research institute of vaccines and serums	SARS-CoV2	Pre-Clinical	
Protein Subunit	COVID-19 XWG-03 truncated S (spike) proteins	Innovax/Xiamen Univ./GSK	SARS-CoV2	Pre-Clinical	HPV
Protein Subunit	Adjuvanted microsphere peptide	VIDO-InterVac, University of Saskatchewan	SARS-CoV2	Pre-Clinical	
Protein Subunit	Synthetic Long Peptide Vaccine candidate for S and M	OncoGen	SARS-CoV2	Pre-Clinical	
Protein Subunit	(RBD-Fc + Adjuvant)	Research Center			
Protein Subunit	OMV-based vaccine	Quadram Institute Biosciences	SARS-CoV2	Pre-Clinical	Flu A, plague
Protein Subunit	OMV-based vaccine	BIOMVIS Srl/Univ. of Trento	SARS-CoV2	Pre-Clinical	
Protein subunit	structurally modified spherical particles of the tobacco mosaic virus (TMV)	Lomonosov Moscow State University	SARS-CoV2	Pre-Clinical	rubella, rotavirus
Protein Subunit	Spike-based	University of Alberta	SARS-CoV2	Pre-Clinical	Hepatitis C
Protein Subunit	Recombinant S1-Fc fusion protein	AnyGo Technology	SARS-CoV2	Pre-Clinical	
Protein Subunit	Recombinant protein	Yisheng Biopharma	SARS-CoV2	Pre-Clinical	
Protein Subunit	Recombinant S protein in IC-BEVS	Vabiotech	SARS-CoV2	Pre-Clinical	
Protein	Orally delivered, heat	Applied Biotechnology Institute,	SARS-CoV2	Pre-Clinical	
Protein Subunit	S-2P protein + CpG 1018	Medigen Vaccine Biologics Corporation/NIAID/Dynavax	SARS-CoV2	Pre-Clinical	

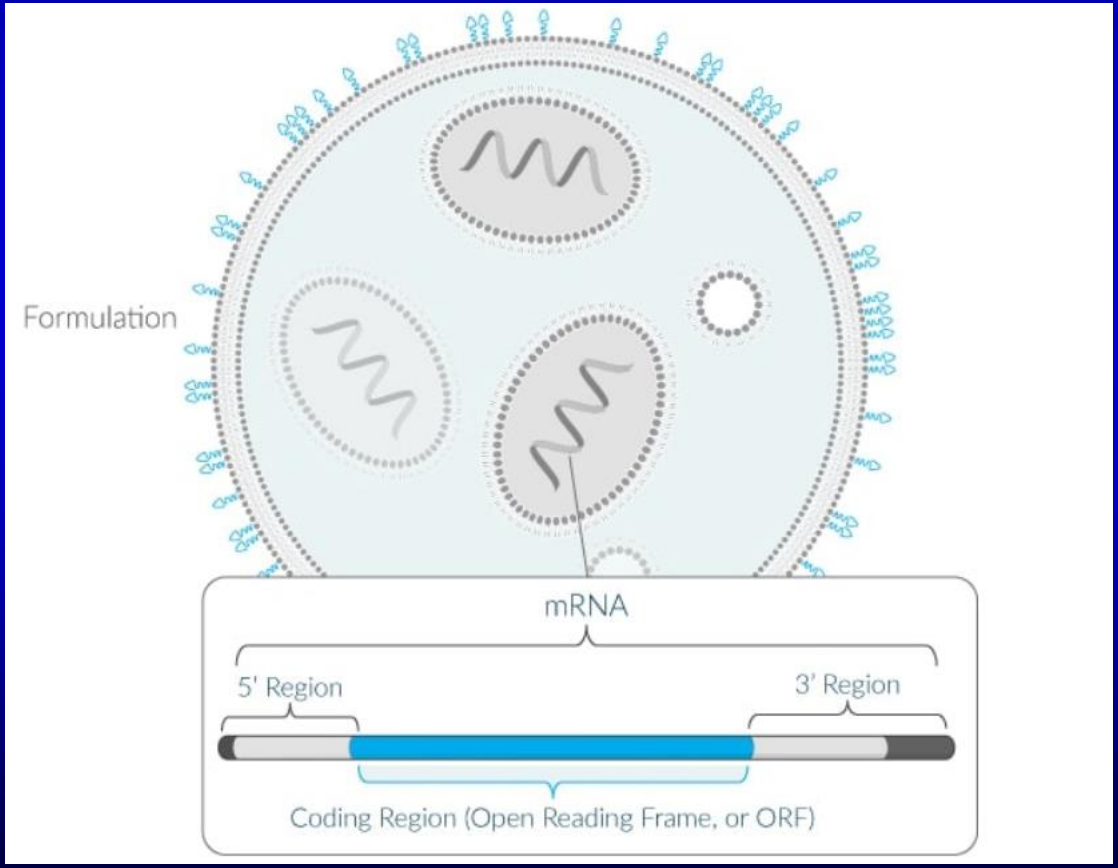
Protein Subunit | S-2P protein + CpG 1018 | Medigen Vaccine Biologics Corporation/NIAID/Dynavax

G.Q.

WHO website.

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

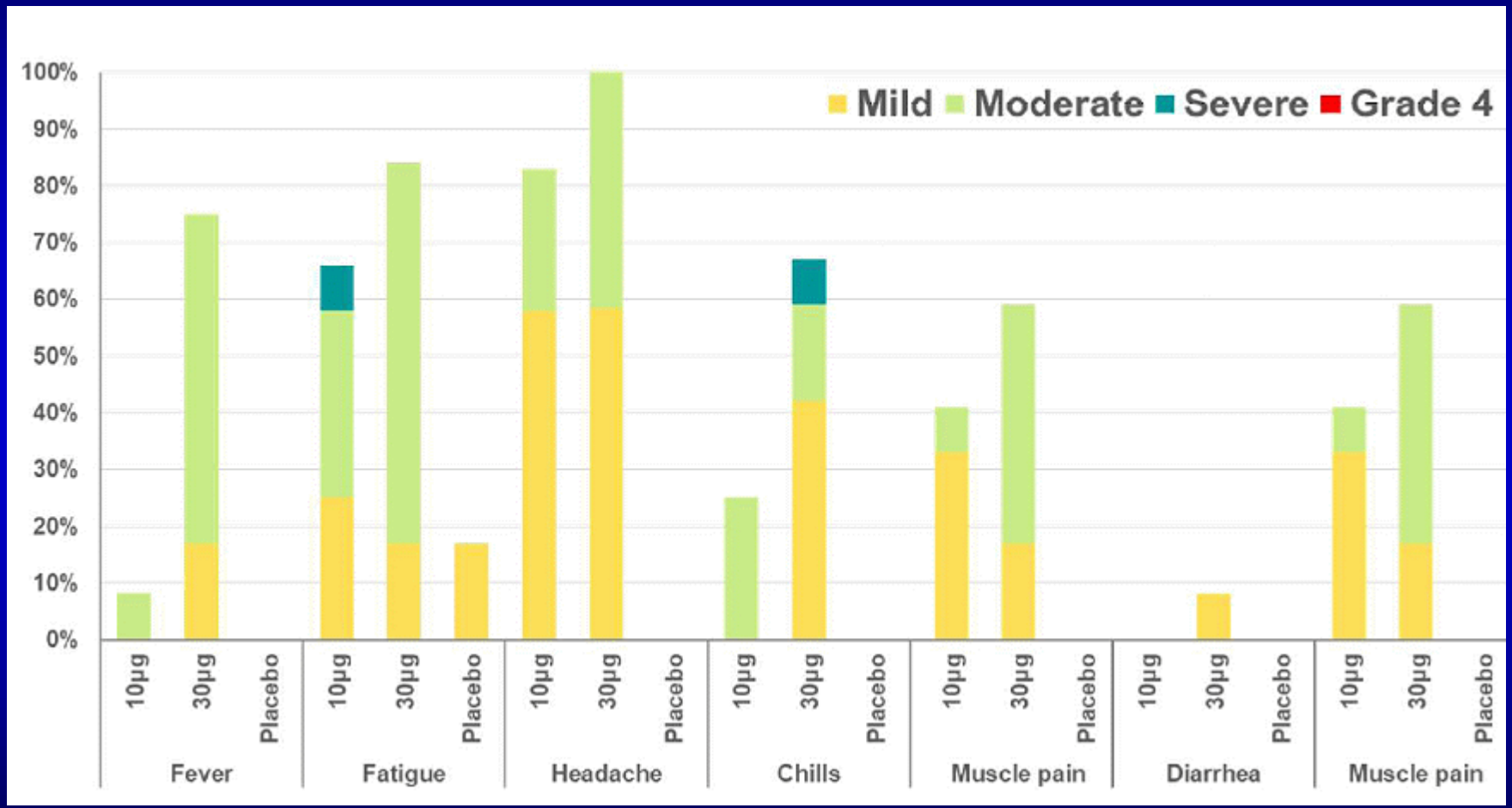
- 設計簡單，快速生產
- 致免性較差，沒有上市疫苗



G.Q. https://www.modernatx.com/mrna-technology/mrna-platform-enabling-drug-discovery-development

COVID-19 RNA vaccine candidate (BNT162b1)

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



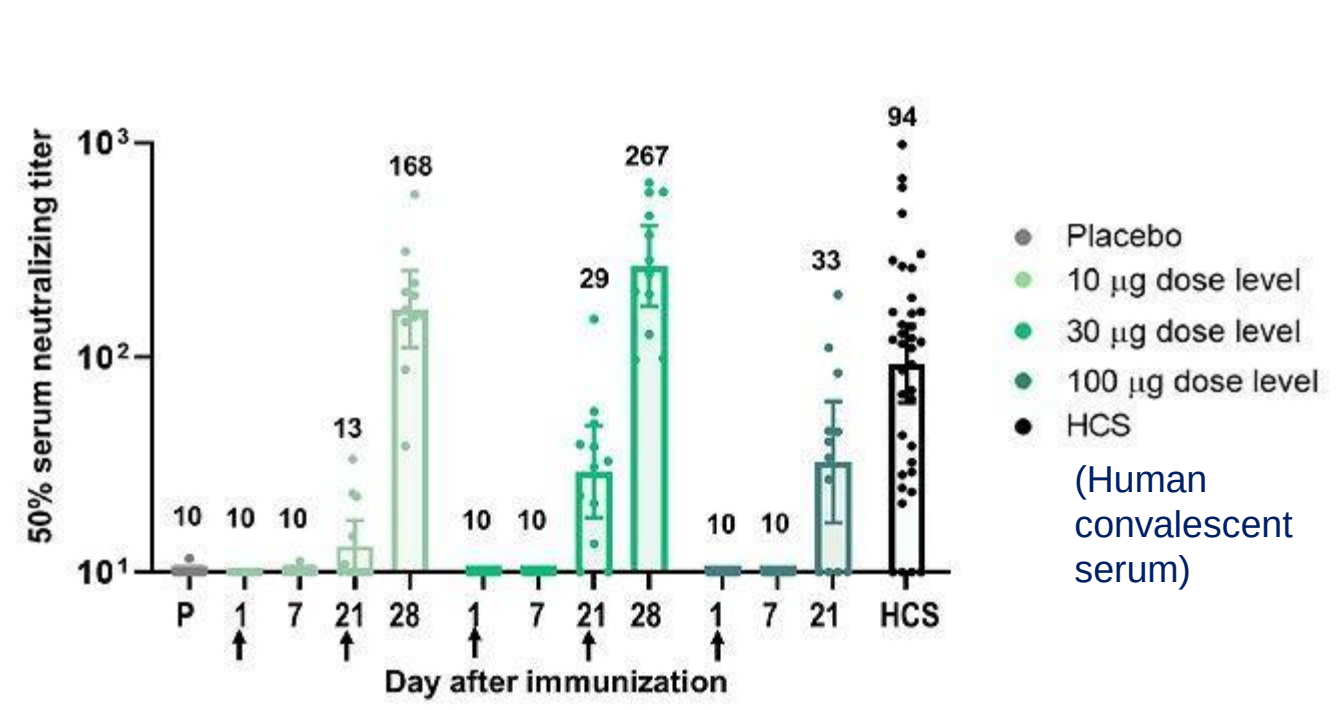
G.Q.

Mulligan MJ. medRxiv 2020; doi.org/10.1101/2020.06.30.20142570.

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

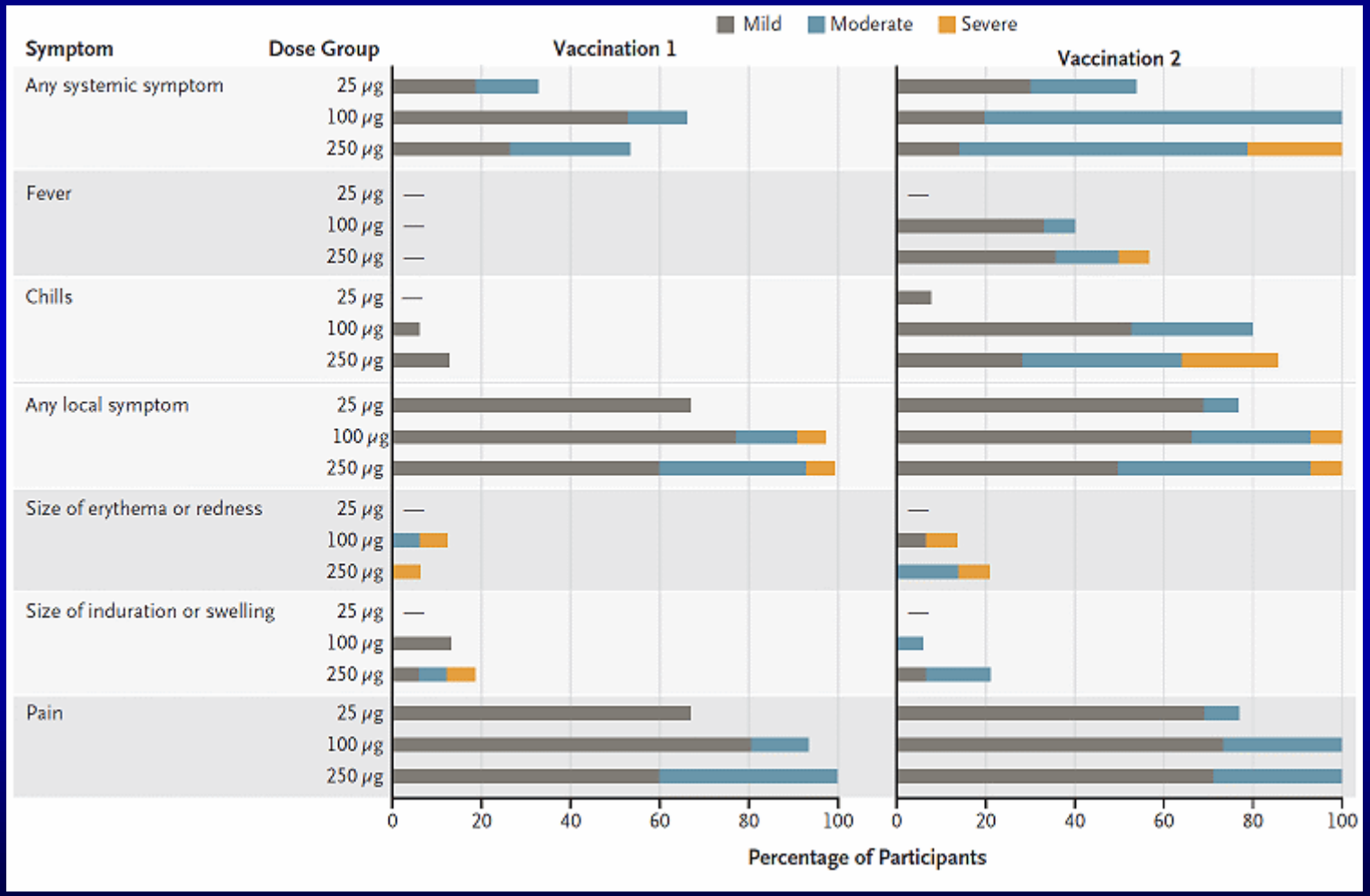


G.Q.

Mulligan MJ. medRxiv 2020; doi.org/10.1101/2020.06.30.20142570.

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

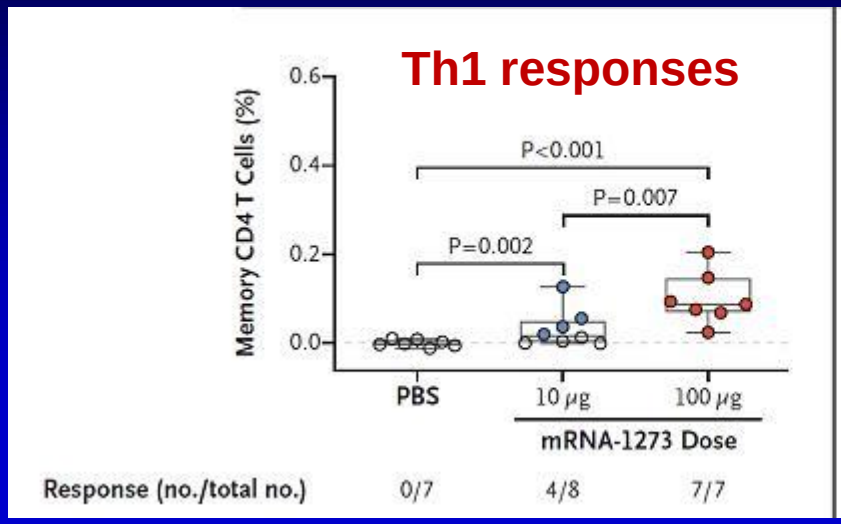
2 doses, N=45, 18-55 yrs, 2020, USA

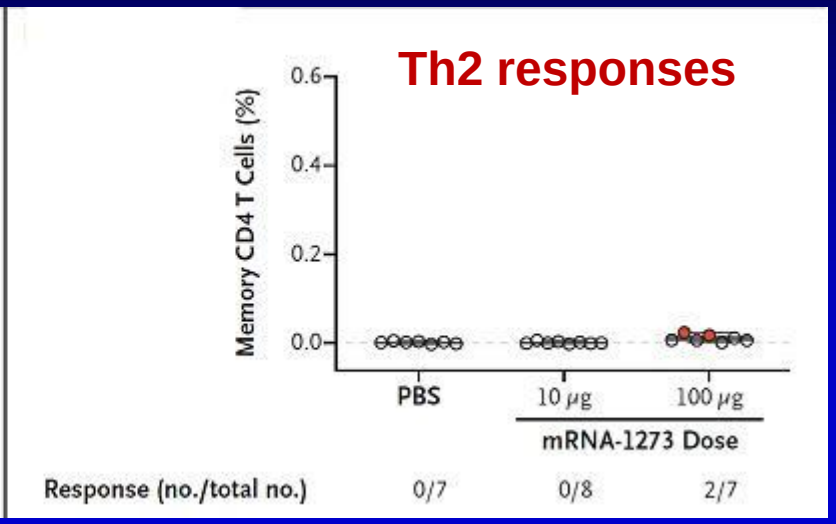


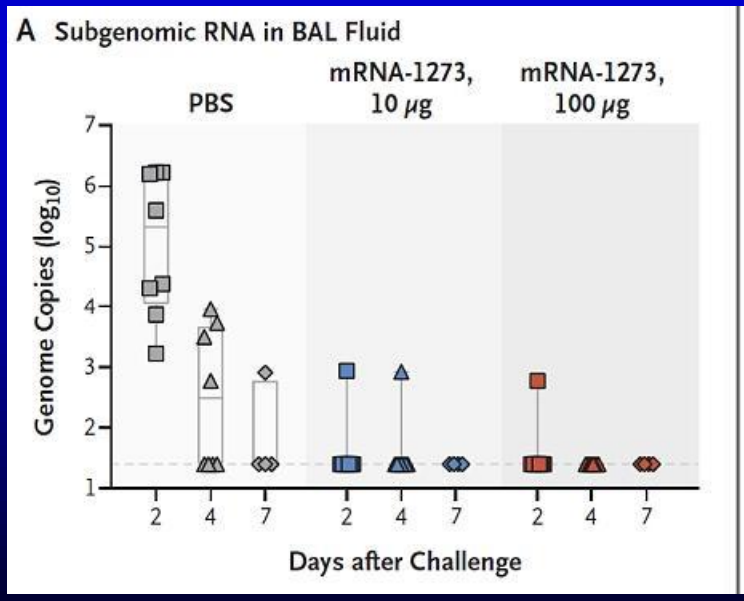
Jackson LA. N Engl J Med 2020; doi: 10.1056/NEJMoa2022483. Onli

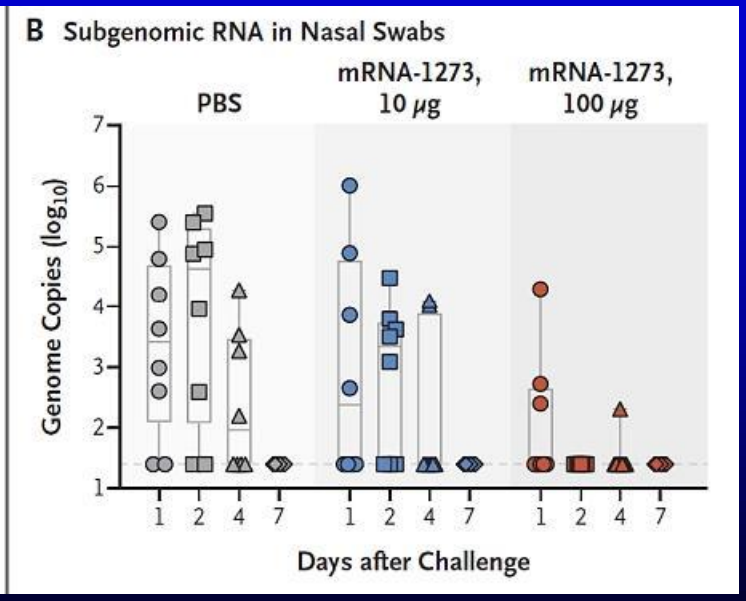
mRNA vaccine (Moderna, Inc.)

Rhesus macaques challenge test, 2020, USA









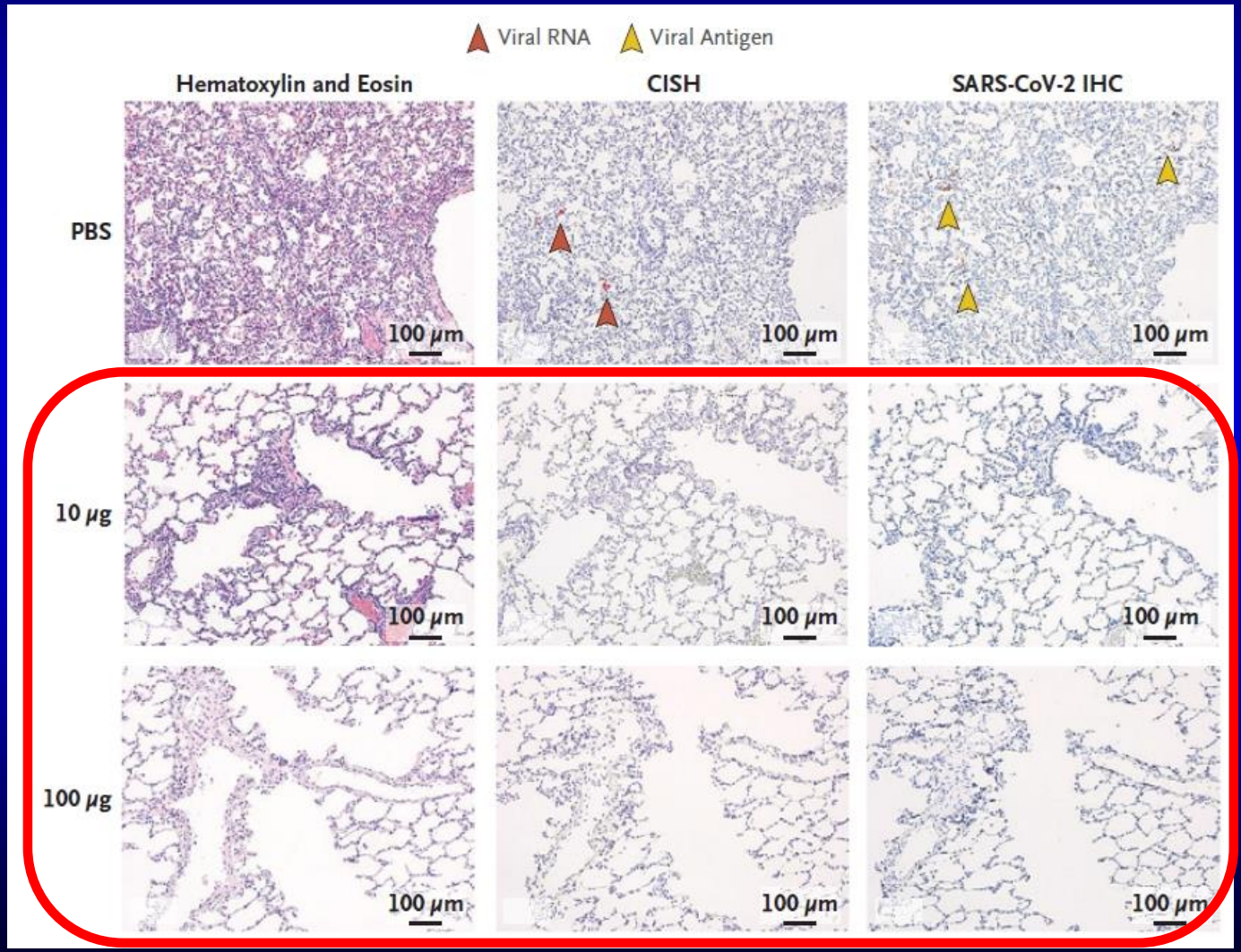
G.Q.

Corbett KS. N Engl J Med 2020; DOI: 10.1056/NEJMoa2024671.

mRNA vaccine (Moderna, Inc.)

Rhesus macaques challenge test, 2020, USA

Limited inflammation in vaccine group



G.Q.

Corbett KS. N Engl J Med 2020; DOI: 10.1056/NEJMoa2024671.

Johnson & Johnson: adenovirus vector

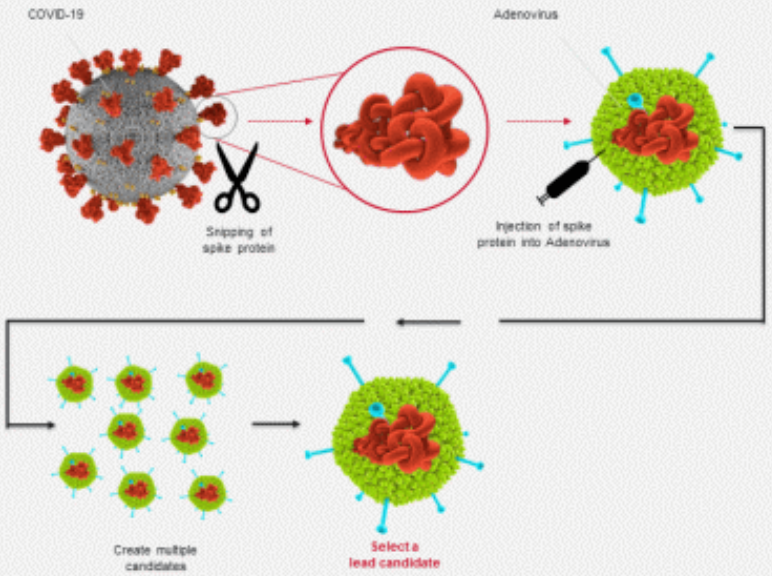
- 設計簡單，快速生產
- 對載體病毒有抗體會降低致免性，不適合重複接種

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

G.Q.

https://news.yahoo.com/jj-coronavirus-vaccine-we-plan-to-begin-production-at-risk-imminently-210204457.html

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

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

	Low dose group (n=36)	Middle dose group (n=36)	High dose group (n=36)	Total (N=108)
All adverse reactions within 0–7 days				
Any	30 (83%)	30 (83%)	27 (75%)	87 (81%)
Grade 3	2 (6%)	2 (6%)	6 (17%)	10 (9%)
Injection site adverse reactions within 0–7 days				
Pain	17 (47%)	20 (56%)	21 (58%)	58 (54%)
Induration	2 (6%)	1 (3%)	1 (3%)	4 (4%)
Redness	2 (6%)	1 (3%)	1 (3%)	4 (4%)
Swelling	4 (11%)	4 (11%)	0	8 (7%)
Itch	2 (6%)	3 (8%)	0	5 (5%)
Muscular weakness	0	0	1 (3%)	1 (1%)
Systemic adverse reactions within 0–7 days				
Fever	15 (42%)	15 (42%)	20 (56%)	50 (46%)
Grade 3 fever	2 (6%)	2 (6%)	5 (14%)	9 (8%)
Headache	14 (39%)	11 (31%)	17 (47%)	42 (39%)
Fatigue	17 (47%)	14 (39%)	16 (44%)	47 (44%)
Grade 3 fatigue	0	0	2 (6%)	2 (2%)

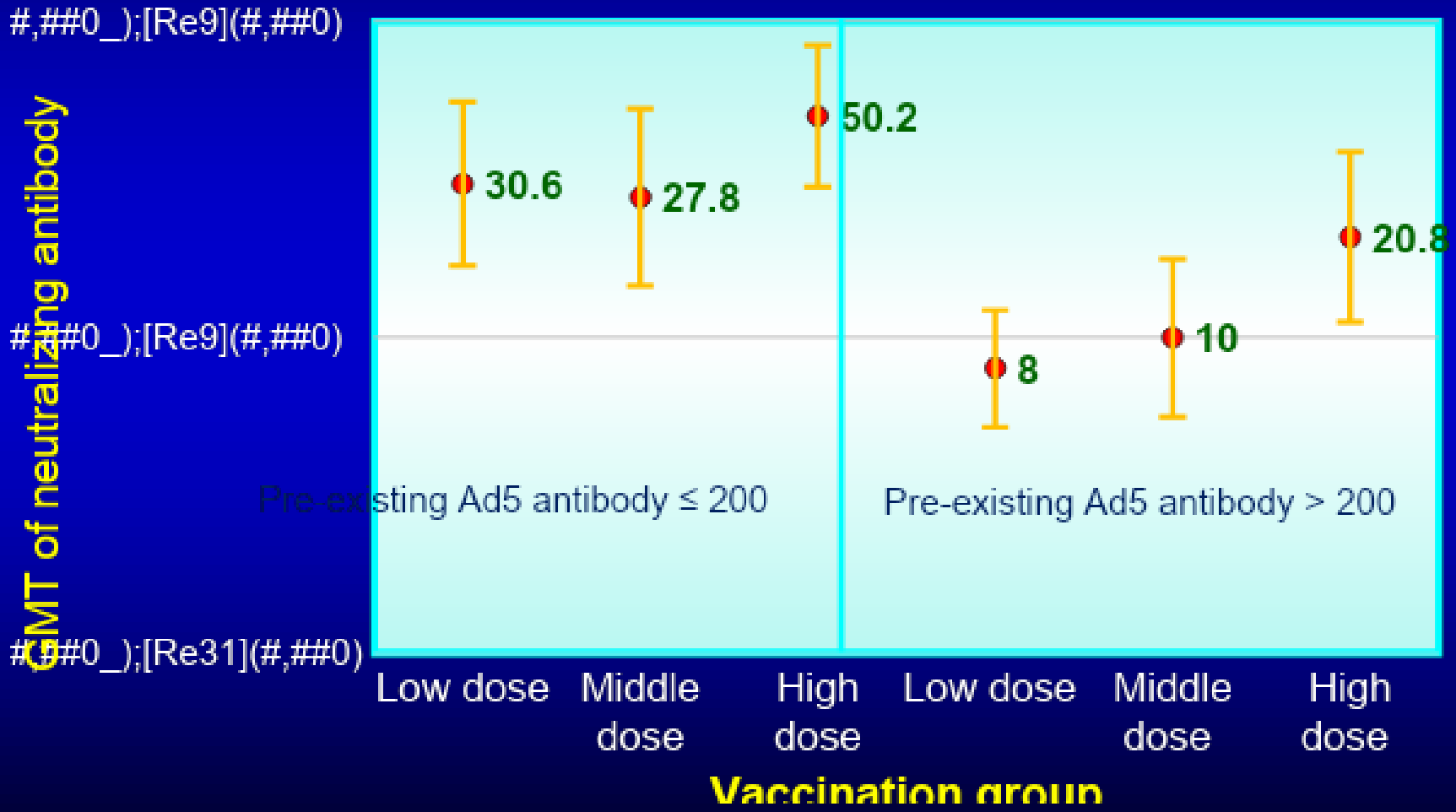
G.Q.

Zhu FC. Lancet 2020;395(10240):1845-1854.

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

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

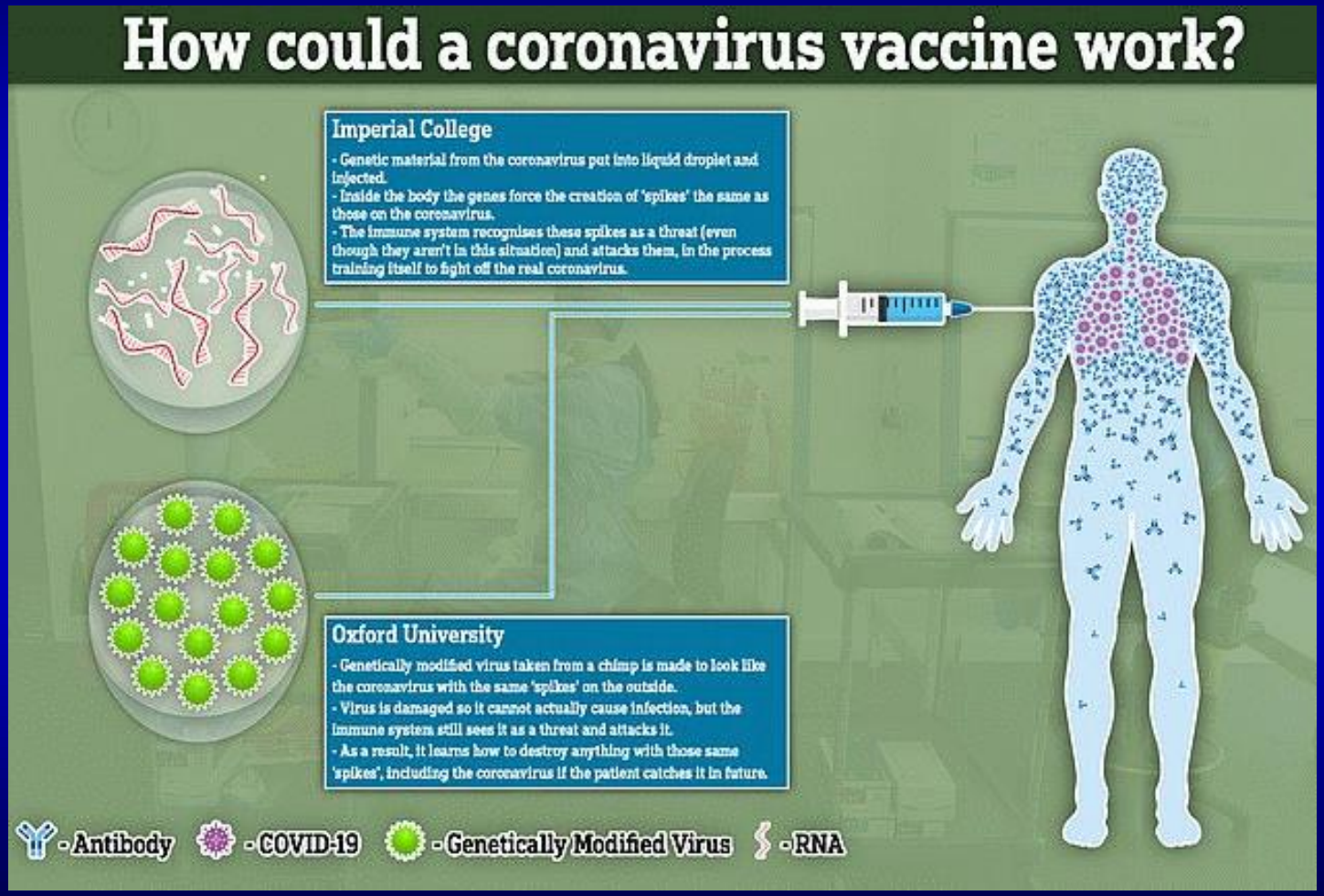
Neutralizing antibodies to live SARS-CoV-2



G.Q. Zhu FC. Lancet 2020;395(10240):1845-1854.

AstraZeneca: adenovirus vector

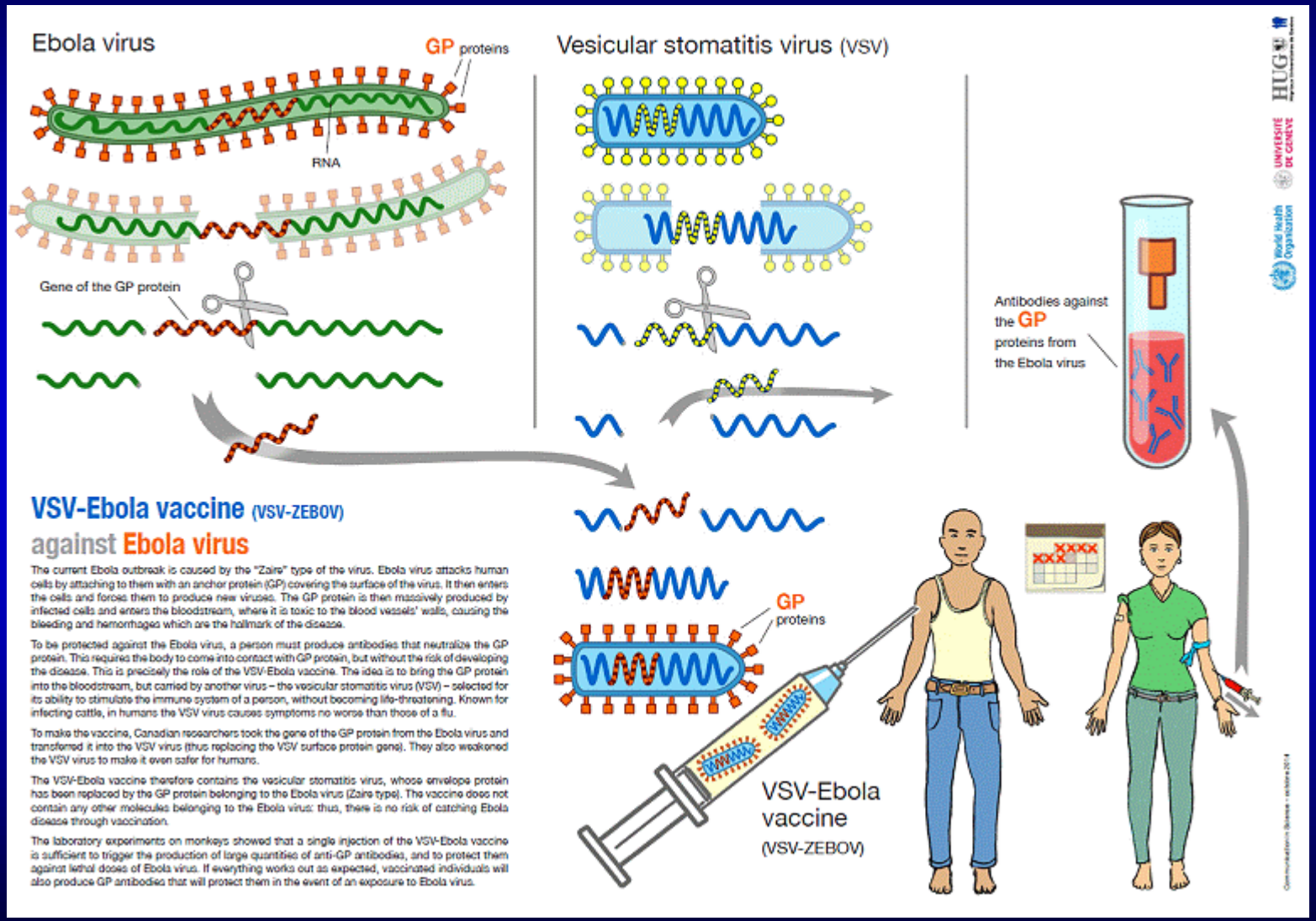
AZD1222 SARS-CoV-2 vaccine



G.Q.

https://internewscast.com/astrazeneca-to-begin-supply-of-covid-19-vaccine-in-september/

Merck Sharp & Dohme : live attenuated chimeric vaccine



G.Q. https://www.hug-ge.ch/sites/interhug/files/structures/ebola_vaccine_candidate/infographie-vaccin-vsv-ebola-english.pdf

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

G.Q.

疫苗的研發

- **第一階段 (2-5年)**：抗原鑑定、疫苗設計及生產
- **第二階段 (1-2年)**：動物試驗
- **第三階段 (4-8年)**：臨床試驗
  - **第一期**：安全性、耐受性
  - **第二期**：免疫原性、安全性、劑量、時程
  - **第三期：確認保護效益與安全性**
- **第四階段 (1-2年)**：審查、領證

G.Q.

天下雜誌 https://www.cw.com.tw/article/article.action?id=5099060
王亞蕾. 當代醫藥法規月刊 2018;98:1.

疫苗保護效力的判定

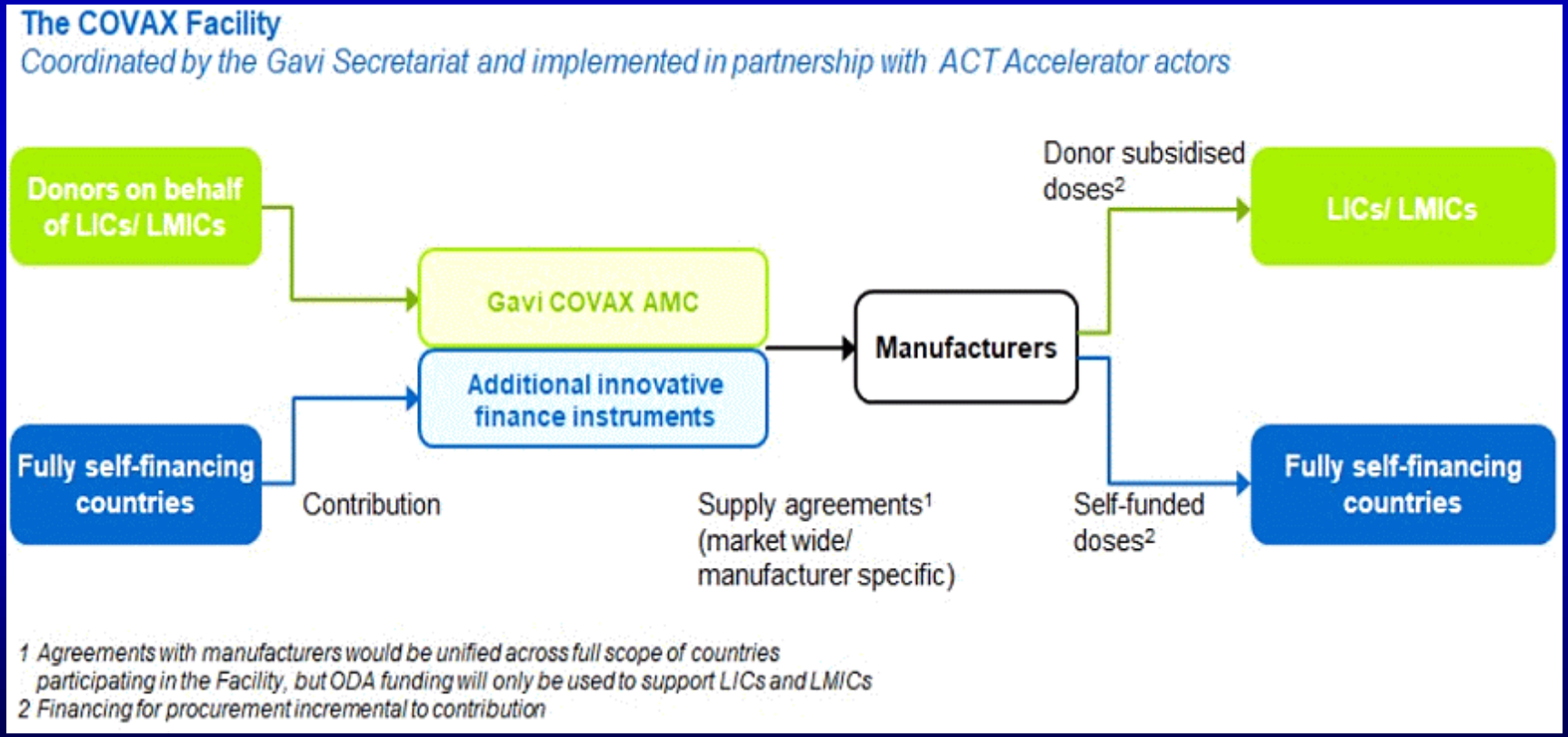
- **已知保護性免疫反應臨界值**：B型肝炎表面抗體 ≥ 10 mIU/mL
- **對照研究**：疫苗組與對照組暴露病原後，發病率減少的比率
- **人類挑戰試驗 (human challenge trial)**：受試者故意接受病原暴露
- **免疫橋接 (immune bridging)**：參考類似疫苗的免疫反應資料

G.Q.

王亞蕾. 當代醫藥法規月刊 2018;98:1.

COVAX：共同投資、共同製造、平均分配新型冠狀病毒疫苗　WHO, Gavi, CEPI

2020.7.15：> 150國家



G.Q.

https://genevahealthfiles.wordpress.com/2020/06/19/gavi-covax-facility-questions-on-access-pricing-governance/

流感疫苗優先順序的考量
降低全人口死亡率的效果

傳播率	**高危險群**	高傳播群
傳入管道	**高危險群**	高傳播群
疫苗獲得	高危險群	**高傳播群**
致死率 *	高危險群	**高傳播群**

其他因素：

- 年齡別死亡率：e.g. 老人罹病率低
- 疫苗大量製造：優先順序不重要

*愈需要重視社會機能相關族群 LPI

G.Q.

Bansal S. PLoS Med 2006;3:1816.

COVID-19疫苗接種對象優先順序草案

2020.7

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

G.Q.

大規模疫苗接種引起的安全性質疑

台灣

- 施打H1N1疫苗身體抽搐　高三女無法練琴 (今日，2009.12.19)
- 國一女打完疫苗 四肢無力! (華視，2009.12.22)
- 打完疫苗！18歲女半癱　現又吐血眼矇 (TVBS，2009.12.23)
- 孕婦死胎.失聰 疫苗問題連爆 (民視，2009.12.24)
- **劉童死亡效應 投訴暴增** (自由，2009.12.23)
- 小五男童突然腦中風　家屬疑疫苗所害 (今日，2010.1.2)
- 疫苗又惹禍？69歲男子昏迷不醒 (中廣，2010.1.3)

G.Q.

集體心因性疾病
Mass psychogenic illness

- 大規模疫苗接種後，許多人出現類似的症狀，但卻沒有明顯的病因，則必須考慮是集體心因性疾病。
- 常見症狀包括頭痛、頭暈、肌肉無力與意識喪失
- 一旦發生，這些症狀很**不容易消退**
- 可因**媒體大幅報導**而快速增加
- **即使專家出面解說，大眾通常無法被說服疫苗沒有問題。**
- 都出現於**較大兒童與成人**的大規模預防接種，而且受到影響的多為**女性**，尤其**社經地位偏低**者。
- 對這些年齡較大族群大規模接種疫苗時，決策者必須預見可能會發生集體心因性疾病。

G.Q. Clements CJ. Drug Safety 2003;26:599.

醫藥界對H1N1新型流感疫苗與政策的批評　台灣 2009-2010

- **疫苗廠牌：**國光疫苗品質堪虞、疫苗蛋不符合標準、含福馬林與硫柳汞、人體試驗人數太少、政府護航本國疫苗
- 疫苗未進行孕婦、免疫功能不全者的人體試驗
- **醫師質疑疫苗安全性**
- 疑似**疫苗傷害**：太快宣布與疫苗無關、太慢確定因果關係、「哪那麼剛好」
- 預防接種諮詢委員與傷害救濟委員多人重複，防疫單位**球員兼裁判**。

G.Q.

H1N1新型流感流行期對政府的建言
台灣 2009-2010

- 民眾可選擇諾華或國光疫苗。
- 資訊應該更透明，包括疑似疫苗不良反應通報等。
- 公布國光疫苗胚胎蛋檢驗證明、試驗詳細過程與結果、詳細藥物審查過程
- 公布諾華與國光兩種疫苗引發的不良反應通報比例、所有疑似疫苗傷害案件、審議委員會名單。
- 增加衛生署預防接種受害救濟委員會非醫界委員比例
- 放寬救濟標準，擴大認定「無法排除與疫苗有關」的範圍，無確切因果關係的死亡案例也給予救濟。
- 提高疫苗傷害相關案件的給付標準。

G.Q.

疫苗安全事件的背景值
台灣健保資料

- 每週發生：
  - Guillain-Barré syndrome 9件
  - 顏面神經麻痺：389件
  - 抽搐、痙攣：842件
  - 急性腦中風：1,532件
  - 急性心肌梗塞：745件
- 一般孕婦自然流產：12.8%

G.Q.

Thanks....