The Evolutionary Future of SARS-CoV-2

Prof. Eddie Holmes

Sydney Institute for Infectious Diseases,
School of Life & Environment Sciences
and School of Medical Sciences,
The University of Sydney, Australia

Australian Government
Australian Research Council

THE UNIVERSITY OF SYDNEY

Australian Government
National Health and Medical Research Council
NHMRC

Possible COVID "Futures" – June 2020

Biological Feature	Future 1 "Vaccines work, antivirals fail"	Future 2 "Antivirals work, vaccines fail"	Future 3 "Medical interventions are effective and evolution works for us"	Future 4 "Medical interventions fail and evolution works against us"
Immunity	• Strong and long-lasting immunity after infection. Immune individuals can be identified through robust biological indicators. Possible immunological cross-protection.	• Very limited natural immunity after infection. Reinfection possible after less than a year. Antibody-dependent enhancement exacerbates disease.	• Some protective immunity, but this is variable and wanes after around two years. False positives make identification of immune individuals unreliable. Possible weak immunological cross-protection.	• Very limited natural immunity after infection. Reinfection possible after less than a year. Antibody-dependent enhancement exacerbates disease.
Vaccines	• Vaccine developed in 12 months. Fully protective and long lasting (~5 years). Relatively easy and quick to produce in large quantities. No antibody-dependent enhancement.	• No effective vaccine developed in the next 5 years because of a lack of protective immunity. Antibody-Dependent Enhancement and/or other negative consequences.	• Vaccines developed providing partial protection developed in 18-24 months. Takes several months to produce so limited doses and global supply chain issues.	• No effective vaccine developed in the next 5 years because of a lack of protective immunity. Antibody-Dependent Enhancement and/or other negative consequences.
Antivirals	• No effective antiviral identified in the next 5 years.	• Multiple effective antivirals are developed that are easy to produce. Antiviral resistance emerges after first year.	• A limited number of partially effective antivirals developed over the next 12 months. Some supply chain issues.	• No effective antiviral identified in the next 5 years.
Antigenic evolution	• No large-scale antigenic evolution/escape in the virus, even following widespread vaccination.	• Widespread and rapid antigenic evolution, even before the onset of widespread vaccination. Reinfection possible on short time-horizons. Vaccines need to be updated annually.	• No large-scale antigenic evolution/escape in the virus, even following widespread vaccination.	• Widespread and rapid antigenic evolution, even before the onset of widespread vaccination. Reinfection possible on short time-horizons. Vaccines need to be updated annually.
Evolution in virulence, transmission and seasonality	• Virulence stays as it is now. Transmission increases in younger cohorts. Develops into a winter seasonal disease after 12-24 months.	• Virulence stays as it is now. Transmission increases in younger cohorts. Develops into a winter seasonal disease after 12-24 months.	• Virulence declines over 12 months with no increase in transmissibility. The use of vaccines and antivirals further reduces virulence. Develops into a winter seasonal disease within 12 months.	• Virulence increases over the next 12 months. Virulence increases in younger cohorts. New transmission routes emerge. No seasonality evolves.
Interaction with other pathogens and/or co-morbidities	• Some interactions with other pathogens in some populations increase COVID-19 morbidity / mortality.	• Some interactions with other pathogens in some populations increase COVID-19 morbidity / mortality.	• Possible weak cross-protective immune responses.	• Interactions with pathogens commonly circulating in some populations increase morbidity / mortality.

Case scenarios: best (no shading), middle (light grey), worse (dark grey)

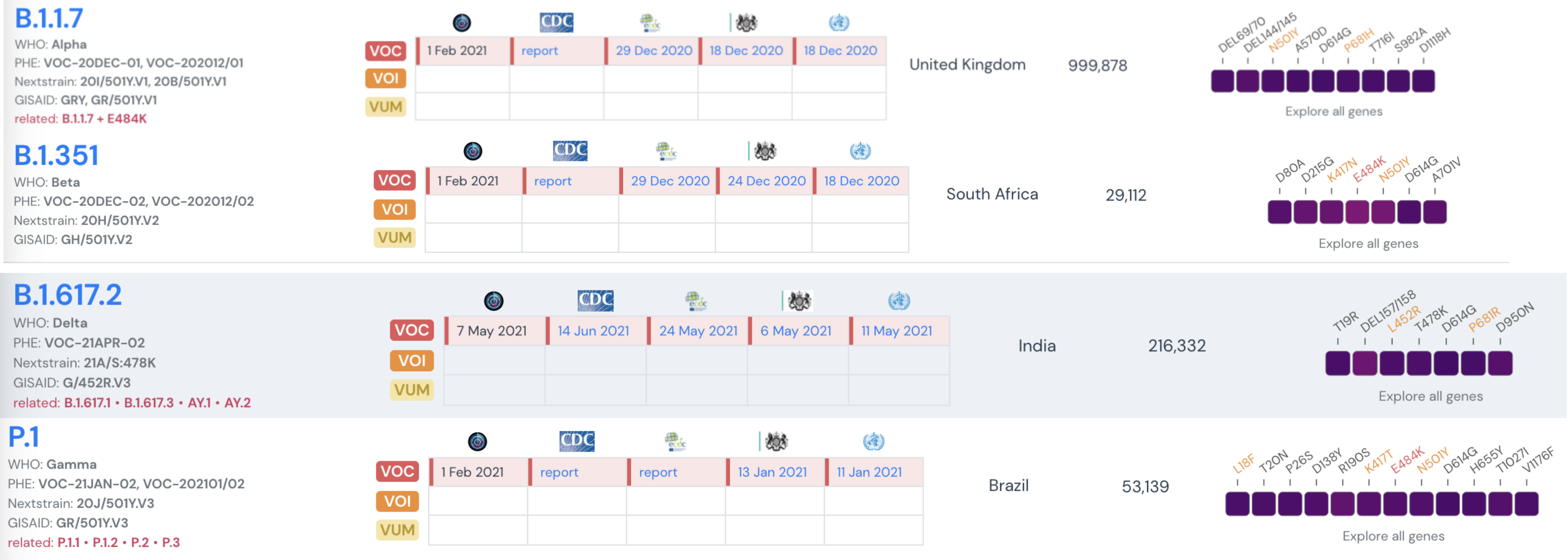
What Actually Happened – December 2021

Biological Feature	Future 1 "Vaccines work, antivirals fail"	Future 2 "Antivirals work, vaccines fail"	Future 3 "Medical interventions are effective and evolution works for us"	Future 4 "Medical interventions fail and evolution works against us"
Immunity	• Strong and long-lasting immunity after infection. Immune individuals can be identified through robust biological indicators. Possible immunological cross-protection.	• Very limited natural immunity after infection. Reinfection possible after less than a year. Antibody-dependent enhancement exacerbates disease.	• Some protective immunity, but this is variable and wanes after around two years. False positives make identification of immune individuals unreliable. Possible weak immunological cross-protection.	• Very limited natural immunity after infection. Reinfection possible after less than a year. Antibody-dependent enhancement exacerbates disease.
Vaccines	• Vaccine developed in 12 months. Fully protective and long lasting (~5 years). Relatively easy and quick to produce in large quantities. No antibody-dependent enhancement.	• No effective vaccine developed in the next 5 years because of a lack of protective immunity. Antibody-Dependent Enhancement and/or other negative consequences.	• Vaccines developed providing partial protection developed in 18-24 months. Takes several months to produce so limited doses and global supply chain issues.	• No effective vaccine developed in the next 5 years because of a lack of protective immunity. Antibody-Dependent Enhancement and/or other negative consequences.
Antivirals	• No effective antiviral identified in the next 5 years.	• Multiple effective antivirals are developed that are easy to produce. Antiviral resistance emerges after first year.	• A limited number of partially effective antivirals developed over the next 12 months. Some supply chain issues.	• No effective antiviral identified in the next 5 years.
Antigenic evolution	• No large-scale antigenic evolution/escape in the virus, even following widespread vaccination.	• Widespread and rapid antigenic evolution, even before the onset of widespread vaccination. Reinfection possible on short time-horizons. Vaccines need to be updated annually.	• No large-scale antigenic evolution/escape in the virus, even following widespread vaccination.	• Widespread and rapid antigenic evolution, even before the onset of widespread vaccination. Reinfection possible on short time-horizons. Vaccines need to be updated annually.
Evolution in virulence, transmission and seasonality	• Virulence stays as it is now. Transmission increases in younger cohorts. Develops into a winter seasonal disease after 12-24 months.	• Virulence stays as it is now. Transmission increases in younger cohorts. Develops into a winter seasonal disease after 12-24 months.	• Virulence declines over 12 months with no increase in transmissibility. The use of vaccines and antivirals further reduces virulence. Develops into a winter seasonal disease within 12 months.	• Virulence increases over the next 12 months. Virulence increases in younger cohorts. New transmission routes emerge. No seasonality evolves.
Interaction with other pathogens and/or co-morbidities	• Some interactions with other pathogens in some populations increase COVID-19 morbidity / mortality.	• Some interactions with other pathogens in some populations increase COVID-19 morbidity / mortality.	• Possible weak cross-protective immune responses.	• Interactions with pathogens commonly circulating in some populations increase morbidity / mortality.

Medical interventions have been effective, but virus evolution has often worked against us

Ongoing Evolution of SARS-CoV-2

- >5,000,000 SARS-CoV-2 genome sequences generated to date

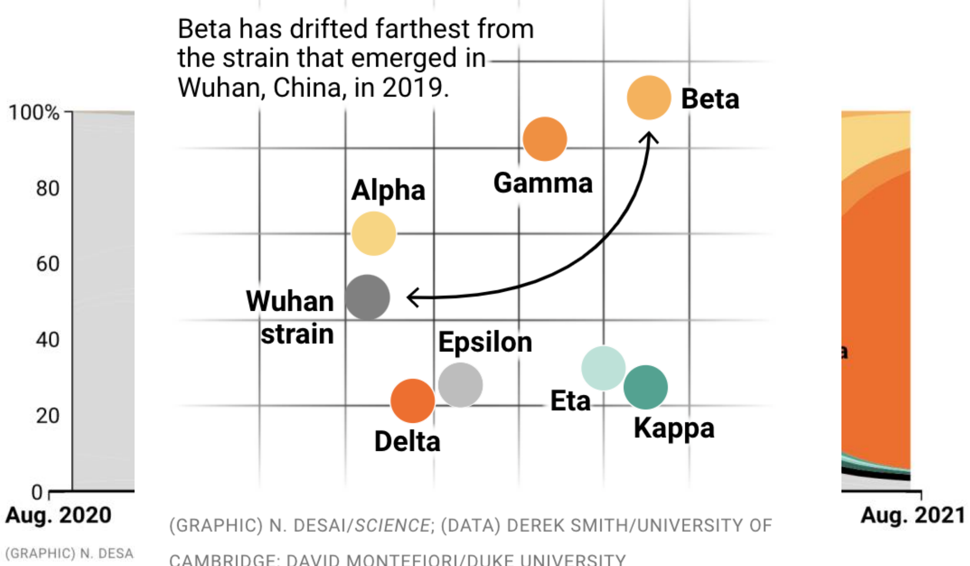


			CDC						
B.1.1.7 WHO: Alpha PHE: VOC-20DEC-01, VOC-202012/01 Nextstrain: 20I/501Y.V1, 20B/501Y.V1 GISAID: GRY, GR/501Y.V1 related: B.1.1.7 + E484K	VOC	1 Feb 2021	report	29 Dec 2020	18 Dec 2020	18 Dec 2020	United Kingdom	999,878	DEL69/70, DEL144/145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H (Explore all genes)
B.1.351 WHO: Beta PHE: VOC-20DEC-02, VOC-202012/02 Nextstrain: 20H/501Y.V2 GISAID: GH/501Y.V2	VOC	1 Feb 2021	report	29 Dec 2020	24 Dec 2020	18 Dec 2020	South Africa	29,112	D80A, D215G, K417N, E484K, N501Y, D614G, A701V (Explore all genes)
B.1.617.2 WHO: Delta PHE: VOC-21APR-02 Nextstrain: 21A/S:478K GISAID: G/452R.V3 related: B.1.617.1 • B.1.617.3 • AY.1 • AY.2	VOC	7 May 2021	14 Jun 2021	24 May 2021	6 May 2021	11 May 2021	India	216,332	T19R, DEL157/158, L452R, T478K, D614G, P681R, D950N (Explore all genes)
P.1 WHO: Gamma PHE: VOC-21JAN-02, VOC-202101/02 Nextstrain: 20J/501Y.V3 GISAID: GR/501Y.V3 related: P.1.1 • P.1.2 • P.2 • P.3	VOC	1 Feb 2021	report	report	13 Jan 2021	11 Jan 2021	Brazil	53,139	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F (Explore all genes)

Scripps Research
https://outbreak.info/situation-reports

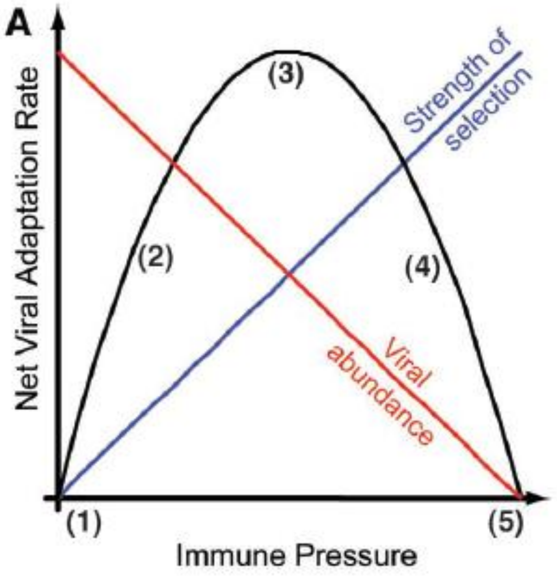
Why convergent evolution and emergence of Variants of Concern?

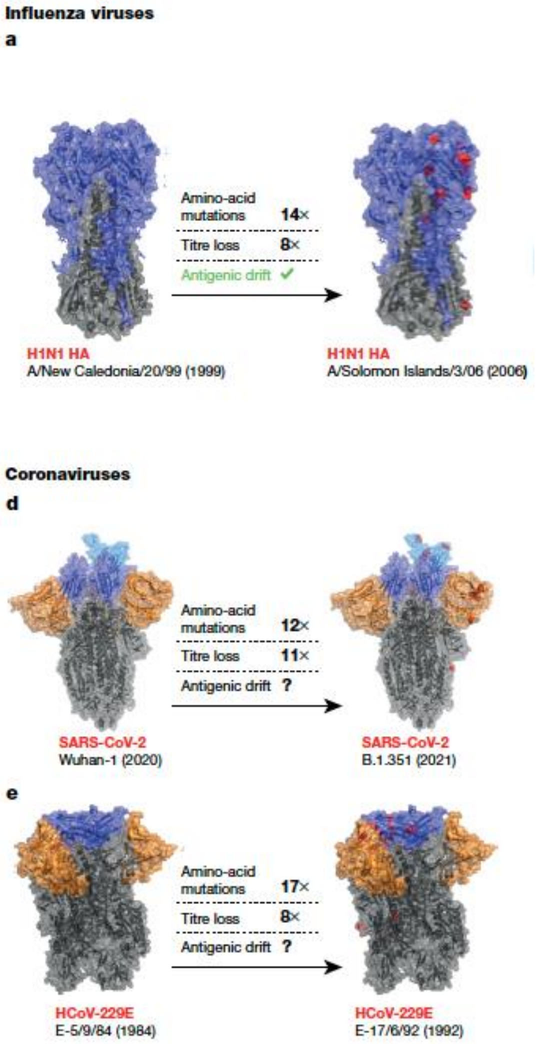
- Increased transmissibility
- Impact of population lockdowns
- Immune evasion (e.g. mounting interferon resistance)
- Inter-host chronic infections (i.e. prolonged shedding and evolution)



One Scenario of SARS-CoV-2 Future Evolution

- Virus is endemic.
- There will be natural selection for immune evasion.
- Ongoing SARS-CoV-2 evolution will necessitate the use booster vaccine shots and likely updated vaccines.
- Immune escape will be strongest in the first years of the pandemic; strongest adaptive evolution at intermediate levels of immune protection.
- As time passes the virus will find it harder to find an escape mutation.
- Virulence evolution depends on whether there is selection to infect cells of the lower or upper respiratory tract (or both).
- Serious disease/mortality will decline with increasing immunity.





Telenti *et al*. *Nature* **596**, 495-504 (2021).

COVID-19: Lessons Learned

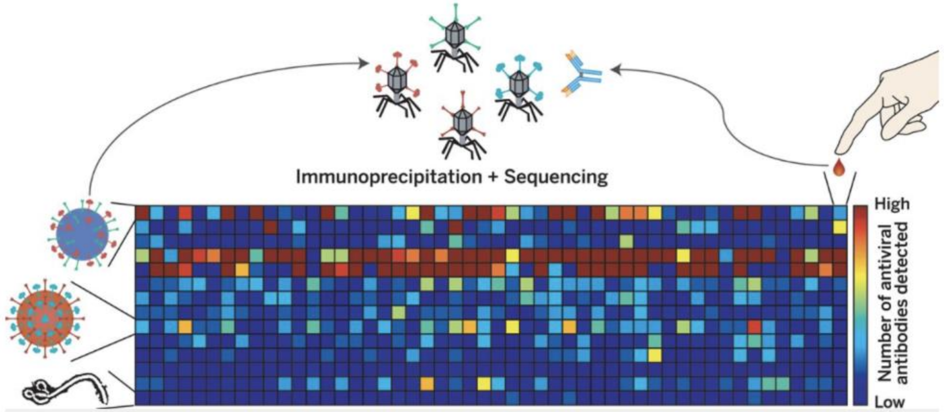
- Need a broader set of pandemic plans, not just those based on influenza
- Continual research funding for cross-protective vaccines and antivirals (for coronaviruses, influenza viruses and paramyxoviruses)
- We need a new global “pandemic radar” to rapidly identify emerging diseases
- Climate change will increase the frequency of disease emergence events
- Scientists and public health officials need to share their data as openly and rapidly as possible
- Open global collaboration between scientists should be encouraged and enriched
- Governments need to listen to and trust in scientists
- Science must be depoliticised

Wuhan Central Hospital, 2016

A Global "Pandemic Radar"

- Active surveillance of people living/working at the human-animal interface: wildlife trade and fur farming, in animal production and slaughter, live animal markets, animal hunting/bushmeat, people living around bat roosts, animal carers and animal rescue centres etc.
- Active surveillance of animal mortality events
- Regular immunological surveillance (e.g. VirScan/GIO) and occasional metagenomic surveillance
- Rapid and open data sharing

VirScan



VirScan, or systematic viral epitope scanning, works by displaying bits of protein from more than 1,000 strains of virus. Antibodies in a blood sample latch onto the bits they recognize. Now, scientists have updated VirScan to include the novel coronavirus. Credit: G. Xu et al./*Science* 2015

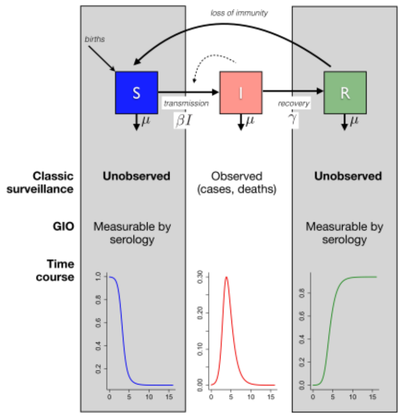
SCIENCE FORUM

A Global Immunological Observatory to meet a time of pandemics

Abstract SARS-CoV-2 presents an unprecedented international challenge, but it will not be the last such threat. Here, we argue that the world needs to be much better prepared to rapidly detect, define and defeat future pandemics. We propose that a Global Immunological Observatory and associated developments in systems immunology, therapeutics and vaccine design should be at the heart of this enterprise.

MICHAEL J MINA†*, C JESSICA E METCALF†*, ADRIAN B MCDERMOTT, DANIEL C DOUEK, JEREMY FARRAR AND BRYAN T GRENFELL

A) Serology as epidemiological 'dark matter'



B) Addressing challenges to establishing GIO

Challenge:	Addressed by:
Funding, sustainability	Distributed model, but with stable, multilateral, multi-year funding. **A transparent, well governed administrative/informatics/laboratory core is essential.**
Global equity and ethics	Strong focus in endemic countries. There are other models of global partnerships which could be looked for inspiration and governance - H3Africa, GISAID, GA4GH, EBI/EMBO, CERN, GIP.
Data dissemination	Open source dissemination of key anonymized immunological data and associated methods and analyses
Intellectual Property issues	Most of these issues can be sorted out with good governance, transparency, being inclusive and by building trust. Lessons can be learned from Human Genome Project, and agencies like Medicine Patent Pool, DNDi, MMV, GAVI, Open Source, and other respected structures who have considered similar issues.