SARS-CoV-2 Variants of concern: What to know?

Swiss Society of Tropical and Travel Medicine FMH - Formation continue

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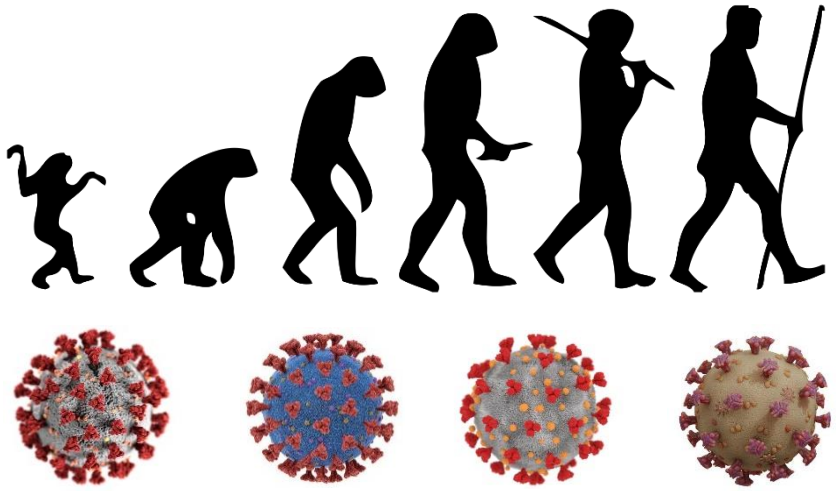


Variant:

Natural evolution of a virus over time (mutations)
Favoured by selection pressure
Acquisition and selection of properties which confer an advantage

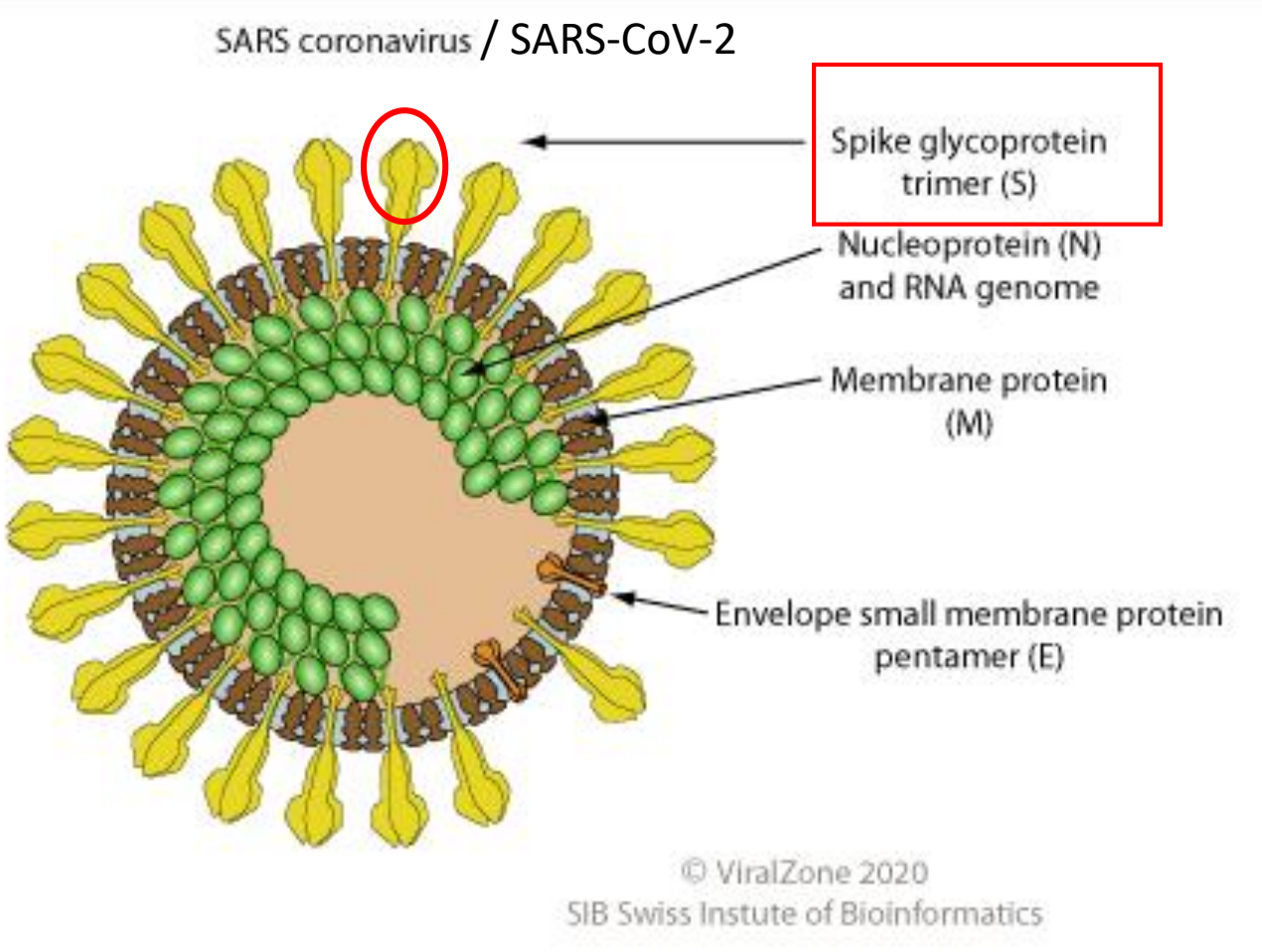
https://unige.zoom.us/rec/share/qlancqK2UNaugN906r-1xS1_oJR9en91sRn3dbdvqXUXHS_fib72M11tjqofKJum.JIDzDrmjrihBV5Qm?startTime=1611902822000

Mutations and impact on viruses

- Types of mutations
  - Insertion
  - Deletion
  - Substitution

- Impact:
  - Neutral
  - Negative
  - Positive

- Synonymous
- Non-synonymous

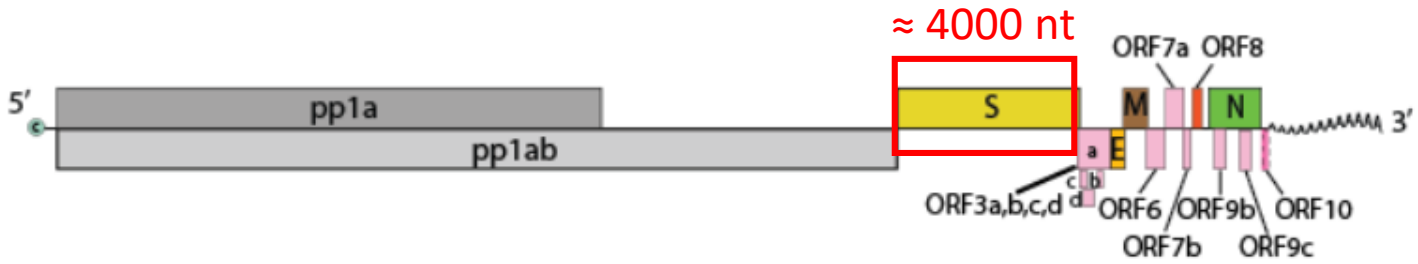


Single-stranded + RNA
Genome size 30 kb

RNA-dependent RNA polymerase (proofreading reacitivity)

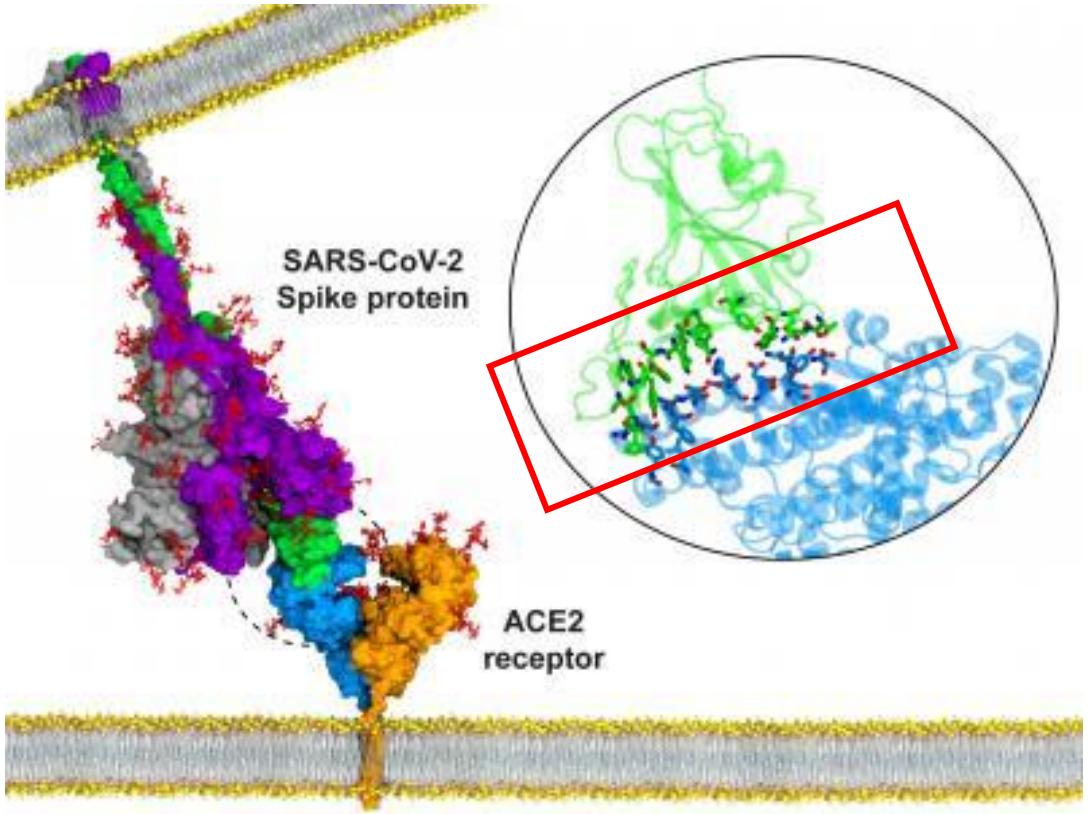
Rate of substitutions: 9.9×10^{-4} to 1.12×10^{-3} substitutions per site per year

SARS-CoV-2: 1-2 nt per month/lineage



Nie, Virus Res. 2 oct 2020;287:198098; Duchenne, Virus Evolution 6 (2): veaa061

Interaction between the Spike protein and its receptor



Mutation of the S protein:

- Modification of the entry efficiency of the cell
- Modification of neutralising antibodies (natural infection and vaccines)

Neutralizing antibodies : prevent infection by targeting the Spike
-> no binding to the receptor ACE2 anymore (principle of vaccination)

Adapted from : https://www.krisp.org.za/ngs-sa/ngs-sa_updates_covid-19_analysis_narratives_reports/token/18

https://www.sciencemuseumgroup.org.uk/blog/coronavirus-the-spike/

«Variants of concern»

Accumulation of high number of mutations (> 10-20)
Most of them on the **S gene**

WHO denomination	Lineage	Country of first identification	Main important mutations
Alpha	**B.1.1.7**	**UK**	**N501Y**, Del 69-70
Beta	**B.1.351**	**South-Africa**	**N501Y**, **E484K**, K417N
Gamma	**P.1**	**Brazil**	**N501Y**, **E484K**, K417T
Delta	**B.1.617**	**India**	**L452R,** P681R, +/-E484Q

- Increase in transmissiblity
- Severity/virulence
- Possible immune escape
  - Reinfection risk
- Reduced vaccine efficacy
- Diagnostic failure
- Treatment failure

B.1.617 – First identified in India

- 3 sub-lineages: B.1.617.1, B.1.617.2, B.1.617.3
- B.1.617.2 (delta) considered a VOC by WHO since May 2021
  (increased transmissibility: dominant in the UK)

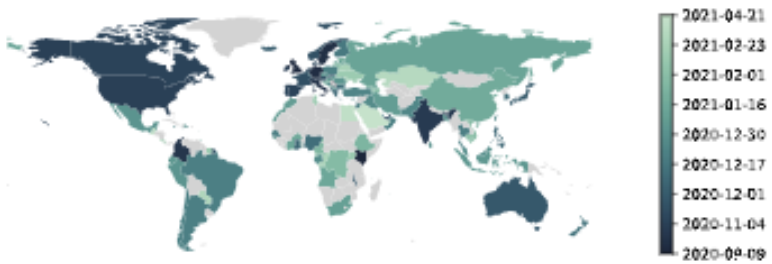
- «Double mutant»?

  7 mutations on the S gene, > 15 mutations along the whole genome

  L452R (RBD): increased affinity of the virus to its ACEII receptor (Chen, JMB, 2020)

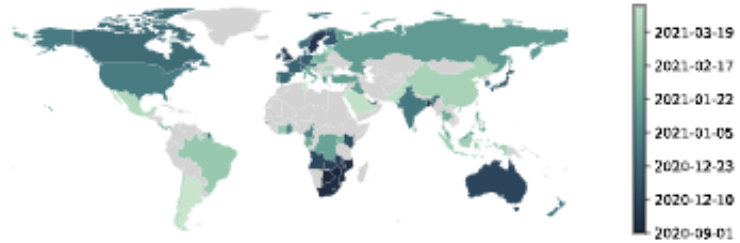
  P681R: increased transmissibility (near furin cleagage site)

  E484Q: (only in B.1.617.1/3) : immune escape



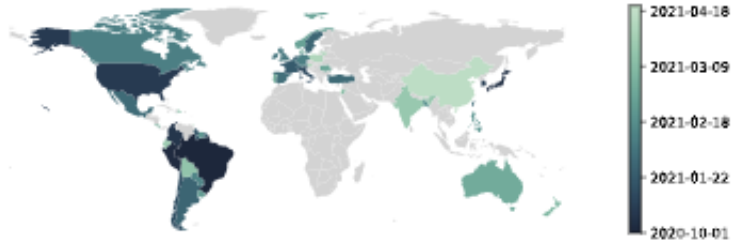
B.1.1.7 report

Alpha
First identification in UK
September 2020



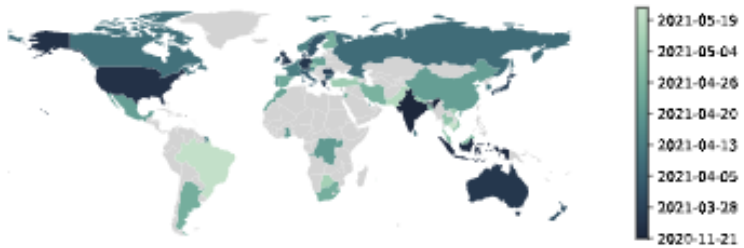
B.1.351 report

Beta
First identification South-Africa
May 2020



P.1 report

Gamma
First identification in returning travellers from Brazil
November 2020

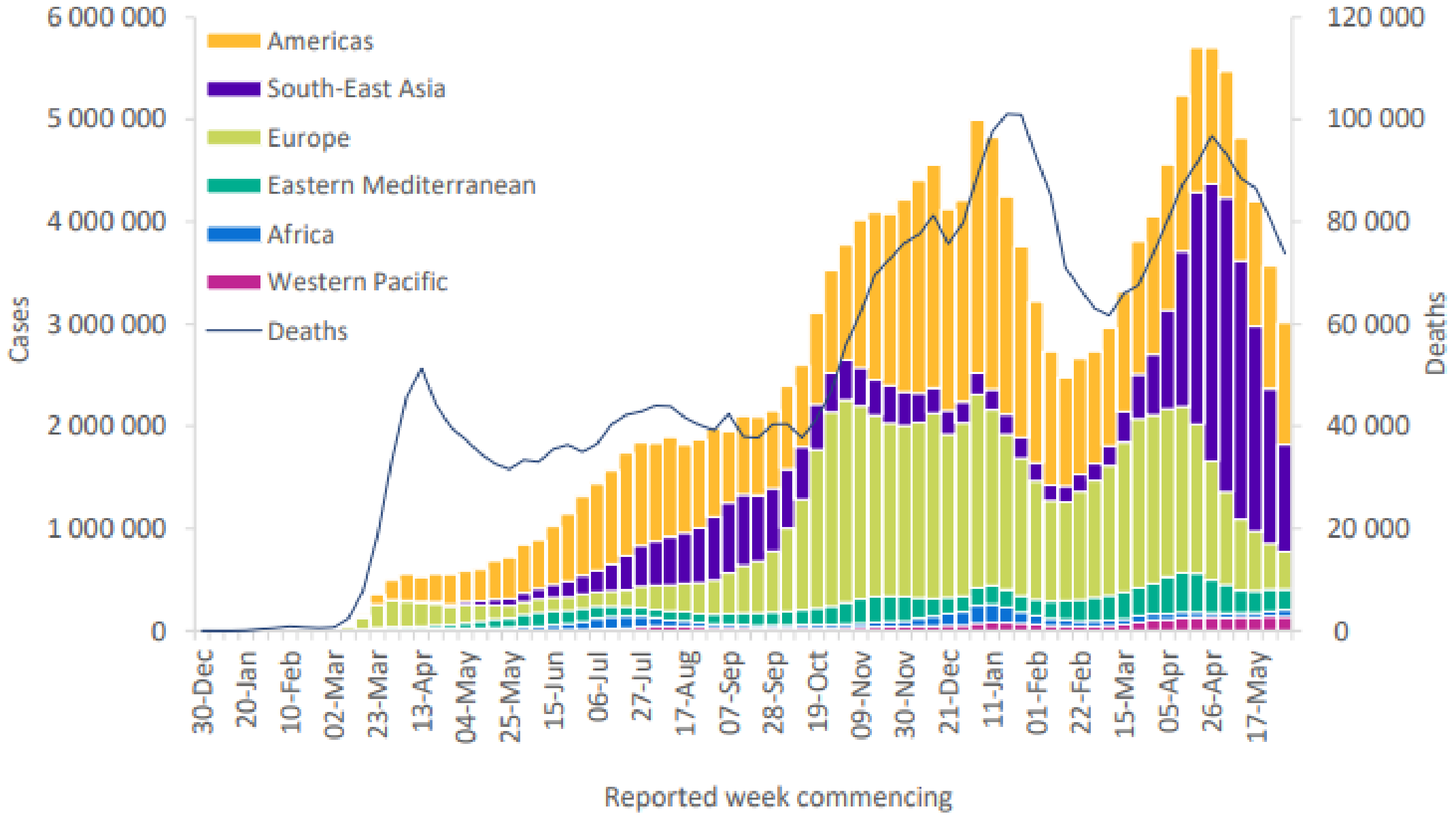


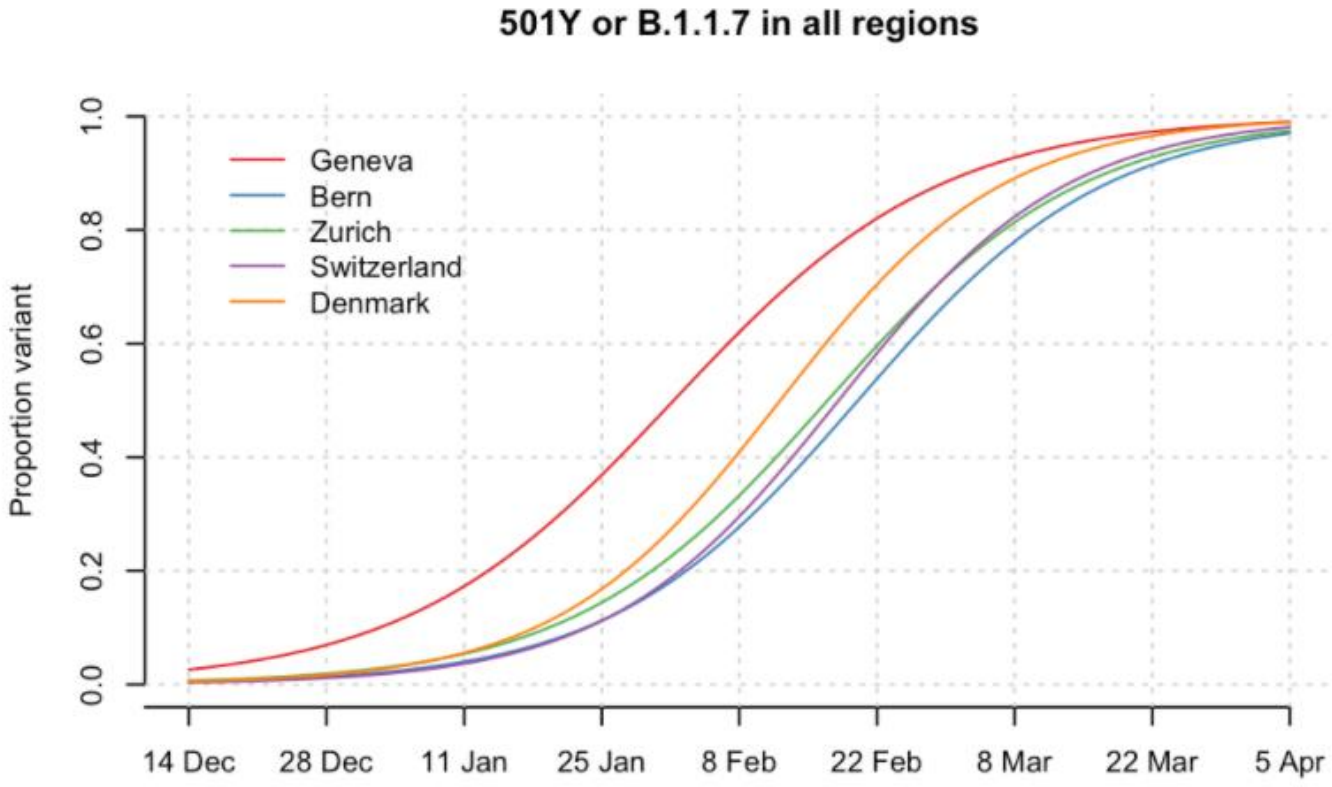
B.1.617.2 report

Delta
First identification en India, October 2020

https://cov-lineages.org/global_report.html; WHO weekly COVID-19 situation report

Figure 1. COVID-19 cases reported weekly by WHO Region, and global deaths, as of 6 June 2021**





C. Althaus' group: https://ispmbern.github.io/covid-19/variants/

https://cevo-public.github.io/Quantification-of-the-spread-of-a-SARS-CoV-2-variant/

B.1.1.7 Alpha variant:

→Increased transmissibility 20-50%

→Replaced previously circulating variants

Increased transmissibility

B.1.1.7 Alpha	B.1.351 Beta	P.1 Gamma	B.1.617.2 Delta
30-50% more transmissible than previous variants (↑ Rt) ↑ secondary attack rate	Increased transmissibility (1.5 time?)	Increased transmissibility (2.5 time?)	≈40% more transmissible than alpha (outcompetes alpha) ↑ (Rt) ↑ secondary attack rate
In all age groups Secondary attack rate still lower in children			Spreading in non vaccinated population (children(?))
Increased in VL? Increased shedding duration? Increased growth rate (shorter generation time)? **Public heath and social measures effective against all variants**			

Davies, Science, 2021; Grabowski, medRxiv, 2021; Leung, Eurosurveillance, 2021; Walker, MedRxiv, 2021; Tegally, Nature, 2021; ECDC; Pearson, github, 2021; Volz, Nature, 2021; Faria, MedRxiv, 2021; Kissler, MedRxiv, 2021; PHE technical briefing 14, June 2, 2021; Frampton, Lancet ID, 2021; WHO weekly epidemiological report, June 8, 2021; Pung, MedRxiv, 2021; Dagpunar, MedRxiv, 2021; Torjesen, MedRxiv, 2021

Severity

B.1.1.7 Alpha	B.1.351 Beta	P.1 Gamma	B.1.617.2 Delta
Possible increased risk of hospitalisation, severity and mortality (epidemiological data) Not confirmed based on data relying on sequencing	Possible increased risk of in-hospital mortality Not confirmed (low evidence data)	Possible increased risk of hospitalization Not confirmed (low evidence data)	Increased risk of hospitalization Under study (?) Increased severity in Syrian Golden Hamster

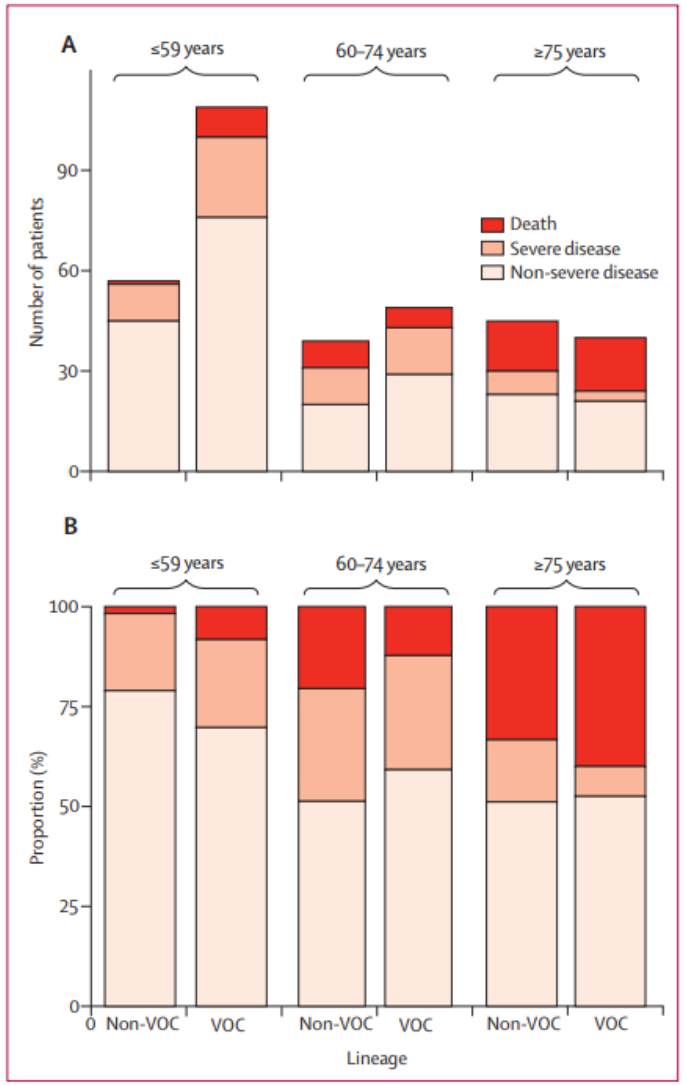


Figure 1: **Severity of illness across patient age groups and by presence of VOC or non-VOC SARS-CoV-2 infection**
Figure shows absolute counts (A) and proportion of patients (B). Non-severe disease was defined as reaching a WHO ordinal scale of less than 6 by day 14 after symptom onset. Severe disease was defined as reaching an ordinal scale point of 6 or higher. Death was defined as those who had died by day 28 after the first positive swab. VOC=variant of concern.

Ons.gov.uk; NERVTAG report 21.01.2021; Public Health England; Santos de Oliveira, MedRxiv, 2021; Bager, Lancet, 2021; Jassat, MedRxiv, 2021; Frampton, Lancet, 2021; Yadav, MedRxiv, 2021

Possible immune escape

- Mechanism:
  - Mutations in antigenic supersites (RBD and N-terminal domain of S) with decreased neutralizing capacities of monoclonal antibodies and polyclonal sera
  - E484K, K417N/T, Del69-70, L452R, …

In vitro neutralization data studies give no indication on the effectiveness of **cell-mediated immunity,** which is conserved against variants

Wang P. et al, BioRxiv 2021, Greaney AJ. BioRxiv 2021, Baum et al. 2020; Weisblum et al. 2020; Tada et a., MedRxiv, 2020; Wibmer, Nat Med, 2021; Planas, Nature, 2021; Cele, Nature, 2021; Wibmer, Nat Med, 2021; Planas, Nature, 2021; Cele, Nature, 2021; Starr, MedRxiv, 2021; Hoffman, BioRxiv, 2021, Yadav, BioRxiv, 2021; Weekly epidemiological report WHO June 8, 2021 ; Graham, Lancet Public Health, 2021; Planas, MedRxiv, 2021; Caniels, MedRxiv, 2021; Riou, MedRxiv, 2021; Reynolds, Science, 2021

Immune escape to monoclonal antibodies

	B.1.1.7	B.1.351	P.1	B.1.617
Monoclonal antibodies Eli Lilly	Partial resistance to etesevimab Conserved efficacy of bamlanivimab	Partial resistance to etesevimab (501Y, E484K, 417N/T) Resistance to bamlanivimab (452R, E484K, 417N/T)		
Regeneron	Conserved efficacy of carisivimab and imdevimab	Partially resistant to casirimivab (E484K, 452R) Neutralization effective with imdevimab		
	Preserved *in vitro* efficacy of the cocktail casirivimab/imdevimab against all variants			
VIR-7831 (GSK)	maintained activity (press release) binds to a highly conserved epitope of the spike protein			(?)

Wang P. et al, BioRxiv 2021, Greaney AJ. BioRxiv 2021, Baum et al. 2020; Weisblum et al. 2020; Tada et a., MedRxiv, 2020; Wibmer, Nat Med, 2021; Planas, Nature, 2021; Cele, Nature, 2021; Starr, MedRxiv, 2021; Planas, MedRxiv, 2021

Variants and vaccines:

In vitro neutralization data (pseudoviruses or full virus)

	B.1.1.7 Alpha	B.1.351 Beta	P.1 Gamma	B.1.617.2 Delta
Pfizer mRNA BTN162b2 **Moderna mRNA 1273**	**From no to minimal decreased neutralization** Impact of age Impact of number of doses	**Mininal to substantial decreased neutralization (esp. only 1 dose)** Effect linked to E484K	**Minimal to moderate decreased neutralization** Effect linked to E484K	**Modest to moderate decreased neutralization (esp. only 1 dose)** Impact of age Impact of number of doses
Astra-Zeneca	**Minimal to moderate decreased neutralization**	**Moderate to substantial decreased neutralization (esp. only 1 dose)**	**Minimal decreasead neutralization**	**Moderate to Substantial loss (esp. only 1 dose)**
Novavax	**From no to minimal decreased neutralization**	Not available	Not available	Not available

Gupta, Preprint, 2021; Tada et al., MedRxiv, 2021; Xie, Nat Med, 2021; Muik, BioRxiv, 2020; Shen, bioRxiv, 2020; Wang, bioRxiv, 2021; Collier, MedRxiv, 2020; Schwartz, EID, 2021; Planas, MedRxiv, 2021; Wall, Lancet, 2021

Variants and vaccine efficacy/effectiveness

	B.1.1.7 Alpha	B.1.351 Beta	P.1 Gamma	B.1.617.2 Delta	Previous circulating variants
mRNA (Pfizer/Moderna)	**51% effective 1d** **> 90% effective 2d**	**76% effective 2 doses** (infection) **100% (?) against severe disease**	No data	(symptomatic disease) **33% effective 1d** **88% effective 2d**	**> 90% efficacy after 2 doses**
Astra-Zeneca	**51% 1d - 73% 2d** (symptomatic disease) **26%** (infection)	**10%** (symptomatic disease)	No data	(symptomatic disease) **33% effective 1d** **60% effective 2d**	**75% - 84% efficacy (2d)**
Janssen (J&J) 1 dose (Ad26.COV2.S)		**57% efficacy** 100% against severe cases	No data	No data	**72% efficacy (USA)**
Novavax NVX-CoV2373 (protein-based)	**85.6% efficacy** N= 62 events, 32 B.1.1.7 Only one severe case	**51% efficacy** (95% CI: 19.9 – 80.1) N= 44 events **No severe case**	No data	No data	**89% efficacy (UK)**

Bernal, MedRxiv, 2021; Abu-Raddad, NEJM, 2021; Haas, Lancet, 2021; Emary, Lancet, 2021; Mahdi, NEJM, 2021; Shinde, NEJM, 2021

Vaccines against SARS-CoV-2 variants

- Decreased effectiveness of some vaccines against some SARS-CoV-2 variants against infection or symptomatic disease

  Retained protection against B.1.1.7 (alpha),

  but decreased against B.1.351 (beta) & B.1.617.2 (delta)

- **Protection depends on:**

  - vaccine type

  - number of vaccine doses

  - time elapsed since the last dose

  - characteristics of the patients: age, immunosuppression, …

- **Preserved protection against severe disease (?)**

Other variants to monitor…

- **All variants that include E484K**
  - P.2 (Zeta)
  - P.3 (Theta): 501Y+484K!
  - B.1.525 (Eta)
  - B.1.526 (Iota): part of the lineage carries E484K, the other S477N
  - B.1.1.7 + E484K (Alpha with the 484K: cluster detected in Switzerland)
  - A.VOI.V2
  - A.23.1 + E484K … and likely more to come
- **All variants that include E484Q**: Likely similar to the E484K mutation
  - B.1.617.1 (Kappa) and B.1.617.3 : L452R+E484Q
- **All variants that include L452R**: slightly more transmissible relative to N501, resistance to bamlanivimab
  - B.1.427/429: (Epsilon): L452R
  - B.1.617.1 (Kappa): L452R+E484Q
  - Paris/Mondor variant HMN.19B : N501Y+L452R
  - C.36.3
- And more to come (?)

Conclusion

- New emerging variants have become dominant
- Public health measures still effective despite higher transmissibility
- **Phenotypic difference** with increased severity (?)
- Some mutations have an **impact on immune therapeutics** (consider local epidemiology when initiating treatment)
- Decreased **vaccine** efficacy *in vitro* but **may still protect against severe disease**
  - Need for real-life clinical data & vaccine adaptation
- No impact yet on RT-PCR detection (multiplex)
- **Monitoring** is crucial

Thank you for you attention!

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