The COVID-19 pandemic: Where are we now? What have we learnt?

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https://media.nature.com/lw100/magazine-assets/d41586-021-02275-2/d41586-021-02275-2_19552098.gif

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Outline of Presentation

- Update on COVID-19 pandemic
- Variants
- Clinical picture
- Pathophysiology
- Treatment
- Vaccines
- 10 Lessons learnt

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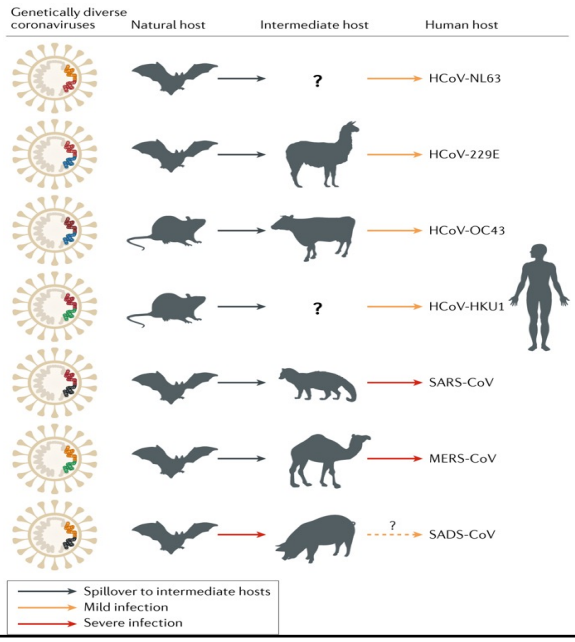
Update on the Pandemic

3

Introduction to Coronaviruses



Jie Cui, Fang Li & Zheng-Li Shi, Nat. Rev. Micro, 2019

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Timeline of COVID-19 Origination and Spread

- Illness with fever, cough, pneumonia reported in Wuhan, China, on New Year's Eve (December 31, 2019)[1]
- Initial exposure linked to seafood and animals in "wet markets"[1]
- Identified as a new coronavirus on January 7, 2020[1]
- January 30, 2020: WHO deemed it a "public health emergency of international concern"[1]
- March 11, 2020: WHO deems it a "pandemic"[1]
- Bat → pangolin? → humans → human to human[2]

1. WHO. Timeline: WHO's COVID-19 response. WHO. Report of the WHO-China Joint Mission on coronavirus disease 2019 (COVID-19). February 16-24, 2020. 2. Morens. Am J Trop Med Hyg. 2020;[Epub]. 3. https://commons.wikimedia.org/wiki/File:Manidae.jpg. 4. https://creativecommons.org/licenses/by-sa/4.0/legalcode.

Slide credit: clinicaloptions.com

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Coronavirus in South Africa

Latest update: 26 August 2021

Previous update: 25 August 2021

CONFIRMED CASES	DEATHS	TESTS
2,734,973	80,826	16,228,941
⬆ 12,771	⬆ 357	+ 66,116
ACTIVE CASES	RECOVERED	
169,039	2,485,108	
	90.9% RECOVERED	

Active cases are confirmed cases minus recoveries and deaths

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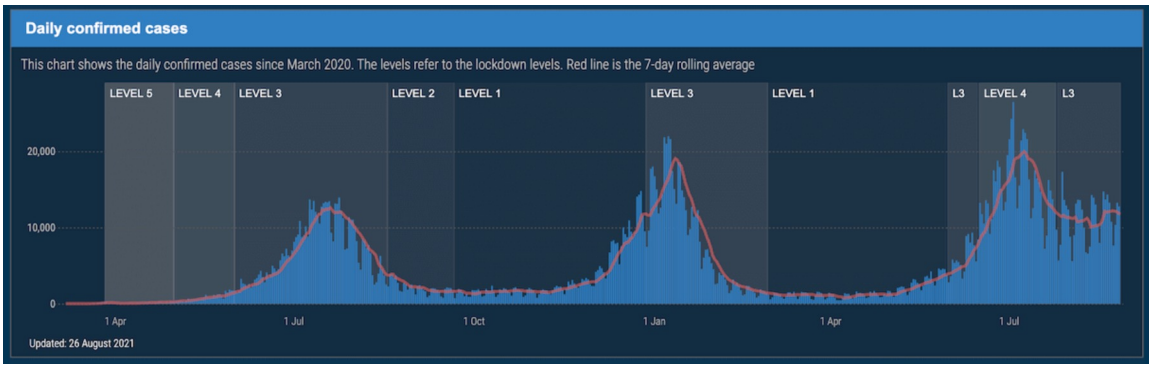

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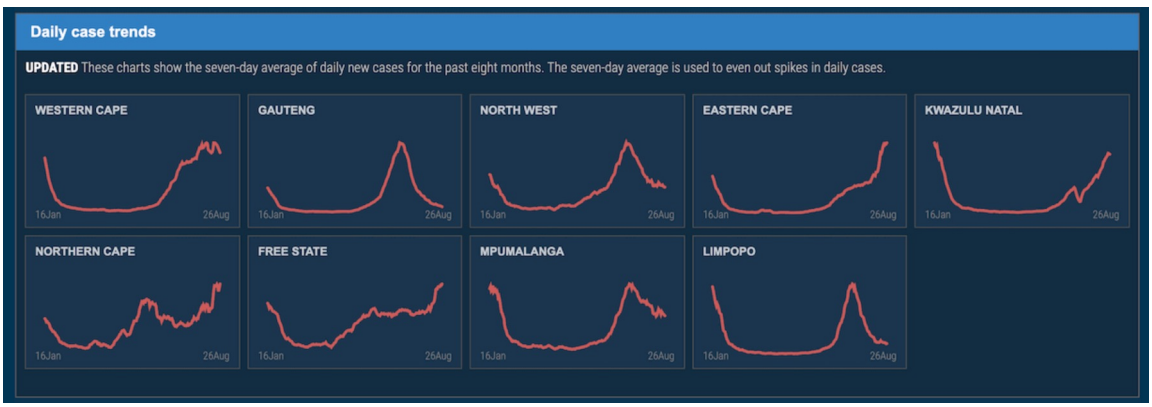
Daily case trends
UPDATED These charts show the seven-day average of daily new cases for the past eight months. The seven-day average is used to even out spikes in daily cases.
WESTERN CAPE
GAUTENG
NORTH WEST
EASTERN CAPE
KWAZULU NATAL
NORTHERN CAPE
FREE STATE
MPUMALANGA
LIMPOPO
16Jan
26Aug

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Total Deaths
Total deaths
Case Fatality Rate (CFR)
80,826
120,000
100,000
80,000
60,000
40,000
20,000
0
10%
9%
8%
7%
6%
5%
4%
3%
2%
1%
0%
01/04
01/07
01/10
01/01
01/04
01/07
Updated: 26 August 2021

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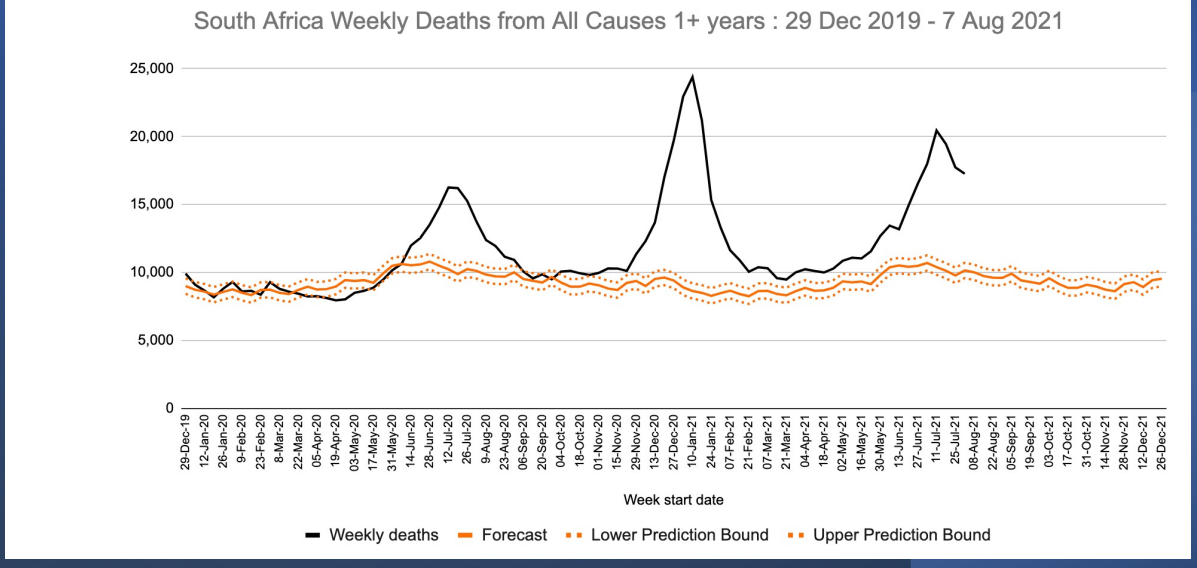
Report on Weekly Deaths in South Africa



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BUSINESS INSIDER | TRENDING

SA estimates 220,000 excess deaths during the pandemic – ranked among the world's worst

Business Insider SA
Aug 11, 2021, 12:54 PM

- >50% in the past seven months
- 85% - 95% excess natural deaths attributable to COVID-19
- Remainder a result of collateral causes
- Excess deaths: 374/100,000

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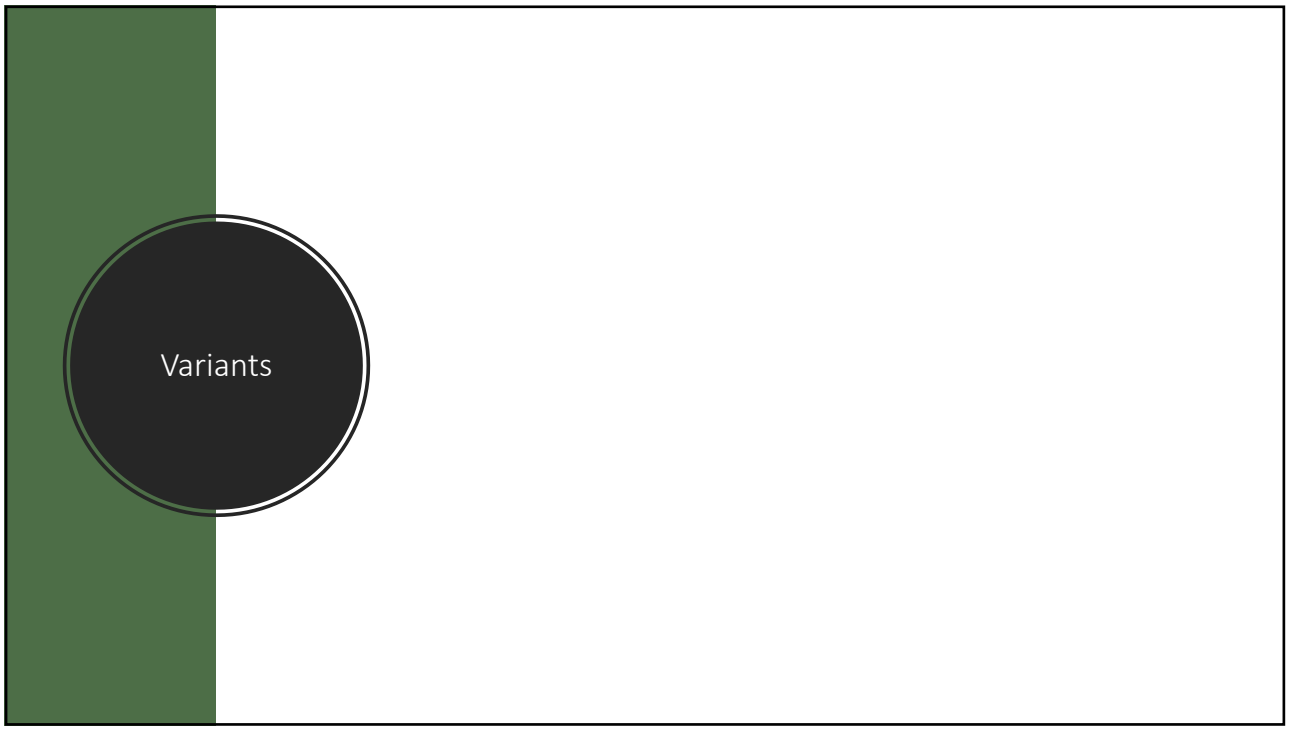

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Variants of Concern (VOC)

- Increase in transmissibility or detrimental change in COVID-19 epidemiology; OR
- Increase in virulence or change in clinical disease presentation; OR
- Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.

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Currently designated Variants of Concern:

WHO label	Pango lineage*	GISAID clade	Nextstrain clade	Additional amino acid changes monitored°	Earliest documented samples	Date of designation
Alpha	B.1.1.7 #	GRY	20I (V1)	+S:484K +S:452R	United Kingdom, Sep-2020	18-Dec-2020
Beta	B.1.351	GH/501Y.V2	20H (V2)	+S:L18F	South Africa, May-2020	18-Dec-2020
Gamma	P.1	GR/501Y.V3	20J (V3)	+S:681H	Brazil, Nov-2020	11-Jan-2021
Delta	B.1.617.2§	G/478K.V1	21A	+S:417N	India, Oct-2020	VOI: 4-Apr-2021 VOC: 11-May-2021

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Variants of Interest (VOI)

- Genetic changes predicted to affect virus characteristics
  - transmissibility, disease severity, immune escape, diagnostic or therapeutic escape; AND
- Identified to cause significant community transmission or multiple COVID-19 clusters, in multiple countries with increasing relative prevalence alongside increasing number of cases over time.

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Currently designated Variants of Interest:

WHO label	Pango lineage*	GISAID clade	Nextstrain clade	Earliest documented samples	Date of designation
Eta	B.1.525	G/484K.V3	21D	Multiple countries, Dec-2020	17-Mar-2021
Iota	B.1.526	GH/253G.V1	21F	United States of America, Nov-2020	24-Mar-2021
Kappa	B.1.617.1	G/452R.V3	21B	India, Oct-2020	4-Apr-2021
Lambda	C.37	GR/452Q.V1	21G	Peru, Dec-2020	14-Jun-2021

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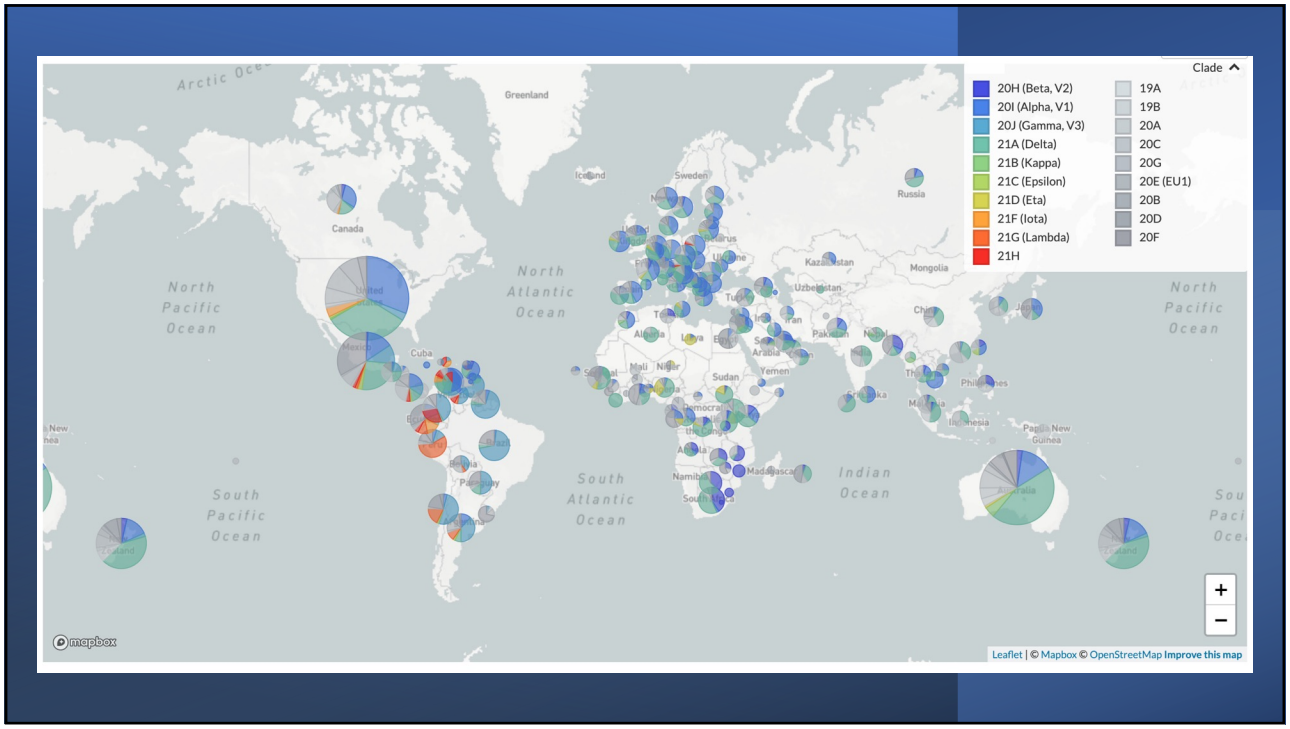

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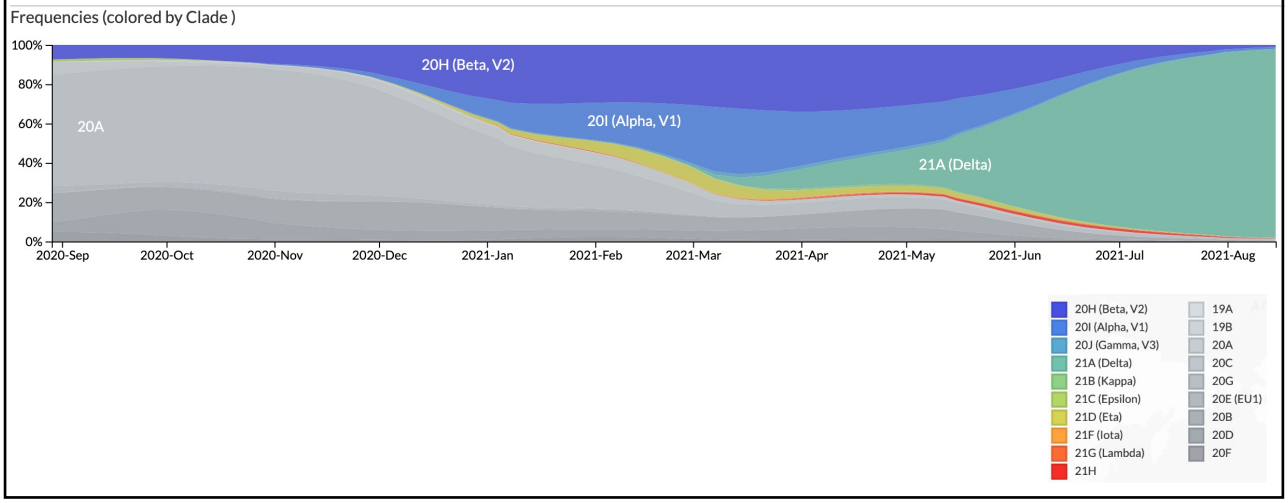
Variants in Africa



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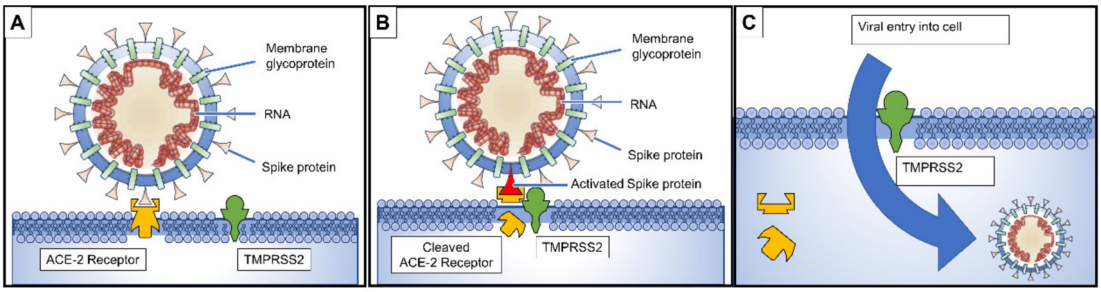
SARS-CoV-2 Binding & Entry of Cells



SARS-CoV-2 spike protein must be cut twice by host proteins

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Mutations Over Time

Alpha variant: 10 changes in the spike-protein sequence → RBD being more likely to stay in the 'up' position → easier for virus to enter into cells

Delta variant: multiple mutations in the S1 subunit, including 3 in RBD → improves RBD's ability to bind to ACE2 and evade immune system

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nature

NEWS | 20 August 2021

The mutation that helps Delta spread like wildfire

- Furin cleavage site: host enzymes can make the first cut as newly formed viral particles emerge from an infected cell
- These pre-activated viral particles can then infect cells more efficiently
- Spike proteins with P681R fuse with plasma membranes ±3 x faster
- In cultured human-airway epithelial cells, Delta rapidly outcompetes Alpha
- It takes more than one mutation to make a difference

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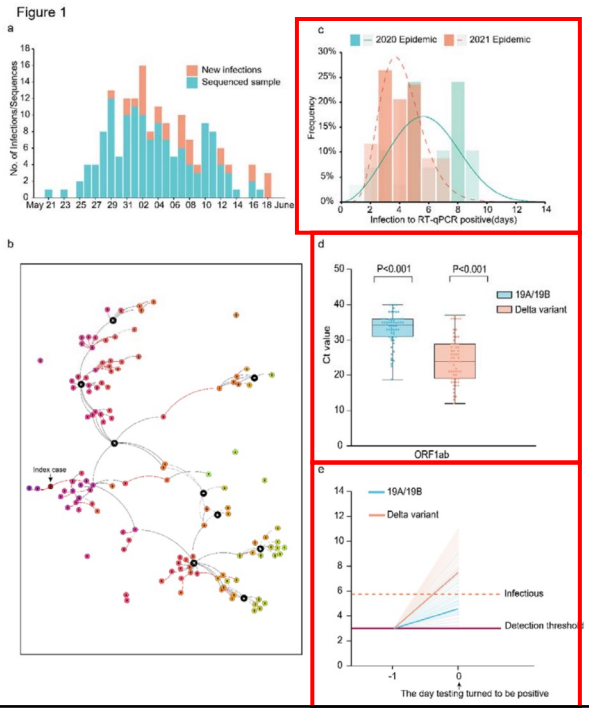
medRxiv
THE PREPRINT SERVER FOR HEALTH SCIENCES

Cold Spring Harbor Laboratory BMJ Yale

Viral infection and transmission in a large, well-traced outbreak caused by the SARS-CoV-2 Delta variant

- Delta: virus detectable in people 4 days after exposure (original strain: 6 days)
- VL up to 1,260 times higher than in the original strain



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Does COVID have a Lower Impact in Africa?

Younger population?

- Median age
  - North/South America, Europe & Asia: 32 - 42.5 years
  - Africa: 18 years

Lack of long-term care facilities?

Potential cross-protection from local circulating coronaviruses?

Limitations of SARS-CoV-2 testing?

Effective government public health response – early lock-down?

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Clinical Picture

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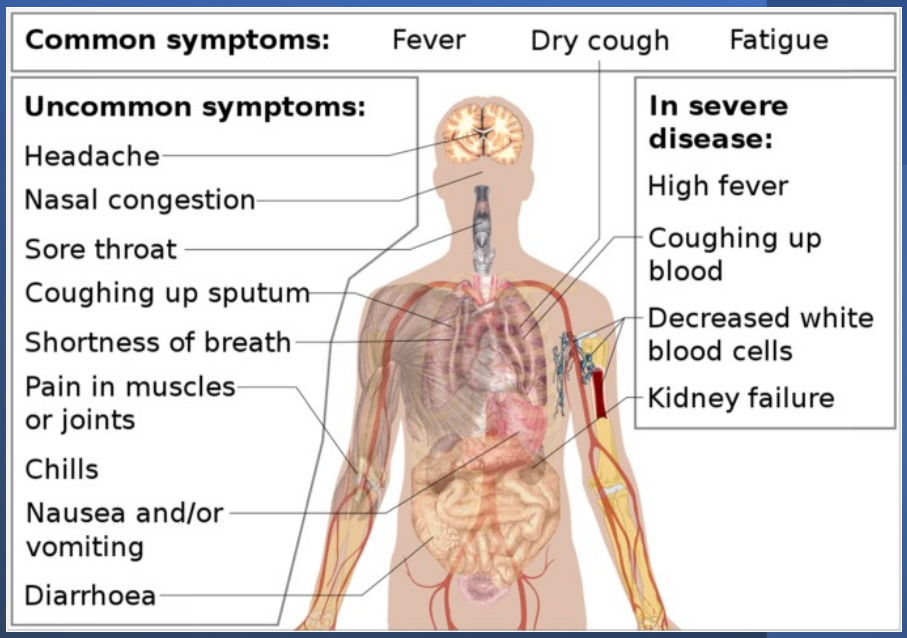

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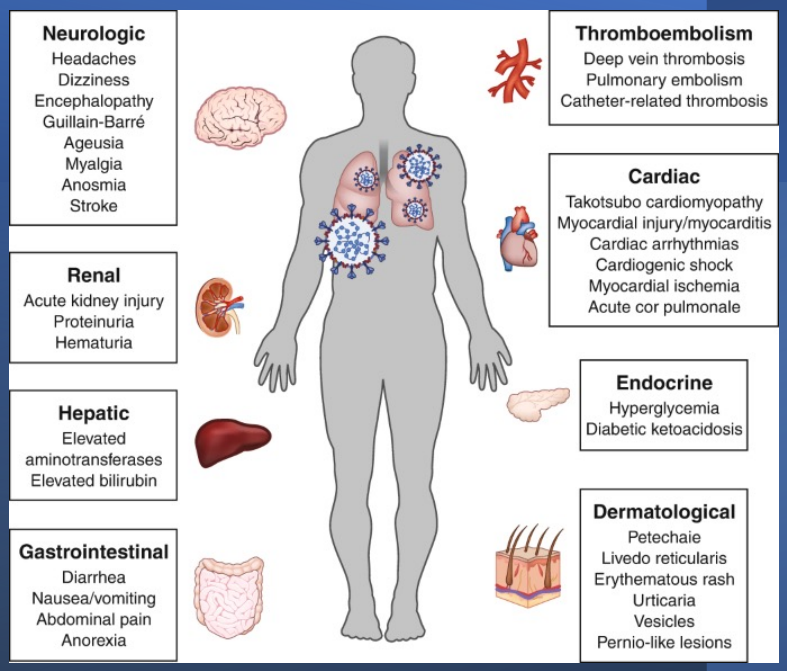

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COVID-19 Clinical Classification

Mild	Moderate	Severe
Oxygen sats > 94%	Oxygen sats < 94%	ARDS
Resp rate < 25bpm	Resp rate > 25bpm	Septic shock
Pulse rate < 120bpm	Pulse rate > 120 bpm	Multiple organ failure
Temp 36 – 39 C	Temp < 36 or > 39 C	Needing critical care
Normal mental status	Confused	

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1. Co-morbidities that are supported by meta-analysis/systematic review: Defined as having a significant association with risk of severe COVID-19 illness in at least one meta-analysis or systematic review.
    - Cancer
    - Cerebrovascular disease
    - Chronic kidney disease*
    - COPD (chronic obstructive pulmonary disease)
    - Diabetes mellitus, type 1 and type 2*
    - Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)
    - Obesity (BMI ≥30 kg/m2)*
    - Pregnancy and recent pregnancy
    - Smoking, current and former

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2. Co-morbidities that are supported by mostly observational (e.g., cohort, case-control, or cross-sectional) studies: These might include systematic review or meta-analysis that represents one condition in a larger group of conditions (for example, kidney transplant under the category of solid organ or blood stem cell transplantation).
    - Children with certain underlying conditions
    - Down syndrome
    - HIV (human immunodeficiency virus)
    - Neurologic conditions, including dementia
    - Overweight (BMI ≥25 kg/m2, but <30 kg/m2)
    - Other lung disease (including interstitial lung disease, pulmonary fibrosis, pulmonary hypertension)*
    - Sickle cell disease
    - Solid organ or blood stem cell transplantation
    - Substance use disorders
    - Use of corticosteroids or other immunosuppressive medications

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4. Co-morbidities that are supported by mixed evidence: Defined as having an association in at least one meta-analysis or systematic review and additional studies or reviews that reached different conclusions about risk associated with a condition.
   - Asthma
   - Hypertension*
   - Immune deficiencies
   - Liver disease

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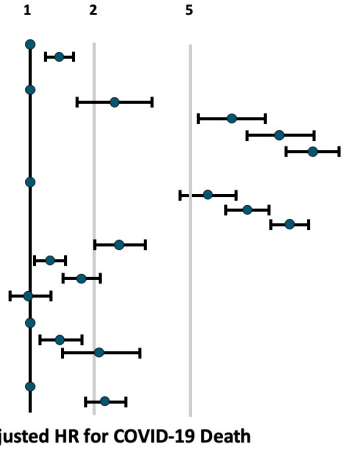
COVID-19 and HIV: Routine Public Sector Data in Western Cape, South Africa

- Evaluated factors among all adult public sector patients (N = 3,460,932)

Patient Characteristics	Adjusted HR	95% CI
Sex		
Female	1.00	
Male	1.45	1.23-1.70
Age		
20-39 yrs	1.00	
40-49 yrs	2.83*	1.92-4.15
50-59 yrs	7.78*	5.51-10.98
60-69 yrs	11.54*	8.11-16.42
≥ 70 yrs	16.79*	11.69-24.11
Noncommunicable diseases		
None	1.00	
Diabetes well controlled (A1C < 7%)	5.37*	3.96-7.27
Diabetes poorly controlled (A1C 7-8.9%)	8.53*	6.60-11.02
Diabetes uncontrolled (A1C ≥ 9%)	12.07*	9.70-15.02
Diabetes, no measure of control	2.91*	2.18-3.89
Hypertension	1.31†	1.09-1.57
Chronic kidney disease	1.86*	1.46-2.33
Chronic pulmonary disease	0.93	0.73-1.17
Tuberculosis		
Never tuberculosis	1.00	
Previous tuberculosis	1.51‡	1.18-1.93
Current tuberculosis	2.70*	1.81-4.04
HIV		
Negative	1.00	
Positive	2.14	1.70-2.70*

*P < .001. †P = .004. ‡P = .001.



22,308 total persons diagnosed with COVID-19; 3978 PWH diagnosed with COVID-19

Standard mortality ratio for COVID-19 death with vs without HIV: 2.39 (95% CI: 1.96-2.86)

Boulle. CID. 2020;[Epub].

Slide credit: clinicaloptions.com

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Commonly Associated with Mortality

- Age
- Comorbidity
- Late presentation
- Acute kidney injury

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Duration of Isolation & Precautions

- Adults with mild to moderate COVID-19: infectious <10 days after symptom onset
- Severe to critical illness or severe immunocompromise: infectious <20 days after symptom onset
- Can shed replication-competent virus >20 days due to severe immunocompromise
- Recovered adults can continue to shed detectable but non-infectious RNA for up to 3 months after illness
- Rely on a symptom-based rather than test-based strategy for ending isolation of most patients

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Severely immunocompromised definition

The studies used to inform this guidance did not clearly define "severely immunocompromised." For the purposes of this guidance, CDC used the following definition:

- Some conditions, such as being on chemotherapy for cancer, hematologic malignancies, being within one year out from receiving a hematopoietic stem cell or solid organ transplant, untreated HIV infection with CD4 T lymphocyte count < 200, combined primary immunodeficiency disorder, and taking immunosuppressive medications (e.g., drugs to suppress rejection of transplanted organs or to treat rheumatologic conditions such as mycophenolate and rituximab, receipt of prednisone >20mg/day for more than 14 days), may cause a higher degree of immunocompromise and inform decisions regarding the duration of Transmission-Based Precautions.

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Symptom-Based Strategy for Discontinuing Transmission-Based Precautions

Patients with mild to moderate illness who are *not* severely immunocompromised:

- At least 10 days have passed *since symptoms first appeared* **and**
- At least 24 hours have passed *since last* fever without the use of fever-reducing medications **and**
- Symptoms (e.g., cough, shortness of breath) have improved

Patients who were asymptomatic throughout their infection and are *not* severely immunocompromised:

- At least 10 days have passed since the date of their first positive viral diagnostic test.

Patients with severe to critical illness or who are severely immunocompromised:

- At least 10 days and up to 20 days have passed *since symptoms first appeared* **and**
- At least 24 hours have passed *since last* fever without the use of fever-reducing medications **and**
- Symptoms (e.g., cough, shortness of breath) have improved
- Consider consultation with infection control experts

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Post-COVID Conditions

- Dyspnea or increased respiratory effort
- Fatigue
- Post-exertional malaise and/or poor endurance
- "Brain fog," or cognitive impairment
- Cough
- Chest pain
- Headache
- Palpitations and/or tachycardia
- Arthralgia
- Myalgia
- Paresthesia
- Abdominal pain
- Diarrhea
- Insomnia and other sleep difficulties
- Fever
- Lightheadedness
- Impaired daily function and mobility
- Pain
- Rash (e.g., urticaria)
- Mood changes
- Anosmia or dysgeusia
- Menstrual cycle irregularities

* Post-exertional malaise (PEM) is the worsening of symptoms following even minor physical or mental exertion, with symptoms typically worsening 12 to 48 hours after activity and lasting for days or even weeks.

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Pathophysiology

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Underlying Pathology

- COVID-19 is best viewed as an inflammatory endotheliïlitis, with direct viral infection of pneumocytes, endothelial and epithelial cells producing inflammatory cytokines and immune-mediated damage to the vasculature and surrounding tissue

Chen LYC, Hoiland RL, Stukas S, et al. Confronting the controversy: Interleukin-6 and the COVID-19 cytokine storm syndrome. Eur Respir J 2020; in press

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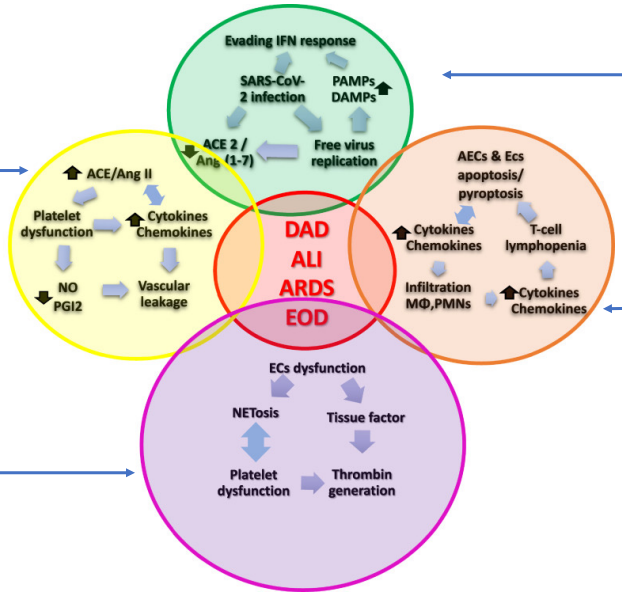
"The Four Horsemen of a Viral Apocalypse"

Result: hyperinflammatory and hypercoagulable state producing acute immune-mediated lung injury and eventually, adult respiratory distress syndrome

Coagulation loop: hypercoagulable state caused by the interplay between inflammation and coagulation



Viral loop: evading host's innate response → uncontrolled viral replication → hyperactive immune response

Inflammatory loop: exuberant inflammatory response, downregulation of ACE2 → excessive production of Angiotensin Ⅱ

https://els-jbs-prod-cdn.jbs.elsevierhealth.com/cms/asset/fb3c2f7a-c24e-4716-b241-16869d5ca9b7/gr1.jpg

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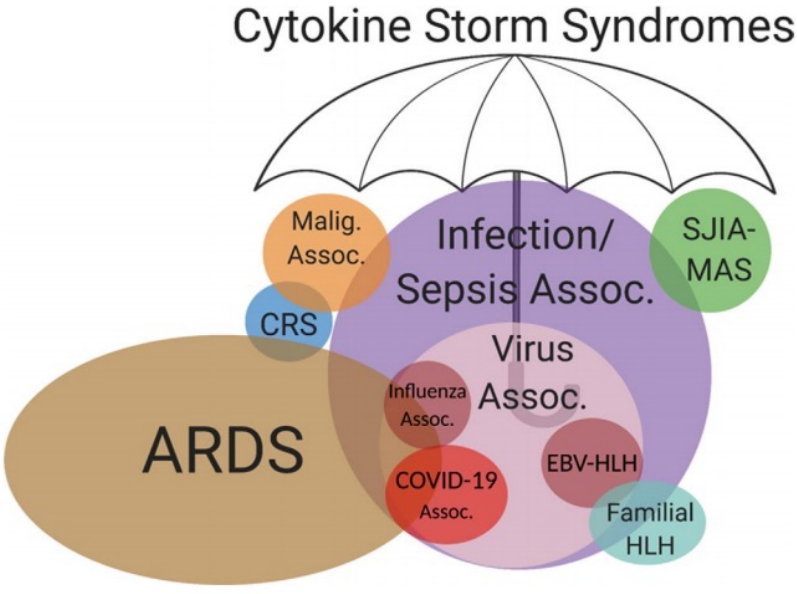

- Arthritis & Rheumatology Vol. 72, No. 7, July 2020, pp 1059–1063 DOI 10.1002/art.41285 © 2020, American College of Rheumatology

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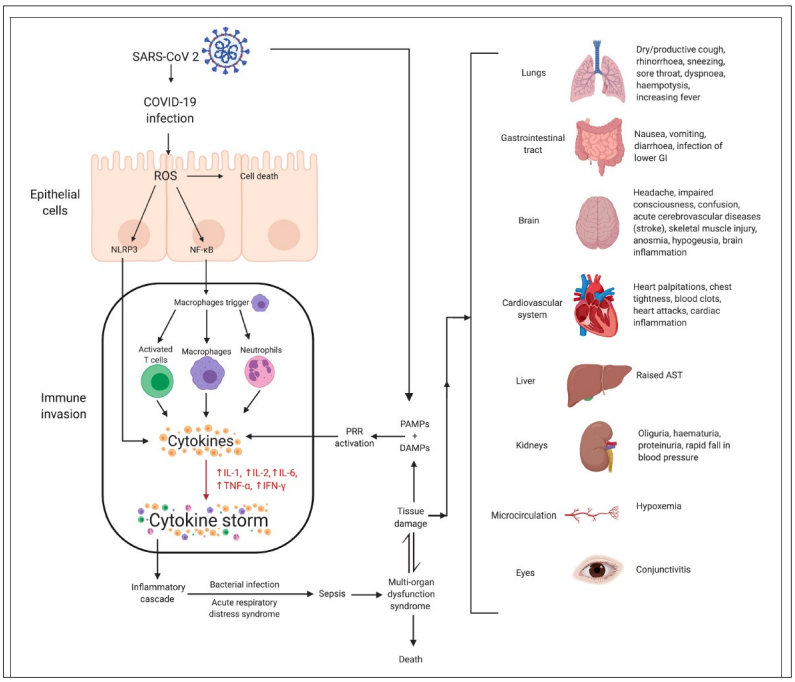

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Product Line	Parameter	Lab abnormalities
Hematology	Neutrophile count	↑
	Lymphocyte count	↓
	Erythrocyte sedimentation rate	↑
Clinical Chemistry	C-reactive protein	↑
	Albumin	↓ *
	Liver enzymes (GOT (AST), GPT (ALT), GGT, ALP, Bilirubin)	↑ *
	Lactate dehydrogenase (LDH)	↑ *
	Kidney parameters (Creatinine, Urea/BUN)	↑ *
	Lactate	↑ *
Cardiac Marker	CK-MB	↑ *
	Myoglobin	↑ *
	Troponin	↑ *
Coagulation	D-dimer	↑ *
	Prothrombin time (sec)	↑ *

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Blood Picture

- Exaggerated release of acute phase reactants
  - CRP, serum amyloid A & ferritin
- CD4+ & CD8+ T-cells, NK & Treg cells much lower than expected
  - Transcriptomic analysis: upregulation of genes involved in apoptosis / P53 pathways
- Highly activated (HLA-DR+ & CD38+)
  - Others show functionally exhausted cells, incapable of generating IFN/ TNF
- CD8+ T cells enriched with perforin & granulysin
  - 31.6% perforin+, 64.2% granulysin+ & 30.5% granulysin & perforin+
  - adds to the reported lung injury
- ⇧ neutrophil/lymphocyte ratio (NLR) in severe cases

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Pregnant Women & Children

Children & pregnant women generally have a mild disease

Immune response skewed toward a Th2 profile with specific generation of related cytokines like IL-4 and IL-10

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Pregnant Women

- Some studies show that women in the 2nd half of pregnancy have increased risk of complications
  - Severe pneumonia
  - Hospitalisation, invasive mechanical ventilation, ICU admission
  - Death
- Increased rates of preterm and stillbirths

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Paediatric Considerations

- Clinical symptoms similar to adults
- Disease usually milder than adults
- Common symptoms
  - Cough or fever
  - Gastrointestinal or other symptoms
- Increased risk of severe illness
  - Certain underlying medical conditions
  - Infants (<12 months of age)

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Multisystem Inflammatory Syndrome in Children (MIS-C)

- Present with persistent fever, abdominal pain, vomiting, diarrhoea, skin rash, mucocutaneous lesions and, in severe cases, hypotension & shock
- Elevated laboratory markers of inflammation
  - CRP, ferritin
- Markers of damage to the heart
  - Troponin; BNP or proBNP
- Some have myocarditis, cardiac dysfunction & acute kidney injury
- MIS-C may begin weeks after a child was infected with SARS-CoV-2

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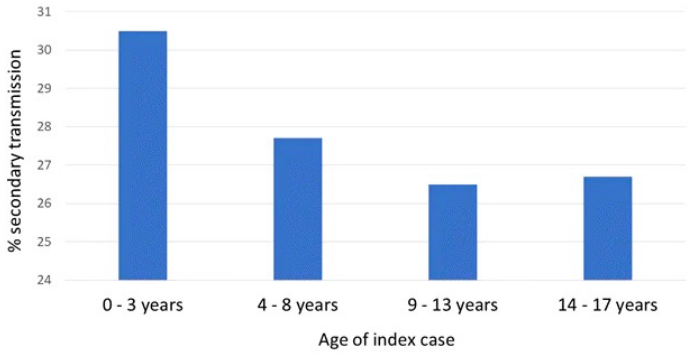
These Kids Are Most Likely to Transmit COVID to Family



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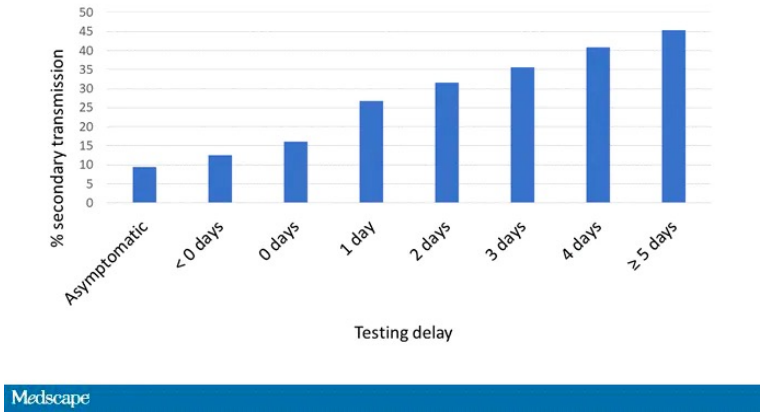
These Kids Are Most Likely to Transmit COVID to Family



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