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Morning Brief : Scientific Review

5 June 2020

The purpose of the Morning Brief is to **summarize** and present key information, research articles and other relevant publications pertaining to critical care and COVID-19. We aim to prioritise information, articles and publications released in the preceding 24-48hours.

Stellenbosch University Research Response Team

STELLENBOSCH UNIVERSITY PULMONOLOGY

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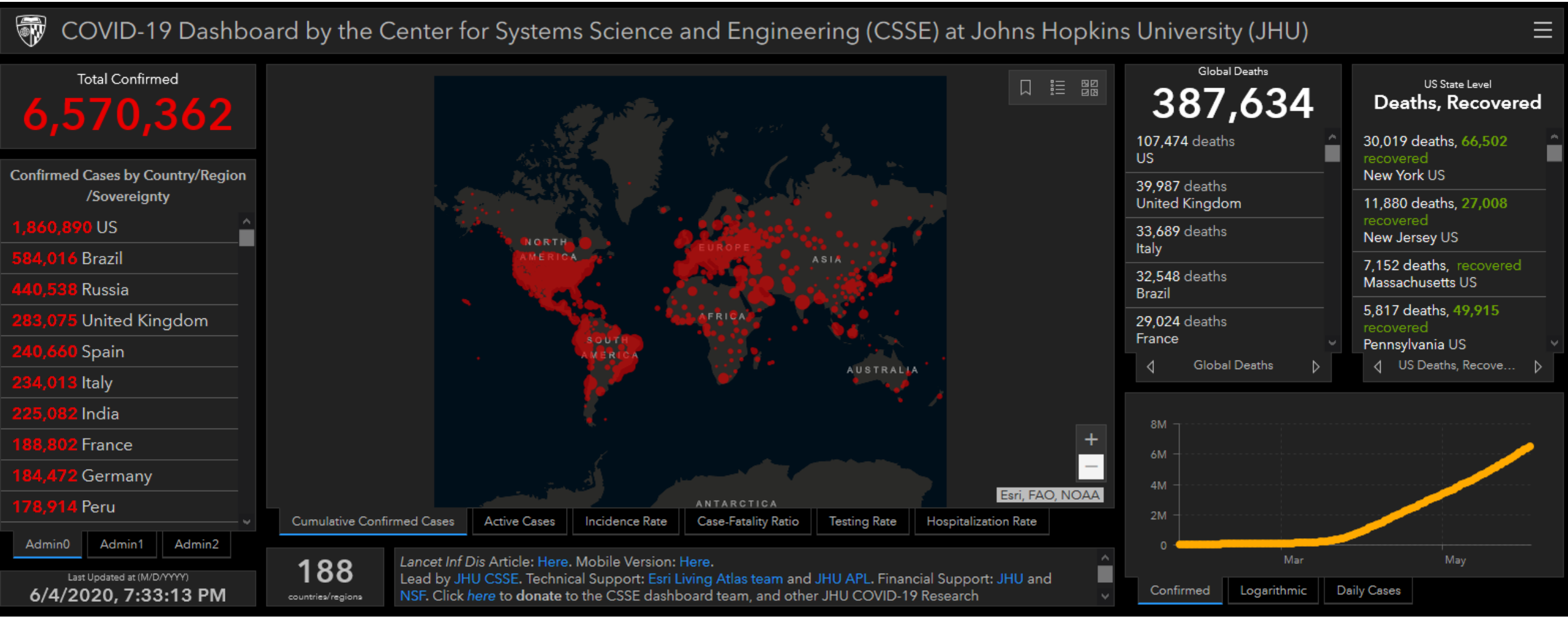
Content of the brief

- Global Statistics
- South African Statistics
- Topic: Human Challenge Studies

Global Statistics



Source: https://coronavirus.jhu.edu/map.html

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South African Statistics

Source: https://sacoronavirus.co.za

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Articles of Interest

World Health Organization

Key criteria for the ethical acceptability of COVID-19 human challenge studies

6 May 2020

"This document aims to provide guidance to scientists, research ethics committees, funders, policy-makers, and regulators in deliberations regarding SARS-CoV-2 challenge studies by outlining key criteria that would need to be satisfied in order for such studies to be ethically acceptable."

Human challenge studies

Deliberate infection of healthy volunteers

Benefits

- Vaccine studies – shorten time to vaccine candidates, rule out non-effective vaccines before larger studies
- Study processes of infection and immunity from their inception – immunity, risk of transmission, evaluate tests

Recent examples

Vaccine studies for typhoid, cholera, immune correlates of protection studies for influenza

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World Health Organization

Key criteria for the ethical acceptability of COVID-19 human challenge studies

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Ethics

Historic examples of unethical deliberate infection – Hepatitis, Syphilis

Must be carefully designed and conducted in order to minimize harm to volunteers and preserve public trust in research.

Substantial public health benefit

Risk

18–30 years Covid-19 hospitalization rates 1% & mortality rates around 0.03%

Higher risk than other diseases, due to many unknowns

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World Health Organization

Key criteria for the ethical acceptability of COVID-19 human challenge studies

6 May 2020

Scientific and ethical assessments		
Criterion 1	Scientific justification	SARS-CoV-2 challenge studies must have strong scientific justification
Criterion 2	Assessment of risks and potential benefits	It must be reasonable to expect that the potential benefits of SARS-CoV-2 challenge studies outweigh risks
Consultation and coordination		
Criterion 3	Consultation and engagement	SARS-CoV-2 challenge research programmes should be informed by consultation and engagement with the public as well as relevant experts and policy-makers
Criterion 4	Coordination	SARS-CoV-2 challenge study research programmes should involve close coordination between researchers, funders, policy-makers and regulators
Selection criteria		
Criterion 5	Site selection	SARS-CoV-2 challenge studies should be situated where the research can be conducted to the highest scientific, clinical and ethical standards
Criterion 6	Participant selection	SARS-CoV-2 challenge study researchers should ensure that participant selection criteria limit and minimize risk
Review and consent		
Criterion 7	Expert review	SARS-CoV-2 challenge studies should be reviewed by a specialized independent committee
Criterion 8	Informed consent	SARS-CoV-2 challenge studies must involve rigorous informed consent

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OPINION

Is it ethical to give someone coronavirus to create a vaccine? Yes

The political spin promising a quick vaccine for COVID-19 is false. The average time to make a vaccine is 20 years.

By Arthur Caplan Updated May 14, 2020, 10:01 a.m.

"And the benefit would be many months, if not years, saved to study different candidates. The hurdle is obvious — **is it ethical to give someone a deadly disease?**

In a pandemic, yes. The number of people who will die from the novel coronavirus while the hunt for a vaccine plods on is exponential. And if the virus ebbs and returns, it will take even longer to learn anything. The stakes are so high that risking volunteers makes sound moral sense."

Caplan, Arthur, The Boston Globe, 14 May 2020

Subject selection

Low risk volunteers

20 – 29yr : 0.03% death rate, 1.1% admission rate

Antiviral / antibody treatment on hand to treat unexpectedly severe cases

Consent

No coercion

Demonstrate understanding of risks, unknowns, no benefit to them

Risk

Society accepts the risk to healthcare workers exposed to Covid-19, live donors of kidneys / liver lobes

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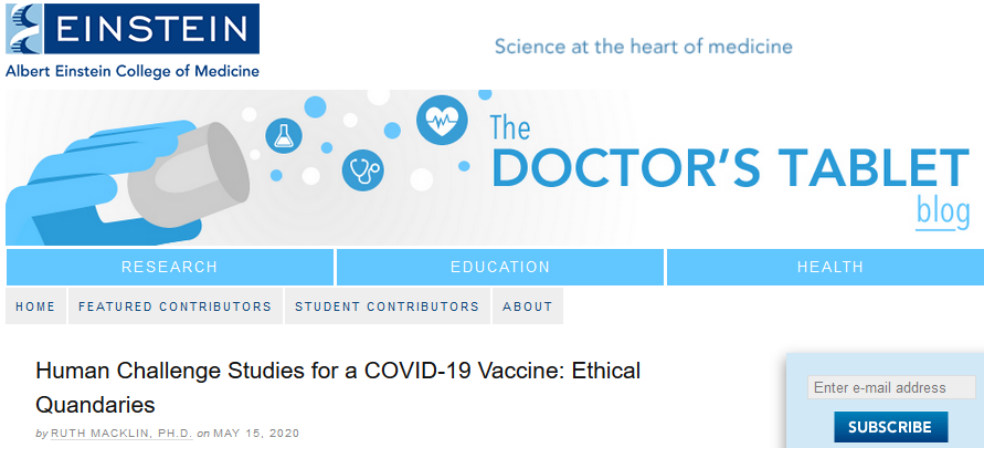

"The situation has all the earmarks of a quintessential ethical dilemma: Is it permissible to intentionally inflict serious harm on a few for a possible benefit to many? With several vaccines already in the pipeline, I conclude that a rush to begin human challenge studies for a grave disease lacking an effective treatment is ethically unjustifiable."

Public-health imperative

- save the most lives
- lower costs
- fewer research subjects

VS

Minimise risks to research participants

- Minimise risks
- Do not unnecessarily expose to risk
- Accepted treatment available

Currently no treatment available for Covid-19

WHO document of criteria does not include the requirement of an available treatment

Concerns with informed consent

- **"prevention misconception" – wrongly thinking that the vaccine under study will necessarily be effective**
- **Payment – vulnerable populations**

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Macklin, R. The Doctor's Tablet, May 15, 2020, http://blogs.einstein.yu.edu/human-challenge-studies-for-a-covid-19-vaccine-ethical-quandaries/

Review of relevant literature and qualitative interviews involving 45 scientists and ethicists with relevant expertise

99% of the >40 000 human volunteers who have participated in HCS worldwide since World War II have been in **high income countries**

Arguably there is an ethical imperative to conduct HCS in LMICs where infection under study is endemic

- Potential benefit to participants
- Burden and benefit of research in the same population
- Building research capacity in LMICs

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Jamrozik E, Selgelid MJ. J Med Ethics .doi:10.1136/medethics-2019-106001

Issues for particular consideration in HCS in LMICs:

- **Generalisability to intended population and context**
  - results beneficial to LMIC populations
  - Use of attenuated vs wild-type strains – ethical trade-offs between

  risks and maximally informative results

- **Benefit sharing with participants and/or local population**
  - Definition of “benefit”

- **Risks / burdens**
  - No reported deaths in recent HCS, lasting harms extremely rare
  - Minimise risks by patient selection, strain selection, early diagnosis and treatment, inpatient care, follow-up of long term outcomes
  - Trade-offs between minimising risk and other burdens – restriction of freedom, time etc.
  - Trade-offs between uncertainty and potential benefits
  - No agreed-upon upper limit of risk – analogous to socially beneficial actions like fire-fighting or live kidney donation
  - Public reaction to severe harm may prevent future research
  - Community engagement important in setting limits of risks in context
  - No consensus on limits of acceptable risk of long term harm

LMIC specific risks / burdens

- Fragile health infrastructure – delays in treatment
- Partial immunity – less severe disease
- Endemic setting inhabitants already at risk of infection – but this risk itself reflects injustices
- Unique burdens of research – eg. beliefs about blood

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Issues for particular consideration in HCS in LMICs:

- Right to withdraw / absconding
  - Risks to untreated and unmonitored participant, risk of transmission to others

- Risks to third parties
  - Transmission, unborn children
  - ? informed consent from at-risk third parties / local communities

- Participant selection
  - "vulnerable" populations (eg. poverty) typically excluded from research
  - Privileged populations benefiting from research in underprivileged populations
  - Excluding vulnerable populations from research often excludes them from benefits of results
  - Education level / consent - several problems with excluding uneducated
  - Children – generalisability, informed consent, public perceptions

- Payment
  Reimbursement / compensation / incentive / undue inducement
  Attitudes vary across cultures
  Volunteers vs "employees" / over –volunteering

- Governance – standard procedures vs special committees

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This summary was prepared by Prof Keymanthri Moodley as part of the daily brief to the TBH ICU team.