Executive Summary: COVID-19
22ND April 2020

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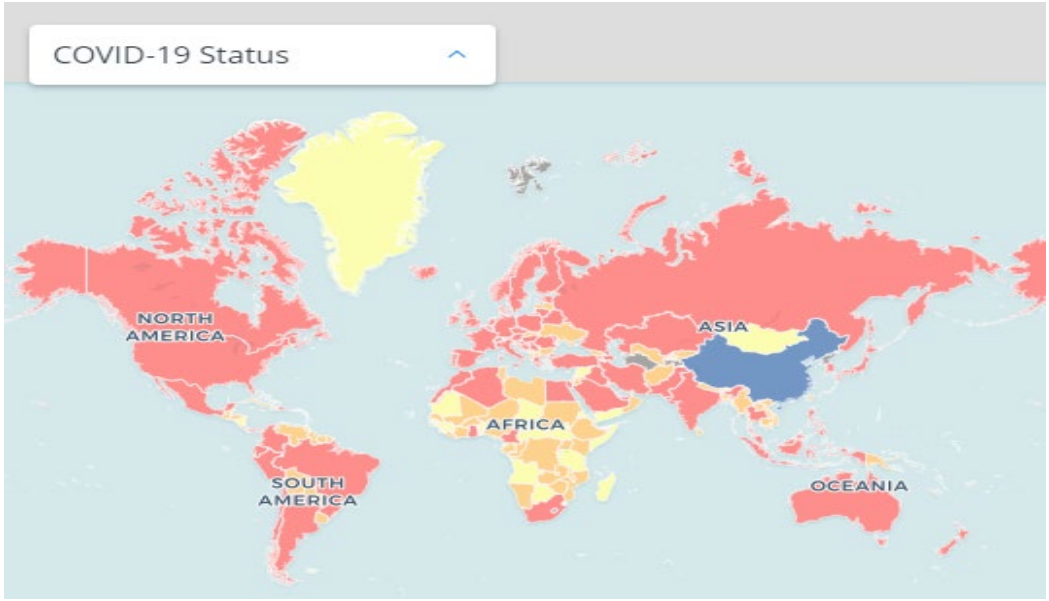
The Executive Summary is produced weekly and contains in-depth analysis.
International SOS publishes a COVID-19 Daily Case Summary.

INTRODUCTION

In this week's edition of the International SOS COVID-19 Executive Summary we explore:

1. International SOS add "Waning" category to COVID-19 status map
2. New Zealand to move from Level 4 to Level 3 interventions
3. Sweden: some herd immunity by May?
4. Focus on Indonesia
5. Serosurveys – a look at the Santa Clara study
6. World roundup
7. The Singapore Experience: moving away from lockdowns may not be easy
8. Recovering from the coronavirus may not make you immune
9. A Virologist's Perspective: Professor John Oxford

INTERNATIONAL SOS ADDS "WANING" CATEGORY TO COVID-19 STATUS MAP



LEGEND

IMPORTED CASES ONLY

LOCAL TRANSMISSION

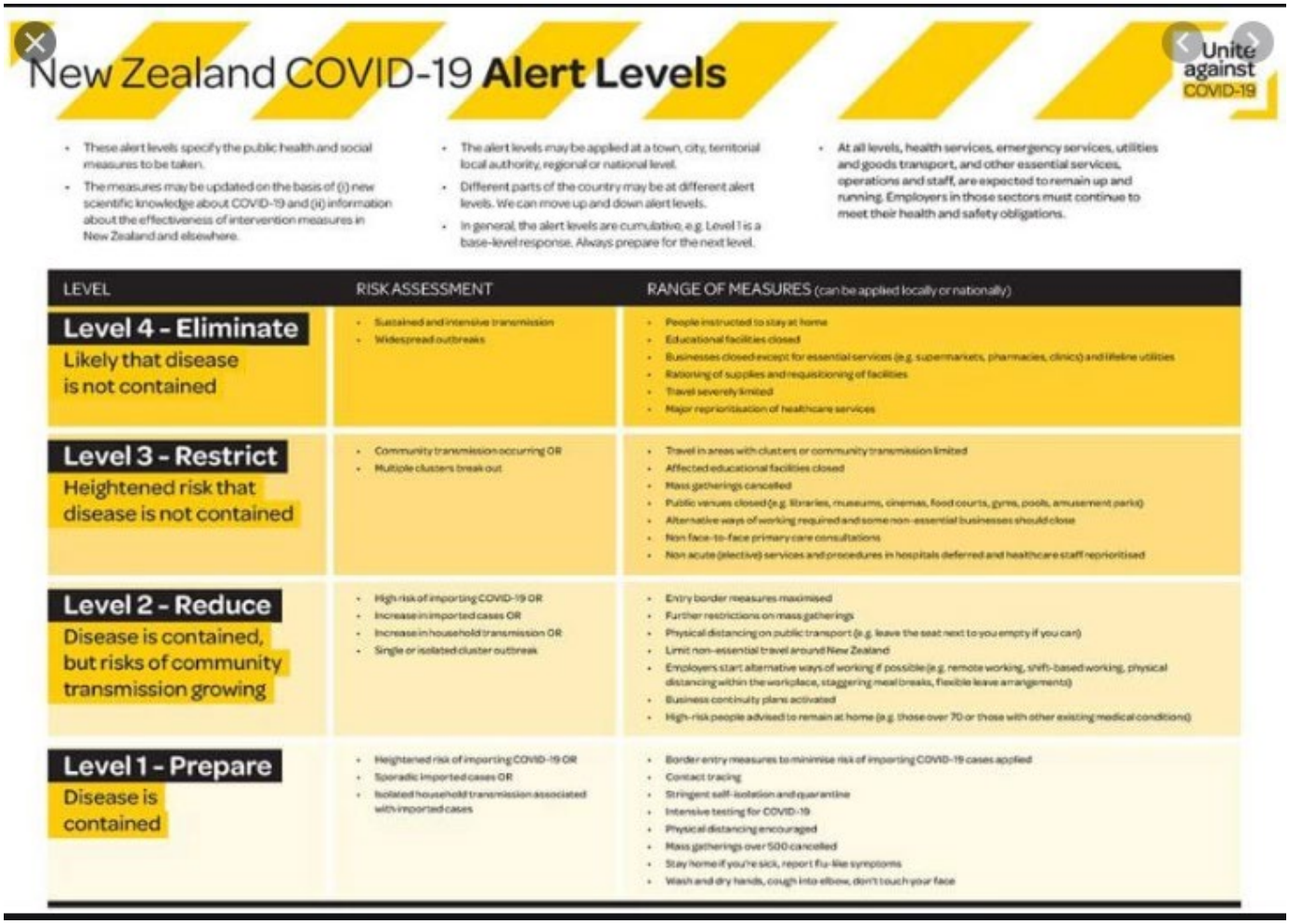
OUTBREAK (>= 1,000 cases, locally acquired in many areas, cases exported)

WANING (<100 cases per day, > 2 weeks of declining numbers, sporadic cases or clusters, restrictions easing)

The only country categorized as WANING so far is Mainland China.

NEW ZEALAND TO MOVE FROM LEVEL 4 TO LEVEL 3

New Zealand has a well-articulated four-level plan for COVID-19 interventions.



Timeline: Level 3: introduced 23 March / Level 4: introduced 25 March

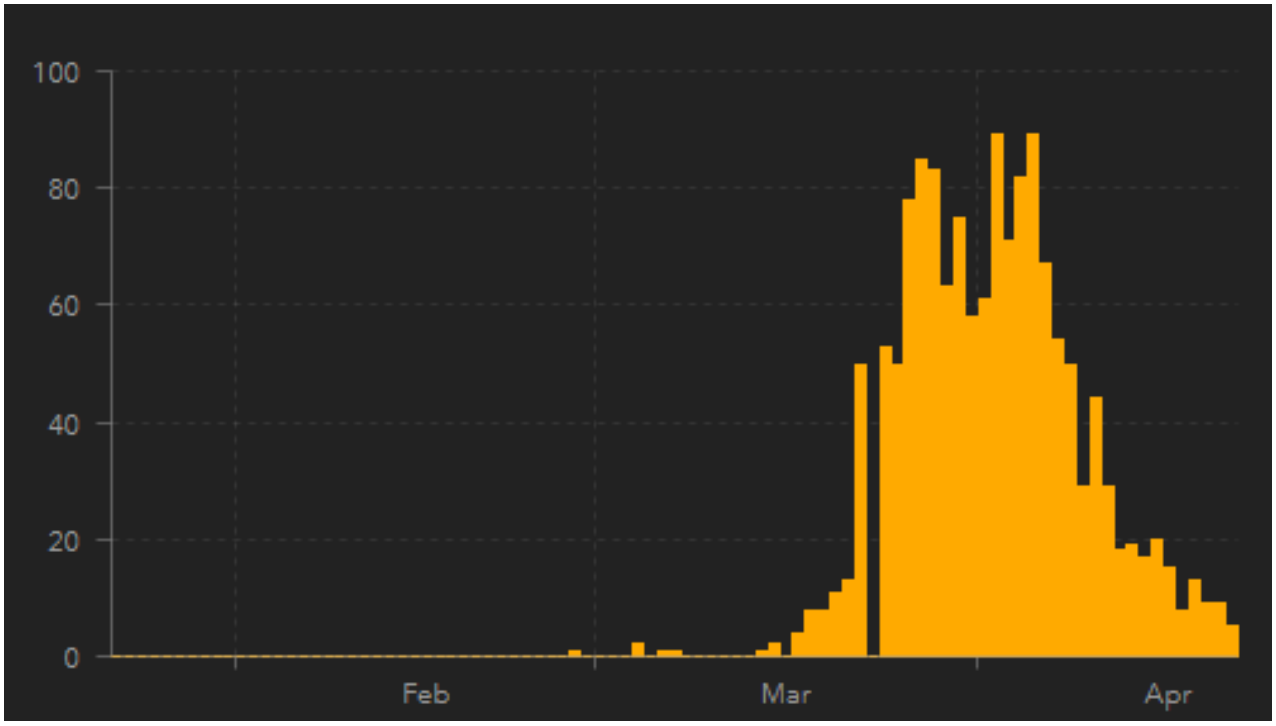
NEW ZEALAND LEVEL 4	
The advice from the Prime Minister is that, unless essential, you should be staying at home and avoiding contact with others.	
• People instructed to stay at home (in their bubble) other than for essential personal movement. • Safe recreational activity is allowed in local area. • Travel is severely limited. • All gatherings cancelled and all public venues closed.	• Businesses closed except for essential services (e.g. supermarkets, pharmacies, clinics, petrol stations) and lifeline utilities. • Educational facilities closed. • Rationing of supplies and requisitioning of facilities possible. • Reprioritisation of healthcare services.

More details on Level 4 here:

RESULTS OF THE LEVEL 4 INTERVENTION

The Level 4 interventions has been very successful; it is possible that New Zealand will eliminate or almost eliminate COVID-19 soon.

Daily confirmed cases in New Zealand: Data: Johns Hopkins University



- **Confirmed cases: 1,445 / Deaths: 14**
-

New Zealand will move to Level 3 interventions on 27 April.

NEW ZEALAND LEVEL 3	
• People instructed to stay home in their bubble other than for essential personal movement – including to go to work, school, if they have to, or for local recreation. • Physical distancing of two metres outside home (including on public transport), or one metre in controlled environments like schools and workplaces. People must stay within their immediate household bubble, but can expand this to reconnect with close family / whānau, or bring in caregivers, or support isolated people. This extended bubble should remain exclusive. • Schools (years 1 to 10) and Early Childhood Education centres can safely open, but will have limited capacity. Children should learn at home if possible. • People must work from home unless not possible.	• Businesses can open premises but cannot physically interact with customers. • Low risk local recreation activities are allowed. • Public venues are closed (e.g. libraries, museums, cinemas, food courts, gyms, pools, playgrounds, markets). • Gatherings of up to 10 people are allowed but only for wedding services, funerals and tangihanga. Physical distancing and public health measures must be maintained. • Healthcare services use virtual, non-contact consultations where possible. • Inter-regional travel is highly limited (e.g. for essential workers, with limited exemptions for others). • People at high risk of severe illness (older people and those with existing medical conditions) are encouraged to stay at home where possible, and take additional precautions when leaving home.

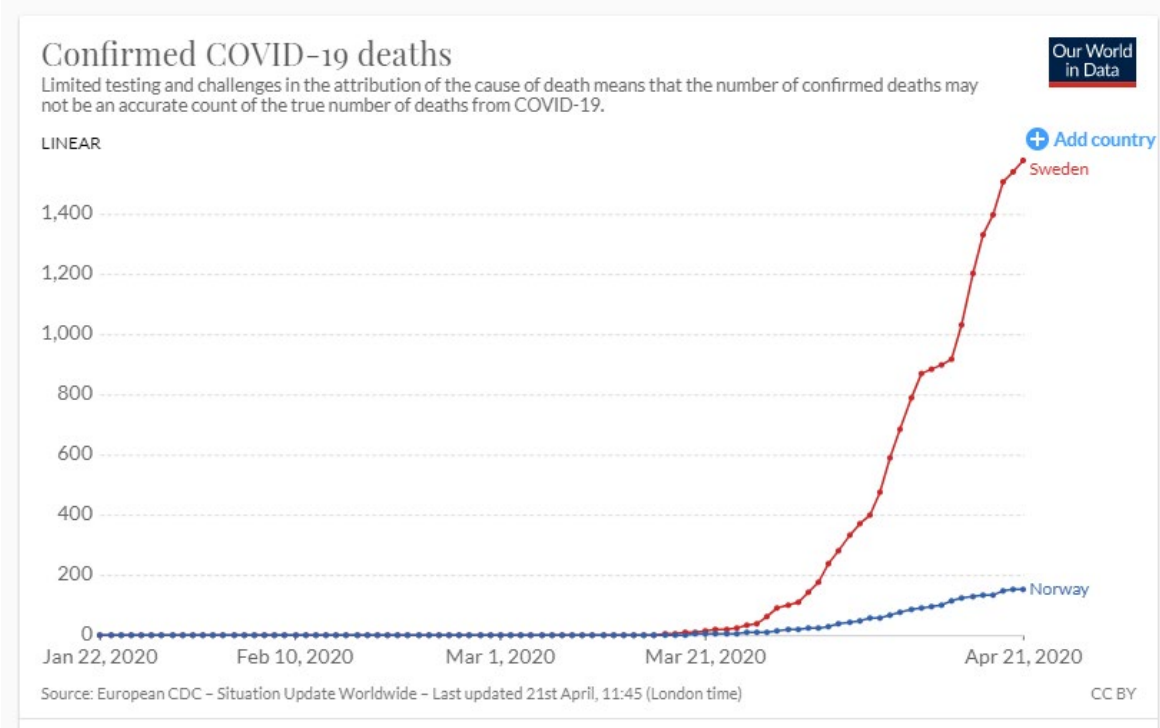
SWEDEN: SOME HERD IMMUNITY BY MAY?

Sweden's top epidemiologist Dr Anders Tegnell says the country's controversial decision not to enforce a quarantine means parts of Stockholm could become largely immune to the virus.

"According to our modellers [at the Public Health Agency of Sweden], we are starting to see so many immune people in the population in Stockholm that it is starting to have an effect on the spread of the infection," Dr Tegnell said. "Our models point to sometime in May."

“Locking people up at home won’t work in the longer term. Sooner or later people are going to go out anyway,” Tegnell told reporters recently. However, Sweden’s somewhat laissez-faire response has come at a cost.

Confirmed deaths: Sweden / Norway: Our World in Data



Population Sweden: 10.23 million

Population Norway: 5.37 million

FOCUS ON INDONESIA

What we know:

- Mid-January: A Dutch man was probably the first case in Indonesia. Fell ill and treated in three hospitals in East Java
- 2 March: First confirmed case, a dance instructor, in West Java:
    - Had held a dance class for more than 12 people in Keman on 14 February
    - One student was Japanese and later tested positive in Malaysia
- 8 March: six people who attended the dance class tested positive
- 20 March: an 11-year-old girl died on Madura Island. She was Indonesia's first confirmed fatality.

Responses:

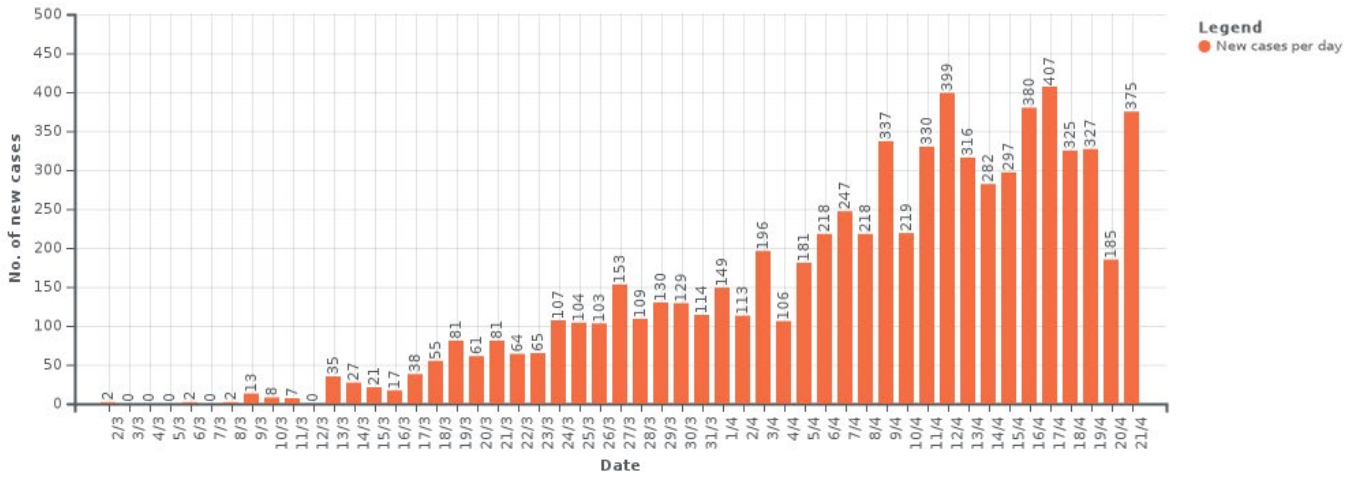
- 5 February: flights from Mainland China banned
- 8 March: flights from certain areas of South Korea and Italy banned
- 15 March: President Joko Widodo called on all Indonesians to practice social distancing
    - Indonesia has quite decentralized government
    - Each province decides on its own interventions
    - The social distancing programme has been described as "fragmented, bureaucratic and full of holes, ignoring the advice of most medical experts that containment requires strict and coherent measures."
- 30 March: no lockdown in Jakarta
- 21 April: President Joko Widodo banned the *mudik* (travel back to the provinces) to curb the spread of COVID-19 ahead of Ramadan.

About Mudik:

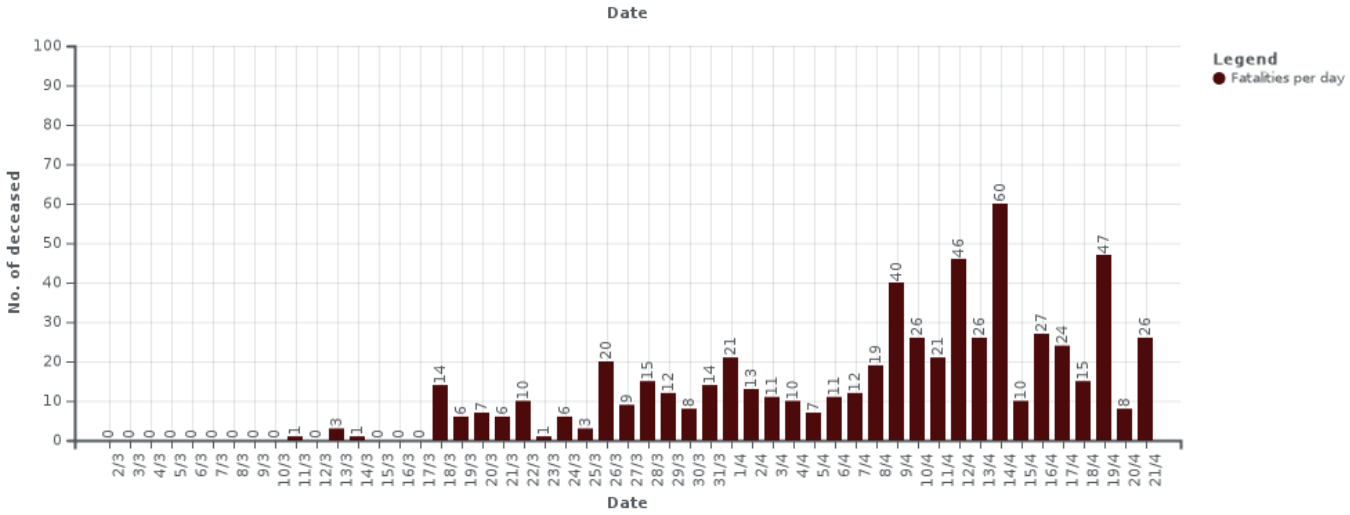
The dates for Ramadan in 2020 are 23 April to 23 May. During Ramadan many workers return to their home villages / towns to be with family – this migration is known as *mudik* and in 2017 involved 33 million Indonesians travelling. Trains, planes and roads are usually extremely busy, if not overwhelmed.

"Based on field research and a survey conducted by the Transportation Ministry, we found that 68% of people had decided to not participate in the annual exodus, while 24% still insisted on leaving and 7% had already left," Jokowi said. Apparently 1 million people have already left Jakarta.

New cases per day. Source: Indonesian National Board of Disaster Management

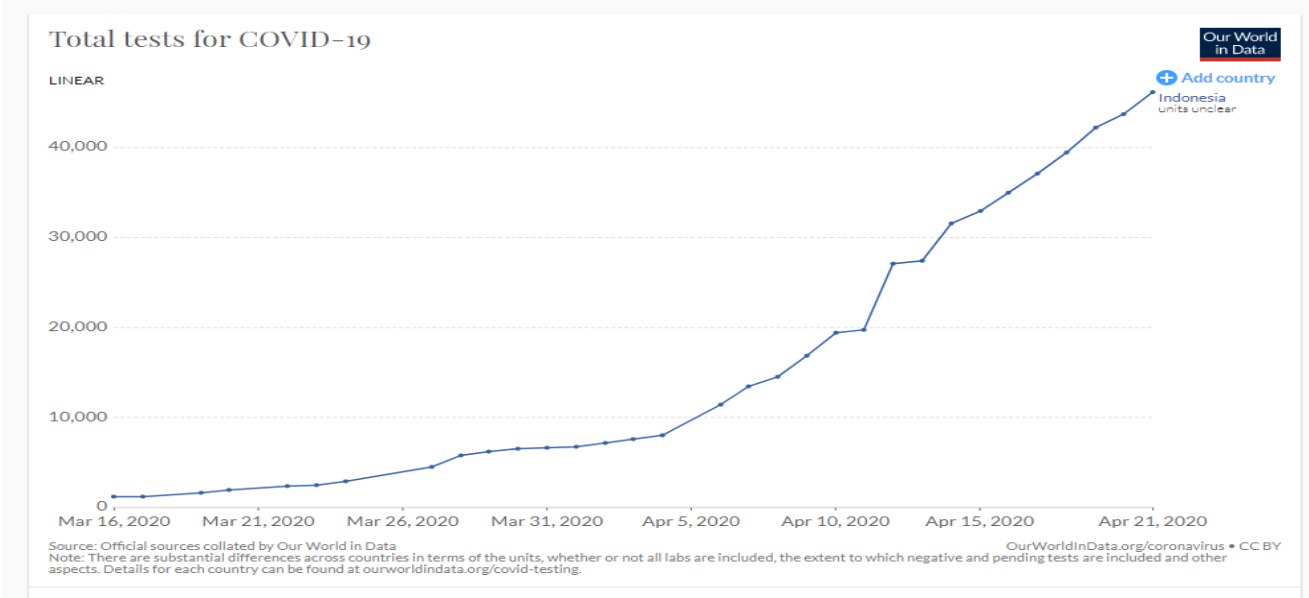


Fatalities per day: Source: [Indonesian National Board of Disaster Management]



Testing has been quite delayed in Indonesia with only 46,173 tests having been performed.

Total tests for COVID-19 in Indonesia: Source [Our World in Data]



Data from: [Our World in Data]

Tests performed per 1,000 people	
Italy	0.7
South Korea	0.08
Taiwan	0.08
Indonesia	<0.01

Comments:

Indonesia has officially recorded 7,135 confirmed cases and 616 deaths giving a CMR of 8.6%. If the true CMR was 2%, the number of cases would be closer to 30,000.

There are also reports of 1,000 burials occurring in Jakarta to COVID-19 standards. These represent more than the reported number of deaths. Using our previous assumption that the true number of cases in any country is at least 15 times the confirmed rate, the number of cases in Indonesia may be 150,000. With such a low level of testing, the reported case doubling time of 11 days may also be incorrect.

Yurdhina Meilissa, chief strategist at the Centre for Indonesia's Strategic Development Initiatives, said insufficient investment had left the healthcare sector unprepared for pandemics. "Without a significant change in the public healthcare strategy, we will lose [the battle against coronavirus],"

SEROSURVEYS

Stanford / Santa Clara study

The first large-scale community test of 3,300 people in Santa Clara County found that 2.5 to 4.2% of those tested were positive for antibodies -- a number suggesting a far higher past infection rate than the official count.

Based on the initial data, researchers estimate that the range of people who may have had the virus to be between 48,000 and 81,000 in the county of 2 million -- as opposed to the approximately 1,000 in the county's official tally at the time the samples were taken.

"Our findings suggest that there is somewhere between 50- and 80-fold more infections in our county than what's known by the number of cases than are reported by our department of public health," Dr. Eran Bendavid, the associate Professor of Medicine at Stanford University who led the study, said in an interview with ABC News' Diane Sawyer.

Dr. John Brownstein, an epidemiologist at Boston Children's Hospital and an ABC News contributor, cautioned that the results for the California county are not necessarily representative of the U.S. population and noted the use of online ads to find participants could skew the candidate pool. But, he said, the work is "adding to this confirmation of what we've expected, which is a much larger number of cases than we ever anticipated."

WORLD ROUND UP

Turkey: Istanbul Death Toll Hints Turkey Is Hiding a Wider Coronavirus Calamity

- Istanbul recorded 2,100 more deaths than over recent years between March and April suggesting a hidden toll.

Mexico: Coronavirus outbreaks at Mexico's hospitals raise alarm, protests

- The coronavirus outbreak in Monclova, Mexico's northern steel capital, started at the very place that was supposed to help stop it. Social Security Hospital No. 7, a towering 240-bed facility, is the main public medical center in Monclova.
- But when a 42-year-old truck driver arrived with pneumonia-like symptoms last month, the hospital didn't isolate him. Within two weeks, he was dead of COVID-19. Soon, a doctor and an administrator had also perished. Ultimately, 41 employees of the hospital wound up testing positive for the virus.

Malawi: Court suspends lockdown in Malawi

- A three-week lockdown due to begin in Malawi this weekend has been suspended following a High Court decision that the Government had not made enough provision to stop poor people going hungry.

- The ruling, the first successful legal challenge to the concept of a lockdown in Africa, adds to a growing debate on the continent about the trade-offs between shutting down economic activity and saving lives.

- In Africa, there have been relatively few reported deaths from coronavirus, with just over 1,000 so far. But the economic consequences of the virus have been palpable as people have been prevented by anti-pandemic measures from earning a living and from leaving often cramped accommodation where social distancing is impossible.

Brazil: Brazil digging large-scale graves ahead of coronavirus peak

- Ahead of an anticipated and dreaded peak of the national COVID-19 epidemic, Brazil has begun digging large-scale graveyards.

- In Sao Paulo's Vila Formosa cemetery, the largest in Latin America, about 20 excavators are digging against the clock. For this they have released a new lot of land "as a precaution", one of the gravediggers of the municipal funeral service said.

THE SINGAPORE EXPERIENCE – MOVING AWAY FROM LOCKDOWN IS NOT EASY

Singapore has been a model of how to control COVID-19. In January it started screening incoming travellers and isolating all who tested positive. It also began quarantining travelers who may have been exposed to the virus. Singapore avoided a "lockdown", businesses and restaurants stayed open, and people were able to leave their houses.

On 11 April, Singapore only had confirmed 191 cases. However, case numbers have grown since then and the number of cases in Singapore has more than doubled over the past week. This increase relates to infections among foreign workers staying in crowded dormitories and now makes up around 60 per cent of Singapore's cases.

Singapore has more than 200,000 migrant workers from Bangladesh, India and other Asian countries living in dormitories that house up to 20 people per room with shared facilities.

As of 21 April, Singapore had 1,100 confirmed cases on 21 April; a lockdown was announced two weeks ago.

It may be that Singapore is a paradigm for intensely urban communities with substantial poverty and "bode poorly for our (the US) ability to remain open for a long time" Aaron Carroll, a professor at Indiana University's medical school and a contributor to The Times, said.

"We will also more and more adapt to the new normal," said Josip Car, a top expert in population health sciences at Nanyang Technological University in Singapore. "This is the likely future for the next 18 months minimum, this being the anticipated time to make a first vaccine available at scale."

RECOVERING FROM THE CORONAVIRUS MAY NOT MAKE YOU IMMUNE

Precis of SBS article 19 April

Do those who recover from the disease have immunity?

There is no clear answer to this question even if many of us have assumed that contracting the disease confers at least temporary immunity. In addition, plans to suppress or eradicate SARS-CoV-2 rely on the assumption that a vaccine that will confer immunity will be developed.

- **Eric Vivier, a Professor of Immunology in the public hospital system in Marseilles:**
    - "For some viral diseases, such as measles, overcoming the sickness confers immunity for life. But for RNA-based viruses such as Sars-Cov-2 - the scientific name for the bug that causes the COVID-19 disease - it takes about three weeks to build up a sufficient quantity of antibodies, and even then they may provide protection for only a few months."

- **Michael Ryan, Executive Director of the World Health Organization's Emergencies Programme:**
    - "We do not have the answers to that - it's an unknown,"

- **Francois Balloux, Director of the Genetics Institute at University College London:**
    - For SARS, which killed about 800 people across the world in 2002 and 2003, recovered patients remained protected "for about three years, on average,"

- **Pasteur Institute researcher Frederic Tangy**
    - Commenting on the recent study (which had not gone through peer review) that reported that rhesus monkeys that had recovered from SARS-CoV-2 did not get re-infected when exposed to the virus again, said "But that doesn't really reveal anything" noting that the experiment unfolded over only a month.

A VIROLOGISTS PERSPECTIVE: PROFESSOR JOHN OXFORD

He X et al. Temporal Dynamics in viral shedding and transmissibility of COVID-19
Nature Medicine (2020) 15th April

The authors studied 94 patients in detail. They observed the highest viral load in throat swabs at the time of symptoms. (This is not unusual for many viruses). The inference is that the infection of others peaked at this time or even just before symptoms. Again, this is not unusual for viruses and was recorded in 2003 during the SARS outbreak. They estimated that 44% of secondary cases were infected from the index case when asymptomatic. Their clear and important message is that "disease control measures should be adjusted to account for probable substantial pre symptomatic transmission."

I feel that this is a very important paper published in a substantial journal and with a well-known authorship! It tells me that we must begin wide testing in the community by PCR for the virus and then identify infected persons, either with or without symptoms and quarantine.

For reasons best known to the decision-makers, this was stopped suddenly in the UK. This was probably our biggest single mistake and I feel we are paying dearly for it!

For example, by 15 April the UK has had 182 deaths per million persons. This compares to 42 in Germany, 349 in Italy and 399 in Spain. These figures have also been used when comparing the approach between the neighbouring countries in Scandinavia, namely Denmark and Sweden.

Sweden decided on "a light touch" to the pandemic and now has a death rate of 118 per million inhabitants compared to neighbouring Denmark who have recorded 55 and Finland 13 per million. These countries were much stricter in lockdown, etc. The Swedes "asked" the population to avoid non-essential travel. Swedes continued shopping normally, going to restaurants and sending children under 16 to school, even if a family member was ill.

Personally, I feel that countries like the USA are risking everything on a wild and unscientific "return to normal" despite warnings from NIH and CDC.

But to return to the paper itself, the author took a reproductive number of 2.2 to 2.5 and rehearsed the important parameters for us. These are the serial interval (the duration between symptoms onsets of successive cases in a

transmission chain) and the incubation period (time between infection and onset of symptoms). The authors noted that if the observed serial interval is shorter than the observed mean incubation time this would indicate that a significant portion of transmission may have occurred before the infected persons developed symptoms.

Obviously, and importantly, under these circumstances control methods such as isolation, contact tracing and enhanced hygiene and face masks for infected persons would be compromised. A total of 414 throat swabs were collected from 94 patients from onset of symptoms to 32 days post onset. High virus loads were detected at the start and decreased to zero by day 21.

Overall, they calculated that the serial interval was 5.8 days with an incubation period of 5.2 days. So, infectiousness started from 2.3 days before symptom onset and peaked at 0.7 days before symptom onset. There was some good news, infectiousness declined quickly within 7 days. I particularly appreciated the detailed graphs from individual patients on virus excretion patterns.

A ferret transmission model for influenza

Science Daily, 16 April 2020

An international consortium from the Peter Doherty Institute in Melbourne, Roche and Imperial College has published data on the treatment of influenza-infected ferrets with their new drug Bolaxivir to see if animal to animal spread can be stopped.

As a reminder, Bolaxivir is a new anti-flu drug which works at the point of virus RNA replication; in fact at the unique "cap snatching" virus protein. So, it is different to Tamiflu, which blocks the influenza virus NA. The two drugs could be used together. Bolaxavir has the advantage of immediately stopping virus replication and in volunteers one tablet is sufficient for treatment of patients.

This study was performed in two laboratories, not an uncommon approach nowadays. Ferrets were infected with influenza A/H1N1 virus which were co-housed with 'sentinel' animals. The infected ferrets were given Bolaxivir as a subcutaneous injection. Bolaxivir reduced virus excretion and the frequency of transmission even when drug treatment was delayed until two days post infection.

The study is an important one and reminds us that influenza A is still a big threat to the world community. It is possible that epidemic influenza next year could cause as many clinical problems as COVID-19. It is also possible that there could be simultaneous outbreaks in both viruses over the winter. Therefore, this work is well worth attention!

Several 'new' drugs inhibit COVID-19 replication in the laboratory

Antiviral Research, 178, June 2020

Choy et al reports that remdesivir, lopinavir, emetine and homo- haringtonne inhibit COVID-19 virus replication. Moreover, remdesivir and emetine showed synergistic effects. In contrast ribavirin, and favipiravir showed no activity.

Classic virology was used with the COVID virus growing in Vero E6 cells. The stock virus had a titre of $10^{7.25}$ $TCID_{50}$/ml The significant finding was that the COVID-19 virus was inhibited by relatively low concentrations of remdesivir and also the HIV protease inhibitor lopinavir.

As a reminder, remdesivir is a Gilead drug (the discoverer of Tamiflu to treat influenza) and is a pro-drug of an adenosine analogue with broad spectrum antiviral activity versus filoviruses (e.g. ebola) as well as coronaviruses. I would have preferred it to be less broad in antiviral effect, thereby hoping for a high specific effect, although I must admit that this logic is not always followed! I do remember the Dr. de Uit study published recently with the drug versus SARS in a primate model.

There are several controlled clinical trials from China about to be published and these will give the first indication of usefulness in the field. I am keeping my fingers crossed especially in view that synergism was noted above.

Post Script

Today the Journal of the Royal Society of Medicine published new data on age related clinical illness in COVID patients. They strongly indicate that 60-69-year olds in the UK should join the 70 plus cohorts in the UK and take special precautions. There are 7.3 million in this group.

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