SARS-CoV-2 viral load and the severity of COVID-19

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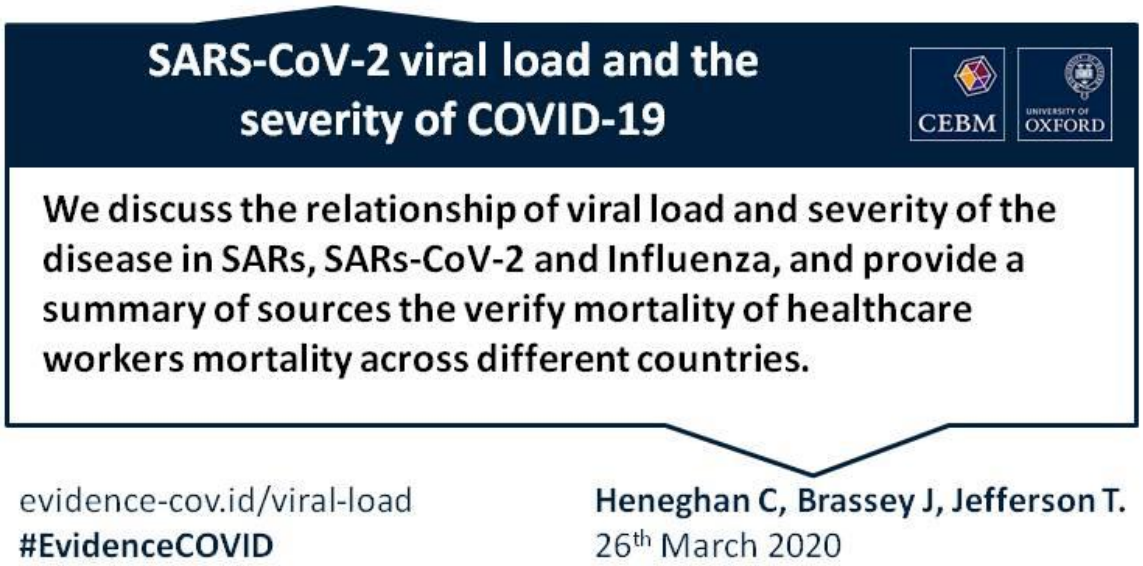

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Every day no matter which European state you live in, you are subject to a deluge of figures and opinions, often at odds. In this post, we look at some of them and draw our conclusions at the bottom.

We discuss evidence in SARs, SARs-CoV-2 and Influenza and the relationship of viral load and severity of the disease. We then present a summary of the sources that verify current healthcare workers who have died across different countries.

Background

The initial dose of virus and the amount of virus an individual has at any one time might worsen the severity of COVID 19 disease. Viral load is a measure of the number of viral particles present in an individual. Higher SARS-CoV-2 viral loads. might worsen outcomes, and data from China suggests the viral load is higher in patients with more severe disease. The amount of virus exposure at the start of infection – the infectious dose – may increase the severity of the illness and is also. linked to a higher viral load

Healthcare workers can be exposed more often due to numerous infected individuals exposures. In the early stages of an outbreak, initial contacts might not be recognized, particularly contacts with those with mild symptoms, or when the use of protective measures is suboptimal. Reducing the frequency and intensity of exposure to SARs-CoV-2 might reduce the infectious dose and result in less severe cases.

What is the evidence linking viral dose, viral load and the severity of disease?

The evidence suggests an association of viral dose with the severity of the disease. However, the evidence of the relationship is limited by the poor quality of many of the studies, the retrospective nature of the studies, small sample sizes and the potential problem with selection bias.

SARs:
An analysis of the nasopharyngeal viral load of 79 SARs patients in Amoy Gardens, Hong Kong, in the 2003 outbreak. reported that while patients admitted to hospital had initially similar illness severity regardless of proximity to the initial case. During the SARS outbreak, Amoy Gardens was placed under active surveillance, and residents underwent frequent

examinations including nasopharyngeal specimens collected at an early stage.

The SARS pandemic in 2002-2003 affected 8,098 people with 774 deaths. An analysis of 142 patients with SARs reported that Viral load in Nasal Pharyngeal Aspirates between days 10 and 15 after the onset of symptoms was associated with:*

- Oxygen desaturation, OR=3.1 (95% CI, 1.6- 6.2),
- Mechanical ventilation, OR =11.3 (95% CI, 3.6-35.1)
- Diarrhoea, OR=2.5 (95% CI, 1.3-5),
- Hepatic dysfunction, OR =2.5 (95% CI, 1.2-5.2) and
- Mortality (OR=54; 95% CI, 7-415).

*The small sample size of this study results in wide confidence intervals and uncertainty over the point estimates. Compared with other common viral respiratory diseases, the onset of peak viral load appeared to be delayed. Only those who sent the specimen on day 10 were included, which further limits firm conclusions to be drawn

SARs-Co-2:
A retrospective, multicentre cohort study, of 191 adult inpatients (median age 56.0) with laboratory-confirmed COVID-19 from Jinyintan Hospital and Wuhan Pulmonary Hospital (Wuhan, China) discharged or died by Jan 31, 2020.

- The median duration of viral shedding was 20·0 days (IQR 17·0–24·0) in survivors,
- The longest observed duration of viral shedding in survivors was 37 days.
- SARS-CoV-2 was detectable until death in non-survivors.
- Severe lymphopenia was observed until death in non-survivors.

A preprint of the temporal patterns of viral shedding in 94 laboratory-confirmed COVID-19 patients and analysis of a separate sample of 77 infector-infectee transmission pairs modelled the following:

- Infectiousness started from 2.5 days before symptom onset and reached its peak at 0.6 days before symptom onset.
- The proportion of transmission before symptom onset (area under the curve) was 44%.
- Infectiousness was estimated to decline relatively quickly within 7 days of illness onset

Influenza:
The link to the initial dose and subsequent severity of the disease is linked with the 1918-19 Spanish Flu pandemic. Simulation models showed that the infectious dose was related to the number of simultaneous contacts a susceptible person has with infectious ones; that severe cases of influenza result from higher infectious doses of the virus; and over-crowded places are the ideal environment for a susceptible person to be exposed to very high infectious doses of influenza.

- High infectious dose and influenza disease progression have been shown in experimental animals;
- The high infectious dose is associated with a higher viral load; and
- The high infectious dose is associated with a smaller period of time to maximum viral load. [2]

[2] Influenza Infectious Dose May Explain the High Mortality of the Second and Third Wave of 1918–1919 Influenza Pandemic. PLoS ONE 5(7): e11655.

An analysis of 147 inpatients with influenza A (H3N2) infection (mean age, 72±16 years) reported major comorbidities and systemic corticosteroid were associated with slower viral clearance. Severe cases of influenza have more active and prolonged viral replication.

Healthcare Workers.

Reports across several countries report healthcare workers are more at risk of catching SARS-CoV-2 and potentially more severe. having COVID-19 disease. We use multiple sources as there is considerable variation in the number of deaths reported, which currently presents a confusing picture.

China:
4th March: Business Insider
– M ore than 3,300 healthcare workers infected (4% of the 81,285 reported infections)
– 13 healthcare workers have died, 0.39% of the 3,300 infected (95% CI, 0.23% to 0.67%).

Italy:
26th March: Independent:
– A t least 37 doctors have died after contracting coronavirus in Italy .
– Italian Federation of Surgeons and Dentists: List of 40 doctors who died during the Covid-19 epidemic.[1]
25th March: Integrated surveillance COVID-19: the main national data:
– 6 ,205 (9.2%) healthcare workers infected out of 67,814 cases
24th March: SBS.au:
– 24 doctors have died, 0.39% of the 6,205 infected (95% CI, 0.26% to 0.58%)
22nd March: CNN
– 4, 826 (9%) healthcare workers infected out of the 53,578 cases
– 18 doctors have died, 0.37% of those infected (95% CI, 0.23% to 0.59%)

[1] It is unclear if the doctors were frontline or treating the infected
[1] Not all died as a direct consequence of infection. E.g., On March 7, an anesthesiologist died due to end-stage disease.

Source data: Italy's National Health Institute (ISS).
– Integrated surveillance COVID-19: the main national data
– infographic available in English (pdf 1,5 Mb)

Spain:

26th March: Metro

– Opposition conservative People's Party leader Pablo Casado said: 'Governments don't send their soldiers to the front without helmets, flak jackets and ammunition. But our health workers don't have any protection.'

25th March: Global News

– A t least three health care workers have died.

– On Wednesday, the number of medical personnel infected was nearly 6,500 nationally, (13.6%) of the country's 47,600 total cases – 1% of the health system's workforce.

24th March: Guardian

– 5,400 (13.6%) healthcare workers infected out of 39,673 cases~

24th March: NY Times

– In Madrid, 426 (6%) the medical staff (6%) have either tested positive or show symptoms of COVID

– In Igualada hospital, Catalonia, 1/3rd of the 1,000 hospital staff has been sent home.

– Protection measures were highly inadequate to protect staff: "When we already knew that the virus was circulating in hospitals, we were still being told that the usage of protective gear should be limited to specific circumstances," said Juanjo Menéndez,

France:

24th March: NY Times

– Three doctors out of five who died of Covid-19 in France were GPs, one was a gynaecologist.

22nd March: The Local Fr

– A total of five doctors have now died in France

– Three doctors worked in the départements of Oise, Haut-Rhin and Moselle in the eastern area of France, worst affected by the coronavirus outbreak.

23rd March: RFI

– Three doctors now dead after being infected by Covid-19*

Philippines:
26th March: Bangkok Post
– Philippine Medical Association said Thursday a ninth doctor had died of the virus, and that health workers were not getting enough protection.
– "If it were up to me, test the frontliners first and test them again after seven days. Doctors could be carriers themselves," Benito Atienza, vice president of the Philippine Medical Association told AFP.
26th March: France 24
– Nine doctors die from coronavirus in the Philippines
– The confirmed virus death toll in the Philippines is 38.
21st March: Philippine Heart Association (PHA) Facebook Post
– Announces one of its members died due to COVID-19:

Indonesia:
23rd March: Jakarta Globe
– Six Indonesian Doctors Die From Covid-19, Cases Exceed 500
22nd March: Jakarta Post
– Indonesian Doctors Association, or IDI, confirmed on Sunday that its six members had died from Covid-19
22nd March: The Star
– Three doctors die of Covid-19 in Indonesia, 23 health officers infected
– The Indonesian government's spokesman for Covid-19-related matters Achmad Yurianto said the government was concerned by deaths of the doctors.

Source verification: Indonesian Doctors Doctors Association Facebook page
– IDI mourned deeply for the passing away of IDI fellow members as victims of the Covid-19 Pandemic

Nurses:
20th March: Nursing Times
– A small number of nurses around the world have died after contracting coronavirus, an international nursing body has confirmed.* Howard Catton,

chief executive of the ICN, told Nursing Times that nurse deaths had been reported in Iran, Indonesia and Spain.
*no study data referred to.

What can we Conclude from the reports on healthcare worker deaths

If readers are confused by the mass of contradictory information, so are we.

What can be desumed by this post is that no one really knows what is going on, least of all governments and professional associations which seem at odds with news outlets as to how many of their members have died.

As our grandfathers used to say, when you do not know what is going on, do nothing. This is what we plan to do from our privileged position: observe and monitor the situation without jumping to conclusions.

List of relevant studies:

Title	URL
Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study	https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2930566-3
Temporal dynamics in viral shedding and	https://www.medrxiv.org/content/10.1101/2020.03.15.20036707v2

transmissibility of COVID-19	
Viral shedding and clinical illness in naturally acquired influenza virus infections	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3060408/
Viral Loads and Duration of Viral Shedding in Adult Patients Hospitalized with Influenza	https://academic.oup.com/jid/article/200/4/492/857773
Comparative and kinetic analysis of viral shedding and immunological responses in MERS patients representing a broad spectrum of disease severity	https://www.nature.com/articles/srep25359
Systematic Review of Influenza A(H1N1)pdm09	https://pubmed.ncbi.nlm.nih.gov/24299099

Virus Shedding: Duration Is Affected by Severity, but Not Age	
Middle East Respiratory Syndrome Coronavirus Infection Dynamics and Antibody Responses among Clinically Diverse Patients, Saudi Arabia	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6433025/
Predictors of mortality in Middle East respiratory syndrome (MERS)	https://thorax.bmj.com/content/73/3/286.abstract
Influenza A Virus Shedding and Infectivity in Households	https://academic.oup.com/jid/article/212/9/1420/1025422
Correlation of Pandemic (H1N1) 2009	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3298297/

Viral Load with Disease Severity and Prolonged Viral Shedding in Children	
Prolonged shedding of type 55 human adenovirus in immunocompetent adults with adenoviral respiratory infections	https://link.springer.com/article/10.1007/s10096-019-03471-9
Epidemiology of human influenza A(H7N9) infection in Hong Kong	https://www.sciencedirect.com/science/article/pii/S1684118215007720
Viral Kinetics and Resistance Development in Children Treated with Neuraminidase Inhibitors: The Influenza Resistance Information	https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciz939/5574924

Study (IRIS)	
Transmission of the First Influenza A(H1N1)pdm09 Pandemic Wave in Australia Was Driven by Undetected Infections: Pandemic Response Implications	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4687009/

Title	URL
Virological assessment of hospitalized cases of coronavirus disease 2019	https://www.medrxiv.org/content/10.1101/2020.03.05.20030502v1.full.pdf
High transmissibility of COVID-19 near symptom onset	https://www.medrxiv.org/content/10.1101/2020.03.18.20034561v1.full.pdf

Duration of viral detection in throat and rectum of a patient with COVID-19	https://www.medrxiv.org/content/10.1101/2020.03.07.20032052v1

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