Estimating disease severity of Omicron and Delta SARS-CoV-2 infections

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The Omicron variant of SARS-CoV-2 has been reported to cause milder disease in adults but lead to increased hospital admissions in children. How can we compare disease severity in Omicron and Delta infections, and how should differences be interpreted?

Measuring COVID-19 disease severity in a population has been important for understanding the public health impact of each variant of concern. It also impacts immunologists and virologists closely as it reflects population immunity and the mechanisms of viral infection. A watershed moment in the COVID-19 pandemic was the emergence of the Omicron (B.1.1.529) variant of SARS-CoV-2 with widespread reports of lower disease severity relative to previous variants such as Delta (B.1.617.2). The lower disease severity seen in populations during the Omicron wave of the SARS-CoV-2 pandemic infection[1] can be attributed to changes in the virus that limit its ability to spread in the lungs and, probably most importantly, to increased immunity in the population from previous SARS-CoV-2 infection and vaccination[2]. However, in children, Omicron infections led to more hospital admissions than in previous waves[3,4]. Does this mean that Omicron is causing more severe disease in children, or is the difference based on how disease severity is defined? While the current Omicron wave is waning globally, a clearer concept of disease severity should help us evaluate the variants to come.

Disease severity is measured using outcomes such as total hospital admissions, requirement for supplemental oxygen and ventilation, and death (FIG. 1a). Hospital admission is a measure that is not very specific: it does not indicate cause, and there can be a wide range of severity. People may also be admitted with, but not because of, SARS-CoV-2 infection. However, severity measures become more specific for lower respiratory tract damage caused by COVID-19 disease as severity increases.

Measurement generally has one of three forms: 1) per unit time, usually daily, for example number of new hospital admissions per day; 2) as an integral over a time interval, for example total excess mortality over an infection wave; and 3) as a fraction of infections, for example fraction of deaths out of the total number of people infected within a defined period. These measurements all involve disease severity but are used differently. Knowing daily hospital admissions would be important for planning sufficient hospital capacity. Total disease or mortality may be important to calculate the human and economic cost of an infection wave. Fraction of infections that are severe is important to know to answer questions such as: "Is my child more or less likely to become severely ill if infected with this variant?" with implications for risk assessment, behaviour and mechanisms of pathogenicity.

In terms of immunological mechanisms, inferring disease severity from a daily or cumulative measure may be misleading because a higher number of deaths, hospital admissions or other metrics may result from an increase in infections, not increased severity. Higher infection prevalence can happen because the virus has evolved to transmit better, or because there was no lockdown or non-pharmacological interventions in place. Normalizing by the number of infections should eliminate this dependence. However, it introduces a new complication: what is the denominator? Not all infections are reported, either because they are asymptomatic, or because people have difficulty accessing testing or choose not to test.

To give an example, a clinical trial recruiting people during the Omicron infection wave in South Africa[5] showed that 31% of apparently healthy individuals arriving to enrol were qPCR positive for SARS-CoV-2. Given the population of South Africa is approximately 59 million, this would equate to about 18 million people infected. By contrast, the total number of reported SARS-CoV-2 cases in South Africa between 25 November 2021 and 15 February 2022 (the Omicron wave) was 692,153 (see Related links). This gives a ratio of 26 to 1 of unreported to reported infections.

A more precise way to estimate unreported infections may be community surveys. The REACT-1 study in the UK randomly surveys about 100,000 people monthly for SARS-CoV-2 and may capture about a 2-week window of infection per sampling, given that SARS-CoV-2 is detectable by qPCR in most people for this period.

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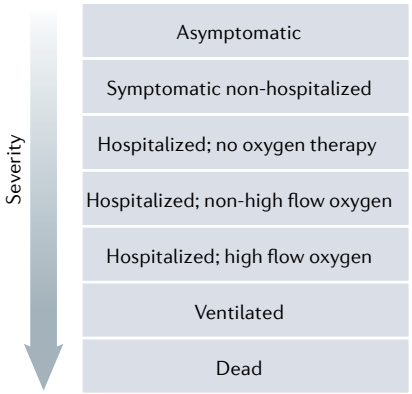
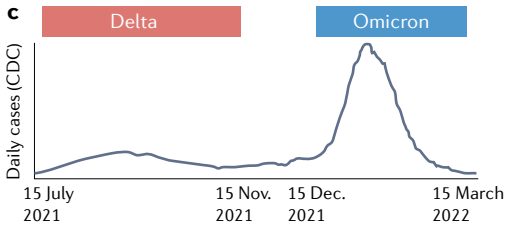
a Simplified severity scale



b Ballpark estimate of unreported infection from UK surveillance

UK Study	Wave	Fraction infected	Estimated infected UK	Confirmed cases GOV.UK dashboard	Fraction unreported
REACT-1 Round 15	Delta (Oct. 2021)	1.6%	1,055,354	609,990 19 Oct.–3 Nov. 2021	42%
REACT-1 Round 18	Omicron (Feb. 2022)	2.9%	1,935,936	528,400 12 Feb.–25 Feb. 2022	73%

c



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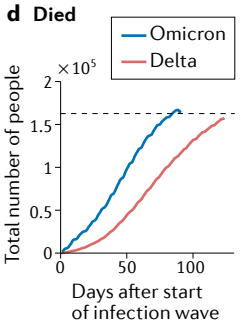
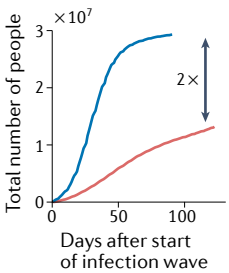
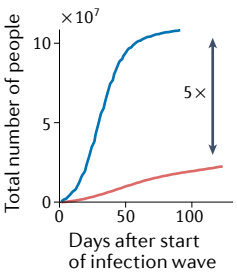


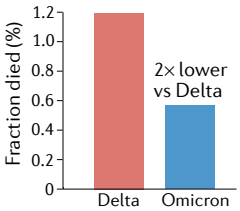
e Reported infected



f Estimated total infected



g Case fatality ratio



h Infection fatality ratio

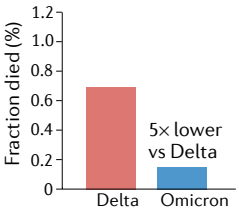


Fig. 1 | **Estimating disease severity. a** | A simplified severity scale for COVID-19 disease. **b** | Ballpark estimate of the fraction of unreported infections based on UK surveillance data. **c** | Periods for the USA Delta (15 July 2021 to 15 November 2021) and Omicron (15 December 2021 to 15 March 2022) infection waves used in the analysis. The period between 15 November and 15 December was not analysed to avoid times when both variants were circulating. **d**,**e** | Cumulative number of deaths (**d**) and reported cases **(e)** since the start of each infection wave from Centers for Disease Control and Prevention (CDC) data. **f** | Cumulative number of estimated total infections in each wave, calculated by dividing the number of cumulative reported cases by the UK estimated fraction of reported to total infections as determined from data in (**b**). **g** | Case fatality ratio, the cumulative number of deaths divided by the cumulative number of reported infections per wave. **h** | Infection fatality ratio, the cumulative number of deaths divided by the cumulative number of estimated total infections per wave.

The study found an infection prevalence of 2.9%[6] between 8 February and 1 March 2022, when Omicron dominated. Between 19 October to 5 November 2021, when Delta was dominant, infections were at 1.6%[7]. Extrapolating this to the UK population of 67 million and comparing the resulting number to the number of UK reported cases (see Related links) in a two-week interval within the surveyed Omicron and Delta periods gives 27% reported and 73% unreported infections for Omicron. The estimate for Delta is 58% reported and 42% unreported infections (FIG. 1b). Estimates for unreported infections may be dependent on vaccination prevalence, age of the infected population, and likely many other factors, and so may be specific to the population surveyed. They are used here as ballpark figures to illustrate how they influence the assessment of relative disease severity between Omicron and Delta.

To compare relative disease severity, we used data from the Delta and Omicron infection waves in the USA (FIG. 1c) available from the Centers for Disease Control and Prevention (see Related links). The number of cumulative deaths in the Omicron wave (analysed from 15 December 2021 to 15 March 2022) was very similar to that seen in the Delta wave (analysed from 15 July 2021 to 15 November 2021; FIG. 1d). However, the number of confirmed cumulative cases during this period was twofold higher with Omicron (FIG. 1e). Based on the ballpark figures for unreported infections stated above, the number of total estimated infections was about fivefold higher for Omicron (FIG. 1f). Normalized by the number of confirmed cases — the case fatality ratio — Omicron infection had about a twofold lower mortality relative to Delta (FIG. 1g). Normalized by the total number of infections — the infection fatality ratio — the difference became approximately fivefold (FIG. 1h). For comparison (see Related links), the same time-windows in South Africa, also corresponding to Delta and Omicron dominated periods, had 699,236 reported cases and 23,894 deaths (Delta) and 492,181 cases and 9,555 deaths (Omicron). This gives a case fatality ratio of 3.4% for Delta and 1.9% for Omicron, again about a twofold difference. Therefore, Omicron does have lower severity by these measures, with the precise severity drop relative to Delta dependent on how the number of infections is estimated.

But is Omicron more severe in children? In children, the fraction of SARS-CoV-2-positive cases admitted to hospital in South Africa doubled during the Omicron wave compared to in the Delta wave[8,9]. This seems to point to higher disease severity. However, the in-hospital case fatality ratio of children under 5 in the Omicron wave was 0.5% versus 0.6% in the Delta wave[9]. A similar trend, but with lower case fatality, was seen in older children. Consistent with this, the fraction of ventilated children under 5 in the UK was 2.9% in the Omicron wave versus 5.1% in other waves[10].

Although the adult severity scale may miss paediatric-specific symptoms such as seizures, which are more prevalent with Omicron[8], it seems that measures of high severity and death do not support that Omicron is more severe than Delta in children. Also, a lower fraction of children than adults die with both variants. So why are more children admitted with Omicron? One possibility is that, like in adults, there were more unreported cases of infection in the Omicron wave and this drove the higher admissions, but admissions did not result in as many severe outcomes as with the other variants. For example, in South Africa, 61% of children were admitted with fever or dehydration from diarrhoea and vomiting[8]. There are clinical protocols for paediatric management that require children to be admitted for fever or fluid management. These are generally short admissions for supportive care and may not lead to the more dangerous respiratory symptoms.

A related explanation is that Omicron leads to a shift in symptoms (for example, more fever). This may be harder to discern in adults possibly because of the gap in immunity between adults and children (that is, adults are more likely to be vaccinated). Also, most adults may not require admission for fever.

What all this may show is that measures of disease severity should be interpreted with caution. As seen in children, the metric of hospital admissions as a fraction of cases may not be a good measure, as it does not fully reflect more severe disease. The number of deaths is an easily accessible measure and captures the most severe outcome, but may be misleading if it is not normalized by the number of infections. The infection fatality ratio may therefore be the most informative metric, and population surveys measuring active infection prevalence should be used to get an accurate estimate of this.

1. Abdullah, F. et al. Decreased severity of disease during the first global Omicron variant Covid-19 outbreak in a large hospital in Tshwane, South Africa. *Int. J. Infect. Dis.* **116**, 38–42 (2021).
2. Sigal, A. Milder disease with Omicron: is it the virus or the pre-existing immunity? *Nat. Rev. Immunol.* **22**, 69–71 (2022).
3. New York State Department of Health. Pediatric COVID-19 update: January 7, 2022 https://www.health.ny.gov/press/releases/2022/docs/pediatric_covid-19_hospitalization_report.pdf (2022).
4. UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England. Technical briefing 34 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1046853/technical-briefing-34-14-january-2022.pdf (2022).
5. Garret, N. et al. High rate of asymptomatic carriage associated with variant strain Omicron. Preprint at *medRxiv* https://doi.org/10.1101/2021.12.20.21268130 (2021).
6. Chadeau-Hyam, M. et al. The Omicron SARS-CoV-2 epidemic in England during February 2022. Preprint at *medRxiv* https://doi.org/10.1101/2022.03.10.22272177 (2022).
7. Chadeau-Hyam, M. et al. REACT-1 round 15 final report: increased breakthrough SARS-CoV-2 infections among adults who had received two doses of vaccine, but booster doses and first doses in children are providing important protection. Preprint at *medRxiv* https://doi.org/10.1101/2021.12.14.21267806 (2021).
8. Cloete, J. et al. Paediatric hospitalisations due to COVID-19 during the first SARS-CoV-2 omicron (B.1.1.529) variant wave in South Africa: a multicentre observational study. *Lancet Child Adolesc. Health* https://doi.org/10.1016/S2352-4642(22)00027-X (2022).
9. Jassat, W. et al. Clinical severity of COVID-19 patients admitted to hospitals during the Omicron wave in South Africa. Preprint at *medRxiv* https://doi.org/10.1101/2022.02.22.21268475 (2022).
10. COVID-19 Clinical Information Network. CO-CIN update January 2022 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1046475/S1483_CO-CIN_Child_admissions_and_severity_by_epoch.pdf (2022).

Competing interests
The authors declare no competing interests.

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