Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Understanding how fast SARS-CoV-2 variants transmit from household studies

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The generation time distribution, $g(t)$, is used by epidemiologists to monitor disease spread and to assess intervention effectiveness on the basis of daily reported new cases, $\chi(t)$, using a simple identity:

$$R_t = \chi(t)/\int_0^\infty \chi(t-s)g(s)ds$$

where R_t is the effective reproductive number at a specific time (t). Additionally, the generation time distribution is used by health authorities to guide isolation and quarantine policies (eg, a close contact of an identified case might be recommended to self-quarantine for a period that corresponds to the maximum generation interval plus the maximum incubation period).

The successive waves of dominant SARS-CoV-2 variants have shown a general trend of increasing transmissibility. The relative transmissibility of emerging variants of concern was reportedly higher than for previous variants, with increases in R_t of 29–90% for the alpha variant (B.1.1.7) and 97% for the delta variant (B.1.617.2).[1,2] Most modelling studies on transmission and control of variants require the generation time distribution as an input. Due to insufficient data, the analysis of novel strains often assumes the same generation time distribution as for an ancestral strain.[1–3] Several studies[4,5] reported a shortened mean incubation period of 3·5–4·4 days for the alpha and delta variants compared with the ancestorial strain, implying shorter generation times given the presymptomatic transmissibility of SARS-CoV-2. Only a few studies have estimated generation times directly for these variants from contact-tracing data.[4] Although some studies estimated the serial interval for variants of concern,[6] this interval cannot reliably approximate the generation time for SARS-CoV-2 because of its presymptomatic transmissibility.

Based on 227 households in the UK, William Hart and colleagues[7] provide long needed estimates of generation time distributions for the alpha and delta variants. The reliability of these estimates is grounded on (1) a rigorously designed prospective household study with a decent sample size, (2) a modelling framework that accounts for uncertainties in both the natural history of disease and transmission within households, (3) refined analyses stratified by age group and vaccination status of index cases and their family contacts, and (4) a comprehensive assessment of estimability of parameters and robustness of results to changing assumptions. The authors provide estimates of both the intrinsic generation time, needed by modellers, and the household generation time, which is similar to most existing estimates for SARS-CoV-2 obtained by traditional methods that identify transmission pairs empirically from contact-tracing data. The current model probably identifies transmission pairs more accurately because it explicitly accounts for competition among cases for susceptible contacts.

The authors estimate the mean intrinsic generation time to be 4·7 days (95% credible interval [CI] 4·1–5·6) and the household generation time to be 3·2 days (2·5–4·2) for the delta variant. These estimates are shorter than those for the alpha variant, which were 5·5 days (4·7–6·5) for the mean intrinsic generation time and 4·5 days (3·7–5·4) for the household generation time. The mean household generation time for the delta variant is clearly shorter than that of its ancestral strains (4·0–5·2)[8] and is similar to another estimate of 2·9 days (2·4–3·3) for the delta variant in a non-household study in China.[4] The authors estimated a mean household serial interval of 1·8 days (95% CI 1·0–2·4) for the delta variant, which is consistent with estimates of 2·0–2·5 days in Asian countries[4,6,7] and is substantially shorter than the 3·5 days (2·7–4·1) estimated for the alpha variant. A proportionally larger decrease in the household serial interval (48·6%) than the household generation time (28%, 95% CI 0–48%) for the delta variant compared with the alpha variant is most likely a consequence of the delta variant's slightly longer (7·8%) presymptomatic infectious period and its higher relative transmissibility (39·3% higher) during this period (calculated on the basis of information in appendix 2 p 24 of the Article from Hart and colleagues).[7]

Vaccines have shown sustainable efficacy and effectiveness at preventing severe disease and death due to SARS-CoV-2 in clinical trials and observational studies, with only moderate reductions in efficacy for new variants of concern.[9] Although slightly longer household generation times were seen for fully vaccinated infectors or infectees versus unvaccinated individuals in the study, there is no unambiguous evidence for considerable

delay of breakthrough transmissions. However, it is possible that the small sample sizes after stratification by vaccination status reduced the power of the study to detect moderate delays. Inadequate effectiveness of vaccines in reducing the generation times of the alpha and delta variants, as shown in the study by Hart and colleagues,[7] suggests that quarantine practices for exposed close contacts should remain unchanged regardless of vaccination status.

The surging omicron variant (B.1.1.529) gained an additional growth rate advantage (2·0–3·5 times) according to the US Centers for Disease Control and Prevention (CDC), which might be explained by a combination of improved inherent transmissibility and immune escape. The observed shorter incubation period of the omicron variant (around 3 days) implies a further shortened generation interval.[10] Household studies with similar designs to the study by Hart and colleagues should be conducted to assess the transmissibility and generation interval of, and vaccine effectiveness against, omicron so that control policies can be amended in a timely manner if necessary.

We declare no competing interests.

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For the **US CDC modelling** see https://www.cdc.gov/coronavirus/2019-ncov/science/forecasting/mathematical-modeling-outbreak.html

CD24Fc: an emerging COVID-19 therapy

In *The Lancet Infectious Diseases,* James Welker and colleagues[1] report a randomised, double-blind, placebo-controlled, phase 3 study of intravenous CD24Fc (480 mg over 60 min on day 1) versus placebo in adults hospitalised with COVID-19 at nine medical centres in the USA. The primary endpoint was time to clinical improvement, defined as time elapsed between a baseline National Institute of Allergy and Infectious Diseases 8-point ordinal scale (NIAID-OS) score of 2–4 and a score of 5 or higher or hospital discharge.[2] Among all 234 participants who were randomly assigned to a treatment group (of whom 62% were male and 38% female, 47% were non-Hispanic White, and median age was 59 years [IQR 48–68]), time to clinical improvement was accelerated among participants who received CD24Fc (median 6·0 days) compared with those who received placebo (10·5 days) over the 28-day study period (hazard ratio [HR] 1·40, 95% CI 1·02–1·92).

The study was well designed, with near-complete protocol adherence and minimal loss to follow-up. However, the trial enrolled participants between April and September, 2020, and preceded landmark clinical trials of dexamethasone,[3] remdesivir,[4] and interleukin-6 (IL-6) receptor antagonists[5] in the treatment of severe COVID-19. As a result, CD24Fc infusion was compared with an outdated standard of care that included a combination of experimental corticosteroids, remdesivir, and convalescent plasma given at the discretion of the treating physician. Since the enrolment period ended, trials have shown that convalescent plasma was not associated with reduced time to clinical improvement,[6] and IL-6 receptor antagonists have emerged as an important part of the COVID-19 treatment framework.[5]

A key component of clinical trial design is ensuring the control group reflects the current standard of


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