such as extreme terminal digit bias and the duplication of blocks of patient records would have been both obvious and immediately interrogable from raw data if provided.

We recommend that meta-analysts who study interventions for COVID-19 should request and personally review IPD in all cases, even if IPD synthesis techniques are not used. In a similar vein, all clinical trials published on COVID-19 should immediately follow best-practice guidelines and upload anonymized IPD so that this type of analysis can occur. Any study for which authors are not able or not willing to provide suitably anonymized IPD should be considered at high risk of bias for incomplete reporting and/or excluded entirely from meta-syntheses.

Hurdles to the release of IPD from clinical trials are well described, and generally addressable with careful anonymization and integration of data sharing plans at the ethical approval stage of trial planning.

We recognize that this is a change to long-accepted practice and is substantially more rigorous than the standards that are typically currently applied, but we believe that what has happened in the case of ivermectin justifies our proposal: a poorly scrutinized evidence base supported the administration of millions of doses of a potentially ineffective drug globally, and yet when this evidence was subjected to a very basic numerical scrutiny it collapsed in a matter of weeks. This research has created undue confidence in the use of ivermectin as a prophylactic or treatment for COVID-19, has usurped other research agendas, and probably resulted in inappropriate treatment or substandard care of patients.

We recognize that by recommending IPD review by default for meta-analysis of potential therapeutic agents in COVID-19 we are calling for change to nearly universally accepted practice over many decades, but the consequent potential for patient harm on a global scale demands nothing less. ❐

Jack M. Lawrence[1], Gideon Meyerowitz-Katz[2], James A. J. Heathers[3], Nicholas J. L. Brown[4] and Kyle A. Sheldrick[5]✉

[1]St George's, University of London, London, UK. [2]School of Health and Society, University of Wollongong, New South Wales, Australia. [3]Cipher Skin, Denver, CO, USA. [4]Linnaeus University, Växjö, Sweden. [5]University of New South Wales, Kensington, Australia.

✉*e-mail: k.sheldrick@unsw.edu.au*

Published online: 22 September 2021
https://doi.org/10.1038/s41591-021-01535-y

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Author contributions

All authors contributed equally to the writing of this manuscript. K.S. and G.M.K. primarily contacted authors requesting IPD for randomized trials.

Competing interests

The authors declare no competing interests.

Check for updates

Monitoring key epidemiological parameters of SARS-CoV-2 transmission

To the Editor — Control of the SARS-CoV-2 pandemic requires targeted interventions, which in turn require precise estimates of quantities that describe transmission. Per-capita transmission rates are influenced by four quantities: (1) the latent period (time from infection to becoming infectious); (2) individual variability in infectiousness (defined by variation in intrinsic transmissibility and contact rate); (3) the incubation period (time from infection to symptom onset); and (4) the serial interval (time between symptom onset of an infector and an infected) (Fig. 1).

Exact knowledge of these four quantities contributes to our ability to control an outbreak[1] but they can vary depending on disease-mitigating interventions[2] and population structure, as well as the inherent properties of the SARS-CoV-2 variant[3,4]. Inaccurate estimates of the four quantities can lead to incorrect estimation of the time-varying reproduction number (R_t) (ref. [5]) and the role or effectiveness of interventions such as testing, isolation and contact tracing on transmission.

As we progress to an even more complicated landscape of SARS-CoV-2 transmission, affected by varying levels of immunity, vaccination and SARS-CoV-2 variants of concern (VOCs), we argue that coordinated studies are needed to continually monitor for changes in transmission behavior.

Changes in virus reproduction numbers are well recognized, but there has been less attention on changes through time in epidemiological parameters that describe other quantities that affect transmission. For example, population-level estimates of infectiousness and the latent period are currently limited to only a few contexts, such as a German hospital population, sports team[6] and returning travellers and healthcare workers[7], all of which have their limitations for generalisability.

As new VOCs arise, the public health community needs to identify quickly what combination of factors contribute to potential increases in transmissibility, so that interventions can be adapted to the specific context within which VOCs emerge. For example, it is hypothesized that higher and earlier peak infectiousness of the Delta variant contributes to higher per-contact transmissibility early in the course of infection[8]. As VOCs will dominate the future of SARS-CoV-2, we will need to monitor the four quantities constantly. If the Delta variant indeed contributes to higher levels of transmission early in an infection, this will change the assessment of the effectiveness of different interventions in reducing transmission.

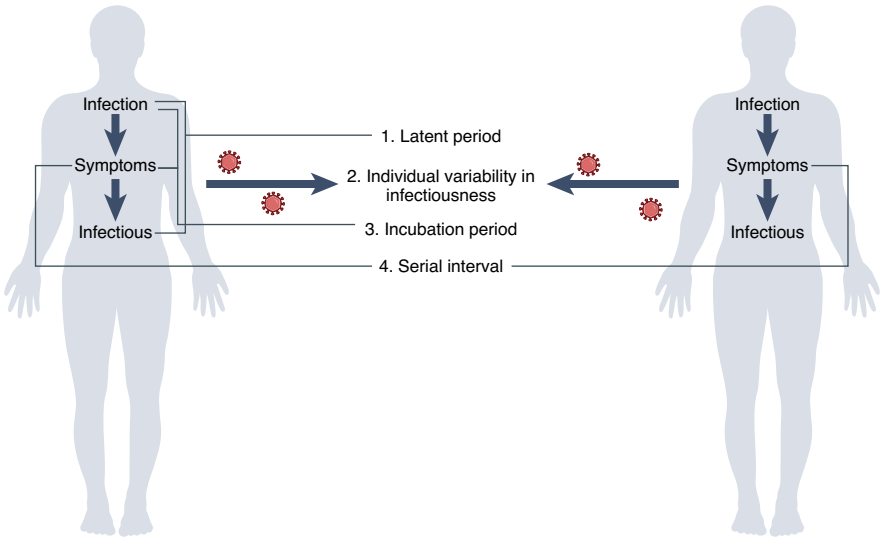

Fig. 1 | Epidemiological parameters of SARS-CoV-2 transmission. Four quantities that affect SARS-CoV-2 transmission are shown.

With sufficient resources, longitudinal studies of about 1,000-case–contact pairs with detailed information of the demographics, genotype, serology and case characteristics (including behavior) as well as regular testing of contacts and their baseline immunity would allow rapid estimation of the four quantities in relation to new VOCs and how they change in relation to pre-existing immunity (from vaccination, previous infection or both)[9]. These longitudinal studies will need to be done in close collaboration with those responsible for contact tracing, and results need to be made available immediately. Further, measuring how individual mutations affect epidemiological quantities such as the incubation period could help anticipate which SARS-CoV-2 lineages may be the ones to follow closest[10].

Opportunities exist when combining contact-tracing data with epidemiological modeling and genomic data to estimate secondary attack rates across settings. When linking modeling and genomic data with digital contact tracing, it may be possible to scale these longitudinal studies to the general population during high levels of virus circulation.

Population-level epidemiological case timeseries may not be highly informative about the four quantities at this stage of the pandemic due to high heterogeneity in SARS-CoV-2 lineage circulation, vaccination and pre-existing immunity. There is therefore a strong need for studies built across disciplinary collaborations between epidemiologists, virologists and clinicians that link together genomic, epidemiological, contact-tracing and context-specific policy information.

Unfortunately, such joint databases rarely exist, and collection methods and protocols vary widely between countries, making it hard to compare findings. There is an urgent need to improve integrated disease surveillance for the COVID-19 pandemic, but investments will not be lost as they are critical for future pandemic and epidemic preparedness and response — a priority recognized by the recently established World Health Organization (WHO) Hub for Pandemic and Epidemic Intelligence and Rockefeller Foundation Pandemic Prevention Institute. ❐

Moritz U. G. Kraemer[1]✉, Oliver G. Pybus[1,2], Christophe Fraser[3], Simon Cauchemez[4], Andrew Rambaut[5] and Benjamin J. Cowling[6]✉

[1]Department of Zoology, University of Oxford, Oxford, UK. [2]Department of Pathobiology and Population Sciences, Royal Veterinary College London, London, UK. [3]Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, Nuffield Department of Medicine, University of Oxford, Oxford, UK. [4]Mathematical Modelling of Infectious Diseases Unit, Institut Pasteur, Université de Paris, CNRS, Paris, France. [5]Institute of Evolutionary Biology, University of Edinburgh, Edinburgh, UK. [6]School of Public Health, The University of Hong Kong, Hong Kong Special Administrative Region, China.
✉*e-mail: moritz.kraemer@zoo.ox.ac.uk; bcowling@hku.hk*

Published online: 8 November 2021
https://doi.org/10.1038/s41591-021-01545-w

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Acknowledgements

M.U.G.K. acknowledges support from The Rockefeller Foundation, Google.org, the EU-H2020 programme MOOD (grant no. 874850), a Branco Weiss Fellowship and the Oxford Martin School. C.F. acknowledges support from the Bill & Melinda Gates Foundation, the Li Ka Shing Foundation, the Wellcome Trust and the UK Department of Health. A.R. is supported by the Wellcome Trust, the Bill & Melinda Gates Foundation and the European Research Council. S.C. acknowledges support from the Investissement d'Avenir program, the Laboratoire d'Excellence Integrative Biology of Emerging Infectious Diseases program (grant 14 ANR-10-LABX-62-IBEID), the European Union's Horizon 2020 research and innovation program under grant 101003589 (RECOVER) and 874735 (VEO), AXA and Groupama. B.J.C. is supported by a fellowship award from the Research Grants Council of the Hong Kong Special Administration, China (project no. HKU SRFS2021-7S03). The contents of this publication are the sole responsibility of the authors and do not necessarily reflect the views of the European Commission or any of the other funders.

Author contributions

M.U.G.K. and B.C. wrote the first draft. All authors edited the manuscript.

Competing interests

C.F. is a consultant for The Public Health Company. B.J.C. has consulted for AstraZeneca, GSK, Moderna, Roche and Sanofi Pasteur. A.R. and O.G.P. have received consulting fees from AstraZeneca. M.U.G.K. and S.C. declare no competing interests.