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.

substantial group of patients who can safely be treated with 3 days of antibiotics. However, of the 706 patients assessed for eligibility on day 3 of therapy, only 310 were eligible for randomisation. Of the 396 who were excluded, many had reasons that would restrict the use of short duration therapy in any health-care setting: 122 were not clinically stable, 80 had severe or complicated community-acquired pneumonia, 22 were homeless or had other reasons that meant they could not be followed up closely, and 80 had advanced renal failure. Why the comparator group was treated for 8 days is unclear, when 5 days are recommended by most experts for patients admitted to hospital with uncomplicated community-acquired pneumonia. No data were provided on the cause of community-acquired pneumonia in this cohort, which is of specific interest because a high prevalence of viral infections has been reported in patients with community-acquired pneumonia.[9] Since many patients with mild illness might have had a non-bacterial cause, it is unlikely that antibiotics, of any duration, could affect their outcome. In fact, among the 50 patients in the placebo group and 57 in the β-lactam group who had procalcitonin levels measured at baseline, those in the β-lactam group had lower levels than those in the placebo group (0·20 μmol/L *vs* 0·55 μmol/L), implying that more patients in the β-lactam group might have had non-bacterial illness and thus no real chance to benefit from extended therapy.[6] Ideally, a study of the duration of therapy should have included only those with bacterial or atypical pathogen infection. However, monotherapy with a β-lactam, as used in Dinh and colleagues' study (US guidelines recommend either a β-lactam plus macrolide combination or fluoroquinolone monotherapy), provides no coverage for atypical pathogens, and could have masked any differences related to duration of therapy.

On the basis of the data from this study, we do not feel that 3 days of treatment can be recommended routinely for patients admitted to hospital for community-acquired pneumonia. We feel that a study using the key features of the current double-blind randomised design should be done, but with more seriously ill patients, with data examining cause of illness, excluding those without documented bacterial or atypical pathogen infection, and taking into account both β-lactam plus macrolide and fluoroquinolone based treatment regimens.

MSN reports grants and personal fees from Shionogi, personal fees from Bayer, Nabriva, and Paratek outside of the area of work commented on here; and has consulted for Fisher Diagnostics on the topic of antimicrobial stewardship of pneumonia. LAM reports personal fees from Merck, Daiichi-Sankyo, Sunovion, and Covance outside of the area of work commented on here.

**Michael S Niederman, Lionel A Mandell*
msn9004@med.cornell.edu

Pulmonary and Critical Care Medicine, New York Presbyterian/Weill Cornell Medical Center, New York, NY 10065, USA (MSN); Division of Infectious Diseases, McMaster University, Hamilton, ON, Canada (LAM)

1 Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. an official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 2019; **200:** e45–67.
2 Uranga A, España PP, Bilbao A, et al. Duration of antibiotic treatment in community-acquired pneumonia: a multicenter randomized clinical trial. *JAMA Intern Med* 2016; **176:** 1257–65.
3 Yi SH, Hatfield KM, Baggs J, et al. Duration of antibiotic use among adults with uncomplicated community-acquired pneumonia requiring hospitalization in the United States. *Clin Infect Dis* 2018; **66:** 1333–41.
4 Schuetz P, Christ-Crain M, Thomann R, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA* 2009; **302:** 1059–66.
5 de Jong E, van Oers JA, Beishuizen A, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. *Lancet Infect Dis* 2016; **16:** 819–27.
6 Dinh A, Ropers A, Duran C, et al. Discontinuing β-lactam treatment after 3 days for patients with community-acquired pneumonia in non-critical care wards (PTC): a double-blind, randomised, placebo-controlled, non-inferiority trial. *Lancet* 2021; 397: 1195–203.
7 Lindenauer PK, Lagu T, Shieh M-S, Pekow PS, Rothberg MB. Association of diagnostic coding with trends in hospitalizations and mortality of patients with pneumonia, 2003–2009. *JAMA* 2012; **307:** 1405–13.
8 el Moussaoui R, de Borgie CAJM, van den Broek P, et al. Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. *BMJ* 2006; **332:** 1355.
9 Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med* 2015; **373:** 415–27.

Risk of SARS-CoV-2 reinfection after natural infection

Published **Online**
March 17, 2021
https://doi.org/10.1016/S0140-6736(21)00662-0

See **Articles** page 1204

Since the start of the COVID-19 pandemic, the question of potential reinfection has been ever present. Although there has been much debate about potential reliance on herd immunity through natural infection, human coronaviruses are well adapted to subvert immunity[1] and reinfection occurs for seasonal coronaviruses (229E, OC43, NL63, and HKU1) that cause the common cold due to ephemeral immunity that is poorly protective between infections.[2] Furthermore, detailed mapping of immune parameters in cohorts such as health-care workers emphasises the heterogeneity of immune responsiveness to SARS-CoV-2, from those with high

Henning Bagger/Getty Images

neutralising antibody titres and broad T-cell repertoires, to the minority with barely detectable immunity.[3] These very low levels of immunity after infection would be hard to equate with protection from reinfection. Furthermore, among the longitudinal studies that have investigated waning antibody levels against SARS-CoV-2, responses have been found to last for 6 months or longer; although, depending on which components of the antibody repertoire are assayed, a substantial minority serorevert to negativity.[4,5]

Despite the substantial advances in all aspects of COVID-19 analysis and data collection over the past year, calculation of the risk of reinfection has been difficult and there are two key reasons for this. The most obvious reason for difficulty is that most individuals around the world who became infected during the first wave of the pandemic did not access a PCR or antibody test and were not admitted to or treated in hospital, and so are not included in many COVID-19 datasets. The second reason is that scientific journals require specific evidence for formal reporting of reinfection, leading to probable under-reporting. For instance, peer reviewers and editors have required evidence from individuals who tested positive by PCR, then recovered and became negative by PCR, and then subsequently tested positive by a second PCR test, with distinct sequenced viral isolates on each occasion.[6] Outside of a research cohort setting, such evidence gathering is rarely achievable and potential confounders exist to reinfection analysis. For example, a minority of individuals can harbour a reservoir of persistent SARS-CoV-2 in the gut,[7] such that distinguishing between true reinfection as opposed to recurrence of the original infection is challenging. A study of health-care workers in Sergipe, Brazil, indicated a relatively high rate of reinfections correlated with the lowest antibody responses,[8] but in most cases the researchers could not confirm de-novo reinfection. From that study, the investigators estimated risk of reinfection to be approximately 7%.[8]

In *The Lancet*, Christian Hansen and colleagues report their population study of a Danish cohort investigating the risk of becoming positive for SARS-CoV-2 by PCR for the second time, presumed to indicate reinfection.[9] The study makes use of data from Denmark's national PCR-testing strategy whereby approximately 4 million people took 10·6 million PCR tests. Because the data in the system were person-identifiable, the authors were able to determine that 3·27% of those who were uninfected during the first surge had a positive test during the second surge, compared with 0·65% among those who had previously recorded a positive test. Thus, they determined from that, in general, past infection confers 80·5% protection against reinfection, which decreases to 47·1% in those aged 65 years and older. Hansen and colleagues acknowledge the many limitations of their analysis being restricted to only PCR data, including the possibility that people might change their behaviour after a positive PCR test. This confounder is addressed by noting that the findings are similar in a sensitivity analysis of nurses, doctors, social workers, and health-care assistants who were tested regularly due to their profession.

Set against the more formal reinfection case reports that are based on differential virus sequence data and make reinfection appear an extremely rare event, many will find the data reported by Hansen and colleagues about protection through natural infection relatively alarming. Only 80·5% protection from reinfection in general, decreasing to 47·1% in people aged 65 years and older are more concerning figures than offered by previous studies. Until now, one of the largest datasets has come from Qatar during a period of high disease burden and reported an estimated reinfection risk of 0·2%.[10] However, a key difference between the studies is that the Danish study is based on a universally accessible national testing programme for both symptomatic and non-symptomatic individuals, whereas the Qatar data are derived from a programme of PCR testing in the context of symptomatic disease. PCR-positive cases within the Danish dataset are thus likely to encompass a far higher proportion of asymptomatic cases presumed to elicit more marginal levels of protective immunity.

The quality, quantity, and durability of protective immunity elicited by natural infection with SARS-CoV-2 are poor relative to the much higher levels of virus-neutralising antibodies and T cells induced by the vaccines currently being administered globally.[11,12] Emergence of variants of SARS-CoV-2 with variable escape from natural and vaccine-induced immunity complicates matters further. Precise correlates of protection against SARS-CoV-2 are not known, but emerging variants of concern might shift immunity below a protective margin, prompting the need for

updated vaccines.[13] Interestingly, vaccine responses even after single dose are substantially enhanced in individuals with a history of infection with SARS-CoV-2.[14] These data are all confirmation, if it were needed, that for SARS-CoV-2 the hope of protective immunity through natural infections might not be within our reach, and a global vaccination programme with high efficacy vaccines is the enduring solution.

RJB and DMA are supported by UK Research and Innovation and Medical Research Council Newton (MR/S019553/1, MR/R02622X/1, and MR/V036939/1), National Institute for Health Research Imperial Biomedical Research Centre: Institute of Translational Medicine and Therapeutics, Cystic Fibrosis Trust Strategic Research Centre, and Horizon 2020 Marie Curie Actions. DMA and RJB have consulted as members of the Global T cell Expert Consortium, Oxford Immunotec, UK, outside of the area of work commented on here.

*Rosemary J Boyton, Daniel M Altmann
r.boyton@imperial.ac.uk

Department of Infectious Disease, Imperial College London, London W12 0NN, UK (RJB); Lung Division, Royal Brompton Hospital, London, UK (RJB); Department of Immunology and Inflammation, Imperial College London, London, UK (DMA)

1 Park A, Iwasaki A. Type I and type III interferons - induction, signaling, evasion, and application to combat COVID-19. *Cell Host Microbe* 2020; **27:** 870–78.
2 Edridge AWD, Kaczorowska J, Hoste ACR, et al. Seasonal coronavirus protective immunity is short-lasting. *Nat Med* 2020; **26:** 1691–93.
3 Reynolds CJ, Swadling L, Gibbons JM, et al. Discordant neutralizing antibody and T cell responses in asymptomatic and mild SARS-CoV-2 infection. *Sci Immunol* 2020; **5:** eabf3698.
4 Manisty C, Treibel TA, Jensen M, et al. Time series analysis and mechanistic modelling of heterogeneity and sero-reversion in antibody responses to mild SARS-CoV-2 infection. *EBioMedicine* 2021; **65:** 103259.
5 Hall V, Foulkes S, Charlett A, et al. Do antibody positive healthcare workers have lower SARS-CoV-2 infection rates than antibody negative healthcare workers? Large multi-centre prospective cohort study (the SIREN study), England: June to November 2020. *medRxiv* 2021; published online Jan 15. https://doi.org/10.1101/2021.01.13.21249642v1 (preprint).
6 To KK-W, Hung IF-N, Ip J, et al. Coronavirus disease 2019 (COVID-19) re-infection by a phylogenetically distinct severe acute respiratory syndrome coronavirus 2 strain confirmed by whole genome sequencing. *Clin Infect Dis* 2020; published online Aug 25. https://doi.org/10.1093/cid/ciaa1275.
7 Robbiani DF, Gaebler C, Muecksch F, et al. Convergent antibody responses to SARS-CoV-2 in convalescent individuals. *Nature* 2020; **584:** 437–42.
8 Dos Santos LA, Filho PGdG, Silva AMF, et al. Recurrent COVID-19 including evidence of reinfection and enhanced severity in thirty Brazilian healthcare workers. *J Infect* 2021; published online Feb 9. https://doi.org/10.1016/j.jinf.2021.01.020.
9 Hansen CH, Michlmayr D, Gubbels SM, Mølbak K, Ethelberg S. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. *Lancet* 2021; published March 17. https://doi.org/10.1016/S0140-6736(21)00575-4.
10 Abu-Raddad LJ, Chemaitelly H, Malek JA, et al. Assessment of the risk of SARS-CoV-2 reinfection in an intense re-exposure setting. *Clin Infect Dis* 2020; published online Dec 14. https://doi.org/10.1101/2020.08.24.20179457.
11 Walsh EE, Frenck RW, Falsey AR, et al. Safety and immunogenicity of two RNA-based COVID-19 vaccine candidates. *N Engl J Med* 2020; **383:** 2439–50.
12 Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* 2020; **396:** 467–78.
13 Altmann DM, Boyton RJ, Beale R. Immunity to SARS-CoV-2 variants of concern. *Science* 2021; **371:** 1103–04.
14 Manistry C, Otter AD, Treibel TA, et al. Antibody response to first BNT162b2 dose in previously SARS-CoV-2-infected individuals. *Lancet* 2021; published online Feb 25. https://doi.org/10.1016/S0140-6736(21)00501-8.

Global health security requires endemic disease eradication

Published **Online** March 4, 2021 https://doi.org/10.1016/S0140-6736(21)00521-3

In 2019, the *Lancet* Commission on malaria eradication contended that malaria can be eradicated within a generation by improving management, operations, and leadership, developing and deploying innovative tools, and spending an additional US$2 billion per year.[1] WHO released a report in 2020 reaffirming its vision for a malaria-free world.[2] These reports described the numerous benefits of malaria eradication, including the synergistic nature of eradication, global health security, and the achievement of universal health coverage. Several countries, regions, and global organisations expressed their commitment to an eradication goal, and enthusiasm in the malaria community was high. Then came the COVID-19 pandemic.

Global health experts were quick to warn of the potential negative impacts of COVID-19 on endemic disease programmes. Modelling studies indicated that disruptions to health services and supply chains from the COVID-19 response could set back efforts to control HIV/AIDS, tuberculosis, and malaria by up to 20 years.[3] In a worst-case scenario, malaria deaths in 2020 were projected to more than double compared with those in 2019.[4] This extreme outcome did not come to pass given the coordinated action by multiple stakeholders to ensure that more than 90% of planned malaria prevention campaigns, including mass net distributions, indoor residual spraying, and seasonal malaria chemoprophylaxis among children, were undertaken in accordance with COVID-19 safety protocols. Still, irregular access to antimalarial treatment could lead to a considerable increase in malaria deaths in sub-Saharan Africa—even a 10% disruption in access could result in 19 000 additional deaths.[5] However, COVID-19 has not universally impacted malaria trends. Countries that recently eliminated malaria, including China, El Salvador, and Malaysia, maintained zero transmission throughout 2020, and El Salvador was certified malaria-free by WHO on Feb 25, 2021.[5–7] Many of the countries that are nearing malaria elimination stayed