COVID-19 containment measures and incidence of invasive bacterial disease

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Interventions implemented amidst ongoing infectious disease outbreaks can act as natural experiments that help to disentangle how pathogens spread and diseases manifest. The most well known example is John Snow's seminal cholera study from mid-19th century London. Suspecting that recurring cholera outbreaks were resulting from drinking water contaminated with sewage, Snow recognised the relocation of water intake pipes to a source upstream from city effluent as an opportunity to test, and ultimately confirm, his hypothesis.

In response to the COVID-19 pandemic declared in early 2020, governments worldwide enacted a range of COVID-19 containment measures to control the spread of SARS-CoV-2, including school and workplace closures, stay-at-home orders, and travel restrictions. These natural experiments have been evaluated for their effects on COVID-19 incidence, human contact behaviour, and other outcomes.[1,2] However, consequences for the spread of pathogens other than SARS-CoV-2 are only just beginning to be revealed.

In this issue of *The Lancet Digital Health*, Angela B Brueggemann and colleagues[3] present results from an extensive international surveillance network uniting 26 countries and territories across six continents, including 24 national reference centres, and use interrupted time series analyses to study the effects of COVID-19 containment measures on invasive disease due to three common respiratory pathogens: *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*. Coincident with COVID-19 containment measures, they observed substantial and sustained reductions in the incidence of hospital-reported invasive disease for each pathogen compared with the years 2018 and 2019. For *S pneumoniae* in particular, which had the largest sample size by an order of magnitude, reductions in incidence were associated with the stringency of containment measures (measured using the Oxford COVID-19 Government Response Tracker) and with corresponding reductions in human mobility (measured using Google COVID-19 Community Mobility Reports). Importantly, in nine countries with available data, they found no change in the incidence of *Streptococcus agalactiae*, a non-respiratory control pathogen, suggesting that neither pandemic-associated breakdowns in surveillance nor changes in health-care seeking behaviours among individuals with invasive disease were responsible for the decreased incidence of *S pneumoniae*, *H influenzae*, and *N meningitidis*.

Indirect efficacy of COVID-19 containment measures for control of respiratory pathogens other than SARS-CoV-2 seems intuitive. Brueggemann and colleagues state that the most plausible explanation for observed reductions in disease incidence is reduction in person-to-person transmission of the bacteria under study. This explanation is supported by an estimated 38% reduction in invasive *S pneumoniae* disease immediately following the implementation of containment measures. However, unlike respiratory viruses, which often spread quickly and infect briefly, these bacteria tend to colonise their hosts as harmless symbionts, only occasionally becoming pathogenic when natural immunological barriers are overcome, causing opportunistic infections such as pneumonia, septicaemia, and meningitis. Colonisation is a necessary precursor to invasive disease, but how the probability of illness varies with time since acquisition remains unclear.

Immediate reductions in disease incidence seem to support the hypothesis that containment measures prevented bacterial disease by blocking bacterial acquisition. However, a competing hypothesis is that containment measures prevented asymptomatic carriers from progressing to disease by blocking transmission of respiratory viruses that trigger bacterial infection. Viral respiratory infection is a known risk factor for invasive bacterial disease, and recent work[4] has identified influenza-like illnesses as important drivers of the seasonal dynamics of invasive pneumococcal disease. In addition to immediate reductions in incidence, the authors estimated a 13% weekly reduction in the incidence of invasive disease due to *S pneumoniae* following implementation of COVID-19 containment measures, for an overall 82% reduction at 8 weeks. It is difficult to interpret the extent to which persistent declines in incidence reflect continued reduction in new

acquisitions versus prevention of disease progression. Future longitudinal studies investigating changes in bacterial carriage and viral infection in different age groups in response to containment measures are needed to help understand these results.

Other factors might have further contributed to the observed trends, including altered transmission of other constituents of the nasopharyngeal microbiome, which can both compete and cooperate with the pathogens under study.[5] Potential interactions between SARS-CoV-2 and respiratory bacteria could also have had a role.[6] More broadly, the pandemic has disrupted antibiotic prescribing and consumption both in hospitals and in the community in many regions.[7–9] These changes might have affected the prevalence of asymptomatic pathogen colonisation, selection for drug-resistant strains, and antibiotic impacts on the microbiome, with potential knock-on effects for susceptibility to colonisation and infection. To date, the impacts of the COVID-19 pandemic on antimicrobial resistance are under-investigated phenomena of potentially great global health significance, for these and other pathogens.[10]

The work by Brueggemann and colleagues shows the importance of maintaining high-quality microbiological surveillance systems during crises, the value of internationally collaborative infectious disease research networks, and together what they can reveal about indirect effects of natural experiments targeting certain pathogens but ultimately affecting others. When John Snow showed that clean drinking water can prevent cholera, *Vibrio cholerae* was not yet discovered. Brueggemann and colleagues show that COVID-19 containment measures in early 2020 protected against invasive diseases caused by respiratory bacteria. However, in the absence of even more comprehensive surveillance data across age groups, including data on asymptomatic carriage of these bacteria and other microorganisms that could influence host susceptibility to disease, the exact reasons remain unclear.

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1 Islam N, Sharp SJ, Chowell G, et al. Physical distancing interventions and incidence of coronavirus disease 2019: natural experiment in 149 countries. *BMJ* 2020; **370:** m2743.
2 Jarvis CI, Gimma A, van Zandvoort K, Wong KLM, Edmunds WJ. The impact of local and national restrictions in response to COVID-19 on social contacts in England: a longitudinal natural experiment. *BMC Med* 2021; **19:** 52.
3 Brueggemann AB, Jansen van Rensburg MJ, Shaw D, et al. Changes in the incidence of invasive disease due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis* during the COVID-19 pandemic in 26 countries and territories in the Invasive Respiratory Infection Surveillance Initiative: a prospective analysis of surveillance data. *Lancet Digit Health* 2021; **3:** e360–70.
4 Domenech de Cellès M, Arduin H, Lévy-Bruhl D, et al. Unraveling the seasonal epidemiology of pneumococcus. *Proc Natl Acad Sci USA* 2019; **116:** 1802–07.
5 Weiser JN, Ferreira DM, Paton JC. *Streptococcus pneumoniae*: transmission, colonization and invasion. *Nat Rev Microbiol* 2018; **16:** 355–67.
6 Amin-Chowdhury Z, Aiano F, Mensah A, et al. Impact of the Coronavirus Disease 2019 (COVID-19) pandemic on invasive pneumococcal disease and risk of pneumococcal coinfection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): prospective national cohort study, England. *Clin Infect Dis* 2021; **72:** e65–75.
7 Malcolm W, Seaton RA, Haddock G, et al. Impact of the COVID-19 pandemic on community antibiotic prescribing in Scotland. *JAC Antimicrob Resist* 2020; **2:** dlaa105.
8 Ryu S, Hwang Y, Ali ST, et al. Decreased use of broad-spectrum antibiotics during COVID-19 epidemic in South Korea. *J Infect Dis* 2021; published online April 15. https://doi.org/10.1093/infdis/jiab208.
9 Rodríguez-Baño J, Rossolini GM, Schultsz C, et al. Key considerations on the potential impacts of the COVID-19 pandemic on antimicrobial resistance research and surveillance. *Trans R Soc Trop Med Hyg* 2021; published online March 27. https://doi.org/10.1093/trstmh/trab048.
10 Knight GM, Glover RE, McQuaid CF, et al. Antimicrobial resistance and COVID-19: intersections and implications. *eLife* 2021; **10:** e64139.