COVID-19, community trials, and inclusion

Richard Baker/Getty images

See **Articles** page 1063

The COVID-19 pandemic has changed the research landscape with the emergence of platform trials. Platform trials are adaptive clinical trials in which patients with a single disease are randomly allocated to different treatments based on an algorithm to investigate whether various agents have clinical benefit.[1] In *The Lancet*, the PRINCIPLE Trial Collaborative Group[2] report no benefit of azithromycin compared with usual care (hazard ratio 1·08, 95% Bayesian credibility interval 0·95–1·23) for suspected COVID-19 in older adults in the community. This result is important for guiding clinical practice, not only for preventing unnecessary treatment of patients with COVID-19 but also for antimicrobial stewardship. Furthermore, the findings accord with the RECOVERY trial and the COALITION II trial of azithromycin for hospitalised patients with COVID-19.[3,4]

Randomised trials provide robust evidence for clinical management with random treatment allocation that ensures no systemic differences between treatment groups, maximising internal validity and reducing both bias and confounding. This community trial recruited a large sample of 2265 participants aged over 65 years, or over 50 with comorbidity, over 6 months, which is remarkable. There were follow-up data for 2120 (94%) of 2265 participants who were included in the Bayesian primary analysis, with 500 participants in the azithromycin plus usual care group, 823 in the usual care alone group, and 797 in other intervention groups. The mean participant age was 60·7 years (SD 7·8), 787 (57%) participants were women and 599 (43%) were men, and 1233 (88%) of 1388 participants had comorbidities. It is important to remember that during this time national guidance and restrictions were in place in the UK, restricting movement of people, and this is reflected in 1586 (70%) participants being recruited online or by telephone. The PRINCIPLE trial and COVID-19 vaccination roll-out in the UK have highlighted the importance of a good primary care platform to address challenges to health of the population. Therefore, primary care is needed now more than ever in the UK and globally.[5]

For the **PRINCIPLE trial news** see https://www.principletrial.org/news

The PRINCIPLE trial goes some way to reflect groups that are vulnerable to the more serious complications of SARS-CoV-2 infection and is a step in the right direction for external validity. External validity can be a particular limitation in clinical trials, where strict inclusion and exclusion criteria mean that participants are usually younger and have fewer comorbidities than the target population of the intervention.[6]

Only 434 (31%) of 1388 participants with suspected COVID-19 had PCR-confirmed SARS-CoV-2 infection because of low availability of community testing, although this increased during the trial. The initial primary endpoint was hospitalisation or mortality within 28 days, which was amended to a coprimary outcome with addition of self-reported illness duration because of lower than expected hospitalisation during the changing pandemic.

Although many of the challenges of conducting a trial during the COVID-19 pandemic were successfully navigated, important limitations remain. First, a lack of representation by people from Black and minority ethnic (BAME) backgrounds, which is also reflected in other COVID-19 clinical trials.[7] Given the large trial and the disproportionate impact of COVID-19 on minority ethnic communities,[8,9] it is surprising that so few participants from these communities were recruited—only seven (1%) participants were Black and 55 (4%) were south Asian. The inclusion strategy is not detailed in the paper. However, the PRINCIPLE website states that a BAME expert joined the collaboration 3 months before the azithromycin group ended to facilitate recruitment from these vulnerable communities.

The reasons for exclusion of minority ethnic groups more generally in clinical trials are complex. These might be related to doctor or researcher factors, language barriers, and cultural and wider societal factors.[10] In reported trials, it might not be clear what the main factors are—eg, planned exclusion, inadvertent exclusion, non-participation, or a mixture of these.[11] Indeed, it has been documented that minority ethnic communities are willing to participate in research if it is directly relevant to them, and if researchers approach them with respect and sensitivity and provide them with relevant and well defined explanations of what participation involves.[12,13] There is a need for researchers to state in their protocol how they will ensure inclusion of marginalised groups, including minority ethnic communities. Guidance exists, with recommendations for research funders to apply a checklist to assess whether research proposals have been codesigned with underserved groups and whether proposed recruitment methods are likely to

successfully recruit underserved groups.[14] Additionally, it is recommended that funders ensure additional funds are available to research teams to support recruitment of underserved groups; indeed, it is incumbent on funders to ensure that funds are available to enable this. Furthermore, policy makers need to question the validity of results before implementation.

A second limitation of the PRINCIPLE trial[2] is that participant deprivation was not considered, although participants were recruited from across the UK. Deprivation is a major determinant of health outcomes[15] and should be reported with baseline characteristics.

One of the many lessons of the SARS-CoV-2 pandemic is the disproportionate effects it has had on vulnerable communities, particularly those from minority ethnic and deprived backgrounds, further widening existing health inequalities.[16] This pandemic provides the opportunity for greater equity in health for all vulnerable populations, with their inclusion in trials in the UK and globally.

PSG is trustee of the South Asian Health Foundation and receives support from the National Institute for Health Research (NIHR) Applied Research Collaborations West Midland, the NIHR Global Health Research Unit on Improving Health in Slums at the University of Warwick (16/136/87), and the NIHR Global Health Group on Addressing Smokeless Tobacco Use and Building Research Capacity in South Asia at the University of York. SP holds an NIHR Academic Clinical Lecturer fellowship. The views expressed in this publication are those of the authors and not necessarily those of the NIHR or the UK Department of Health and Social Care. RI reports grants from the NIHR Global Health Research Unit on Improving Health in Slums at the University of Warwick, grants from NIHR Global Health Group on Addressing Smokeless Tobacco Use and Building Research Capacity in South Asia at the University of York, grants from Medical Research Council Trials—Children Learning About Second Hand Smoke at the University of York, grants from Bloomberg—Campaign for Tobacco-Free Kids Smoke-Free Karachi at the Aga Khan University, and is co-investigator on a grant (time is not budgeted) from Hamilton Health Sciences—Prospective Urban and Rural Epidemiological Studies at the Population Health Research Institute, Canada. JST declares no competing interests.

Paramjit S Gill, Shoba Poduval, Jarnail S Thakur, Romaina Iqbal
p.gill.1@warwick.ac.uk

Warwick Medical School, University of Warwick, Coventry CV4 7AL, UK (PSG); UCL eHealth Unit, Department of Primary Care and Population Health, University College London, London, UK (SP); Department of Community Medicine and School of Public Health, Post Graduate Institute of Medical Education and Research, Chandigarh, India (JST); Department of Community Health Sciences, Aga Khan University. Karachi, Pakistan (RI)

1 Berry SM, Connor JT, Lewis RJ. The platform trial: an efficient strategy for evaluating multiple treatments. *JAMA* 2015; **313:** 1619–20.
2 PRINCIPLE Trial Collaborative Group. Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet* 2021; **397:** 1063–74.
3 RECOVERY Collaborative Group. Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021; published online Feb 2. https://doi.org/10.1016/S0140-6736(21)00149-5.
4 Furtado RHM, Berwanger O, Fonseca HA, et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. *Lancet* 2020; **396:** 959–67.
5 WHO. The World Health Report 2008—primary health care (now more than ever). Geneva: World Health Organization, 2008.
6 He J, Morales DR, Guthrie B. Exclusion rates in randomized controlled trials of treatments for physical conditions: a systematic review. *Trials* 2020; **21:** 228.
7 Chastain DB, Osae SP, Henao-Martínez AF, Franco-Paredes C, Chastain JS, Young HN. Racial disproportionality in Covid clinical trials. *N Engl J Med* 2020; **383:** e59.
8 Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; **584:** 430–36.
9 Public Health England. Disparities in the risk and outcomes of COVID-19. August, 2020. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/908434/Disparities_in_the_risk_and_outcomes_of_COVID_August_2020_update.pdf (accessed March 5, 2021).
10 Treweek S, Forouhi NG, Narayan KMV, Khunti K. COVID-19 and ethnicity: who will research results apply to? *Lancet* 2020; **395:** 1955–57.
11 Redwood S, Gill P. The under-representation of ethnic minority groups in research studies. *Br J Gen Pract* 2013; **63:** 342–43.
12 Gill PS, Plumridge G, Khunti K, Greenfield S. Under-representation of minority ethnic groups in cardiovascular research: a semi-structured interview study. *Fam Pract* 2013; **30:** 233–41.
13 Ekezie W, Czyznikowska BM, Rohit S, et al. The views of ethnic minority and vulnerable communities towards participation in COVID-19 vaccine trials. *J Public Health (Oxf)* 2020; published online Oct 30. https://doi.org/10.1093/pubmed/fdaa196.
14 National Institute for Health Research. INCLUDE Roadmap can help researchers make trials more inclusive. Nov 9, 2020. https://evidence.nihr.ac.uk/alert/include-roadmap-can-help-researchers-make-trials-more-inclusive/ (accessed March 5, 2021).
15 Institute of Health Equity. Health equity in England: the Marmot review 10 years on. 2020. http://www.instituteofhealthequity.org/the-marmot-review-10-years-on (accessed March 9, 2021).
16 Blundell R, Costa Dias M, Joyce R, Xu X. COVID-19 and inequalities. *J Appl Econ* 2020; published online June 27. https://doi.org/10.1111/1475-5890.12232.

Sustained neutralising antibodies in the Wuhan population suggest durable protection against SARS-CoV-2

SARS-CoV-2 infections were first reported in Wuhan, China, in 2019,[1] and quickly became a global pandemic, as declared on March 11, 2020.[2] SARS-CoV-2 is highly infectious[3] and COVID-19 is variable in its presentation, with many infected individuals, as detected by viral nucleic acid screening, being asymptomatic.

In *The Lancet*, Zhenyu He and colleagues[4] report their cross-sectional study of serological responses of more than 9500 individuals from 3600 households in Wuhan, the early epicentre for the COVID-19 outbreak. The study was initiated shortly after lockdown in Wuhan ceased in April, 2020, with follow-up over two timepoints

See **Articles** page 1075