rhetoric must soon translate into action to prevent the disastrous consequences of an even greater humanitarian crisis in Afghanistan. Taliban rule threatens to reverse significant achievements in health equity and public health infrastructure over the past two decades, and international aid organizations and states must seek out innovative approaches to avoid such regression. These responsibilities include comprehensive refugee resettlement and sustainable healthcare aid deployment to protect the vulnerable and reduce dependency over the long term. While Western policies have abandoned Afghanistan to the Taliban, the world cannot abandon the Afghan people; the stakes to global health are too high. ❑

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Check for updates

The lesson of ivermectin: meta-analyses based on summary data alone are inherently unreliable

To the Editor — The global demand for prophylactic and treatment options for COVID-19 has in turn created a demand for both randomized clinical trials, and the synthesis of those trials into meta-analyses by systematic review. This process has been fraught, and has demonstrated the inherent risks in current approaches and accepted standards of quantitative evidence synthesis when dealing with high volumes of recent, often unpublished trial data of variable quality.

Research into the use of ivermectin (a drug that has an established safety and efficacy record in many parasitic diseases) for the treatment and/or prophylaxis of COVID-19 has illustrated this problem well. Recently, we described flaws in one randomized control trial of ivermectin[1], the results of which represented more than 10% of the overall effect in at least two major meta-analyses[2,3]. We described several irregularities in the data that could not be consistent with them being experimentally derived[4]. That study has now been withdrawn by the preprint server[5] on which it was hosted. We also raised concerns about unexpected stratification across baseline variables in another randomized controlled trial for ivermectin[6], which were highly suggestive of randomization failure. We have requested data from the authors but, as of

6 September 2021, have not yet received a response. This second ivermectin study has now been published[6], and there is still no response from the authors in a request for data.

The authors of one recently published meta-analysis of ivermectin for COVID-19[3] have publicly stated that they will now reanalyze and republish their now-retracted meta-analysis and will no longer include either of the two papers just mentioned. As these two papers[1,6] were the only studies included in that meta-analysis to demonstrate an independently significant reduction in mortality, the revision will probably show no mortality benefit for ivermectin.

Several other studies that claim a clinical benefit for ivermectin are similarly fraught, and contain impossible numbers in their results, unexplainable mismatches between trial registry updates and published patient demographics, purported timelines that are not consistent with the veracity of the data collection, and substantial methodological weaknesses. We expect further studies supporting ivermectin to be withdrawn over the coming months.

Since the above primary studies were published, many hundreds of thousands of patients[7] have been dosed with ivermectin,

relying on an evidence base that has substantially evaporated under close scrutiny.

Relying on low-quality or questionable studies in the current global climate presents severe and immediate harms. The enormous impact of COVID-19 and the consequent urgent need to demonstrate the clinical efficacy of new therapeutic options provides fertile ground for even poorly evidenced claims of efficacy to be amplified, both in the scientific literature and on social media. This context can lead to the rapid translation of almost any apparently favorable conclusion from a relatively weak trial or set of trials into widespread clinical practice and public policy.

We believe that this situation requires immediate remediation. The most salient change required is a change in perspective on the part of both primary researchers and those who bring together the results of individual studies to draw wider conclusions. Specifically, we propose that clinical research should be seen as a contribution of data toward a larger omnibus question rather than an assemblage of summary statistics. Most, if not all, of the flaws described above would have been immediately detected if meta-analyses were performed on an individual patient data (IPD) basis. In particular, irregularities

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. ❏

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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.