does not lie in wasteful personalized disease overtreatment but in timely and appropriate personalized health care for at-risk populations. ❐

Editorial note: This article has been peer reviewed.

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Competing interests

D.A.H. consults for Johnson & Johnson, Verily Life Sciences, and Worrell. He has received research support from Olympus. A.P. is on the Advisory Boards of Pear Therapeutics. G.P.P. consults for Johnson & Johnson, Takeda, Bristol-Myers Squibb, Eli Lilly and Tolero, and serves on the Board of Directors of Axcella Health and Celixir.

Diagnostics and the coronavirus: don't let the standards slip

To the Editor — The development of rapid and reliable molecular diagnostic tests for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is paramount for controlling the COVID-19 pandemic. A similar scenario was faced in the Ebola virus outbreak in West Africa, in which rapid, reliable tests were key to controlling the outbreak. However, in the rush to scale up testing availability, the importance of standardization, though critical, is often overlooked by laboratories when setting up assays. As an example, different sensitivities of real-time reverse transcriptase PCR (RT-PCR) kits can have considerable clinical impact because different tests might yield undetectable results at different time points, which could inappropriately prolong or shorten patient isolation times. Standardization is also important for accelerating clinical trials for novel preventive (vaccines) and therapeutic approaches. Here, we argue that standardization should be built into the COVID-19 response and should be considered in future epidemics and pandemics.

A recent *Nature* news item[1] highlighted the need to develop rapid and reliable molecular diagnostic tests for SARS-CoV-2. A similar situation occurred during the Ebola virus outbreak in West Africa, when rapid and reliable tests were crucial to controlling disease spread. The importance of standardization is illustrated in a study by Cherpillod et al.[2], which noted that the different sensitivities of real-time RT-PCR kits for Ebola detection had considerable clinical impact, as different tests could yield undetectable results at different time points, potentially influencing how long patients were kept in isolation. The authors recommended that results be reported in international units (IU) per milliliter using an international quantification standard. At the time of the outbreak, it was recognized that the use of reference standards would help provide reliable and robust assays[3,4], and current recommendations are to use a World Health Organization (WHO) International Standard (IS) in assays as and when one becomes available. Moreover, the WHO produces Target Product Profiles that include the need to include standards in assays.

The WHO and its collaborating centers for standards, the Paul Ehrlich Institute (Germany), the US Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER) and the UK's National Institute for Biological Standards and Control (NIBSC), have an ongoing program to develop an IS to harmonize the measurement of pathogens in diagnostic assays. For emerging diseases that require biocontainment (Biosafety Levels 3 and 4), packaging pathogen-specific sequences in lentiviral vectors proved to be very effective in harmonizing the measurement of ebolavirus by nucleic acid test (NAT)[5]. As has been consistently shown in collaborative studies performed to establish an IS, the varying performance of individual laboratories' assays against an in-house standard typically leads to a wide variety of results for the same sample (Fig. 1a). It is possible that this could result in different clinical decisions for patients, depending on which lab their sample was tested in. However, calibration against an IS effectively eliminates this variability to a large degree (Fig. 1b). This has important implications not just for individual patients, but also for the reproducibility and reliability of data in clinical trials, such as those to establish the immunogenicity of novel vaccines.

Urgent work is ongoing, in collaboration with the WHO, to develop interim reference materials that will assist in harmonizing NAT-based diagnostics for SARS-CoV-2. Although these materials will not be available immediately as formal standards, similarly produced full-genome reagents are already available from the NIBSC (via covid19_reagents@nibsc.org, catalog number 19/304). The consistent use of standards will help to establish diagnostic assay performance and support the early development of accurate and reliable tests with comparable sensitivity. We strongly encourage the scientific community and diagnostic labs to strive for standardization and employ relevant reference materials as

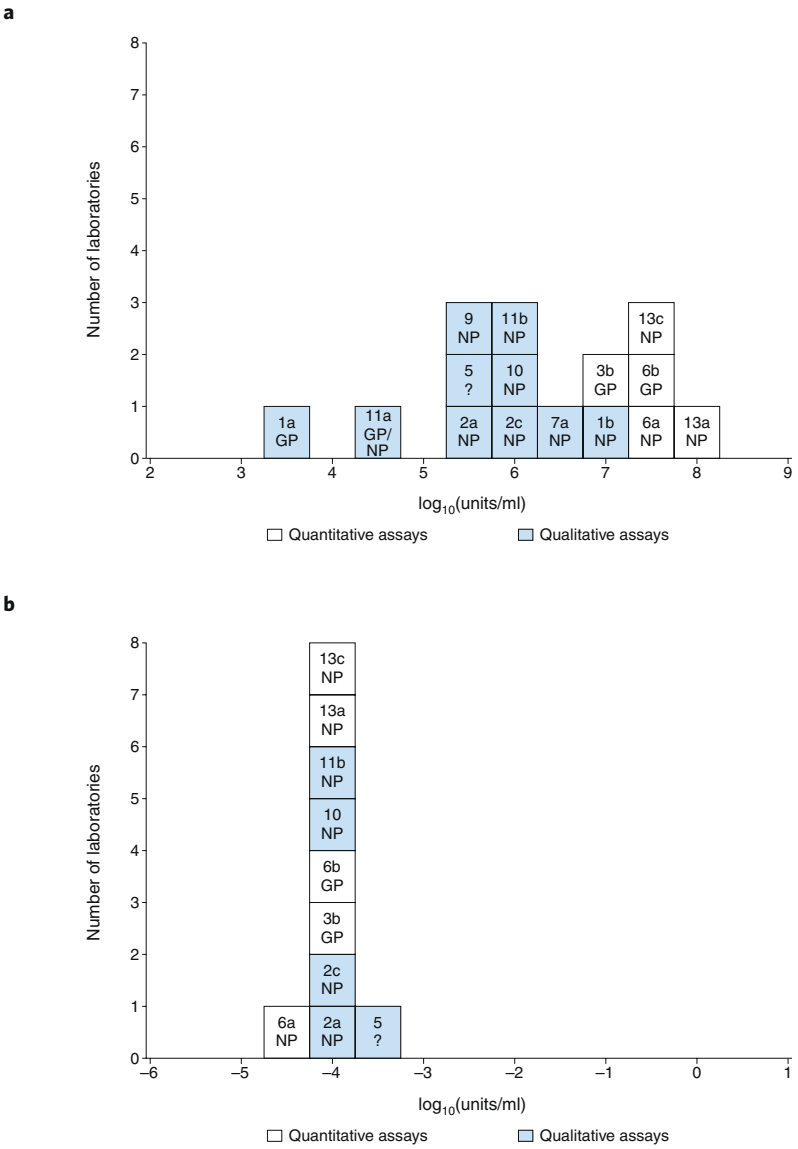

Fig. 1 | An example of how an external reference standard can harmonize data and reduce inter-lab variation. a,**b**, Potency estimates for an Ebola RNA sample relative to an in-house standard (**a**) and reporting of the sample relative to an independent reference reagent (**b**). Histograms of the mean laboratory estimates in quantitative (white squares) or qualitative (blue squares) NAT assays. The estimated values are shown on the horizontal axis and the number of laboratories is indicated on the vertical axis. The results are reported as $\log_{10}$(copies/ml) for quantitative assays and $\log_{10}$(NAT-detectable units/ml) for qualitative assay. Each box represents the mean estimate from one laboratory assay and is labeled with the alphanumeric laboratory code and assay target. Harmonization was independent of the assay target commonly used by laboratories (nucleoprotein (NP) or glycoprotein (GP)). Adapted from ref. [6].

they become available so as to establish the relative sensitivity and limit of detection of assays. This will be a key determinant for success in handling the COVID-19 crisis and future infectious disease outbreaks. ❐

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Competing interests

The National Institute for Biological Standards and Control (NIBSC) is a center of the Medicines and Healthcare Products Regulatory Agency, an Agency of the UK Government's Department of Health and Social Care. It fulfils its public health role through the standardization and control of biologicals used in medicine. NIBSC's strategy includes anticipating emerging quality and safety issues associated with existing and future biological medicines, and facilitation of the development of novel biological medicines and diagnostics. In some instances, it is appropriate for NIBSC to charge commercial and other organizations for its products and services, in line with guidance issued from Her Majesty's Treasury ('Fees & Charges Guide' and 'Selling into Wider Markets'). NIBSC endeavors to make the same products and services equally available to commercial organizations, without prejudice.