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adds substantial costs to health care,⁸ and the risk-benefit ratio of IMV varies considerably with age, comorbidities, and baseline functional status. It is time that we looked beyond short-term survival and define which populations of patients with acute hypoxaemic respiratory failure are most likely to meaningfully benefit from IMV. In addition to drawing from the evidence base, engagement with patients is central to making this decision.

The pandemic has certainly allowed us to reimagine the future management of acute hypoxaemic respiratory failure. There are many approaches clinicians can take to delay IMV or avoid IMV altogether. The risk-benefit ratio and the costs of this approach requires investigation in clinical trials. The majority of patients with acute hypoxaemic respiratory failure who receive IMV do so because of worsening hypoxaemia and respiratory muscle fatigue from an increased work of breathing.⁹ In addition to awake prone positioning, pharmacological adjuncts such as nitric oxide gas, which were introduced in attempt to improve oxygenation in non-intubated patients during the pandemic, need further testing in clinical trials. Environmental modifications, staff education, patient compliance, and the pharmacological management of anxiety and agitation are all critical components to the success of awake strategies that aim to avoid IMV. Minimising the reliance on the diseased native lungs for gas exchange with the use of extracorporeal techniques merits consideration too. For example, extracorporeal carbon dioxide removal might allow better control of respiratory effort and in select patients might help prevent IMV. Awake extracorporeal membrane oxygenation¹⁰ without IMV might be a viable option in select patients. Moving forward, although IMV is inevitable in some patients, there might be room for better integration and greater personalisation of respiratory supports that allow patients to be awake, ambulatory, and rehabilitate while maintaining their autonomy.

A concerted, collaborative undertaking of research across disciplines is needed to tackle acute hypoxaemic respiratory failure globally. Inequities in health-system access is morally confronting. Future acute hypoxaemic respiratory failure research should also focus on low-cost, high-value respiratory supports, such as awake prone positioning, which are tailored for resource poor settings. Hopefully, in the post-pandemic world, we will be one step closer to offering more personalised, equitable, value-driven, and evidence-based respiratory supports for patients with acute hypoxaemic respiratory failure.

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Ending the tuberculosis syndemic: is COVID-19 the (in)convenient scapegoat for poor progress?

Tuberculosis is a syndemic. Elimination requires a syndemic approach that addresses the individual and societal vulnerabilities that determine whether

we become infected, get sick, die, or get better with disability and an impact on livelihoods.¹ The WHO End TB Strategy, a global initiative launched in 2015,



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signifies that syndemic approach. End TB outlines fundamentals required to modify determinants of ill health, promote prevention of disease and early diagnosis with prompt treatment to save lives, prevent economic hardships, and reduce transmission. Yet, even before COVID-19 emerged, we were on track to miss all targets.² The situation is unlikely to improve without a shift in our attitude to tuberculosis elimination.

2 years on from the start of the global response to COVID-19, it is a good time to reflect on what the pandemic has taught us about our elimination efforts and ability to handle threats to tuberculosis control. In a Series of papers published in *The Lancet Respiratory Medicine* and *eBioMedicine* to coincide with World TB Day 2022, the authors provide an account of current threats to tuberculosis control. Keertan Dheda and colleagues³ give a painful synopsis of the impact of COVID-19 on tuberculosis, while Ruvandhi Nathavitharana and colleagues⁴ and Hanif Esmail and colleagues⁵ address the ongoing threat of paucibacillary and subclinical tuberculosis.

Tuberculosis was declared a public health emergency in 1993.⁶ However, the years that followed this declaration proved tuberculosis to be the most non-urgent emergency. COVID-19, by contrast, was declared an emergency in January, 2020. The new pandemic starkly revealed the impact of underlying health inequalities, but it also demonstrated what can be achieved with sufficient global effort. The response was a model of public health action in an emergency. Within months of the emergence of SARS-CoV-2, we often saw high-quality science informing the response and shaping policy. Nothing was off the table, from use of multidisease big data and multinational collaboration to discover novel diagnostics and therapies, to innovation in service delivery.^{7,8}

Even when the COVID-19 response has failed, it has provided lessons for future tuberculosis research and control, and an indication of how we should deliver the benefits of research, construct equitable partnerships, and source and share funding. Failure to enact the Trade-Related Aspects of Intellectual Property Rights (TRIPS) waiver⁹ and the resulting vaccine apartheid provides a clear warning of global health inequalities and threats to the right to benefit from future tuberculosis science. Access to SARS-CoV-2 vaccines has since improved, but when these reach countries in need, roll-out is often hindered by vaccine hesitancy and operational challenges,

a poignant lesson in preparedness for novel tuberculosis vaccines and products. COVID-19 also triggered an unprecedented influx of funds for innovation; however, the most value added, with respect to people and expertise, remains in richer countries. US\$104 billion was spent on COVID-19 research and development in the first 11 months of the pandemic, in contrast to \$5.5 billion on tuberculosis research and development in the past decade. Less than \$60 billion has been spent on tuberculosis activities over this period.¹⁰

COVID-19 wiped out 10 years of gains in tuberculosis outcomes in less than 10 months. Evidently, we did not build and prepare resilient health programmes for tuberculosis. Programmes for other diseases appear to be more resilient and were affected less. The number of tuberculosis deaths (excluding those caused by HIV) rose for the first time in 10 years in 2020–21.³ By contrast, the number of HIV deaths has stayed low. Since 2015, when HIV was announced as the number 1 cause of death from an infectious agent, we have seen better-funded HIV programmes substantially lower mortality to below that of tuberculosis. The HIV response evolved to become patient-centric and offer inspired, decentralised care (eg, community antiretroviral clubs and HIV self-testing¹¹) and robust distribution systems for antiretrovirals, and successfully incorporated its goals within other programmes to reflect HIV priorities.¹² As a result, the delivery of care for HIV has been less affected by COVID-19. The observation by Dheda and colleagues³ that we need similar patient-centric, whole-systems approaches for tuberculosis is on point. The End TB Strategy is the foundation for this, but it needs better funding and a more innovative approach to spending.

Threats to tuberculosis elimination can be inherent to the disease area, but can also come from outside, as observed with the emergence of COVID-19. For example, subclinical tuberculosis has re-emerged as a threat of daunting proportions.¹³ In their papers, Nathavitharana and colleagues and Esmail and colleagues highlight specific diagnostic and therapeutic research gaps, and propose inspiring solutions for addressing subclinical tuberculosis.^{4,5} However, the current research funding gap, US\$900 million annual expenditure against a target of \$2 billion, continues to hamper success.

Multimorbidity and failure to develop integrated care pathways is another new threat. Integration is deemed to be complex, needing extensive systems innovation,

and therefore costly. This neglect of multimorbidity in poorer countries has resulted in major gaps in care and in data.¹⁴ COVID-19 revealed how vulnerable both populations and health programmes are to external threats when multimorbidity is neglected. But it also revealed how multidisease platforms and approaches could be used. Pandemic preparedness should not only be about algorithms to predict unknown threats, but equally address prevention and care of prevalent conditions, even during a co-emergency. We need a multidisease framework funded and implemented across multiple disease programmes to achieve this, eventually moving away from a single-disease focus. This would see the tuberculosis community invest in interventions that benefit tuberculosis as well as associated multimorbidities, with the goal to improve health overall. Benefits of the framework would be greater cooperation with other disease sectors, mutual funding, and human resource support.

We have failed to address health inequities and tackle inadequacies in care, systems, and innovation. The global community has fallen short in providing the tools and funding needed to enable us to achieve our goals. As we chart the way forward, we need to reimagine the End TB agenda, and do so within a well-funded, multidisease framework to guarantee resilient systems and better preparedness for future extrinsic threats.

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The crucial need for tuberculosis translational research in the time of COVID-19



The world is still grappling with the devastating effects of COVID-19 more than 2 years into the pandemic. Countries with high COVID-19 vaccination rates are transitioning to the new normal of living with SARS-CoV-2, but low-income and middle-income countries (LMICs) are struggling to vaccinate their populations while concurrently fighting other communicable diseases, key among them tuberculosis. The burden of tuberculosis, the leading cause of death

from an infectious disease before COVID-19 emerged, has been deeply affected by the pandemic.^{1,2} In the first of a Series of three papers published in *The Lancet Respiratory Medicine* and *eBioMedicine*, Keertan Dheda and colleagues³ discuss the effects of COVID-19 on efforts to end tuberculosis and the need for wide-ranging interventions to restore tuberculosis control, including the need to implement and enhance tuberculosis diagnostic tests to reduce under-diagnosis.

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