Title: The impact of COVID-19 on tuberculosis burden: a review of the data available to evaluate and respond

Running title: Impact of COVID-19 on TB: a review of the data

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Early in the COVID-19 pandemic, models predicted hundreds of thousands of additional tuberculosis (TB) deaths as a result of health service disruptions. To date, empirical evidence of the effects of COVID-19 on TB outcomes has been limited. Here we summarize the evidence available at a country level, identifying broad mechanisms by which COVID-19 may modify TB burden and mitigation efforts.

Where data are available, it is clear that there have been substantial TB health service disruptions and an increase in vulnerability to TB. Evidence for changes in *Mycobacterium tuberculosis* transmission is limited, and it is unclear how the resources required and available for the TB response have changed. To advocate for additional funding to mitigate the impact of COVID-19 on the global TB burden, and to efficiently allocate resources for the TB response, a significant improvement in TB data is required.

Introduction

Given concerns for maintaining TB care and prevention services during the COVID-19 pandemic,[1] mathematical modelers have attempted to estimate the potential impact of program disruptions on TB incidence and mortality.[2-5] Despite the use of different methods and assumptions about the future of the pandemic, as well as modelling a variety of settings including India, China, South Africa, Kenya, Ukraine and Brazil, these analyses reached broadly similar conclusions. Specifically, TB incidence, and especially TB mortality, are projected to increase by around 5-15% over the next 5 years, amounting to hundreds of thousands of additional TB deaths worldwide during that time. These early modeling analyses, however, relied on a number of assumptions, which should ideally be re-evaluated in the context of empirical data. Since these analyses were produced, little empirical evidence has been systematically collected to quantify the impact of COVID-19 on TB burden. A data-driven understanding of this impact is necessary to support efforts to mitigate it, revising the implementation of TB services and the allocation of resources to different TB interventions. To implement and prioritise effectively, it is essential to understand the current situation.

We expect COVID-19 to affect TB outcomes differently by setting. For example, countries with large TB burden such as India and Viet Nam have experienced very different COVID-19 incidence.[6] Countries with similar COVID-19 burden such as Brazil and Argentina have experienced very different health system disruptions.[7] Indeed, within individual countries the impact will further vary between rural and urban areas, by socioeconomic status, and as response measures vary spatially. With all of this variation, it is therefore important to focus on the measurement of setting-specific impact. It is also important to identify when the impact was measured, as the temporal effect of the pandemic varies between countries.

Here we review the evidence available, to inform the revision of both implementation and allocation of resources by TB programmes. We identify where country-specific data and evidence can be found to quantify the impact of COVID-19 on TB outcomes, and the costs of any mitigation. We outline in Figure 1 the conceptual framework to scope our narrative review, specifying how COVID-19 may impact across the TB care cascade, identifying disruptions to TB health service delivery and changes in demand, alterations in vulnerability to TB (including comorbidities and risk factors), and opportunities for *Mycobacterium tuberculosis* (*Mtb*) transmission. Lastly, we identify data on the impact of COVID-19 on both availability and requirements of TB resources. We collate this evidence in Table 1, and end by highlighting knowledge gaps which should be prioritized for study.

Search strategy and selection criteria

We conducted a narrative and bibliometric review, combining a rapid semi-systematic search and convening a range of experts. For the rapid review references were identified through searches of PubMed, medRxiv and bioRxiv for articles published from January 2020 to January 2021, using the terms “COVID” or “SARS” or “corona”, and “TB” or “tuberculosis”. In addition, literature relevant to TB vulnerabilities, *Mtb* transmission and TB resources was identified through the authors’ personal libraries. Additional relevant grey literature was identified through communication with the WHO Global TB Department, as well as through a virtual meeting of the TB Modelling and Analysis Consortium, where a group of TB experts from global agencies, academic institutions and country programmes were invited to identify additional sources of data and to confirm and highlight priority knowledge gaps. Grey literature were included in this instance as they represent a significant proportion of the relevant data available to country-level TB decision makers when making policy choices. Articles resulting from these searches and relevant references cited in those articles were reviewed.

Articles which contained data on country-specific quantitative changes to TB health service indicators, burden of TB vulnerabilities, *Mtb* transmission and TB resources for the World Health Organization high TB, TB/HIV and multidrug-resistant (MDR) TB burden countries were included, and data extracted from these articles. A summary of sources found by country on each topic is presented in Table 1. We provide a narrative synthesis of our findings below. Ethical approval was not required for this study.

Tuberculosis health services

The provision of TB health services (TB diagnosis, care and prevention services), and access to these services, has been severely disrupted by COVID-19.[8-10] TB service providers across many high TB burden contexts have faced difficulties in service provision, due to lack of appropriate equipment and capacity, restrictions to movement (affecting health care workers, commodities and stock), and reallocation of resources.[9] Meanwhile, individual TB patients have struggled to access TB services, whether through fear of SARS-CoV-2 infection, fear of stigma, restrictions to movement, reduced health facility opening hours, or reductions in ability to pay for care or transport.[8] Globally, TB diagnosis, care and prevention has been affected as a result. However, nearly a year after these disruptions first hit, very little high-level information is available, focused primarily on reductions in the number of TB patients.[11] Most data that are available focus on the first two quarters of 2020, with very little data except for patient numbers available for quarters three and four when services might be expected to be somewhat restored.

Most high TB burden countries have observed some changes in TB case numbers or notifications (when TB is diagnosed in a patient and this is reported through the national surveillance system) that have resulted due to COVID-19.[12-31] Continuous surveillance systems and current data collection efforts[32,33] suggest that additional data may also be forthcoming. In general, TB notifications decreased significantly during the early stages of the pandemic compared to previous years. The United States Agency for International Development preliminarily estimates that over 1 million fewer cases in 24 high TB burden countries alone may have been notified in 2020 as a result of the pandemic, with a 7% relative reduction in Africa, a 15% reduction in Central Asia and Europe and a 27% reduction in Asia compared to 2019.[34] A limited number of countries appear to have either avoided this trend (such as Mozambique and Tanzania) or have seen notifications dip and since recover to pre-pandemic levels (such as China and Viet Nam).[12] However, without data on TB testing and positivity rates it is difficult to determine whether this widespread decrease in notifications reflects a true decrease in incidence, or a decrease in access to TB diagnostic services. In several countries where testing data, including for drug sensitivity testing, are available (China,[15-17] Nigeria,[35] the Philippines[36] and South Africa[37], with further studies underway in Kenya, Malawi and Zimbabwe[38], as well as Brazil, Uganda and Viet Nam[39]), testing decreased. In South Africa this was accompanied by a corresponding increase in TB test positivity (the proportion of TB tests which were positive).[37] The implication of this is that there are likely to be large numbers of undiagnosed cases of TB in the community, who may now face poorer treatment outcomes due to delayed diagnosis and treatment.

In addition to reducing TB diagnosis, COVID-19 related disruptions may hamper treatment for TB patients due to limited treatment support and medication stockouts. Such disruptions could increase the risk of treatment interruption and delay, and decrease treatment adherence, which can be expected to result in worsening TB treatment outcomes. Due to the long duration of TB treatment, definitive data on changes in TB treatment outcomes as a result of COVID-19 may not be available for several months. In small reports of patients in private-sector centres in Pakistan,[40] a Chinese province[16] and cities in Ethiopia[41] and Zimbabwe,[24] treatment outcomes and support have worsened slightly (~5-15% relative reduction). On the other hand, analysis of data from China[17] and of a small number of patients in cities in Kenya and Malawi[24] did not show strong evidence of a significant reduction in treatment success, and non-TB-specific data in a South African province showed that numbers of clinic visits in general did not decline, although there was a significant (but temporary) decrease in child healthcare visits.[42] Further studies are underway in Brazil, Uganda and Viet Nam.[39] At this point, it is difficult to determine how effective calls for the use of digital technologies, additional medicines to take home and other approaches to ensure adequate treatment[43] have been, although many patients have reported feeling insufficiently supported.[8]

TB prevention services such as routine BCG vaccination, household contact management and preventive therapy are also likely to have been impacted by the COVID-19 pandemic. Routine reporting on these indicators is limited, and this challenges efforts to quantify the impact of COVID-19 on provision of these preventive services. TB centres in Brazil,[25] Kenya,[25] the Philippines[36], Russia,[25] South Africa,[44] Sierra Leone[25] and Zambia[45] reported relative declines in preventive therapy enrollment of 30-70%, although in the Philippines this decline appears to be consistent with pre-pandemic recent trends, and in South Africa as well as one Brazilian centre, preventive therapy enrollment seems to have recovered to pre-COVID levels. Meanwhile, India[31,46] and Pakistan[47,48] reported major decreases in relative BCG vaccination coverage of up to 60%, with significant potential consequences for paediatric TB mortality in particular.[49]

Vulnerability to tuberculosis

As the COVID-19 pandemic has impacted TB burden, so it has also impacted global vulnerability to TB, through a general decrease in health care access, an increase in poverty and the potential for post-COVID-19 lung diseases. These vulnerabilities could increase progression to TB disease amongst those with *Mtb* infection, as well as worsen treatment outcomes for patients on treatment. Modelling evidence broadly suggests that an increase in these vulnerabilities is likely,[4,50,51] but clear evidence of an increase is thus far scarce.

There is growing evidence to suggest that previous or current TB infection or disease are associated with poor COVID-19 outcomes, including a roughly two- to threefold increase in mortality (which occurred more quickly) and a 25% relative decrease in risk of recovery (which occurred more slowly) for COVID-19 coinfection with current TB disease.[52-55] However, while there is little evidence as yet that previous SARS-CoV-2 infection or COVID-19 disease affect either progression to TB disease or TB treatment outcomes, the possibility of post-COVID-19 lung damage and subsequent vulnerability to TB is a major concern.[11,56,57] A number of different studies are underway to investigate this issue.[58-60]

At the same time, a similar decrease in health care provision to that described above for TB could significantly impact TB vulnerabilities such as HIV and diabetes. Data for HIV health services are available from UNAIDS [61] for many, but not all, high TB/HIV burden countries. This includes both testing and treatment data for Botswana, Ethiopia, Indonesia, Kenya, Lesotho, Mozambique, Myanmar, Peru, Sierra Leone, Tajikistan, Ukraine and Zimbabwe, testing data only for Brazil, Cambodia, Liberia, Uganda and Tanzania, (as well as the capital cities of Kenya, Malawi and Zimbabwe[24]) and treatment data only for Cameroon, Kyrgyzstan and Nigeria. Broadly, HIV testing has declined significantly due to COVID-19, particularly in the early stages of the pandemic. However, in many settings this has recovered somewhat, in particular HIV self-testing.[61] In addition, the proportion of tests that are positive has generally not changed, suggesting that there has likely been relative stability in testing practices if not coverage. Meanwhile, although numbers on treatment have been less affected, numbers initiating treatment have declined precipitously and generally not returned to pre-COVID-19 levels.[61] However, it is not yet clear how the actual burden of HIV, diabetes and other TB vulnerabilities has increased due to COVID-19.

Poverty is expected to increase due to COVID-19,[50] and in particular surveys show it is driving people with TB into poverty and increasing inequities.[8] Although data on changes to costs faced by TB patients are not yet available, national surveys were underway in 2020 or planned for 2021 in 13 of the 48 high TB, TB/HIV or MDR-TB burden countries.[12] In particular, one survey recently completed in India contains samples from both pre- and mid-pandemic periods. The effects of an increase in poverty and inequality include a likely increase in catastrophic costs (>20% of household annual income) faced by TB patients and a resulting inability to access TB health services as discussed above.[62] Increases in poor living conditions and malnutrition can also drive increases in TB.[63,64] With as much as 30-50% of TB incidence attributable to malnutrition, the potential longer term consequences for these economic effects on the TB epidemic will be important to investigate.[65]

***Mycobacterium tuberculosis* transmission**

We do not yet know how *Mtb* transmission has been affected by COVID-19 and the use of interventions to reduce SARS-CoV-2 transmission. A reduction in respiratory contacts in the community and healthcare settings, in addition to the widespread use of masks, may reduce transmission of *Mtb* as has been observed for influenza.[66] However, a potential increase in contact within household settings, and the long duration of latent TB infection and TB disease as compared to COVID-19, may increase transmission in these settings. This effect could be compounded if decreasing access to TB health services leads to greater durations of TB infectiousness and increasing vulnerabilities lead to greater risk of TB disease.

Studying TB transmission in general is challenging. One approach to estimate potential changes in *Mtb* transmission is to consider changes in contacts in different social settings over time, particularly as these data are collected elsewhere to understand changes to SARS-CoV-2 transmission. Unfortunately, for most high TB burden countries contact surveys are limited. While synthetic contact matrices are available for all high TB burden countries except Somalia,[67-70] only 10 high TB, TB/HIV or MDR-TB burden countries have contact surveys available from before the pandemic.[71-84] Furthermore, only China[85], Kenya[86] and South Africa[87] have contact surveys available from during the pandemic (with a survey currently underway in Pakistan), showing a marked decrease in contacts outside of the household.

New sources of mobility data, for example from Google [88] or mobile phone providers, suggest massive, time-varying changes in population movements as a result of COVID-19. Although this does not provide information on how contacts have changed, it does allow for a better understanding of locations (such as public transport or places of worship) where contacts have decreased. This can be used, alongside contact surveys where the location of contact was recorded, to estimate likely reductions in contacts. A major caveat is that those surveyed include mobile phone owners only, which may underrepresent both TB patients[89] and potentially those unable to practice physical distancing.

Again as a result of efforts to understand the pandemic, data on mask-wearing are widely available for all high TB burden countries, and shows a major increase,[90,91] which has the potential to be of great benefit to the TB response.[92] Although the impact of mask use on *Mtb* transmission is poorly understood,[93] it may be significant in some settings, particularly if sustained for significant time periods.[94]

The impact on *Mtb* transmission of changes in contacts or mask-wearing in particular locations is dependent on the extent to which transmission occurs in those locations and the potential for changes in per-contact risk to affect overall risk of transmission. Studies from before the pandemic suggest that even for children as little as 10-30% of population-attributable transmission is due to household exposures.[95,96] Presuming contact saturation within the home limits the amount of additional transmission that could occur as a result of increased time spent there,[97] decreased community contact and mask-wearing could significantly reduce overall *Mtb* transmission per person with TB disease. The relative importance of this reduction in community transmission is likely to be dependent on the extent to which transmission occurs outside of the home. Some evidence of the proportion of *Mtb* transmission attributable to the household or other locations is available for a number of countries, where this may depend in part on the burden of disease.[95,98-108]

Tuberculosis resources

To both understand and mitigate the consequences of COVID-19 on TB interventions and outcomes, it is necessary to understand how the resource needs of TB services have changed, and the impact of COVID-19 on the resources available to TB. Firstly, approaches to delivering TB interventions are likely to have changed, either through design (such as an increased need for personal protective equipment or additional staff time required to undertake infection control and physical distancing measures), or through shortages or constraints to some inputs (such as staffing and diagnostic capacity).[43] Secondly, prices for different intervention inputs could change substantially as demand increases. Thirdly, the costs of providing services are linking to service volumes (for example, a short term reduction in demand may result in temporary over capacity of some TB focused resources). Lastly, the available budget for supporting TB services may be lower, with resources reprogrammed to COVID-19 care or mitigation. Indeed, nearly half of high TB burden countries reported reallocation of TB funding to the COVID-19 response,[12] with TB funding broadly decreasing significantly,[8]. Although additional funding to most countries (apart from Brazil, Cambodia, China, DPR Korea, Guinea-Bissau, Indonesia, Russian Federation, Sierra Leone, Tajikistan, Thailand and Tanzania) has been made available by funders such as the Global Fund to Fight AIDS, Tuberculosis and Malaria,[109] this is aimed at mitigating the impact on the HIV, TB and malaria programmes in general, and does not shed light on any changes to domestic budget available to the TB programme. We found no country-level quantitative data currently publicly available on the impact of COVID-19 on the resources available to or required for the TB response. During the expert meeting, researchers confirmed that in the main cost data collection had been suspended during the COVID-19 period.

Conclusions

In general, where data are available TB health services appear to have decreased significantly in most settings due to COVID-19. Numbers of patients, as well as testing and prevention coverage, have decreased more noticeably than treatment outcomes, although few data are available on the latter. Ensuring adequate treatment for known TB patients, through provision of additional medicine and digital treatment support, certainly appears to be more amenable to physical distancing than TB diagnosis, which requires more direct contact between individuals. Meanwhile, vulnerability to TB has widely increased. HIV services appear to have recovered somewhat, although the potential for COVID-19-related lung damage to lead to widespread vulnerability to TB is still unknown, as are the impacts of changes in other vulnerabilities such as diabetes and malnutrition. Data on the impact of an increase in poverty on TB patient costs are currently unavailable, although in many countries studies are underway to address this. Unlike TB health services, which have in a number of cases been restored to some extent, vulnerabilities are likely to continue to increase despite COVID-19 vaccines, as widespread poverty remains and SARS-CoV-2 infections continue to climb. While community transmission of *Mtb* has likely decreased significantly, the effect of household transmission and a potential increase in cases means that it is difficult to draw any conclusions on changes to *Mtb* transmission, and indeed this may never be possible, although the location of transmission events is certainly highly likely to have shifted. Lastly, while some additional funding has been allocated by global agencies to countries for their TB response, it remains unclear how overall health system resource constraints and the changing resources of service delivery are impacting TB. Although it is difficult to draw any conclusions on the geographic availability of data, we note that little appear to be available for the high MDR-TB burden countries of Central Asia, while many smaller studies are available for countries in sub-Saharan Africa. In general, in only a limited number of countries such as China and South Africa are good data available across a range of indicators.

When identifying priority gaps that remain for understanding and mitigating the impact of COVID-19 on TB, it is important to be clear on what these data will be used for; here we suggest that this would primarily be to allocate TB resources more efficiently and to help advocate for additional resources for the TB response. The first of these requires a good understanding of the effect on health services, and the resources available and required to restore these to at least pre-pandemic levels. The second requires in addition an understanding of how vulnerability to TB and *Mtb* transmission have changed. In an online meeting of 60 TB experts (TB Modelling and Analysis Consortium meeting on the impact and mitigation of COVID-19 on TB, held 12 January 2021), a range of priorities were identified from across the four broad areas identified above; these are outlined in Figure 2. The most strongly supported of these included data on delays to diagnosis and treatment, changes to patient costs of TB services, the impact of COVID-19 infection and disease on vulnerability to TB and mortality, and the effect of changing contacts and mobility on household and community transmission of *Mtb*. A key priority was the longer-term requirement for more responsive TB information systems. While this has not been as much of a problem in the past, the rapid nature of the COVID-19 pandemic has highlighted the need for frequently reported, disaggregated TB health service availability and use data, to allow for an appropriate response. A lack of real-time data to make decisions suggests that investment in a change to TB information and reporting systems to enhance real-time empirical evidence (as can be seen for COVID-19) is required. Data collation and monitoring efforts, by an appropriate global stakeholder, should additionally be strengthened.

In conclusion, while numbers of TB patients have declined globally, it is not yet possible to determine the key causes for these declines, what they represent in terms of changing TB burden, and what action is required to mitigate them. In advocating for additional funding to mitigate the impact of COVID-19 on the global TB burden, and to allocate available resources efficiently for the TB response, a significant improvement in the availability of TB data is required.

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Declaration of Interests

The authors report no conflicts of interest.

Author Contributions

CFM and RGW conceptualized this project. CFM reviewed papers and drafted the manuscript. All authors read and revised the draft manuscript.

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Table 1: Available or upcoming data on the impact of COVID-19 on TB by country for World Health Organization high TB, TB/HIV and multidrug-resistant TB burden countries.[12]

COUNTRY	HEALTH SERVICES DATA							VULNERABILITY DATA			TRANSMISSION DATA					RESOURCE DATA		
	Diagnosis			Treatment		Prevention		HIV		Poverty	No control measures		Under control measures			Required		Available
	Cases	Testing	Drug sensitivity testing	Delays	Outcomes	BCG coverage	Preventive therapy	Testing	ART	Patient costs	Household transmission	Contacts	Contacts	Mobility	Mask-wearing	Resource utilisation	Prices	Budgets
Angola	13											67		88	90			109
Azerbaijan												67			90			109
Bangladesh	13									12	98	67		88	90			109
Belarus												67		88	90			109
Botswana								61	61		98	67		88	90			109
Brazil	23,25	39		39	39		25	61		12	98,99	67		88	90			
Cambodia	12							61				67		88	90			
Cameroon									61	12		67		88	90			109
Central African Republic												67			90			109
Chad												67			90			109
China	12,14-17,30	15-17		17	16,17							67,68,71,72	85		91			
Congo												67			90			109
DPR Korea	13											67			90			
DR Congo												67			90			109
Eswatini												67			90			109

Ethiopia	13				41			61	61	12		67			90		109
Ghana												67		88	90		109
Guinea-Bissau											98	67		88	90		
India	12,20,21 25,27,28 31					31,46				12	98	67,68		88	91		109
Indonesia	12							61	61	12	98	67		88	91		
Kazakhstan												67		88	90		109
Kenya	12,24,25	38	38		24		25	24,61	61		95,98	67,73,74	86	88	90		109
Kyrgyzstan									61			67		88	90		109
Lesotho	13							61	61			67			90		109
Liberia								61				67			90		109
Malawi	24	38	38		24			24		12	95,100	67,75			90		109
Mozambique	12							61	61	12		67		88	90		109
Myanmar	13							61	61			67		88	90		109
Namibia	12									12		67		88	90		109
Nigeria	18	35							61		98	67		88	90		109
Pakistan	22				40	47 48						67		88	90		109
Papua New Guinea												67		88	90		109
Peru	13							61	61	12	98,101,102	67,76		88	90		109
Philippines	12,25,29	36	36				36					67		88	91		109
Republic of Moldova												67		88	90		109
Russian Federation	13,25						25					67,68,77,78			90		
Sierra Leone	12,19,25						25	61	61		98	67			90		

Somalia															90			109
South Africa	12,26	37	37	42			44	61	61	12	95,98,103-106	67,68,79-81	87,110	88	90			109
Tajikistan								61	61			67		88	90			
Thailand	12									12		67,69		88	91			
Uganda	111	39			39			61			95,98,99,107	67,82		88	90			109
Ukraine								61	61			67		88	90			109
Tanzania	12							61				67		88	90			
Uzbekistan												67			90			109
Viet Nam	12	39			39						98,108	67,83		88	91			109
Zambia	12						45			12		67,80,81		88	90			109
Zimbabwe	13,24	38	38		24			24,61	61			67,84		88	90			109

98
99

Figure 1: Potential impact of the COVID-19 pandemic on the TB care cascade. Arrows indicate an increase or a decrease in number of patients at that point of the cascade, including the logic behind the change. Dark blue arrows indicate an impact of health service delivery and demand, grey arrows indicate an impact on vulnerability to TB, and light blue arrows indicate an impact on *Mtb* transmission.

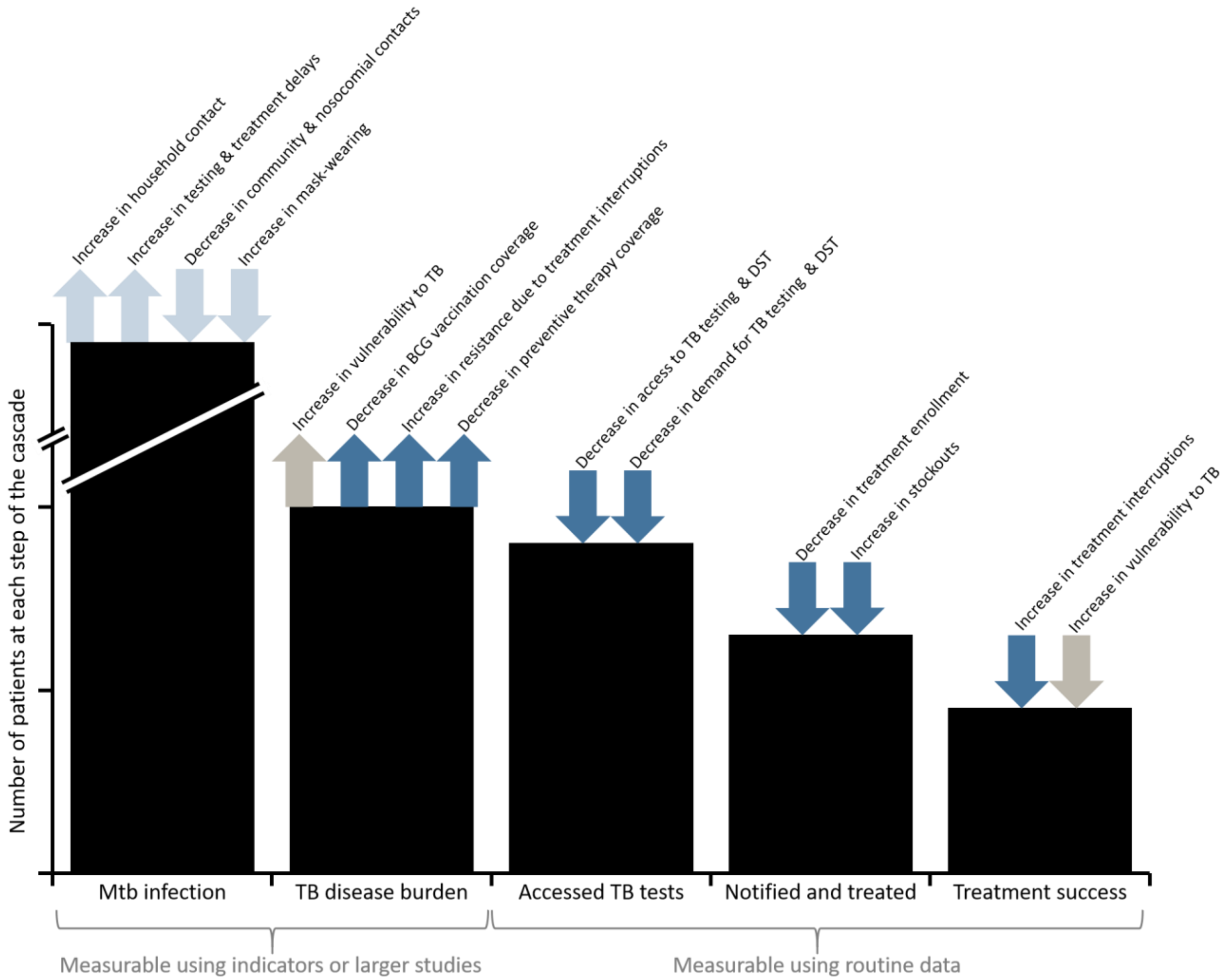

Figure 2: Outline of priority gaps that remain for understanding and mitigating the impact of COVID-19 on TB.