



Capacity Building in Sub-Saharan Africa as Part of the INTENSE-TBM Project During the COVID-19 Pandemic

E. Ariza-Vioque · F. Ello · H. Andriamamonjisoa · V. Machault · J. González-Martín · M. C. Calvo-Cortés · S. Eholié · G. A. Tchabert · T. Ouassa · M. Raberahona · R. Rakotoarivelo · H. Razafindrakoto · L. Rahajamanana · R. J. Wilkinson · A. Davis · M. Maxebengula · F. Abrahams · C. Muzoora · N. Nakigozi · D. Nyehangane · D. Nanjebe · H. Mbega · R. Kaitano · M. Bonnet · P. Debeaudrap · J. M. Miró · X. Anglaret · N. Rakotosamimanana · A. Calmy · F. Bonnet · J. Ambrosioni  · INTENSE-TBM Group

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ABSTRACT

Tuberculous meningitis (TBM) is the most severe and disabling form of tuberculosis (TB), with at least 100,000 cases per year and a mortality rate of up to 50% in individuals co-infected with human

immunodeficiency virus type 1 (HIV-1). To evaluate the efficacy and safety of an intensified anti-tubercular regimen and an anti-inflammatory treatment, the INTENSE-TBM project includes a phase III randomised clinical trial (TBM-RCT) in four countries in sub-Saharan Africa (SSA). Within this framework, we designed a comprehensive capacity-building work package ensuring all centres had, or would acquire, the ability to conduct the TBM-RCT and developing a network of skilled researchers, clinical centres and microbiology laboratories. Here, we describe these activities, identify strengths/challenges and share tools

A. Calmy, F. Bonnet and J. Ambrosioni contributed equally to this work.

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E. Ariza-Vioque · J. M. Miró · J. Ambrosioni
Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

F. Ello · G. A. Tchabert · X. Anglaret
Programme ANRS Coopération Côte d'Ivoire (PAC-CI), Abidjan, Ivory Coast

H. Andriamamonjisoa · N. Rakotosamimanana
Institut Pasteur de Madagascar, Antananarivo, Madagascar

V. Machault · X. Anglaret · F. Bonnet
INSERM U1219, Bordeaux Population Health (BPH), Université de Bordeaux, Bordeaux, France

J. González-Martín
Servei de Microbiologia, Centre de Diagnòstic Biomèdic (CDB), Hospital Clínic de Barcelona, Barcelona, Spain

J. González-Martín
Institut de Salut Global (ISGlobal), Barcelona, Spain

J. González-Martín · J. M. Miró · J. Ambrosioni
Facultat de Medicina i Ciències de la Salut, Universitat de Barcelona, Barcelona, Spain

M. C. Calvo-Cortés
Agence Nationale de Recherche sur le SIDA et les Hépatites Virales (ANRS), Maladies Infectieuses Émergentes, Paris, France

S. Eholié
Centre Hospitalier Universitaire (CHU) Treichville, Abidjan, Ivory Coast

T. Ouassa
Centre de Diagnostic et de Research sur le SIDA et les autres maladies infectieuses (CeDRoS), Abidjan, Ivory Coast

adaptable to other projects, particularly in low- and lower-middle income countries with heterogeneous settings and during the coronavirus disease 2019 (COVID-19) pandemic. Despite major challenges, TBM-RCT initiation was achieved in all sites, promoting enhanced local healthcare systems and encouraging further clinical research in SSA. In terms of certified trainings, the achievement levels were 95% (124/131) for good clinical practice, 91% (39/43) for good clinical laboratory practice and 91% (48/53) for infection prevention and control. Platform-based research, developed as part of capacity-building activities for specific projects, may be a valuable tool in fighting future infectious diseases and in developing high-level research in Africa.

PLAIN LANGUAGE SUMMARY

The INTENSE-TBM project aimed to design a comprehensive work-package on capacity building, ensuring all centres would acquire the ability to conduct a phase III randomised

clinical trial on TBM in sub-Saharan Africa, to reduce tuberculous meningitis mortality and morbidity in patients with/without HIV-1 co-infection. Therefore, the INTENSE-TBM project is an example of how an international clinical research consortium can provide opportunities to enhance local capacity building and promote centres without previous experience in clinical research. This article provides practical approaches for implementing effective capacity-building programmes. We highlight how to overcome limitations imposed by the COVID-19 pandemic to successfully complete clinics, laboratory set-ups and personnel training, so as to optimise resources and empower African institutions on a local level. At the same time, our experience shows how capacity-building programmes can deliver long-lasting impact that extends beyond the original aims of the project (e.g. HIV and TB), and support local health systems in fighting other infectious disease (e.g. COVID-19). Research projects in low- and lower-middle income countries with heterogeneous settings could stand to benefit the most.

M. Raberahona · H. Razafindrakoto ·
L. Rahajamanana
Centre d'Infectiologie Charles Mérieux (CICM),
Antananarivo, Madagascar

M. Raberahona
Université d'Antananarivo, Antananarivo,
Madagascar

M. Raberahona
Centre Hospitalier Universitaire (CHU) Joseph
Raseta Befalatanana, Antananarivo, Madagascar

R. Rakotoarivelo
Université de Fianarantsoa, Fianarantsoa,
Madagascar

R. Rakotoarivelo
Centre Hospitalier Universitaire (CHU) Tambohobe,
Fianarantsoa, Madagascar

R. J. Wilkinson · A. Davis · M. Maxebengula ·
F. Abrahams
Wellcome Centre for Infectious Diseases Research in
Africa, Cape Town, Republic of South Africa

R. J. Wilkinson
Francis Crick Institute, London, UK

R. J. Wilkinson
Department Infectious Diseases, Imperial College
London, London, UK

C. Muzoora · N. Nakigozi · D. Nyehangane ·
D. Nanjebe · H. Mbega · R. Kaitano
Médecins Sans Frontières (MSF) Epicentre, Mbarara,
Uganda

C. Muzoora
Mbarara University of Science and Technology
(MUST), Mbarara, Uganda

M. Bonnet
Université de Montpellier, Montpellier, France

M. Bonnet · P. Debeaudrap
Recherches Translationnelles sur le VIH et les
Maladies Infectieuses (TransVIHMI), Institut de
Recherche pour le Développement (IRD), INSERM,
Paris, France

J. M. Miró · J. Ambrosioni (✉)
HIV Unit, Infectious Diseases Service, Hospital
Clínic de Barcelona, Barcelona, Spain
e-mail: jambrosioni@intramed.net

J. M. Miró · J. Ambrosioni
Centro de Investigación Biomédica en Red de
Enfermedades Infecciosas (CIBERINFEC), Madrid,
Spain

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Key Summary Points

Tuberculous meningitis (TBM) is the most severe and disabling form of tuberculosis.

The INTENSE-TBM project includes a phase III randomised clinical trial on TBM in sub-Saharan Africa. Using a factorial design, the INTENSE-TBM is evaluating the efficacy of an intensified anti-tubercular treatment (increased rifampicin dose and added linezolid during intensive phase vs. WHO standard regimen) and an anti-inflammatory treatment (aspirin vs. placebo), with a view to reducing TBM mortality and morbidity in patients co-infected/not co-infected with human immunodeficiency virus (HIV).

We aimed to design a comprehensive work-package on capacity building, ensuring all centres would acquire the ability to conduct a phase III randomised clinical trial on TBM in sub-Saharan Africa.

The initiation of the INTENSE-TBM clinical trial was achieved at all sites - despite major challenges imposed by the coronavirus disease 2019 (COVID-19) pandemic - enhancing local healthcare systems and encouraging further clinical research in sub-Saharan Africa.

INTRODUCTION

Tuberculosis (TB) is one of the worldwide leading causes of death from a single infectious agent. A quarter of the world's population carries *Mycobacterium tuberculosis* (*M.tb*), of whom about 10% progress to active TB. According to the latest global report [1], ten million people became ill with the disease in 2020; among these, 8% were people living with human immunodeficiency virus (PLWH), a population with a higher risk of developing the disease. The most common clinical presentation is pulmonary TB, which affects the lungs, although other organs are susceptible to extrapulmonary TB. The most severe and disabling form of TB is tuberculous meningitis (TBM), which causes illness in at least 100,000 people each year. In areas of high TB/human immunodeficiency virus (HIV) prevalence, as many as 50% of TBM cases may be in patients co-infected with HIV type 1 (HIV-1), in which the mortality rate can also approach 50%, with severe disability frequently affecting survivors [2–4]. Indeed, TBM outcomes reflect the existing gaps in TB healthcare, which more severely impact PLWH: from incidence to diagnosis (inadequate or unavailable tools), from diagnosis to treatment (delays/subsequent only to neurological damage) and from treatment initiation to successful outcome (suboptimal treatment, inadequate management of drug toxicities and insufficient integration of TB/HIV services) [2–6]. The way forward, therefore, urgently requires investment via clinical research and capacity building [3, 4, 7–9].

INTENSE-TBM (<https://intense-tbm.org/>) is a 5-year international project with the aim to improve the overall care of patients with TBM. It includes a phase III multicentre randomised controlled clinical trial ('TBM-RCT'; ClinicalTrials.gov Identifier: NCT04145258) in four countries in sub-Saharan Africa (SSA). Using a factorial design, the INTENSE-TBM is evaluating the efficacy of an intensified anti-tubercular treatment (increased rifampicin dose and added linezolid during intensive phase vs. WHO standard regimen) and an anti-inflammatory treatment (aspirin vs. placebo), with a view to

A. Calmy
Université de Genève (UNIGE), Geneva, Switzerland

F. Bonnet
Service de Médecine Interne et Maladies
Infectieuses, Saint-André Hospital, Centre
Hospitalier Universitaire (CHU) de Bordeaux,
Bordeaux, France

reducing mortality and morbidity in patients with TBM co-infected/not co-infected with HIV.

The project encompasses eight highly interactive work programmes (Fig. 1a), each led or co-led by an SSA partner. With a focus on capacity building, the second workpackage (WP2-CB) coordinates and organises the activities, approaches, strategies and methodologies that will help researchers, clinical centres and laboratories enhance performance, foster development and achieve two main objectives: (1) align participating centres' capacity (infrastructure, equipment, network) and capabilities (skills, training, know-how) with INTENSE-TBM criteria, and (2) develop a network of skilled researchers, clinical centres and microbiology laboratories not only to facilitate TBM-RCT roll-out but also to conduct future clinical research. To achieve these aims, WP2-CB was structured around four main tasks: (1) establishing clinical centres; (2) establishing microbiology laboratories; (3) conducting training on good clinical practice/good clinical laboratory practice (GCP/GCLP); and (4) conducting training on infection prevention and control (IPC).

INTENSE-TBM began on 1 January 2019, and initial patient recruitment was expected in the first half of 2020. However, this period saw the coronavirus disease 2019 (COVID-19) pandemic imposing huge challenges on healthcare services worldwide; these were acutely felt in developing countries and significantly delayed the initiation of research projects. In this article, we report on our capacity-building activities (development/successful completion), identifying our strengths and challenges and describing our tools and how they are adaptable to other projects, particularly in low- and lower-middle income countries (LMIC) with their heterogeneous settings and in the context of the ongoing COVID-19 pandemic.

This article is based on authors' knowledge and experiences prior to conducting clinical research and, therefore, it does not contain any data from human participants or animals. Written consent was obtained from the individuals shown in Fig. 4.

Fig. 1 a Work-packages in the INTENSE-TBM project. ▶ INTENSE-TBM is organised in 8 work-packages (*WP*). WP1 is related to the overall coordination and management of the project. WP2 is a longitudinal package with the aim to provide the required infrastructures, resources and trainings before, during and after the randomised controlled trial (*RCT*), with the ultimate aim that the created capacities be permanently used to reinforce the local health systems in these countries. WP3 and WP4 are related to the clinical trial implementation and development. WP5–8 are related to specific clinical, laboratory or research issues. INTENSE-TBM project website: <https://intense-tbm.org/>; ClinicalTrials.gov Identifier: NCT04145258. *HIV* Human immunodeficiency virus, *PK* pharmacokinetics, *TBM* tuberculous meningitis, **b** African sites participating in the INTENSE-TBM clinical trial.

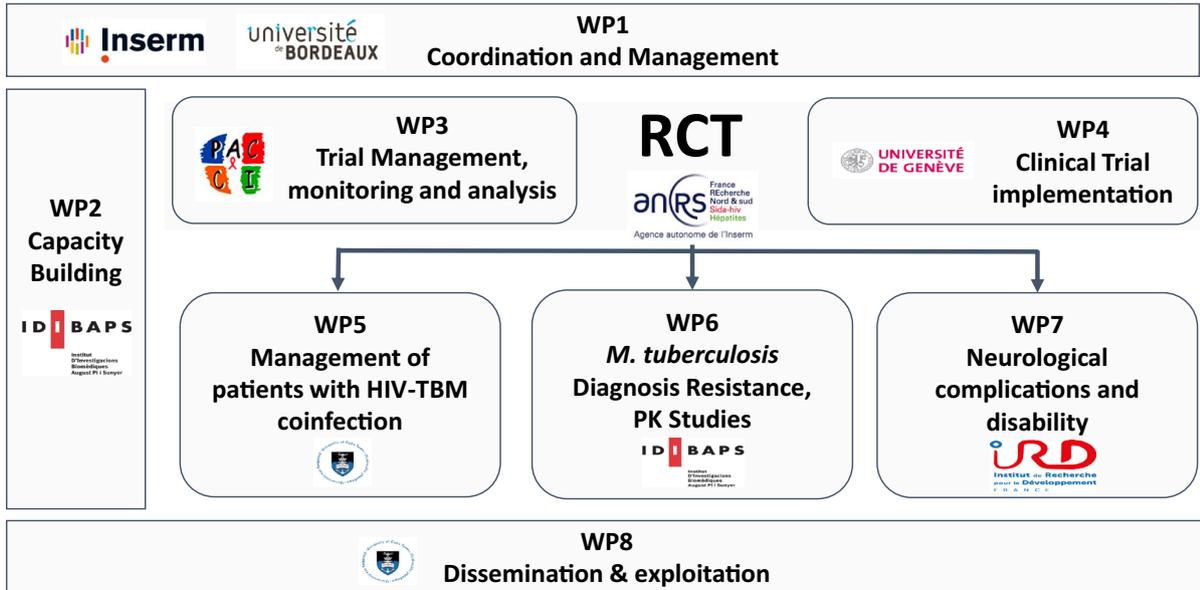
CLINICAL RESEARCH IN HETEROGENEOUS, COVID-19 CONTEXTS

The INTENSE-TBM is designed to be conducted in 12 clinical centres in four SSA countries: three in the Ivory Coast, two in Madagascar, five in South Africa and two in Uganda (Fig. 1b). Centres were selected according to the experience of clinicians in TBM management, participatory feasibility and geographical distribution (TB/HIV burden varies across western, eastern and southern Africa). Most sites were already experienced in clinical research ($n = 10$), whereas others ($n = 2$) required comprehensive development. Further, our in-detail evaluation of the sites identified a high level of heterogeneity, both among countries and within each participating country, between referral and regional centres. In the light of these features, our capacity-building activities had to be tailored to each individual centre, taking into close account geographical location, levels of infrastructure and resource centralisation, network access to other institutions and existing international collaborations.

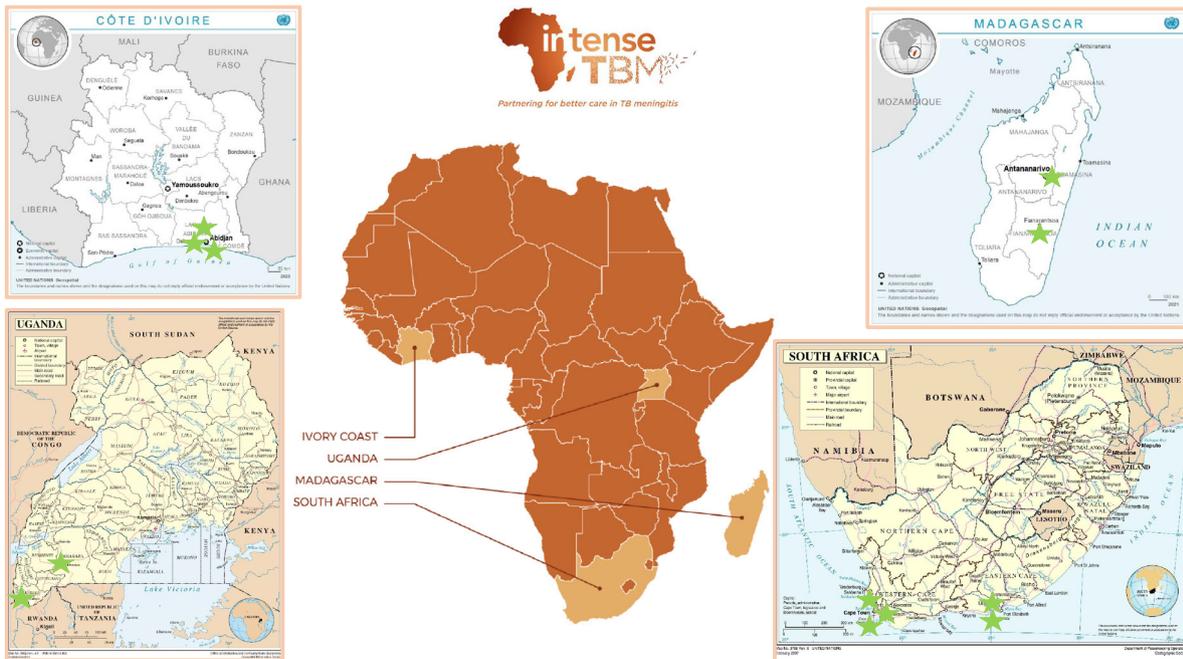
In addition to these structural factors, the COVID-19 pandemic also forced centres to suspend many aspects of their activities and adapt to the prevailing circumstances, including:

- staff shortages;

a



b



- restrictions on air-traffic and at borders;
- delays in receiving equipment;
- supply shortages;
- local movement restrictions;
- missed deadlines for external quality programmes and equipment maintenance;
- resorting to remote technical support and monitoring visits;
- resorting to online training;
- lockdowns, making it difficult for patients to attend facilities and raising the fear of attending such facilities.
- in Cape Town (South Africa), the research ethical committee also suspended non-COVID-19 trials and the faculty banned non-COVID-19 laboratory research.

METHODOLOGICAL APPROACH FOR CAPACITY BUILDING

To ensure capacity building was tailored, the activities relating to site preparation were divided into four phases (Fig. 2). This ensured that, despite the differences among centres, all centres met the same criteria and the requirements for INTENSE-TBM development. By the end of phase 1, the essential aspects of TBM-RCT implementation were defined and evaluation tools were developed. In phase 2, each centre was empowered to identify its own needs and to define its own action plan in accordance with those needs. In this way, we delegated leadership to each national country team, supporting

and monitoring their activities through monthly virtual meetings and annual face-to-face visits which were scheduled up to project completion. In phase 3, the following strategies were applied:

- mentorship from experienced research institutions (national and international);
- networking among sites, such as resource optimisation and sample transfer;
- infrastructure renovation;
- purchasing equipment;
- supporting implementation of diagnostic techniques;
- drafting standard operational procedures (SOP) and logbooks;
- reinforcing quality assurance;
- reinforcing equipment maintenance;
- training staff.

In phase 4, initiation visits were conducted to check that sites complied with all the requirements and that training had taken place prior to recruiting the first patients.

SPECIFIC CAPACITY-BUILDING TASKS

As described in the [Introduction](#), WP2-CB was structured around four main tasks, explained in the following subsections.

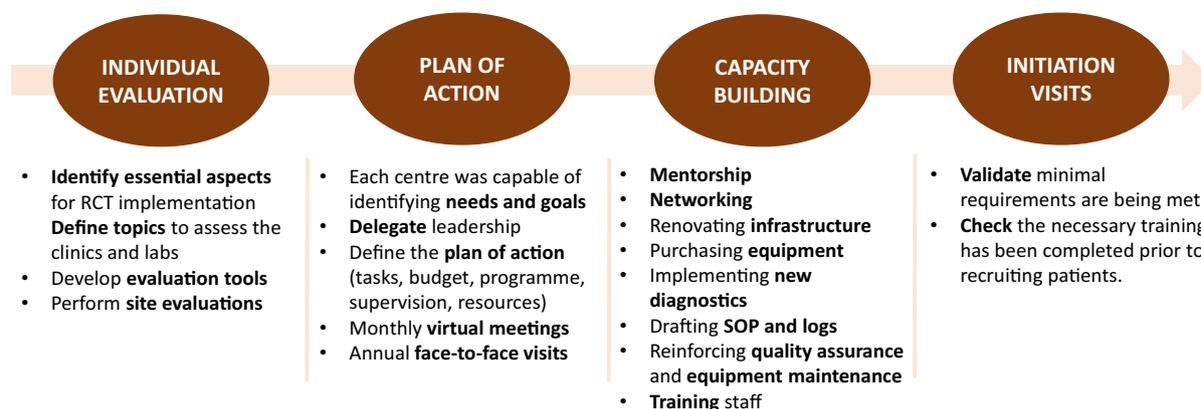


Fig. 2 Methodological approach to capacity building. *SOP* Standard operational procedure

To Establish Clinical Centres

The INTENSE-TBM project began in February 2021, and currently all 12 sites have been successfully initiated (Fig. 1b).

Ivory Coast Patient recruitment in the Ivory Coast is being carried out by three university hospitals located in the capital city of Abidjan, although research is conducted at the Service des Maladies Infectieuses et Tropicales (SMIT) and the Centre de Diagnostic et de Recherche sur le SIDA et les autres maladies infectieuses (CeDReS), also located in Abidjan. SMIT and CeDRes are supported by Mereva, a bilateral clinical trial unit between Ivory Coast (PAC-CI, Treichville Hospital and Abidjan University) and France (Bordeaux University and INSERM). The existence of these previous international collaborations presumably led to the main capacity building interventions being readily achieved, and this country was the first to have all sites operational in February 2021.

Madagascar Two university hospitals in two regions in Madagascar were selected for INTENSE-TBM participation, both of which already part of collaborations with the Centre d'Infectiologie Charles Mérieux de Madagascar (CICM) and the Institut Pasteur de Madagascar (IPM). These latter two national research institutions granted access to HIV viral load and *M. tb* culture resources, albeit only through physical presence in the capital city of Antananarivo. Indeed, the main challenges in this context were lack of experience in clinical trials, resource decentralisation, infrastructure deficits and travel times between regional and reference centres. At the time of writing, both sites are up and running (Antananarivo in January 2021 and Fianarantsoa in July 2021).

South Africa There are five participating hospitals in South Africa, all in the region of Cape Town and Port Elizabeth. These institutions work closely with the University of Cape Town (UCT), which has an established clinical research team and recognised researchers in HIV/TB whose work includes the LASER-TBM (NCT03927313) phase II clinical trial evaluating the safety and tolerability of increased dosages

of rifampicin and adjunctive linezolid with or without aspirin for HIV-associated TBM. It is this trial that will supply the relevant safety information to INTENSE-TBM. Given this context, all capacity-building activities were in place: INTENSE-TBM activities would follow on from the LASER-TBM trial. All five sites were initiated between March and June 2021.

Uganda The INTENSE-TBM involve two regional reference hospitals in Uganda, one in Mbarara at the Mbarara Regional Reference Hospital (MRRH) and one in Kabale at the Kabale Regional Reference Referral Hospital (KRRH). MRRH is the teaching hospital of the Mbarara University of Science and Technology (MUST). MUST hosts the Epicentre Uganda Research Centre of the research organisation Médecins Sans Frontières (MSF)-Epicentre, and this collaboration has been conducting clinical research on HIV/TB for more than 10 years. Conversely, KRRH has never participated in clinical trials and therefore has required comprehensive training, infrastructure renovation, additional resources (including essentials, such as internet, stable power supply) and systems for quality control and documentation. MRRH was the first site initiated (August 2021), followed by KRRH (February 2022), with the delay due to institutions and local borders being temporarily closed due to COVID-19.

To Establish Microbiology Laboratories

Minimum requirements (Fig. 3) for compliance with the study protocol, standard guidelines and GCLP were defined to standardise laboratory performance and to ensure confidence in the research to be conducted. [10–12].

Ivory Coast The analytical procedures in the Ivory Coast are centralised at CeDReS, a reference laboratory involved in international research, which already had the infrastructure, equipment and resources to participate in the INTENSE-TBM. In terms of procedure, Xpert MTB/RIF (a WHO-recommended first-line TB diagnosis test, which is PCR-based and allows simultaneous *M. tb*-DNA/rifampicin-resistance detection) [13] was upgraded to the more

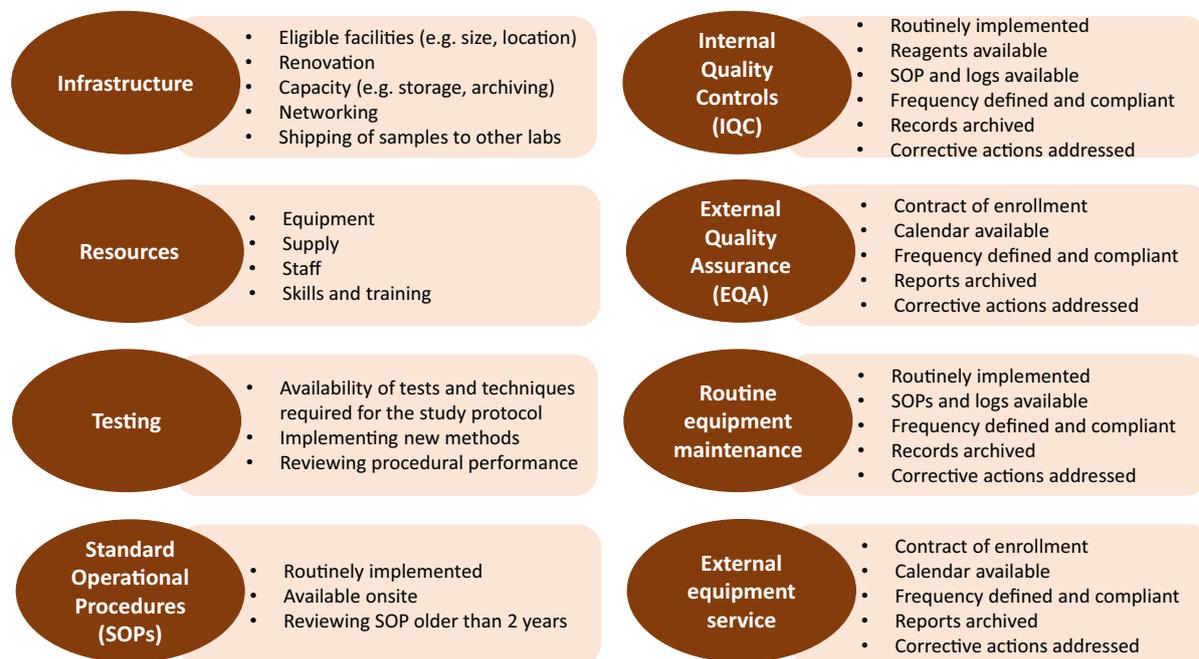


Fig. 3 Requirements applied to laboratory standardisation

sensitive Ultra version [14], and drug susceptibility testing (DST) for pyrazinamide was introduced. Overall, capacity-building activity focused on enhancing quality, maintenance and documentation systems. Notably, 42% (15/36) of the required standard operating procedures (SOPs) had to be drafted, and 58% (21/36) needed reviewing as they were > 2 years old. CeDReS was already enrolled in an external quality assurance programme, and its equipment was being serviced annually by accredited technicians, despite the challenge of procuring this service domestically.

Madagascar The main challenges in Madagascar were related to renovating infrastructure, purchasing equipment, establishing laboratory networks, providing training and introducing diagnostic techniques. A research laboratory was built at CICM (Fig. 4). BACTEC MGIT960 (a WHO reference phenotypic method for *M.tb* bacteriological confirmation and DST, based on liquid culture) [15] was introduced at IPM, and Xpert MTB/RIF Ultra was scaled-up in the regional TB laboratories. The regional sites underwent significant renovations, particularly the regional TB laboratory, all of which were

necessary to improve staff well-being and ensure the proper functioning of the installations.

South Africa The laboratories were already operational in South Africa and were conducting a similar trial. Therefore, our approach was simply to adapt those procedures to the INTENSE-TBM trial.

Uganda MSF-Epicentre already acts as a reference laboratory in Uganda, and it satisfied the infrastructure and resource criteria for the INTENSE-TBM trial, such as presence of staff with experience in clinical research. All diagnostic tests are available, except for the HIV viral load test and *M.tb* DST; both will be tested at the national reference laboratory. In this context, capacity building translated into providing support to the implementation of INTENSE-TBM and at the same time upgrading laboratory performance. By contrast, Uganda's second site had never participated in clinical research, receives little external support and faces the common problems of regional districts (excessive workloads, limited staffing and resources, frequent supply interruptions, unstable power supply, lack of internet, etc.).



Fig. 4 Research laboratory built at the Centre d'Infectiologie Charles Mérieux (CICM) in Madagascar. Picture taken during remote study initiation visit

Work is currently ongoing to complete the capacity-building activities at KRRH. At the time of writing, only rapid diagnostic tests are done. A referral system for samples to be tested at MSF-Epicentre has also been put in place.

To Provide training on GCP and GCLP Training

GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. This standard provides assurance that the rights, the safety and the well-being of subjects are protected, and that trial data are credible [16]. GCLP applies GCP principles to laboratory practice regarding sample analysis, and ensuring the reliability and integrity of data generated by analytical laboratories [12]. Accordingly, GCP and/or GCLP certification (valid for 3 years) was a requirement for all staff involved in INTENSE-TBM. Where GCP certification was unavailable, alternative GCP training modalities were offered depending on previous experience: (1) online (through the Training and Resources in

Research Ethics Evaluation); (2) on-site (according to national availability of accredited institutions); (3) hybrid (local team working face-to-face on-site and external experts working online). Regarding GCLP, not one person was found to be certified, and online training was recommended through the Global Health Network. GCP and GCLP certification achievement levels were 95% (124/131) and 91% (39/43), respectively, reflecting the sites at initiation.

To provide Training on IPC

IPC is a practical approach to protecting patients and healthcare workers from harm due to avoidable/preventable infections [17, 18]. This specialised training was provided to all sites by the Infection Control African Network, which is based in South Africa, because difficulties in procuring the service were reported in the other countries. Due to budgetary concerns (and lately pandemic-related restrictions), it was decided to deliver the bilingual French/English course online, covering the essential contents of IPC with a focus on TB. In total, 91% (48/53) of

healthcare workers completed the course successfully.

The overview of activities initially planned and the modifications introduced to face the challenges of the COVID-19 pandemic are shown in Table 1.

DISCUSSION: LESSONS LEARNED AND TOOLS FOR SHARING

Developing new strategies to tackle TBM and other emerging or re-emerging diseases, including COVID-19, requires clinical research [19–21]. The major global burden of

communicable diseases is borne by SSA, but, in stark contrast, this region is only a minor beneficiary of clinical research funding [19, 21, 22]. Although highly competitive institutions have increased their presence in some countries in the region, many other countries lack such research capacity and are left behind; hence, resources remain centralised and significant disparities persist both between and within countries [20, 23]. In this context, clinical research combined with capacity building is an effective strategy to promote fairer resource distribution, to redress healthcare inequalities and to achieve minimum research capacity. These three features are crucial to the fight

Table 1 Overview of activities initially planned and modifications introduced to face the COVID-19 pandemic

List of activities	Before COVID-19	After COVID-19
Meetings	Routine meetings online	All meetings online
	Annual investigators meeting centralised in 1 country (e.g. kick-off meeting in Ivory Coast)	Budget saved will cover part of the COVID-19 unexpected expenses
Visits and monitoring activities	On-site displacement of national/international staff	Local leadership
	On-site evaluation visits	On-site monitoring by national team
	Online monthly monitoring	On-line monitoring by international team
	On-site annual monitoring	
	On-site opening visits	Hybrid (online/on-site) opening visits (Fig. 4)
Establishing clinical centres and microbiology laboratories	On-site displacement of external experts	Local leadership
	Hands-on training	Remote technical advice (hands-on training cancelled and internships postponed)
	Staff internship in other national/international institutions	Remote monitoring tools
	Shared working platform and source of resources on the Cloud	Increased of activities reporting and procedures documentation
Trainings	Specialised training (GCP, GCLP, IPC) adapted by country according to previous knowledge and resources available (on-site/online/hybrid)	Resorted to online trainings
	On-site technical trainings	Large-scale webinars with local researchers on-site and external experts online
	On-site study initiation trainings	

COVID-19 Coronavirus disease 2019, *GCP* good clinical practice, *GCLP* good clinical laboratory practice, *ICP* infection prevention and control

against endemic diseases and the prevention of future outbreaks [19–21, 23]. Moreover, research platforms developed for a given disease (e.g. TBM) may later serve in tackling others (e.g. COVID-19).

It is of concern that several African countries have documented a rise in infectious diseases during the COVID-19 pandemic [24–26]. A major factor driving this increase was the reallocation of existing resources from endemic diseases to COVID-19 and the overwhelming of healthcare systems [24–26]. In the field of TB and HIV, the WHO warns about the backward trend in the preventive and control programmes [1, 27]; similar concerns are raised with other infectious diseases that are emerging and re-emerging in SSA [28–30], with the prediction that the long-term consequences are still to come due to late diagnosis and treatment. Although infectious disease outbreaks have long posed a public health threat, especially in Africa, little attention has been given to strengthening the health surveillance systems [24, 28, 30, 31].

According to United Nations Sustainable Development Goal (SDG) 17: “Partnerships for the Goals” [22, 32], humanity’s way forward requires strong global partnerships to enhance North–South and South–South cooperation, if we are to meet all other SDG targets, including SDG 3: “Good health and well-being” [22, 33]. This approach has been adopted by the European and Developing Countries Clinical Trials Partnership (EDCTP), which promotes international consortia that are owned and co-led by European and African scientists. EDCTP aims to eliminate gaps in research by nurturing teams and synergetic networks that provide mutual assistance in promoting skills, experience, expertise and infrastructure, and that are collectively capable of conducting high-level clinical trials, even in complex settings [19, 34–36]. The INTENSE-TBM project is a good example of how the international consortium represents an opportunity to drive local capacity-building programmes, particularly by creating prosperous collaborations and attracting research funding.

Conducting capacity-building activities to create homogeneous, highly competitive and

long-lasting consortia has always been a major challenge [37], but it has become even more complicated in the context of the COVID-19 pandemic. Although the INTENSE-TBM consortium had been mostly successful in overcoming the usual difficulties, the pandemic had serious consequences on the project’s research agenda, such as delays in initiation, and led us to consider innovative strategies to push forward the project despite the disruption of the national and international healthcare systems and our inability to travel on-site as expected.

In order to be sustainable, capacity building requires a long-term perspective, as it is expensive and time-consuming [19, 38]. With this in mind, we invested in developing capacity (infrastructure, equipment, resources, staff, networks) and capability (mentorship, skills, certified training, know-how), knowing that these will last beyond the lifespan of the project and enhance healthcare systems, ensure positive spill-overs to local institutions and attract further clinical research. In order to be effective, capacity-building interventions and support should be site specific, thereby reflecting the disparities in research capacity and experience among countries, regions and institutions [20, 21, 23, 37]. This approach optimises and equitably distributes resources where they are needed, and is inclusive when strengthening sites where clinical research has never been performed. Another key element of capacity-building programmes is professional development (e.g. mentorship, knowledge exchange, professional internships, training) [23, 39, 40]. Not only does professional development programmes improve clinical expertise and overall confidence in the study being conducted, but they also help to promote career advancement and to retain scientists. Despite the difficulties in procuring specialised training services (e.g., GCP/GCLP, IPC) in some countries, we were able to demonstrate the feasibility of dispensing large-scale training in a hybrid format with local researchers on-site and external experts online.

The dissemination of reports on capacity-building programmes may provide useful practical guides for implementing clinical trials in other resource-limited settings and for raising

the barriers perceived by donors and partners [20, 21]. In our case, some challenges were underestimated, potentially compromising the conduct of the trial at some sites; however, we were able to identify temporary solutions that kept the centers on track and that were in line with the goal of helping scale-up and decentralise national healthcare and clinical research.

The COVID-19 pandemic forced us to innovate and dematerialise many activities, causing us to reflect on the optimisation of resources. Remote activities (Table 1) were revealed to be feasible, largely cheaper, more sustainable and respectful of local and global environments; however, they required more paperwork and working hours to ensure good planning and to avoid overwhelming the staff on-site. In our case, even site initiation visits were successfully performed remotely (Fig. 4), with the sponsor and international managers guiding the visit online and the principal investigators and country managers conducting the visit on-site.

The ongoing COVID-19 crisis highlights the need for global health research, and national healthcare systems may indirectly benefit from capacity building related to clinical trials. In this regard, strengthening research capacity in LMIC may form the foundations for their self-reliance in the fight against endemic diseases and in coping with future health emergencies [19, 41, 42]. Many of platforms developed as part of INTENSE-TBM will continue to exist after the trial and may contribute to tackling new potential threats from infectious diseases.

In conclusion, the INTENSE-TBM project designed and developed a comprehensive capacity-building programme and has demonstrated its effectiveness by initiating the TBM-RCT at all planned sites, despite the COVID-19 pandemic. Capacity building develops infrastructure, provides resources, transfers knowledge, fosters capabilities and creates networks of skilled researchers—in the present case to ensure optimal conditions for conducting the TBM-RCT, to improve HIV/TB standards of care and to promote further clinical research in SSA. This is why capacity building must extend beyond the lifespan of individual projects and why this approach should be advocated for

enhancing and decentralising healthcare services and clinical research.

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Compliance with Ethics Guidelines. This article is based on authors knowledge and experiences prior to conducting clinical research and, therefore, it does not contain any data from human participants or animals. Written consent was obtained from the individuals appearing in Fig. 4.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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