



OPEN LETTER

REVISED **Cross- Wellcome Africa Asian Programmes (AAPs) Acceleration of Genomics for Escalating infectious Diseases, (CAGED) Consortium**

[version 2; peer review: 2 approved, 1 approved with reservations]

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Abstract
The Cross-Wellcome Africa Asian Programmes (AAPs) Acceleration of Genomics for Escalating Infectious Diseases (CAGED) Consortium is a collaboration among six institutions: the Africa Health Research Institute, the Center for Infectious Disease Research in Africa, the KEMRI-Wellcome Trust Research Programme, the Malawi Liverpool Wellcome Programme, the Mahidol Oxford Tropical Medicine Research Unit and the Oxford University Clinical Research Unit. The consortium focuses on studying pathogens posing major public health threats in Africa and Southeast Asia including chikungunya virus (CHIKV) dengue virus (DENV), multidrug-resistant (MDR) *Klebsiella pneumoniae* (*Kpn*), and drug-resistant *Mycobacterium tuberculosis* (Mtb) with climate change considered one of the several factors influencing the distribution, transmission or burden of some of these pathogens. In this paper, we outline the consortium goals, planned activities, discuss challenges and future directions. By

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leveraging cross-continent expertise, CAGED aims to unravel the molecular epidemiology of escalating infectious diseases of public health importance in Africa and Southeast Asia, and build sustainable local sequencing capacity, helping the region better prepare for future emerging infectious disease outbreaks.

Any reports and responses or comments on the article can be found at the end of the article.

Plain Language Summary

The CAGED consortium seeks to leverage the capability of six institutions spread across Africa and South East Asia: the Africa Health Research Institute (AHRI) in South Africa, the Center for Infectious Disease Research in Africa (CIDRI-Africa) in the University of Cape Town in South Africa, KEMRI-Wellcome Trust Research Programme (KWTRP) in Kenya; the Malawi Liverpool Wellcome Programme (MLW) in Malawi; the Mahidol Oxford Tropical Medicine Research Unit (MORU) in Thailand and Laos; the Oxford University Clinical Research Unit (OUCRU) in Vietnam and Indonesia. The consortium seeks to scale up genomic surveillance for diseases driven by climate change and of public health importance in these regions. Specifically, we aim to advance multi-pathogen genomic epidemiology for characterizing transmission dynamics, tracking the emergence and spread of outbreak-associated variants, and assessing their potential to evade treatments, host immunity, and vaccines.

We will use a multi-pathogen genomic surveillance approach to study the following pathogens: chikungunya (CHIKV), dengue (DENV), multidrug-resistant *Klebsiella pneumoniae* (Kpn), and drug-resistant *Mycobacterium tuberculosis* (Mtb) to bolster pathogen sequences in this region and inform improved diagnostics for these pathogens, while delineating drug resistance markers. We will share the data analysis tools developed from this study with the National Public Health Laboratory (NPHL) to improve their genomic surveillance capabilities. Additionally, we propose working closely with the policymakers to ensure that the results generated feed into policy-making decisions.

Keywords

chikungunya virus, dengue virus, *Mycobacterium tuberculosis* (Mtb), multidrug-resistant *Klebsiella pneumoniae*, genomic surveillance



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REVISED Amendments from Version 1

In the introduction, we initially noted that genomic data on the pathogens we are studying are limited, especially compared to SARS-CoV-2, which had over 3 million genomes available on GISAID. We have since revised this section to include updated information on the current availability of genomic data for each pathogen, as well as an overview of surveillance platforms in the countries where our study is being conducted. These additions strengthen the justification for our study.

Any further responses from the reviewers can be found at the end of the article

Introduction

Genomic surveillance has become a top priority for the World Health Organization, through their strategy to “focus on the specialized role of genomics as a cross-cutting capacity within the broader health system from a public health lens”. Genomics can provide insights into pathogen evolution, transmission, drug resistance, the emergence of clinically important variants and disease epidemiology. Such insights are critical for the development of intervention strategies and health policies as demonstrated during the COVID-19 pandemic, and equally relevant to endemic and escalating infections. Given the heterogeneity in infectious disease epidemiology in Africa and Asia, a multi-site and multi-pathogen approach across different geographical regions will provide a rich source of clinical and epidemiological data linked to genomics to enhance public health impact.

The Wellcome Africa Asian Programmes (AAPs) (know termed the Major International Programmes, MIPs) include: the Africa Health Research Institute (AHRI) in South Africa, the Center for Infectious Disease Research in Africa (CIDRI-Africa) in the University of Cape Town in South Africa, KEMRI-Wellcome Trust Research Programme (KWTRP) in Kenya; the Malawi Liverpool Wellcome Programme (MLW) in Malawi; the Mahidol Oxford Tropical Medicine Research Unit (MORU) in Thailand and Laos; the Oxford University Clinical Research Unit (OUCRU) in Vietnam and Indonesia. Together, the AAPs/CIDRI-A have a wealth of experience conducting genomic surveillance on multiple pathogens, through a single researcher led focus, such as Chikungunya (KWTRP),¹ Dengue (MORU, OUCRU),^{2,3} HIV (AHRI), respiratory syncytial virus (KWTRP),⁴ *Klebsiella pneumoniae* (MLW, MORU, OUCRU),^{5–7} malaria (KWTRP, MORU, OUCRU),⁸ metagenomics (OUCRU)⁹ and *Mycobacterium tuberculosis* (AHRI, CIDRI-A, OUCRU).^{10,11} The sequencing of these pathogens at all the sites is primarily conducted in-house on multiple next-generation sequencing platforms, such as Illumina and Oxford Nanopore Technology (ONT), anchored on strong platforms of infectious disease epidemiology, detailed surveillance to interrogate the impact of these infections in cohorts, communities and health facilities, while also examining the biology and immunology of the infections to inform drug and vaccine design. Furthermore, our rich resource of archived samples linked to well-characterized clinical and epidemiological data informs the historical context of these infectious diseases. Notably, we have conducted amplicon-based, whole genome and agnostic metagenomics sequencing, allowing us to overcome technical challenges posed by the diversity of the pathogens. This is supported by established bespoke pathogen specific bioinformatics workflows. Thus, we can move rapidly from samples to data analysis and policy impact.

Collectively we used SARS-CoV2 genomic surveillance to determine national and subnational routes of entry and dispersion^{12,13} and the drivers of regional transmission, while regularly sharing the data with public health professionals and policy makers. These are the similar analyses conducted on the single-focus pathogens to define, for example, the emergence and trends of drug resistance markers locally and regionally, and the outbreak and transmission of new variants.¹⁴ We are proposing to scale up and deploy this expertise to a multi-pathogen genomic surveillance approach to bolster our research capacity in the four pathogens, while maximizing on our strategic geographic locations to ensure research uptake into policy. We selected high burden endemic pathogens, Chikungunya virus (CHIKV), dengue virus (DENV), *Klebsiella pneumoniae* (*Kpn*) and *Mycobacterium tuberculosis* (*Mtb*), with currently limited use of genomics to support disease surveillance efforts, in Africa and Asia. This is in comparison to over 3 million SARS-CoV-2 genomes deposited on GISAID since the beginning of the COVID-19 pandemic.¹⁵

DENV is ubiquitous in the tropics, causing around 390 million infections globally every year, however only 96 million are symptomatic.¹⁶ Currently, there are 3.9 billion people at risk of contracting DENV, 70% of whom are from the Western Pacific and South-East Asia regions.¹⁷ In Africa, the estimated number of DENV infections exceeds 60 million,¹⁸ and half a million people require hospitalization as per WHO estimates, with a ~2.5% mortality rate.¹⁹ CHIKV which initially caused small outbreaks, has recently expanded beyond the Indian Ocean Islands.²⁰ Since, its initial description in Tanzania in 1952²¹ one of the largest epidemics, in 2004, resulted from its re-emergence in Coastal Kenya affecting millions of people and spreading along the Indian Ocean islands, India, Southeast Asia and Europe, with a new emergent lineage^{22,23} CHIKV mortality rates are low (~0.1%), however morbidity has a substantial impact on the quality

of life as the virus can lead to neurological disease and chronic disability.^{24,25} CHIKV and DENV symptoms are similar, and the infections are often confused,²⁶ thus molecular diagnostics are an imperative. Climate change is a key driver of the spread and transmission of CHIKV and DENV. Arbovirus distribution is predicted to be strongly affected by climate change. The distribution of the *Aedes* mosquito vectors responsible for transmission of CHIKV and DENV have been extensively studied, investigating the effects of temperature^{27,28} and humidity²⁹ on habitat suitability and suggesting a climate-driven expansion into new ranges,³⁰ and a corresponding increased urban population at risk from mosquito-borne disease.³¹

Genomic data from DENV and CHIKV is available for many of the countries in the CAGED consortium, however this is not evenly distributed by country. We assessed the data used by the Nextstrain real-time tracking of viral evolution³² to determine the availability of public sequence data for these two viruses. While Thailand and Vietnam have over 2000 available dengue genomes deposited in public databases, the majority were sampled before 2020. For Laos, Nepal, and Kenya, there are fewer than 150 genomes per country, and for Indonesia there are 555 genomes. For chikungunya, there are over 150 complete genomes for Thailand, but fewer than 50 for all other countries in this consortium, and no genomes for Vietnam or Nepal. Although some countries have existing surveillance policies for the pathogens in this consortium, others do not. Thailand has a national disease surveillance program which includes case reporting for chikungunya and dengue³³ viruses and Extensively Drug-Resistant (XDR) *Mtb*. Laos has a national surveillance program for dengue which only includes clinical case reporting. A WHO/TDR survey of 47 African countries reported that although most countries have adequate capacity for general disease surveillance, arbovirus diagnosis, notification and preparedness for disease outbreaks due to their long experience in the control of malaria and other diseases, they lack integrated, nationwide dengue–chikungunya surveillance platform <https://fctc.who.int/resources/publications/i/item/9789240052918>.

Hospital and community acquired *Kpn* infections in Asia and Africa, predominantly affect neonates, young children and adults in intensive care units (ICUs).³⁴ The burden of disease is exacerbated by the emergence and spread of multidrug-resistant (MDR) and hypervirulent *Kpn* strains.³⁵ *Kpn* is the second leading cause of death due to antimicrobial resistance (AMR), with over 200,000 fatalities attributed to AMR in 2019.³⁶ The accumulation of AMR is primarily due to horizontal gene transfer aided by plasmids and mobile genetic elements.^{35,37} These resistance mechanisms can be interrogated using whole genome data. Existing global surveillance platforms for *Klebsiella pneumoniae* such as KlebNET Genomic Surveillance Platform (KlebNET-GSP) was established in 2018, currently hosting 110,891 *Kpn* genomes with associated metadata (<https://next.pathogen.watch/genomes/573-klebsiella-pneumoniae>, assessed on 16th March 2026). This global platform also incorporates a set of standardized bioinformatic pipelines and genomic reporting frameworks, which greatly facilitate data harmonization and the interpretation of AMR genotypes. It further supports global efforts to develop a genomic risk framework, to assess K (capsule) and O (lipopolysaccharide) antigen distributions and track the transmission of high-risk lineages associated with neonatal sepsis. However, national policies on *Kpn* genomic surveillance remain largely lacking across countries within the AAPs.

For *Mtb*, the treatment success for rifampicin-resistant TB (RR-TB) is ~63%, however of the ~410,000 patients with RR-TB in 2022, only 2 in 5 people were enrolled on RR-TB therapy.³⁸ In 2022, the WHO announced that RR-TB could be treated with a new regimen of bedaquiline (B), pretomanid (Pa), linezolid (L) (BPaL), with or without moxifloxacin (M).³⁹ The BPaL(M) regimen is up to 50% more effective than the previous standard-of-care, it is fully oral and given over a shorter (6 months) time period.⁴⁰ This regimen is prescribed in at least 40 countries, but without an adequate companion molecular diagnostic to monitor resistance.³⁸ Though in 2023, targeted next-generation sequencing was recommended by WHO for RR-TB.⁴¹ Large WGS datasets for *Mtb* are now widely available, though no single platform tracks global totals. Key collections include the CRYPTIC dataset of 12,289 sequenced isolates,⁴² the Afro-TB dataset with 17,641 strains (13,753 curated) from 26 African countries,⁴³ and the NIAID TB Portals resource housing genomic-linked data from over 28,000 TB cases (<https://www.niaid.nih.gov/research/tb-portals>). Additional raw reads are deposited across the NCBI SRA <https://sra-explorer.info> and ENA <https://www.ebi.ac.uk/ena/browser/home>, the primary global repositories, although neither provides organism-specific counts. Tools like Pathogenwatch <https://next.pathogen.watch/en>, CRYPTIC, and the TB-Resources index <https://github.com/a-r-j/TB-Resources> help researchers identify and navigate these distributed datasets. Despite the large volume of data, global coverage is uneven: most publicly available genomes derive from high-income settings and dominant Eurasian lineages, while many regions - including much of Africa and parts of Asia and the Pacific - remain under sampled.

All countries hosting AAP-affiliated sites maintain National TB Programmes, but surveillance systems differ substantially in diagnostic reach and laboratory capacity. WHO regional analyses highlight persistent gaps in case detection and incomplete linkage of diagnostic data to national reporting systems in several high-burden settings <https://www.who.int/publications/i/item/9789240116924>. Laboratory assessments similarly report limited access to culture, Drug-Susceptibility Testing (DST), and advanced molecular diagnostics across many countries,⁴⁴ despite wide uptake of Xpert MTB/RIF as the primary test for rifampicin resistance.⁴⁵ As a result, surveillance in many AAP-region settings

remains heavily Xpert-based, providing drug-resistance screening but lacking the resolution required for genomic epidemiology or monitoring emerging resistance.

Moreover, for *Mtb*, climate change acts primarily through indirect pathways. It has been shown that climate change has potential to worsen the TB epidemic by among others contributing to population displacement which often leads to overcrowding living conditions that accelerates TB transmission.⁴⁶ Healthcare disruption can cause TB treatment interruption, leading to longer infectious period and ultimately increased risk of development of drug resistance.⁴⁷ Moreover climate-related and socioeconomic disruptions contribute to food insecurity and malnutrition, which weakens the immune system and increasing the risk of TB infection and transmission.⁴⁸

The MIPs will collectively utilise their broad expertise, lessons from the COVID-19 pandemic and their current research strengths, to provide comprehensive genetic profiles for these four pathogens. More importantly, we will work towards integrating the genomic surveillance by moving platforms developed and data generated to the National Public Health Laboratory (NPHL) such that the data is used to accelerate evidence-based policy decision making, for instance, antimicrobial stewardship. The aim of this consortium is to advance multi-pathogen genomic epidemiology for characterizing transmission dynamics, tracking the emergence and spread of outbreak-associated variants and assessing their potential to evade treatments, host immunity and vaccines. This will be done through; coordinating and synergizing the strengths across AAPs/CIDRI-A and data integration of all 4 pathogens to explore the following objectives; i) determine the transmission networks of CHIKV and DENV outbreaks and the potential of these rapidly evolving viruses to escape host immunity and vaccination; ii) map out the emergence and transmission of multidrug-resistant *Kpn* in hospital facilities and community settings; and iii) evaluate the emergence of resistance to bedaquiline, pretomanid, linezolid and moxifloxacin among rifampicin resistant *Mtb* strains.

Methodology

The project will be delivered through five work packages (WPs), linked by sharing resources, analytical approaches and governance to ensure the consortium realizes its synergies. We will build on existing investments in sample collection and surveillance to analyse archived and prospective samples that we have established through long-term local partnerships. Thus, ethical approvals have already been obtained for these studies for future work or for molecular analyses.

All archived samples will form part of the retrospective observational study for each pathogen and will be selected based on the availability of requisite meta-data to support the genomic epidemiology analyses. All prospective samples from ongoing studies in these sites will be obtained from consenting participants. A standard data collection tool will be used across all AAPs/CIDRI-A for each pathogen to support easy access, data sharing and analyses. [Table 1](#) lists details of the samples to be used for this study.

WP 1 Project management

Overall goal

Provide coordination across the pathogen WPs to ensure timely delivery of the overall project milestones. In addition, the project management WP will be responsible for planning periodic project meetings to bring together all teams across AAP/CIDRI-A to ensure alignment on project goals and to provide a forum for sharing site-specific updates.

Governance and management of the consortium

The consortium operates under a transparent governance framework to ensure effective coordination and management of the programs of work across participating institutions. Overall leadership is shared between two coordinating institutions KWTRP and OUCRU.

The consortium's governance is organized across three primary committees to ensure strategic oversight, operational management, and support for execution of the project activities [Figure 1](#). The Advisory Committee (AC) serves as the highest decision-making committee. The AC is composed of the Directors of the AAP/CIDRI-A, a selection of independent external experts, and an observer from the Wellcome Infectious Disease Strategic team. The AC serves to provide strategic direction, scientific critique and policy guidance on consortium activities.

The project will be managed by the Steering Committee (SC), who are the lead applicants, co-applicants and WP leads from the AAPs/CIDRI-A. The SC will: oversee and set the priorities and scope of research activities of the consortium, manage project resources, and coordinate the various Work Packages. The SC will convene for quarterly virtual

Table 1. Description of the prospective and retrospective samples to be used for this study across the different sites.

Work package	Site	Source of sample and sample type	Sample type
CHIKV and DENV	MORU	Hospital samples	Blood
	KWTRP	Archived blood samples in the biobank at KWTRP and from collaborators such as NPHI and KEMRI CVR	Blood
	AHRI	National Health Laboratory Service of South Africa and AHRI-Durban cohort of participants with respiratory and febrile illness based at Inkosi Albert Luthuli Central Hospital, King Edward Hospital, Clairwood Hospital, and KwaDabeka community clinic	Blood
	MLW	Multiple health facilities and from ongoing studies under the vector programme	Mainly serum and plasma as well as NP and CSF, mosquitoes
<i>Kpn</i>	COMRU	Angkor Hospital for Children	Blood
	KWTRP	Kilifi County Hospital (neonates and paediatrics (retrospective and prospective, from HDU and normal wards) adults (retrospective from wards)), Mbagathi County Hospital, Nairobi (neonates and paediatrics from neonate and children wards and the acute room (not exactly a HDU)), Community health facilities in Kilifi (3 health centres catering to the community) (children and adults)	Blood, urine, CSF
	CIDRI-A	Tertiary referral hospital for Infectious diseases, tertiary general hospital and community carriage studies	
	MLW	Queen Elizabeth Central Hospital, Zomba Central Hospital	Blood, CSF
	OUCRU	Tertiary referral hospital for Infectious diseases & tertiary general hospital	Blood, Urine
Mtb	SMRU	Hospitals and centralised DR-TB clinics	Sputum and cultures
	KWTRP	Kilifi County Hospital, Malindi sub-county Hospital and Mariakani sub-county hospital	
	AHRI	National Health Laboratory Service of South Africa and AHRI-Somkhele Demographic Surveillance Site based in uMkhanyakude district, KwaZulu-Natal province	Sputum and isolated cultures
	CIDRI-A	Nkqubela Chest Hospital, a public referral hospital in the Buffalo City Municipality, East London, Eastern Cape, South Africa	

Mahidol Oxford Tropical Medicine Research Unit (MORU); KEMRI-Wellcome Trust Research Programme (KWTRP); Africa Health Research Institute (AHRI); Malawi (MLW); Center for Infectious Diseases Research in Africa (CIDRI-A); Oxford University Clinical Research Unit (OUCRU); Cambodia-Oxford Medical Research Unit (COMRU); Shoklo Malaria Research Unit (SMRU).

meetings. Its responsibilities also extend to actively engaging with policymakers and producing reports on project outputs for dissemination to stakeholders.

The consortium research activities are carried out through Work Packages (WPs). Each WP is led by a designated Lead and Co-Lead, and relevant members from each AAP/CIDRI-A. These teams are responsible for developing and implementing detailed work plans, engaging stakeholders and collaborators to implement project activities, reviewing whole-genome sequencing (WGS) assays and bioinformatics pipelines, conducting country-level and cross AAPs/CIDRI-A data analysis, and holding monthly coordination meetings to ensure harmonised progress.

Reports will be generated biannually to evaluate project progress at all sites. It will include information on samples, sources and sequencing, variants detected, expenditure, dissemination activities, publications, health facility reports, and policy briefs shared and stakeholder engagements.

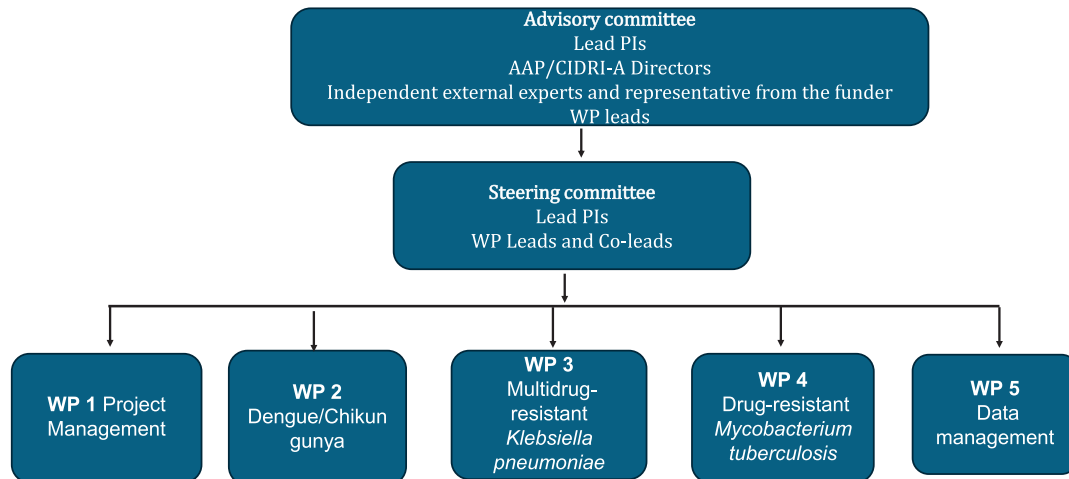


Figure 1. The project governance and management structure. The advisory committee will provide strategic leadership, the steering committee oversees the research activities while the work package lead will provide the day to day management of the study activities.

Expected outcomes

The terms of reference for the AC and SC will be developed, strategic directions will be set and revised as appropriate, and quarterly reports demonstrating the project progress and outputs from SC will be shared with the AC and funder. We will develop a list of use cases for each pathogen to develop standard lab and data tools. The advice from the AC will support the project's public health impact within the AAPs/CIDRI-A countries and beyond. Successful coordination by the SC will result in the achievement of the project milestones through the WP teams. The quarterly reports will track the progress of the project.

WP 2 CHIKV and DENV

Overall goal

To characterize the genetic diversity and evolutionary dynamics of CHIKV and DENV across Asia and Africa through genomic surveillance and phylogenetic analysis, and to assess the implications of this diversity for vaccine efficacy via neutralization assays, thereby generating critical evidence to inform regional outbreak response and vaccine deployment strategies.

Methodological approach

We will utilise retrospective and prospective confirmed (by Reverse Transcription (RT)-quantitative PCR CHIKV blood samples. Additional febrile surveillance retrospective and prospective samples, serum or plasma will be screened by RT-qPCR for CHIKV and DENV. Sequencing and bioinformatics pipeline methodologies will be standardized across the sites. WGS of CHIKV and DENV will be done using an amplicon-based approach on the Illumina and ONT platforms, according to the platforms available in each site. Whole genomes will be amplified by generating between 4 and 8 long overlapping RT-PCR fragments in separate RT-PCRs, or small fragments in two pools of RT-PCRs, according to the procedures in place on each site. The RT-PCR products will then be pooled and cleaned, and the library will be built using either Rapid Barcoding or Native Barcoding ONT kits, or Illumina library preparation kits according to the technique available at each site. The read analysis will be performed using established pipelines such as the artic network amplicon pipeline <https://artic.network/resources/amplicon-nf>, which processes both Illumina and ONT data. While sites will not harmonise sequencing protocols, owing to different platform availability, we will standardize the data QC and metrics to ensure we use high quality sequences for the downstream analysis, and an internal EQA process will allow comparison of sequences between sites.

Consensus genomes will be generated and both maximum likelihood and Bayesian phylogenetic trees will then be constructed in the context of global CHIKV and DENV sequences obtained from GenBank, representing the 3 distinct CHIKV clades from East/Central/South Africa, West Africa and Asia. For DENV, the representative sequences will include the four distinct serotype strains DENV-1, 2, 3 and 4. We aim to identify distinct CHIKV and DENV lineages, any

global transmission trends such as lineage replacements or movement of lineages between continents and detect any new emerging outbreak strains.

To assess neutralizing antibodies against CHIKV and DENV a minimum of 20 participant samples per group will be selected to examine strain differences related to immune/vaccine escape. The selection of a minimum of 20 participant samples per group was based on a formal sample size determination conducted specifically for neutralization assays comparing responses between viral strains. A bootstrap-based power analysis was performed assuming neutralization titres (FRNT50) follow a normal distribution with high inter-sera variability ($\sigma \approx \mu$), which is typical for neutralization assays. The analysis further assumed that biologically meaningful differences correspond to approximately a three-fold difference in neutralization titres between strains. Using 1000 bootstrap iterations and a two-sided t-test with $\alpha = 0.05$, the analysis demonstrated that approximately 20 sera samples are sufficient to detect such differences with statistical power ≥ 0.8 . The purpose of this assessment is not to estimate population-level seroprevalence or overall immunity, but rather to experimentally compare neutralization capacity across viral lineages and assess potential immune escape at the virological and immunological level.

Representative live virus strains from each location, as informed by phylogenetic analysis, will be isolated and tested against geography specific sera from convalescent individuals (~3 months following the initial febrile episode). We will perform multiplexed serological epitope mapping approaches using data from live virus neutralization assays, to discern correlates of immune protection and escape across strains.^{49,50} The geometric mean titres per group of sera against each DENV and CHIKV viral isolate will be determined and the Racmacs package for antigenic cartography will be used to determine antigenic distance between viral isolates.^{51,52}

Furthermore, the existing Dengue Advanced Readiness Tools consortium (DART) <https://www.dartdengue.org>, a separately funded project which is also lead by OUCRU-Vietnam, are integrating climatic factors into dengue outbreak forecasting, and we will work with them to expand their tools to sites in this consortium and to integrate genetic factors into their model.

Expected outcomes

The WGS data will be deposited on GenBank (doubling the number of genomes) and GISAID. The phylogenetic analysis of historical and contemporary CHIKV and DENV sequences will identify new lineages, the spread of lineages across Asia and Africa and potential imports within each geographic location. The neutralisation assays will provide a better understanding of the potential protective effect of DENV and CHIKV vaccines given the DENV and CHIKV genetic diversity defined in this project and its consequences for immune escape.

WP 3 Kpn

Overall goal

To achieve three complementary objectives: (1) establish accessible genomic data infrastructure through the ACORN platform and Pathogenwatch to facilitate real-time data sharing with Ministries of Health and research collaborators; (2) elucidate the temporal emergence, community-hospital linkages, and national and international transmission patterns of MDR strains through in-depth phylogenetic analysis; and (3) characterize the genetic elements (plasmids, genes, chromosomal insertions) associated with AMR and virulence and their horizontal transfer dynamics, thereby strengthening the evidence base for outbreak detection and antimicrobial resistance containment.

Methodological approach

We will randomly select *Kpn* positive samples collected from hospital and community carriage surveillance. We will utilize an equivalent number of *Kpn* community carriage strains as hospital facilities (HF) strains. We will also leverage existing surveillance efforts such as the Wellcome-funded A Clinically Oriented Antimicrobial Resistance Network (ACORN) study⁵³ to collect patient, microbiology and clinical metadata using the available standard protocols to ensure data harmonization. In addition, we will collect information on any previous and current antibiotics prescribed.

We will use a single whole genome sequencing (WGS) standard operating procedure (SOP) and bioinformatics pipeline. All *Kpn* isolates identification from blood and CSF cultures will undergo the routine antimicrobial susceptibility testing to support clinical care and will subsequently be cultured for DNA for extraction using either the Wizard[®] Genomic DNA Purification Kit (Promega, USA) or the DNeasy Blood & Tissue Kit (Qiagen, Germany), depending on local availability. DNA libraries will be prepared using the Nextera XT DNA Library Preparation Kit or the NEBNext Ultra II FS DNA

Library Prep Kit for Illumina. WGS will be done on locally established Illumina platform MiSeq (Miseq, Hiseq or Novaseq), with the OTN platform used for selected samples. Except for South Africa most sites will do shot-read Illumina sequencing.

We will use well-established bioinformatics tools such as Kleborate⁵⁴ for the characterisation of *Kpn* genomes including multilocus sequence typing (MLST), delineating the *Kpn* complex into species, screening for AMR and virulence genes and the mobile elements (including plasmids) harbouring them. We will use Kleborate with Kaptive⁵⁵ to identify capsule K and the lipopolysaccharide O antigen loci. Short read sequence typing (SRST2) for bacterial pathogens,⁵⁶ will determine the emergence of MDR and/or hypervirulent strains/variants. The genomic and clinical metadata will be uploaded to Pathogenwatch (<https://next.pathogen.watch/en>), a comprehensive global platform dedicated to genomic surveillance of microbial pathogens, including 110,891 *Kpn* publicly available genomes, and featuring real-time analytics. Genomic data will be analyzed within the local, regional, and global contexts, including clinical parameters, enabling visualization and real-time data sharing across the sites.

We will infer transmission of high-risk lineages using phylodynamic modelling and SNP analyses. SNP calling will be performed using the Snippy pipeline (<https://github.com/tseemann/snippy>). Maximum likelihood phylogenies will be inferred from the core SNP alignment, using IQ-TREE v2.2.0.3 with best-fit substitution models and 1,000 ultrafast bootstraps and these phylogenetic trees will serve as the basis for time-scaled phylodynamic analysis using BEAST X.⁵⁷ The phylogenetic analyses will identify clinically relevant lineages that emerge within a HF, network of HFs and the community that could cause a local outbreak. The data across-sites will determine whether a MDR clonal outbreak in SE Asia seeds MDR outbreaks in Africa and vice versa. We will also define the prevalence of sequence types, serotypes, AMR genes and virulence factors circulating in the different countries, hospitals and the community. These *Kpn* components will then be associated with clinical outcomes and the antimicrobial sensitivity test data, to determine which components are associated with, for instance, third-generation cephalosporin-resistance to inform treatment strategies in our populations. Similarly, the prevalence of hypervirulent clones will be defined in SE Asia and particularly in Africa where this data is limited.

Expected outcomes

WGS data will be on the ACORN platform and Pathogenwatch for easy data sharing with collaborators and the Ministry of Health (MoH). The archived samples will provide insights into the temporal emergence of variants. The in-depth phylogenetic analyses will elucidate the links between community carriage and hospital transmission, national and international transmission patterns of MDR strains between Asia and Africa and characterize potential outbreaks. Furthermore, we will describe the genetic elements (genes, plasmids, chromosomal insertions) associated with AMR and virulence and determine the transmission of these elements within and between strains/variants, both at a national and international scale.

WP 4 Mtb

Overall goal

To characterize the emergence of resistance to bedaquiline, pretomanid, linezolid, and moxifloxacin among rifampicin-resistant *Mtb* strains, thereby strengthening predictive capacity for drug resistance in this population.

Methodological approach

We will focus on prospective sampling from *Mtb* clinics within level 3 HFs and above. The standard data variables will be agreed upon across institutions and data on previous *Mtb* episodes and *Mtb* treatments and use of BPaL(M) drugs will be collected. Sputum will be collected from patients with RR-TB confirmed by Xpert MTB/RIF. Isolates will be cultured to purity in category 3 laboratory facilities and DNA extracted from pure isolates prior to Illumina/ONT sequencing. We will use the Illumina and ONT platforms and the bioinformatics analyses will be based on a standardised and validated pipelines familiar to CIDRI-A and OUCRU.

Consensus genomes will be generated and variants called using an automated pipeline, MTBseq⁵⁶ or GPAS <https://gpas.global>. For historical and wider geographic context, we will select additional publicly available genomes for comparison. Resistance mutations relevant to fluoroquinolones, bedaquiline, pretomanid, and linezolid will be identified using the WHO mutation catalogue⁵⁸ with phenotypic DST performed on isolates with mutations of uncertain significance. Lineages associated resistance mutations will be determined using an automated pipeline. Similar to *Kpn*, we will use Pathogenwatch for the cross-site analysis since it supports easy data sharing.

A logistic regression analysis will be conducted to assess epidemiological risk factors for the presence of drug resistance mutations. Time-scaled, Bayesian phylogenetic reconstruction will also be used to estimate the date of emergence of drug resistance mutations. This will form the basis for the discovery, identification and prevalence of drug resistance variants to bedaquiline, pretomanid, linezolid, and moxifloxacin.

Expected outcomes

The data will be on Pathogen watch for easy data sharing with our collaborators and the MoH. The in-depth phylogenetic analyses will elucidate the national and international transmission patterns of MDR strains between Asia and Africa and characterize potential outbreaks. We will describe the mutations associated with MDR-Mtb and their prevalence. Expertise in the use of MTBseq will be developed as an additional tool for the bioinformatics analyses of WGS data from clinical Mtb strains. This WP will advance resistance prediction, provide genomic MDR-Mtb genomic surveillance data to support the diagnosis of MDR-Mtb infections (those not identified by Xpert MTB/RIF) and minimise treatment failures. Thus, it will improve the optimal treatment of patients and reduce MDR-TB resistance transmission.

WP 5 Data management

Project goal

To foster integrated data management across sites to carry out unified analyses and enable interoperability between AAPs/CIDRI-A and national-level surveillance systems.

Methodological approach

We will achieve our goal through roll out and implementation of FAIR data principles.

Findable: We will aim to employ standardised metadata policies and formats for example those developed by the PHA4GE network. The sequence data will be deposited on additional publicly available repositories such as Nextstrain, European Nucleotide Archive and GenBank. The standardized bioinformatic pipelines will be made available on Github.

Accessible: We will utilize both paper and digital systems, predominantly REDCap, Open data kit, Kobo Toolbox, and CommCare, and a mix of on-premise and cloud-based servers. We will use openly accessible data formats, with licensing that supports broader usage while respecting personal data privacy.

Interoperable: To harmonize these systems and link the data with the national Mtb, AMR and vector borne diseases programs dashboards or health information services, we will utilize the HL7 Fast Healthcare Interoperability Resources (FHIR)⁵⁹ data standard that is endorsed by WHO to enable data interoperability. The MoH of each country has initiated transition to the FHIR standard, with most having drafted FHIR implementation guides (IG). We will adopt and expand these to integrate our genomics and clinical meta-data. Each site will map their current and planned data schemas to their country-level FHIR IG, and we will jointly agree on harmonization encoding across countries. This process will be facilitated by engagement with the FHIR HL7 genomics working group and the FHIR GenomeX initiative, and with specific tools, such as REDCap's Clinical Data Interoperability Services (CDIS). We will deploy the FHIR HL7 clinical quality language (CQL) or real time assessment of data quality and completeness.

Reusable: Documentation (data dictionaries, user manuals) will accompany each dataset, making re-analysis or meta-analysis straightforward for external researchers. Whenever feasible, we aim for a CC-BY 4.0 license, except where restricted by ethical constraints.

Expected outcome

Ultimately, we hope that our project will produce interoperable data in line with the FHIR standards and establish mechanisms across the sites for a federated data analysis pipeline.

Opportunities, challenges and future directions

The CAGED study consortium serves as an excellent platform for building local sequencing capacity across its sites and anchoring additional research. By leveraging the AAPs network the consortium will enhance the surveillance of *Kpn*, support national AMR reference laboratories in tracking the spread of carbapenem-resistant *Kpn* lineages across hospital surveillance systems (e.g. in Vietnam) or to assist collaborative hospitals in confirming and responding to nosocomial *Kpn* outbreaks (e.g. in Kenya). To build sustainable local sequencing capacity, for Mtb, CIDRI-A and OUCRU will

transfer standardized protocols and provide hands-on training to AAPs that do not currently conduct these assays, including MLW and KWTRP, with SOPs shared across all sites. MORU and OUCRU (DENV) and KWTRP (CHIKV), based on their existing expertise, will lead the standardization of sequencing and bioinformatic pipeline methodologies across AAPs. SOPs will be shared and training provided, where needed, to support the deployment of the tools in each AAP. The consortium has also leveraged on this platform to secure further grant funding including resources to expand the consortium's work into Zika virus sequencing. Capacity building efforts have also leveraged on the platform to support short-term MSc projects and partial PhD projects.

Operating across diverse partner institutions and global regions necessitates navigating country-specific regulations, including protocol approvals, data and sample sharing mechanisms, and institutional bureaucracies related to Material Transfer Agreements (MTAs).

While challenging these processes present valuable opportunities to strengthen collaborative frameworks and enhance our standing in international research. To ensure effective coordination, the consortium has established regular communication channels and formed an advisory committee. This committee, comprising heads of all partner institutions and key external stakeholders, secures high-level institutional buy-in and strategic guidance for consortium activities.

Looking beyond the current project cycle, future directions include individual countries' National Public Health Institutes and Ministries of Health. This ongoing collaboration is crucial to ensure the evidence generated directly informs national policy decisions.

Communication/engagement and dissemination plans

The consortium activities will be implemented across three years for all the pathogen specific activities. The overall aim is to strengthen national public health institutions by providing enhanced genomic surveillance data on priority pathogens and improving outbreak response mechanisms. To achieve this, we will engage regularly with national and subnational policymakers to foster stronger collaboration. At project initiation we will hold engagement meetings with subnational and national level policy makers to introduce the project objectives, planned activities, expected outputs and potential policy implications. These initial project engagement meetings will also serve to establish communication channels between the researchers and the policy makers. Throughout the project, we will regularly share the data and results obtained. Through WP 5, we will develop data dashboards based on the genomic surveillance and epidemiological data generated across the AAPs/CIDRI-A. The dashboard will be made freely available to policy makers and the NPHL to support outbreak preparedness and response planning in addition to evidence-based decision making. The dashboard and the associated data tools will be handed over to the NPHL for project sustainability. Final project results generated from the consortium will also be translated into policy brief tailored to national and sub-national decision-makers. The policy briefs will be disseminated through structured policy engagement meetings, stakeholder workshops and to the relevant MoHs relevant technical working groups (TWGs). These engagements will provide a forum to discuss policy implications, foreseeable implementation challenges and recommendations for strengthening the regions outbreak response strategies. Moreover, partners are committed to promptly publishing results and refining the collaboration's dissemination strategy through quarterly steering committee meetings.

Workplan

Table 2. Project timelines and milestones across the three-year implementation period of the study.

Activity	Year 1		Year 2		Year 3	
	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec
Work package 2, CHIKV & DENV						
<i>Sub-Aim 2.1 generation of a centralized sample database</i>						
Setting up sequencing plan and central database						
<i>Sub-Aim 2.2 capacity development and sequencing</i>						
Sequencing using Oxford Nanopore or Illumina						
<i>Sub-Aim 2.3 sequence analysis and tracking variants</i>						
Phylogenetic analysis to define lineages and new variants						
<i>Sub-Aim 2.4 characterization of neutralising antibody responses</i>						

Table 2. Continued

Activity	Year 1		Year 2		Year 3	
	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec	Jan-Jun	Jul-Dec
Setting up neutralisation assays across the AAPs and serological analysis						
Work package 3, <i>Klebsiella pneumoniae</i>						
<i>Sub-Aim 3.1 generation of a centralized sample database</i>						
Harmonization of <i>Kpn</i> bioinformatics pipelines and setting up central database						
<i>Sub-Aim 3.2 capacity development and sequencing</i>						
Sample DNA extraction and WGS in all sites						
<i>Sub-Aim 3.3 sequence analysis and tracking variants</i>						
Phylogenetic analysis to define lineages and new variants						
<i>Sub-Aim 3.4 Characterisation of antimicrobial resistance (AMR)</i>						
Identification of clinically relevant MDR lineages in Africa and Southeast Asia						
Work package 4, <i>Mycobacterium tuberculosis</i> (Mtb)						
<i>Sub-Aim 4.1 Generation of a centralized sample database</i>						
Prospective sample collection in all sites and Xpert RR-TB screening						
<i>Sub-Aim 4.2 Capacity development and sequencing</i>						
Training and setting up Mtb sequencing at all sites						
<i>Sub-Aim 4.3 sequence analysis and tracking variants</i>						
Overall cross AAPs/CIDRI-A sequence analysis and submission to MTBseq and Pathogenwatch						
<i>Sub-Aim 4.4 Characterisation of AMR</i>						
Determination of local emergence and prevalence of drug resistance mutations						
Work package 5, Data management						
Integration of current data platforms into the FHIR standard						

Ethics and consent

Ethical approval and consent were not required for this study.

Disclaimer

The views expressed in this article are those of the author(s). Publication in Wellcome Open Research does not imply endorsement by Wellcome.

Data availability**Underlying data**

No data are associated with this article.

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References

1. Nyamwaya DK, Otiende M, Omuoy DO, *et al.*: **Endemic Chikungunya fever in Kenyan children: a prospective cohort study.** *BMC Infect Dis.* 2021; **21**(1): 186.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
2. Castonguay-Vanier J, Klitting R, Sengvilaipaseuth O: **Molecular epidemiology of Dengue Viruses in three provinces of Lao PDR 2006-2010.** *PLoS Negl Trop Dis.* 2018; **12**(1): e0006203.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
3. Dang TT, Pham MH, Bui HV, *et al.*: **First full-length genome sequence of Dengue Virus serotype 2 circulating in Vietnam in 2017.** *Infect Drug Resist.* 2020; **13**: 4061–4068.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
4. Owuor DC, de Laurent ZR, Nyawanda BO, *et al.*: **Genetic and potential antigenic evolution of influenza a(H1N1)pdm09 viruses circulating in Kenya during 2009-2018 influenza seasons.** *Sci Rep.* 2023; **13**(1): 22342.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
5. Chomkatekaw C, Thaipadungpanit J, Hearn P, *et al.*: **Detection of maternal transmission of resistant gram-negative bacteria in a Cambodian hospital setting.** *Front Microbiol.* 2023; **14**: 1158056.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
6. Musicha P, Msefula CL, Mather AE, *et al.*: **Genomic analysis of *Klebsiella pneumoniae* isolates from Malawi reveals acquisition of multiple ESBL determinants across diverse lineages.** *J Antimicrob Chemother.* 2019; **74**(5): 1223–1232.
[Publisher Full Text](#) | [Free Full Text](#)
7. Trang NHT, Nga TVT, Campbell JI, *et al.*: **The characterization of ESBL genes in *Escherichia coli* and *Klebsiella pneumoniae* causing nosocomial infections in Vietnam.** *J Infect Dev Ctries.* 2013; **7**(12): 922–928.
[PubMed Abstract](#) | [Publisher Full Text](#)
8. Osoti V, Akinyi M, Wamae K, *et al.*: **Targeted amplicon deep sequencing for monitoring antimalarial resistance markers in Western Kenya.** *Antimicrob Agents Chemother.* 2022; **66**(4): e0194521.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
9. Tan LV, NTT H, Ngoc NM, *et al.*: **SARS-CoV-2 and co-infections detection in nasopharyngeal throat swabs of COVID-19 patients by metagenomics.** *J Infect.* 2020; **81**(2): e175–e177.
[Publisher Full Text](#) | [Free Full Text](#)
10. Srinivasan V, VTN H, Vinh DN, *et al.*: **Sources of multidrug resistance in patients with previous isoniazid-resistant tuberculosis identified using whole genome sequencing: a longitudinal cohort study.** *Clin Infect Dis.* 2020; **71**(10): e532–e539.
[Publisher Full Text](#) | [Free Full Text](#)

11. Wasserman S, Louw G, Ramangoela L, *et al.*: **Linezolid resistance in patients with drug-resistant TB and treatment failure in South Africa.** *J Antimicrob Chemother.* 2019; **74**(8): 2377–2384. [Publisher Full Text](#) | [Free Full Text](#)
12. Githinji G, de Laurent ZR, Mohammed KS, *et al.*: **Tracking the introduction and spread of SARS-CoV-2 in coastal Kenya.** *Nat Commun.* 2021; **12**(1): 4809. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
13. Joonlasak K, Batty EM, Kochakarn T, *et al.*: **Genomic surveillance of SARS-CoV-2 in Thailand reveals mixed imported populations, a local lineage expansion and a virus with truncated ORF7a.** *Virus Res.* 2021; **292**: 198233. [Publisher Full Text](#)
14. Chau NVV, Thuong TC, Hung NT, *et al.*: **Emerging enterovirus A71 subgenogroup B5 causing severe hand, foot, and mouth disease, Vietnam, 2023.** *Emerg Infect Dis.* 2023; **30**(2): 363–367. [Publisher Full Text](#) | [Free Full Text](#)
15. Fumagalli SE, Padhiar NH, Meyer D, *et al.*: **Analysis of 3.5 million SARS-CoV-2 sequences reveals unique mutational trends with consistent nucleotide and codon frequencies.** *Virol J.* 2023; **20**(1): 31. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
16. Brady OJ, Gething PW, Bhatt S, *et al.*: **Refining the global spatial limits of Dengue Virus transmission by evidence-based consensus.** *PLoS Negl Trop Dis.* 2012; **6**(8): e1760. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
17. WHO: **Dengue and severe dengue.** 2024; Accessed May 15, 2025. [Reference Source](#)
18. Bhatt S, Gething PW, Brady OJ, *et al.*: **The global distribution and burden of dengue.** *Nature.* 2013; **496**(7446): 504–507. [Publisher Full Text](#) | [Free Full Text](#)
19. WHO A: **Dengue** | WHO | Regional Office for Africa. May 14, 2025; Accessed May 15, 2025. [Reference Source](#)
20. Weaver SC, Forrester NL: **Chikungunya: evolutionary history and recent epidemic spread.** *Antiviral Res.* 2015; **120**: 32–39. [PubMed Abstract](#) | [Publisher Full Text](#)
21. Ross RW: **The Newala epidemic. III. The virus: isolation, pathogenic properties and relationship to the epidemic.** *J Hyg (Lond).* 1956; **54**(2): 177–191. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
22. Chretien JP, Anyamba A, Bedno SA, *et al.*: **Drought-associated Chikungunya emergence along coastal East Africa.** *Am J Trop Med Hyg.* 2007; **76**(3): 405–407. [Free Full Text](#)
23. Wahid B, Ali A, Rafique S, *et al.*: **Global expansion of Chikungunya Virus: mapping the 64-year history.** *Int J Infect Dis.* 2017; **58**: 69–76. [PubMed Abstract](#) | [Publisher Full Text](#)
24. Renault P, Jossereau L, Pierre V: **Chikungunya-related fatality rates, Mauritius, India, and Reunion Island.** *Emerg Infect Dis.* 2008; **14**(8): 1327a–1327a. [Publisher Full Text](#)
25. Schilte C, Staikovskiy F, Couderc T, *et al.*: **Chikungunya Virus-associated long-term arthralgia: a 36-month prospective longitudinal study.** *PLoS Negl Trop Dis.* 2013; **7**(3): e2137. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
26. Halstead SB: **Reappearance of Chikungunya, formerly called Dengue, in the Americas.** *Emerg Infect Dis.* 2015; **21**(1): 557–561. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
27. Huber JH, Childs ML, Caldwell JM, *et al.*: **Seasonal Temperature Variation Influences Climate Suitability for Dengue, Chikungunya, and Zika Transmission.** *PLoS Neglected Tropical Diseases.* 2018; **12**(5): e0006451. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
28. Mordecai EA, Cohen JM, Evans MV, *et al.*: **Detecting the Impact of Temperature on Transmission of Zika, Dengue, and Chikungunya Using Mechanistic Models.** *PLoS Negl Trop Dis (United States).* 2017; **11** (4): e0005568. [Publisher Full Text](#)
29. Hales S, de Wet N, Maindonald J, *et al.*: **Potential Effect of Population and Climate Changes on Global Distribution of Dengue Fever: An Empirical Model.** *Lancet (England).* 2002; **360**(9336): 830–834. [Publisher Full Text](#)
30. Campbell LP, Luther C, Moo-Llanes D, *et al.*: **Climate Change Influences on Global 46 Distributions of Dengue and Chikungunya Virus Vectors.** *Philos Trans R Soc Lond B Biol Sci (England).* 2015; **370** (1665). [Publisher Full Text](#)
31. Messina JP, Brady OJ, Golding N, *et al.*: **The Current and Future Global Distribution and Population at Risk of Dengue.** *Nature Microbiology.* 2019; **4**(9): 1508–1515. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
32. Hadfield J, Megill C, Bell SM, *et al.*: **Nextstrain: Real-Time Tracking of Pathogen Evolution.** *Bioinformatics.* 2018; **34**(23): 4121–4123. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
33. Thawillarp S: **Comparison of Data and Performance Indicators: Before and After the Transition of Thailand's National Disease Surveillance System, 2023–2024.** *Outbreak, Surveillance, Investigation & Response (OSIR) Journal.* 2025; **18**(2): 70–77. [Publisher Full Text](#)
34. Podschun R, Ullmann U: **Klebsiella spp. As nosocomial pathogens: epidemiology, taxonomy, typing methods, and pathogenicity factors.** *Clin Microbiol Rev.* 1998; **11**(4): 589–603. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
35. Pendleton JN, Gorman SP, Gilmore BF: **Clinical relevance of the ESKAPE pathogens.** *Expert Rev Anti Infect Ther.* 2013; **11**(3): 297–308. [PubMed Abstract](#) | [Publisher Full Text](#)
36. Antimicrobial Resistance Collaborators: **Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis.** *Lancet.* 2022; **399**(10325): 629–655. [Publisher Full Text](#) | [Free Full Text](#)
37. Wyres KL, Holt KE: **Klebsiella pneumoniae as a key trafficker of drug resistance genes from environmental to clinically important bacteria.** *Curr Opin Microbiol.* 2018; **45**: 131–139. [Publisher Full Text](#)
38. WHO: **Global tuberculosis report 2023.** 2023; Accessed May 15, 2025. [Reference Source](#)
39. WHO: **Rapid communication: key changes to the treatment of drug-resistant tuberculosis.** 2022; Accessed May 15, 2025. [Reference Source](#)
40. Conradie F, Bagdasaryan TR, Borisov S, *et al.*: **Bedaquiline–pretomanid–linezolid regimens for drug-resistant tuberculosis.** *N Engl J Med.* 2022; **387**(9): 810–823. [Publisher Full Text](#) | [Free Full Text](#)
41. WHO: **Use of targeted next-generation sequencing to detect drug-resistant tuberculosis.** 2023; Accessed May 15, 2025. [Reference Source](#)
42. The CRYPTIC Consortium: **A Data Compendium Associating the Genomes of 12,289 Mycobacterium Tuberculosis Isolates with Quantitative Resistance Phenotypes to 13 Antibiotics.** *PLoS Biology.* 2022; **20**(8): e3001721. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
43. Laamarti M, El Fathi Lalaoui Y, Elfermi R, *et al.*: **Afro-TB Dataset as a Large Scale Genomic Data of Mycobacterium Tuberculosis in Africa.** *Scientific Data.* 2023; **10**(1): 212. [Publisher Full Text](#)
44. Iragena J d D, Katamba A, Affolabi D, *et al.*: **Tuberculosis Laboratory Capacity Building in the WHO African Region: The Past, the Present and the Future: A Viewpoint.** *PLoS Glob Public Health.* 2025; **5**(11): e0004979. [Publisher Full Text](#)
45. Kohli M, Schiller I, Dendukuri N, *et al.*: **Xpert MTB/RIF Ultra and Xpert MTB/RIF Assays for Extrapulmonary Tuberculosis and Rifampicin Resistance in Adults.** *Cochrane Database Syst Rev.* 2021; **1**(1): CD012768. [Publisher Full Text](#)
46. Goscé L, Pescarini JM, Houben RMGJ, *et al.*: **Tuberculosis and the Climate Crisis in Latin America: A Predicament of Poverty, Migration and Displacement.** *BMJ Global Health.* 2025; **10**(4): e018674. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
47. Saunders MJ, Boccia D, Khan PY, *et al.*: **Climate Change and Tuberculosis: An Analytical Framework.** *The Lancet Respiratory Medicine.* 2026; **14**(3): 267–280. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
48. Shadi Y, Morasae EK, Khazaei S, *et al.*: **Understanding the Mechanisms of Climate Change Impact on Tuberculosis: A Complex Systems Approach.** *BMC Public Health.* 2025; **25**(1): 3382. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
49. Khan K, Karim F, Ganga Y, *et al.*: **Omicron BA.4/BA.5 escape neutralizing immunity elicited by BA.1 infection.** *Nat Commun.* 2022; **13**: 4686. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
50. Khan K, Lustig G, Römer C, *et al.*: **Evolution and neutralization escape of the SARS-CoV-2 BA.2.86 subvariant.** *Nat Commun.* 2023; **14**: 8078. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
51. Lustig G, Ganga Y, Rodel HE, *et al.*: **SARS-CoV-2 infection in immunosuppression evolves sub-lineages which independently accumulate neutralization escape mutations.** *Virus Evol.* 2023; **10**(1): vead075. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

52. Smith DJ, Lapedes AS, de Jong JC, *et al.*: **Mapping the antigenic and genetic evolution of influenza virus.** *Science*. 2004; **305**(5682): 371–376.
[PubMed Abstract](#) | [Publisher Full Text](#)
53. Mo Y, Ding Y, Cao Y, *et al.*: **AACORN (A Clinically-Oriented Antimicrobial Resistance Surveillance Network) II: protocol for case based antimicrobial resistance surveillance [version 2; peer review: 2 approved].** *Wellcome Open Res*. 2023; **8**: 179.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
54. Lam MMC, Wick RR, Watts SC, *et al.*: **A genomic surveillance framework and genotyping tool for *Klebsiella pneumoniae* and its related species complex.** *Nat Commun*. 2021; **12**(1): 4188.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
55. Wick RR, Heinz E, Holt KE, *et al.*: **Kaptive web: user-friendly capsule and lipopolysaccharide serotype prediction for *Klebsiella* genomes.** *J Clin Microbiol*. 2018; **56**(6): e00197–e00118.
[Publisher Full Text](#) | [Free Full Text](#)
56. Inouye M, Dashnow H, Raven LA, *et al.*: **SRST2: rapid genomic surveillance for public health and hospital microbiology labs.** *Genome Med*. 2014; **6**(11): 90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
57. Didelot X, Croucher NJ, Bentley SD, *et al.*: **Bayesian Inference of Ancestral Dates on Bacterial Phylogenetic Trees.** *Nucleic Acids Research*. 2018; **46**(22): e134.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
58. WHO: Catalogue of mutations in Mycobacterium tuberculosis complex and their association with drug resistance, 2nd ed. 2023; Accessed May 15, 2025.
[Reference Source](#)
59. Vorisek CN, Lehne M, Klopfenstein SAI, *et al.*: **Fast Healthcare Interoperability Resources (FHIR) for interoperability in health research: systematic review.** *JMIR Med Inform*. 2022; **10**(7): e35724.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

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Gerald Mboowa 

Makerere University, Kampala, Uganda

I have reviewed the revised version of this Open Letter. The authors have addressed the major concerns raised in the previous review and have substantially improved the clarity, rationale and structure of the current manuscript.

The revised manuscript now provides a clearer justification for the CAGED consortium, including the public health importance of the selected pathogens, the need for multi-pathogen genomic surveillance across Africa and Southeast Asia, and the importance of strengthening local sequencing and bioinformatics capacity. The added information on current genomic data availability, existing surveillance platforms, surveillance gaps, and country-level differences strengthens the rationale for the work.

The work packages are now described more clearly, including project governance, CHIKV/DENV genomic surveillance, MDR *Klebsiella pneumoniae* surveillance, drug-resistant *Mycobacterium tuberculosis* surveillance, and data management. The methodological approaches, expected outcomes, capacity-building plans, data-sharing intentions and policy-engagement activities are sufficiently explained for an Open Letter.

Overall, the article is scientifically sound, accessible, adequately referenced, and suitable for indexing.

Is the rationale for the Open Letter provided in sufficient detail?

Yes

Does the article adequately reference differing views and opinions?

Yes

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Yes

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Yes

Competing Interests: No competing interests were disclosed.**Reviewer Expertise:** Pathogen genomics**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Version 1

Reviewer Report 28 February 2026

<https://doi.org/10.21956/wellcomeopenres.28217.r146799>

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**Marina Igorova Reyne**

Queen's University Belfast, Belfast, UK

Summary: The open letter describes the formation of a new consortium involving several organizations across Africa and Asia, aimed at strengthening genomic surveillance for four high-burden pathogens. Its goal is to enhance knowledge and monitoring of disease outbreaks and to integrate genomic data into management practices and policy development, enabling more informed and effective decision-making.

The manuscript would benefit from improvements to its structure to make it easier to follow. There is also considerable repetition throughout the manuscript, and it would benefit from being more concise. Clearer subheadings are needed, beginning with an Introduction that explains why the consortium is needed, defines the problem, and outlines the overall goals. This should be followed by distinct sections describing each work package with more details. In its current form, the manuscript feels somewhat limited in its discussion of capacity building and the anticipated impact on policy decisions. The section stating that the consortium will "engage regularly with national and subnational policymakers, fostering stronger collaboration and sharing project outcomes" would benefit from elaboration and could be expanded into a standalone section.

Abstract: The pathogens discussed in the manuscript are chikungunya virus and dengue virus, which cause the diseases chikungunya and dengue, respectively. These names should be corrected and used consistently throughout the manuscript.

Introduction: The abstract indicates that one focus of the study is on pathogens influenced by

climate change, but this is not clearly reflected in the Introduction. Additional detail is needed on how climate change affects these pathogens, for example through expansion of mosquito vector distributions and increasing environmental suitability for flavivirus transmission. This context would strengthen the link between climate drivers and pathogen dynamics. When presenting each pathogen, the authors should provide a brief description of the disease it causes and separate the discussion into individual paragraphs for clarity. Information on the current availability of genomic data, as well as existing surveillance practices and policies relevant to each pathogen, should also be included. In addition, *Klebsiella* and tuberculosis should be separated into distinct paragraphs, as they represent different pathogen groups and public health challenges. The manuscript should maintain consistency in the use of terminology, choosing either abbreviations or full pathogen names and applying them uniformly throughout.

Methodology: The section requires clearer organization to improve readability. It would benefit from being divided into work packages, with each one outlining the overall goal, methodological approach, and expected outcomes. For each pathogen, the manuscript should specify the sample types to be collected, how they will be processed in the laboratory, the sequencing methods to be used, the bioinformatics pipeline, and the planned downstream analyses. Tables should be numbered based on the order they are cited in the text. Expected outcomes should be presented in subsections dedicated to each pathogen. The manuscript currently refers to “Real-Time (RT)-quantitative PC,” but in this context RT should stand for Reverse Transcription. The approach for viral sequencing also needs clarification. Viral whole-genome sequencing can be challenging, so the authors should specify which enrichment protocol or strategy will be used. For *Klebsiella*, it is unclear how whole-genome sequences will be obtained, whether pure culture followed by shotgun sequencing will be used, and whether both short-read and long-read technologies will be combined for assembly. For the bacterial pathogens in general, the manuscript should clarify whether they will be cultured, tested for resistance, and then sequenced from pure isolates. The section on building sustainable local sequencing capacity should also be expanded to provide more detail.

In Figure 1, WP1 appears to be missing, and captions for all figures require additional information.

Is the rationale for the Open Letter provided in sufficient detail?

Partly

Does the article adequately reference differing views and opinions?

Yes

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Yes

Is the Open Letter written in accessible language?

Partly

Where applicable, are recommendations and next steps explained clearly for others to follow?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: pathogen genomics, molecular biology, epidemiological modelling, disease ecology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 11 May 2026

Patience Kiyuka

We thank the reviewer for the insightful comments, below is our response to the issues raised;

The manuscript would benefit from improvements to its structure to make it easier to follow. There is also considerable repetition throughout the manuscript, and it would benefit from being more concise. Clearer subheadings are needed, beginning with an Introduction that explains why the consortium is needed, defines the problem, and outlines the overall goals. This should be followed by distinct sections describing each work package with more details.

We have reorganized the manuscript into distinct sections with clear subheadings. In the revised version of the manuscript there is the introduction, methodology which has all the work packages described followed by the opportunities, challenges and future directions and communication/engagement and dissemination plans.

In its current form, the manuscript feels somewhat limited in its discussion of capacity building and the anticipated impact on policy decisions. The section stating that the consortium will “engage regularly with national and subnational policymakers, fostering stronger collaboration and sharing project outcomes” would benefit from elaboration and could be expanded into a standalone section.

We have added the following text under communication/engagement and dissemination plans; The overall aim is to strengthen national public health institutions by providing enhanced genomic surveillance data on priority pathogens and improving outbreak response mechanisms. To achieve this, we will engage regularly with national and subnational policymakers to foster stronger collaboration. At project initiation we will hold engagement meetings with subnational and national level policy makers to introduce the project objectives, planned activities, expected outputs and potential policy implications. These initial project engagement meetings will also serve to establish communication channels between the researchers and the policy makers.

Throughout the project, we will regularly share the data and results obtained. Through WP 5, we will develop data dashboards based on the genomic surveillance and epidemiological data generated across the AAPs/ CIDRI-A. The dashboard will be made freely available to

policy makers and the NPHL to support outbreak preparedness and response planning in addition to evidence-based decision making. The dashboard and the associated data tools will be handed over to the NPHL for project sustainability. Final project results generated from the consortium will also be translated into policy brief tailored to national and sub-national decision-makers. The policy briefs will be disseminated through structured policy engagement meetings, stakeholder workshops and to the relevant MoHs relevant technical working groups (TWGs). These engagements will provide a forum to discuss policy implications, foreseeable implementation challenges and recommendations for strengthening the regions outbreak response strategies.

Abstract: *The pathogens discussed in the manuscript are chikungunya virus and dengue virus, which cause the diseases chikungunya and dengue, respectively. These names should be corrected and used consistently throughout the manuscript.*

We have made this correction.

Introduction: *The abstract indicates that one focus of the study is on pathogens influenced by climate change, but this is not clearly reflected in the Introduction. Additional detail is needed on how climate change affects these pathogens, for example through expansion of mosquito vector distributions and increasing environmental suitability for flavivirus transmission. This context would strengthen the link between climate drivers and pathogen dynamics.*

We thank the reviewer for this comment. We have added the following statements to the relevant sections; Arbovirus distribution is predicted to be strongly affected by climate change. The distribution of the *Aedes* mosquito vectors responsible for transmission of dengue and chikungunya viruses have been extensively studied, investigating the effects of temperature (Mordecai et al. 2017; Huber et al. 2018) and humidity (Hales et al. 2002) on habitat suitability and suggesting a climate-driven expansion into new ranges (Campbell et al. 2015), and a corresponding increased population at risk from mosquito-borne disease (Messina et al. 2019). We will aim to integrate with existing studies looking at the impact of climate change on our chosen pathogens. For dengue, the existing Dengue Advanced Readiness Tools consortium (DART) <https://www.dartdengue.org>, a separately funded project which is also lead by OUCRU-Vietnam, are integrating climatic factors into dengue outbreak forecasting, and we will work with them to expand their tools to sites in this consortium and to integrate genetic factors into their model. For TB, climate change acts primarily through indirect pathways. It has been shown that climate change has potential to worsen the TB epidemic by among others contributing to population displacement which often leads to overcrowding living conditions that accelerates TB transmission (Goscé et al. 2025). Healthcare disruption can cause TB treatment interruption, leading to longer infectious period and ultimately increased risk of development of drug resistance (Saunders et al. 2026). Moreover climate-related and socioeconomic disruptions contribute to food insecurity and malnutrition, which weakens the immune system and increasing the risk of TB infection and transmission (Shadi et al. 2025).

When presenting each pathogen, the authors should provide a brief description of the disease it causes and separate the discussion into individual paragraphs for clarity.

Information on the current availability of genomic data, as well as existing surveillance practices and policies relevant to each pathogen, should also be included.

We have added the following to capture current availability of genomic data, as well as existing surveillance practices and policies relevant to each pathogen. Genomic data from dengue is available for many of the countries in the CAGED consortium, however this is not evenly distributed by country. We assessed the data used by the Nextstrain real-time tracking of viral evolution (Hadfield et al. 2018) to determine the availability of public sequence data for dengue and Chikungunya. While Thailand and Vietnam have over 2000 available dengue genomes deposited in public databases, the majority were sampled before 2020. For Laos, Nepal, and Kenya, there are fewer than 150 genomes per country, and for Indonesia there are 555 genomes. For Chikungunya, there are over 150 complete genomes for Thailand, but fewer than 50 for all other countries in this consortium, and no genomes for Vietnam or Nepal. Although some countries have existing surveillance policies for the pathogens in this consortium, others don't. Thailand has a national disease surveillance program which includes case reporting for Chikungunya and dengue (Thawillarp 2025) viruses and XDR TB. Laos has a national surveillance program for dengue which only includes clinical case reporting. Existing global surveillance platform for *Klebsiella pneumoniae* (KlebNET-GSP) was established in 2018, currently hosting 110,891 Kpn genomes with associated metadata (<https://next.pathogen.watch/genomes/573-klebsiella-pneumoniae>, assessed on 16th March 2026). This global platform also incorporates a set of standardized bioinformatic pipelines and genomic reporting frameworks, which greatly facilitate data harmonization and the interpretation of AMR genotypes. It further supports global efforts to develop a genomic risk framework, assess K and O antigen distributions and track the transmission of high-risk lineages associated with neonatal sepsis. However, national policies on Kpn genomic surveillance remain largely lacking across countries within the AAPs. For TB, large WGS datasets are now widely available, though no single platform tracks global totals. Key collections include the CRyPTIC dataset of 12,289 sequenced isolates (The CRyPTIC Consortium 2022), the Afro-TB dataset with 17,641 strains (13,753 curated) from 26 African countries (Laamarti et al. 2023), and the NIAID TB Portals resource housing genomic-linked data from over 28,000 TB cases <https://www.niaid.nih.gov/research/tb-portals>. Additional raw reads are deposited across the NCBI SRA <https://sra-explorer.info> and ENA <https://www.ebi.ac.uk/ena/browser/home>, the primary global repositories, although neither provides organism-specific counts. Tools like Pathogenwatch <https://next.pathogen.watch/en>, CRyPTIC, and the TB-Resources index <https://github.com/a-r-j/TB-Resources> help researchers identify and navigate these distributed. Despite the large volume of data, global coverage is uneven: most publicly available genomes derive from high-income settings and dominant Eurasian lineages, while many regions - including much of Africa and parts of Asia and the Pacific - remain under sampled. All countries hosting AAP-affiliated sites maintain National TB Programmes, but surveillance systems differ substantially in diagnostic reach and laboratory capacity. WHO regional analyses highlight persistent gaps in case detection and incomplete linkage of diagnostic data to national reporting systems in several high-burden settings <https://www.who.int/publications/i/item/9789240116924>. Laboratory assessments similarly report limited access to culture, Drug-Susceptibility Testing (DST), and advanced molecular

diagnostics across many countries (Iragena et al. 2025), despite wide uptake of Xpert MTB/RIF as the primary test for rifampicin resistance (Kohli et al. 2021). As a result, surveillance in many AAP-region settings remains heavily Xpert-based, providing drug-resistance screening but lacking the resolution required for genomic epidemiology or monitoring emerging resistance.

The manuscript should maintain consistency in the use of terminology, choosing either abbreviations or full pathogen names and applying them uniformly throughout.

Thank you for this comment. We have revised to ensure consistency.

Methodology The section requires clearer organization to improve readability. It would benefit from being divided into work packages, with each one outlining the overall goal, methodological approach, and expected outcomes.

Thank you for this comment. We have restructured all pathogen work packages to include three sections: overall goal, methodological approach, and expected outcome. For the project management work package, we renamed "methodological approach" to "management and governance of the consortium." This wording reflects the content more accurately and makes the section easier for readers to navigate, as a methodological approach is more appropriate for the pathogen-specific work packages.

For each pathogen, the manuscript should specify the sample types to be collected, how they will be processed in the laboratory, the sequencing methods to be used, the bioinformatics pipeline, and the planned downstream analyses.

We have added the following text to provide clarity on the laboratory processing, sequencing and the bioinformatics pipeline that will be used. *CHIK and DENV work package* We will utilize retrospective and prospective confirmed (by Reverse Transcription (RT)-quantitative PCR CHIKV blood samples. Additional febrile surveillance retrospective and prospective samples, serum or plasma, will be screened by RT-qPCR for CHIKV and DENV. Sequencing and bioinformatics pipeline methodologies will be standardized across the sites. WGS of CHIKV and DENV will be done using amplicon-based approach using the Illumina or ONT platforms, according to the technique available on each site. Whole genomes will be first amplified by overlapping RT-PCR amplifying 4 to 8 long fragments in separated RT-PCRs, or small fragments in two pools of RT-PCRs, according to the procedures in place on each site. The RT-PCR products will then be pooled and cleaned, and the library will be built using either Rapid Barcoding or Native Barcoding ONT kits, or Illumina library preparation kits according to the technique available at each site. The read analysis will be performed using established pipelines such as the artic network amplicon pipeline <https://artic.network/resources/amplicon-nf> which processes both Illumina and ONT data. While sites will not harmonise sequencing protocols, owing to different platform availability, we will standardize the data QC and metrics to ensure we use high quality sequences for the downstream analysis, and an internal EQA process will allow comparison of sequences between sites. *Kpn work package* We will use a single whole genome sequencing (WGS) standard operating procedure (SOP) and bioinformatics pipeline. All Kpn

isolates identified from blood and CSF cultures will undergo routine antimicrobial susceptibility testing to support clinical care, and will subsequently be cultured for DNA extraction, using either the Wizard® Genomic DNA Purification Kit (Promega, USA) or the DNeasy Blood & Tissue Kit (Qiagen, Germany), depending on local availability. DNA libraries will be prepared using the Nextera XT DNA Library Preparation Kit or the NEBNext Ultra II FS DNA Library Prep Kit for Illumina. WGS will be done on a locally established Illumina platform (Miseq, Hiseq or Novaseq), with the OTN platform used for selected samples. We will infer transmission of high-risk lineages using phylodynamic modelling and SNP analyses. SNP calling will be performed using the Snippy pipeline (<https://github.com/tseemann/snippy>). Maximum likelihood phylogenies will be inferred from the core SNP alignment, using IQ-TREE v2.2.0.3 with best-fit substitution models and 1,000 ultrafast bootstraps and these phylogenetic trees will serve as the basis for time-scaled phylodynamic analysis using BEAST X (Didelot et al. 2018). *Mtb work package* Sputum will be collected from patients with RR-TB confirmed by Xpert MTB/RIF. Isolates will be cultured to purity in category 3 facilities and DNA extracted from pure isolates prior to Illumina/ONT sequencing. Consensus genomes and variant calling will use MTBseq (Kohl et al. 2018) or GPAS. Resistance mutations relevant to fluoroquinolones, bedaquiline, pretomanid, and linezolid will be identified using the WHO mutation catalogue, with phenotypic DST performed on isolates with mutations of uncertain significance.

Tables should be numbered based on the order they are cited in the text.

We have made this correction to the revised version of the manuscript.

Expected outcomes should be presented in subsections dedicated to each pathogen.

We have aligned expected outcomes to each pathogen work package in the revised manuscript.

The manuscript currently refers to “Real-Time (RT)-quantitative PC,” but in this context RT should stand for Reverse Transcription.

We have made this correction to the revised version of the manuscript to read as reverse transcription.

The approach for viral sequencing also needs clarification. Viral whole-genome sequencing can be challenging, so the authors should specify which enrichment protocol or strategy will be used.

We have made clarifications that WGS of CHIKV and DENV will be done using amplicon-based approach using the Illumina or ONT platforms according to the technique available on each site. Whole genomes will be first amplified by overlapping RT-PCR amplifying 4 to 8 long fragments in separated RT-PCRs, or small fragments in two pools of RT-PCRs, according to the procedures in place on each site. The RT-PCR products will then be pooled and cleaned, and the library will be built using either Rapid Barcoding or Native Barcoding ONT kits, or Illumina library preparation kits according to the technique available at each

site. The read analysis will be performed using established pipelines such as the artic network amplicon pipeline <https://artic.network/resources/amplicon-nf>, which processes both Illumina and ONT data. While sites will not harmonise sequencing protocols, owing to different platform availability, we will standardize the data QC and metrics to ensure we use high quality sequences for the downstream analysis, and an internal EQA process will allow comparison of sequences between sites.

For Klebsiella, it is unclear how whole-genome sequences will be obtained, whether pure culture followed by shotgun sequencing will be used, and whether both short-read and long-read technologies will be combined for assembly.

We have clarified in the text that we will use whole genome sequencing and that Kpn isolated obtained from blood or CSF will undergo culture before sequencing. We will not use shot-gun sequencing rather it will be whole genome sequencing from pure cultures. Except for South Africa, most sites have capacity for shot-read Illumina sequencing

For the bacterial pathogens in general, the manuscript should clarify whether they will be cultured, tested for resistance, and then sequenced from pure isolates.

We have clarified that sputum will be collected from patients with RR-TB confirmed by Xpert MTB/RIF. Isolates will be cultured to purity in category 3 laboratory facilities and DNA extracted from pure isolates prior to Illumina/ONT sequencing. *Kpn* isolates identification from blood and CSF cultures will undergo the routine antimicrobial susceptibility testing to support clinical care and will subsequently be cultured for DNA extraction then sequencing performed.

The section on building sustainable local sequencing capacity should also be expanded to provide more detail.

We thank the reviewer for this comment. We have added the following information to provide more clarity on how we will build sustainable local sequencing capacity under the section on opportunities, challenges and future direction. For the *Kpn*, we will leverage this cross-AAP platform to support national AMR reference laboratories in tracking the spread of carbapenem-resistant *Kpn* lineages across hospital surveillance systems (e.g in Vietnam) or to assist collaborative hospitals in confirming and responding to nosocomial *Kpn* outbreaks (e.g in Kenya). To build sustainable local sequencing capacity, for Mtb, CIDRI-A and OUCRU will transfer standardized protocols and provide hands-on training to AAPs that do not currently conduct these assays, including MLW and KWTRP, with SOPs shared across all sites. MORU and OUCRU (DENV) and KWTRP (CHIKV), based in their existing expertise, will lead the standardization of sequencing and bioinformatic pipeline methodologies across AAPs. SOPs will be shared and training provided, where needed, to support the deployment of the tools in each AAP.

In Figure 1, WP1 appears to be missing, and captions for all figures require additional information. We have included WP 1 in figure 1 and improved the captions across all the figures

- References** Campbell, Lindsay P., Caylor Luther, David Moo-Llanes, Janine M. Ramsey, Rogelio Danis-Lozano, and A. Townsend Peterson. 2015. "Climate Change Influences on Global Distributions of Dengue and Chikungunya Virus Vectors." *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* (England) 370 (1665). <https://doi.org/10.1098/rstb.2014.0135>.
- Didelot, Xavier, Nicholas J. Croucher, Stephen D. Bentley, Simon R. Harris, and Daniel J. Wilson. 2018. "Bayesian Inference of Ancestral Dates on Bacterial Phylogenetic Trees." *Nucleic Acids Research* 46 (22): e134. <https://doi.org/10.1093/nar/gky783>.
- Goscé, Lara, Julia M. Pescarini, Rein M. G. J. Houben, and Christopher Finn McQuaid. 2025. "Tuberculosis and the Climate Crisis in Latin America: A Predicament of Poverty, Migration and Displacement." *BMJ Global Health* 10 (4): e018674. <https://doi.org/10.1136/bmjgh-2024-018674>.
- Hadfield, James, Colin Megill, Sidney M. Bell, et al. 2018. "Nextstrain: Real-Time Tracking of Pathogen Evolution." *Bioinformatics* 34 (23): 4121–23. <https://doi.org/10.1093/bioinformatics/bty407>.
- Hales, Simon, Neil de Wet, John Maindonald, and Alistair Woodward. 2002. "Potential Effect of Population and Climate Changes on Global Distribution of Dengue Fever: An Empirical Model." *Lancet (London, England)* (England) 360 (9336): 830–34. [https://doi.org/10.1016/S0140-6736\(02\)09964-6](https://doi.org/10.1016/S0140-6736(02)09964-6).
- Huber, John H., Marissa L. Childs, Jamie M. Caldwell, and Erin A. Mordecai. 2018. "Seasonal Temperature Variation Influences Climate Suitability for Dengue, Chikungunya, and Zika Transmission." *PLoS Neglected Tropical Diseases* 12 (5): e0006451. <https://doi.org/10.1371/journal.pntd.0006451>.
- Iragena, Jean de Dieu, Achilles Katamba, Dissou Affolabi, Moses Joloba, and Willy Ssengooba. 2025. "Tuberculosis Laboratory Capacity Building in the WHO African Region: The Past, the Present and the Future: A Viewpoint." *PLOS Global Public Health* 5 (11): e0004979. <https://doi.org/10.1371/journal.pgph.0004979>.
- Kohl, Thomas Andreas, Christian Utpatel, Viola Schleusener, et al. 2018. "MTBseq: A Comprehensive Pipeline for Whole Genome Sequence Analysis of Mycobacterium Tuberculosis Complex Isolates." *PeerJ* 6: e5895. <https://doi.org/10.7717/peerj.5895>.
- Kohli, Mikashmi, Ian Schiller, Nandini Dendukuri, et al. 2021. "Xpert MTB/RIF Ultra and Xpert MTB/RIF Assays for Extrapulmonary Tuberculosis and Rifampicin Resistance in Adults." *The Cochrane Database of Systematic Reviews* 1 (1): CD012768. <https://doi.org/10.1002/14651858.CD012768.pub3>.
- Laamarti, Meriem, Yasmine El Fathi Lalaoui, Rachid Elfermi, Rachid Daoud, and Achraf El Allali. 2023. "Afro-TB Dataset as a Large Scale Genomic Data of Mycobacterium Tuberculosis in Africa." *Scientific Data* 10 (1): 212. <https://doi.org/10.1038/s41597-023-02112-3>.
- Messina, Jane P., Oliver J. Brady, Nick Golding, et al. 2019. "The Current and Future Global Distribution and Population at Risk of Dengue." *Nature Microbiology* 4 (9): 1508–15. <https://doi.org/10.1038/s41564-019-0476-8>.
- Mordecai, Erin A., Jeremy M. Cohen, Michelle V. Evans, et al. 2017. "Detecting the Impact of Temperature on Transmission of Zika, Dengue, and Chikungunya Using Mechanistic Models." *PLoS Neglected Tropical Diseases* (United States) 11 (4): e0005568. <https://doi.org/10.1371/journal.pntd.0005568>.
- Saunders, Matthew J., Delia Boccia, Palwasha Y. Khan, et al. 2026. "Climate Change and Tuberculosis: An Analytical Framework." *The Lancet Respiratory Medicine* 14 (3): 267–80. [https://doi.org/10.1016/S2213-2600\(25\)00329-7](https://doi.org/10.1016/S2213-2600(25)00329-7).
- Shadi, Yahya, Esmaeil Khedmati Morasae, Salman Khazaei, et al. 2025. "Understanding the Mechanisms of Climate Change Impact on Tuberculosis: A Complex Systems Approach." *BMC Public Health* 25 (1): 3382. <https://doi.org/10.1186/s12889-025-24709-6>.
- Thawillarp, Supharerk. 2025. "Comparison of Data and Performance Indicators: Before and After the Transition of Thailand's National Disease Surveillance System, 2023–2024." *Outbreak*,

Surveillance, Investigation & Response (OSIR) Journal 18 (2): 70–77.

<https://doi.org/10.59096/osir.v18i2.272949>. The CRyPTIC Consortium. 2022. "A Data Compendium Associating the Genomes of 12,289 Mycobacterium Tuberculosis Isolates with Quantitative Resistance Phenotypes to 13 Antibiotics." *PLoS Biology* 20 (8): e3001721. <https://doi.org/10.1371/journal.pbio.3001721>.

Competing Interests: No competing interests were disclosed.

Author Response 14 May 2026

Patience Kiyuka

The manuscript would benefit from improvements to its structure to make it easier to follow. There is also considerable repetition throughout the manuscript, and it would benefit from being more concise. Clearer subheadings are needed, beginning with an Introduction that explains why the consortium is needed, defines the problem, and outlines the overall goals. This should be followed by distinct sections describing each work package with more details.

We have reorganized the manuscript into distinct sections with clear subheadings. In the revised version of the manuscript there is the introduction, methodology which has all the work packages described followed by the opportunities, challenges and future directions and communication/engagement and dissemination plans.

In its current form, the manuscript feels somewhat limited in its discussion of capacity building and the anticipated impact on policy decisions. The section stating that the consortium will "engage regularly with national and subnational policymakers, fostering stronger collaboration and sharing project outcomes" would benefit from elaboration and could be expanded into a standalone section.

We have added the following text under communication/engagement and dissemination plans; The overall aim is to strengthen national public health institutions by providing enhanced genomic surveillance data on priority pathogens and improving outbreak response mechanisms. To achieve this, we will engage regularly with national and subnational policymakers to foster stronger collaboration. At project initiation we will hold engagement meetings with subnational and national level policy makers to introduce the project objectives, planned activities, expected outputs and potential policy implications. These initial project engagement meetings will also serve to establish communication channels between the researchers and the policy makers. Throughout the project, we will regularly share the data and results obtained. Through WP 5, we will develop data dashboards based on the genomic surveillance and epidemiological data generated across the AAPs/ CIDRI-A. The dashboard will be made freely available to policy makers and the NPHL to support outbreak preparedness and response planning in addition to evidence-based decision making. The dashboard and the associated data tools will be handed over to the NPHL for project sustainability. Final project results generated from the consortium will also be translated into policy brief tailored to national and sub-national decision-makers. The policy briefs will be disseminated through structured policy engagement meetings, stakeholder workshops and to the relevant MoHs relevant technical working groups (TWGs). These engagements will provide a forum to discuss policy implications, foreseeable

implementation challenges and recommendations for strengthening the regions outbreak response strategies.

Abstract: The pathogens discussed in the manuscript are chikungunya virus and dengue virus, which cause the diseases chikungunya and dengue, respectively. These names should be corrected and used consistently throughout the manuscript.

We have made this correction. **Introduction: The abstract indicates that one focus of the study is on pathogens influenced by climate change, but this is not clearly reflected in the Introduction. Additional detail is needed on how climate change affects these pathogens, for example through expansion of mosquito vector distributions and increasing environmental suitability for flavivirus transmission. This context would strengthen the link between climate drivers and pathogen dynamics.**

We thank the reviewer for this comment. We have added the following statements to the relevant sections; Arbovirus distribution is predicted to be strongly affected by climate change. The distribution of the *Aedes* mosquito vectors responsible for transmission of dengue and chikungunya viruses have been extensively studied, investigating the effects of temperature (Mordecai et al. 2017; Huber et al. 2018) and humidity (Hales et al. 2002) on habitat suitability and suggesting a climate-driven expansion into new ranges (Campbell et al. 2015), and a corresponding increased population at risk from mosquito-borne disease (Messina et al. 2019). We will aim to integrate with existing studies looking at the impact of climate change on our chosen pathogens. For dengue, the existing Dengue Advanced Readiness Tools consortium (DART) <https://www.dartdengue.org>, a separately funded project which is also lead by OUCRU-Vietnam, are integrating climatic factors into dengue outbreak forecasting, and we will work with them to expand their tools to sites in this consortium and to integrate genetic factors into their model. For TB, climate change acts primarily through indirect pathways. It has been shown that climate change has potential to worsen the TB epidemic by among others contributing to population displacement which often leads to overcrowding living conditions that accelerates TB transmission (Goscé et al. 2025). Healthcare disruption can cause TB treatment interruption, leading to longer infectious period and ultimately increased risk of development of drug resistance (Saunders et al. 2026). Moreover climate-related and socioeconomic disruptions contribute to food insecurity and malnutrition, which weakens the immune system and increasing the risk of TB infection and transmission (Shadi et al. 2025).

When presenting each pathogen, the authors should provide a brief description of the disease it causes and separate the discussion into individual paragraphs for clarity.

Information on the current availability of genomic data, as well as existing surveillance practices and policies relevant to each pathogen, should also be included.

We have added the following to capture current availability of genomic data, as well as existing surveillance practices and policies relevant to each pathogen. Genomic data from dengue is available for many of the countries in the CAGED consortium, however this is not evenly distributed by country. We assessed the data used by the Nextstrain real-time tracking of viral evolution (Hadfield et al. 2018) to determine the availability of public sequence data for dengue and Chikungunya. While Thailand and Vietnam have over 2000 available dengue genomes deposited in public databases, the majority were sampled before 2020. For Laos, Nepal, and Kenya, there are fewer than 150 genomes per country, and for Indonesia there are 555 genomes. For Chikungunya, there are over 150 complete

genomes for Thailand, but fewer than 50 for all other countries in this consortium, and no genomes for Vietnam or Nepal. Although some countries have existing surveillance policies for the pathogens in this consortium, others don't. Thailand has a national disease surveillance program which includes case reporting for Chikungunya and dengue (Thawillarp 2025) viruses and XDR TB. Laos has a national surveillance program for dengue which only includes clinical case reporting. Existing global surveillance platform for *Klebsiella pneumoniae* (KlebNET-GSP) was established in 2018, currently hosting 110,891 Kpn genomes with associated metadata (<https://next.pathogen.watch/genomes/573-klebsiella-pneumoniae>, assessed on 16th March 2026). This global platform also incorporates a set of standardized bioinformatic pipelines and genomic reporting frameworks, which greatly facilitate data harmonization and the interpretation of AMR genotypes. It further supports global efforts to develop a genomic risk framework, assess K and O antigen distributions and track the transmission of high-risk lineages associated with neonatal sepsis. However, national policies on Kpn genomic surveillance remain largely lacking across countries within the AAPs. For TB, large WGS datasets are now widely available, though no single platform tracks global totals. Key collections include the CRYPTIC dataset of 12,289 sequenced isolates (The CRYPTIC Consortium 2022), the Afro-TB dataset with 17,641 strains (13,753 curated) from 26 African countries (Laamarti et al. 2023), and the NIAID TB Portals resource housing genomic-linked data from over 28,000 TB cases <https://www.niaid.nih.gov/research/tb-portals>. Additional raw reads are deposited across the NCBI SRA <https://sra-explorer.info> and ENA <https://www.ebi.ac.uk/ena/browser/home>, the primary global repositories, although neither provides organism-specific counts. Tools like Pathogenwatch <https://next.pathogen.watch/en>, CRYPTIC, and the TB-Resources index <https://github.com/a-r-j/TB-Resources> help researchers identify and navigate these distributed. Despite the large volume of data, global coverage is uneven: most publicly available genomes derive from high-income settings and dominant Eurasian lineages, while many regions - including much of Africa and parts of Asia and the Pacific - remain under sampled. All countries hosting AAP-affiliated sites maintain National TB Programmes, but surveillance systems differ substantially in diagnostic reach and laboratory capacity. WHO regional analyses highlight persistent gaps in case detection and incomplete linkage of diagnostic data to national reporting systems in several high-burden settings <https://www.who.int/publications/i/item/9789240116924>. Laboratory assessments similarly report limited access to culture, Drug-Susceptibility Testing (DST), and advanced molecular diagnostics across many countries (Iragena et al. 2025), despite wide uptake of Xpert MTB/RIF as the primary test for rifampicin resistance (Kohli et al. 2021). As a result, surveillance in many AAP-region settings remains heavily Xpert-based, providing drug-resistance screening but lacking the resolution required for genomic epidemiology or monitoring emerging resistance.

The manuscript should maintain consistency in the use of terminology, choosing either abbreviations or full pathogen names and applying them uniformly throughout.

Thank you for this comment. We have revised to ensure consistency.

Methodology The section requires clearer organization to improve readability. It would benefit from being divided into work packages, with each one outlining the overall goal, methodological approach, and expected outcomes.

Thank you for this comment. We have restructured all pathogen work packages to include three sections: overall goal, methodological approach, and expected outcome. For the project management work package, we renamed "methodological approach" to "management and governance of the consortium." This wording reflects the content more accurately and makes the section easier for readers to navigate, as a methodological approach is more appropriate for the pathogen-specific work packages.

For each pathogen, the manuscript should specify the sample types to be collected, how they will be processed in the laboratory, the sequencing methods to be used, the bioinformatics pipeline, and the planned downstream analyses. We have added the following text to provide clarity on the laboratory processing, sequencing and the bioinformatics pipeline that will be used. *CHIK and DENV work package* We will utilize retrospective and prospective confirmed (by Reverse Transcription (RT)-quantitative PCR CHIKV blood samples. Additional febrile surveillance retrospective and prospective samples, serum or plasma, will be screened by RT-qPCR for CHIKV and DENV. Sequencing and bioinformatics pipeline methodologies will be standardized across the sites. WGS of CHIKV and DENV will be done using amplicon-based approach using the Illumina or ONT platforms, according to the technique available on each site. Whole genomes will be first amplified by overlapping RT-PCR amplifying 4 to 8 long fragments in separated RT-PCRs, or small fragments in two pools of RT-PCRs, according to the procedures in place on each site. The RT-PCR products will then be pooled and cleaned, and the library will be built using either Rapid Barcoding or Native Barcoding ONT kits, or Illumina library preparation kits according to the technique available at each site. The read analysis will be performed using established pipelines such as the artic network amplicon pipeline <https://artic.network/resources/amplicon-nf> which processes both Illumina and ONT data. While sites will not harmonise sequencing protocols, owing to different platform availability, we will standardize the data QC and metrics to ensure we use high quality sequences for the downstream analysis, and an internal EQA process will allow comparison of sequences between sites. *Kpn work package* We will use a single whole genome sequencing (WGS) standard operating procedure (SOP) and bioinformatics pipeline. All Kpn isolates identified from blood and CSF cultures will undergo routine antimicrobial susceptibility testing to support clinical care, and will subsequently be cultured for DNA extraction, using either the Wizard® Genomic DNA Purification Kit (Promega, USA) or the DNeasy Blood & Tissue Kit (Qiagen, Germany), depending on local availability. DNA libraries will be prepared using the Nextera XT DNA Library Preparation Kit or the NEBNext Ultra II FS DNA Library Prep Kit for Illumina. WGS will be done on a locally established Illumina platform (Miseq, Hiseq or Novaseq), with the OTN platform used for selected samples. We will infer transmission of high-risk lineages using phylodynamic modelling and SNP analyses. SNP calling will be performed using the Snippy pipeline (<https://github.com/tseemann/snippy>). Maximum likelihood phylogenies will be inferred from the core SNP alignment, using IQ-TREE v2.2.0.3 with best-fit substitution models and 1,000 ultrafast bootstraps and these phylogenetic trees will serve as the basis for time-scaled phylodynamic analysis using BEAST X (Didelot et al. 2018). *Mtb work package* Sputum will be collected from patients with RR-TB confirmed by Xpert MTB/RIF. Isolates will be cultured to purity in category 3 facilities and DNA extracted from pure isolates prior to Illumina/ONT sequencing. Consensus genomes and variant calling will use MTBseq (Kohl et al. 2018) or GPAS. Resistance mutations relevant to fluoroquinolones, bedaquiline, pretomanid, and linezolid will be identified using the WHO

mutation catalogue, with phenotypic DST performed on isolates with mutations of uncertain significance.

Tables should be numbered based on the order they are cited in the text.

We have made this correction to the revised version of the manuscript.

Expected outcomes should be presented in subsections dedicated to each pathogen. We have aligned expected outcomes to each pathogen work package in the revised manuscript.

The manuscript currently refers to “Real-Time (RT)-quantitative PC,” but in this context RT should stand for Reverse Transcription.

We have made this correction to the revised version of the manuscript to read as reverse transcription.

The approach for viral sequencing also needs clarification. Viral whole-genome sequencing can be challenging, so the authors should specify which enrichment protocol or strategy will be used.

We have made clarifications that WGS of CHIKV and DENV will be done using amplicon-based approach using the Illumina or ONT platforms according to the technique available on each site. Whole genomes will be first amplified by overlapping RT-PCR amplifying 4 to 8 long fragments in separated RT-PCRs, or small fragments in two pools of RT-PCRs, according to the procedures in place on each site. The RT-PCR products will then be pooled and cleaned, and the library will be built using either Rapid Barcoding or Native Barcoding ONT kits, or Illumina library preparation kits according to the technique available at each site. The read analysis will be performed using established pipelines such as the artic network amplicon pipeline <https://artic.network/resources/amplicon-nf>, which processes both Illumina and ONT data. While sites will not harmonise sequencing protocols, owing to different platform availability, we will standardize the data QC and metrics to ensure we use high quality sequences for the downstream analysis, and an internal EQA process will allow comparison of sequences between sites.

For Klebsiella, it is unclear how whole-genome sequences will be obtained, whether pure culture followed by shotgun sequencing will be used, and whether both short-read and long-read technologies will be combined for assembly.

We have clarified in the text that we will use whole genome sequencing and that *Kpn* isolated obtained from blood or CSF will undergo culture before sequencing. We will not use shot-gun sequencing rather it will be whole genome sequencing from pure cultures. Except for South Africa, most sites have capacity for shot-read Illumina sequencing

For the bacterial pathogens in general, the manuscript should clarify whether they will be cultured, tested for resistance, and then sequenced from pure isolates.

We have clarified that sputum will be collected from patients with RR-TB confirmed by Xpert MTB/RIF. Isolates will be cultured to purity in category 3 laboratory facilities and DNA extracted from pure isolates prior to Illumina/ONT sequencing. *Kpn* isolates identification from blood and CSF cultures will undergo the routine antimicrobial susceptibility testing to support clinical care and will subsequently be cultured for DNA extraction then sequencing

performed.

The section on building sustainable local sequencing capacity should also be expanded to provide more detail.

We thank the reviewer for this comment. We have added the following information to provide more clarity on how we will build sustainable local sequencing capacity under the section on opportunities, challenges and future direction. For the *Kpn*, we will leverage this cross-AAP platform to support national AMR reference laboratories in tracking the spread of carbapenem-resistant *Kpn* lineages across hospital surveillance systems (e.g in Vietnam) or to assist collaborative hospitals in confirming and responding to nosocomial *Kpn* outbreaks (e.g in Kenya). To build sustainable local sequencing capacity, for *Mtb*, CIDRI-A and OUCRU will transfer standardized protocols and provide hands-on training to AAPs that do not currently conduct these assays, including MLW and KWTRP, with SOPs shared across all sites. MORU and OUCRU (DENV) and KWTRP (CHIKV), based in their existing expertise, will lead the standardization of sequencing and bioinformatic pipeline methodologies across AAPs. SOPs will be shared and training provided, where needed, to support the deployment of the tools in each AAP.

In Figure 1, WP1 appears to be missing, and captions for all figures require additional information.

We have included WP 1 in figure 1 and improved the captions across all the figures

References Campbell, Lindsay P., Caylor Luther, David Moo-Llanes, Janine M. Ramsey, Rogelio Danis-Lozano, and A. Townsend Peterson. 2015. "Climate Change Influences on Global Distributions of Dengue and Chikungunya Virus Vectors." *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* (England) 370 (1665). <https://doi.org/10.1098/rstb.2014.0135>. Didelot, Xavier, Nicholas J. Croucher, Stephen D. Bentley, Simon R. Harris, and Daniel J. Wilson. 2018. "Bayesian Inference of Ancestral Dates on Bacterial Phylogenetic Trees." *Nucleic Acids Research* 46 (22): e134. <https://doi.org/10.1093/nar/gky783>. Goscé, Lara, Julia M. Pescarini, Rein M. G. J. Houben, and Christopher Finn McQuaid. 2025. "Tuberculosis and the Climate Crisis in Latin America: A Predicament of Poverty, Migration and Displacement." *BMJ Global Health* 10 (4): e018674. <https://doi.org/10.1136/bmjgh-2024-018674>. Hadfield, James, Colin Megill, Sidney M. Bell, et al. 2018. "Nextstrain: Real-Time Tracking of Pathogen Evolution." *Bioinformatics* 34 (23): 4121–23. <https://doi.org/10.1093/bioinformatics/bty407>. Hales, Simon, Neil de Wet, John Maindonald, and Alistair Woodward. 2002. "Potential Effect of Population and Climate Changes on Global Distribution of Dengue Fever: An Empirical Model." *Lancet (London, England)* (England) 360 (9336): 830–34. [https://doi.org/10.1016/S0140-6736\(02\)09964-6](https://doi.org/10.1016/S0140-6736(02)09964-6). Huber, John H., Marissa L. Childs, Jamie M. Caldwell, and Erin A. Mordecai. 2018. "Seasonal Temperature Variation Influences Climate Suitability for Dengue, Chikungunya, and Zika Transmission." *PLoS Neglected Tropical Diseases* 12 (5): e0006451. <https://doi.org/10.1371/journal.pntd.0006451>. Iragena, Jean de Dieu, Achilles Katamba, Dissou Affolabi, Moses Joloba, and Willy Ssengooba. 2025. "Tuberculosis Laboratory Capacity Building in the WHO African Region: The Past, the Present and the Future: A Viewpoint." *PLOS Global Public Health* 5 (11): e0004979. <https://doi.org/10.1371/journal.pgph.0004979>. Kohl, Thomas Andreas, Christian Utpatel, Viola Schleusener, et al. 2018. "MTBseq: A Comprehensive Pipeline for Whole Genome Sequence Analysis of Mycobacterium Tuberculosis Complex Isolates." *PeerJ* 6: e5895. <https://doi.org/10.7717/peerj.5895>. Kohli, Mikashmi, Ian Schiller, Nandini Dendukuri, et al.

2021. "Xpert MTB/RIF Ultra and Xpert MTB/RIF Assays for Extrapulmonary Tuberculosis and Rifampicin Resistance in Adults." *The Cochrane Database of Systematic Reviews* 1 (1): CD012768. <https://doi.org/10.1002/14651858.CD012768.pub3>. Laamarti, Meriem, Yasmine El Fathi Lalaoui, Rachid Elfermi, Rachid Daoud, and Achraf El Allali. 2023. "Afro-TB Dataset as a Large Scale Genomic Data of Mycobacterium Tuberculosis in Africa." *Scientific Data* 10 (1): 212. <https://doi.org/10.1038/s41597-023-02112-3>. Messina, Jane P., Oliver J. Brady, Nick Golding, et al. 2019. "The Current and Future Global Distribution and Population at Risk of Dengue." *Nature Microbiology* 4 (9): 1508–15. <https://doi.org/10.1038/s41564-019-0476-8>. Mordecai, Erin A., Jeremy M. Cohen, Michelle V. Evans, et al. 2017. "Detecting the Impact of Temperature on Transmission of Zika, Dengue, and Chikungunya Using Mechanistic Models." *PLoS Neglected Tropical Diseases* (United States) 11 (4): e0005568. <https://doi.org/10.1371/journal.pntd.0005568>. Saunders, Matthew J., Delia Boccia, Palwasha Y. Khan, et al. 2026. "Climate Change and Tuberculosis: An Analytical Framework." *The Lancet Respiratory Medicine* 14 (3): 267–80. [https://doi.org/10.1016/S2213-2600\(25\)00329-7](https://doi.org/10.1016/S2213-2600(25)00329-7). Shadi, Yahya, Esmaeil Khedmati Morasae, Salman Khazaei, et al. 2025. "Understanding the Mechanisms of Climate Change Impact on Tuberculosis: A Complex Systems Approach." *BMC Public Health* 25 (1): 3382. <https://doi.org/10.1186/s12889-025-24709-6>. Thawillarp, Supharerk. 2025. "Comparison of Data and Performance Indicators: Before and After the Transition of Thailand's National Disease Surveillance System, 2023–2024." *Outbreak, Surveillance, Investigation & Response (OSIR) Journal* 18 (2): 70–77. <https://doi.org/10.59096/osir.v18i2.272949>. The CRYPTIC Consortium. 2022. "A Data Compendium Associating the Genomes of 12,289 Mycobacterium Tuberculosis Isolates with Quantitative Resistance Phenotypes to 13 Antibiotics." *PLoS Biology* 20 (8): e3001721. <https://doi.org/10.1371/journal.pbio.3001721>.

Competing Interests: No competing interests were disclosed.

Reviewer Report 27 February 2026

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This manuscript details the establishment and operational framework of the Cross-Wellcome Africa Asian Programmes (AAPs) Acceleration of Genomics for Escalating Infectious Diseases (CAGED) Consortium. The consortium's strength lies in its ability to leverage expertise across six major institutions in Africa and Southeast Asia. This geographic diversity allows for a unique "multi-site and multi-pathogen approach" that is essential for understanding the heterogeneous nature of infectious diseases in these regions. Furthermore, the focus on chikungunya, dengue, multidrug-resistant *Klebsiella pneumoniae*, and drug-resistant Mtb is highly relevant, particularly as

these diseases are increasingly driven by climate change and pose significant public health threats.

The manuscript clearly outlines the use of both Illumina and Oxford Nanopore Technology platforms. This dual-platform approach is a robust choice for handling the diverse genomic architectures of viruses (CHIKV/DENV) and bacteria (Kpn/Mtb). The reliance on established pipelines such as Kleborate for Kpn and MTBseq for Mtb ensures that the data analysis is standardized and scientifically rigorous.

The manuscript emphasizes FAIR (Findable, Accessible, Interoperable, and Reusable) data principles. The plan to use the HL7 Fast Healthcare Interoperability Resources (FHIR) standard is a particularly forward-thinking approach to ensure data can be integrated with national health dashboards. A central goal is the transfer of capacity to National Public Health Laboratories and Ministries of Health. This ensures that the research doesn't remain academic but directly informs evidence-based policy making.

Points to be considered:

The consortium repeatedly states that it focuses on pathogens "driven by climate change". However, the provided methodology does not explicitly detail how environmental, meteorological, or climate data will be integrated with the genomic data. Without a specific analytical plan to correlate genomic shifts with climate variables, the "climate-driven" aspect remains a thematic justification rather than a core scientific inquiry.

For the CHIKV and DENV work package, the plan to select a "minimum of 20 participant samples per group" for assessing neutralizing antibodies may lack sufficient statistical power. Given the high genetic diversity and the goal of assessing "immune escape" across multiple lineages in both Africa and Asia, such a small sample size might not be representative of the broader population immunity or the full spectrum of viral variants.

The manuscript justifies the project by noting the "limited use of genomics" for these pathogens compared to the 3 million SARS-CoV-2 genomes on GISAID. However, it does not fully address how the consortium will overcome the specific biological challenges—such as the low symptomatic-to-asymptomatic ratio in Dengue which makes representative genomic surveillance significantly more difficult.

Overall, the manuscript presents a well-coordinated plan to enhance genomic surveillance in regions with historically limited resources compared to the global response to SARS-CoV-2.

Is the rationale for the Open Letter provided in sufficient detail?

Yes

Does the article adequately reference differing views and opinions?

Yes

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Yes

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to

follow?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Environmental surveillance, Genomics, epigenetics

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 11 May 2026

Patience Kiyuka

We thank the reviewer for the thoughtful and insightful comments that have improved the rigor of our manuscript. Below is our responses to the comments:

The consortium repeatedly states that it focuses on pathogens "driven by climate change". However, the provided methodology does not explicitly detail how environmental, meteorological, or climate data will be integrated with the genomic data. Without a specific analytical plan to correlate genomic shifts with climate variables, the "climate-driven" aspect remains a thematic justification rather than a core scientific inquiry.

We sincerely thank the reviewer for pointing it out. We agree that not all the pathogens we are studying are directly driven by climate change and because we don't have a dedicated methodological section where we provide details of how climatic variables will be incorporated into the genomic data except for DENV and CHIKV, we have changed the abstract to reflect that climate change is one of the factors driving transmission of some of these pathogens with the statement "*with climate change considered one of the several factors influencing the distribution, transmission or burden of some of these pathogens.*" We have also added the following text to the appropriate sections of the manuscript. Arbovirus distribution is predicted to be strongly affected by climate change. The distribution of the *Aedes* mosquito vectors responsible for transmission of dengue and chikungunya viruses have been extensively studied, investigating the effects of temperature (Mordecai et al. 2017; Huber et al. 2018) and humidity (Hales et al. 2002) on habitat suitability and suggesting a climate-driven expansion into new ranges (Campbell et al. 2015), and a corresponding increased population at risk from mosquito-borne disease (Messina et al. 2019). We will aim to integrate with existing studies looking at the impact of climate change on our chosen pathogens. For dengue, the existing Dengue Advanced Readiness Tools consortium (DART) <https://www.dartdengue.org>, a separately funded project which is also lead by OUCRU-Vietnam, are integrating climatic factors into dengue outbreak forecasting, and we will work with them to expand their tools to sites in this consortium and to integrate genetic factors into their model. For TB, climate change acts primarily through indirect pathways. It has been shown that climate change has potential to worsen the TB epidemic by among others contributing to population displacement which often leads to overcrowding living conditions that accelerates TB transmission (Goscé et al. 2025). Healthcare disruption can cause TB treatment interruption, leading to longer infectious period and ultimately increased risk of development of drug resistance (Saunders et al. 2026). Moreover climate-related and socioeconomic disruptions contribute to food

insecurity and malnutrition, which weakens the immune system and increasing the risk of TB infection and transmission (Shadi et al. 2025).

For the CHIKV and DENV work package, the plan to select a "minimum of 20 participant samples per group" for assessing neutralizing antibodies may lack sufficient statistical power. Given the high genetic diversity and the goal of assessing "immune escape" across multiple lineages in both Africa and Asia, such a small sample size might not be representative of the broader population immunity or the full spectrum of viral variants.

Thank you for the thoughtful comment regarding the proposed sample size of approximately 20 participants per group for assessing neutralizing antibodies against CHIKV and DENV. We carefully considered the concern about statistical power, representativeness of population immunity, and viral diversity across African and Asian lineages. We have address this by adding the paragraph below The selection of a minimum of 20 participant samples per group was based on a formal sample size determination conducted specifically for neutralization assays comparing responses between viral strains. A bootstrap-based power analysis was performed assuming neutralization titres (FRNT50) follow a normal distribution with high inter-sera variability ($\sigma \approx \mu$), which is typical for neutralization assays. The analysis further assumed that biologically meaningful differences correspond to approximately a three-fold difference in neutralization titres between strains. Using 1000 bootstrap iterations and a two-sided t-test with $\alpha = 0.05$, the analysis demonstrated that approximately 20 sera samples are sufficient to detect such differences with statistical power ≥ 0.8 . Importantly, the purpose of this component is not to estimate population-level seroprevalence or overall immunity, but rather to experimentally compare neutralization capacity across viral lineages and assess potential immune escape at the virological and immunological level.

The manuscript justifies the project by noting the "limited use of genomics" for these pathogens compared to the 3 million SARS-CoV-2 genomes on GISAID. However, it does not fully address how the consortium will overcome the specific biological challenges—such as the low symptomatic-to-asymptomatic ratio in Dengue which makes representative genomic surveillance significantly more difficult.

We acknowledge the limitation of not including asymptomatic dengue cases; however, this study is based on existing surveillance of clinical cases in health facilities across the different sites and therefore does not include sequencing of asymptomatic cases. The focal area of the project is to expand the use of genomics in these pathogens, once it is routine it can be deployed on other samples sets as they become available from community surveys. We chose to start with all the pathogens through surveillance in health facilities where it can also support diagnostic detection where this is not available.

Competing Interests: No competing interests were disclosed.