South & Southeast Asia

Pathogen Genomics Prioritization & Implementation Workshop

Case study #1: Tuberculosis

Presented by: Eby Sim

WORKSHOP PARTNERS

CDC U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION

DukeNUS Medical School

ASIA PATHOGEN GENOMICS Initiative

CENTRE FOR PATHOGEN GENOMICS

THE UNIVERSITY OF SYDNEY

Sydney Infectious Diseases Institute

CIDM centre for infectious diseases & microbiology Public Health

But before we begin…

Group 1	Bangladesh
	Malaysia
	Sri Lanka
	Timor-Leste
	Vietnam

Group 2	Cambodia
	Fiji
	Laos
	Mongolia

Group 3	Bhutan
	Brunei
	Indonesia
	Nepal

Group 4	Maldives
	Pakistan
	Philippines
	Thailand

Overview of case study #1

Item
Setting the scene: “WHO, TB & genomic sequencing”
Activity 1: “Using genomics for TB”
Activity 2: “Closer to home”
Open discussion

Setting the Scene

“WHO, TB & genomic sequencing”

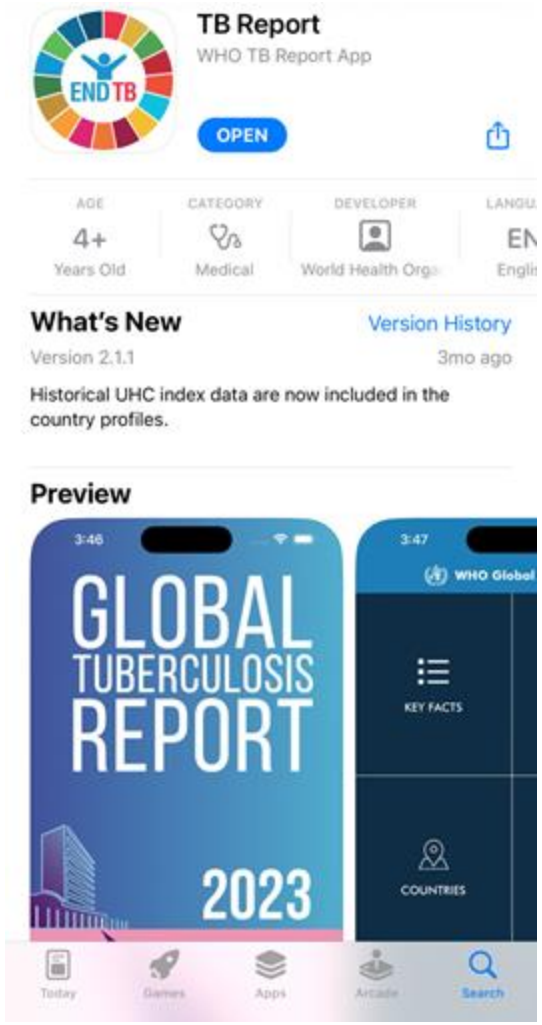
END-TB strategy

	MILESTONES		TARGETS	
			SDG*	END TB
	2020	2025	2030	2035
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20%	50%	80%	90%
TB-affected families facing catastrophic costs due to TB (%)	0%	0%	0%	0%

- Ending of the global TB epidemic.
- Relative to the year 2015:
  - 95% reduction of TB deaths
  - 90% reduction of TB incidence rate

WHO REFERENCE NUMBER: WHO/HTM/TB/2015.19

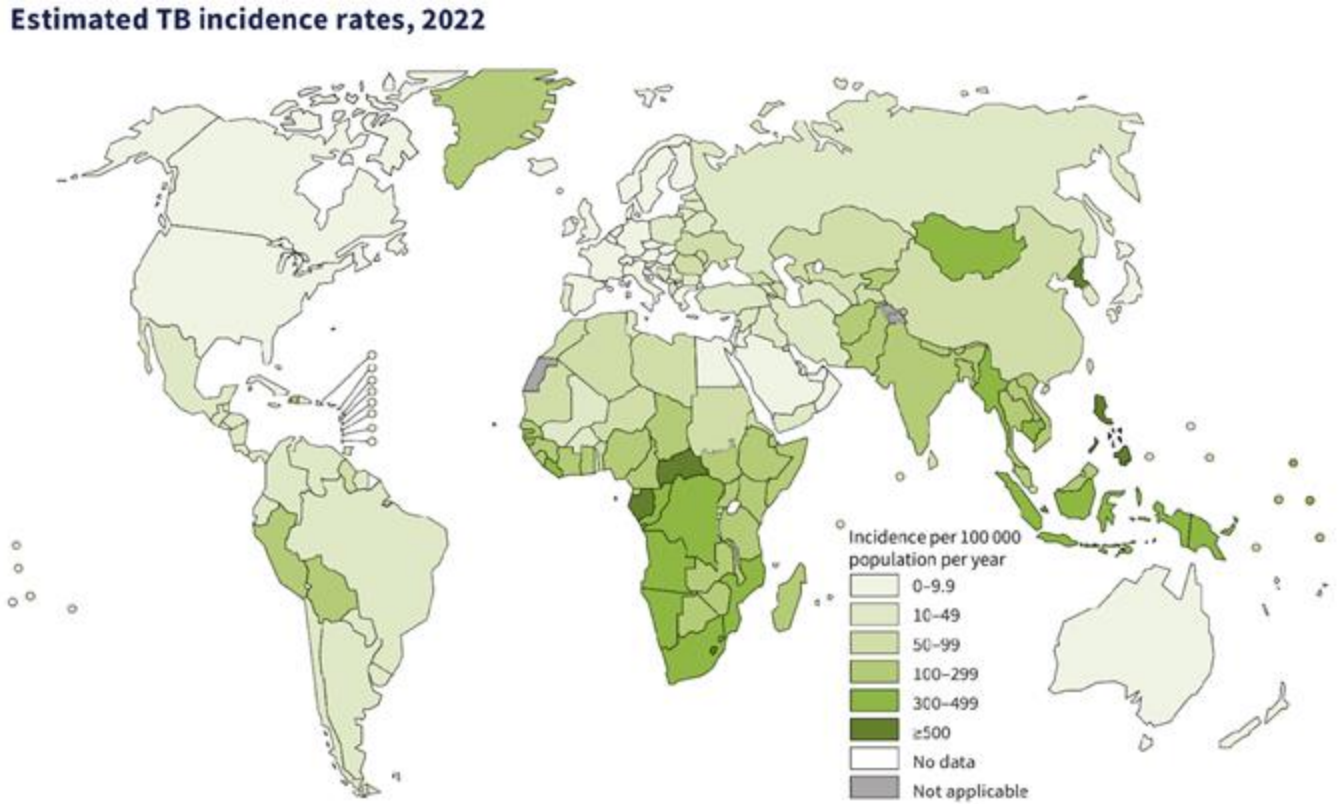
Global report at your fingertips



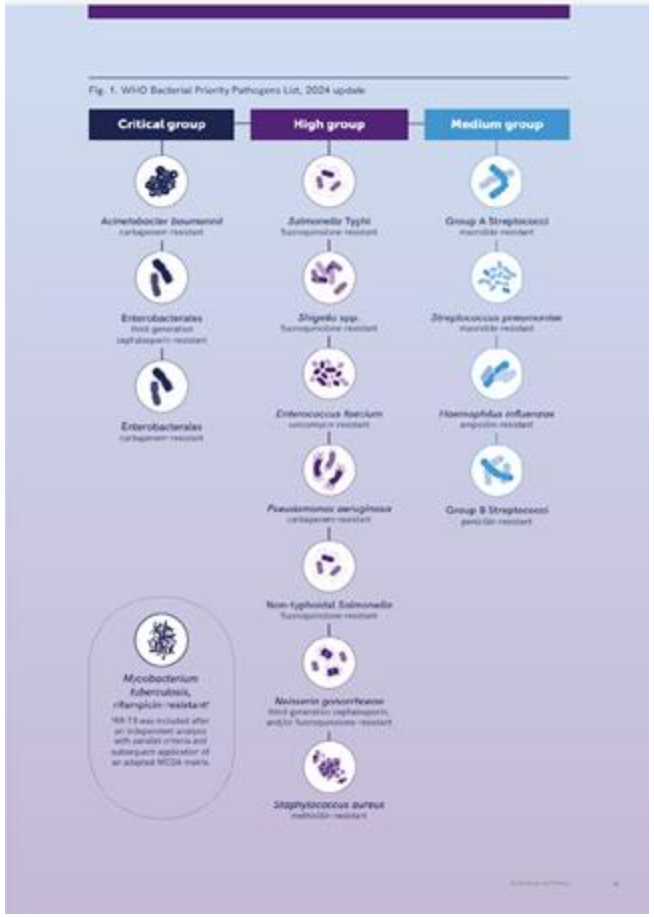
- Available in both Google play and Apple app store.
- Pulls data from the WHO Global TB report
- We will be conferring with this app during this case study.

Global estimated TB incidence rates (2022)

- South-east Asia region has the highest:
  - Incidence
    - 234 per 100K population
  - MDR/RR-TB incidence
    - 3.9 per 100K population

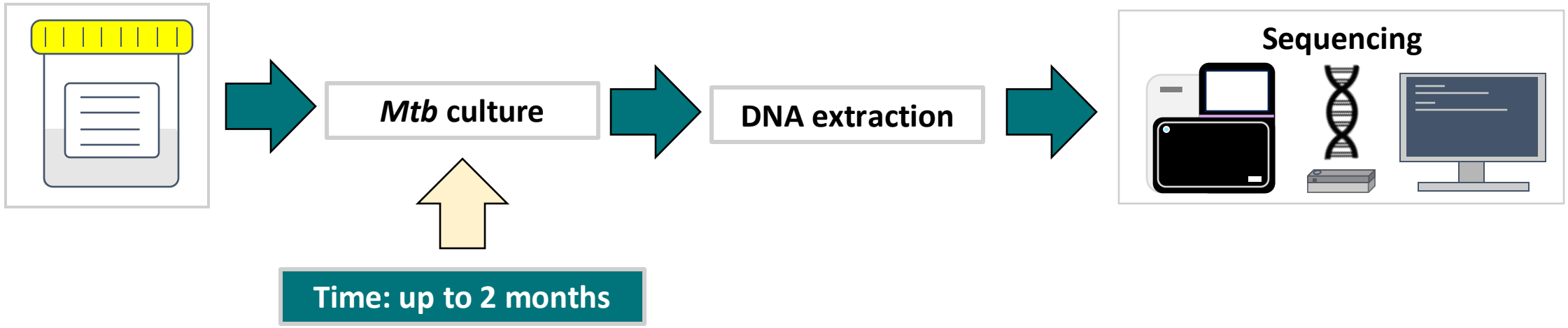


WHO bacterial priority pathogens list 2024



- *Mycobacterium tuberculosis*, rifampicin-resistant
  - *"RR-TB was included after an independent analysis with parallel criteria and subsequent application of an adapted MCDA matrix"*

Culture dependent sequencing of TB



TB genomics to support/monitor public health activities

> Lancet Reg Health West Pac. 2022 Aug 18:28:100556. doi: 10.1016/j.lanwpc.2022.100556. eCollection 2022 Nov.

Whole genome sequencing for tuberculosis in Victoria, Australia: A genomic implementation study from 2017 to 2020

Katie Dale [1], Maria Globan [2], Kristy Horan [3], Norelle Sherry [3], Susan Ballard [3], Ee Laine Tay [4], Simone Bittmann [1], Niamh Meagher [5 6], David J Price [5 6], Benjamin P Howden [7 3], Deborah A Williamson [2 6 8], Justin Denholm [1 7]

Affiliations + expand

PMID: 36034164 PMCID: PMC9405109 DOI: 10.1016/j.lanwpc.2022.100556

> Lancet Reg Health West Pac. 2023 Sep 27:41:100910. doi: 10.1016/j.lanwpc.2023.100910. eCollection 2023 Dec.

Exploring programmatic indicators of tuberculosis control that incorporate routine *Mycobacterium tuberculosis* sequencing in low incidence settings: a comprehensive (2017–2021) patient cohort analysis

Xiaomei Zhang [1 2 3], Elena Martinez [2 3 4], Connie Lam [2 3], Taryn Crighton [3 4], Eby Sim [2 3], Mailie Gall [2 3], Ellen J Donnan [5], Ben J Marais [1 2], Vitali Sintchenko [1 2 3 4]

Affiliations + expand

PMID: 37808343 PMCID: PMC10550799 DOI: 10.1016/j.lanwpc.2023.100910

> Sci Rep. 2021 Jul 28;11(1):15333. doi: 10.1038/s41598-021-94297-z.

Implementation of whole genome sequencing for tuberculosis diagnostics in a low-middle income, high MDR-TB burden country

Monica Vogel [# 1], Christian Utpatel [# 2 3], Caroline Corbett [# 1], Thomas A Kohl [# 2 3], Altyn Iskakova [# 4], Sevim Ahmedov [5], Uladzimir Antonenka [1], Viola Dreyer [2 3], Ainura Ibrahimova [6], Chynara Kamarli [7], Dilorom Kosimova [6], Vanessa Mohr [2 3], Evgeni Sahalchyk [1], Meerim Sydykova [4], Nagira Umetalieva [1], Abdylat Kadyrov [8], Gulmira Kalmambetova [4], Stefan Niemann [2 3], Harald Hoffmann [9 10]

Affiliations + expand

PMID: 34321545 PMCID: PMC8319420 DOI: 10.1038/s41598-021-94297-z

> Microb Genom. 2023 Nov;9(11):001139. doi: 10.1099/mgen.0.001139.

Implementation of national whole-genome sequencing of *Mycobacterium tuberculosis*, National Public Health Laboratory, Singapore, 2019–2022

Ansel Yi Herh Lim [1], Michelle L T Ang [1], Sharol S L Cho [1], Deborah H L Ng [2], Jeffery Cutter [2], Raymond T P Lin [1]

Affiliations + expand

PMID: 38010371 PMCID: PMC10711301 DOI: 10.1099/mgen.0.001139

Can be used to identify missed resistant *Mtb*

Observational Study > Lancet Infect Dis. 2024 Mar;24(3):297-307.
doi: 10.1016/S1473-3099(23)00498-X. Epub 2023 Nov 10.

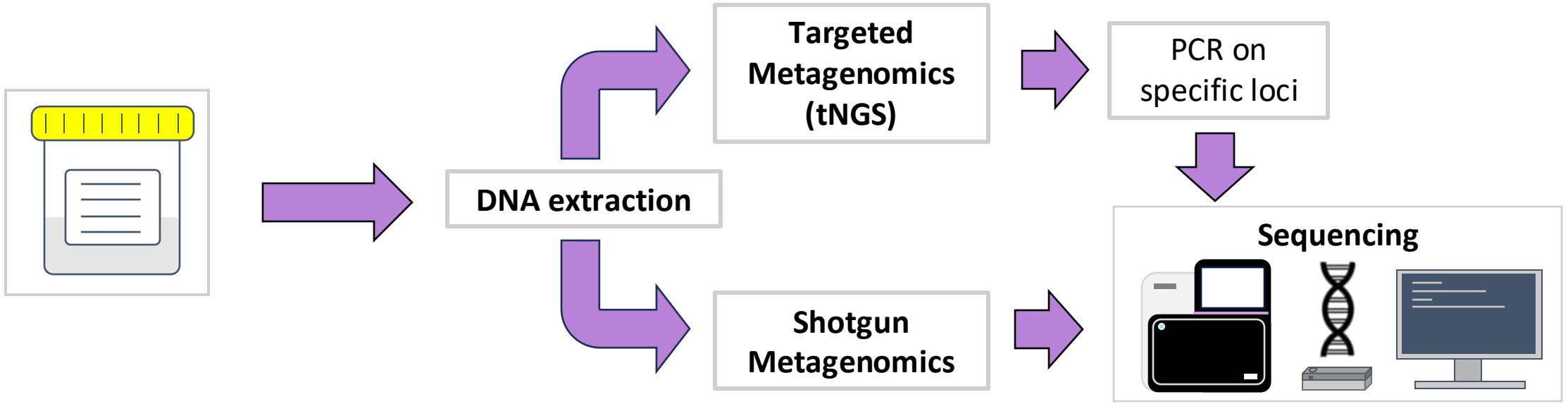
Emergence of bedaquiline–resistant tuberculosis and of multidrug–resistant and extensively drug–resistant Mycobacterium tuberculosis strains with rpoB Ile491Phe mutation not detected by Xpert MTB/RIF in Mozambique: a retrospective observational study

Ivan Barilar [1], Tatiana Fernando [2], Christian Utpatel [1], Cláudio Abujate [2], Carla Maria Madeira [2], Benedita José [3], Claudia Mutaquiha [3], Katharina Kranzer [4], Tanja Niemann [1], Nalia Ismael [2], Leonardo de Araujo [1], Thierry Wirth [5], Stefan Niemann [6], Sofia Viegas [2]

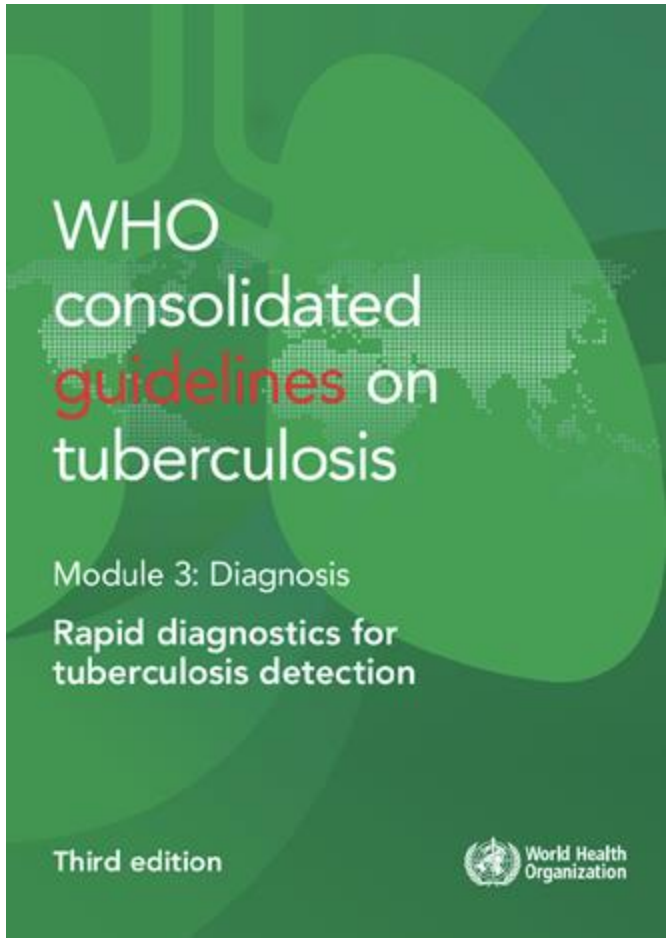
Affiliations + expand

PMID: 37956677 DOI: 10.1016/S1473-3099(23)00498-X

Culture independent sequencing



Associated tNGS products



Deeplex® Myc-TB

- Species ID
- Genotyping
- Drug resistance
- Illumina sequencing
- Cloud analysis

AmPORE-TB®

- Species ID
- Genotyping
- Drug resistance
- Nanopore sequencing
- Cloud or local analysis

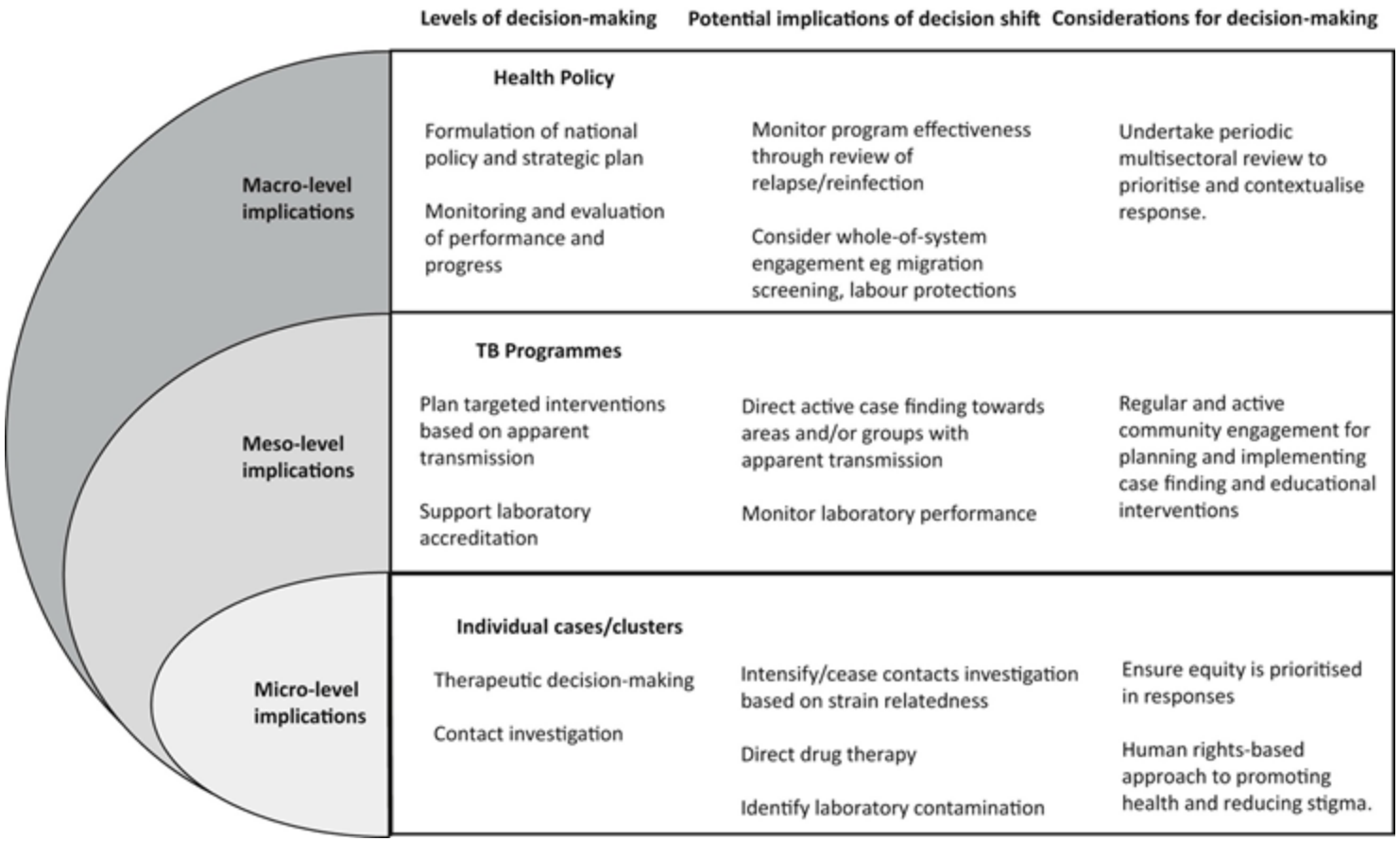
TBseq®

- Species ID
- Drug resistance
- Nanopore sequencing
- Local and cloud analysis

Pros & cons

	Culture dependent sequencing	Shotgun Metagenomics	Targeted Metagenomics
Coverage of *Mtb* genome	Complete to near complete coverage	Ranges from incomplete to complete coverage	Incomplete coverage
Lineage designation	Yes	Yes, with caveats	Dependent on scheme
Drug Resistance predictions	Yes	Yes, with caveats	Only targeted mutations
Turn around time	Slow	Fast	Fast to Very Fast
Transmission tracking using SNPs	Yes	Possible	No
Customisation (Wet lab)	Yes	No	Yes

Integration of genomic sequencing in public health



Denholm JT, *et al*., (2024). *Lancet Reg Health West Pac*. 46:101014. doi:10.1016/j.lanwpc.2024.101014

Activity 1

“Using genomics for TB”

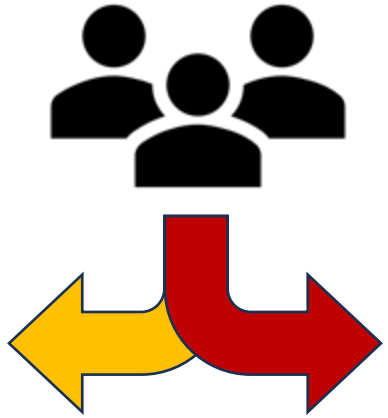
Capacity for Pathogen genomics for TB

Limited capacity	Moderate capacity	High capacity
• TB usually **endemic** • High startup cost could mean minimal interest in genomics for TB control.	• TB usually **endemic** • Genomics to strengthen TB control activities • More stringent inclusion criteria for sequencing.	• Low TB incidence • Genomics to aid in TB elimination. • Complementing or transitioning away from pDST. • Ability to pivot onto culture-independent sequencing.

Case assignments

Moderate capacity

- TB usually endemic
- Genomics to strengthen TB control activities
- More stringent inclusion criteria for sequencing.



High capacity

- Low TB incidence
- Genomics to aid in TB elimination.
- Complementing or transitioning away from pDST.
- Ability to pivot onto culture-independent sequencing.

Assumptions for exercise

- Moderate capacity *Mtb* incidence: Greater than 50 per 100,000.
- High capacity *Mtb* incidence: Less than 50 per 100,000.
- You are part of a team working in a genomics laboratory which does sequencing on a variety of bacterial pathogens.
- Your affiliated diagnostic/public health laboratory is fully stocked for rapid molecular testing and culturing.
- Current workload is sustainable for the foreseeable future.

Questions for considerations

- Does current sampling strategy support their goals?
- Do current sequencing activities support their goals?
- Is there a pathway to expand the current scope of TB genomics activities?
- If there is a pathway to expand, consider what will be required for it to be sustainable?
- Are current reporting pathways adequate? is there a need to enhance it?

Setting the scene: Scenario 1

Moderate capacity

Aim	• Sequencing of drug resistant *Mtb*
Stakeholder(s)	• Local private hospital
Sampling for genomics	• Opportunistic sequencing of samples
Current genomics activities	• Culture dependent sequencing only • Lineage designation • Drug resistance conferring mutations
Sequencing platforms (status)	• Illumina Nextseq 500 (workhorse)
Reporting	• Individual reports for all sequenced isolates

Setting the scene: Scenario 2

Moderate capacity

Aim	• Strengthening current TB control
Stakeholder(s)	• TB control program and clinicians
Sampling for genomics	• Adhoc referral of samples (Primarily from clinicians)
Current genomics activities	• Culture dependent sequencing only • Lineage designation • Drug resistance conferring mutations • Transmission tracking (if requested)
Sequencing platforms (status)	• Illumina Nextseq 500 (workhorse) • Oxford Nanopore GridION (have access if required)
Reporting	• Results reported back for all referrals

Setting the scene: Scenario 3

High capacity

Aim	• Elimination of local transmission
Stakeholder(s)	• TB control program and pathology services
Sampling for genomics	• All culture confirmed, per episode, sequenced
Current genomics activities	• Culture dependent sequencing only • Lineage designation • Drug resistance conferring mutations • Transmission tracking and genomic surveillance
Sequencing platforms (status)	• Illumina Nextseq 500 (workhorse) • Oxford Nanopore GridION (have access if required)
Reporting	• Weekly reports to TB control program and pathology network

Setting the scene: Scenario 4

High capacity

Aim	• Local TB elimination
Stakeholer(s)	• TB control program and pathology services
Sampling for genomics	• All confirmed cases, regardless of clinical episodes
Current genomics activities	• Culture dependent sequencing & tNGS • Lineage designation • Drug resistance conferring mutations • Transmission tracking and genomic surveillance
Sequencing platforms	• Illumina Nextseq 500 and Oxford Nanopore platforms
Reporting	• Weekly reports to TB control program for culture dependent sequencing. • tNGS reports within 24 hrs of end of sequencing run.

Questions for considerations

- Does current sampling strategy support their goals?
- Do current sequencing activities support their goals?
- Is there a pathway to expand the current scope of TB genomics activities?
- If there is a pathway to expand, consider what will be required for it to be sustainable?
- Are current reporting pathways adequate? is there a need to enhance it?

Activity 2

“Closer to home”

Landscape assessment

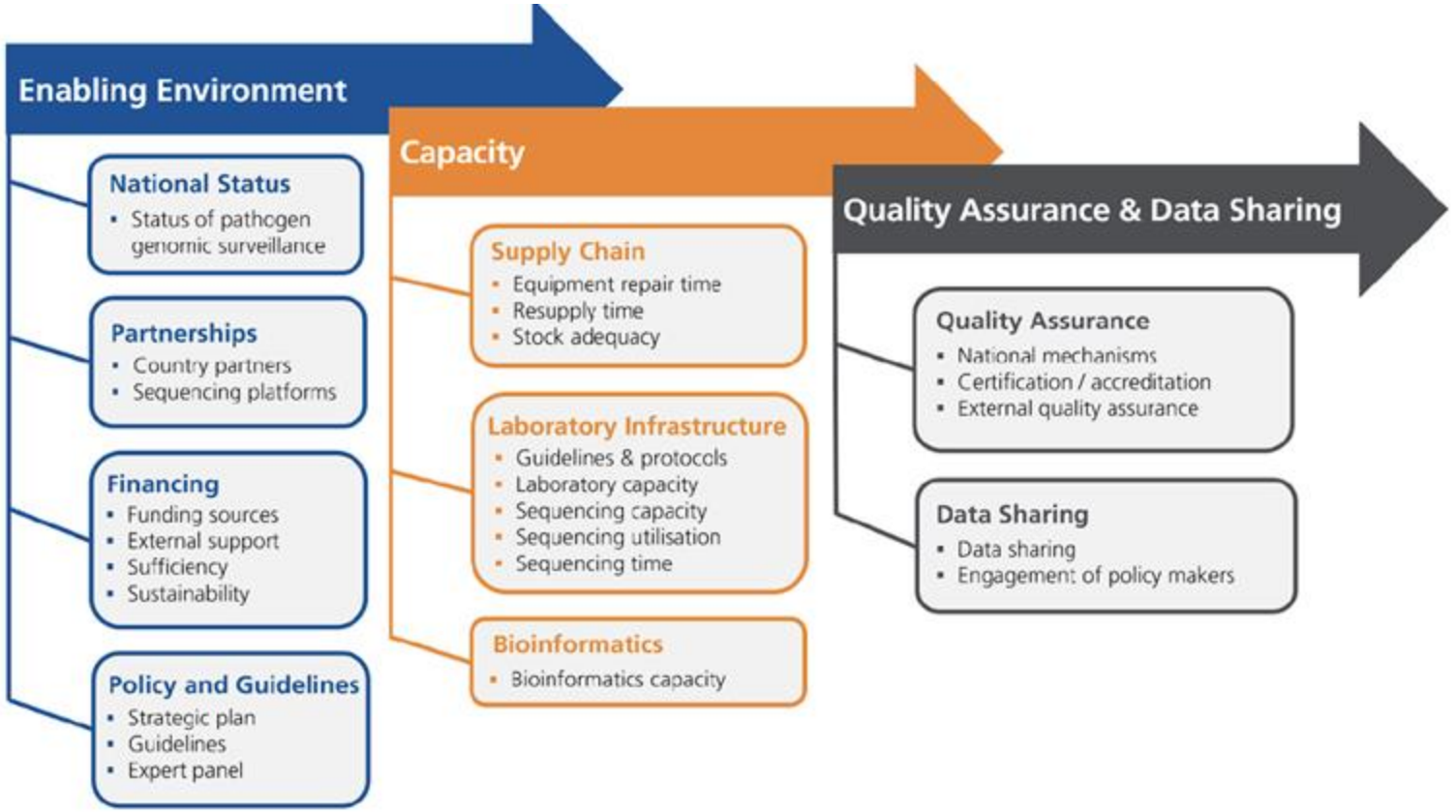
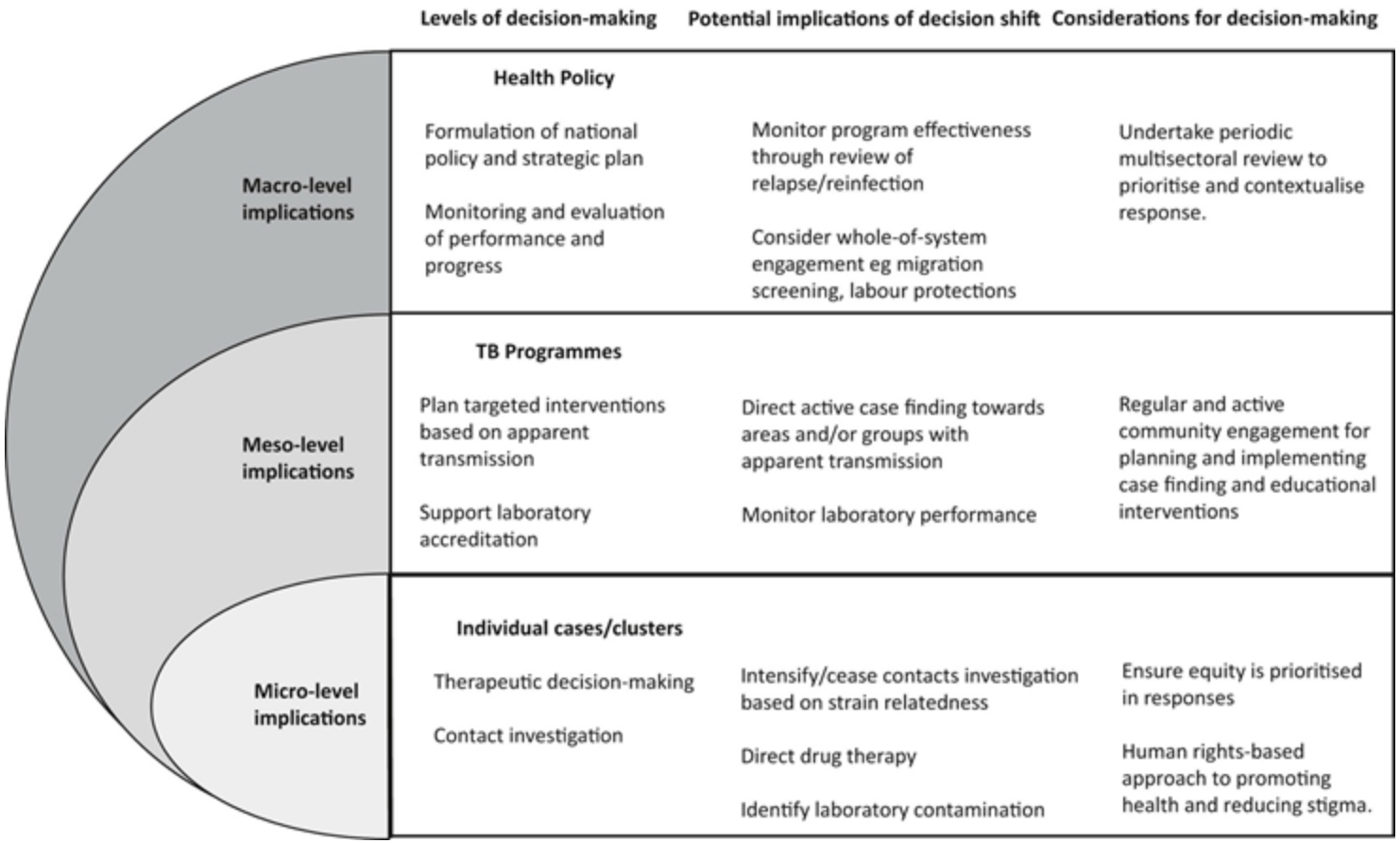


Figure 2. Landscape assessment framework for pathogen genomic surveillance

Considerations for infrastructure.

- Consideration of existing genomics infrastructure.
  - Industry partners
  - Sequencing capacity: in-house or outsourced?
  - Supply chains
  - Computational power
  - People power

Consider public health implications

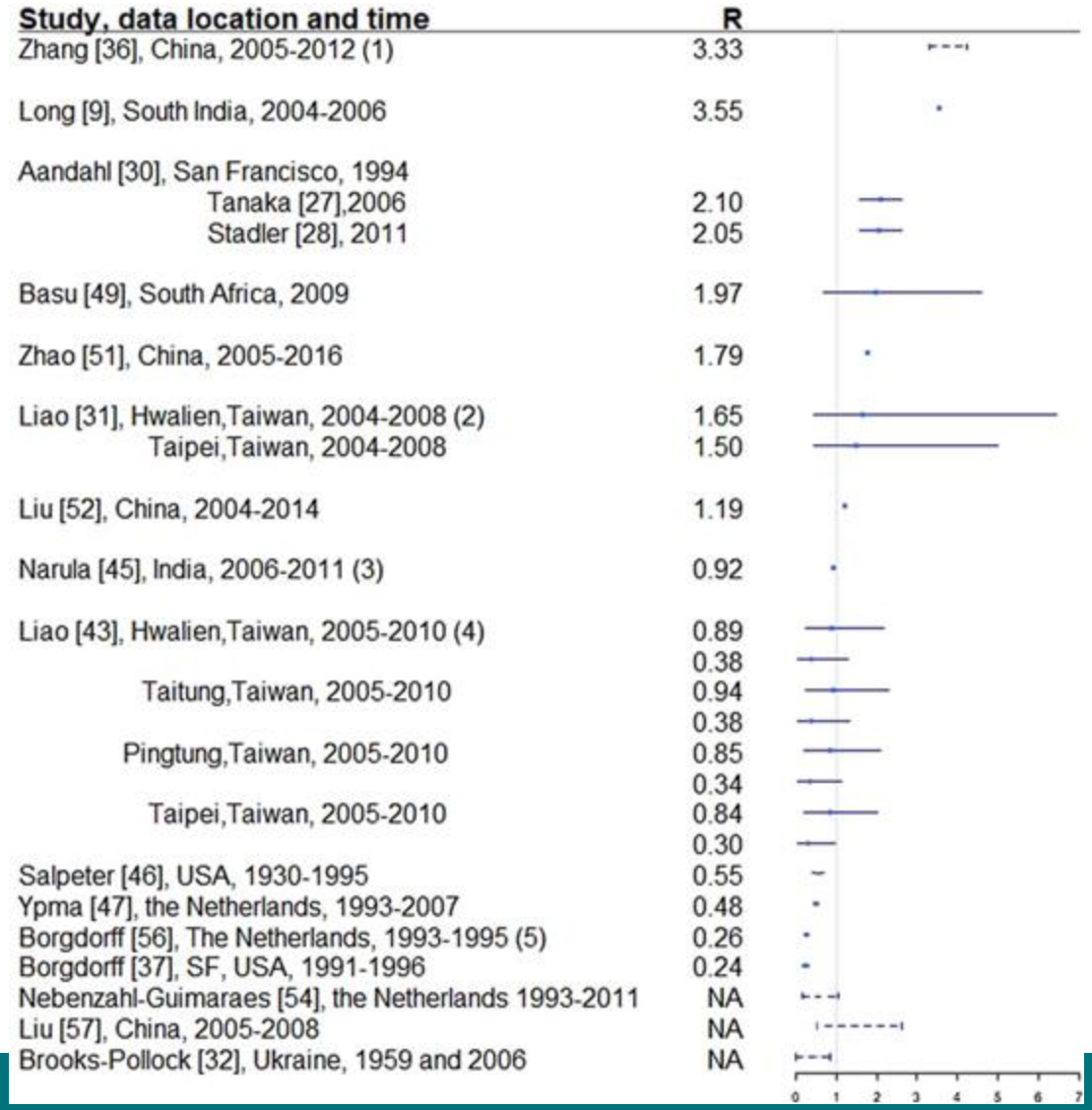


Denholm JT, *et al*., (2024). *Lancet Reg Health West Pac*. 46:101014. doi:10.1016/j.lanwpc.2024.101014

Pathogen prioritization toolkit

- Pathogen significance
  - For prevalence and case fatality ratio, we will use the WHO TB report app.
  - R0 however, is very variable
    - Low incidence countries: Less than 1

Ranges of R0



> Epidemiol Infect. 2018 Sep;146(12):1478-1494. doi: 10.1017/S0950268818001760. Epub 2018 Jul 4.

Quantifying TB transmission: a systematic review of reproduction number and serial interval estimates for tuberculosis

Y Ma [1], C R Horsburgh [2], L F White [1], H E Jenkins [1]

Affiliations + expand

PMID: 29970199 PMCID: PMC6092233 DOI: 10.1017/S0950268818001760

Activity

- Take the time now to:
  - Fill up the pathogen priority toolkit for *Mycobacterium tuberculosis*.
  - Reflect on your current country's current capacity.
  - Consider the possible implementation steps for the integration of genomic sequencing into your country's TB control program.

Pathogen prioritisation tool

Open discussion

Thank you!

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