Leveraging COVID-19 for TB diagnosis

World Health Organization

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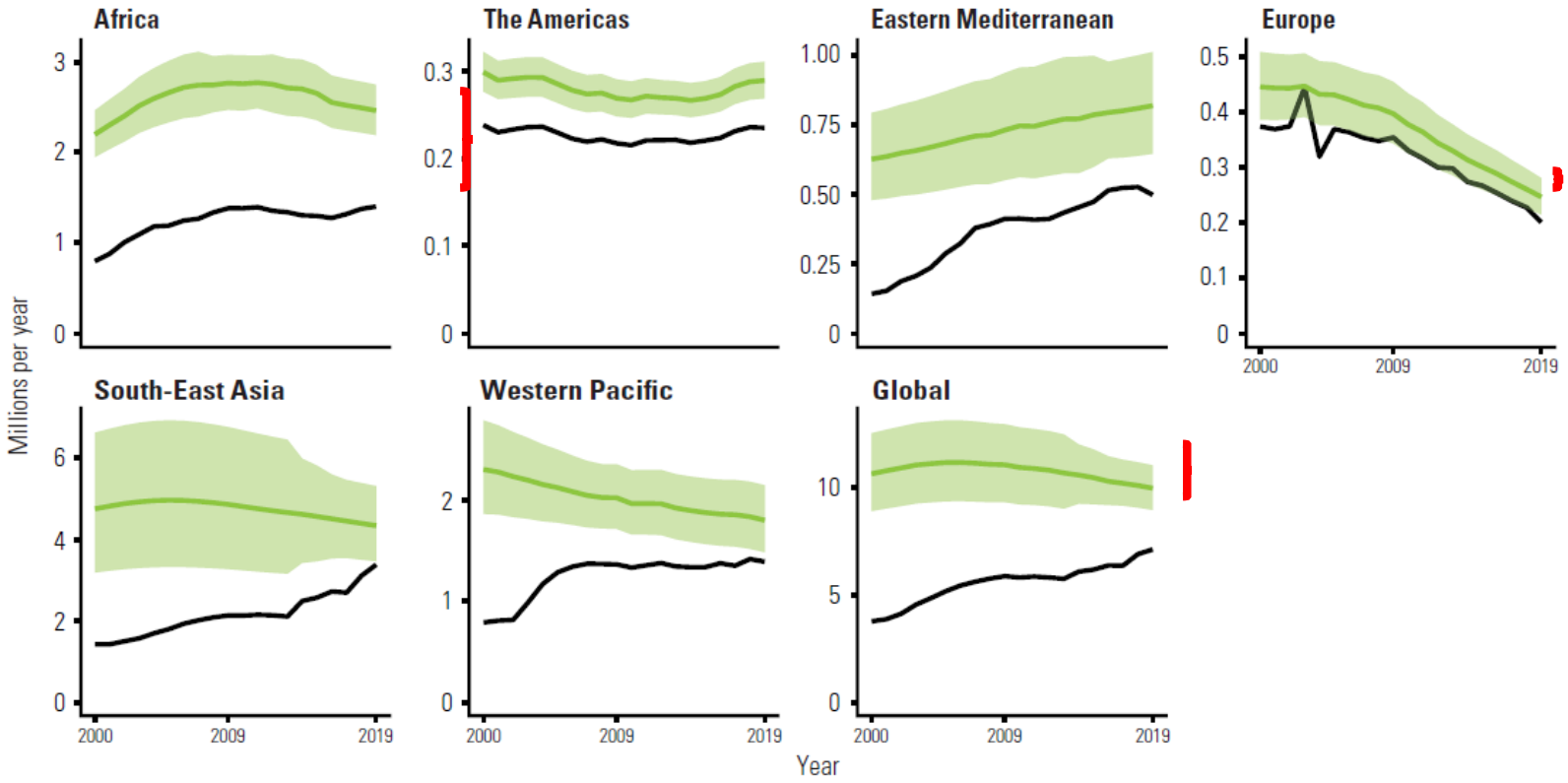
Tuberculosis: estimates and trends

FIG. 5.1

Notifications of TB cases (new and relapse cases, all forms) (black) compared with estimated TB incident cases (green), 2000–2019, globally and for WHO regions

Shaded areas represent uncertainty intervals.



Globally, gap between estimated TB cases and notified on treatment is large: approximately 3 million

Gap is narrowing but unacceptably large varies by region but smaller in higher income countries

WHO diagnostic policies recommended the latest technologies for the diagnosis of TB

https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf

Global TB Situation in the context of COVID-19

84 countries representing 84% of global burden

Figure 1. *Countries reporting monthly or quarterly TB case notification data for 2020 (as of 17 March 2021)*

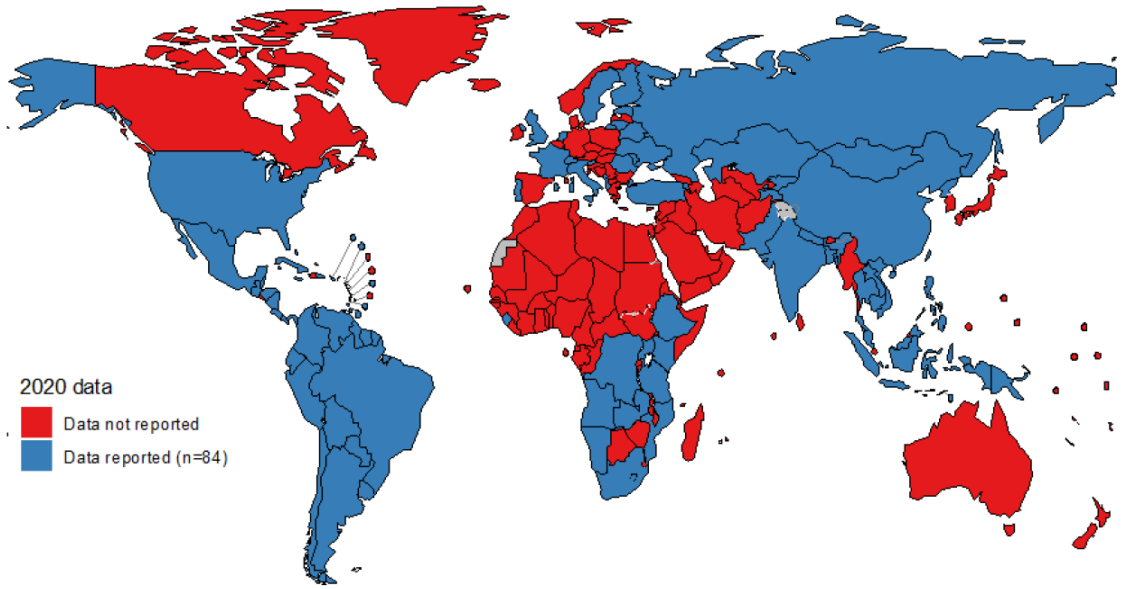
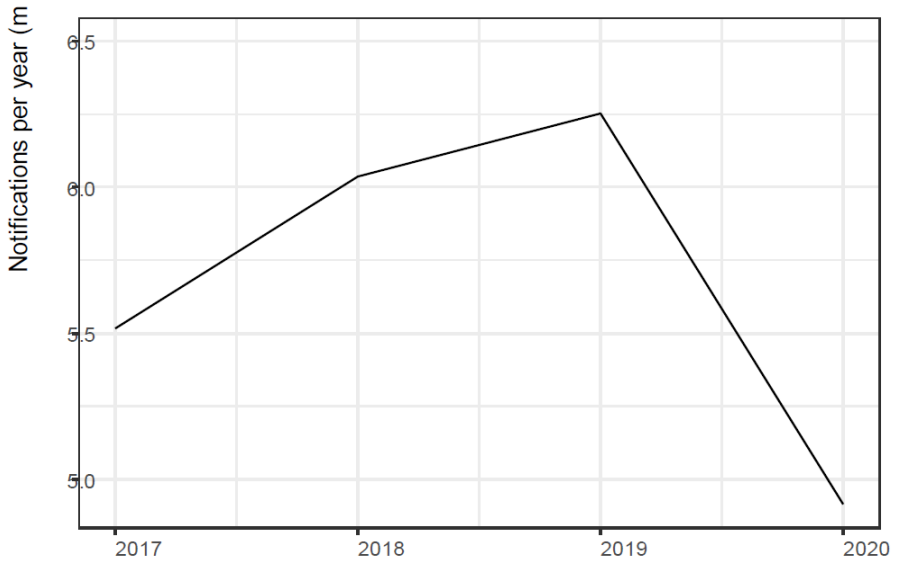


Figure 2. *Case notifications in 84 countries, 2017-2020*



1.4 million fewer people received TB care in

The relative **shortfall in TB case notifications (2020 vs. 2019) was 21%.**

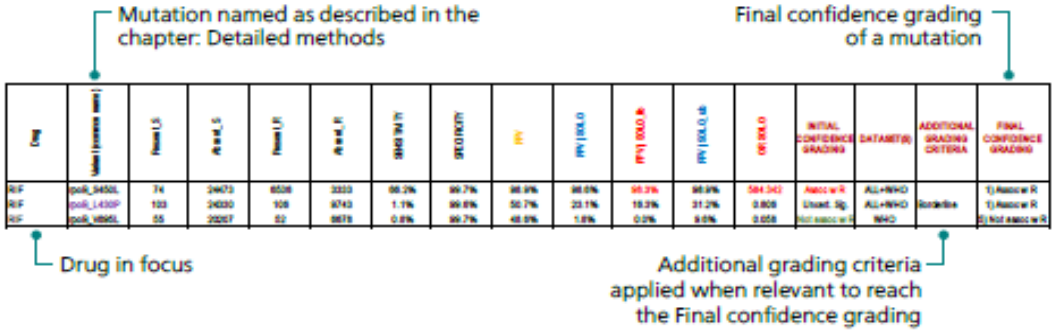
Half a million additional TB deaths could result

https://www.who.int/publications/m/item/impact-of-the-covid-19-pandemic-on-tb-detection-and-mortality-in-2020

WHO catalogue of Mycobacterium tuberculosis mutations

- A list of Mtb mutations and their association with phenotypic drug resistance.
- It provides a reference standard for the interpretation of mutations conferring resistance to all first-line and a variety of second-line drugs.
- It summarises the analysis of over 38,000 isolates with matched data on whole genome sequencing and phenotypic drug susceptibility testing from over 40 countries for 13 anti-TB medicines.
- It lists over 17,000 mutations, their frequency and association with or not with resistance and includes methods used, mutations identified and summaries of important findings for each drug.

An illustrative example



In the first example above, the drug considered is RIF. The variant is in the *rpoB* gene, the amino acid change is at codon 450, and the change is from serine to leucine (this corresponds to codon 531 in the old *Escherichia coli* nomenclature *(4, 18)*). This variant was found in 74 phenotypically susceptible isolates and in 6536 resistant isolates. The mutation was not found in 24 473 susceptible isolates or in another 3333 resistant isolates.

The sensitivity, specificity and PPV represent the performance of this mutation in the dataset. The next four columns indicate the statistical performance of this mutation when it occurs solo in the genomic regions selected when assessing RIF resistance. The values given are the midpoint PPV

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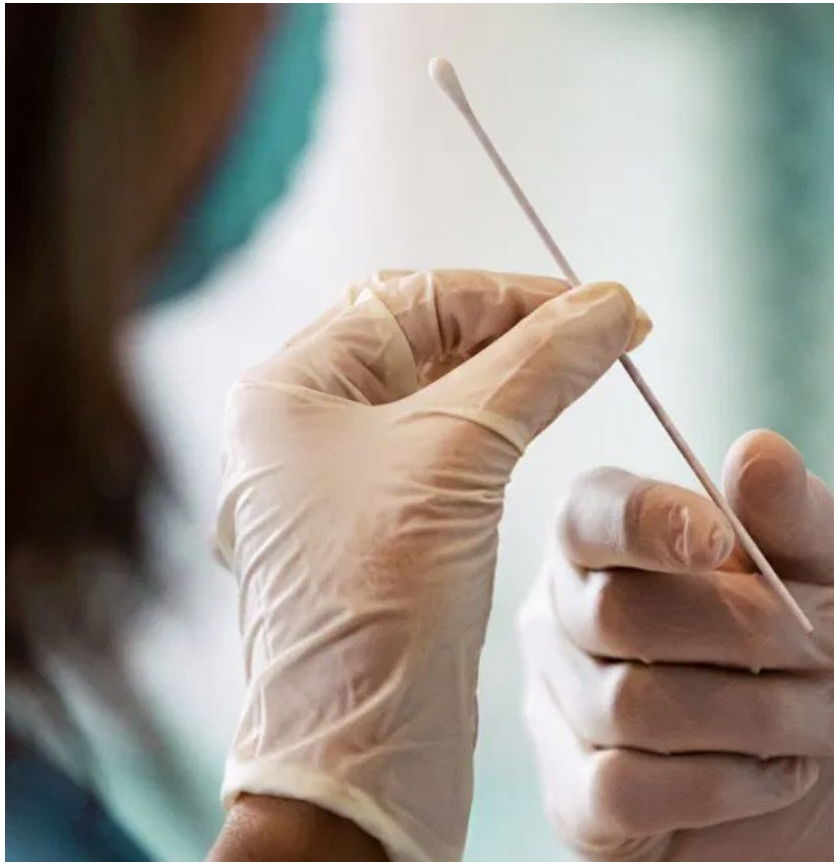
Use of digital tools and artificial intelligence

- **Digital solutions** used in mass dissemination of COVID-19 information sparked wide uptake of **smartphone apps and chatbots** for **interactive education, risk assessment, referrals, and contact tracing**.
- Repurpose for TB programmes to use these tools for information sharing and patient centred care.
- COVID-19 has sparked several **innovations in artificial intelligence** (AI). E.g. Systems for automated interpretation of chest x-ray images with computer-aided design software.
- When combined with improved battery operated, ultra-portable, digital x-ray systems, this technology can be used throughout the health-care system and offer promise for high throughput screening and **integrated COVID-19 and tuberculosis testing**.
- Cough analysers using AI and digital stethoscopes with ambient noise cancelling are in early in development

Budd J, Miller BS, Manning EM, et al. Digital technologies in the public-health response to COVID-19. Nat Med 2020; 26: 1183–92.
Morten Ruhwald, Sergio Carmona, Madhukar Pai. Learning from COVID to reimagine tuberculosis diagnosis Lancet, 2021

Making TB diagnosis simpler, closer to homes

- COVID-19 led to innovation in new sample types and sample collection methods.
- Improved and **affordable polyester swabs** and new approaches to sampling using saliva, mouthwash, oral swabs, and absorbent strips in face masks have shown promise for COVID-19 sample collection and are now being tried for tuberculosis.
- An **easy to obtain sample** that also could be used to SARS-CoV-2 would be revolutionary for TB.
- Improved access to **decentralised testing** of COVID-19 with drive-through facilities, mobile testing sites, community health-care workers, pharmacies, schools, and workplaces.
- COVID-19 **self-testing kits** detecting SARS-CoV-2 antigen, a single-use PCR present new opportunities for rapid diagnostics
- **TB diagnosis** could be revolutionised by even simpler sampling options, such as **oral swabs**.



Ref: Morten Ruhwald, Sergio Carmona, Madhukar Pai. Learning from COVID-19 to reimagine tuberculosis diagnosis Lancet, 2021

Exploiting multi-disease molecular technologies

- To control COVID-19, countries have scaled up their capacity to run molecular tests.
- This capacity was enabled from pre-existing HIV and TB programmes that had centralised multi-disease molecular platforms (eg,HIV viral load assays) and could be expanded to meet demand.
- Several countries have leveraged **automated, cartridge-based molecular technologies** (eg, **GeneXpert and TrueNAT**) for TB and COVID-19.
- This wide use of molecular technologies and bi-directional testing will be good for TB diagnosis and will reduce the reliance on suboptimal tools, such as smear microscopy.

- MacLean E, Kohli M, Weber SF, et al. Advances in molecular diagnosis of tuberculosis. J Clin Microbiol 2020; 58: e01582–19.
- 9 Venkatesan, P. COVID-19 diagnostics—not at the expense of other diseases. Lancet Microbe 2020; 1: e64.

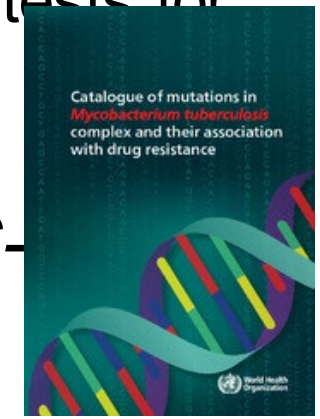
Making data visible, sharing of data

- COVID-19 is a digitalised disease with **real time data sharing, aggregation** and **analysis** to visualise the pandemic and direct the public health response.
- TB remains an analogue disease relying on paper-based systems and annual summary reporting.
- The opportunities brought on by COVID-19 big data aggregators should be applied to TB.
- Investments in data systems, connected diagnostics, and use of crowd sourced data offers the opportunity to rethink TB surveillance and case notification.

Ref: Morten Ruhwald, Sergio Carmona, Madhukar Pai. Learning from COVID-19 to reimagine tuberculosis diagnosis Lancet, 2021

Emerging technologies: in the context of Covid-19 pandemic

- Biomarker based Point of Care tests (*similar to RDTs for SARS-CoV2*)
  - GDG planned for 2nd generation LF-LAM tests 2022, promising performance in PLHIV
  - 3rd generation LF-LAM tests undergoing clinical evaluation, potential POC for all PTB
    - Addressing **ACCESS**
- Multi-disease diagnostic platforms recommended for TB (*includes SARS-CoV2*)
  - GeneXpert, Abbott, Roche, BD Max, Truenat – offering highly accurate tests for TB and used for other diseases including SARS-CoV2, HIV, etc.
    - Addressing **COST and EFFECIENCY**
- Next generation sequencing for TB (*increasingly used for SARS-*
  - WHO Catalogue of mutations for Tuberculosis and Drug Resistance
    - First WHO reference source released July 2021 and with future updates planned
  - WHO GDG planned for 2022.



https://www.who.int/publications/i/item/9789240028173

Summary

- The gap between estimated TB burden and notifications has increased in the COVID-19 pandemic period
- WHO policies address gaps to ensure the best solutions are used
- Adoption is lagging and important gaps need to be closed
- Three major new domains paralleled in the COVID-19 response are key diagnostics going forward for TB
  - Point of care biomarker/RDT tests
  - Multi-disease platforms
  - Next generation sequencing

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