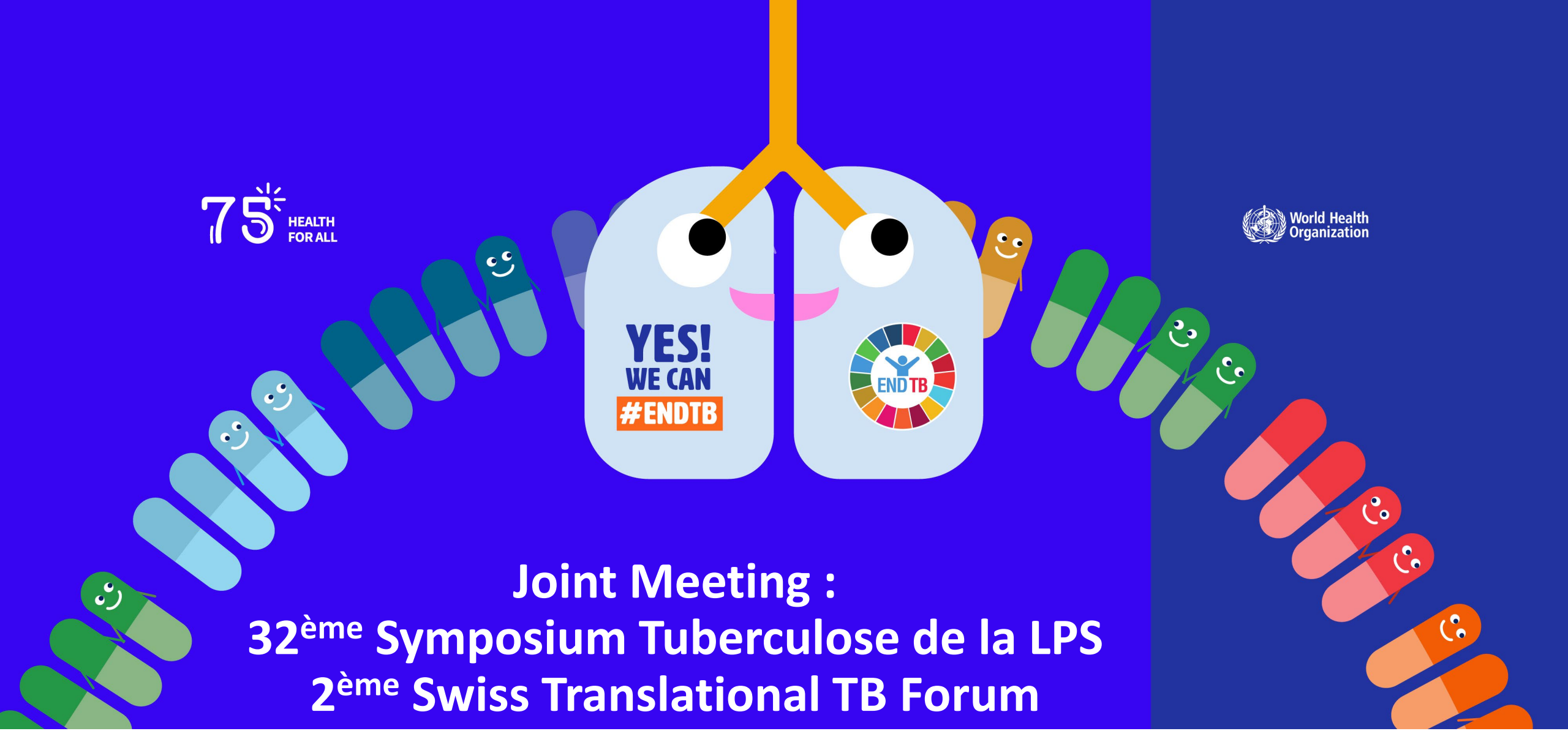
Joint TB-Meeting:
32. Tuberkulose-Symposium der LLS
2. Swiss Translational TB Forum

Willkommen!

Swiss Translational TB Forum

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA



Joint Meeting :
32ème Symposium Tuberculose de la LPS
2ème Swiss Translational TB Forum

Bienvenue !

Swiss Translational TB Forum

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA

Willkommensgruss der Lungenliga Schweiz
Bienvenue de la Ligue pulmonaire suisse

- Vertrag mit dem BAG 2023 – 2027
- Neues TB-Handbuch
- TB-Bericht 2023 Finalisierung
- Neues Team!
  - Melody Schmid, Verantwortliche Kompetenzzentrum Tuberkulose Lungenliga Schweiz
    Biologin / Bilingue
    Seit Februar 2024
  - Sara Magadzio-Ulmann, Administrative Assistentin Kompetenzzentrum Tuberkulose
    Seit März 2023

Danke!
Merci!

- Alle Teilnehmenden
- Organisations-Komitee, Michael Berney, Jan Fehr, Gunar Günther, Jean-Paul Janssens, Peter Keller, Jesica Mazza-Stalder, Melody Schmid und Otto Schoch
- Mitarbeitende Lungenliga Schweiz – Sara Magadzio & Melody Schmid
  Swiss Translational TB Forum – Flavia Gürtler
- Dolmetschende
- Eventforum & Technik
- IMK
- Sponsoren
  - DiaSorin & Qiagen

Mit Unterstützung von
Avec le soutien de

QIAGEN

Diasorin

Swiss Translational
TB Forum

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA


BIG
DEBATE

VORMITTAG:

TB-Erkennung in der Schweiz und ihre Forschung

Moderation: Jesica Mazza-Stalder & Jan Fehr

09.00 **Begrüssung**
Jörg Spieldenner, Direktor | Lungenliga Schweiz
Jan Fehr, Departementsleiter Public & Global Health | Universität Zürich | Translational TB Forum

09.15 **Aktuelles zur TB-Epidemiologie in der Schweiz und weltweit**
Ekkehardt Altpeter, Wissenschaftlicher Mitarbeiter | Bundesamt für Gesundheit

09.45 **Pause und Gruppenverteilung**

News aus der Forschung (auf Englisch)

10.00 **What are B cells doing during TB, and does it matter?**
Carolyn King, Leiterin der Forschungsgruppe Universität Basel

10.30 **Kurze Forschungs-Vorträge ausgewählt aus den Abstracts**
Diverse Referentinnen und Referenten

News aus der Praxis

10.00 **Das neue Handbuch**
Otto Schoch, Facharzt Pneumologie und Schlafmedizin | Kantonsspital St. Gallen

10.15 **Vorstellung von zwei Fällen komplexer Umgebungsuntersuchungen**
Diverse Referentinnen und Referenten von den Kantonen VD & SG

11.00 **Pause und Zusammenführung**

11.15 **Kurze Forschungs-Vorträge ausgewählt aus den Abstracts**
Diverse Referentinnen und Referenten

12.45 **Mittagessen**

NACHMITTAG:

Aktuelles aus der TB

Moderation: Otto Schoch & Jean-Paul Janssens

14.00 **Paradigmenwechsel in der klinischen Behandlung von drug resistent TB? Aktuelle Empfehlungen und Herausforderungen.**
Gunar Günther, Pneumologe | Inselspital Bern & Universität Namibia

14.30 **Subklinische TB - was ist ihre Bedeutung?**
Klaus Reither, Leiter der Abteilung Klinische Forschung, Gruppenleiter Klinische TB-Forschung | Swiss TPH

15.00 **AlpE - neue Medikamentenkombination zur Behandlung von TB**
Michel Pieren, Teamleiter des klinischen Programms | BioVersys AG

15.30 **Pause**

16.00 **Künstliche Intelligenz in der TB-Diagnostik**
Annie Heartley | Universität Yale & EPFL

16.30 **Zugang zu TB-Medikamenten im Jahr 2024**
Christophe Perrin, Apotheker | Ärzte Ohne Grenzen

17.00 **Ende**

MATIN :

La tuberculose en Suisse et les recherches réalisées

Modération : Jesica Mazza-Stalder et Jan Fehr

09.00 **Mots de bienvenue**
Jörg Spieldenner, Directeur | Ligue Pulmonaire Suisse
Jan Fehr, Chef du département de la santé publique et mondiale | Université de Zurich | Translational TB-Forum

09.15 **Point sur l'épidémiologie de la tuberculose en Suisse et dans le monde**
Ekkehardt Altpeter, collaborateur scientifique | Office fédéral de la santé publique

09.45 **Pause et répartition par groupe d'intérêt**

Actualités de la recherche (en anglais)

10.00 **What are B cells doing during TB, and does it matter?**
Carolyn King, responsable du groupe de recherche | Université de Bâle

10.30 **Brèves présentations de recherche sélectionnées parmi les abstracts**
Divers oratrices et orateurs

Actualités du terrain

10.00 **Le nouveau manuel**
Otto Schoch, spécialiste en pneumologie et médecine du sommeil | Hôpital cantonal de St-Gall

10.15 **Présentation de deux cas d'enquêtes d'entourage complexes**
Divers oratrices et orateurs des cantons VD & SG

11.00 **Pause et regroupement**

11.15 **Brèves présentations de recherche sélectionnées parmi les abstracts**
Divers oratrices et orateurs

12.45 **Repas de midi**

APRÈS-MIDI :

Les actualités de la tuberculose

Modération : Otto Schoch & Jean-Paul Janssens

14.00 **Changement de paradigme dans la prise en charge clinique de la tuberculose résistente ? Recommandations et défis actuels.**
Gunar Günther, pneumologue | Hôpital de l'Île à Berne & Université de Namibie

14.30 **La tuberculose subclinique - quel est son intérêt ?**
Klaus Reither, Chef de l'unité de recherche clinique, chef du groupe de recherche clinique sur la tuberculose | Swiss TPH

15.00 **AlpE - nouvelle combinaison de médicaments pour le traitement de la tuberculose**
Michel Pieren, Chef d'équipe du programme clinique | BioVersys SA

15.30 **Pause**

16.00 **L'intelligence artificielle dans le diagnostic de la tuberculose (présentation en ligne)**
Annie Heartley | Université de Yale & EPFL

16.30 **Accès aux médicaments contre la tuberculose en 2024**
Christophe Perrin, pharmacien | Médecins Sans Frontières

17.00 **Fin**

Swiss Translational TB Forum

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA

Overview Abstracts

Time Slot	Titel	Speaker	Affiliation
TB immunology			
10:30 – 10:40	cMYC expression determines the outcome of macrophages maturation and *Mycobacterium tuberculosis* infection	Edoardo Sarti	Department of Infectious Diseases and Hostpial Epidemiology, University Hospital of Zürich
10:40 – 10:50	Exploring Immune-Stromal cell interactions during Tuberculosis	Tiphaine Camarasa	Infection Immunology Lab, Department of Biomedicine, University of Basel
10:50 – 11:00	Exploring the mechanisms of Mycobacteria-mediated membrane damage: Small or catastrophic, two types of damages leading to different bacterial fates.	Céline Michard	Department of Biochemistry, Faculty of Science, University of Geneva
Pause 11:00 – 11:15			
11:15-11:25	Context-dependent Macrophage Activation by Clofazimine via TNF-α	Rebekka Wolfensberger	Department of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich and University of Zurich
Drug resistance and discovery			
11:25 – 11:35	Mycobacterial drug tolerance assessments reveal clinical outcomes	Alexander Jovanovic	Pulmonary Infection Biology, Department of Biomedicine, University Hospital Basel
11:35 – 11:45	Drug tolerance in *Mycobacterium tuberculosis:* it's all in the family.	Valerie March	Tuberculosis Research Unit, Department of Medical Parasitology & Infection Biology, Swiss Tropical and Public Health Institute and University of Basel
11:45 – 11:55	Shedding light on TB's genomic dark matter	Bei Shi Lee	Department of Public and Global Health, Epidemiology, Biostatitics and Prevention Institute, University of Zurich
11:55 – 12:05	Characterization of a novel compound class targeting the *M. tuberculosis* RNA degradosome	Tizian Griesser	National Reference Laboratory for Mycobacteria, Institute of Medical Microbiology, University of Zurich
12:05 – 12:15	Epistasis as a driver of MDR-TB epidemics	Selim Bouaouina	Tuberculosis Ecology & Evolution Unit, Department of Medical Parasitology & Infection Biology, Swiss Tropical and Public Health Institute and University of Basel
Tranlational and clinical studies			
12:15 – 12:25	Tuberculosis Drug Resistance Prediction by Nanopore Targeted Next-Generation Sequencing: A Field Application Study in Sub-Saharan Africa	Tiana Schwab	Institute of Social and Preventive Medicine, University of Bern
12:25 – 12:35	Primary bedaquiline resistance in an Afghan migrant to Switzerland – rare event or upcoming threat?	Nasstasja Wassilew	Department of Infectious Diseases, Bern University Hospital
12:35 – 12:45	ULTR-AI: Ultrasound-Led TB Triage using AI	Julia Wolleb	Laboratory for intelligent Global Health and Humanitarian Response Technologies (LiGHT), Yale School of Medicine, Department of Biomedical Informatics and Data Science, New Haven, Connecticut, USA
Lunch Break 12:45			

Swiss Translational TB Forum

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Swiss Confederation

Bundesamt für Gesundheit BAG
Office fédéral de la santé publique OFSP
Ufficio federale della sanità pubblica UFSP
Federal Office of Public Health FOPH

Epidemiology of Tuberculosis in Switzerland and worldwide

1988 to 2023

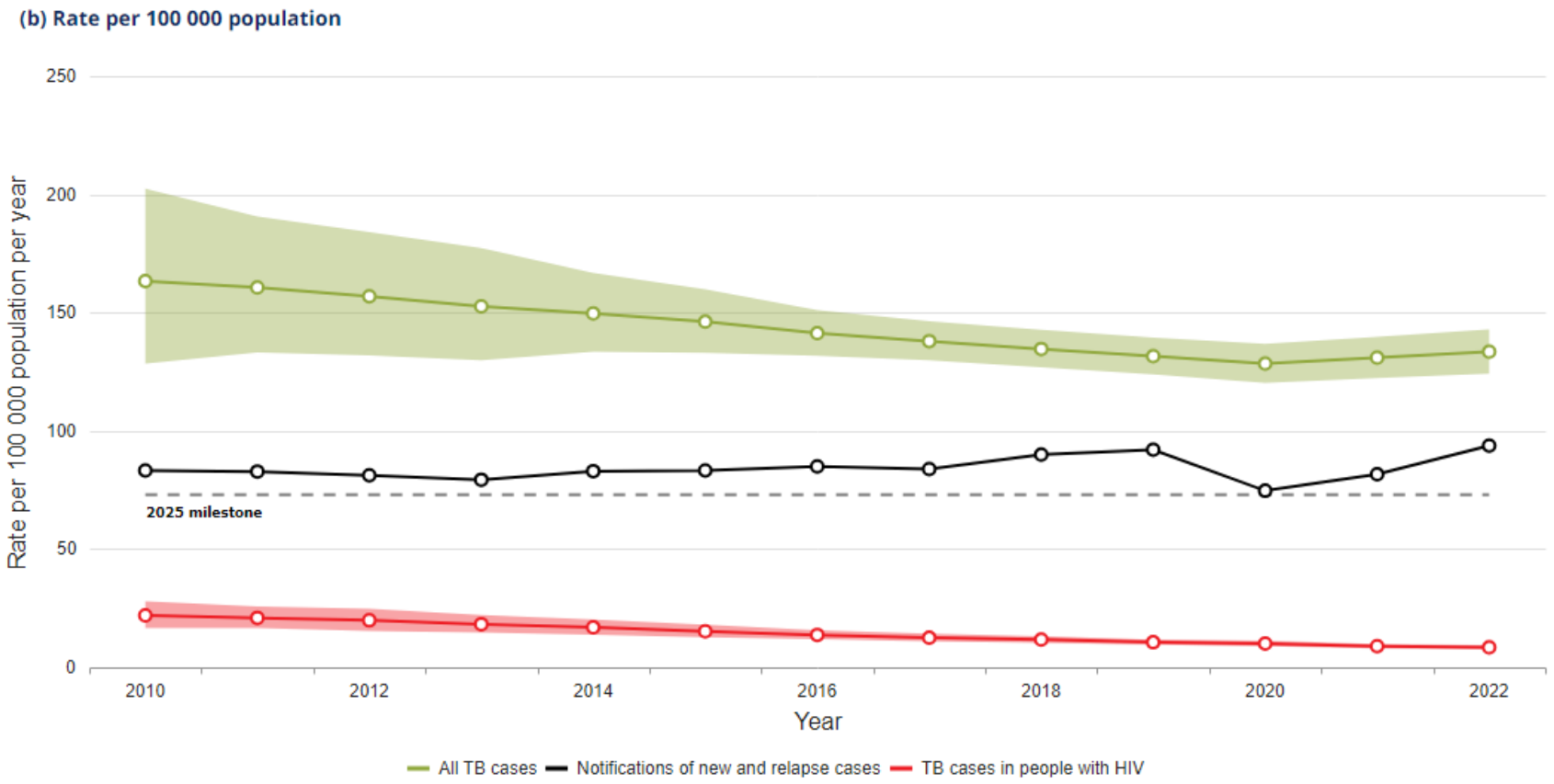
Is Tuberculosis on the rise?

Outline

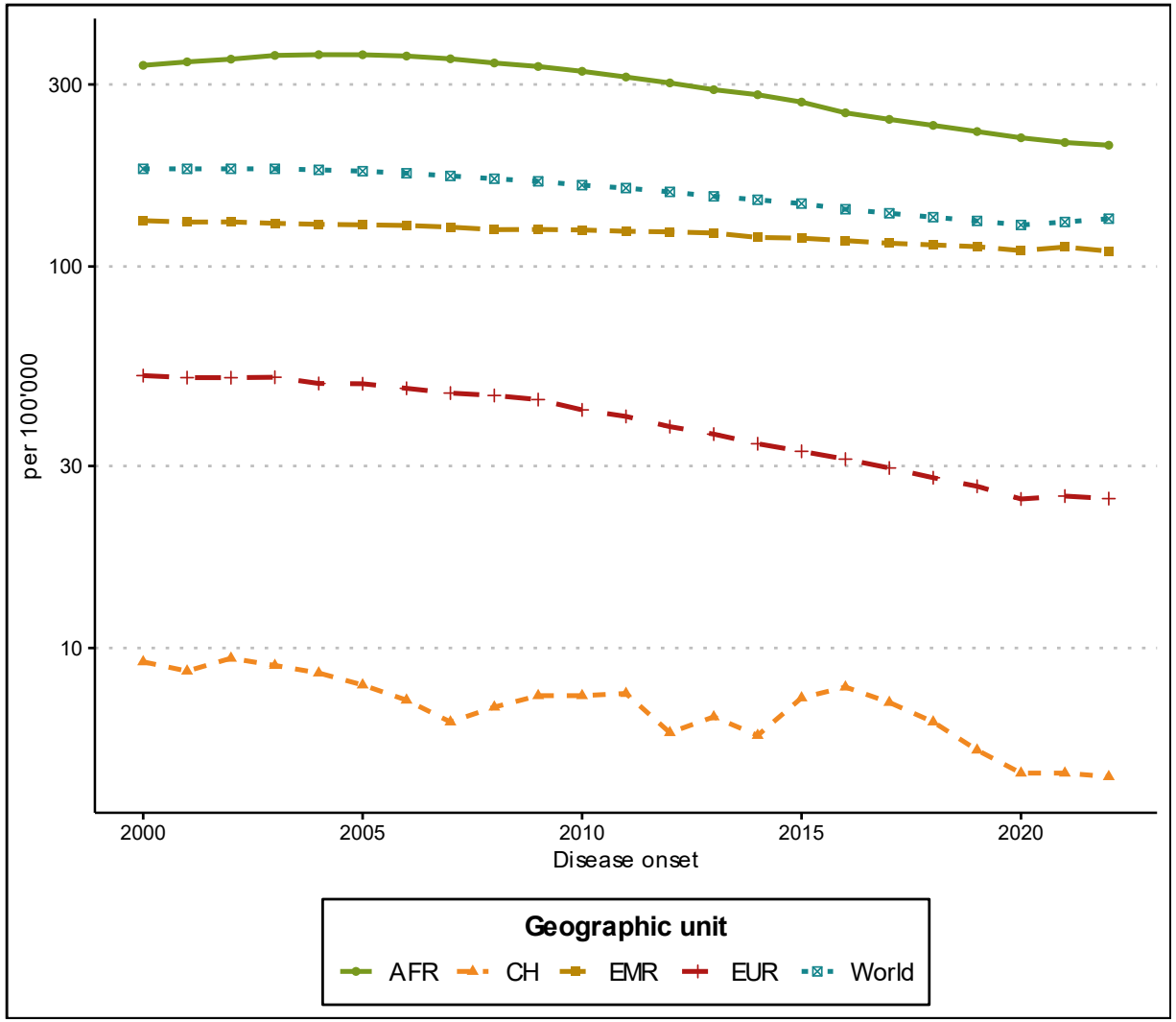
1. Incidence
2. Mortality
3. R-resistance
4. Treatment outcome measurements
5. Conclusion

Tuberculosis in Switzerland (CH) and the Global Context

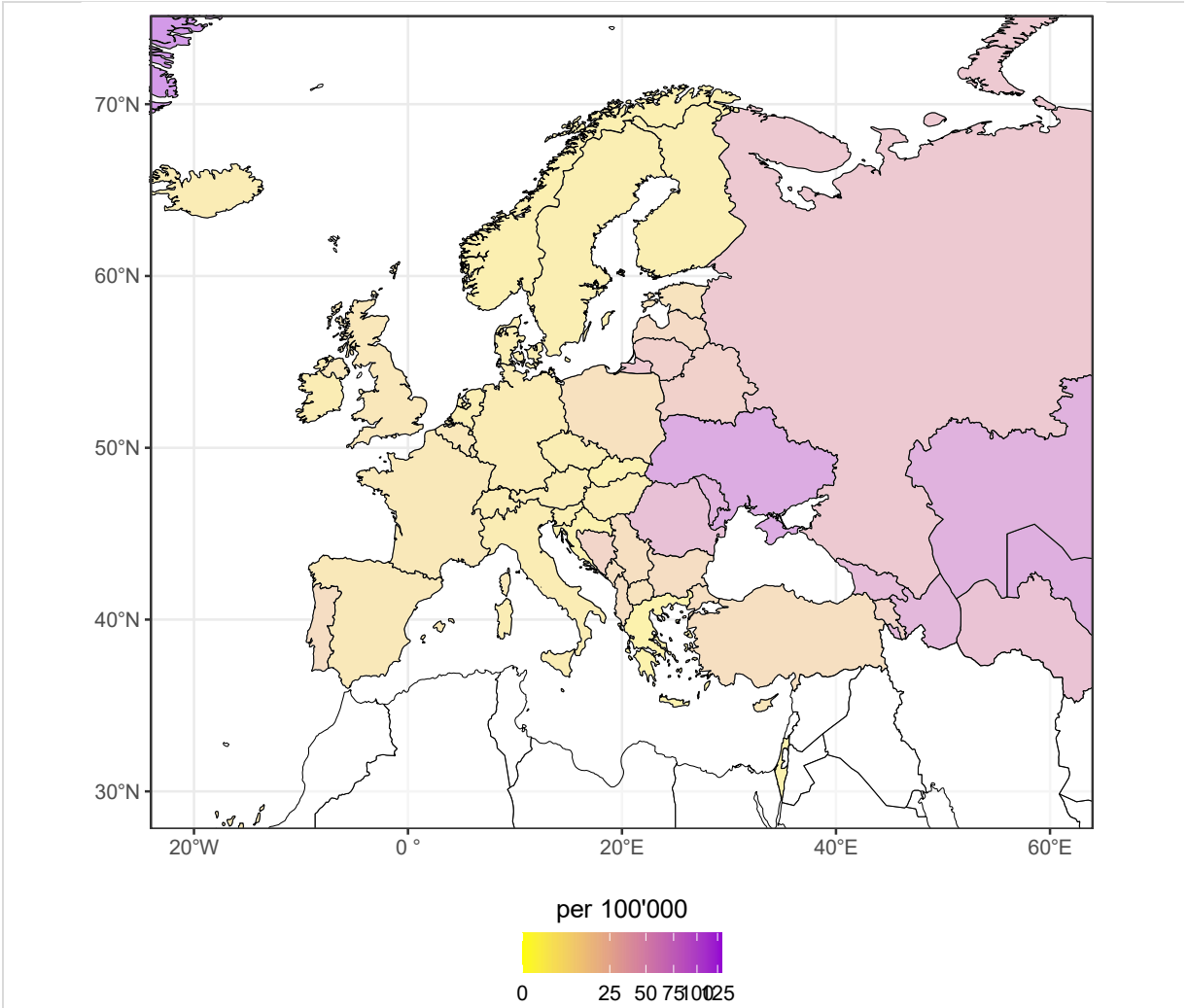
Tuberculosis Incidence: Global Context



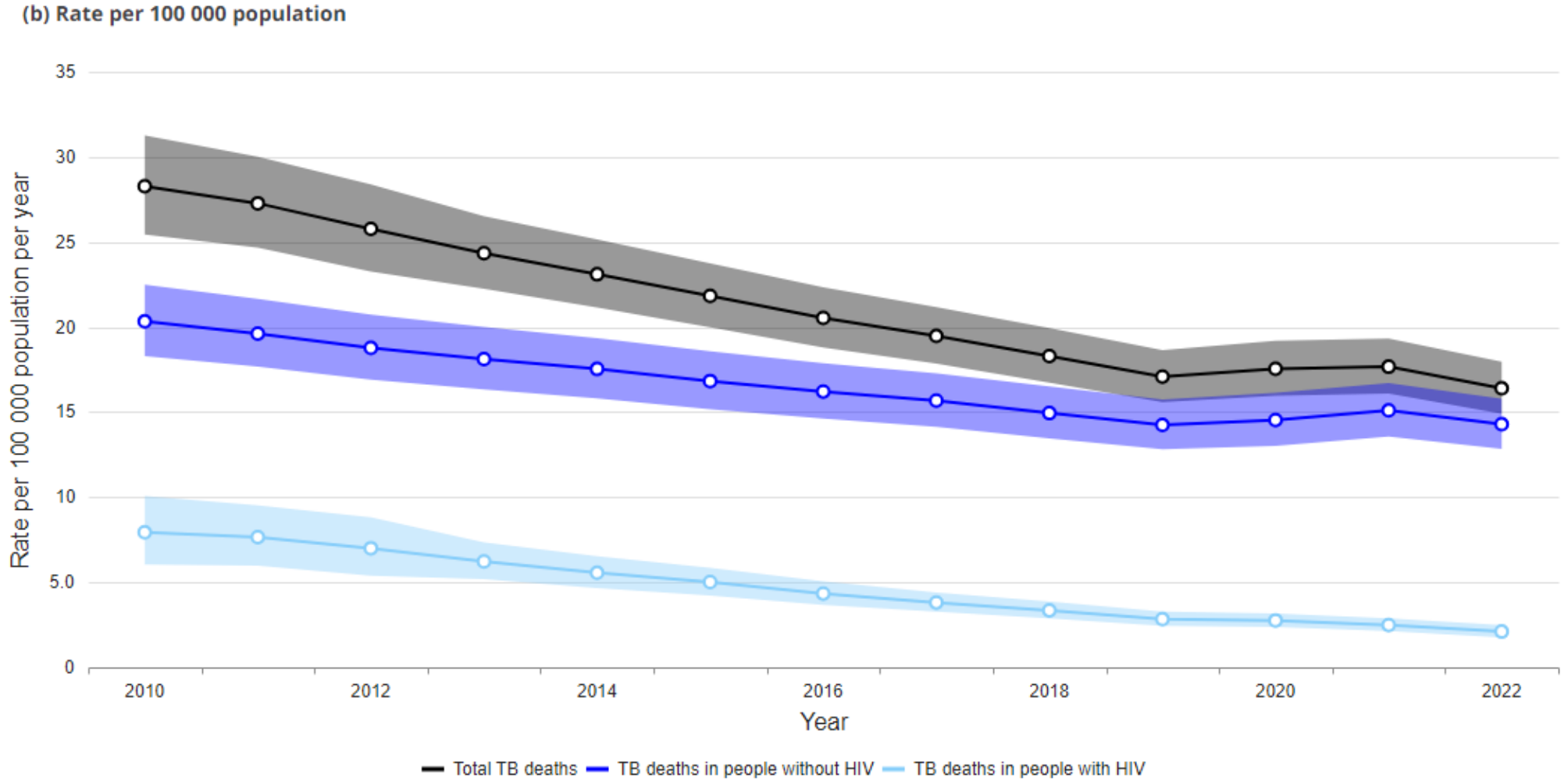
Tuberculosis Incidence: Global and CH



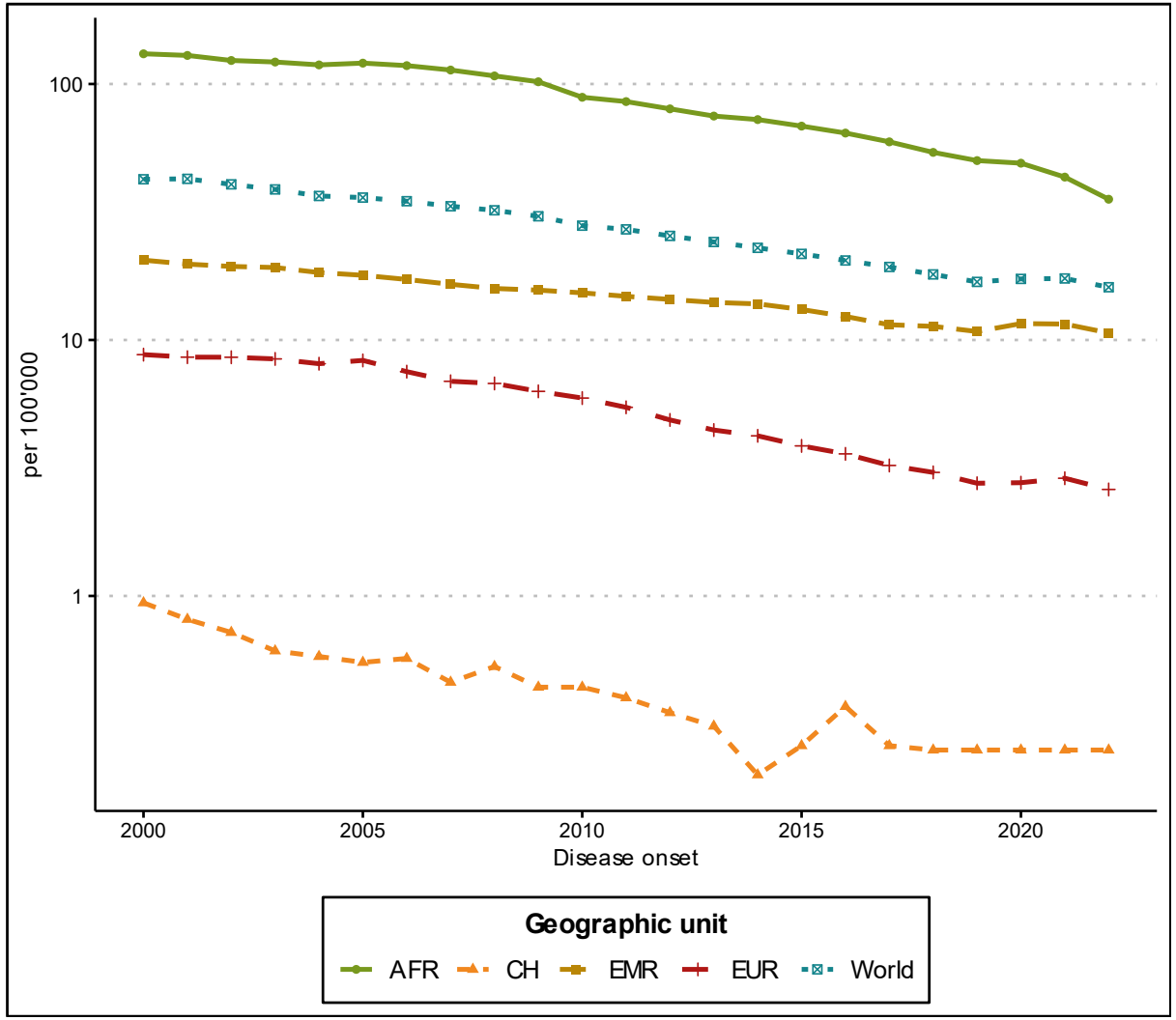
Tuberculosis Incidence in 2022



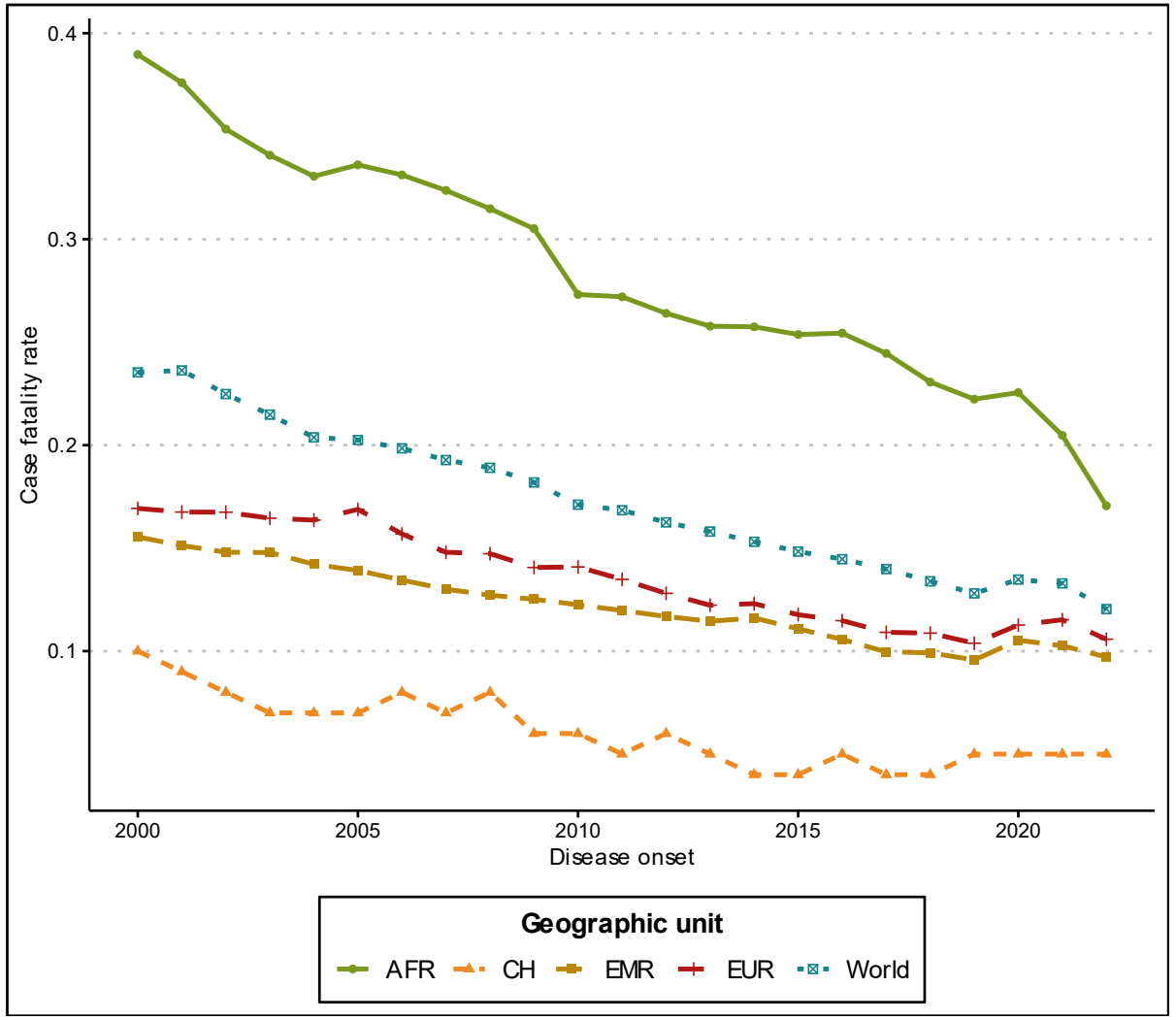
Tuberculosis Mortality: Global



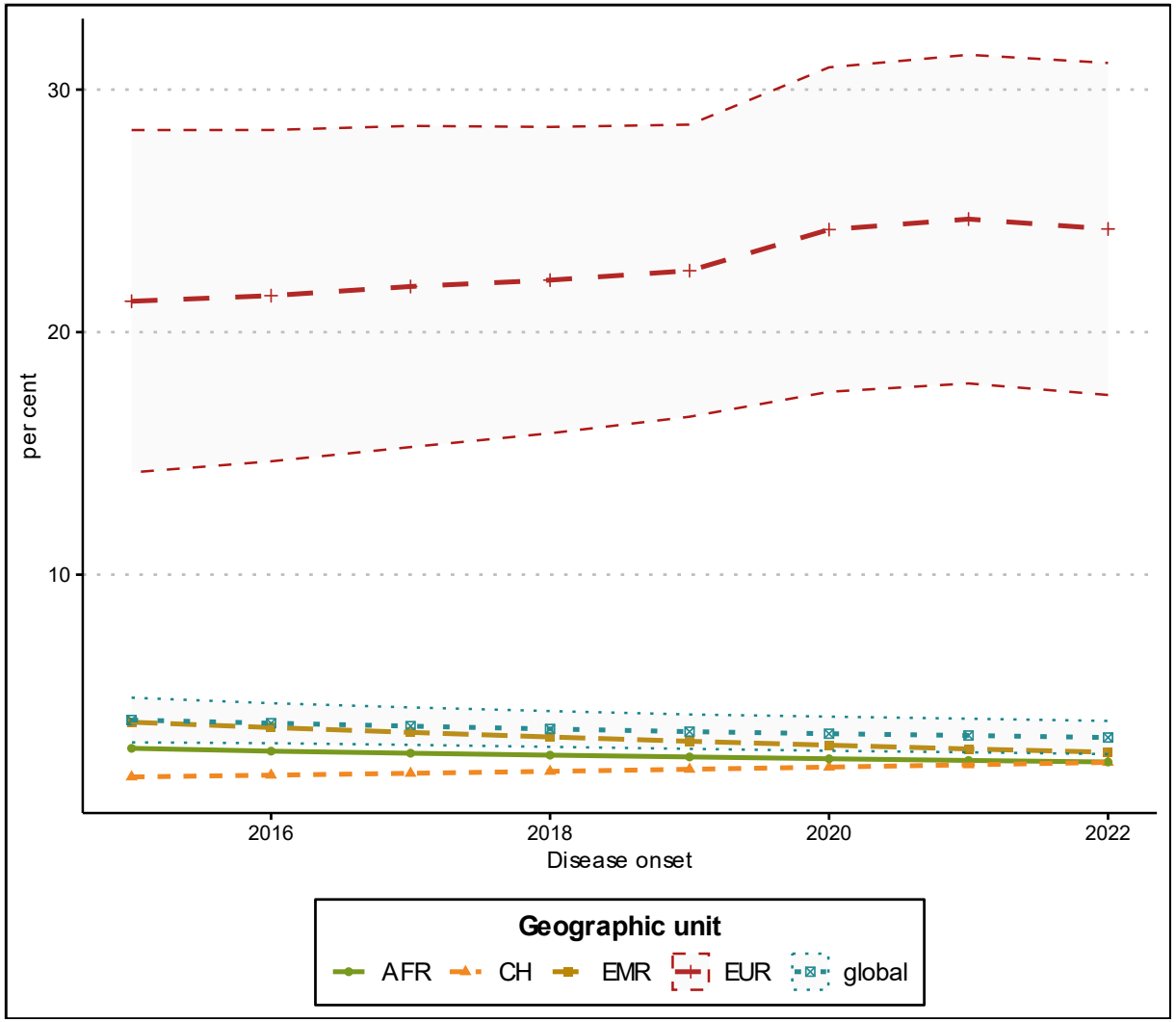
Tuberculosis Mortality: Global and CH



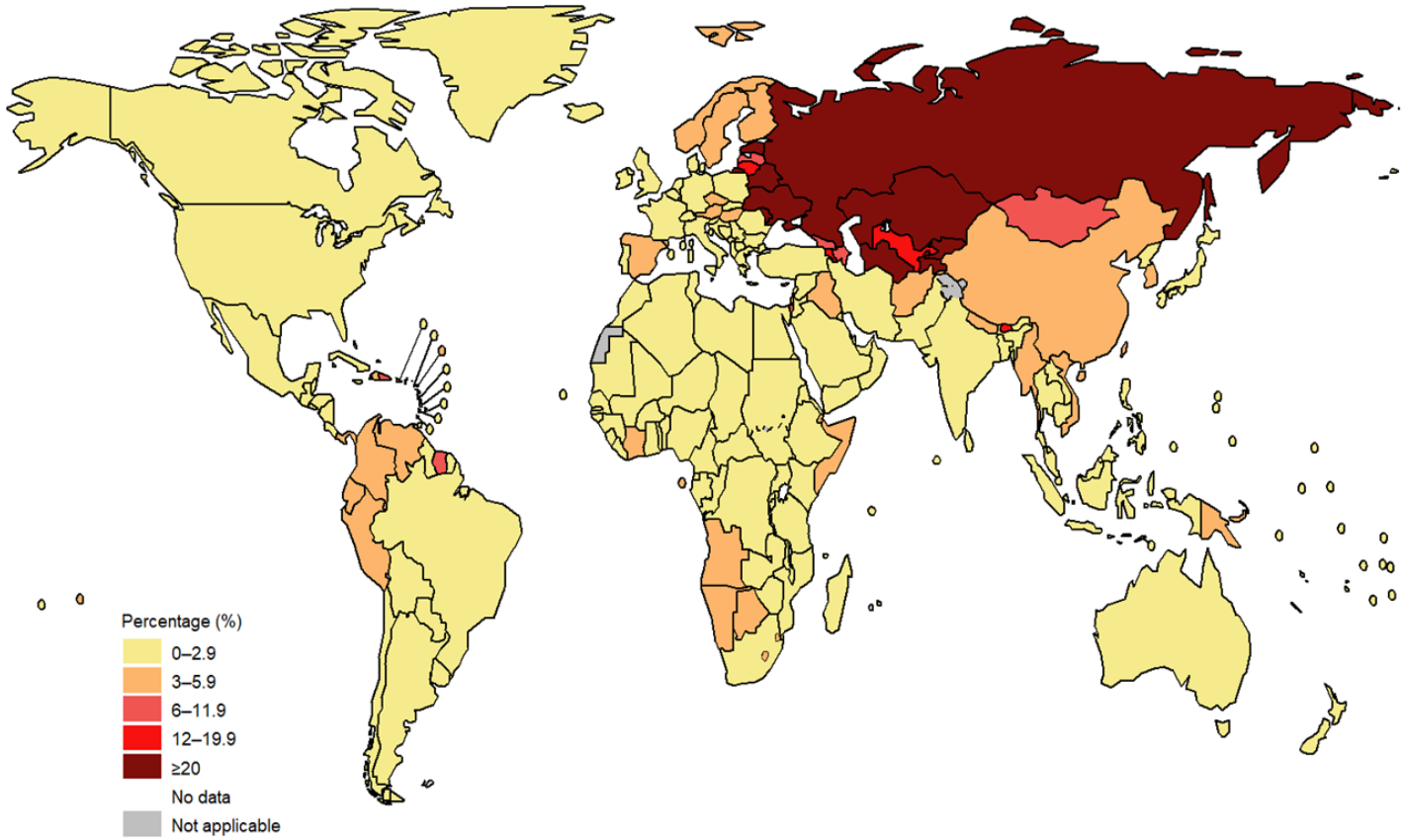
Tuberculosis Case Fatality Rate: Global and CH



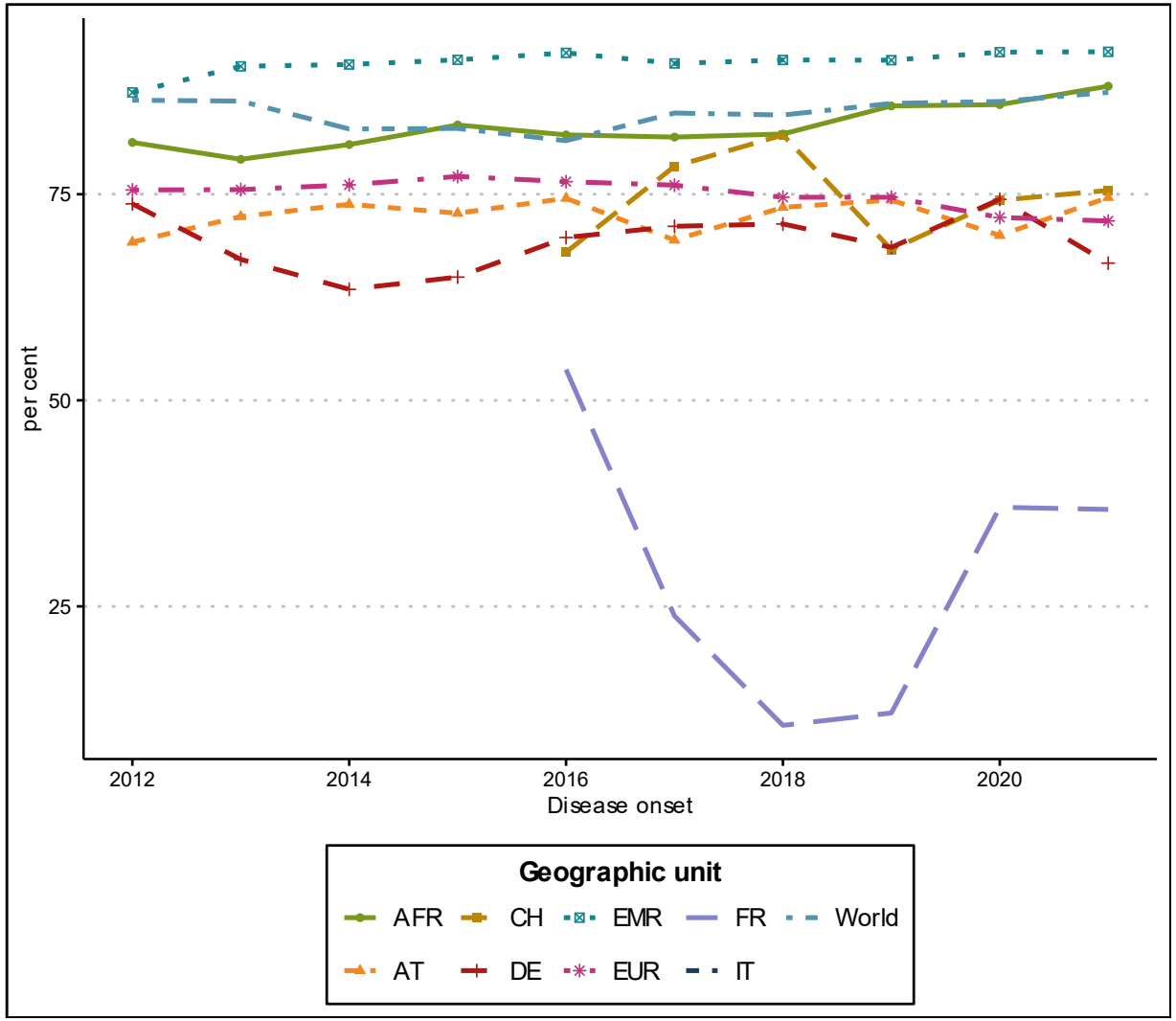
Tuberculosis R-Resistance for those with no previous history of TB treatment: Global and CH



Tuberculosis R-Resistance in 2022 with no previous history of TB treatment

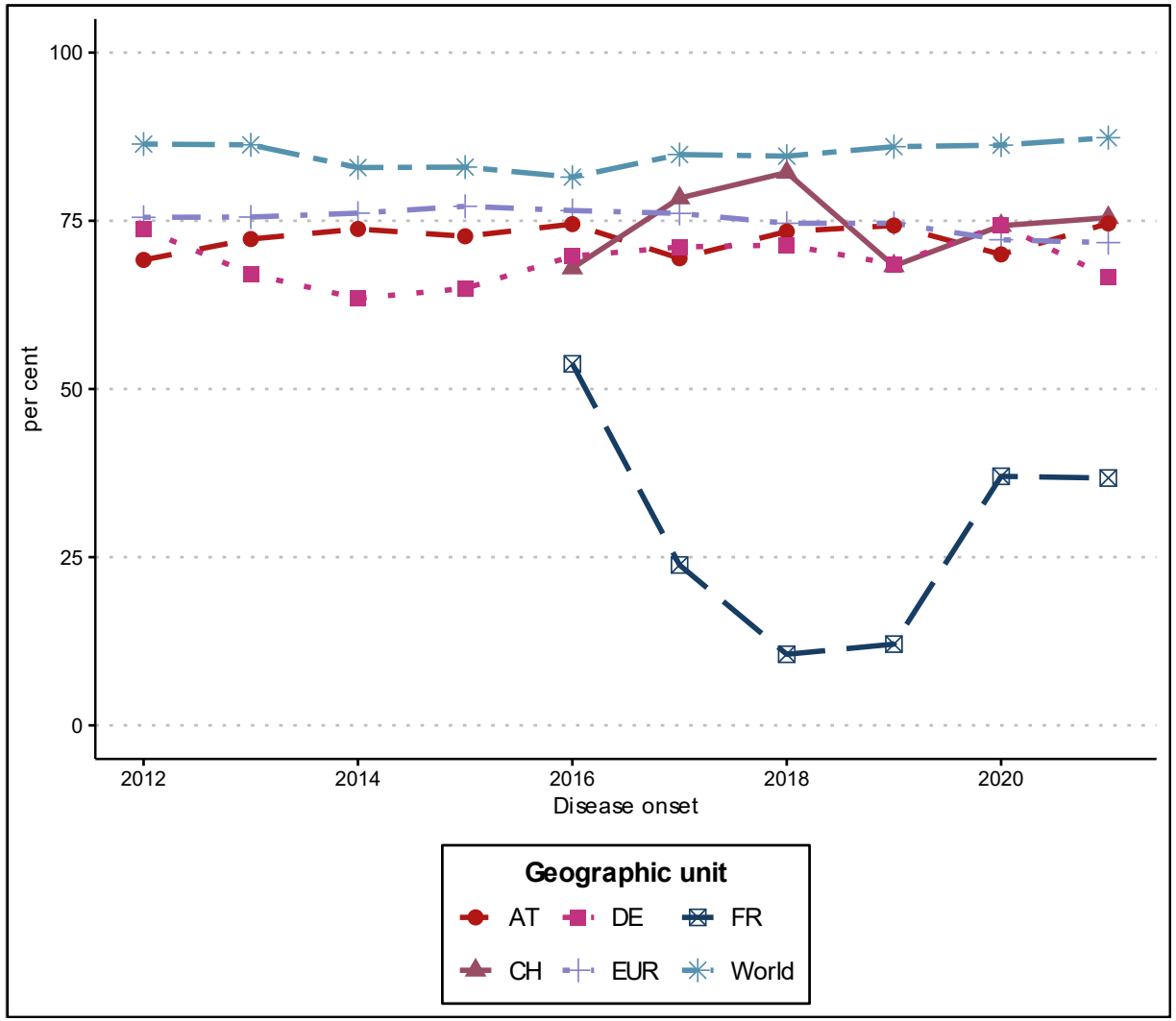


Tuberculosis Treatment Success: Global and CH

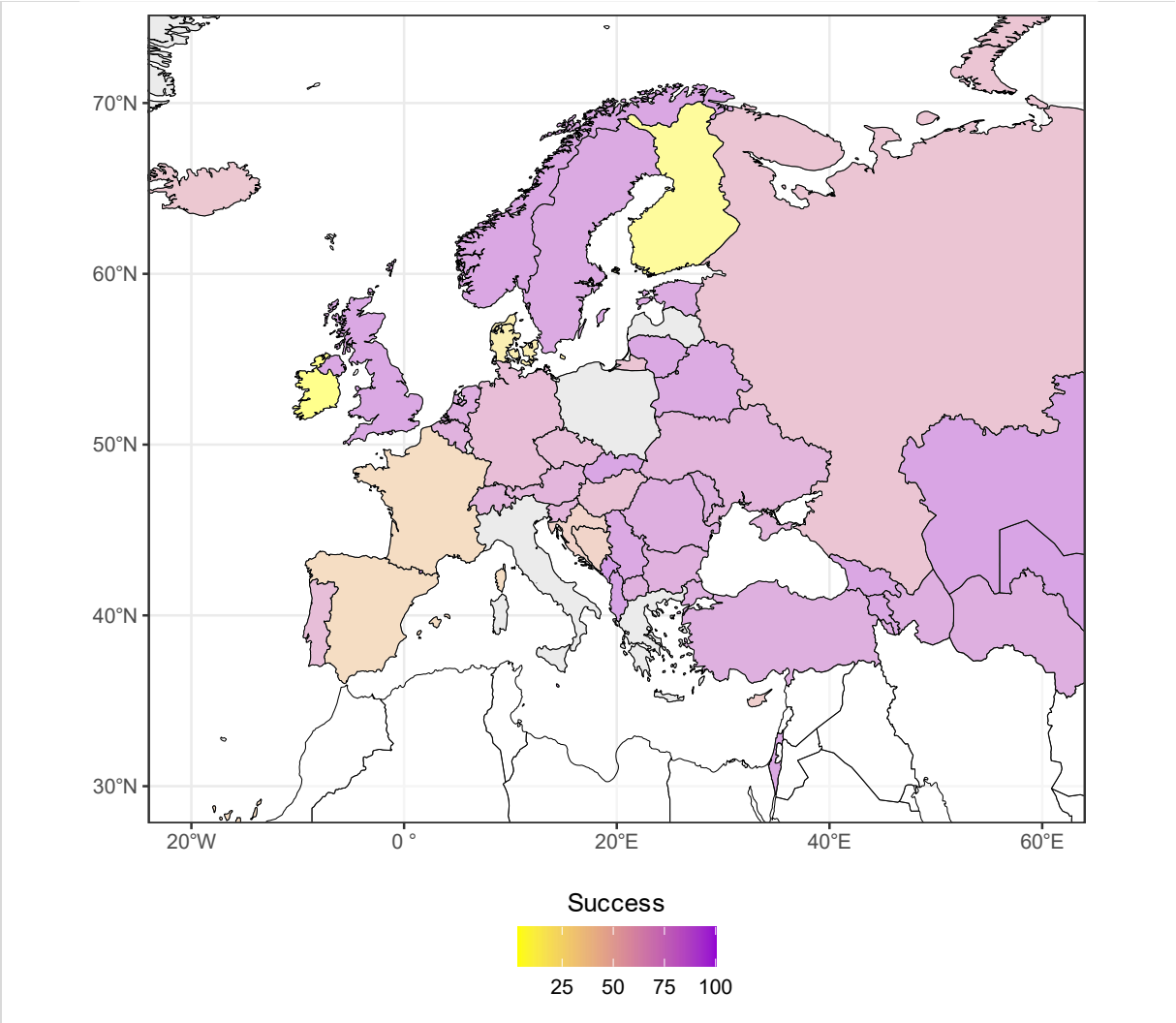


Tuberculosis Treatment Success: CH and Neighbouring Nations

IT does not report treatment success



Tuberculosis Treatment Success in 2021

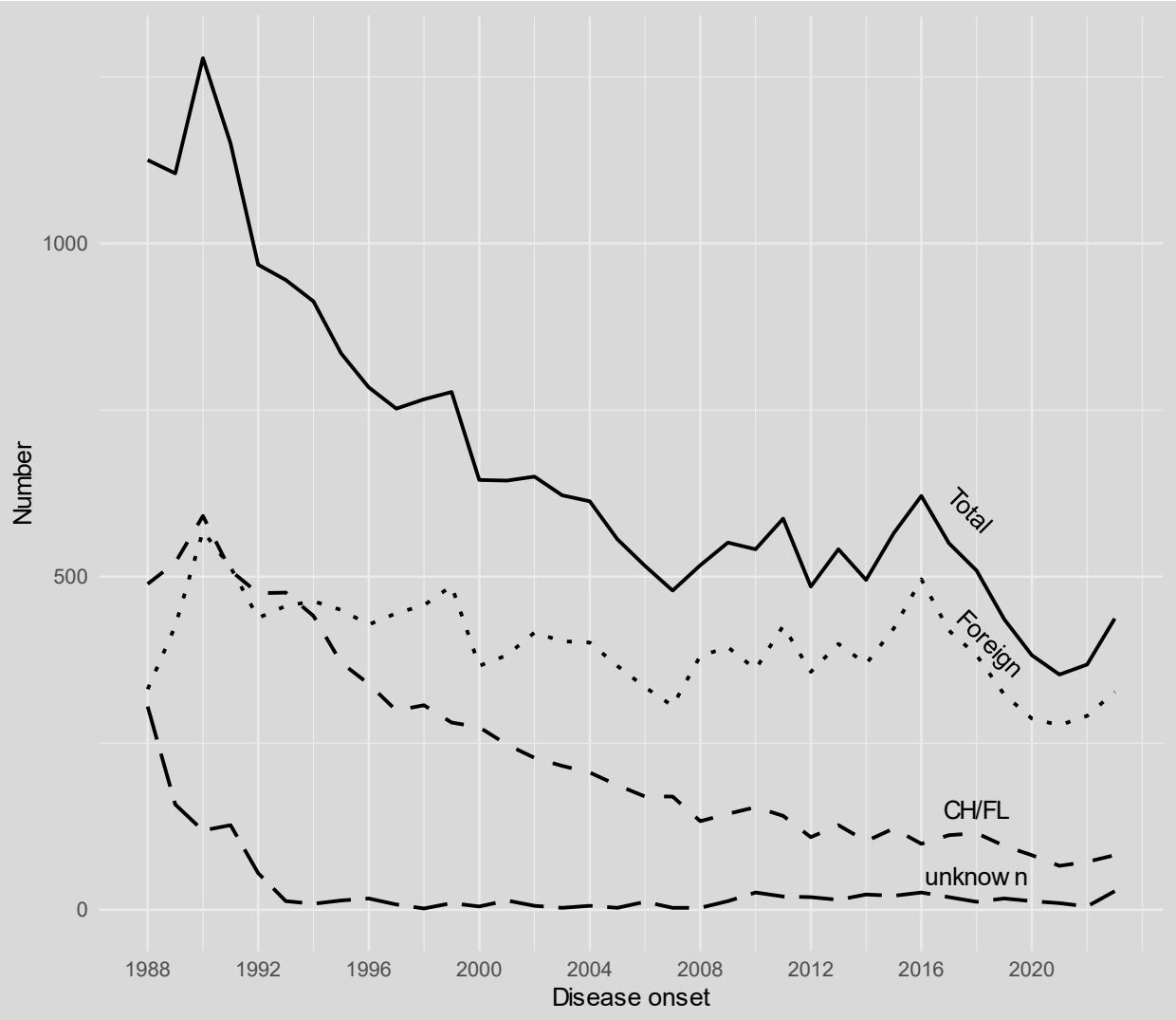


Tuberculosis in Switzerland (CH) and the Principality of Liechtenstein (FL)

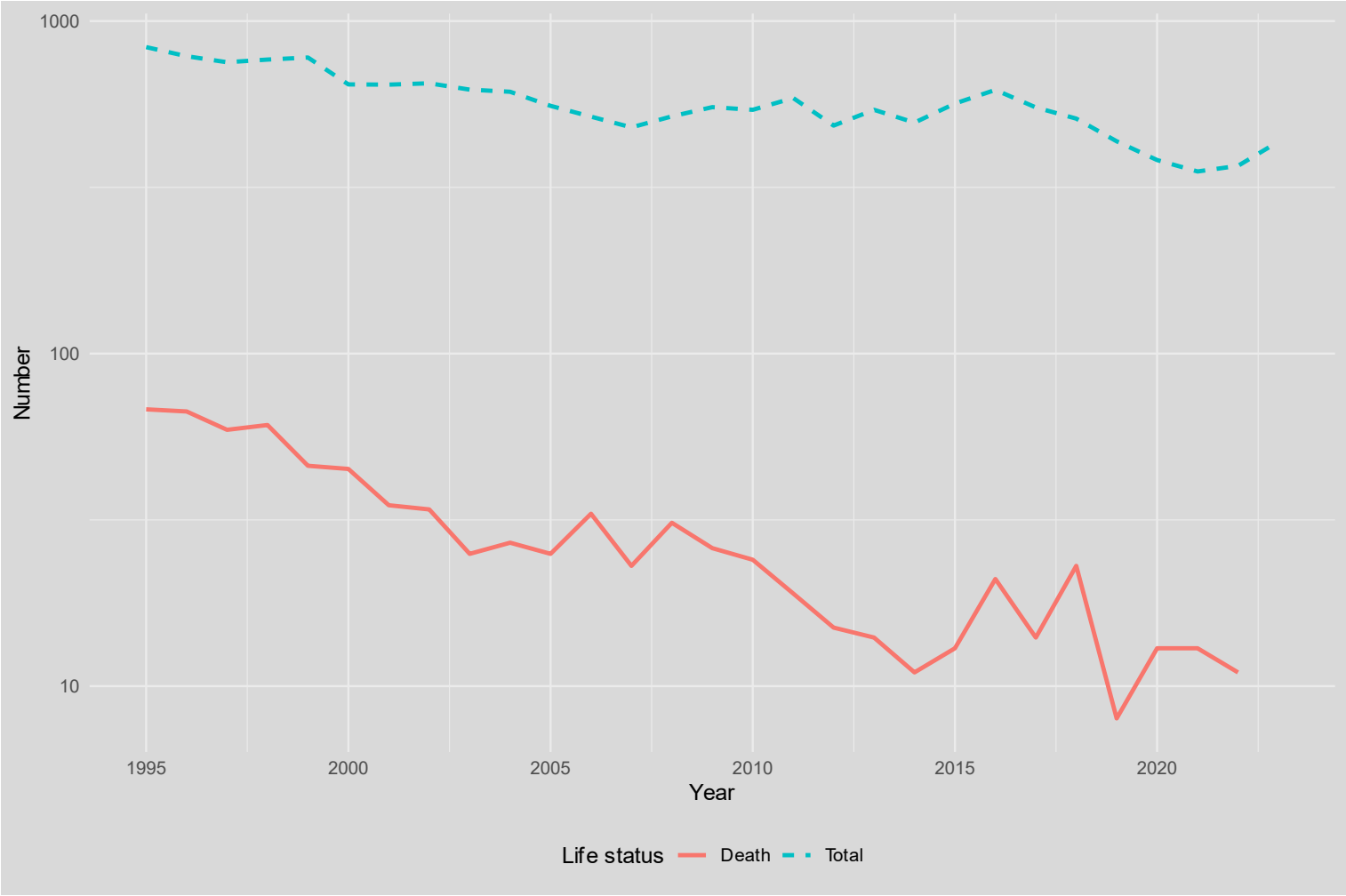
1988 to 2023

Tuberculosis in CH and FL

1. Data quality improved between 1988 to 2023.
2. Migration influences case numbers.
3. The pandemic led to a dip in case numbers.

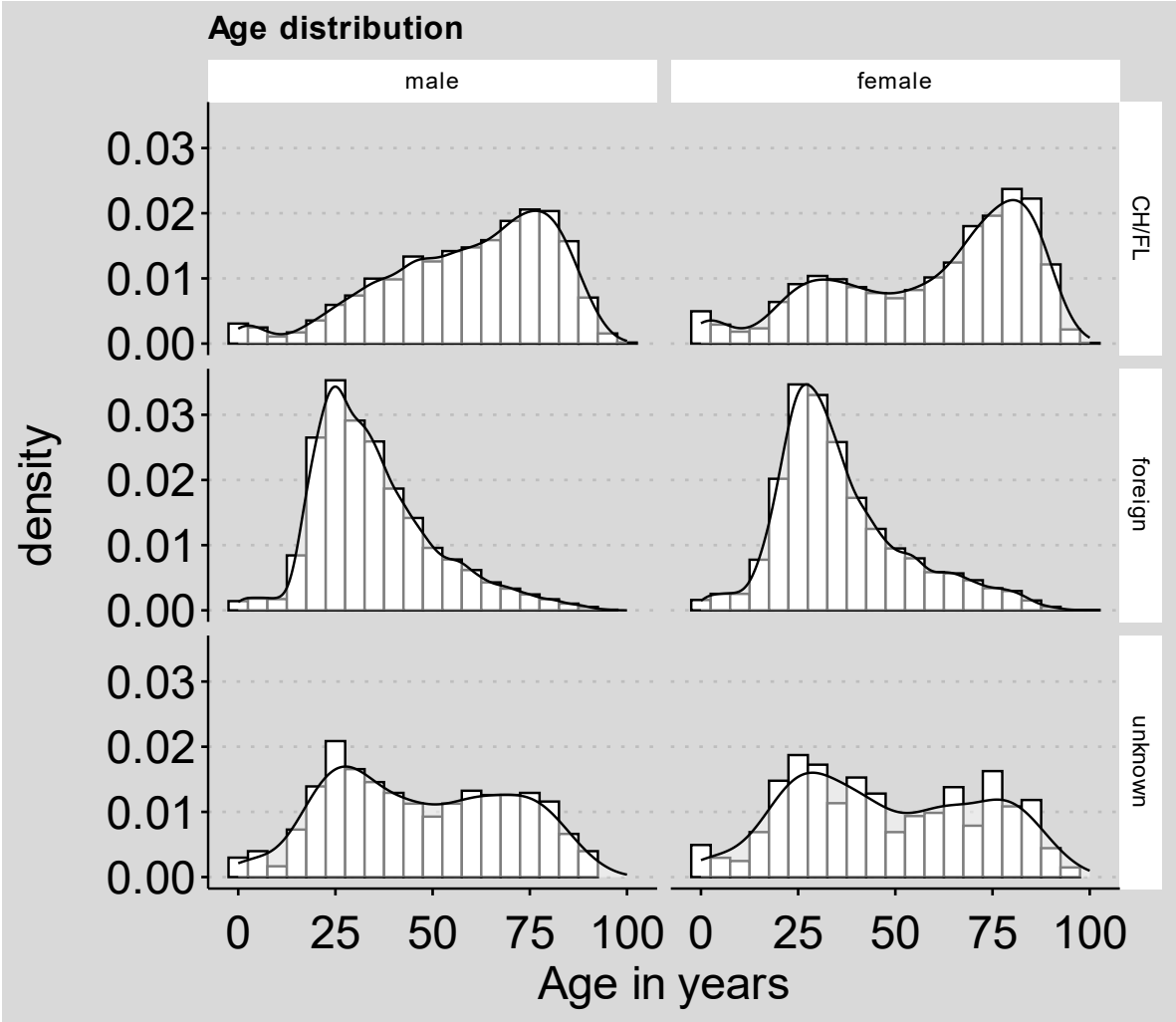


Tuberculosis in CH and FL by Life status



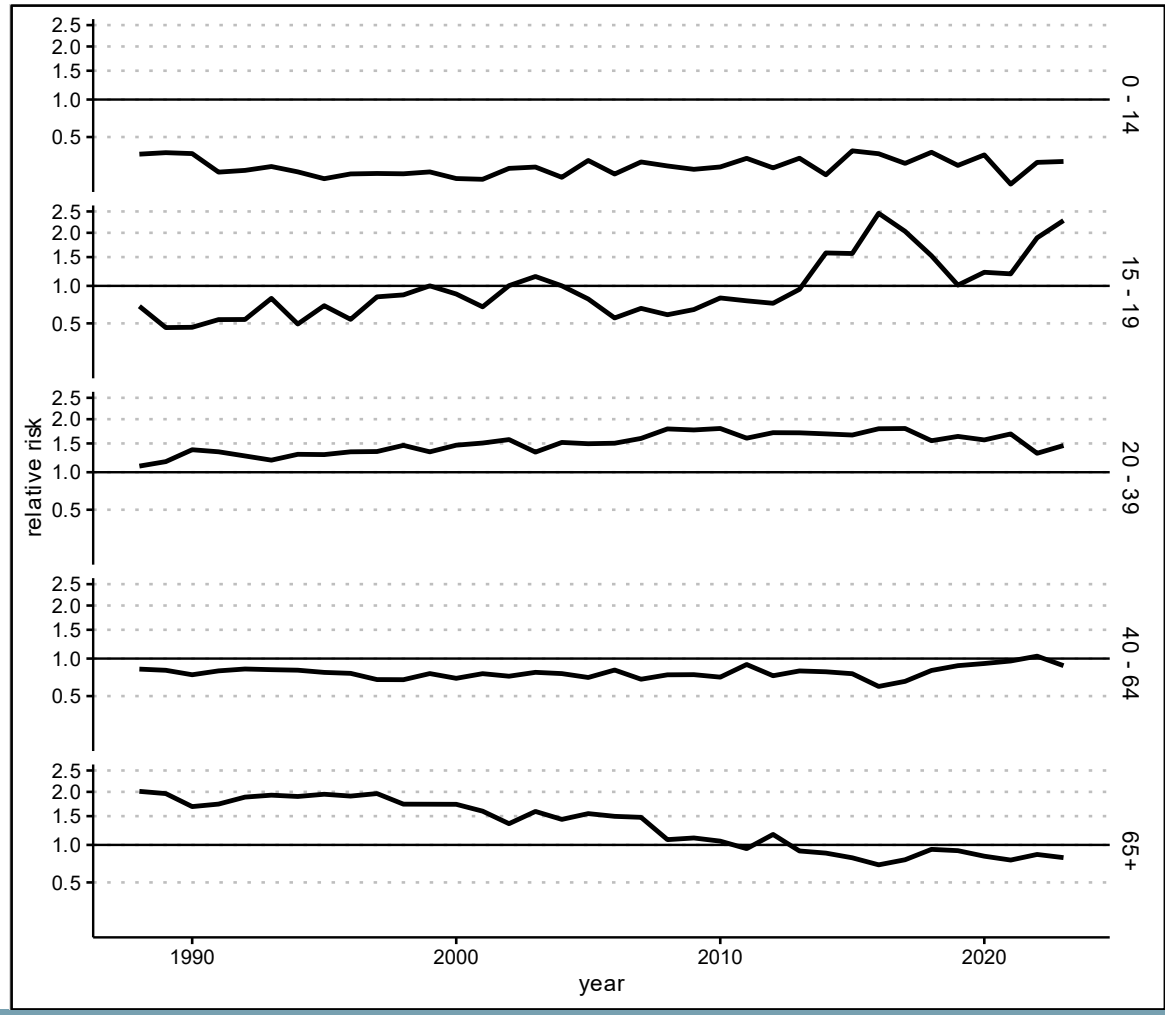
Tuberculosis: Age distribution - 1988 to 2023

1. Majority of cases are foreigners
2. Cases of foreign origin are mainly young adults (UMA)
3. Broad age distribution in the CH/FL population.
4. Constant over time?



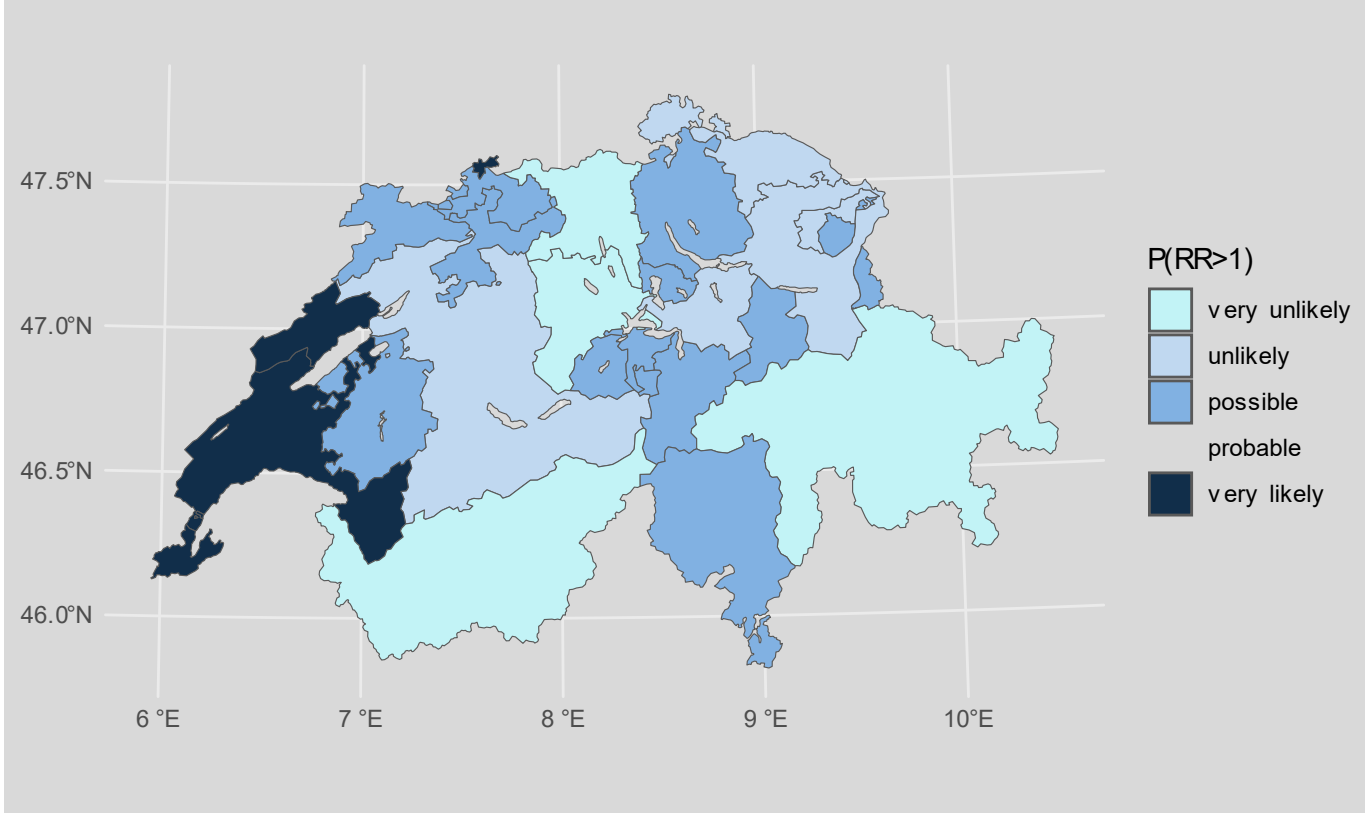
Tuberculosis: Age distribution - 1988 to 2023

1. The relative risk is the ratio of the age-specific incidence and the raw incidence.
2. Children have lower and constant incidences.
3. The relative risk of adolescents increases over time.
4. Young adults have higher incidences than expected and is constant over time.
5. Elderly adults have lower and constant relative risks.
6. The relative risk in seniors is decreasing over time.



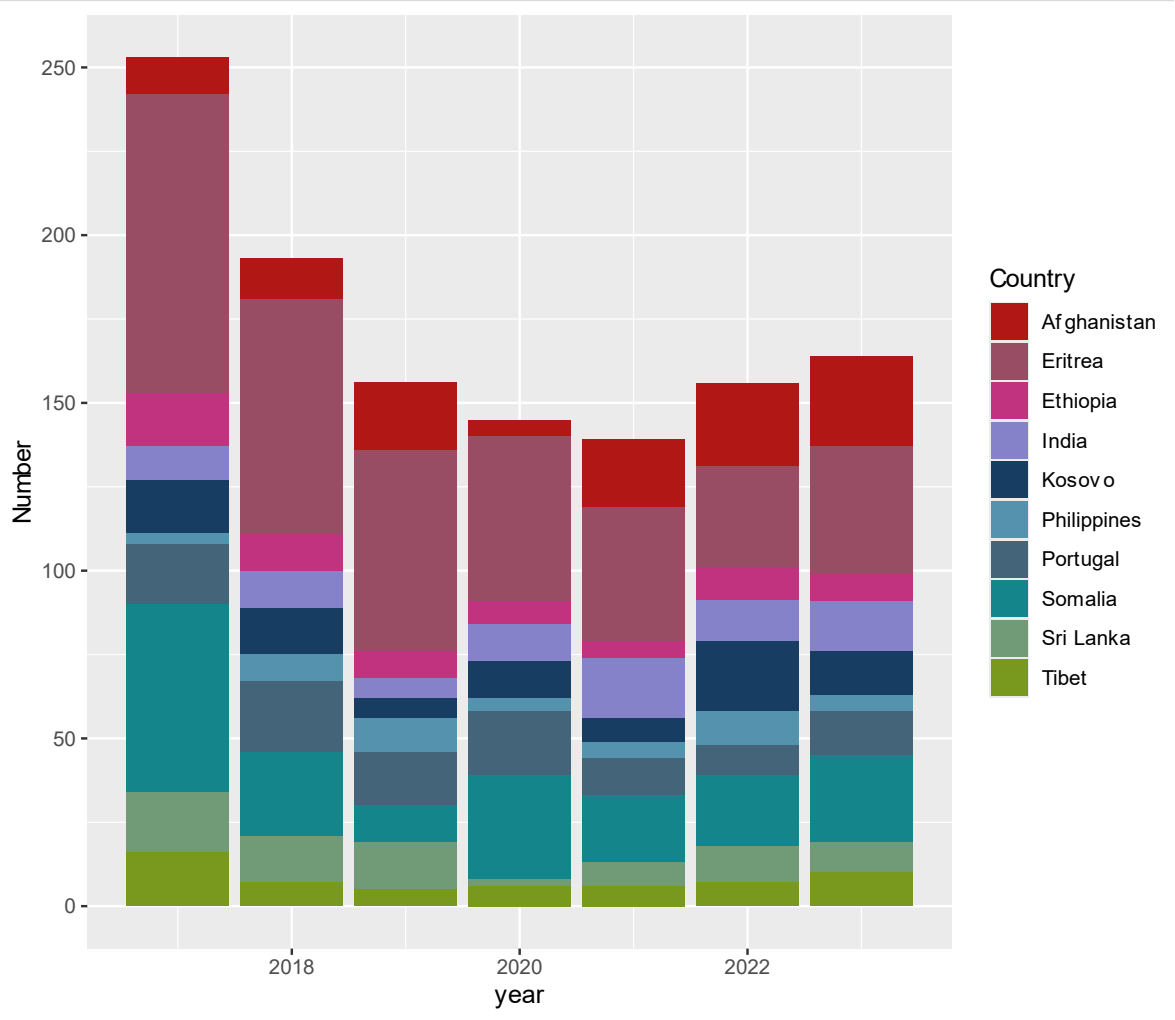
Tuberculosis: Clustering - 2021 to 2023

1. The relative risk is the ratio of observed case numbers to the expected numbers.
2. The expected case numbers are calculated by assuming constant incidence over Switzerland.
3. The random fluctuation of the RR is calculated by a Bayesian model which allows to estimate the probability that the RR is higher than one. This probability is classified: 0 to 0.05, 0.05 to 0.20, 0.20 to 0.80, 0.80 to 0.95 and 0.95 to 1.00
4. Increased RR in GE, VD, JU, BS.
5. Decreased RR in VS, GR, LU, SH.



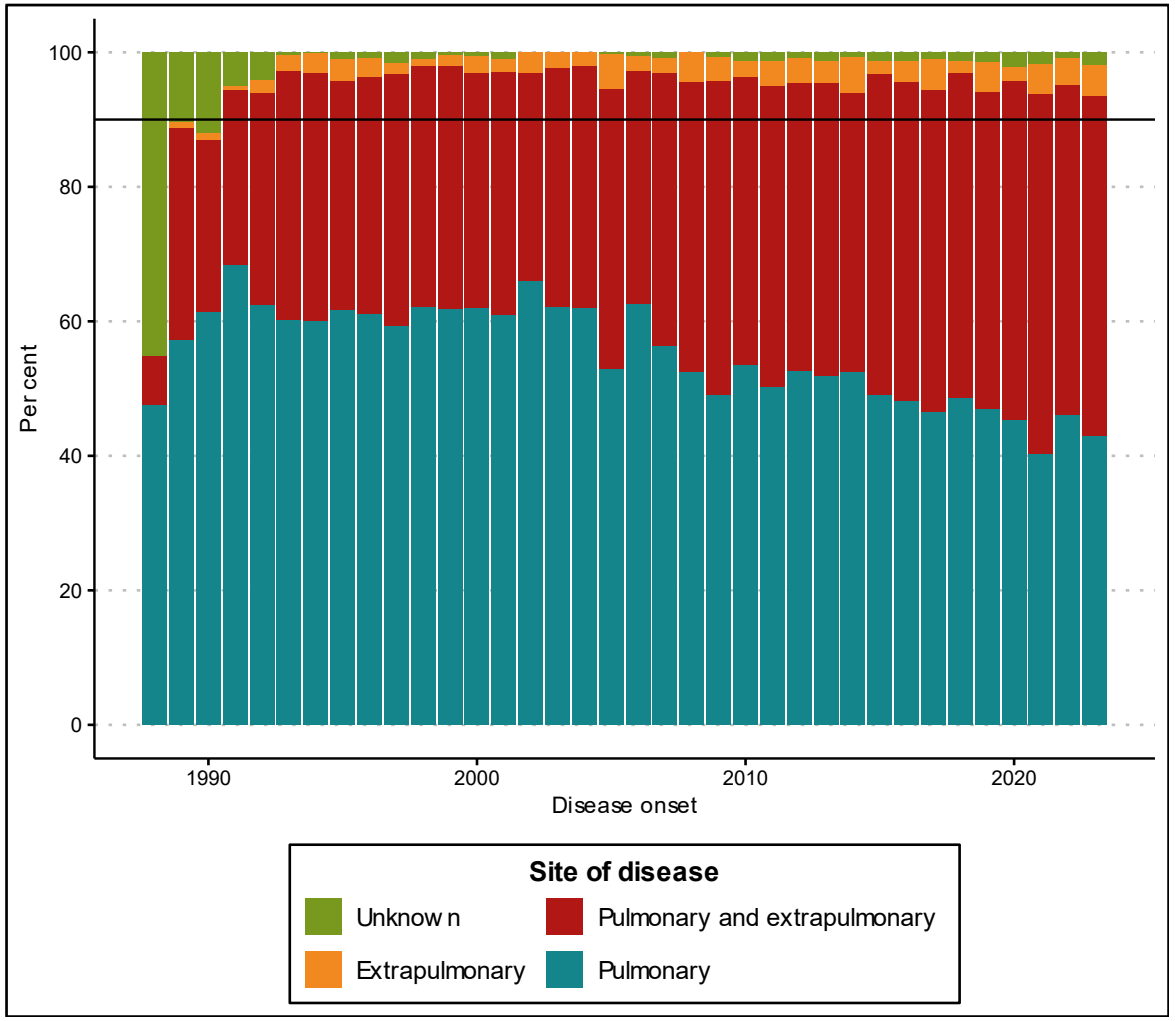
Tuberculosis: Top 10 Origin - 2017 to 2023

1. Most cases from Somalia/Eritrea
2. Increasing proportion from Afghanistan.



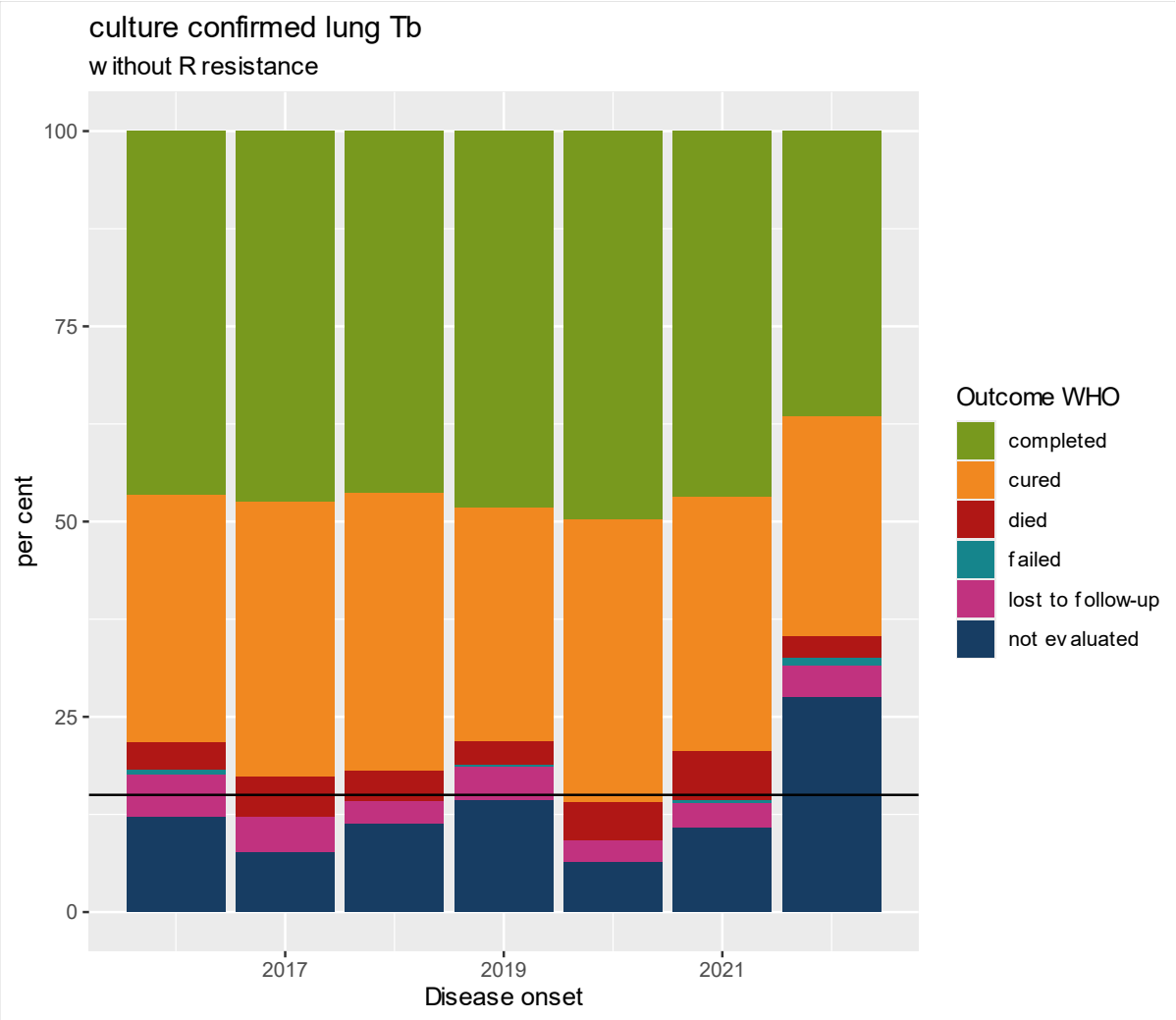
Tuberculosis: Site of Disease 1988 to 2023

1. Data quality improved.
2. Over 90% with lung involvement.
3. Purely extrapulmonary involvement is rare.



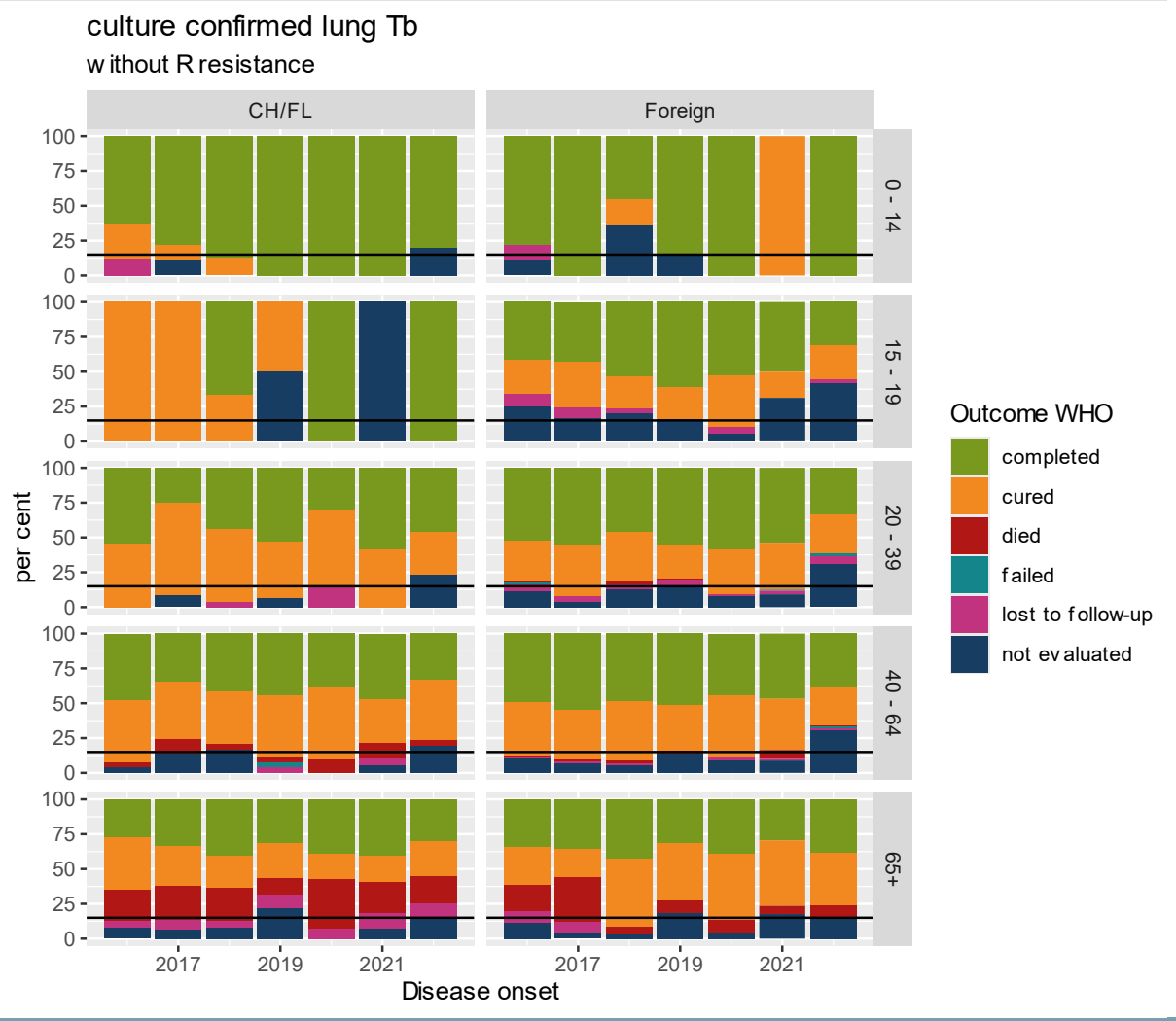
Tuberculosis: Treatment Outcomes since 2016

1. WHO targets not reached.
2. Success is frequent, failure is rare.
3. Cave: lost to follow-up and not evaluated is too frequent and has increased substantially in 2022.



Tuberculosis: Treatment Outcomes since 2016 in CH and FL

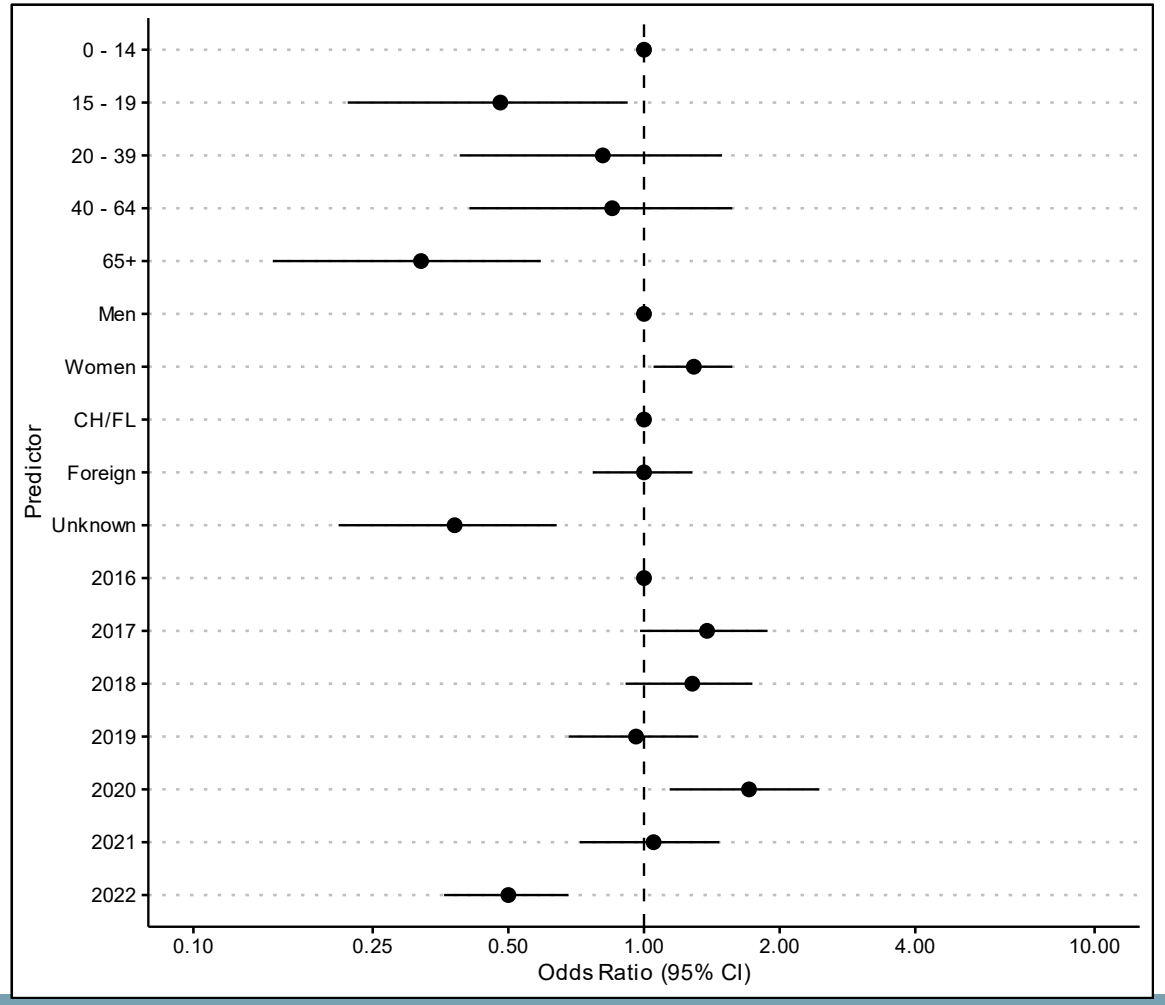
1. WHO targets not reached in most situations.
2. Success is frequent, failure is rare.
3. Cases of lost to follow-up and not evaluated are too frequent.
4. Lost to follow-up and not evaluated increases more or less during the pandemic especially in the foreign population and in the over 15 years old.
5. What is the driving force to predict success?



Tuberculosis: Treatment Outcomes since 2016 in CH and FL

Bayesian logistic regression model (N=2741)

- The reference are male children under 14 years been born in CH/FL with an estimated success of 85% in 2016.
- 15 to 19 years old and 65+ have lower success.
- Women have higher success odds.
- People of unknown origin have lower success.
- The treatment cohort of 2022 has a lower success. The one of 2020 has a higher success



Conclusions

Conclusions

1. Tuberculosis is decreasing over time worldwide with respect to
    1. Incidence
    2. Mortality
    3. Case Fatality Rate
2. Migration drives the epidemiology of TB in CH and FL.
3. RR/MDR-TB is a disease of eastern European countries and is increasing there.
4. TB affects mainly the lung, however, purely extrapulmonary disease is present.
5. Treatment outcome monitoring is of limited value due to substantial gaps.

    The proportion of lost to follow-up and not evaluated cases is too high.

    The target of 85% success is not met and the new WHO-target of 95% is unachievable without additional measures.
6. TB is not yet on the rise worldwide or in CH and FL until 2022, but rises afterwards.

Acknowledgement

- Hazim Timimi, WHO, Geneva
- Annora Mack, FOPH, Bern
- Mirjam Mäusezahl, FOPH, Bern
- Philipp Ludin, FOPH, Bern
- All my colleagues from the FOPH for their support
- The declaring physicians, hospitals, laboratories in Switzerland and the Principality of Liechtenstein.
- The cantonal physicians and the Landesphysicus of Liechtenstein for their patience with me during the process of cleaning the data.
- The lung leagues for caring of the TB patients.

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Swiss Confederation

Bundesamt für Gesundheit BAG
Office fédéral de la santé publique OFSP
Ufficio federale della sanità pubblica UFSP
Federal Office of Public Health FOPH

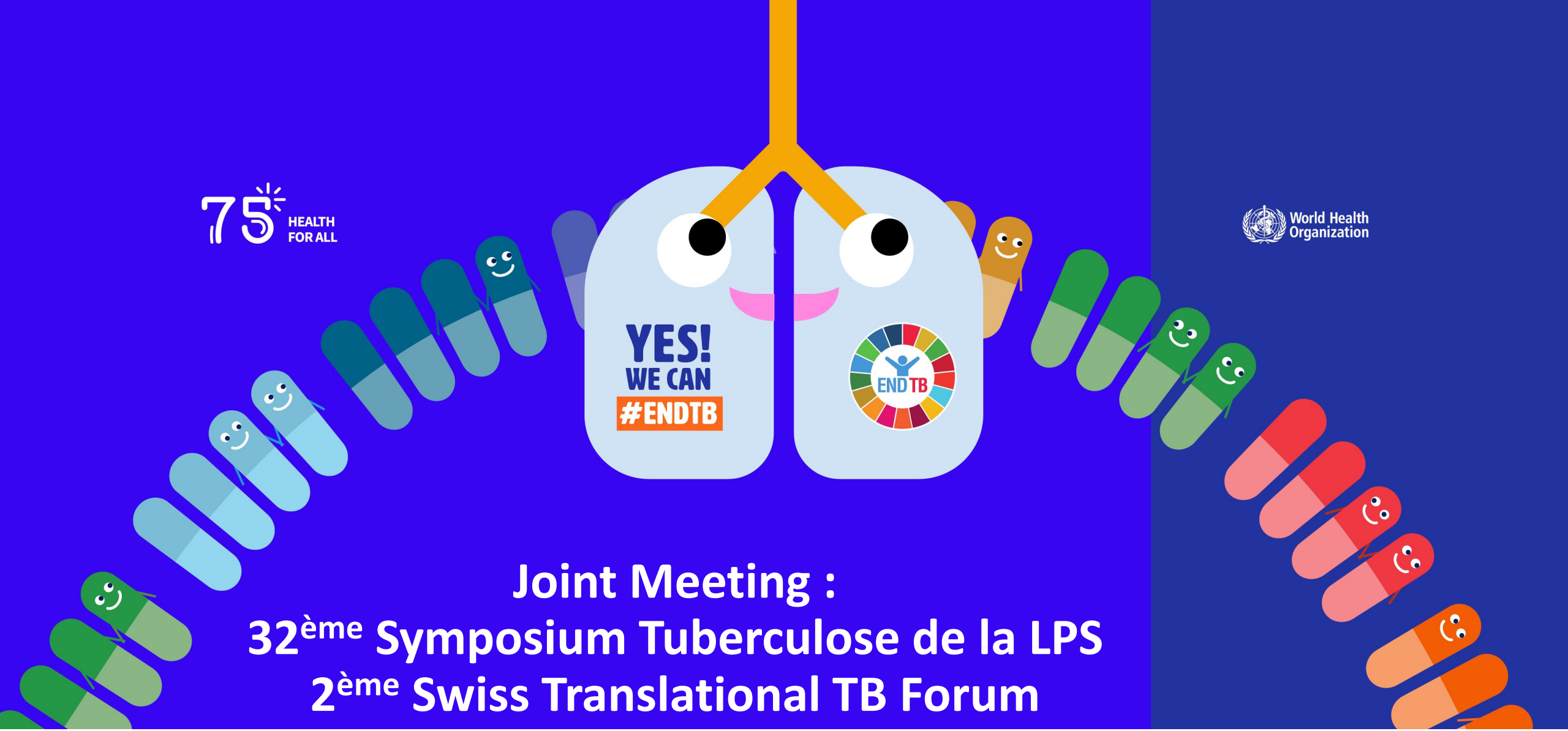
Thank you for your interest in TB.

Joint TB-Meeting:
32. Tuberkulose-Symposium der LLS
2. Swiss Translational TB Forum

Pause und Gruppenverteilung

Swiss Translational TB Forum

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA



Pause et répartition par groupe

Swiss Translational TB Forum

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA

News aus der Forschung (EN) | Raumwechsel!
Actualité de la recherche (ANG) | Changement de salle !

10.00 **What are B cells doing during TB, and does it matter?**

Carolyn King, Research group Leader

10.30 **cMYC expression determines the outcome of macrophages**

Edoardo Sarti, University Hospital of Zürich

10.40 **Exploring Immune-Stromal cell interactions during Tuberculosis**

Tiphaine Camarasa, Infection Immunology Lab, Department of Biomedicine, University of Basel

10.50 **Exploring the mechanisms of Mycobacteria-mediated membrane damage: Small or catastrophic, two types of damages leading to different bacterial fates**

Céline Michard, Department of Biochemistry, Faculty of Science, University of Geneva

News aus der Praxis | Hauptsaal
Actualités du terrain | Salle principale

10.00 **Das neue Handbuch**

Otto Schoch, Facharzt Pneumologie und Schlafmedizin | Kantonsspital St. Gallen

Le nouveau manuel

Otto Schoch, spécialiste en pneumologie et médecine du sommeil | Hôpital cantonal de St-Gall

10.15 **Vorstellung von zwei Fällen komplexer Umgebungsuntersuchungen**

Annett Hunger, Lungenliga Ost

Veronica Maglio, Lungenliga Waadt

Présentation de deux cas d'enquêtes d'entourage complexes

Annett Hunger, Ligue pulmonaire Est

Veronica Maglio, Ligue pulmonaire vaudoise

Mit Unterstützung von
Avec le soutien de

QIAGEN

Diasorin

Swiss Translational
TB Forum

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA

Geschichte Tuberkulose Handbuch

- 2003 erstmals erstellt durch ***Jean-Pierre Zellweger***, Lungenliga Schweiz / BAG
- Revision 2011

- 2014 neues Konzept als Leitfaden mit Einbezug von «organizational authors», koordiniert durch ***Hans Rieder***

- 2017/2018 Überarbeitung koordiniert durch ***Otto Schoch*** mit Einbezug weiterer Organisationen, zB SUVA, Spitalhygiene, (kleinere Anpassungen 2019 und 2021)

- 2023/2024 Neue Erarbeitung der aktuellen Version des Handbuchs

Lungenliga Schweiz (LLS)
Sägestrasse 79
3098 Köniz
info@lung.ch
www.lungenliga.ch

Auskunft Tuberkulose
Kompetenzzentrum Tuberkulose
Sägestrasse 79
3098 Köniz
Tel. 031 378 20 50
tbinfo@lung.ch
www.tbinfo.ch

Herausgeber
Lungenliga Schweiz
Bundesamt für Gesundheit

Konzept und Layout
Giessform GmbH, Bern

28 Einzelautoren
16 «organizational authors»
>> COVID
>> Stellenwechsel TB Kompetenzzentrum

Einzelautoren, einschliesslich Vertreter der institutionellen Autoren

Otto D. Schoch (coordinating author), Ekkehardt Altpeter, Christian Auer, Susanne Bänninger, Jürg Barben, Reka Blazsik, Jan Fehr, Lukas Fenner, Sebastien Gagneux, Nathalie Gasser, Gunar Günther, Christopher Huddleston, Jean-Paul Janssens, Philipp Ludin, Jesica Mazza-Stalder, Céline Moser, Johannes Nemeth, Stefan Neuner-Jehle, Adjua Alexandra N'Goran, Parham Sendi, Marco Pons, Nicole Ritz, Peter Sander, Matthias Schlegel, Melody Schmid, Bettina Schulthess, Michèle Widmer, Jean-Pierre Zellweger.

Institutionelle Autoren

Bundesamt für Gesundheit
Lungenliga Schweiz
Nationales Zentrum für Mykobakterien
Pädiatrische Infektiologiegruppe Schweiz
Schweizerische Fachgesellschaft für Tropen- und Reisemedizin
Schweizerische Gesellschaft der Fachärztinnen und -ärzte für Prävention und Public Health
Schweizerische Gesellschaft für Infektiologie
Schweizerische Gesellschaft für Pädiatrische Pneumologie
Schweizerische Gesellschaft für Pneumologie
Schweizerische Gesellschaft für Spitalhygiene
Schweizerische Tropen- und Public Health-Institut
Schweizerische Unfallversicherung Suva
Schweizerisches Kollegium für Hausarztmedizin
Staatssekretariat für Migration
Tuberkulose-Zentrum LUNGE ZÜRICH
Vereinigung der Kantonsärztinnen und Kantonsärzte der Schweiz

Inhalt / Struktur

- **Neu mit Glossar, 12 Kapitel plus Literaturverzeichnis**
  - Rolle der behandelnden Ärztin / des behandelnden Arztes
  - Epidemiologie
  - Übertragung/Pathogenese/Klinik
  - Infektion
  - Umgebungsuntersuchung
  - Diagnose der Tuberkulose
  - Behandlung
  - Meldeverfahren
  - BCG Impfung
  - Screening bei Asylsuchenden
  - Finanzielle Aspekte und Gesetzesgrundlagen
  - Informationen und nützliche Adressen

Glossar

Directly observed therapy	DOT	Direkte Beobachtung des Schluckens der Tabletten zur Tuberkulosebehandlung
Interferon-gamma release assay	IGRA	Bluttest, der einen immunologischen Kontakt mit *M. tuberculosis* nachweist
Kantonale Tuberkulose-Fachstelle		Der Kantonsarzt oder die Kantonsärztin beauftragt eine Tuberkulose-Fachstelle, in den meisten Kantonen die kantonale Lungenliga
Latente tuberkulöse Infektion	LTBI	Historischer Begriff für TBI. Gemäss WHO Empfehlung wird der Begriff nicht mehr verwendet. Eine Infektion muss nicht immer latent (schlafend) sein
Multiresistente Tuberkulose	MDR-TB	Eine Form der TB-Erkrankung, die durch einen Stamm des *M. tuberculosis* complex verursacht wird, der gegen Rifampicin und Isoniazid resistent ist
Mycobacterium tuberculosis	*M. tuberculosis*	Säurefeste Stäbchen welche Tuberkulose verursachen
Tuberkulin Haut Test	TST	Hauttest der einen immunologischen Kontakt mit *M. tuberculosis* nachweist
Tuberkulose	TB	Durch *M. tuberculosis* ausgelöste Krankheit
Tuberkulöse Infektion	TBI	Ein Zustand von anhaltender Immunantwort auf Stimulation mit *Mycobacterium tuberculosis* antigenen ohne Hinweis auf klinisch erkennbare Tuberkulose
Weltgesundheitsorganisation	WHO	Eine Sonderorganisation der Vereinten Nationen, die für die internationale öffentliche Gesundheit zuständig ist

Epidemiologie

- **Aktualisierung mit neuen Zahlen von BAG und WHO**
- **Erwähnung des BAG Strategie-Ziele**
- **Eigenes Kapitel zum Einfluss von COVID**

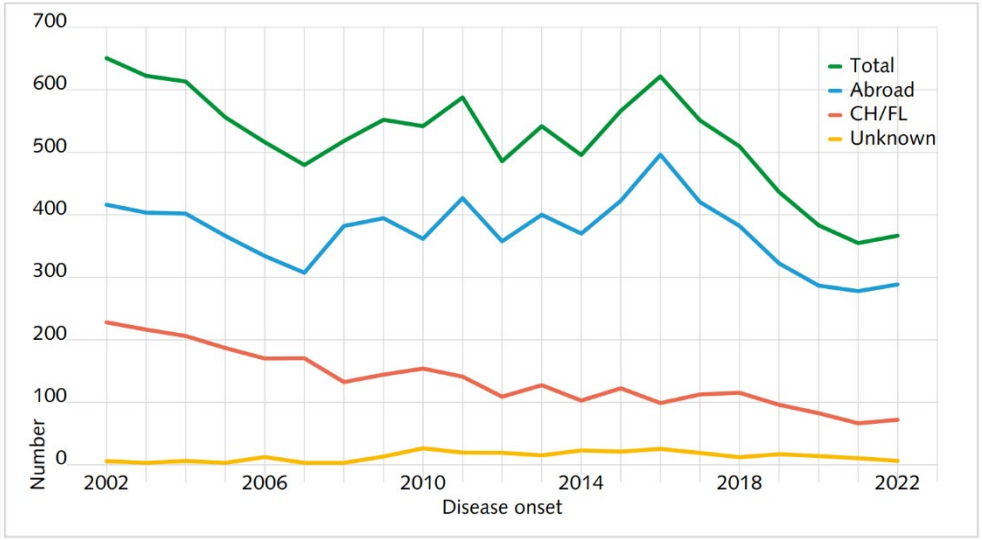
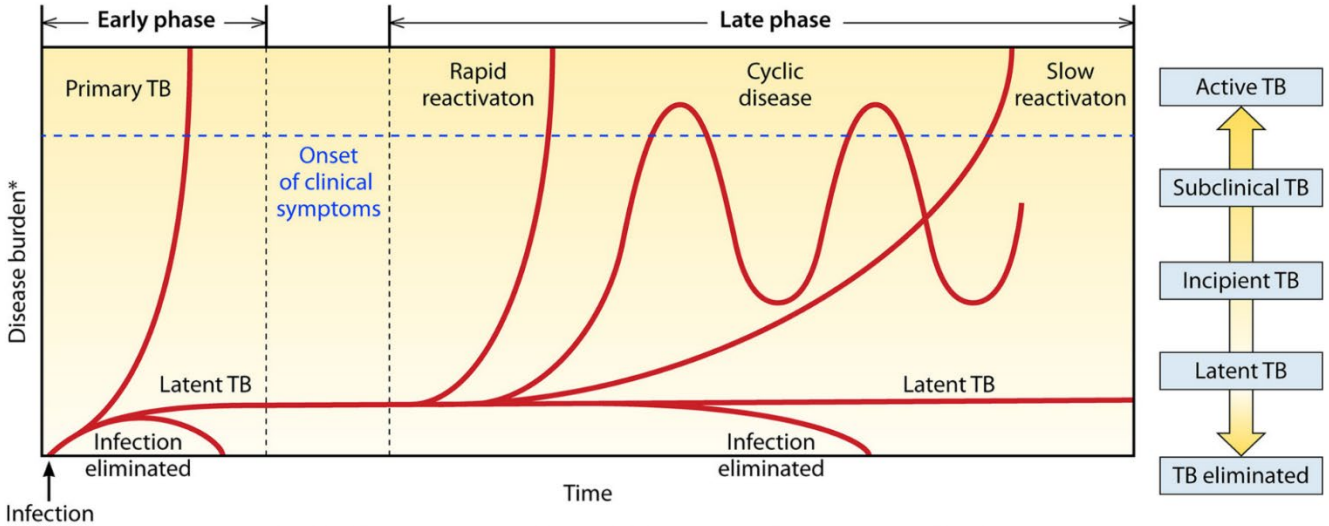


Abbildung 2-1 Dem Bundesamt für Gesundheit gemeldete Tuberkulose-Fälle in der Schweiz nach Herkunft, 2002–2022.

Übertragung/Pathogenese/Klinik

- **Konzept der «subklinischen Tuberkulose» und des «kontinuierlichen Krankheitsspektrums»**

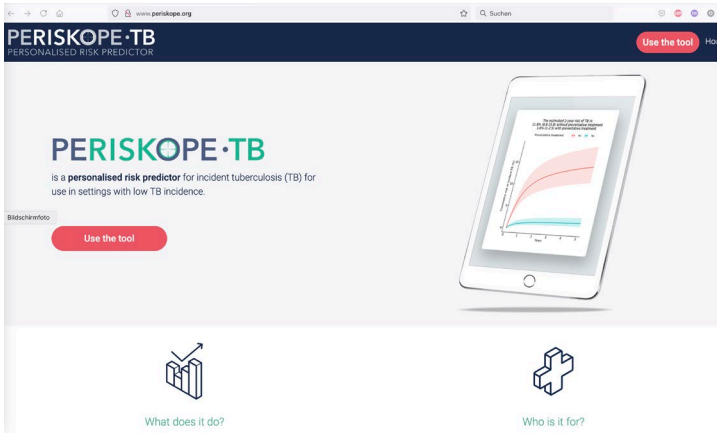


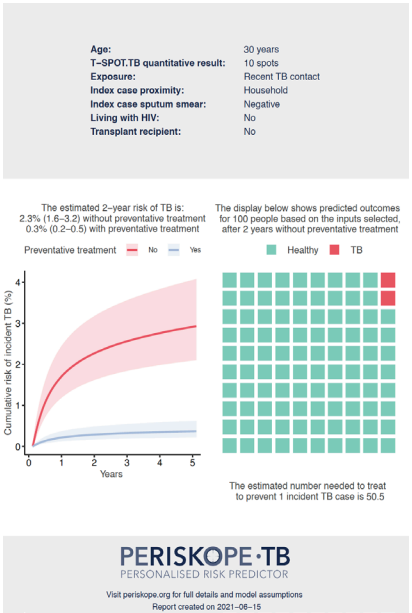
*Rising TB burden implies an increase in abundance of TB and pathogen biomarkers, compartment-specific changes in immunological responses, and a decrease in the probability of disease resolution in the absence of treatment.

Clinical Microbiology Reviews 2018, 31(4), e00021-18

Präventive TBI Behandlung

- **Aufnahme von Informationen zum «Periskope-TB»**
- **Erwähnung von Resultaten der TBI Behandlung mit wöchentlich Rifapentin / INH**





Diagnose der Tuberkulose

- **Aktualisierung des Abschnitts zu Mikrobiologischen Testverfahren**

Assay Information

Assay	Assay Version	Assay Type
Xpert MTB-RIF Ultra	4	In Vitro Diagnostic

Test Result: MTB DETECTED VERY LOW; RIF Resistance NOT DETECTED

Analyte Result

Analyte Name	Ct	EndPt	Analyte Result	Probe Check Result
SPC	23.4	160	NA	PASS
IS1081-IS6110	19.8	621	NA	PASS
rpoB1	28.4	333	POS	PASS
rpoB2	28.6	212	POS	PASS
rpoB3	29.8	147	POS	PASS
rpoB4	31.8	108	POS	PASS

Abb. 6-1. Ergebnisse von Xpert MTB/RIF Ultra. Die Analyse zeigt eine geringe Menge *M. tuberculosis* (Nukleinsäuren) ohne Hinweise auf eine RIF-Resistenz.

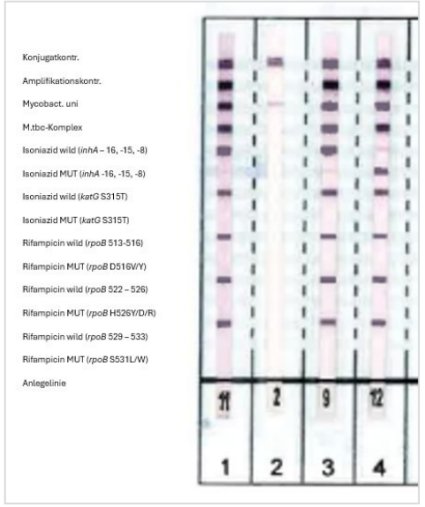


Abb. 6-2. Nachweis von Isoniazid-(INH-) und Rifampicin-(RIF-) Resistenzmutationen mittels Line-Probe-Assay (AID Diagnostika). Tests in Spur 1 und 3 zeigen Wildtyp-Banden für *inhA-Promotor, katG und rpoB* an Positionen, die häufig mit INH- und RIF-Resistenz assoziiert sind. Das Muster weist daher auf die Empfindlichkeit gegenüber INH und RIF hin. Der Test in Spur 2 ist nicht interpretierbar (geringe DNA-Menge). Der Test in Spur 4 zeigt ein Bandenmuster, das auf eine Mutation des *inhA*-Promotors hinweist, die mit der INH-Resistenz assoziiert ist.

Behandlung der Tuberkulose

- **Neu 3 MDR-TB Behandlungsschemata aufgenommen**
  - Sechs Monate Bedaquilin, Pretomanid, Linezolid und Moxifloxacin (BPaLM) als feste Medikamentenkombination. Bei einigen Patienten kann eine Verlängerung der Behandlung über 6 Monate hinaus sinnvoll sein.
  - >18 Monate individualisierte MDR-TB Therapieoption

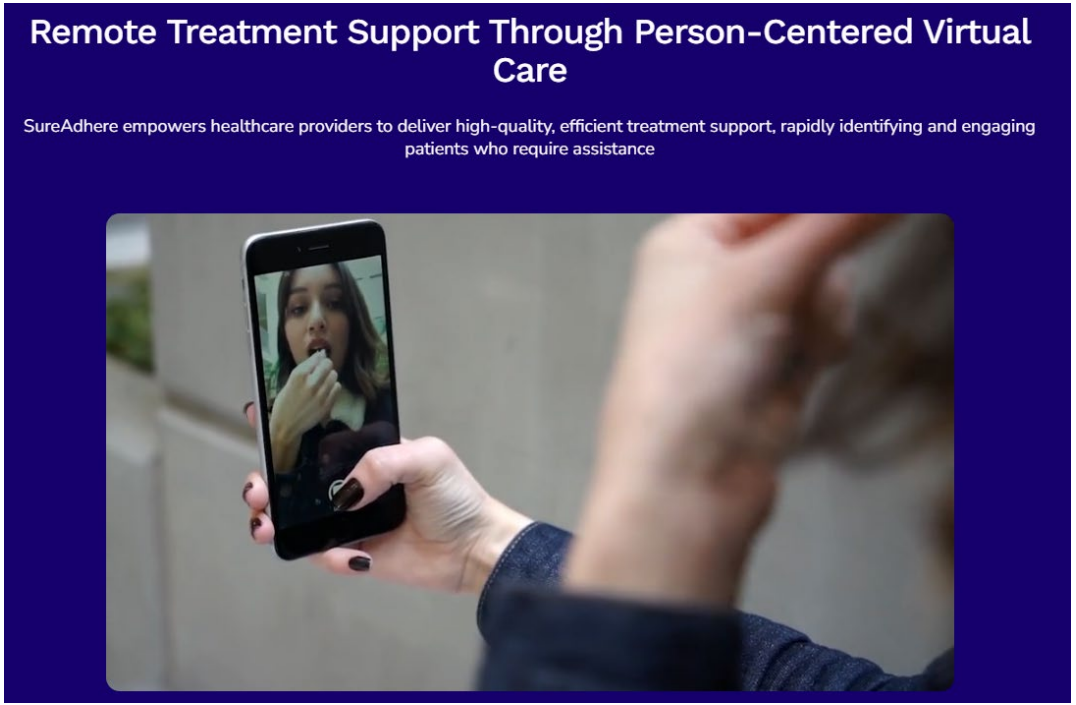
- **MDRTB-Expertengruppe kontaktieren !**

Behandlungsempfehlungen für Kinder

- **Neuerarbeitung mit Verkürzung der Behandlungsdauer bei nicht-schwerer Tuberkulose**
- **Erwähnung laufender Studien zur Meningealen Tuberkulose mit erhöhten Rifampizin-Dosen**

Therapiebegleitung

- **Erfahrungen mit «Video-observed Therapy» werden erwähnt**



Therapiebegleitung

- **Nachkontrollen nach TB- Behandlungsabschluss zur Erkennung der verschiedenen Formen der post-tuberkulösen Lungenerkrankung werden empfohlen**

Tuberkulose- Screening bei Asylsuchenden

- **Ausbau und Neuorganisation des Kapitels mit umfassender Diskussion** (S 49-53)
  - Einführung
  - Zeitrahmen des TB Screenigs bei Asylsuchenden
  - Ziele
  - Screening in Bundesasylzentren
  - Screening nach Aufenthalt in Bundesasylzentren

  - **«Screening auf eine tubekulöse Infektion kann in bestimmten Settings in Betracht gezogen werden»**

Vielen Dank
für das Interesse !

Vorstellung eines komplexen Falles

Annett Hunger
Dipl. Pflegefachfrau HF
Fachverantwortliche Tuberkulose, Lungenliga Ost

LUNGENLIGA OST
SG / AR / AI / GL
Mehr Luft fürs Leben

Vorstellung Indexpatient

- Männlich, 18 Jahre
- Aus Afghanistan, asylsuchend
- M. tuberculosis- Komplex: Lunge
- Symptome zur Diagnosestellung: Husten, Schmerzen Thorax
- Kultur, Amplifikationsverfahren, direkte Mikroskopie vom Sputum: positiv
- Resistenzlage: keine

Unsere Aufgaben

- Anamnese
- Aufklärungsarbeiten
- Vertrauen schaffen
- Umgebungsuntersuchung
- TB- und LTB- Therapieverlaufskontrolle
- DOT

Komplexibilität Indexpatient

- Sprach- und Schriftbarriere
- «offene» Lungentuberkulose mit schon länger bestehenden Symptomen
- Psychosoziale Belastung
- Mehrmaliger Schul- und Jobwechsel in den letzten 3 Monaten vor Therapiebeginn
- Gemeindetransfer während Therapie

Komplexibilität Kontaktpersonen

- Sprach- und Schriftbarriere
- Ausserkantonale UU`s
- Psychosoziale Belastung
- Gesundheitskompetenz
- Finanzielle Ängste
- Auffindbarkeit nach Transfer in anderen Gemeinden

Umgebungsuntersuchung

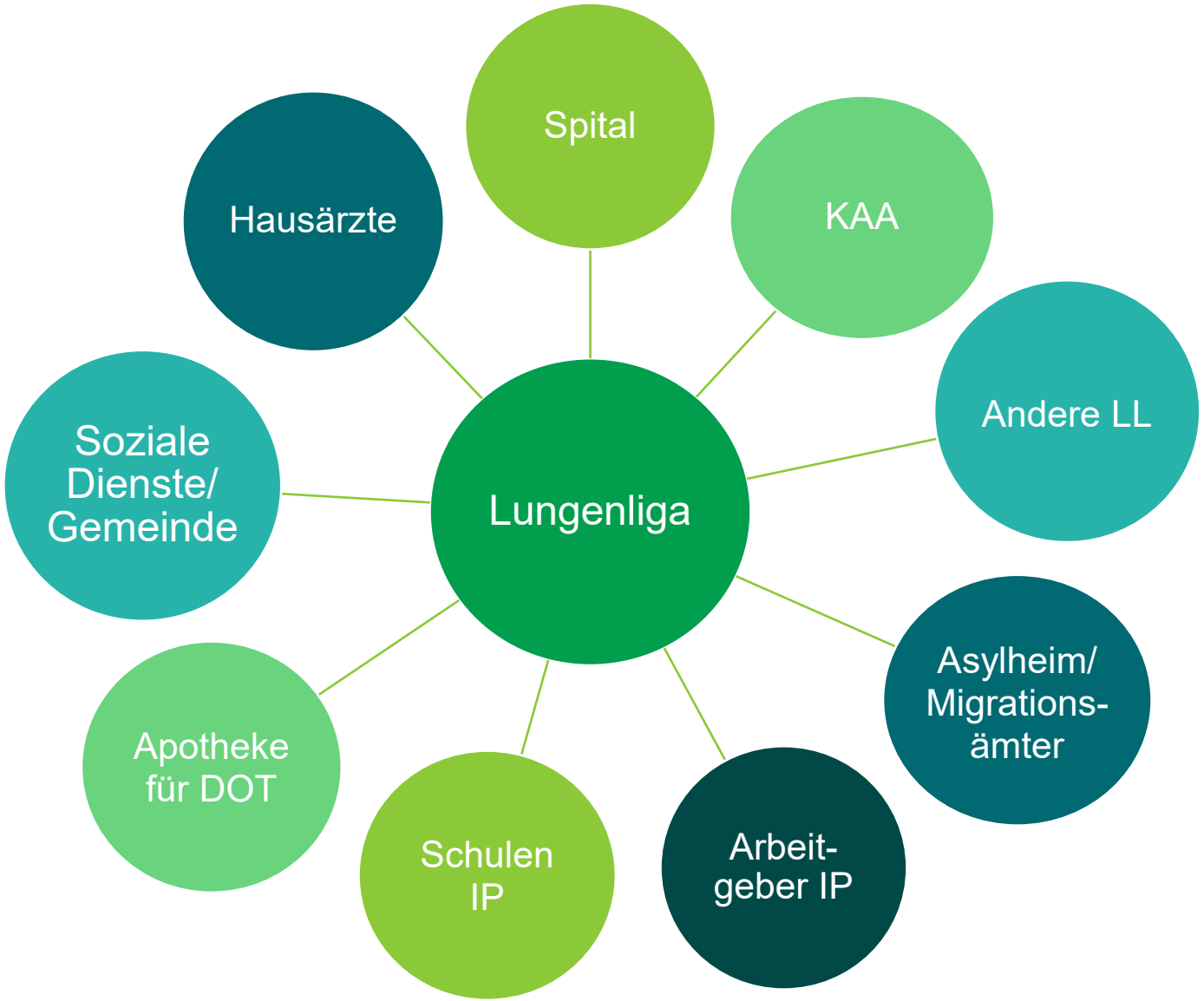
44 Kontaktpersonen aus 5 verschiedenen Institutionen

(2 Schulen, 2 Arbeitsstellen, Asylheim)

- 2x Status nach TB
- 1x ausserkantonale UU
- 4x durch Hausarzt
- 37x in den verschiedenen Institutionen oder vor Ort in der LLO

→ Davon 12 infiziert – 3 abgebrochene Therapie, 9 aktive LTB-Therapien

Interdisziplinäres Netzwerk



LUNGENLIGA OST
SG / AR / AI / GL
Mehr Luft fürs Leben

Fazit

Um einen komplexen Fall **erfolgreich** zu Bearbeiten braucht es:

- **gute Organisation** und **Zusammenarbeit** mit allen beteiligten Institutionen
- **Vertrauen** zwischen: Patient und **UNS**.

Patient schliesst am 02.11.2024 seine Therapie erfolgreich ab

Herzlichen Dank

Lungenliga Ost
Kolumbanstrasse 2
9008 St.Gallen
Tel. +41 71 228 47 47
info@lungenliga-ost.ch
www.lungenliga-ost.ch

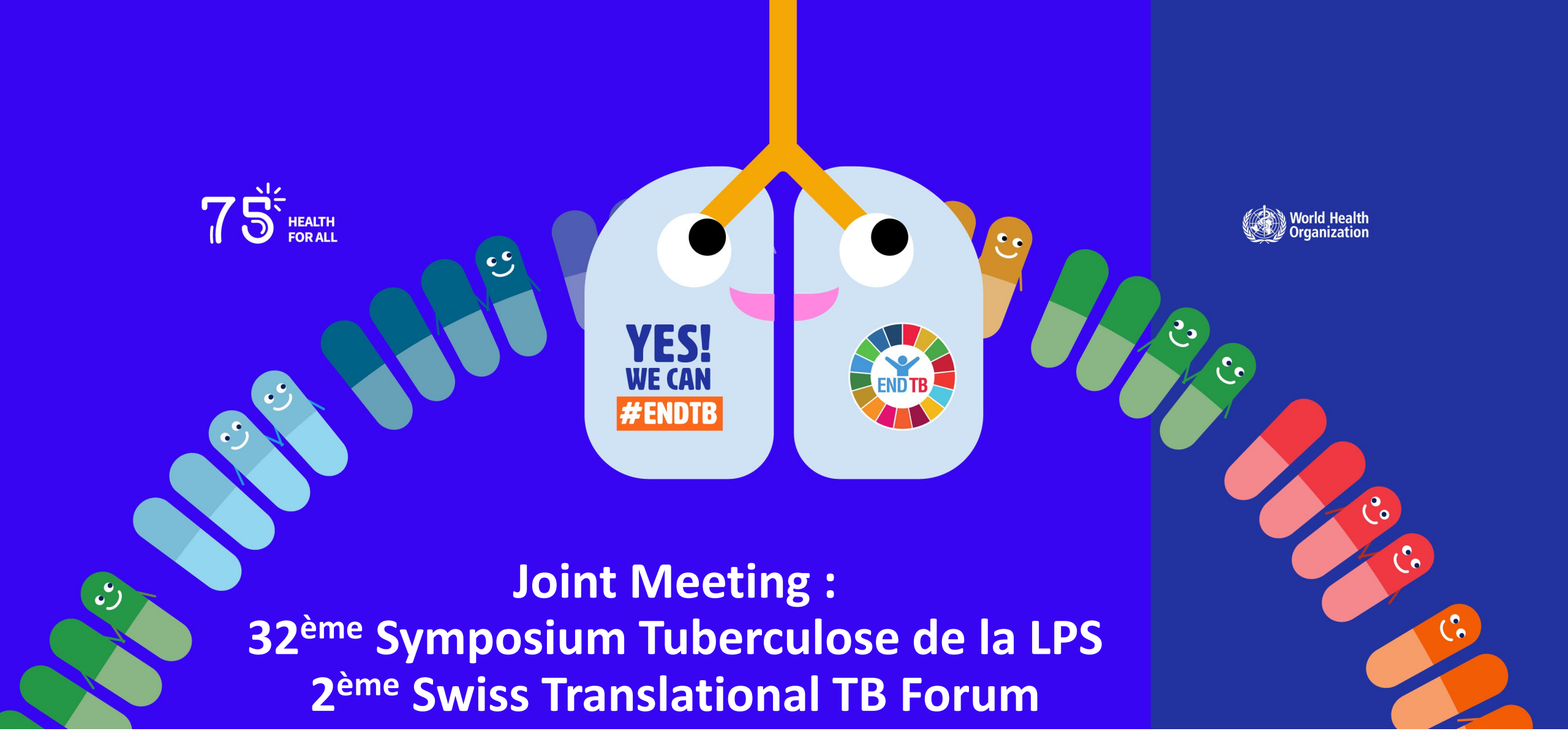
Spendenkonto
IBAN CH54 0078 1015 5255 7430 7

LUNGENLIGA OST
SG / AR / AI / GL
Mehr Luft fürs Leben

Pause und Zusammenführung

Swiss Translational TB Forum

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA



Pause et regroupement

Swiss Translational TB Forum

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA

Mit Unterstützung von
Avec le soutien de

QIAGEN

Diasorin

Swiss Translational
TB Forum

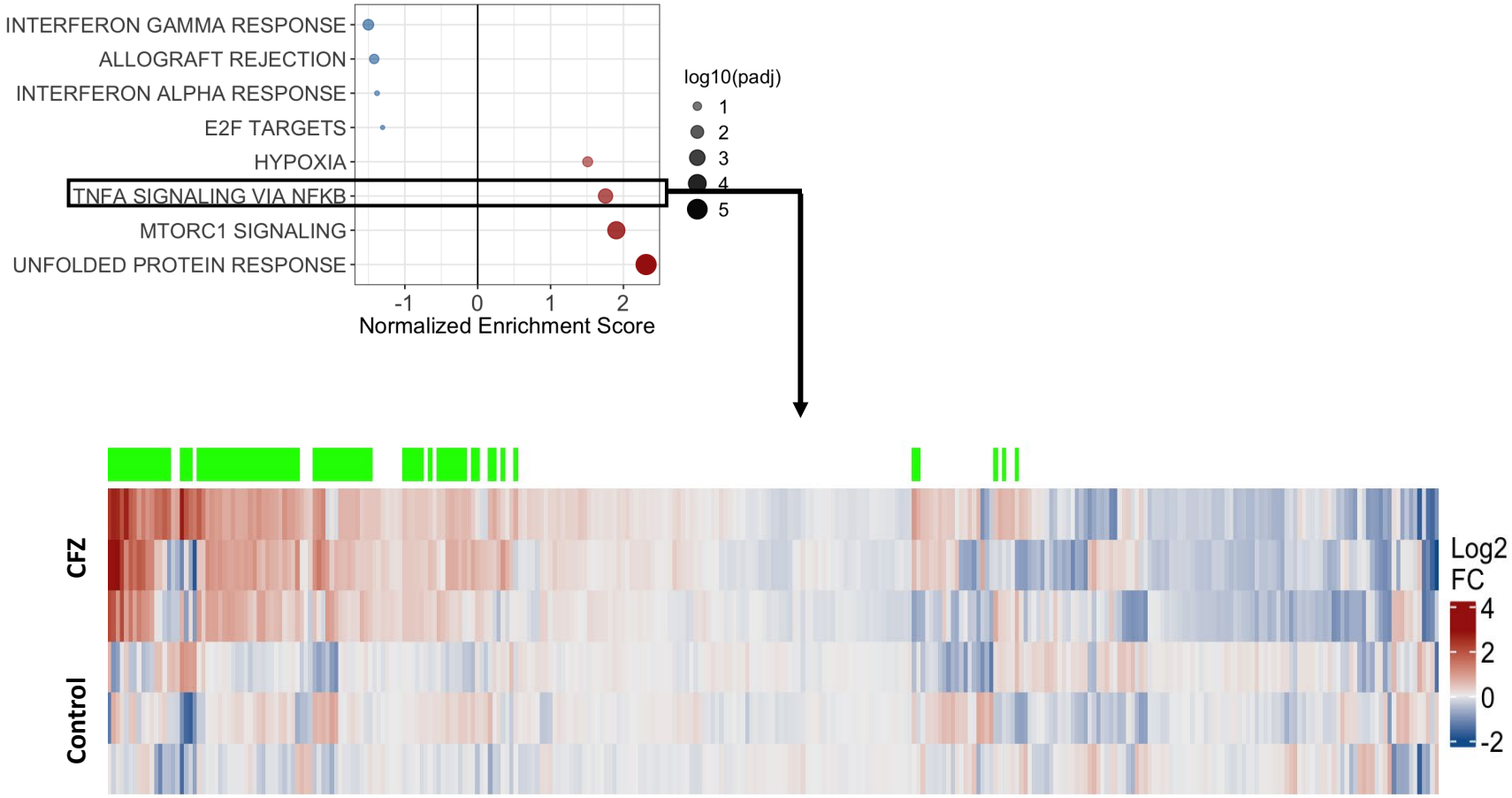
LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA

Context-dependent Macrophage Activation by Clofazimine

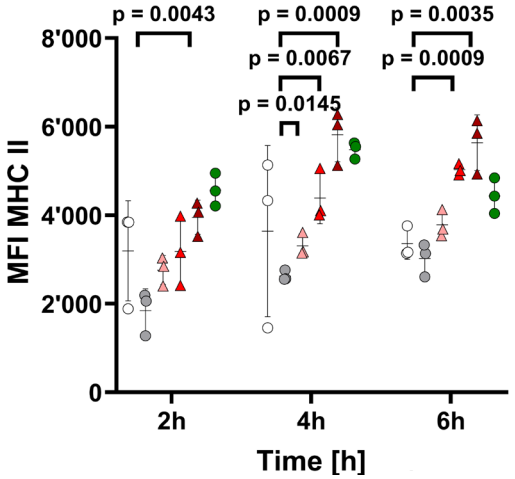
Rebekka Wolfensberger

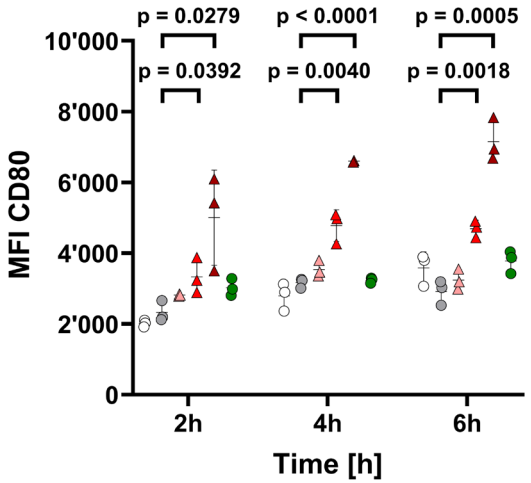
Department of Infectious Diseases and Hospital Epidemiology,
University Hospital Zurich and University of Zurich

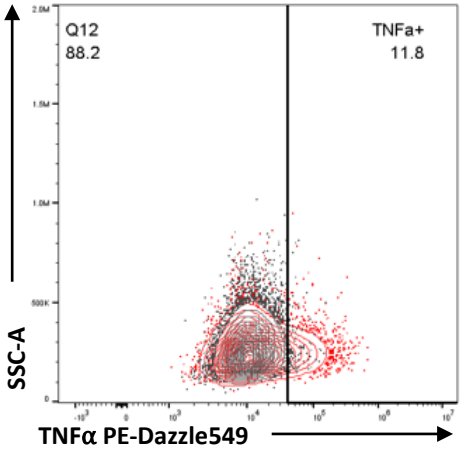
Clofazimine induces transcriptional changes in murine Macrophages



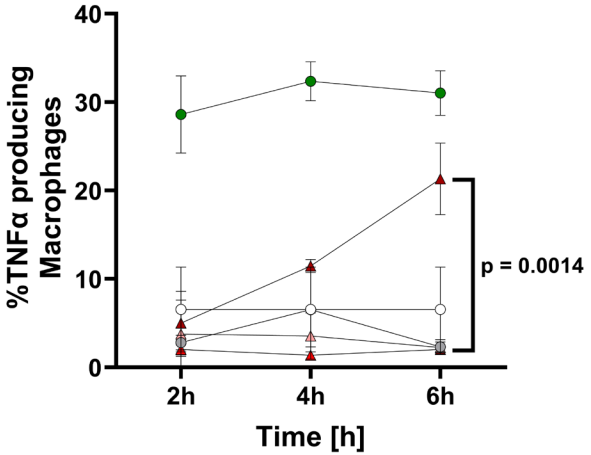
Clofazimine activates Macrophages in a pro inflammatory direction



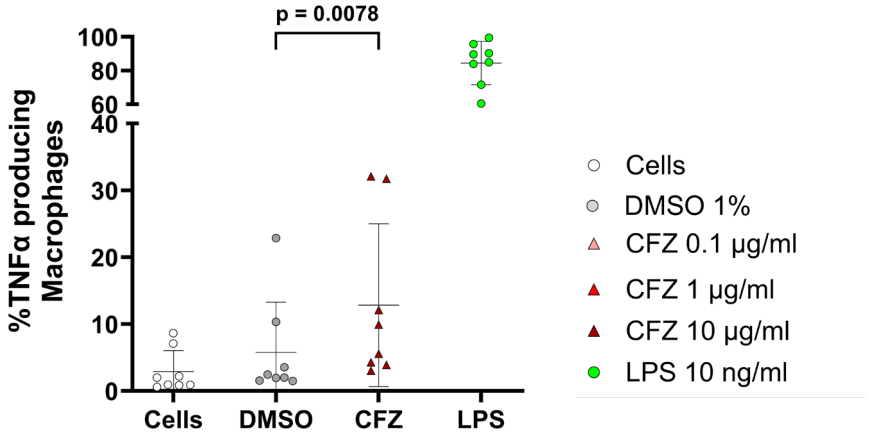


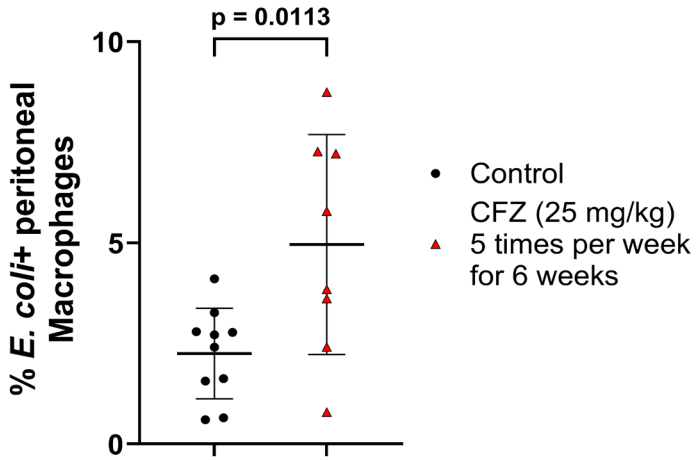


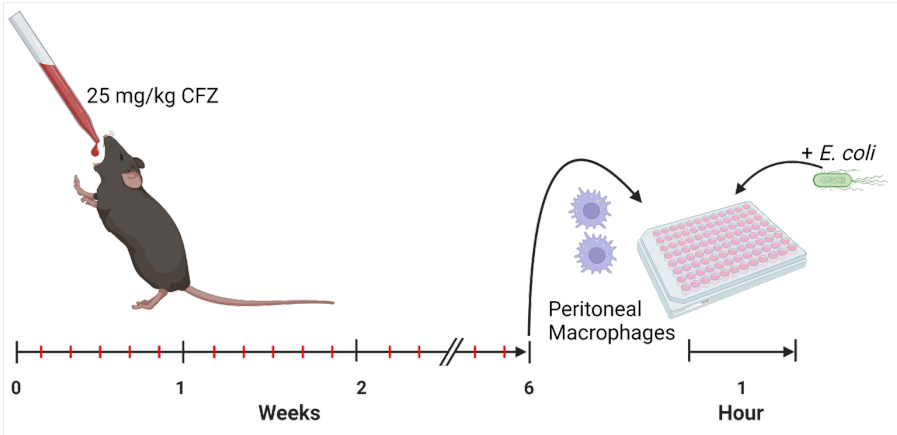
- Cells
- DMSO 1%
- CFZ 0.1 µg/ml
- CFZ 1 µg/ml
- CFZ 10 µg/ml
- LPS 10 ng/ml
- PMA 50 ng/ml + Ionomycin 2 µg/ml



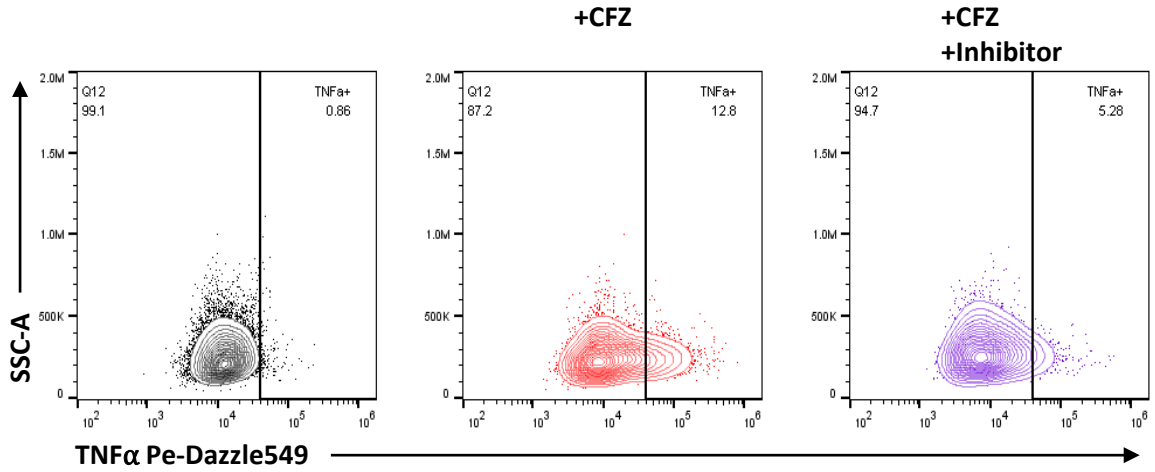
Macrophage activation also present in human cells and *in vivo*

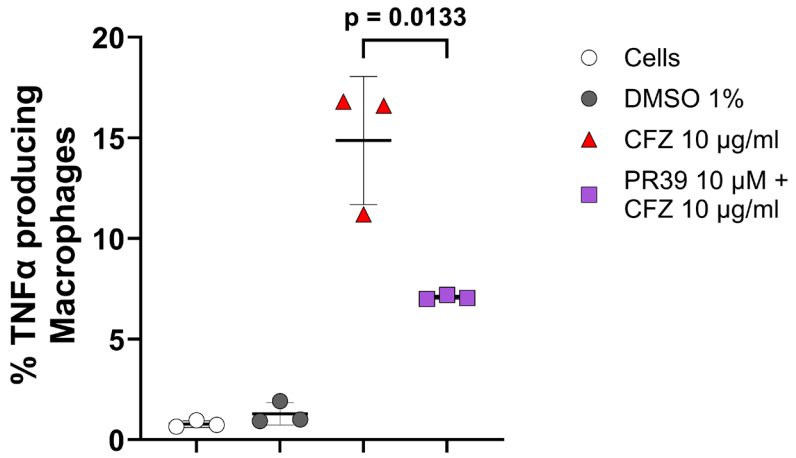




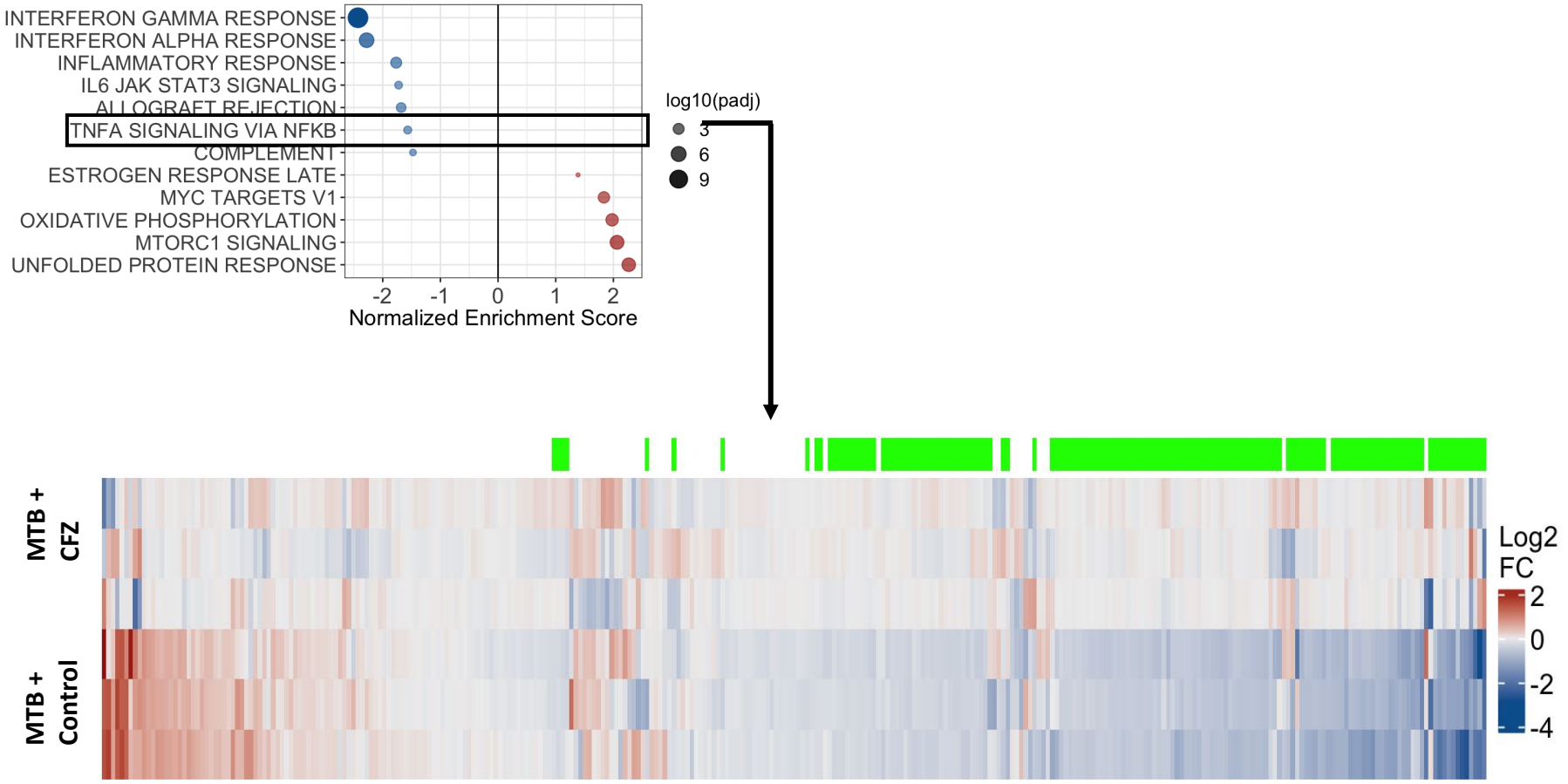


NFκB inhibition partially reverses Clofazimine effects

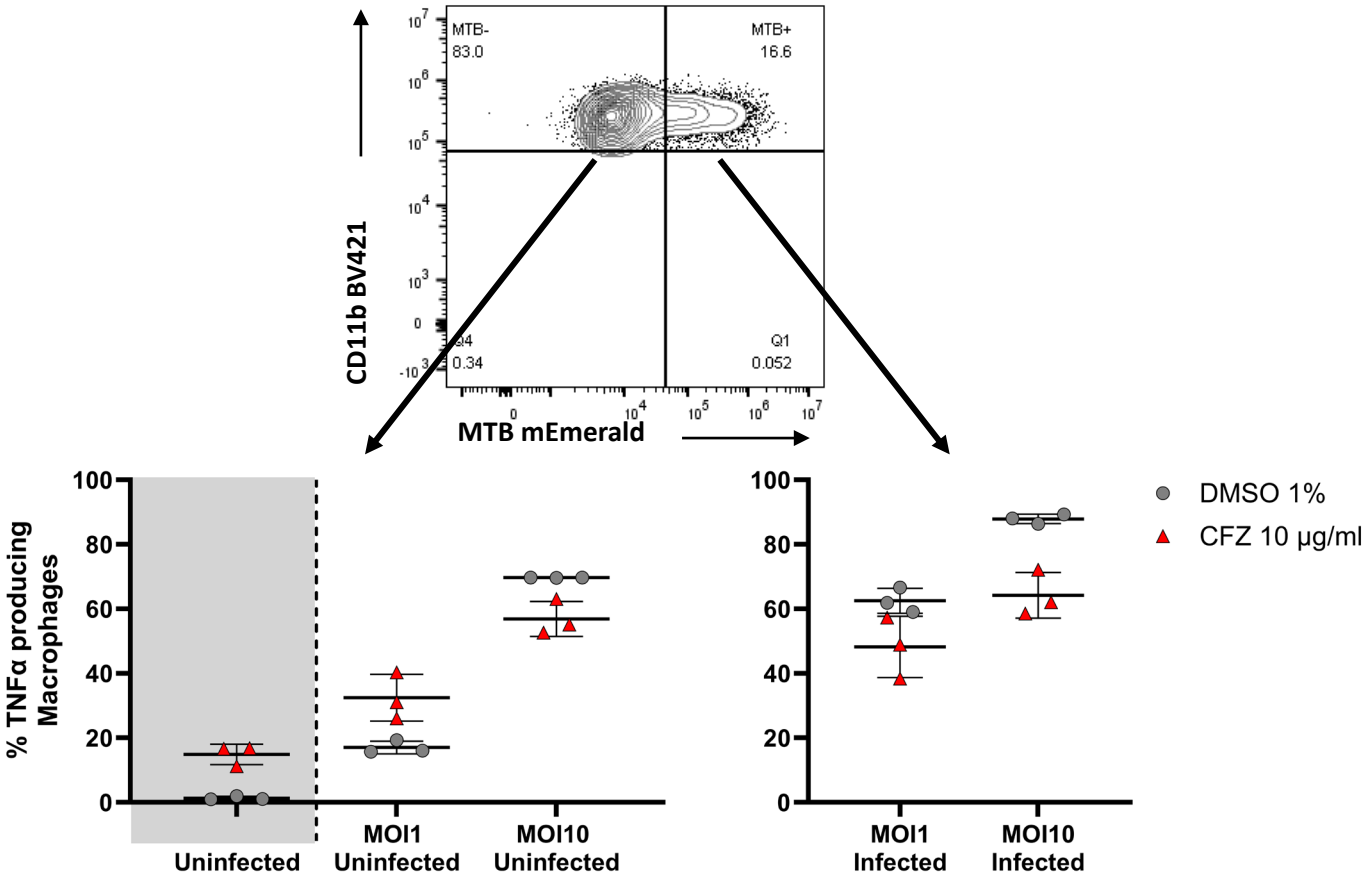




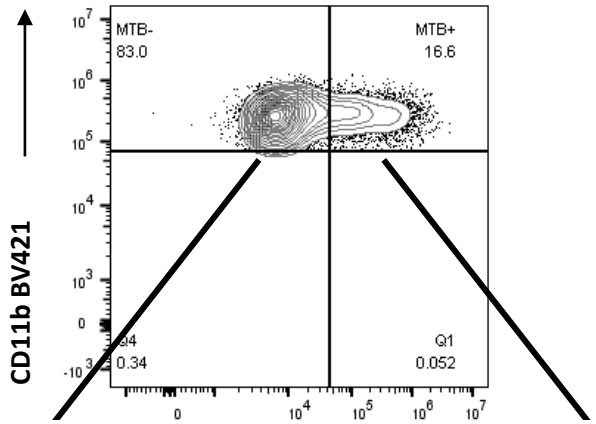
Infection limits Clofazimine mediated effects

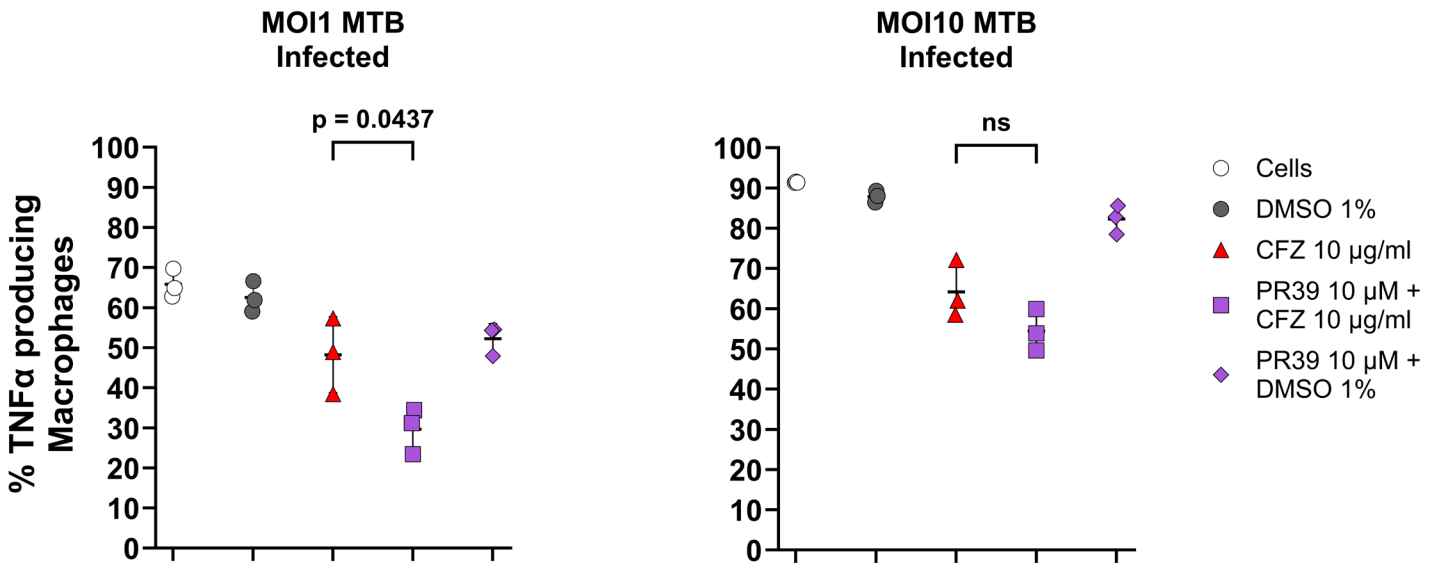


Infection limits Clofazimine mediated effects



Infection limits Clofazimine mediated effects





USZ Universitäts Spital Zürich

Thank you for your attention

Group of PD Dr. med. Johannes Nemeth
- Cédric Dollé
- Terence Tutumlu
- Dr. Edoardo Sarti
- Doris Russenberger

Group of Prof. Dr. med. Roberto F. Speck
- Doris Russenberger
- Laura Ihm
- Sophia Stewart
- Dr. Nicole Kadzioch
- Dr. Sabrina Traxel
- Florian Schmidt
- Benjamin Müller
- Dr. Simon Bredl

Group of Prof. Dr. Peter Sander
- Tizian Griesser
- Michael Meuli

- Prof. Dr. Katharina Kusejko
- Dr. Marius Zeeb
- Prof. Dr. Melanie Greter
- Dr. Sébastien Wielgoss
- Prof. Dr. Sébastien Gagneux

DBM Basel

University Hospital Basel

University of Basel

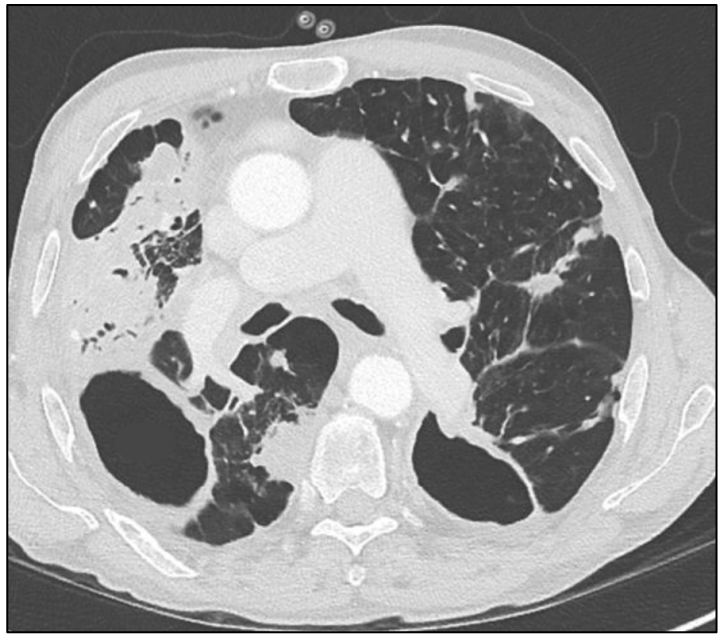
Mycobacterial drug tolerance assessments reveal clinical outcomes

Alexander Jovanovic
PhD student

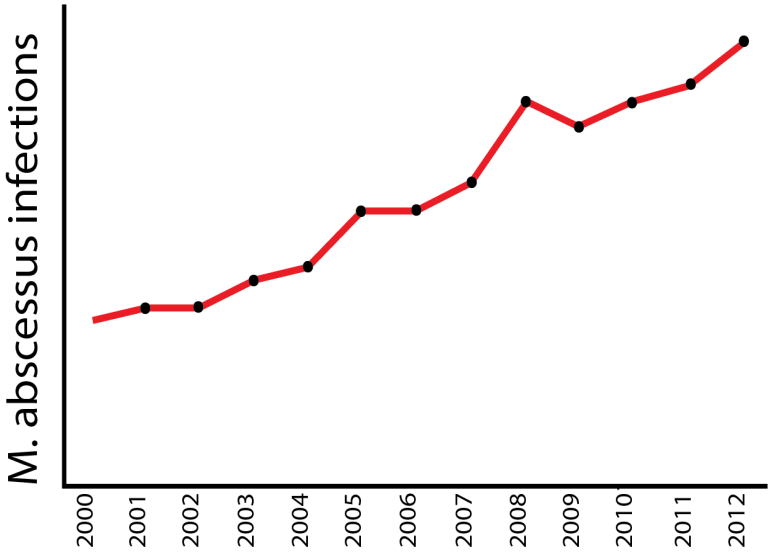
Boeck Lab

Relevance of *Mycobacterium abscessus*

Lung damage



Increasing incidence



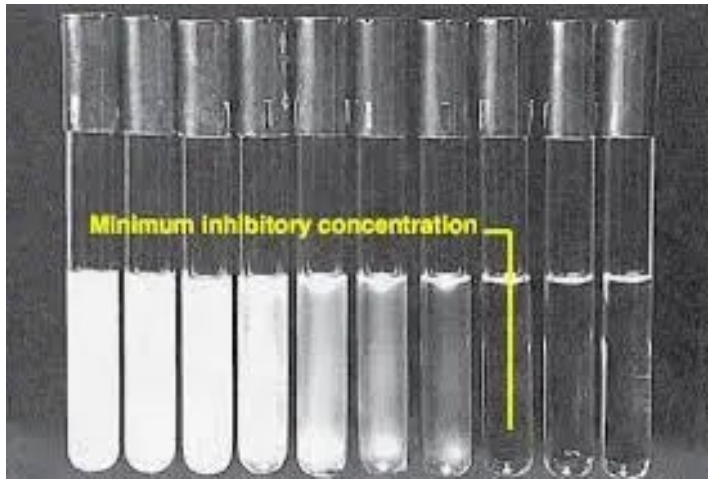
Griffith *et al. Chest* 2015

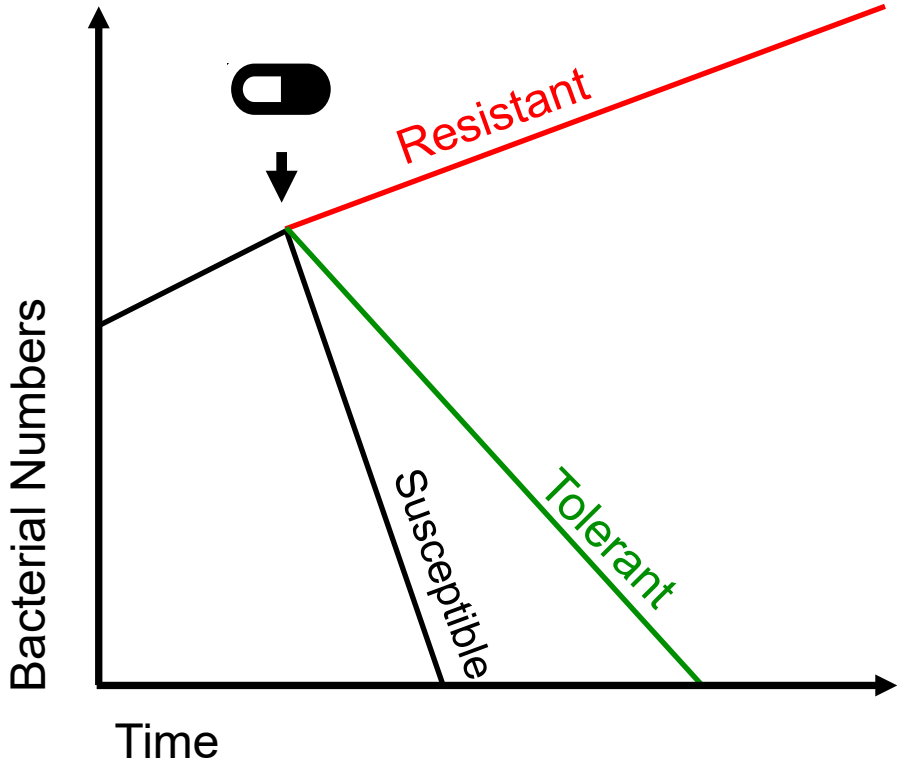
Antibiotic treatment failures

Drug resistant MAB
(n=30)

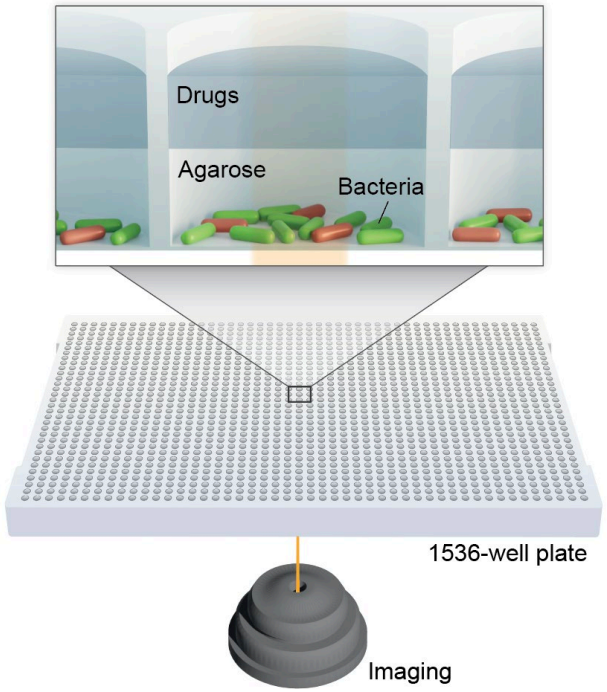
Drug susceptible MAB
(n=106)

Drug resistance is different from drug tolerance

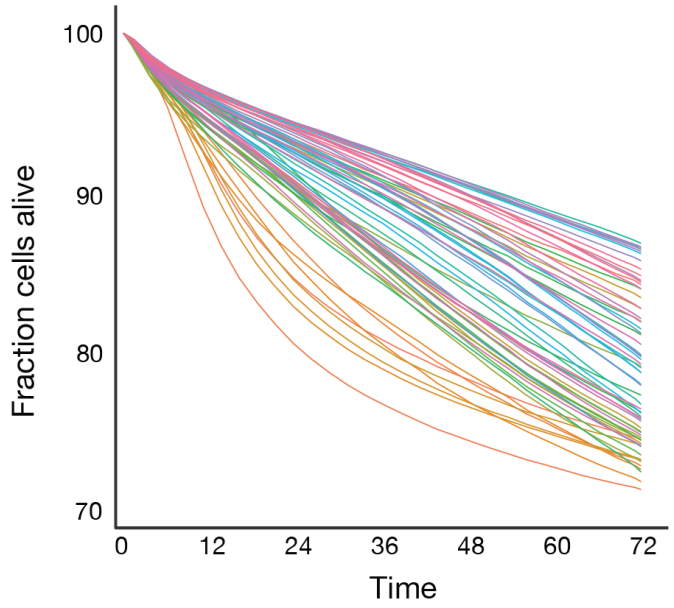


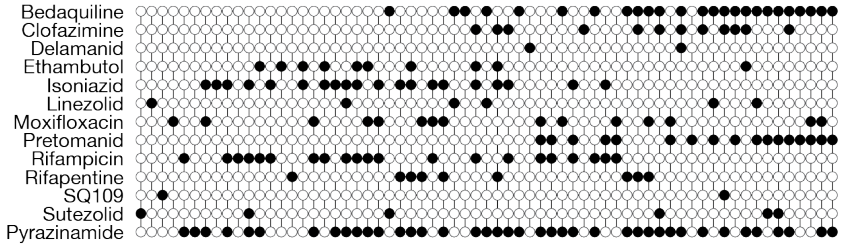


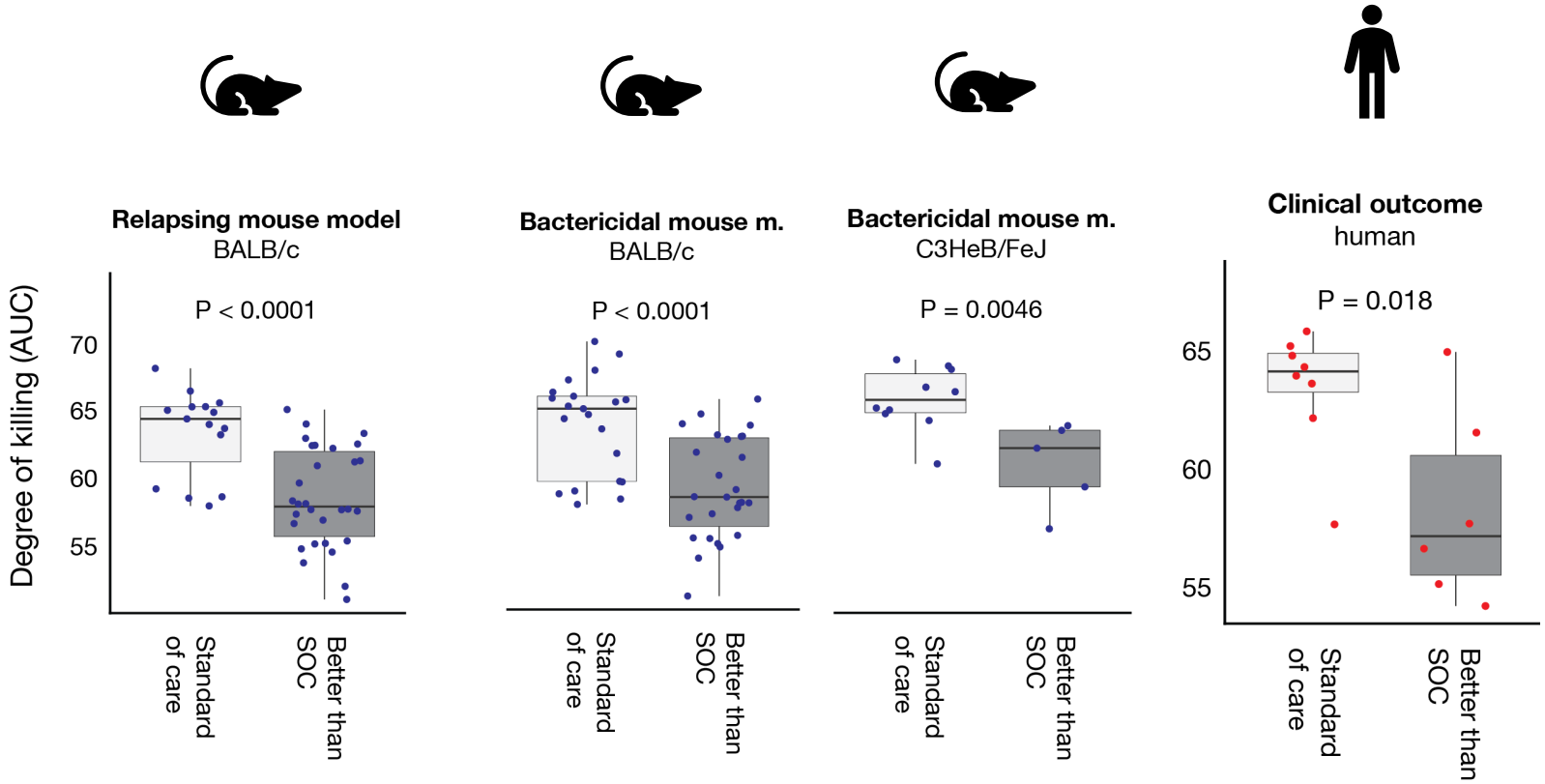
Antimicrobial Single-Cell Testing (ASCT)



ASCT predicts successful *M. tuberculosis* regimens







Larkins-Ford J et al, Cell Systems 2021
Larkins-Ford J et al, Cell Reports Med 2022

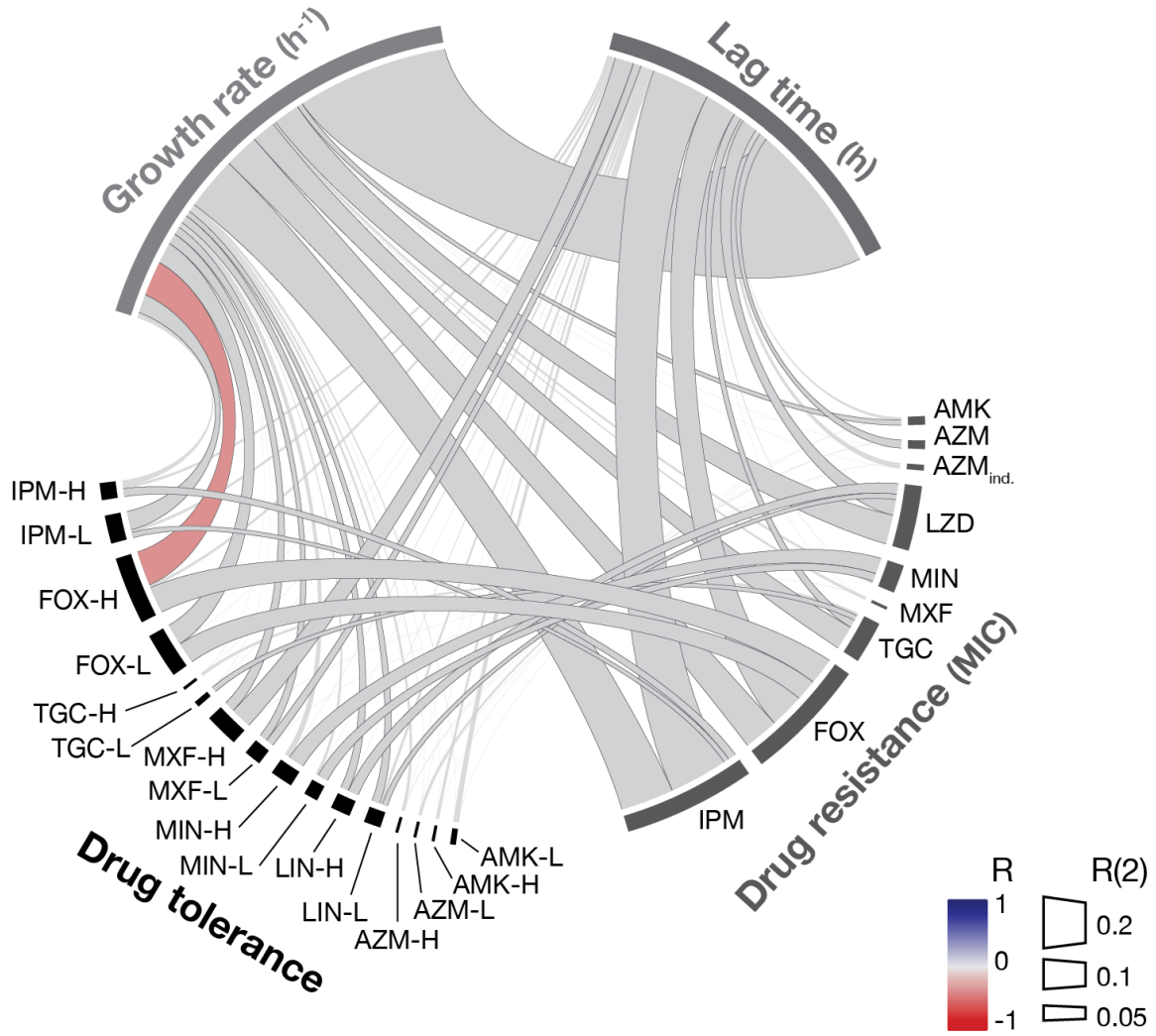
Large-scale killing assessment in *M. abscessus*

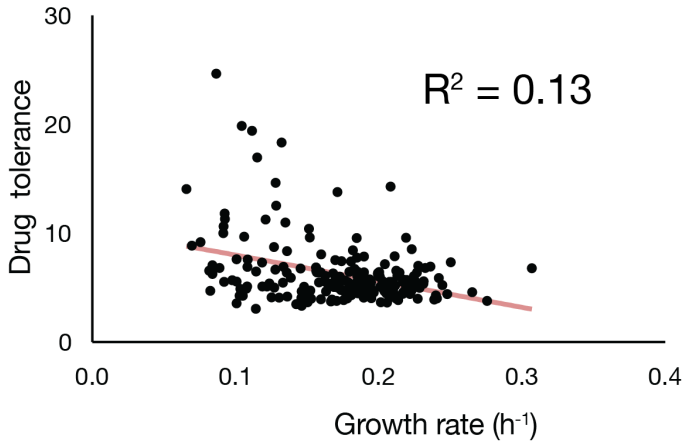
> 400 clinical isolates

> 10 000 time-kill curves

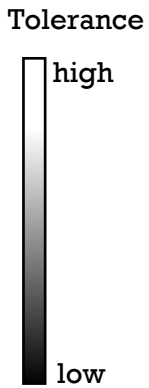
> 300 000 viability assessments

Drug tolerance is a distinct phenotype

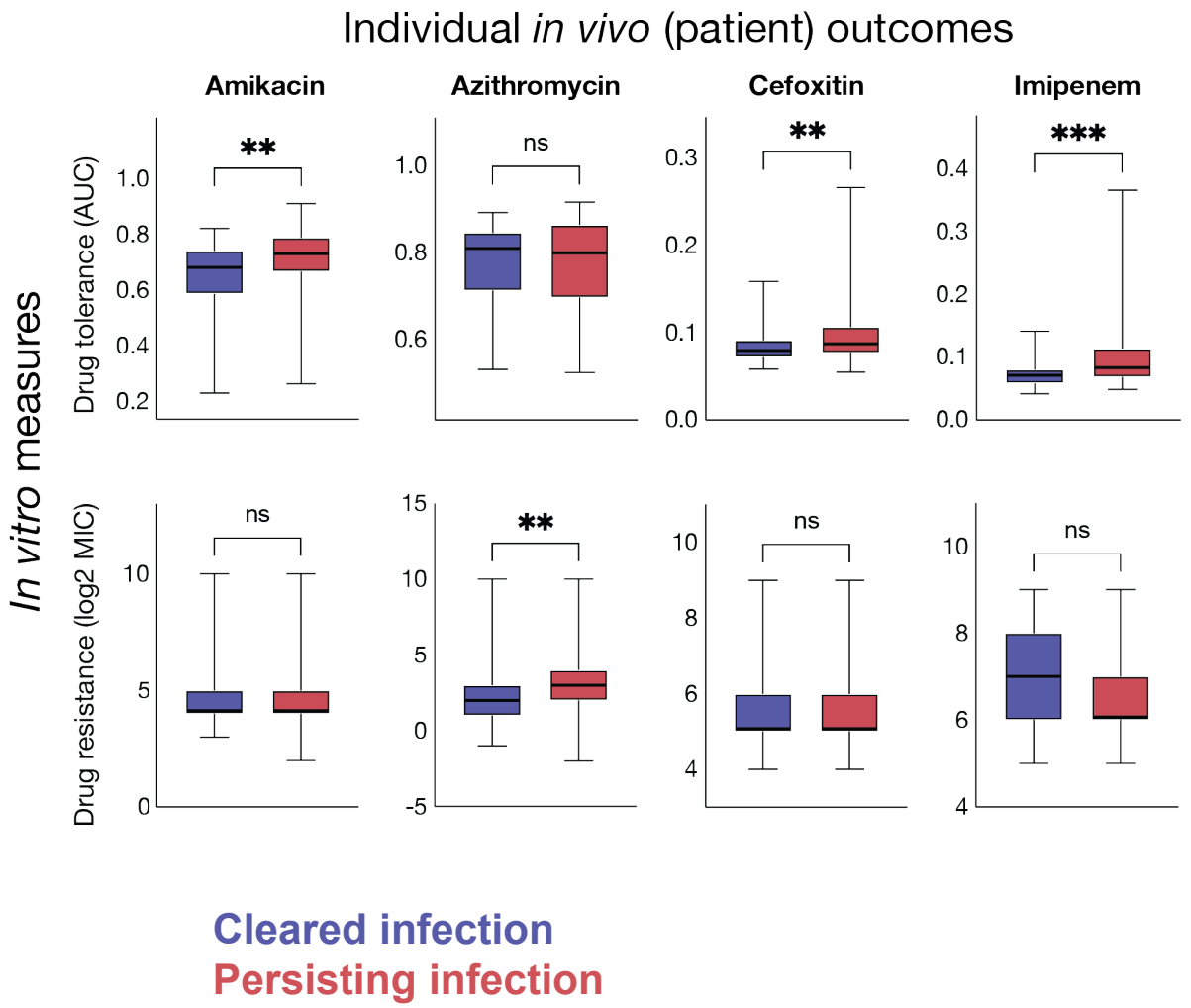




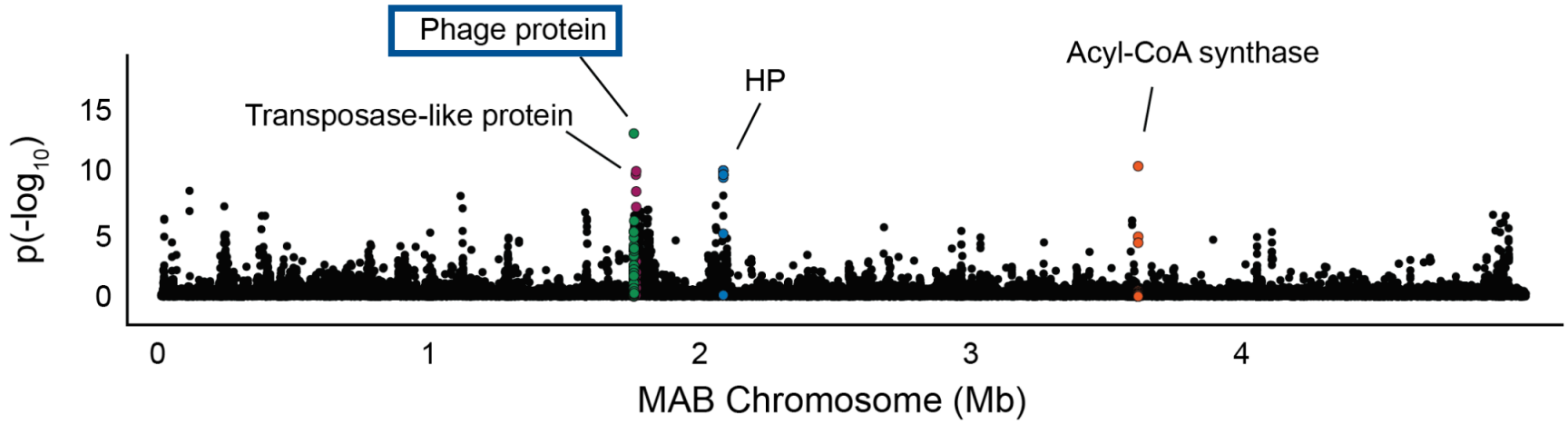
Drug tolerance is a heritable bacterial trait

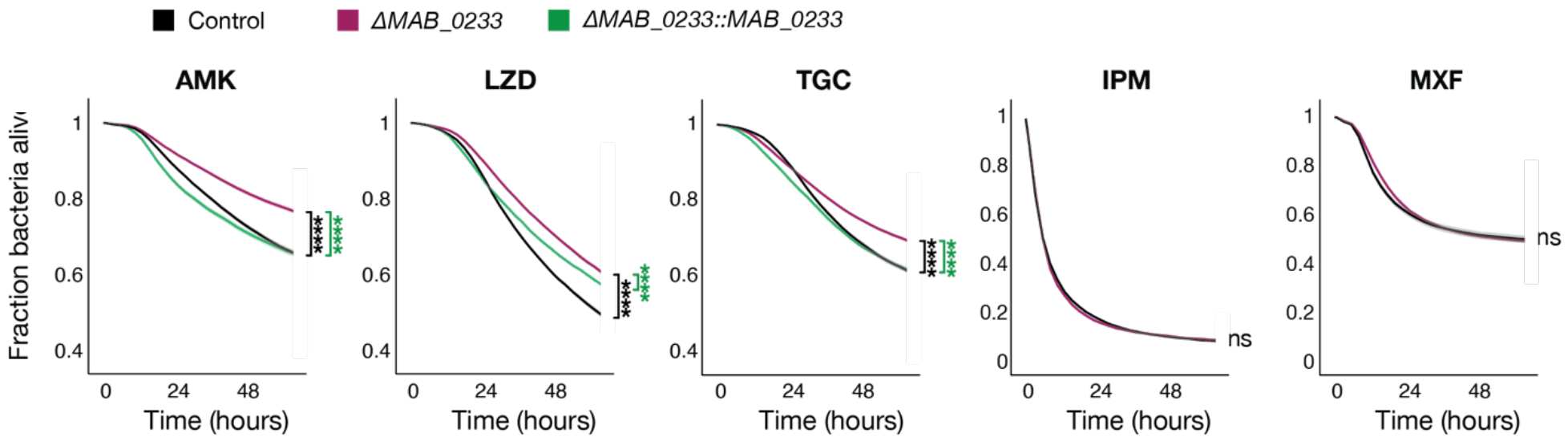


Drug tolerance is associated with infection outcomes



Drug tolerance mechanisms revealed through GWAS





Summary

Through **Antimicrobial Single-Cell Testing**

- Identify drug combinations successful *in vivo*
- Reveal that antibiotic killing is a bacterial phenotype (drug tolerance)
  - Different from resistance
  - Driven by the bacterial genetic background
  - Associated with clinical outcomes
- Identify mechanisms underlying antibiotic killing

Acknowledgments

Boeck lab
Frederick Bright
Dr. Ahmad Sadeghi
Basil Wicki
Dr. Santiago Muniz
Anna Rodoni
Melis Kir
Sara Toprak

University of Basel
Benoit Laventie
Leoni Swart
Urs Jena
Mike Abanto
Loïc Sauteur
Ruben Cabezon

SwissTPH Basel
Sebastien Gagneux

University of Bern
Markus Orsi
Jean-Louis Reymond

University of Cambridge
Andres Floto
Julian Parkhill

Wellcome Sanger Inst.
Josie Bryant

Tufts University
Bree Aldridge

Rockefeller University
Jeremy Rock

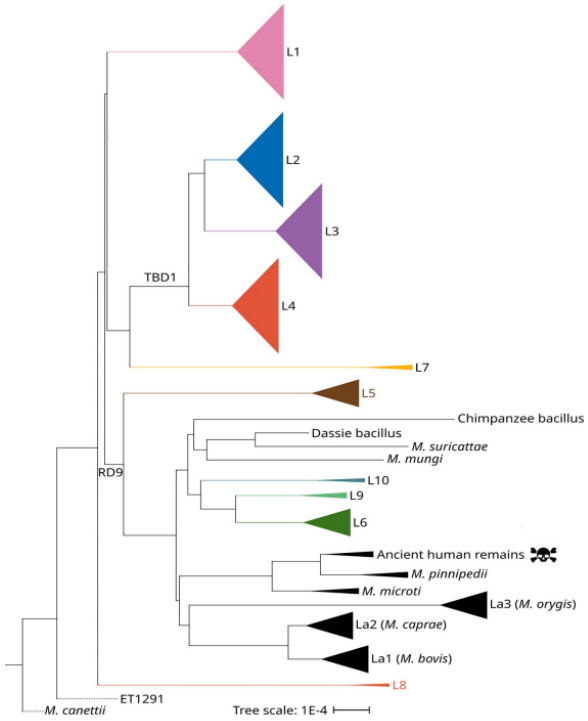
Helmut Horten Stiftung
FNSNF
Cystische Fibrose Schweiz
Goldschmidt-Jacobson Foundation
Gottfried & Julia Bangerter-Rhyner Stiftung
SCHWEIZERISCHE GESELLSCHAFT FÜR PNEUMOLOGIE
SOCIÉTÉ SUISSE DE PNEUMOLOGIE
SOCIETÀ SVIZZERA DI PNEUMOLOGIA
DBM Basel
University Hospital Basel
University of Basel

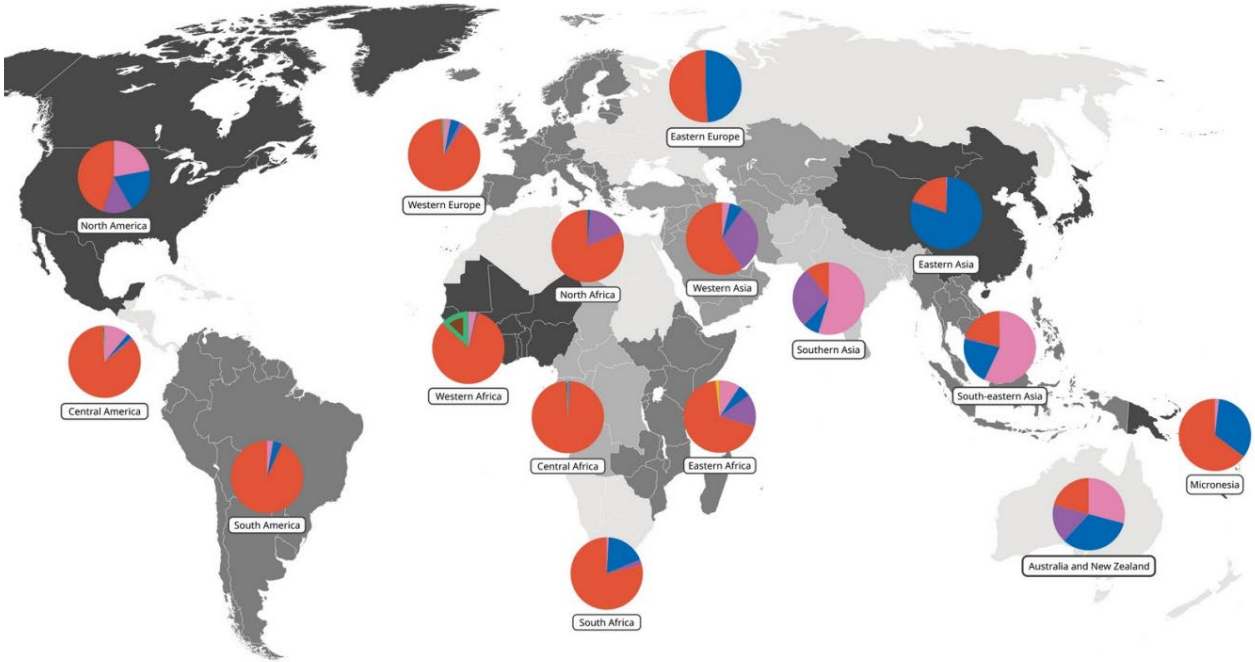
Swiss TPH

Drug tolerance in *Mycobacterium tuberculosis*: it's all in the family

Valerie March
Tuberculosis Ecology & Evolution Unit
TB symposium 30.10.2024

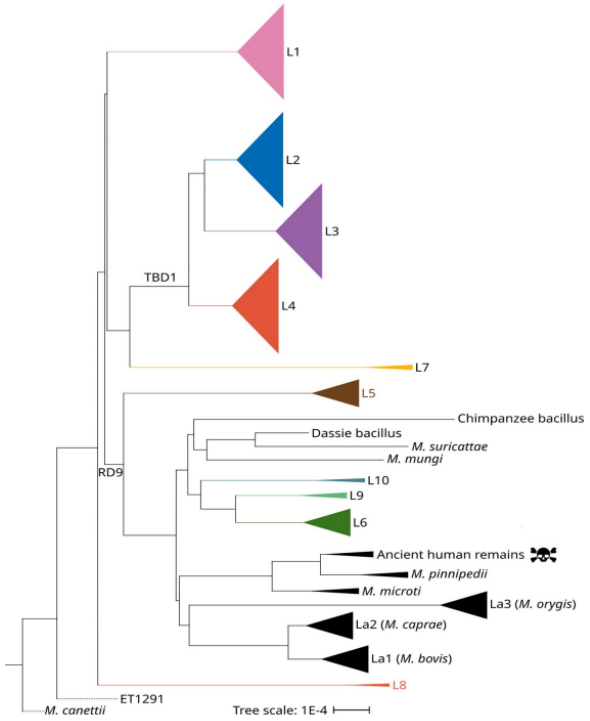
The Mycobacterium tuberculosis complex has evolved 10 human lineages with a distinct phylogeography

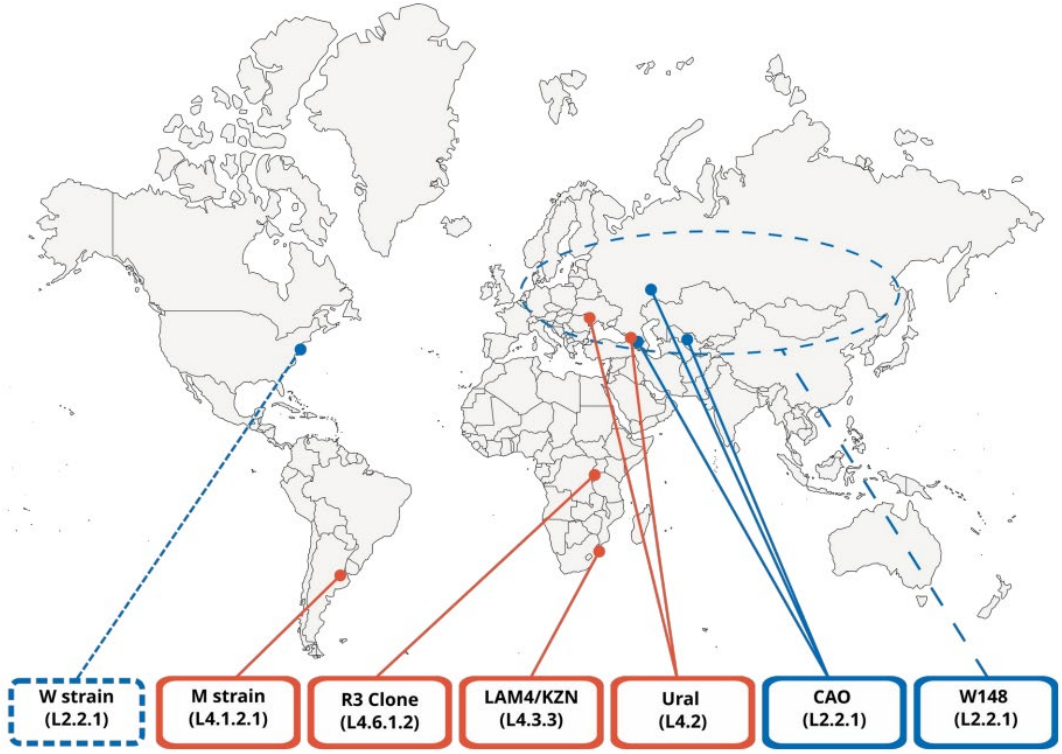




Goig et al., Unpublished

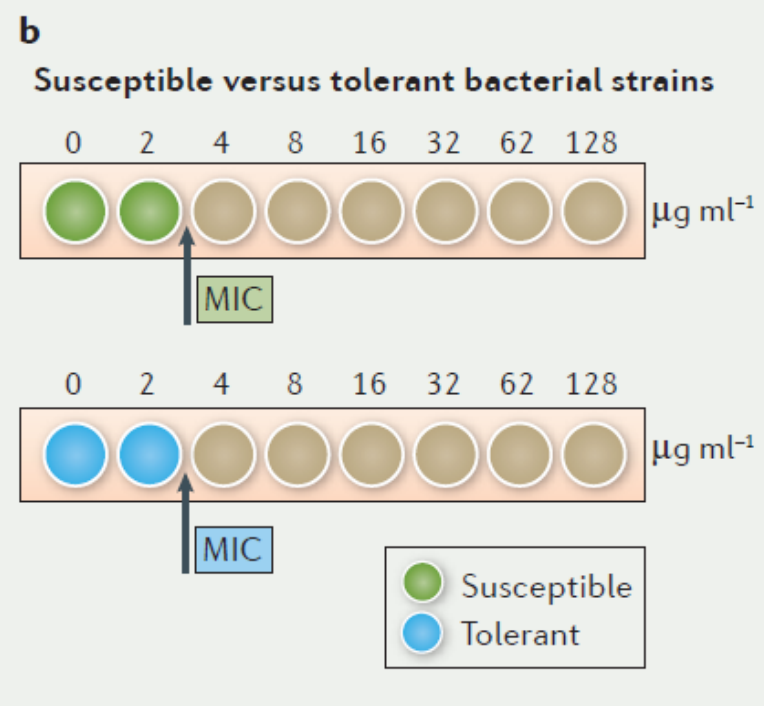
The Mycobacterium tuberculosis complex has evolved 10 human lineages with a distinct phylogeography

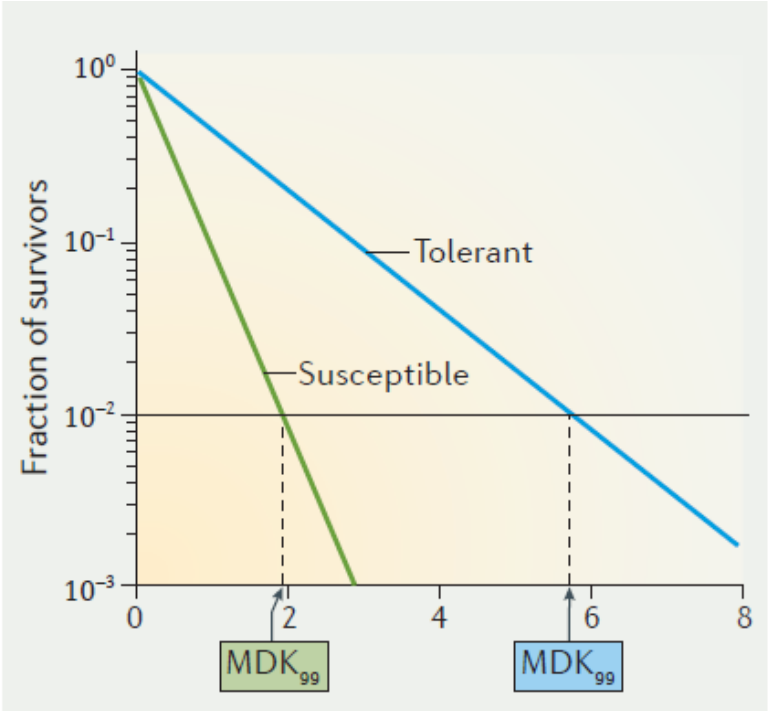




Goig et al., Unpublished

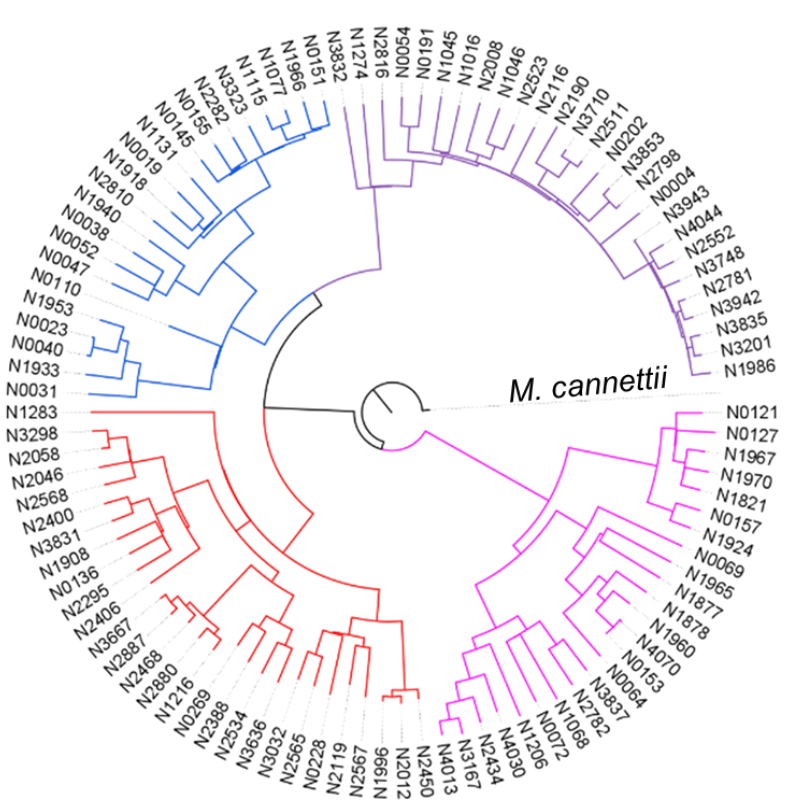
Tolerance: A means by which to evade antibiotic action

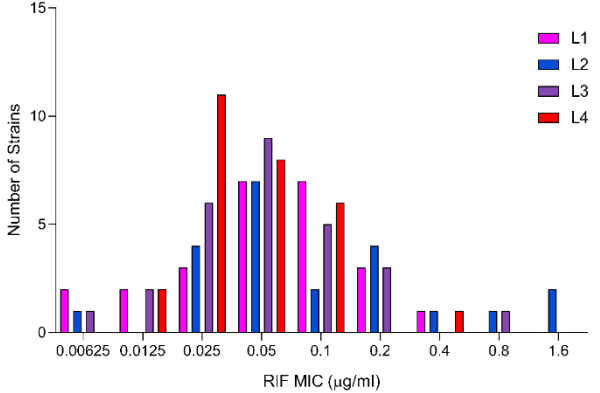


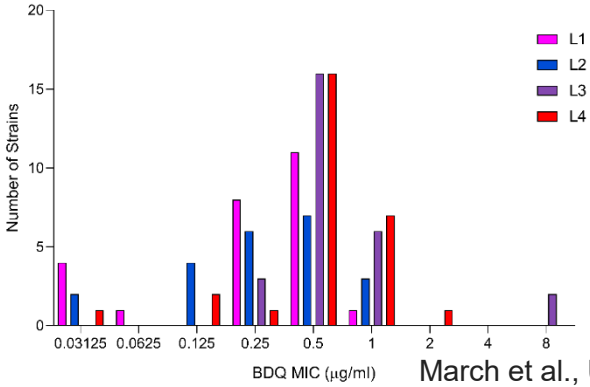


Brauner et al., *Nature Microbiology*, 2016

A diverse panel of Mtb strains to investigate the role of phylogeny in intrinsic antibiotic tolerance



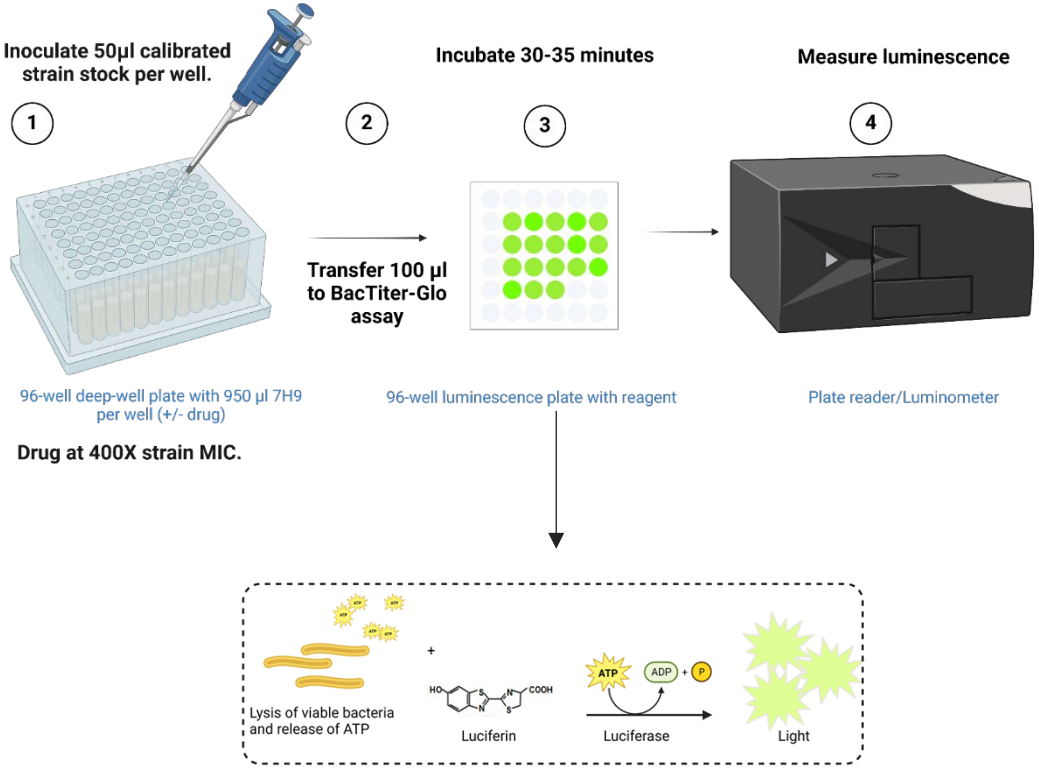




March et al., Unpublished

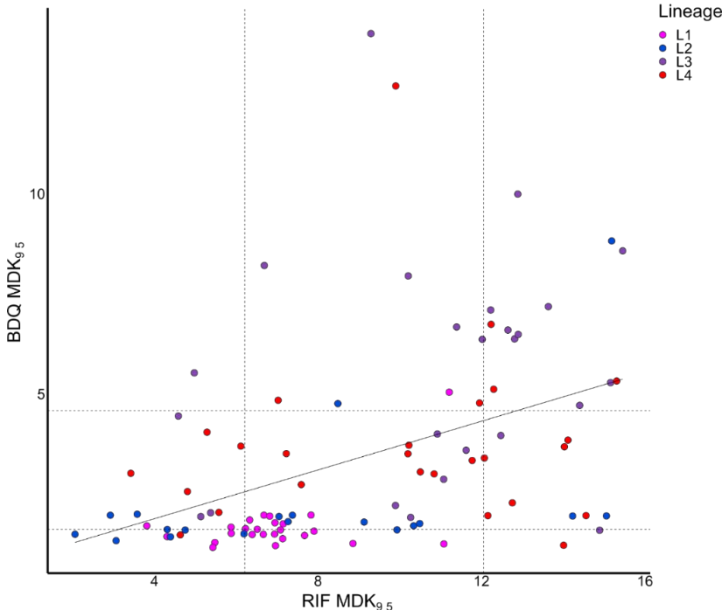
n = 102

An ATP-based time-killing assay to measure tolerance in Mtb



March et al., Unpublished

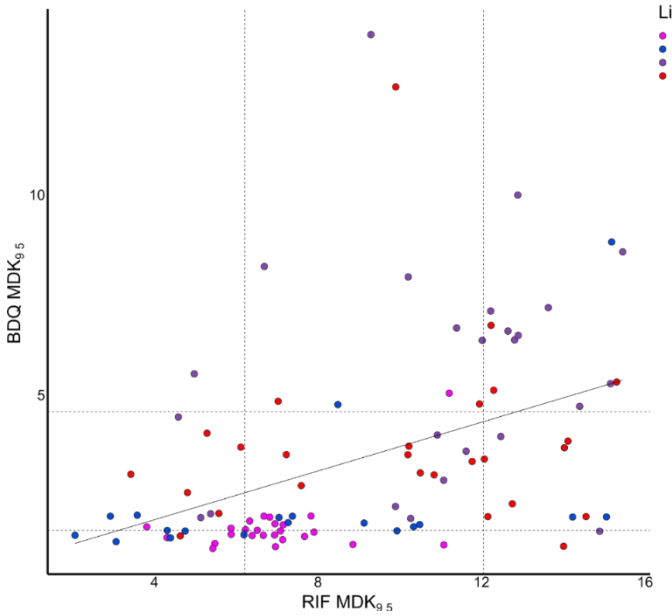
While tolerance varies by strains, members of L3 and L4 show higher intrinsic tolerance to Rifampicin and Bedaquiline

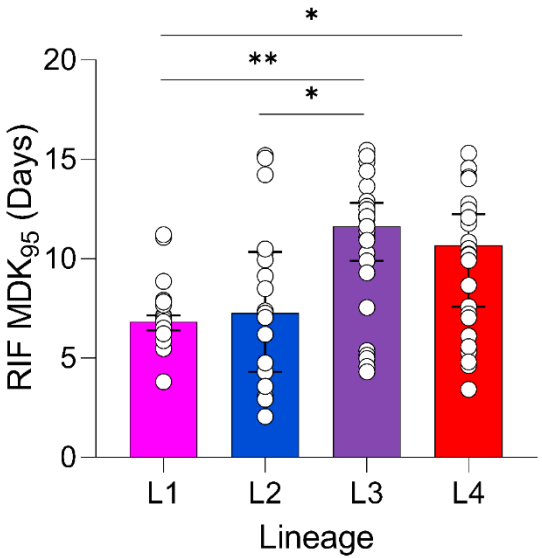


n = 95

March et al., Unpublished

While tolerance varies by strains, members of L3 and L4 show higher intrinsic tolerance to Rifampicin and Bedaquiline

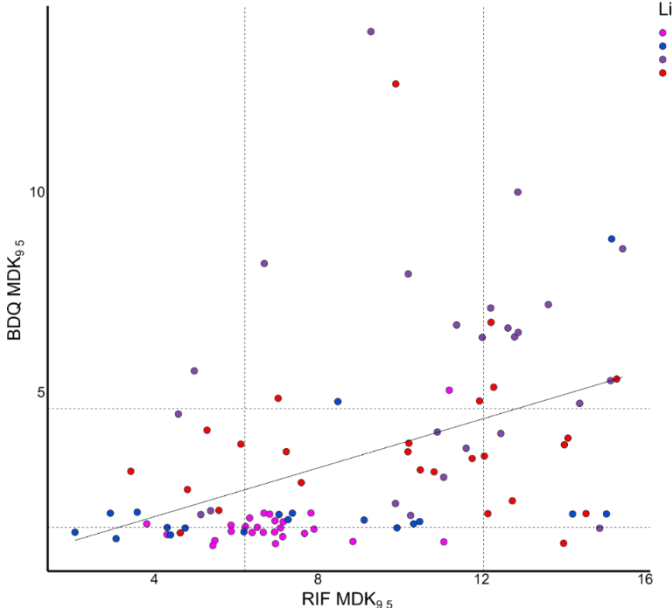


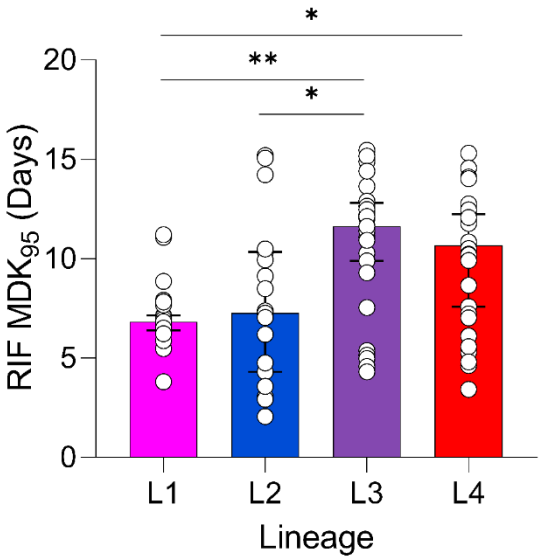


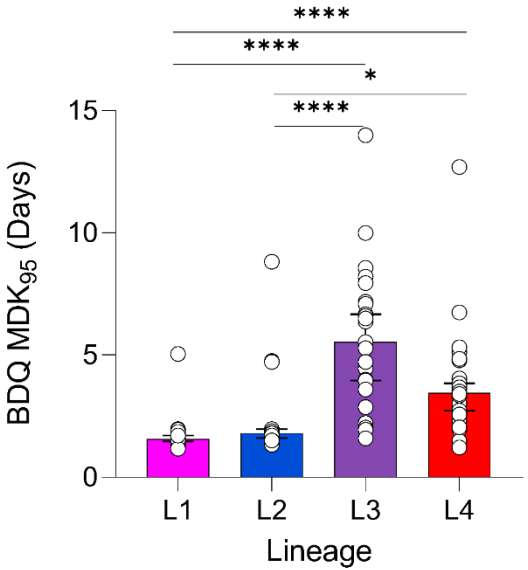
n = 95

March et al., Unpublished

While tolerance varies by strain, members of L3 and L4 show higher intrinsic tolerance to Rifampicin and Bedaquiline







n = 95

March et al., Unpublished

Conclusion: It's a mixed bag

	L1	L2	L3	L4
Associated with MDR-TB	No	Yes	No	Yes
General tolerance	Low	Low	High	High

- It's likely that the importance of tolerance is lineage-specific
- The general clinical relevance of tolerance in TB needs to be explored

Thank you!

erc

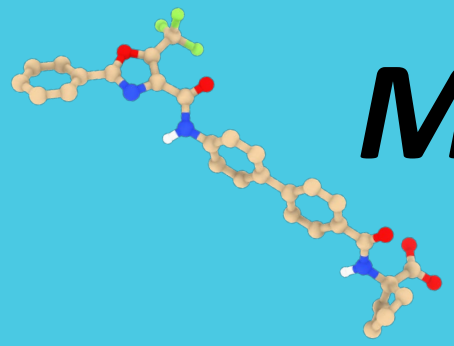
Swiss National Science Foundation

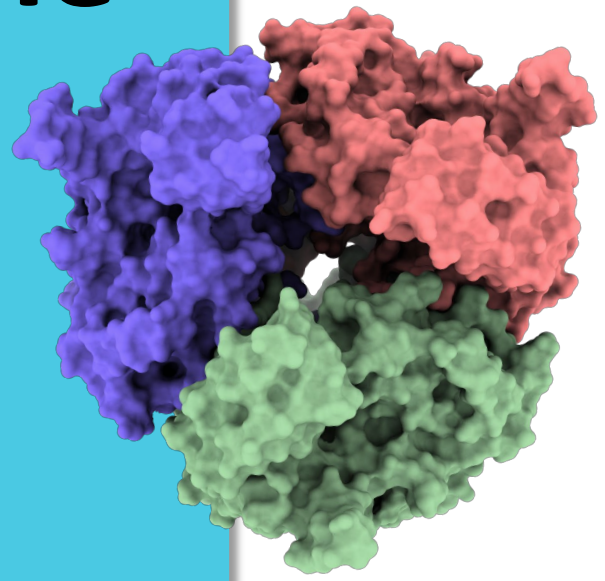
Universität Zürich[UZH]

MiM Microbiology Immunology

Swiss National Science Foundation

Characterization of a novel compound class targeting the *M. tuberculosis* RNA degradosome





T. Griesser, R. Wang, J. Rogenmoser, J. Obrist, P. Sander

Institute of Medical Microbiology, National Reference Laboratory for Mycobacteria

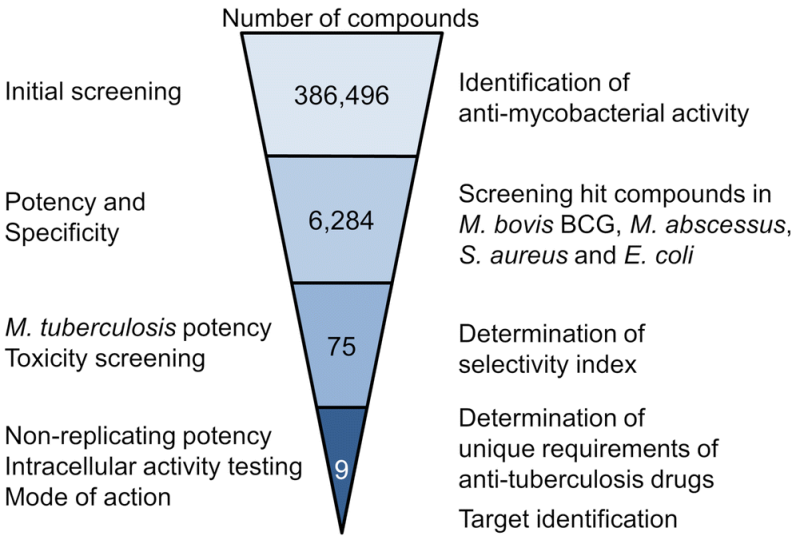
Introduction – the current Problem with Mtb

“The major challenge of managing TB, with current drugs, is the emergence and spread of multidrug resistance strains. Hence, we need new compound classes with novel modes of action that are not targeted by current resistance mechanism.”

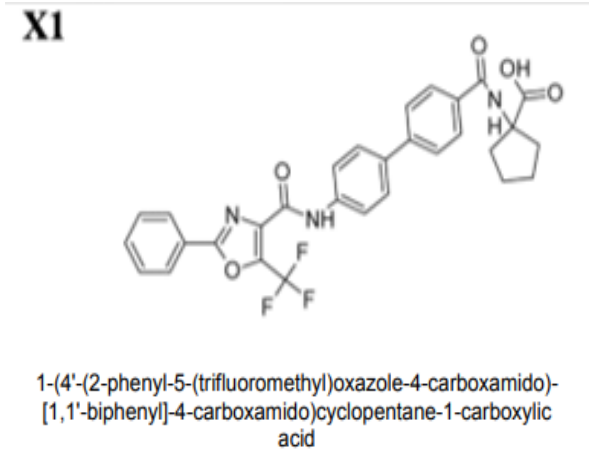
Quote from the talk : Discovering and developing new treatments for tuberculosis –
Nader Fotouhi CSO TB Alliance US, *24.03.2021,* GARDP Seminars

<u>Treatment of DS TB:</u>
Long lasting combination therapy
2 Months : RIF, INH, EMB, PZA
4 months: RIF, INH

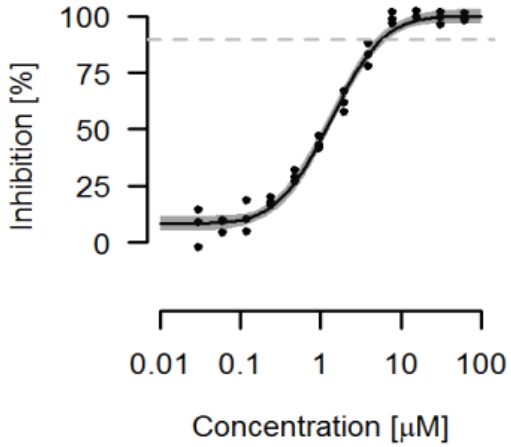
Compound identified by phenotypic whole cell screening



Dal Molin et. al, 2019



Dal Molin et. al, 2019

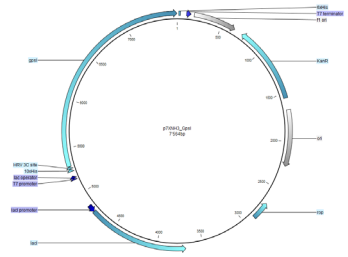


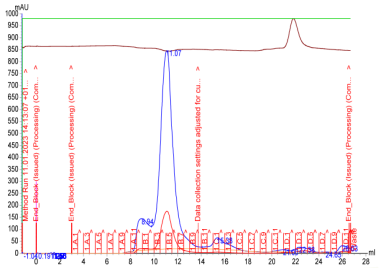
MIC90 Mtb	Selection	Substitution in *gpsI* (Rv2783)	Mutant frequency
7.81 µM	64 µM	A527D	8.75*10^-9

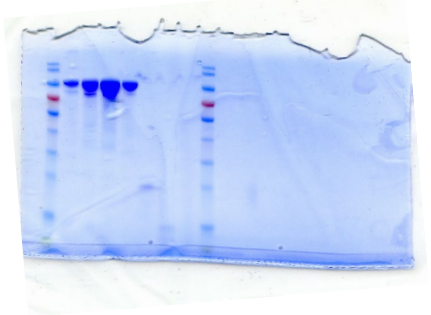
Dal Molin et. al, 2019

Assumption: Mode of action and mode of resistance two side of one coin

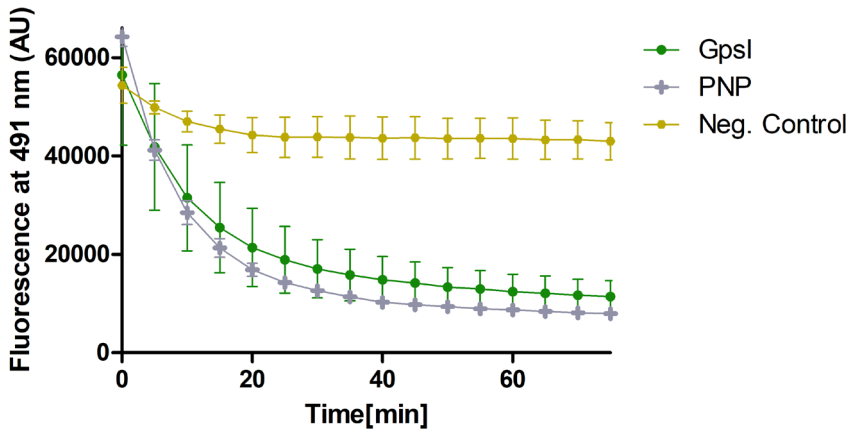
Enzymatic characterization of Mtb GpsI

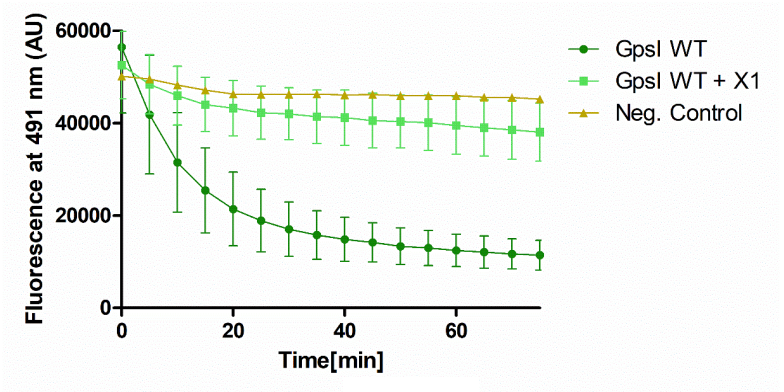


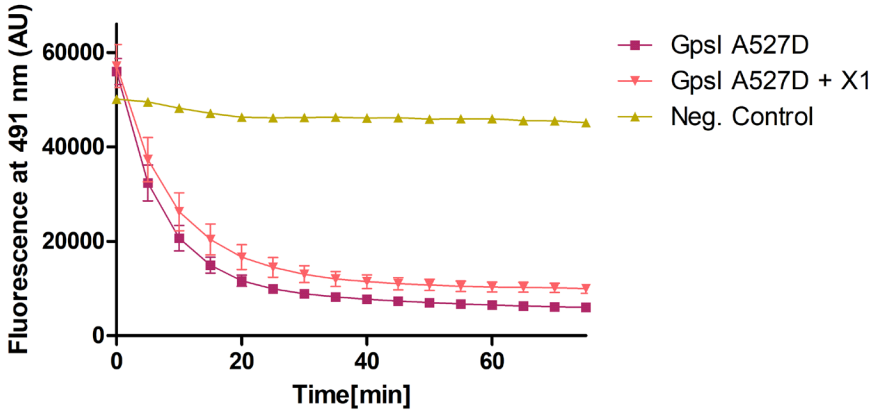




Poly(A) degradation

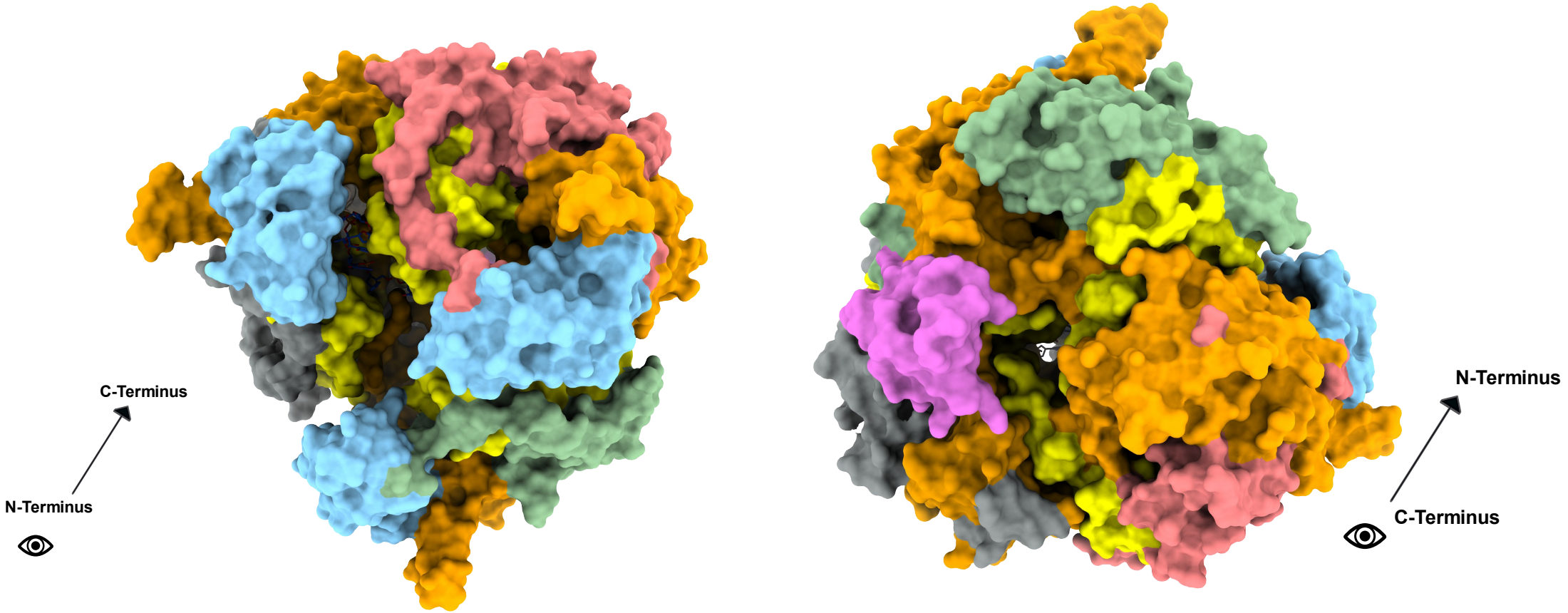




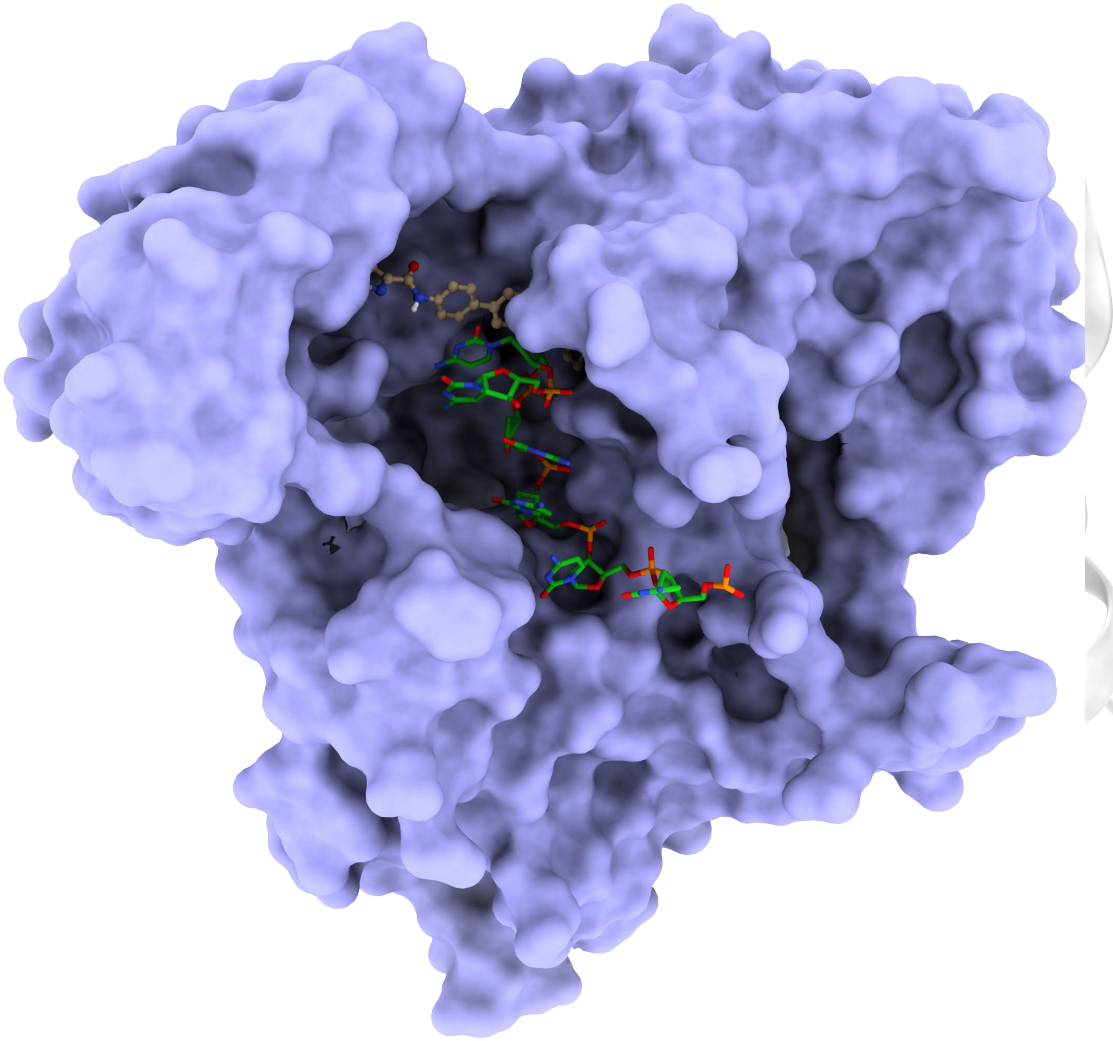


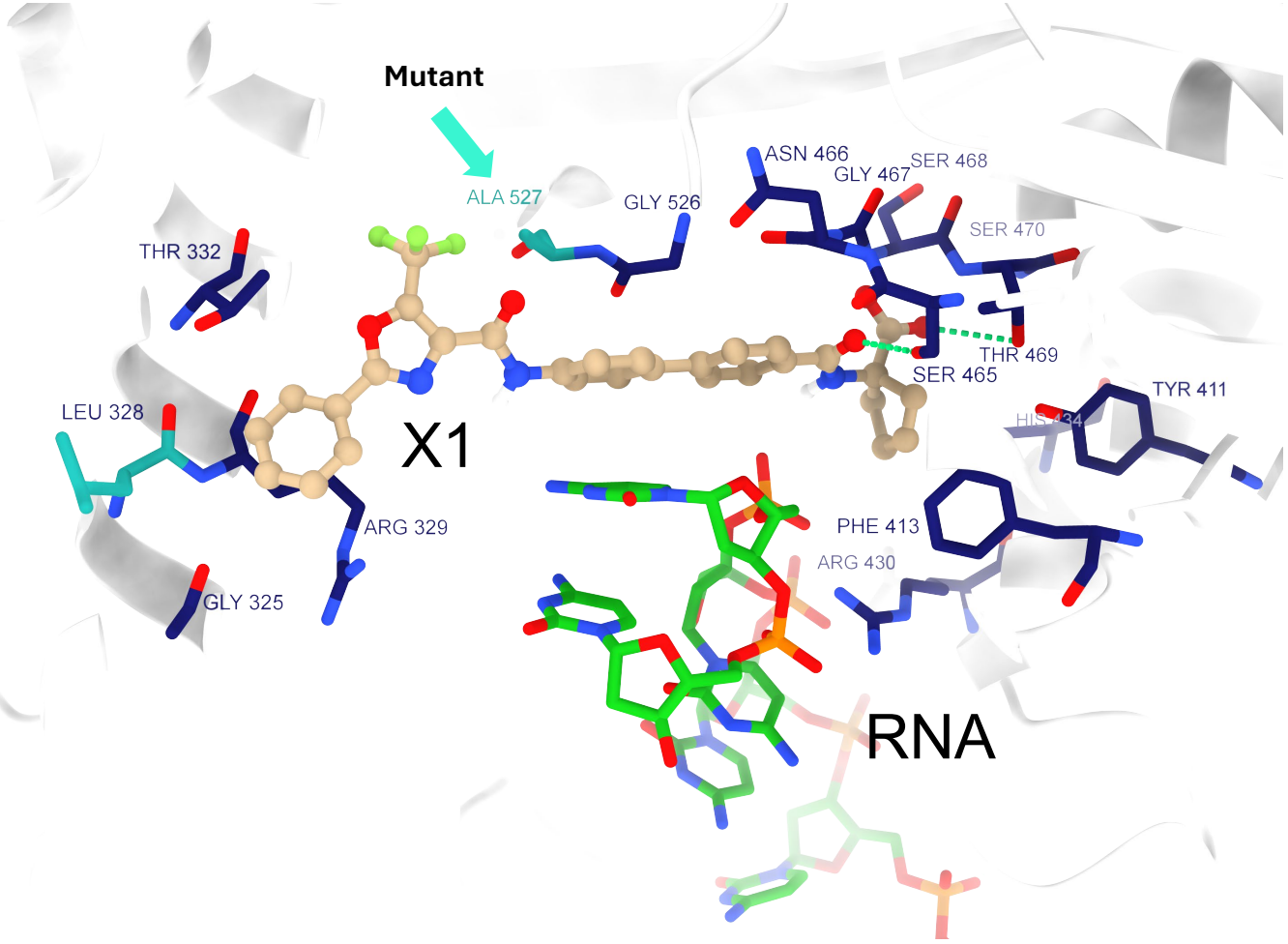
$$RNA_n + P_i \rightarrow NDP + RNA_{n-1}$$

Structural investigation of Mtb GpsI in complex with X1 and RNA



Binding site of compound X1

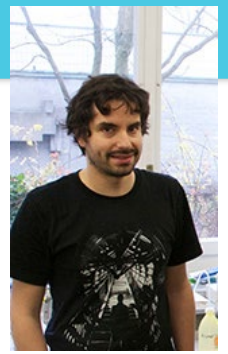




Take Home Message

We provide the basis for the development of a novel compound class that target an yet unexplored and unexploited pathway, the RNA degradation

Acknowledgement



Michael Dal Molin

Rui Wang

Julia Obrist

Janis Rogenmoser

Institute of Medical Microbiology

Peter Sander

Roche

DUBOCHET CENTER FOR IMAGING

Swiss National Science Foundation

BAG OFSP UFSP

Question?

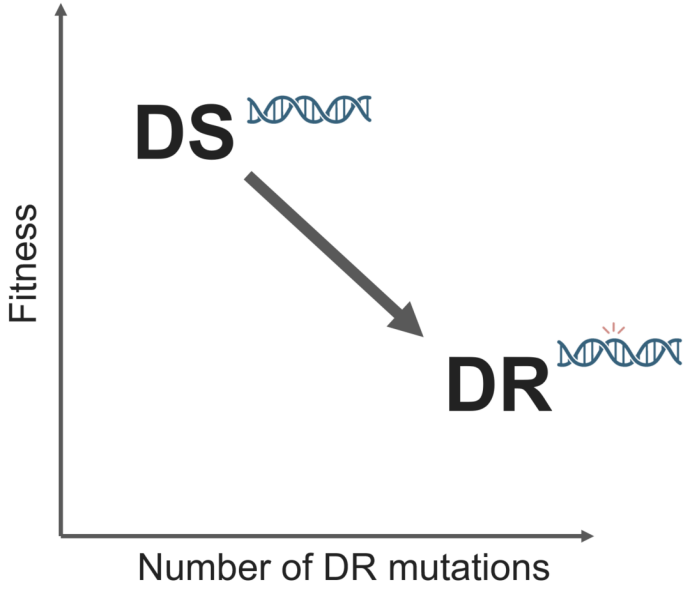
Swiss TPH

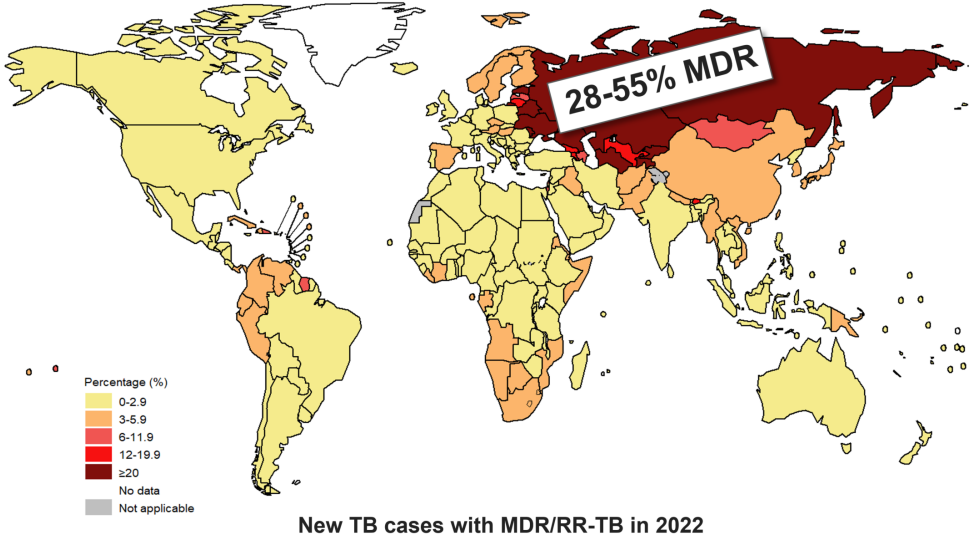
Epistasis as a driver of pre-XDR-TB epidemics

Selim Bouaouina
PhD student
Tuberculosis Ecology & Evolution
Medical Parasitology and Infection Biology

Tuberkulose Symposium 2024 – Joint TB-Meeting
30. October 2024

“Fitness cost” of drug resistance



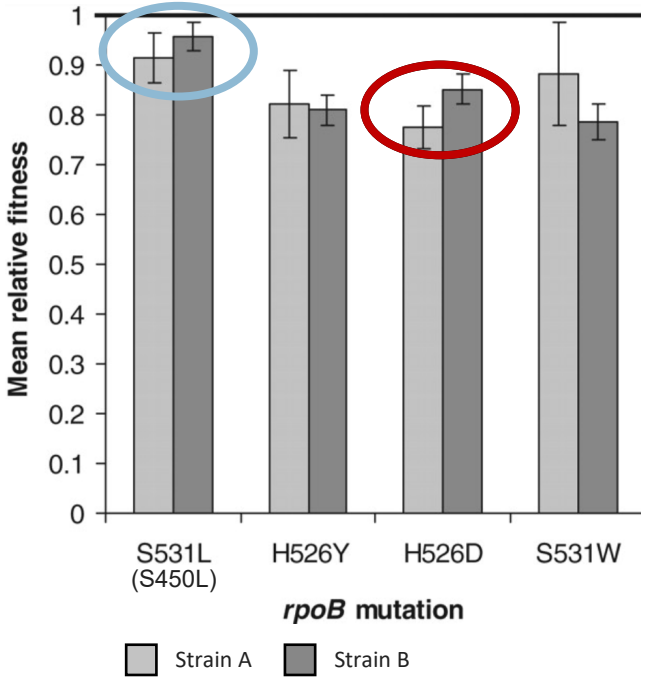


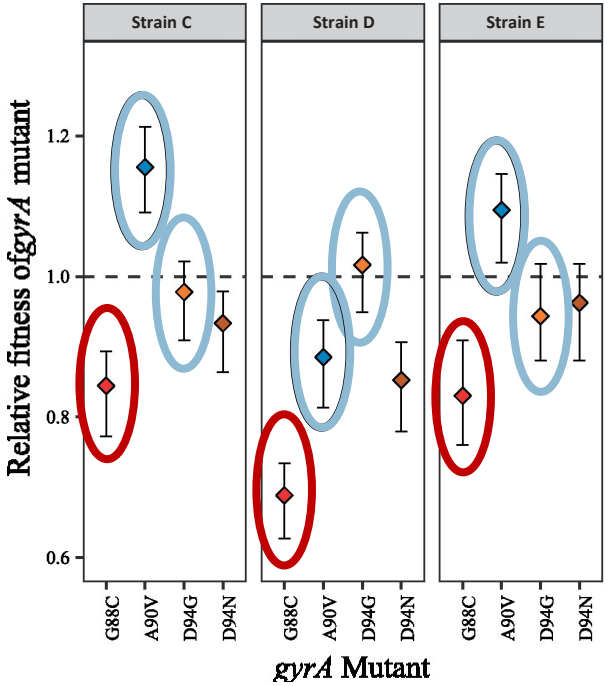
New TB cases with MDR/RR-TB in 2022

Swiss TPH

Global Tuberculosis Report (2023)

Genetic background influences fitness cost

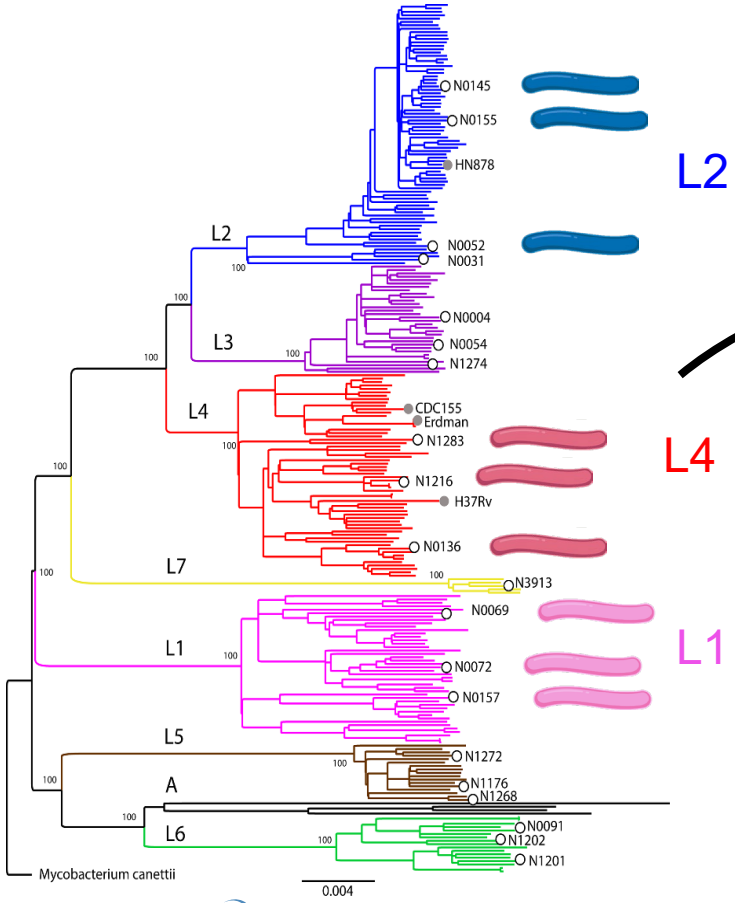




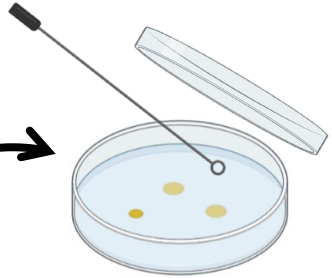
Swiss TPH

Gagneux et al., Science (2006)
Castro et al.,Mol. Biol. Evol. (2021)

Picking and phenotyping mutants



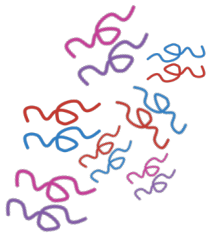
RIF^R and/or FQ^R



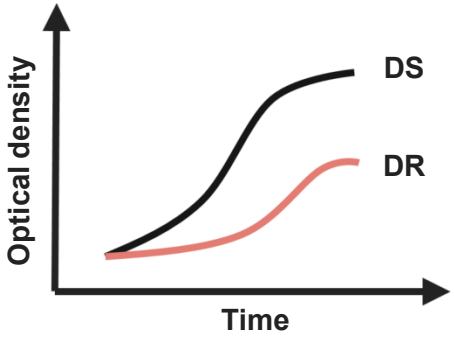
Spontaneous drug resistant mutants

Low-/no-cost	High-cost
rpoB S450L	*rpoB* H445R
gyrA A90V	*gyrA* G88C
gyrA D94G	

Proteome



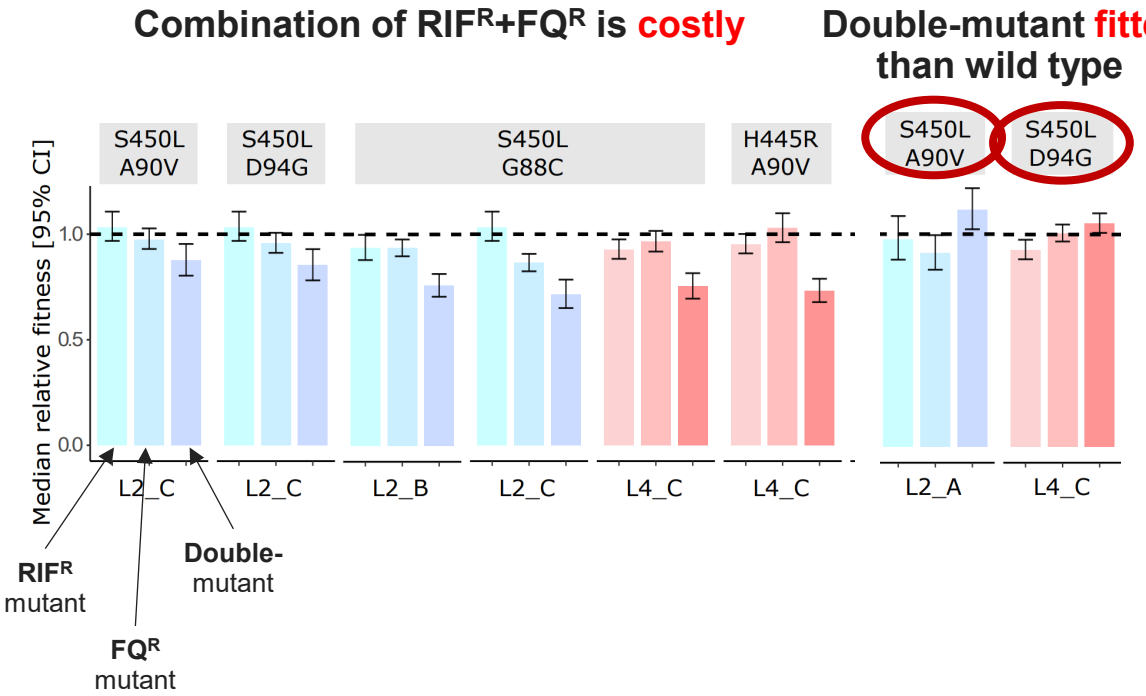
Relative fitness
(by in vitro growth)

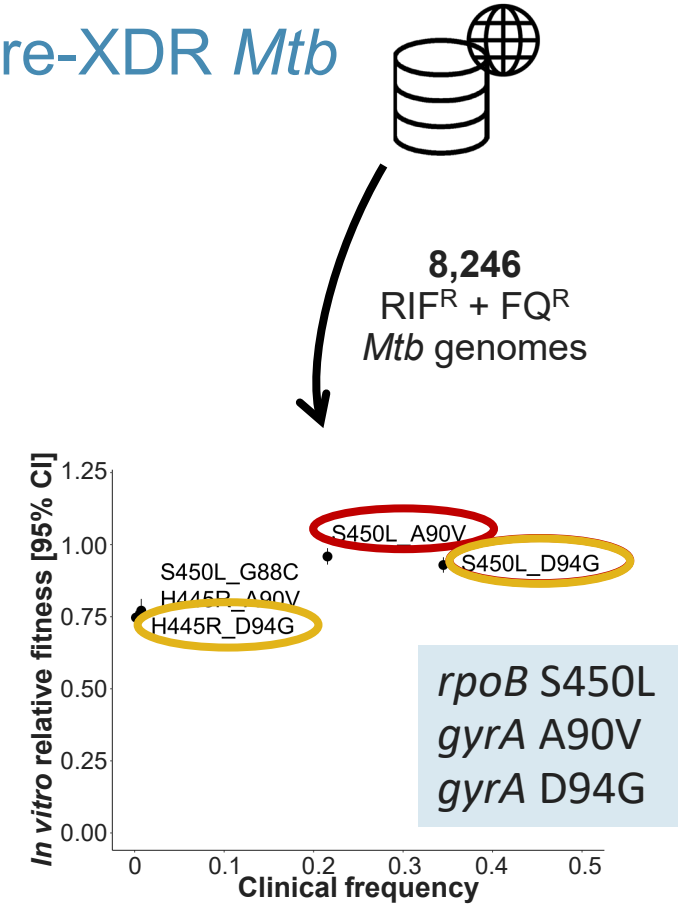


Swiss TPH

Borrell et al., PLOSOne (2019)

In vitro and *in clinico* relative fitness of pre-XDR *Mtb*



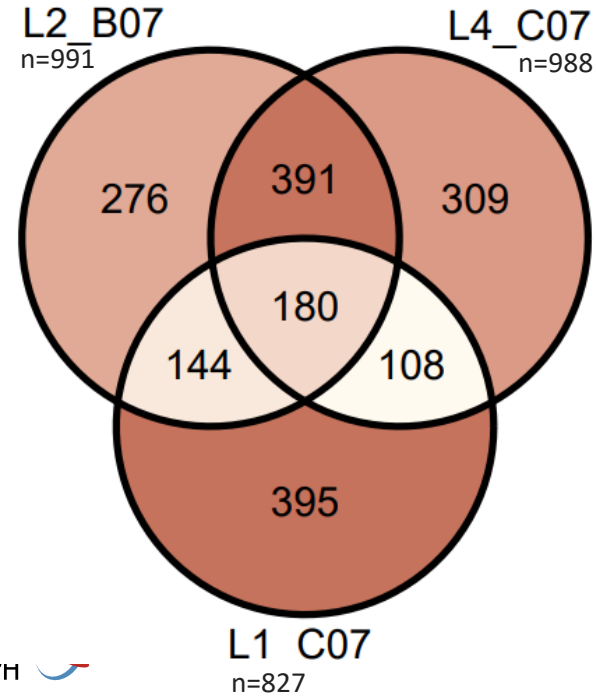


Swiss TPH

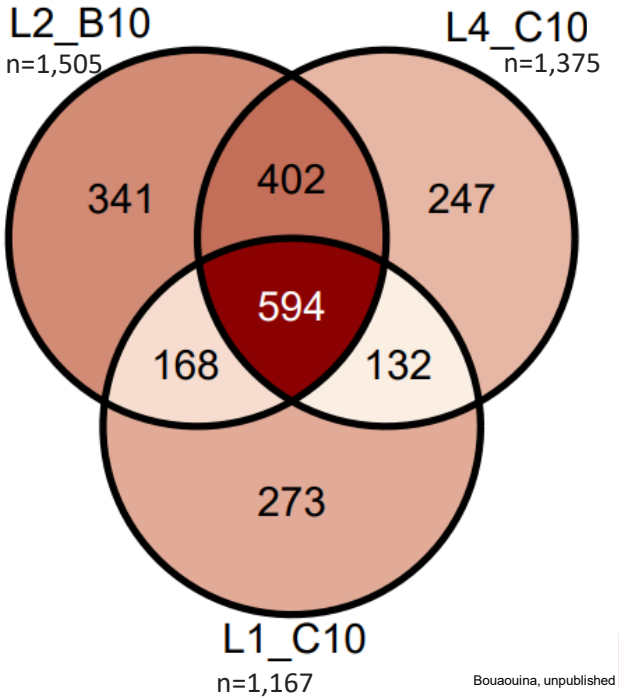
Bouaouina, unpublished

More proteins differentially abundant in low-fitness mutant

***rpoB* S450L-*gyrA* D94G mutant**
vs.
wild type



***rpoB* H445R-*gyrA* D94G mutant**
vs.
wild type



Bouaouina, unpublished

Thanks!

Swiss TPH

TB Ecology
Jérôme Azizaj
Chloé Loiseau
Valerie March
Sevda Kalkan
Miriam Reinhard
Sonia Bòrrell
Sébastien Gagneux
Daniela Brites
Galo Goig
Levan Jugheli
Nino Maghradze
Kakha Mchedlishvili
Gian Schüpbach
Elizaveta Skomorokhova
Christoph Stritt
Venus Rojas
Nestani Tukvadze
Etthel Windels
Michaela Zwyer

former members:
Anna Dötsch
Rhastin Castro
Julia Feldmann
Vanessa Trefzer

TB Immunology
Jasmin Albiez
Liwen Huang
Damien Portevin
Sarah Schmidiger
Laura Zaragoza Infante

Biostatistics
Amanda Ross

BSL3 Infrastructure
Thierry Brun
Fabien Haas

Civil servants
Romain Baechler
Sebastian Jossi
Vincent Grumbacher
Thomas Ruckli

Digital Health Unit
Hélène Langet
Marco Pereira

Biozentrum

Proteomics CF
Thomas Bock
Klemens Fröhlich
Ulrike Lanner
Alexander Schmidt

ETH Zürich

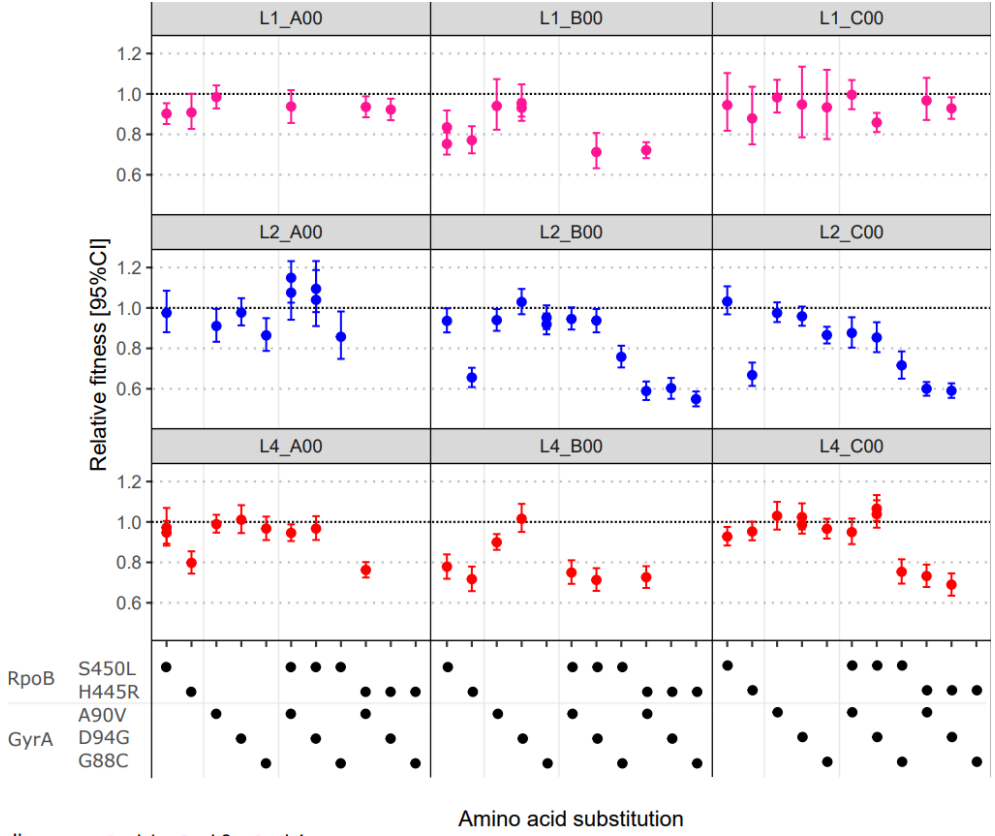
Molec. Systems Bio
Jan-Philipp Quast
Elena Krismer

erc

Swiss National Science Foundation

Swiss TPH

S1: in vitro fitness of single- and double mutants



S2: clinical frequencies of double mutants

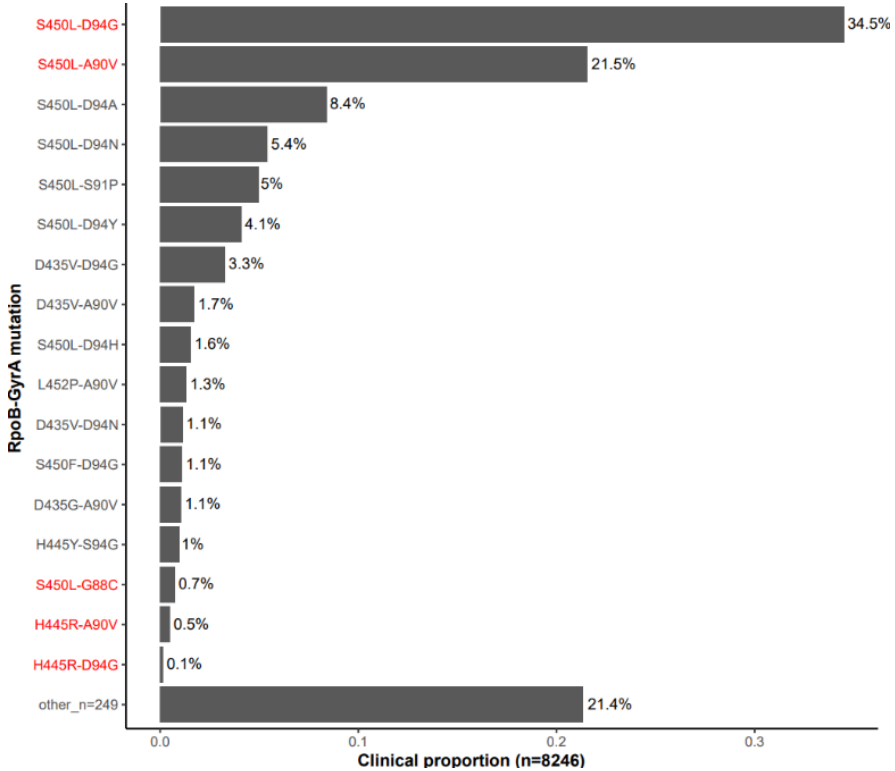
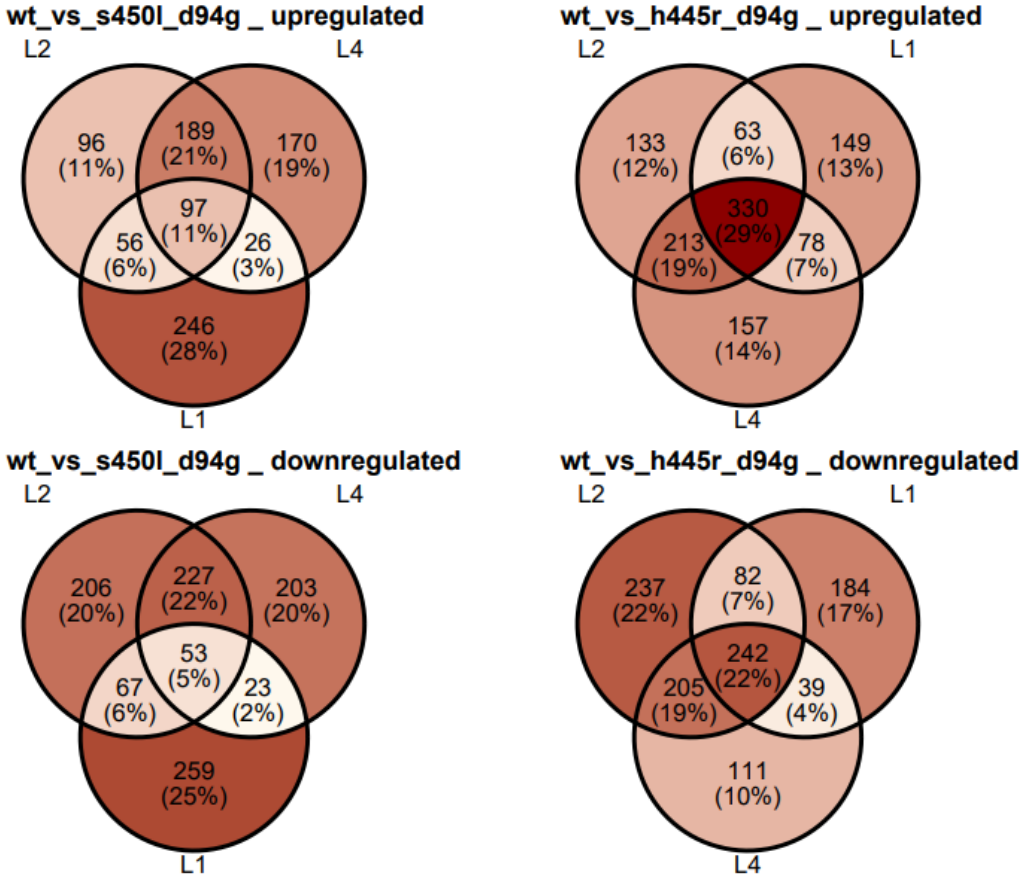


Fig. 4 | Clinical frequency of RpoB-GyrA DR mutations in combination. A) The clinical frequency of each combination of RpoB and GyrA DR mutation, which occurred in the data set of clinical isolates (n=8,246) at a rate of ≥0.1% is depicted.

Bouaouina, unpublished

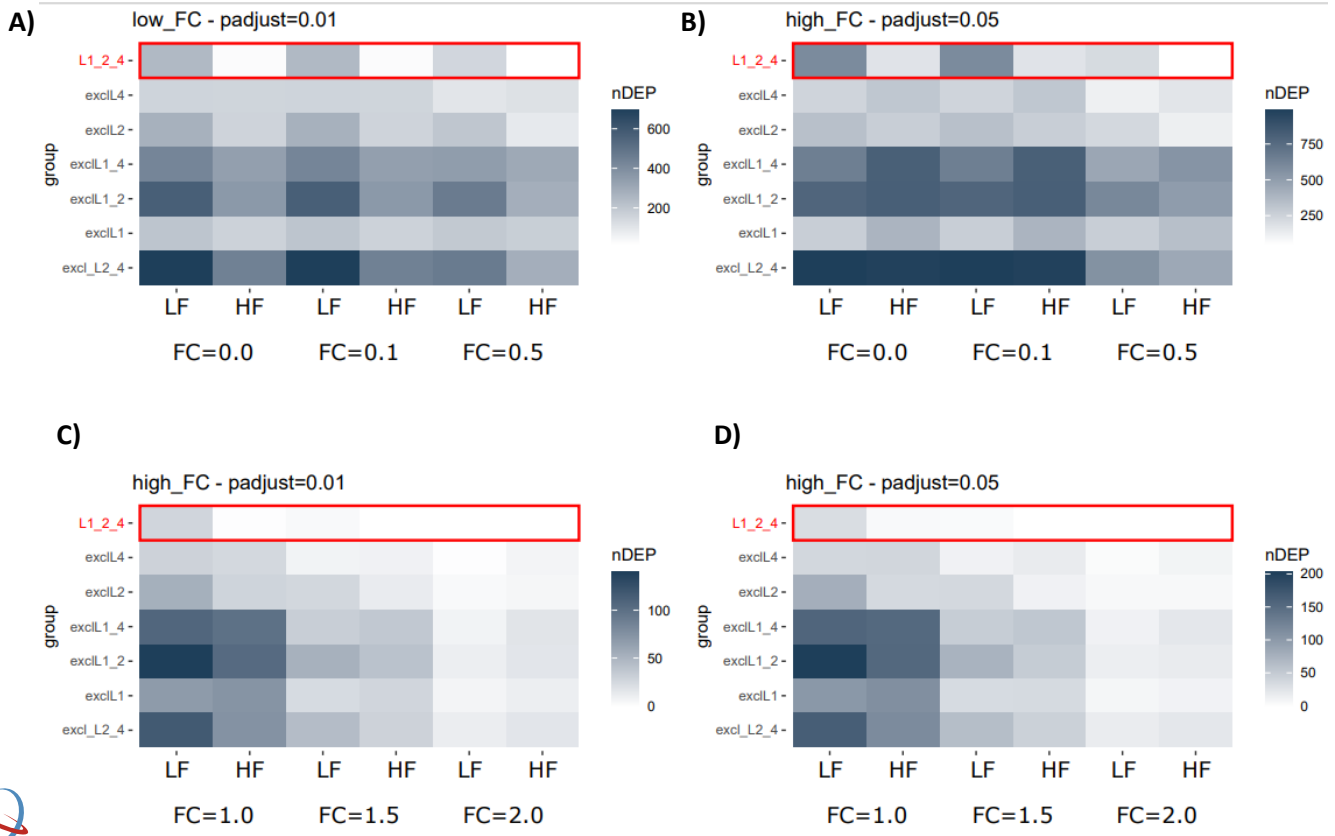
S3: Higher- and lower-abundant proteins



Swiss TPH

Bouaouina, unpublished

S4: log2FC and significance-thresholds



Bouaouina, unpublished

Tuberculosis Drug Resistance Prediction by Targeted Next-Generation Sequencing

Joint Swiss TB Day and Translational TB Forum
30 October 2024

Tiana Schwab

Institute of Social and Preventive Medicine, University of Bern, Switzerland

Tuberculosis drug susceptibility testing (DST) remains a major bottleneck

Of an estimated 62,000 incident drug-resistant TB cases in Africa in 2022, only 22,495 (36%) were diagnosed[1]

Molecular amplification tests

+ Rapid results
+ Simple to use
- Individual drug targets

Culture-based DST

+ Phenotypic testing
- Time-consuming
- Requires BSL-3 infrastructure

Targeted sequencing

+ Large panels of gene targets
+ Results in days

[1] World Health Organization. *Global Tuberculosis Report 2023*

Studies on TB targeted sequencing have been conducted worldwide

Figure: Samples collected in 79 studies across 53 countries

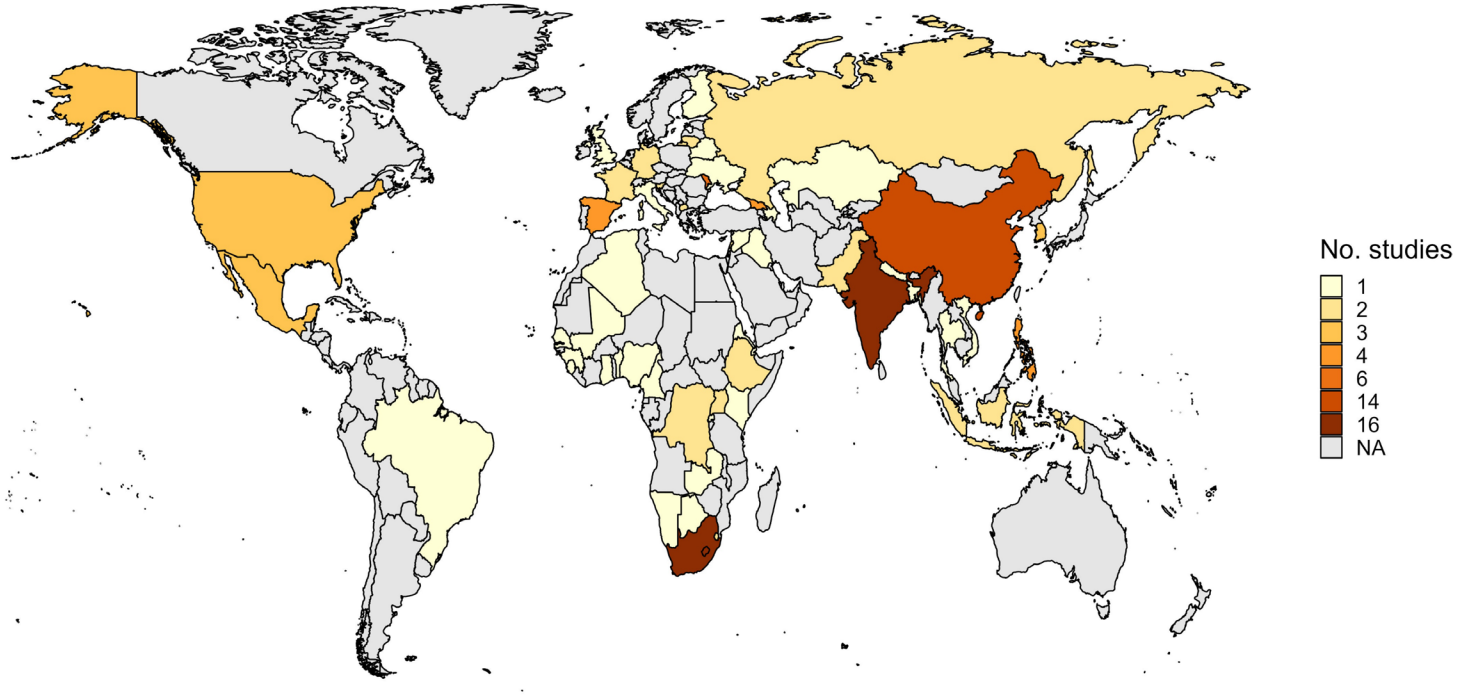


Table: Pooled test accuracy estimates from meta-analysis of 24 diagnostic test accuracy studies

	Primary samples	Culture isolates
Sensitivity (95% CI)	**90.5%** (86.2–93.9)	**95.2%** (93.0–96.9)
Specificity (95% CI)	**97.6%** (96.6–98.3)	**98.2%** (97.2–99.0)

Schwab et al. (2024), *Lancet Infect Dis*

There is a lack of local sequencing in TB high-burden countries

Figure: Country of sequencing reported in 68 studies

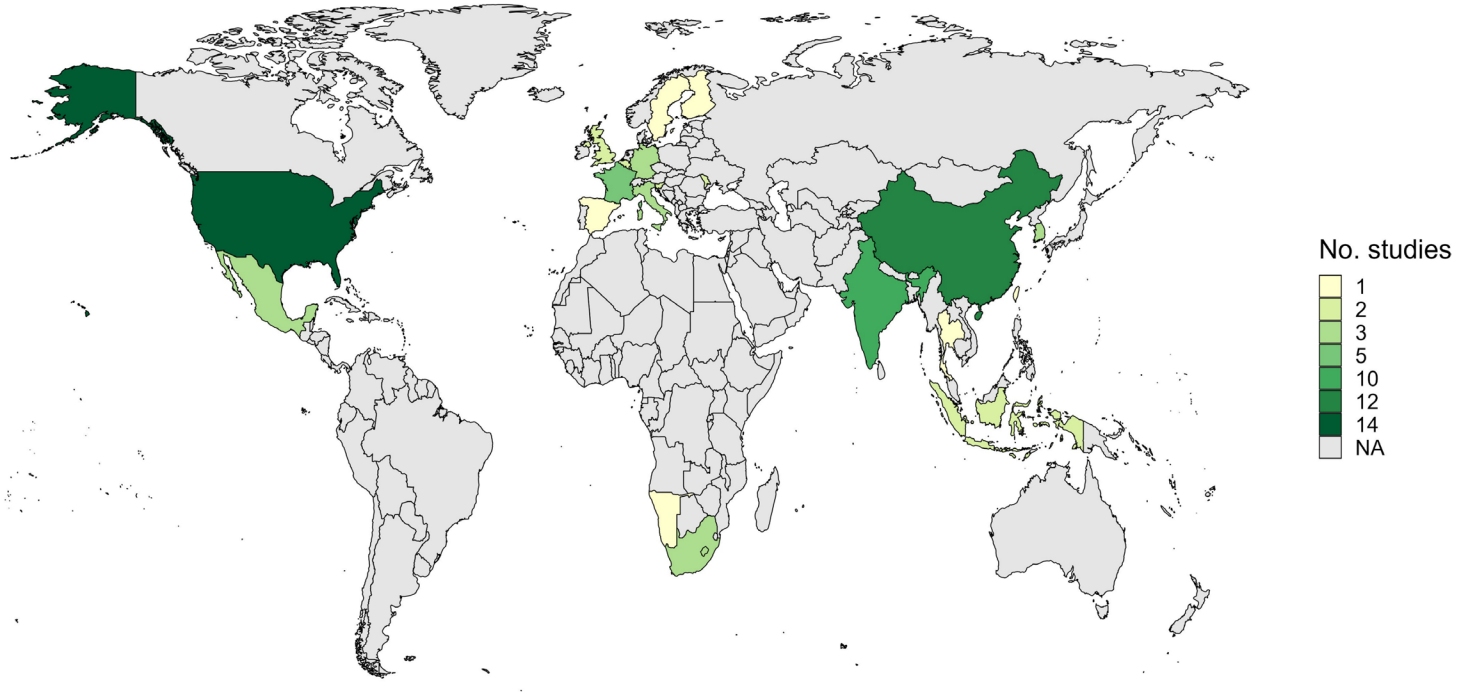


Table: Pooled test accuracy estimates from meta-analysis of 24 diagnostic test accuracy studies

	Primary samples	Culture isolates
Sensitivity (95% CI)	**90.5%** (86.2–93.9)	**95.2%** (93.0–96.9)
Specificity (95% CI)	**97.6%** (96.6–98.3)	**98.2%** (97.2–99.0)

Schwab et al. (2024), *Lancet Infect Dis*

Implementing targeted sequencing in high-burden, routine setting

Tuberculosis Drug Resistance Test (TBDR)

- Oxford Nanopore Diagnostics Ltd., United Kingdom
- Nanopore-based sequencing technology
- Predicts drug resistance to 16 TB drugs

CIDRZ for a healthy Zambia

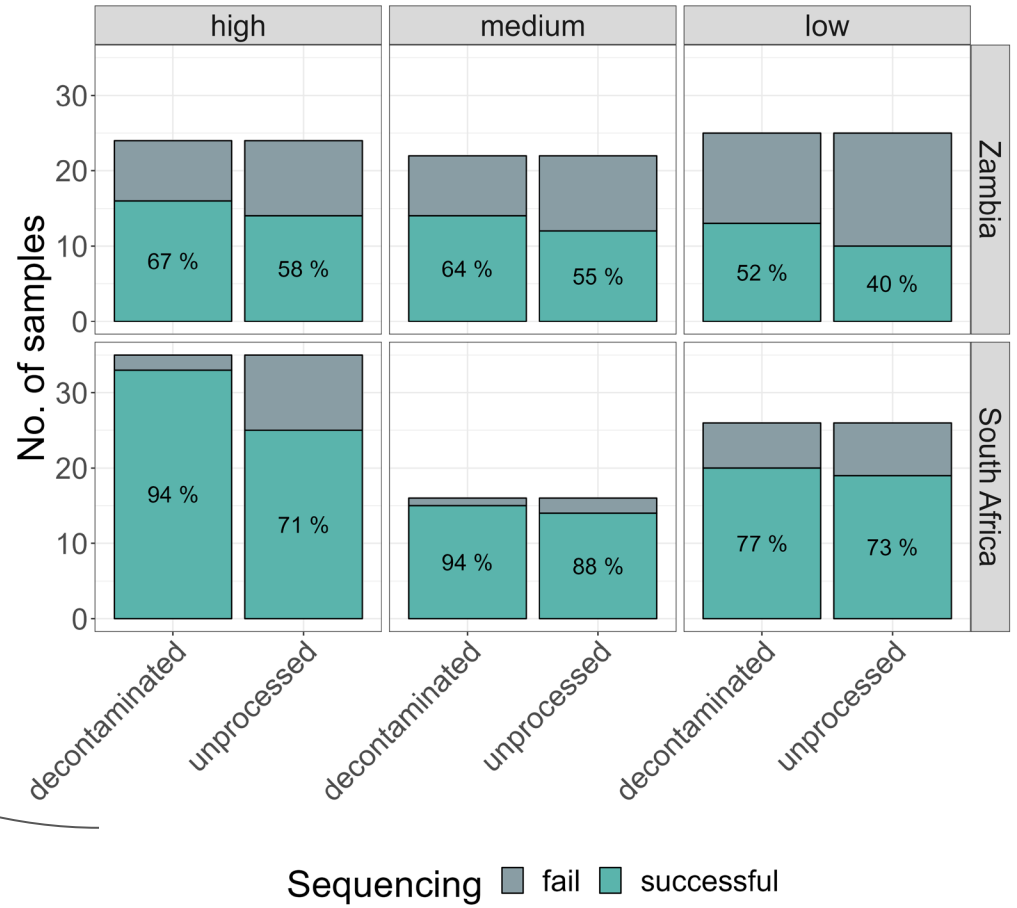
Lusaka, Zambia
District diagnostic laboratory

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Johannesburg, South Africa
National TB reference laboratory

TBDR successfully implemented at two laboratories in Sub-Saharan Africa

Successful sequencing = drug susceptibility predicted for at least one TB drug



Successful sequencing from decontaminated and unprocessed sputum samples

Higher sequencing success rates in South Africa

TBDR test accuracy compared to local DST was variable

TB drug	n	Sensitivity (95% CI)	Specificity (95% CI)
Rifampicin (RIF)	103	94% (81–98%)	99% (93–100%)
Isoniazid (INH)	92	62% (42–78%)	99% (93–100%)
Ethambutol (EMB)	97	64% (39–83%)	94% (86–98%)
Pyrazinamide (PZA)	94	37% (19–59%)	100% (95–100%)
Streptomycin (STM)	34	29% (8–64%)	96% (81–100%)
Amikacin (AMK)	72	50% (9–91%)	100% (95–100%)
Capreomycin (CAP)	70	100% (21–100%)	100% (95–100%)
Kanamycin (KAN)	71	100% (21–100%)	100% (95–100%)
Ethionamide (ETH)	69	38% (14–70%)	97% (89–99%)
Levofloxacin (LFX)	35	75% (30–95%)	97% (84–100%)
Moxifloxacin (MFX)	14	67% (21–94%)	91% (62–98%)
Bedaquiline (BDQ)	14	100% (21–100%)	92% (66–99%)
Clofazimine (CFZ)	10	100% (21–100%)	86% (60–96%)
Linezolid (LZD)	14	-	100% (78–100%)
Delamanid (DLM)	13	-	92% (66–99%)

Compared to a combined reference standard of local DST (Xpert® MTB/RIF Ultra, phenotypic DST, whole-genome sequencing, or Xpert® MTB/XDR). Drug-resistant if resistance was detected by any test.

Main takeaways

- Targeted sequencing is a valuable addition to current DST methods:
  - Rapid results
  - Information-rich
  - Predicted drug resistance to panels of multiple TB drugs

- Nanopore-based TBDR targeted sequencing is possible in diverse settings.
  - Standardized protocols and automated bioinformatics pipeline
  - Flexible and robust when adapting to local context

- Technical and logistic issues complicate implementation.

Acknowledgements

Institute of Social and Preventive Medicine, University of Bern
Lukas Fenner
Matthias Egger
Beatrice Minder
Orestis Efthimiou
Freddy F. G. De la Hoz
Adrien P. Lahousse

National Institute for Communicable Diseases
Shaheed V. Omar
Lavania Joseph
Mamello Motsei

Centre for Infectious Disease Research in Zambia
Carolyn Bolton
Guy Muula
Andrew Moono
Bertha Chibwe
Nyambe Kakula
Jackson Daka

Institute of Medical Microbiology, University of Zürich
Pauline C. Göller

Department of Pulmonology and Allergology, Inselspital
Gunar Günther

Clinical Bacteriology/Mycology, University Hospital Basel
Peter M. Keller

Institute für Infektionskrankheiten, University of Bern
Alban Ramette
Stefan Neuenschwander
Sonja Gempeler
Miguel Terrazos

Health Economics and Epidemiology Research Office, University of the Witwatersrand
Denise Evans
Nelly Jinga,
Sinethemba Madlala,
Nkateko Lebognag Ngolele

Many thanks especially to the participants of the study.

This research was supported by the U.S. National Institutes of Health's National Institute of Allergy and Infectious Diseases (NIAID) under Award Number U01AI069924.
The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

INSELGRUPPE

Joint TB Forum 2024

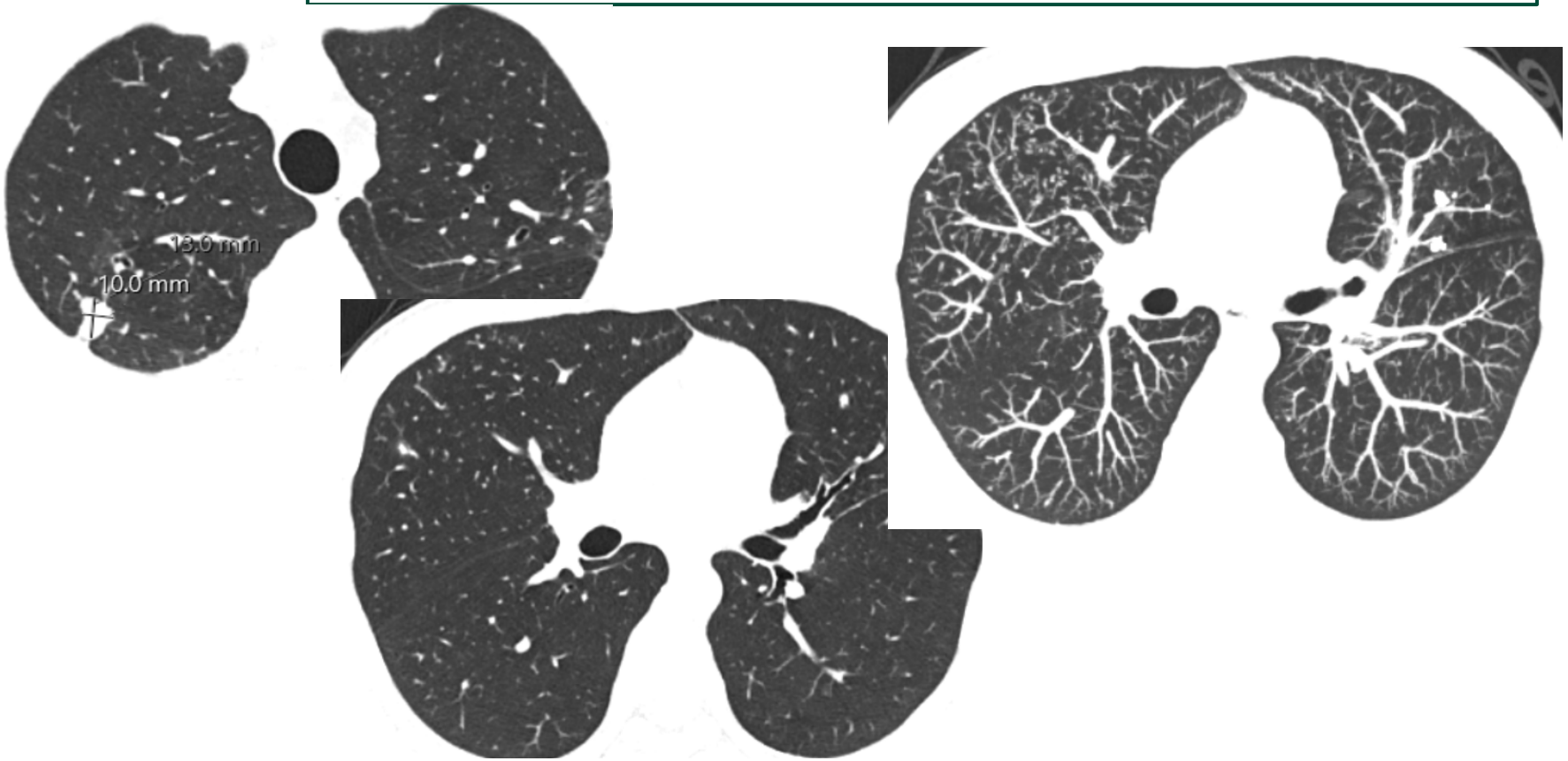
30.10.2024 Nasstasja Wassilew, Inselspital Infektiologie, Infektionsprävention

Case presentation

19 yr old male, asylum seeker from Afghanistan (Balkan route)

Anamnesis:	Weight loss, intermittent cough, no fever, no night sweats
History:	Pulmonary TB 4 years ago in Afghanistan, treated with standard regimen, stop after 5mths due to side effects
Clinical exam:	unremakable, unless BMI 16 kg/m²
X-ray:	Multiple small areas of decreased transparency both upper lobes

CT Thorax 12/2023



Microbiologic investigations

- 11/2023 4x Sputum smear and PCR neg
- 12.12.23 BAL: AFB neg, GeneXpert neg
- HIV: negative

6.5 weeks later:

- **culture positive for *M. tuberculosis***

Auftrag	Eingang	Entnahme	Material
			bronchoalveoläre Lavageflüssigkeit
4037590	13.12.2023	12.12.2023 15:29	Mittellappen
			Mutation H526D
Selektivkultur			
Mykobakterien			POSITIV
1)2)Identifikation			Mycobacterium tuberculosis
Resistenzprüfung			
Isoniazid	0.1 mg/l		sensibel
Rifampicin	1.0 mg/l		resistent
Ethambutol	5.0 mg/l		sensibel
Streptomycin	1.0 mg/l		sensibel
Moxifloxacin	0.25 mg/l		sensibel
Pyrazinamid	100 mg/l		sensibel
			Das Isolat wird ans Nationale Zentrum für Mykobakterien in Zürich verschickt.

Treatment

Rifampicin monoresistant Tuberculosis

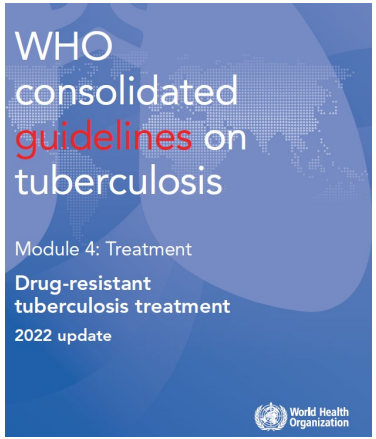
→ BPaLM regimen

BUT Pretomanid not available in Switzerland

→ Start 30.1.2024

Bedaquilline
Linezolid
Moxifloxacin
Clofazimine
Pyrazinamid

} replaced by Pretomanid on 11.02.24



5 weeks later

Kulturergebnisse

[1] *Mycobacterium tuberculosis*

National Reference Center for Mycobacteria, Zürich

Antibiogramm	[1]		[1]
Isoniazid 0.1 mg/l	S	Ethionamid 5.0 mg/l	S
Ethambutol 5 mg/l	S	Levofloxacin 1.0 mg/l	S
Rifabutin 0.1 mg/l	R	Prothionamid 2.5 mg/l	S
Rifabutin 0.4 mg/l	R	p-Aminosalicylsäure 4 mg/l	S
Rifabutin 2 mg/l	R	Cycloserin 50 mg/l	S
Rifampicin 0.5 mg/l	R	Capreomycin 2.5 mg/l	S
Rifampicin 1 mg/l	R	Pyrazinamid 100 mg/l	S
Rifampicin 4 mg/l	R	Linezolid 1 mg/l	S
Rifampicin 20 mg/l	R	Clofazimin 1.0 mg/l	R
Amikacin 1 mg/l	S	Clofazimin 2.0 mg/l	I
Streptomycin 1 mg/l	R	Kanamycin 2.5 mg/l	S
Streptomycin 4 mg/l	S	Delamanid 0.06 mg/l	S
Streptomycin 20 mg/l	S	Bedaquilin 1.0 mg/l	R
Moxifloxacin 0.25 mg/l	S	Bedaquilin 2.0 mg/l	R

Primary bedaquilin/clofazimine resistant

fluoroquinolone (and isoniazid) sensitive

Tuberculosis

Pretomanid: MIC = 0.125 mg/L (S)

NGS: *M. tuberculosis* lineage 3, intragenic insertion of IS*6110* into *mmpR5 (Rv0678)* .

Bedaquiline resistance: challenges

- How would you treat BDQ resistant, FQ sensitive TB?
- And how long?

→ No definition of bedaquiline resistant, fluorquinolone sensitive TB

→ No evidence for the best treatment and duration

Bedaquiline Resistance

Primary BDQ resistance
no prior exposure to Bedaquiline
(Metaanlysis[1]: 2.4% (95% CI 1.7–3.5))

Acquired BDQ resistance
after exposure to Bedaquiline, documented prior Bedaquiline susceptibility
(Metaanalysis[1]: 2.1% (95% CI 1.4–3.0))

Transmission of BDQ resistance
revealed by cluster analyses
(retrospectiv observ. study[2]:
76% MDR -> 94% XDR TB)

[1]Perumal ERJ 2024
Mallick JAC 2022
[2]Barilar JAC 2024
Antoine et al. Mic Spec 2021

No wide scale surveillance on bedaquiline resistance prevalence

Bedaquiline Resistance - Mozambique

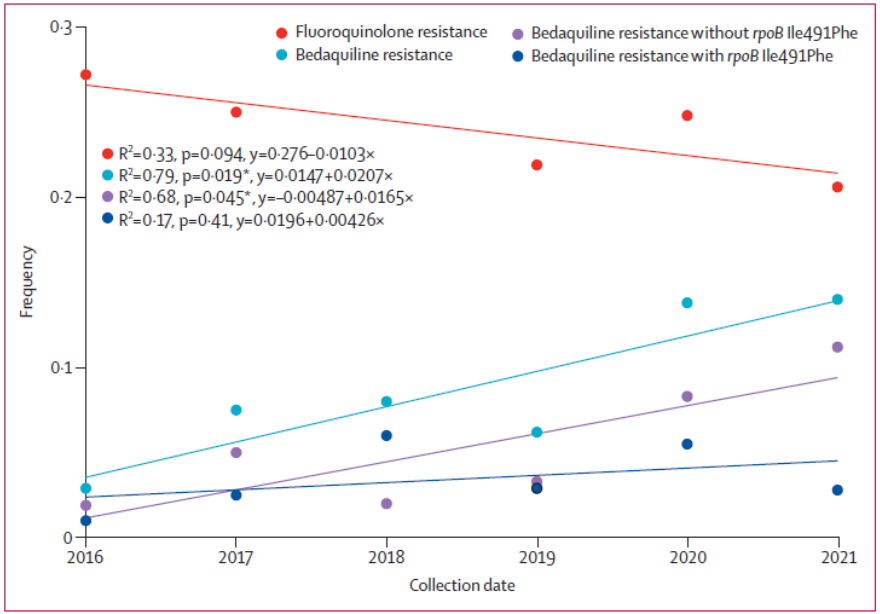


Figure 1: **Frequency of bedaquiline and fluoroquinolone resistance in *Mycobacterium tuberculosis* complex strains over time**

Linear regression analysis of correlation of bedaquiline and fluoroquinolone resistance frequency with the year of strain isolation, additionally stratified by presence or absence of the *rpoB* Ile491Phe mutation for bedaquiline. Frequencies of resistant strains were calculated over the period 2016–21.

- 61 (8·7%)/ 704 Mtbc strains: evidence of BDQ resistance (>90% due to mutations in *Rv0678)*
- BDQ resistance found in 5 RMP-resistant strains and 32 MDR strains

  → emerged independently from FQ resistance.
- **Prevalence of BDQ resistance increased significantly over time:**

  3% in 2016 → 14% in 2021

Mtbc isolates from the NTRL biobank Mocambique; 964 Mtbc strains cultured; 809 Mtbc strains WGS

Barilar Lancet ID 2024

Treatment

Bedaquilline
Pretomanid
Linezolid
Moxifloxacin

→ Pyrazinamid + Isoniazid

→ duration: 9 -12 months

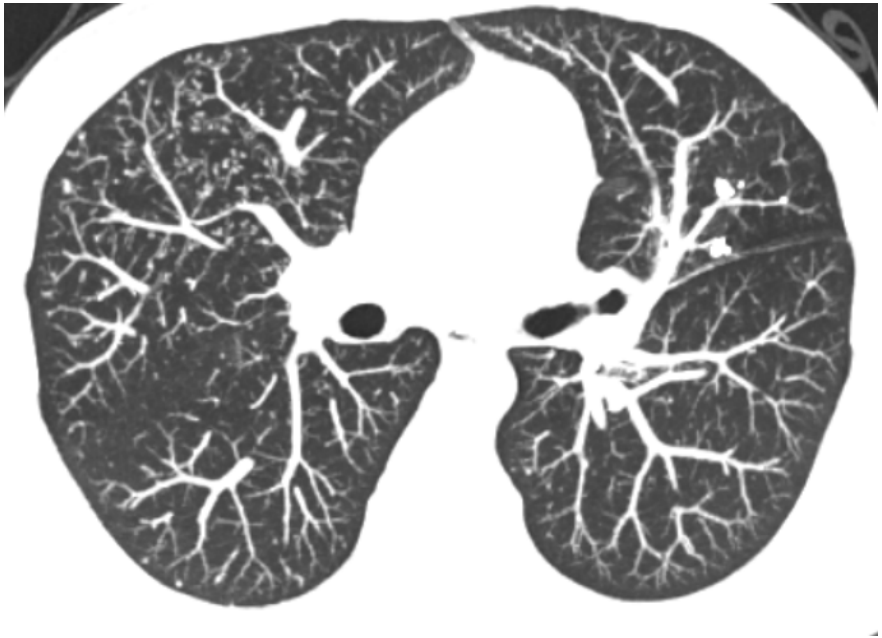
04/2024:

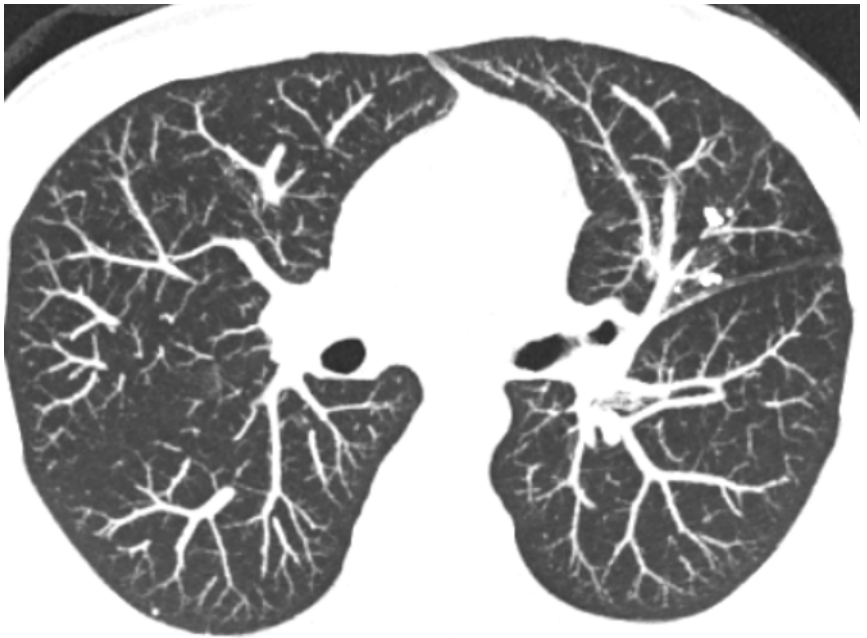
Linezolid induced optic neuropathy

→ Linezolid dose reduction 600mg → 300mg/d

Mok, Lancet 2022

CT Thorax 12/2023 → 10/24





Conclusions

- Diagnostic latency

- BDQ resistance occurs in patients - not previously treated for TB
  - with RMP monoresistance
  - in our setting

- Second line drugs (Pretomanid) difficult to obtain

- No evidence for how to treat BDQ-R, FQ-S TB

INSELGRUPPE

Acknowledgments

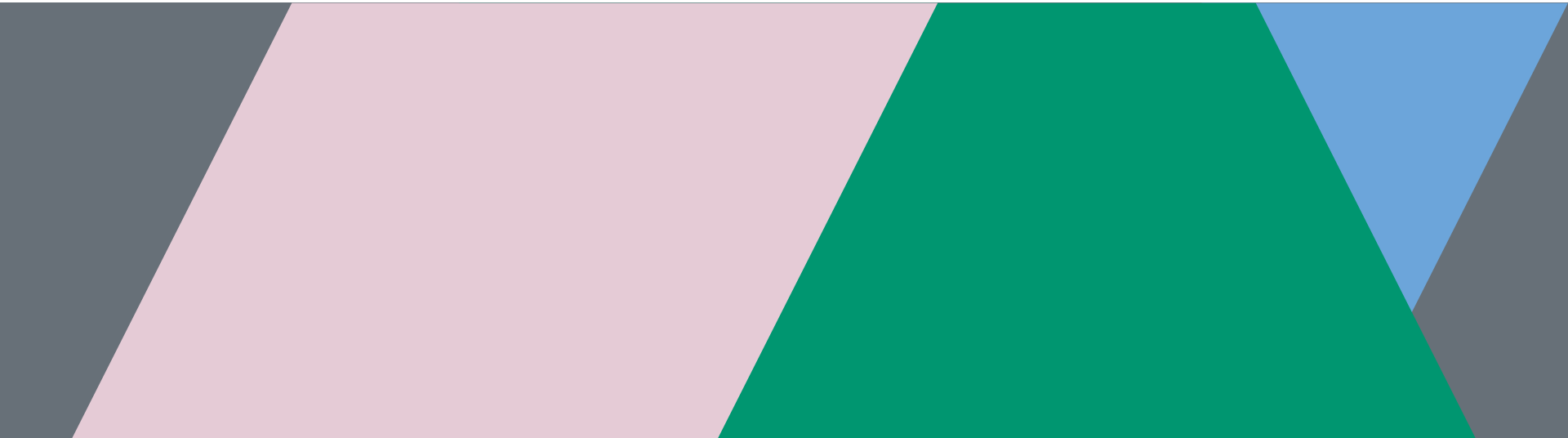
- Anna Eichenberger, Oberärztin Infektiologie Inselspital
- Cornelia Staehelin, Leitende Ärztin Infektiologie Inselspital
- Gunar Günther, Leitender Arzt Pneumologie Inselspital

Ref

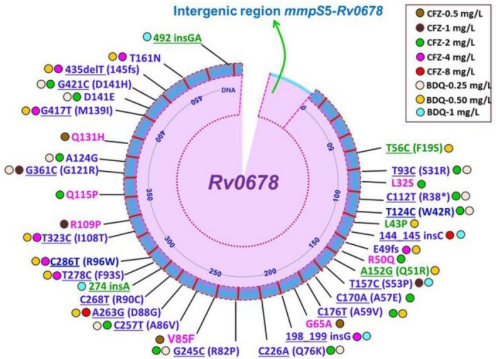
INSELGRUPPE

Thank you for your attention

nasstasja.wassilew@insel.ch



Bedaquiline Resistance



- mainly off-target resistance-associated variants (RAV) in the *mmpR5* (*Rv0678*) gene, regulator of an efflux pump
- can confer cross-resistance to clofazimine
- variable relationship with phenotypic bedaquiline resistance
- no defined genetic hotspot to target to develop a rapid molecular test (Xpert tests/LPAs)

Primary Bedaquiline Resistance:

- reservoirs of bedaquiline RAV exist prior to its use (and that of clofazimine)
- might expand under drug pressure with increasing use of bedaquiline/clofazimine

Villellas JAC 2017; Wu Front Microbiol 2021; Nimmo Gen Med 2024; Islam Front Med 2024

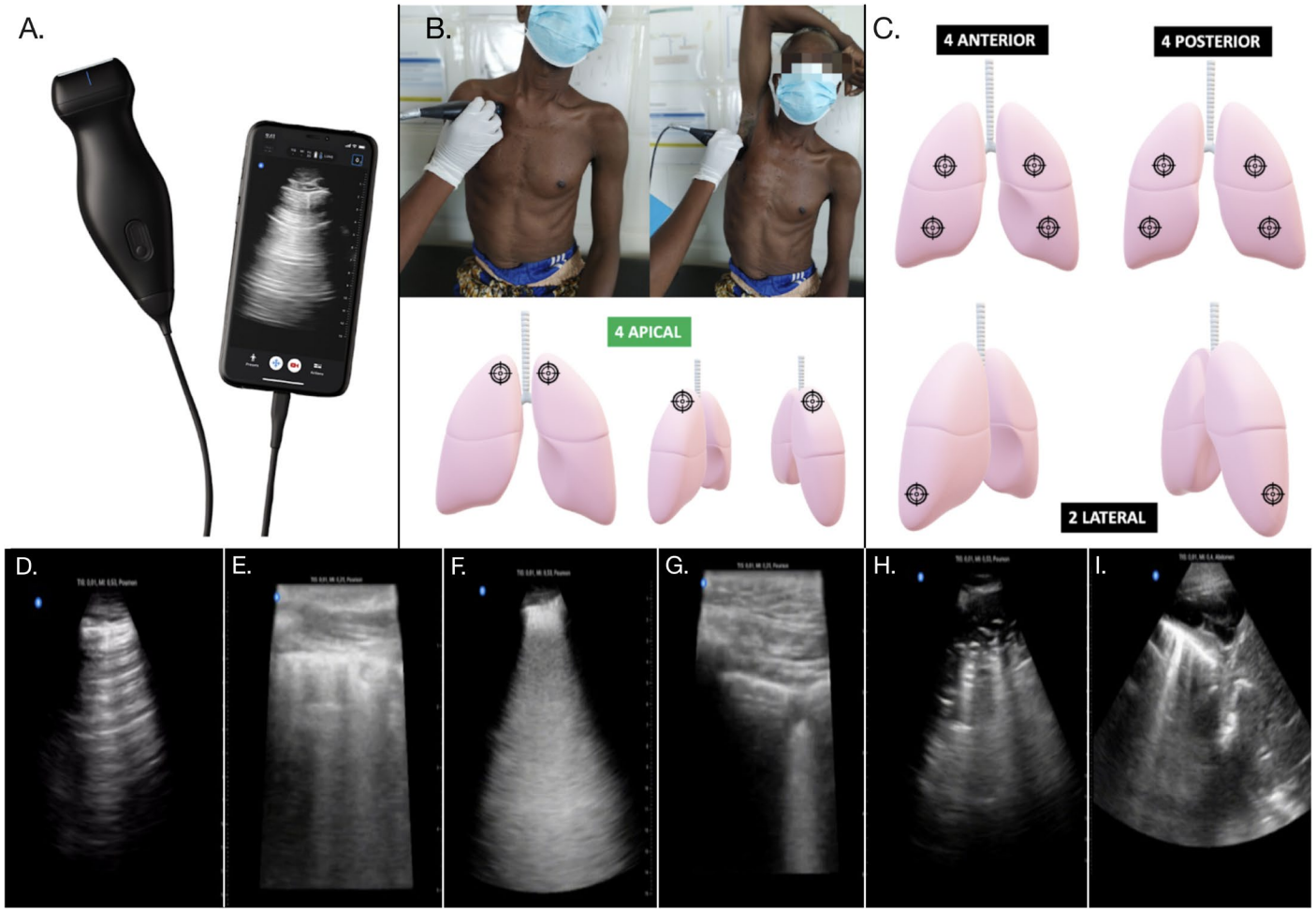
ULTR-AI: Ultrasound-Led TB Triage using AI

Véronique Suttels *, Trevor Brokowski *, Julia Wolleb, Prudence Ablo Wachinou, Aboudou Rasisou Hada, Jacques Daniel Du Toit, Arnauld Attannon Fiogbé, Brice Guendehou, Frederic Alovokpinhou, Elena Garcia, Thomas Brahier, Onya Opota, Jonathan Doenz, Julien Vignoud, Gildas Agodokpessi, Dissou Affolabi, Noemie Boillat-Blanco§, and Mary-Anne Hartley§

Julia Wolleb
October 30, 2024
julia.wolleb@yale.edu

EPFL LiGHT Yale LiGHT

Motivation & Data Collection

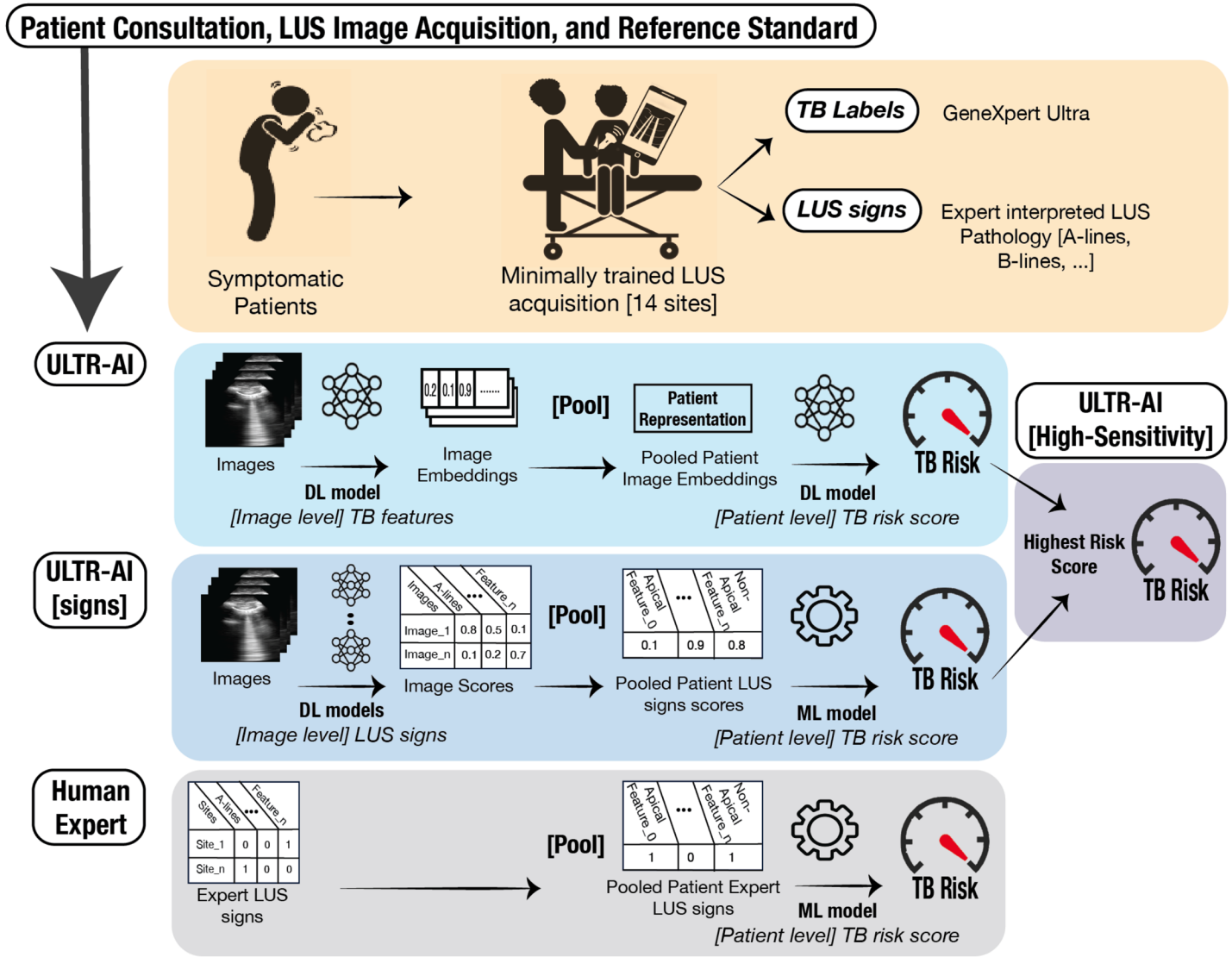


- Lung ultrasound (LUS) offers a non-invasive TB triage solution
- Interpretation requires expertise → We propose **AI algorithms to automatically generate a triage score** from LUS images
- Standardized 14 point LUS acquisition protocol
- Images were acquired from 504 adult patients with LRTI at an outpatient facility in Cotonou, Benin
- GeneXpert MTB/RIF® as reference standard.

Credits: Véronique Suttels

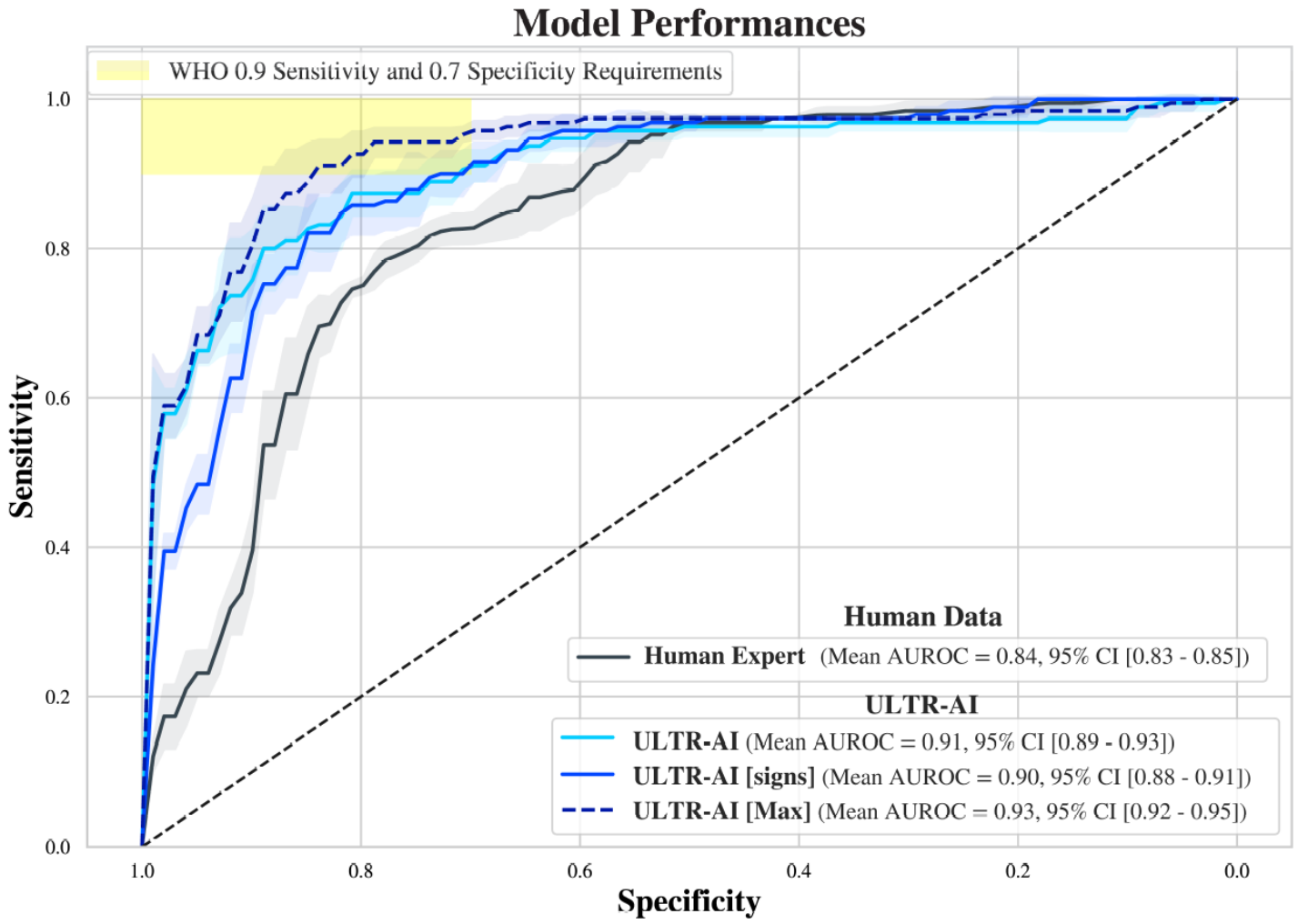
EPFL Yale
LiGHT LiGHT

AI Models



Credits: Trevor Brokowski

Results



AI-driven LUS interpretation has the potential to be a reliable, point-of-care TB triage tool,

- ✓ meeting WHO criteria,
- ✓ expanding diagnostic capacity,
- ✓ enhancing consistency and efficiency in interpretation.

Further exploration of **model interpretability and robustness** is needed for reliable application in diverse low-resource settings.

Discussion/Questions

More content on AI for TB diagnosis in the afternoon…

julia.wolleb@yale.edu

LUS signs

LUS Acquisition

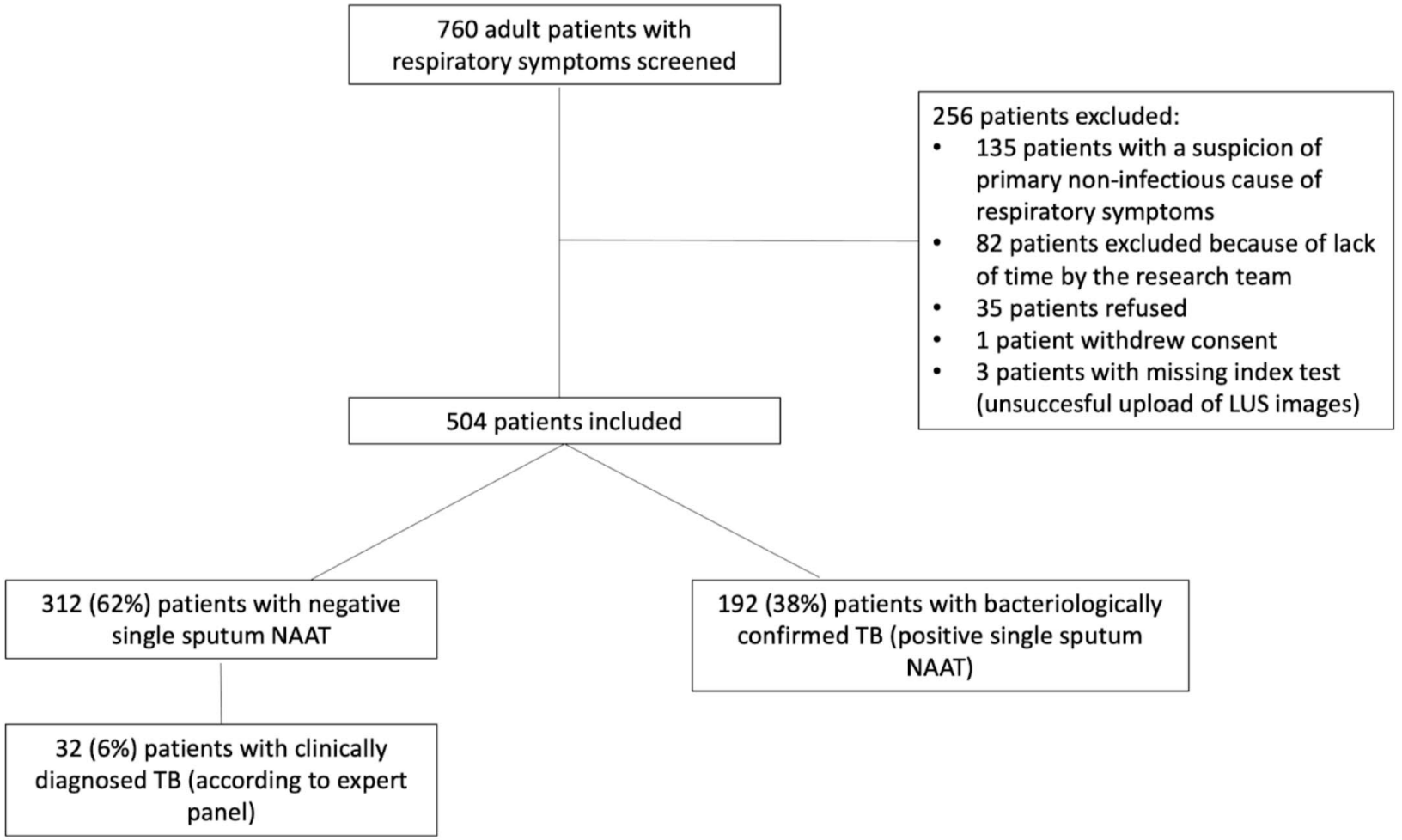
LUS imaging was conducted using a ButterflyIQ 2.0 single-probe whole-body handheld device, operated by a locally trained healthcare worker. The operator (GM) was trained in LUS acquisition and relevant pathological pattern recognition with more than 50 supervised exams. We used a standardized 14-point sliding scan protocol, which involved imaging at 14 predefined anatomical sites, including subclavicular and axillary views of the lung apexes (Figure. 2).

For each anatomical site, two still images were obtained, selected for relevant pathological features: One 5-cm depth image (corresponding to a linear probe view), and one 12-cm depth image. This resulted in approximately 28 high-quality LUS images per patient. To identify pleural effusions, an additional abdominal probe view was used in the lower lateral lung quadrants. Patients were asked to sit upright when possible during the exam, alternatively, the patient was installed in a 45-degree supine position. Posterior images were not obtained in clinically unstable patients.

LUS Signs

Following LUS acquisition, images from all 14 sites were reviewed by a POCUS expert certified through standardized LUS training courses (referred to as the “first reader”). The first reader reviewed the images through standardized criteria, assigning a single categorical class label to each site. The sites were classified into one of six pre-defined diagnostic categories for pulmonary imaging, including 1) dry lung (A-lines), 2) interstitial syndrome with B-lines, 3) interstitial syndrome with confluent B-lines, 4) subpleural consolidations (<1 cm) or irregular/broken pleural line, 5) larger consolidations (≥1 cm), and 6) pleural effusion.

Study Flow Chart



Summary of Patient Charateristics

	all (n=504)	TB+	TB- and TBc	p-value	More in TB+	More in TB- and TBc
Demography						
Patients N	504 (100)	192 (38)	312 (62)			
Male N(%)	308 (61)	151 (79)	157 (50)	<0.001	X	
Age (years); median (IQR)	40 (30-52)	36 (27-46)	45 (33-55)	<0.001	X	
Comorbidities						
Former TB N(%)	66 (13)	13 (7)	53 (17)	0.002		X
Diabetes	18 (4)	5 (3)	13 (4)	0.502		
Hypertension	66 (13)	5 (3)	61 (20)	<0.001		X
BMI >= 25 N(%)	72 (14)	4 (2)	68 (22)	<0.001		X
Co-infections						
Malaria positive N(%)	26 (5)	4 (2)	22 (7)	0.024		
COVID positive N(%)	59 (12)	17 (9)	42 (14)	0.149		
HIV positive N(%)	78 (15)	17 (9)	61 (20)	0.002		X
CD4 count; median (IQR)	92 (43-358)	76 (46-319)	100 (30-352)	0.927		
Symptoms						
Cough as main symptom N(%)	484 (97)	185 (97)	299 (97)	0.981		
Weigth loss N(%)	378 (75)	176 (93)	202 (66)	<0.001	X	
Hemoptysis N(%)	99 (20)	39 (21)	60 (20)	0.880		
Night sweats N(%)	189 (38)	105 (55)	84 (7)	<0.001	X	
Main symptom duration (days); median (IQR)	30 (14-90)	60 (30-90)	30 (14-75)	<0.001	X	
Signs						
BMI <18.5 N(%)	217 (43)	126 (66)	91 (30)	<0.001	X	
Temperature >38°C N(%)	18 (4)	12 (6)	6 (2)	0.022	X	
Temperature =<35°C N(%)	36 (7)	16 (8)	20 (7)	0.536		
Heart rate >100 bpm N(%)	207 (41)	116 (61)	91 (30)	<0.001	X	
Respiratory rate >=22 cpm N(%)	433 (86)	180 (95)	253 (82)	<0.001	X	
Systolic blood pressure <100 mmHg N(%)	89 (18)	52 (27)	37 (12)	<0.001	X	
SpO2 <95% N(%)	83 (16)	40 (21)	43 (14)	0.054		
GCS ≤ 14 N(%)	17 (3)	9 (5)	8 (3)	0.310		
Bad general state (>=4 on a 5-point scale) N(%)		46 (24)	56 (18)	0.137		
Blood formula						
Anemia (Hemoglobin <12 g/dL in female patients,; <13 g/dL in male patients) N(%)	167 (33)	66 (42)	101 (40	0.733		
MCV <80 fl N(%)	181 (36)	97 (51)	84 (27)	<0.001	X	
Platelets >450 G/L N(%)	123 (24)	78 (41)	45 (15)	<0.001	X	
Leukocytes >11 G/L N(%)	385 (76)	140 (74)	245 (80)	0.134		
Clinical evolution						
Follow-up day 7 completed	483 (96)	184 (96)	299 (96)	1		
Follow-up day 28 completed	465 (92)	178 (93)	287 (92)	0.882		
Hospitalized by day 7	86 (17)	37 (19)	49 (16)	0.377		
7-day mortality	9 (2)	4 (2)	5 (2)	0.967		
Hospitalized by day 28	90 (18)	39 (21)	51 (17)	0.327		

EPFL Yale
LIGHT LIGHT

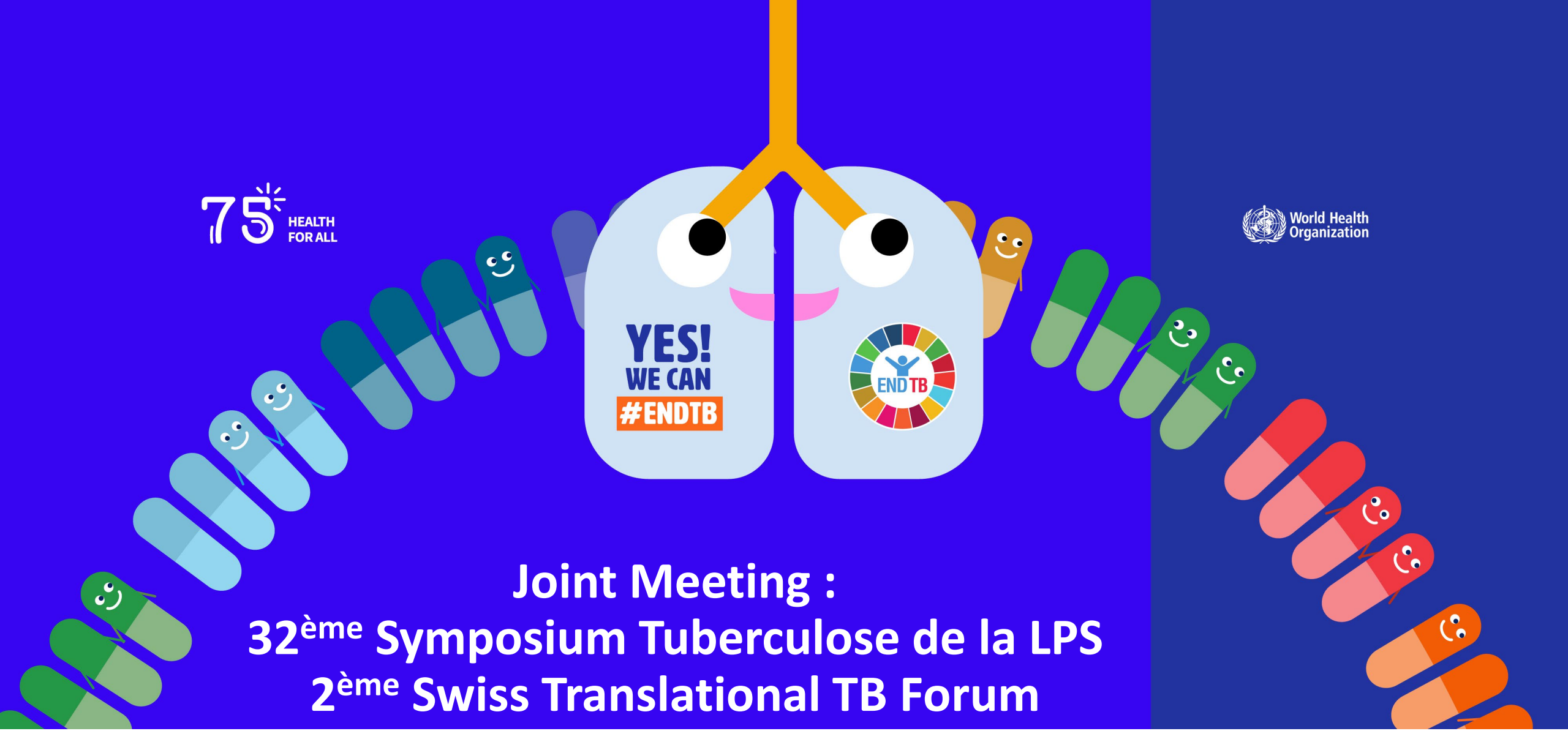
Feature importance

Lung ultrasound pattern and localisation	Prevalence n(%)		Univariate logistic regression			Human Expert (ML) with RFE
	TB+. (n=192)	TB- and TBc (n=312)	OR	95% CI	p-value	Feature importance
Any Non-Apical quadrant						
A-lines	167 (87)	303 (97)	0,20	[0.1, 0.4]	<0,001	0.06
B-lines	145 (76)	188 (60)	2,03	[1.4, 3.0]	<0,001	
Confluent B-lines	121 (63)	188 (60)	1,12	[0.8, 1.6]	0,536	0.02
Subpleural consolidations of <1cm or irregular/broken pleural lines	179 (94)	237 (76)	4,36	[2.3, 8.1]	<0,001	0.02
Consolidations ≥ 1cm	153 (80)	64 (21)	15,20	[9.7, 23.8]	<0,001	0.4
Pleural effusion	12 (6)	15 (5)	1,32	[0.6, 2.9]	0,486	
Any Apical Quadrant						
A-lines	108 (57)	288 (92)	0,11	[0.1, 0.2]	<0,001	0.04
B-lines	58 (30)	69 (22)	1,52	[1.0, 2.3]	0,043	0.04
Confluent B-lines	48 (25)	59 (19)	1,43	[0.9, 2.2]	0,105	0.01
Subpleural consolidations of <1cm or irregular/broken pleural lines	114 (60)	89 (29)	3,66	[2.5, 5.3]	<0,001	0.08
Consolidations ≥ 1cm	109 (57)	20 (6)	19,17	[11.2, 32.8]	<0,001	0.32
A-line pattern in all 4 apical quadrants	12 (6)	144 (46)	0,08	[0.0, 0.1]	<0,001	

Mittagessen bis 14.00 Uhr

Swiss Translational TB Forum

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA



Joint Meeting :
32ème Symposium Tuberculose de la LPS
2ème Swiss Translational TB Forum

Pause de midi jusqu'à 14h00

Swiss Translational TB Forum

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA

Mit Unterstützung von
Avec le soutien de

QIAGEN

Diasorin

Swiss Translational
TB Forum

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA

Paradigm change (?) in the clinical management of drug- resistant TB

32. Tuberculosis S ymposium of theSwiss Lung Association

2. Translational Tuberculosis Forum

Bern, 30.10.2024

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE

Gunar Günther

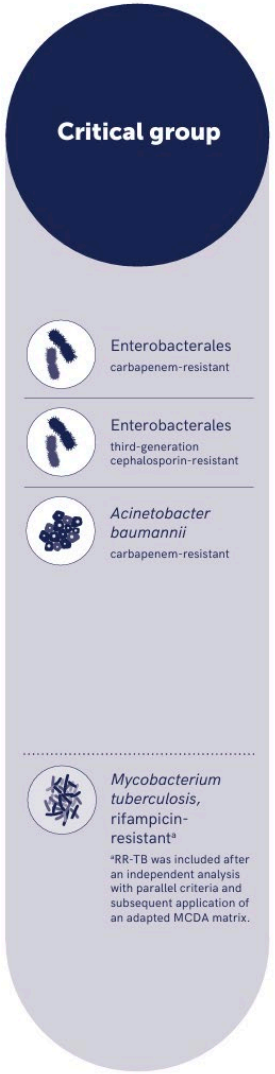
UNAM
UNIVERSITY OF NAMIBIA

Global burden of MDR/RR- TB

WHO Priority pathogens 2024

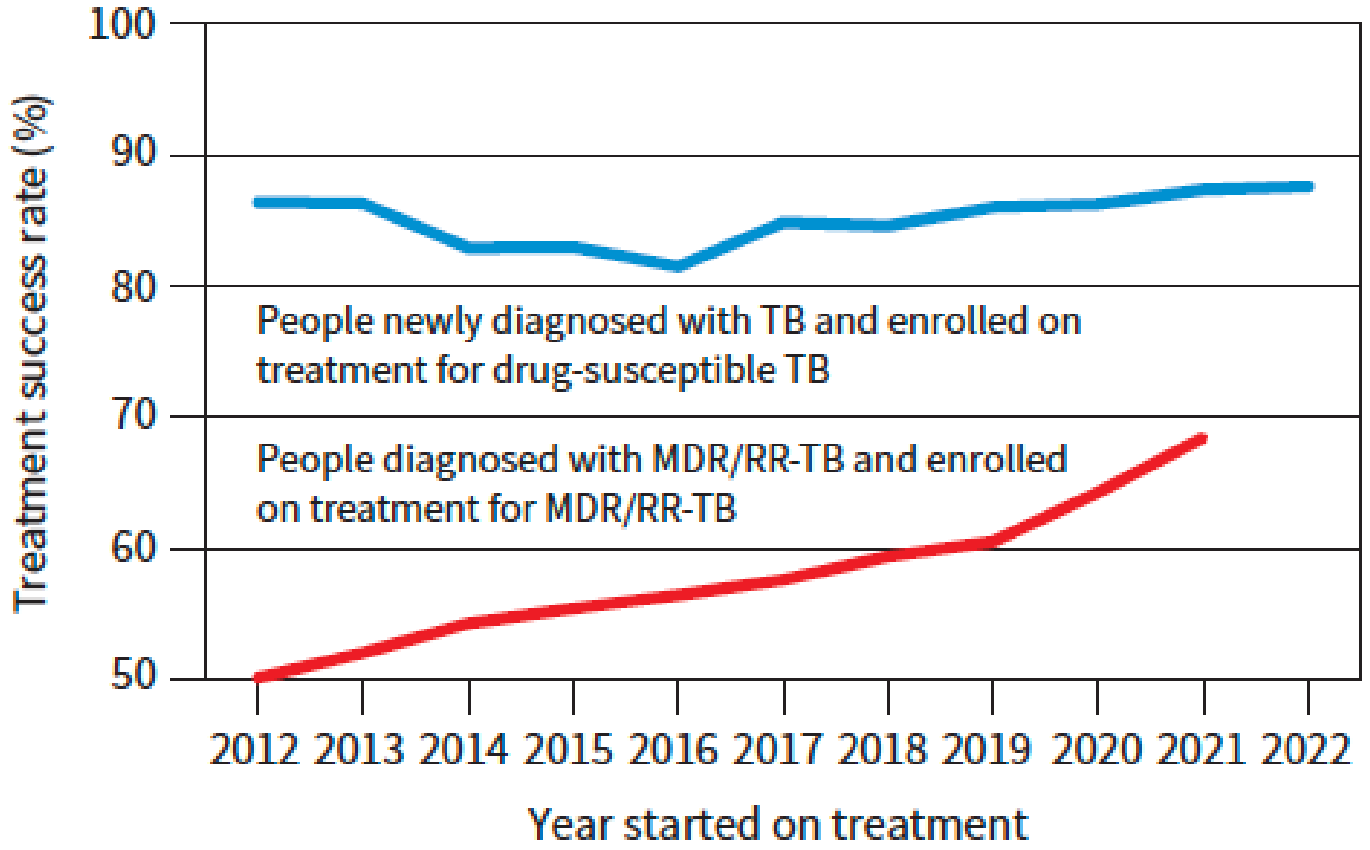
Global MDR/RR – TB burden: 400.000 new 2023 / 176.000 started treatment (44%)

	World	Europe	Ukraine	Russia	Switzer-land	Afrika	South-Afrika
TB incidence 2022 (n/100.000)	134	24	112	38	5.4	206	427
New MDR (%)	3.2	24.0	28.0	37.0	2.6	2.1	3.1
MDR in Retreatment (%)	16.0	53.0	41.0	67.0	29	12.0	16
Total RR TB number of cases	400.000	65.000	13.000	30.000	24	60.000	13.000



WHO 2024

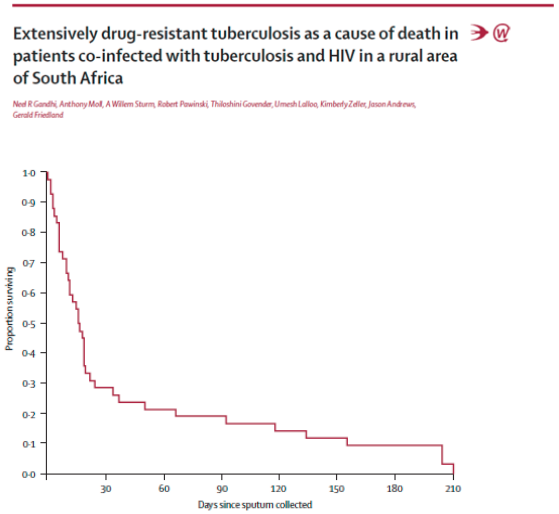
Treatment outcomes of TB according to WHO 2022

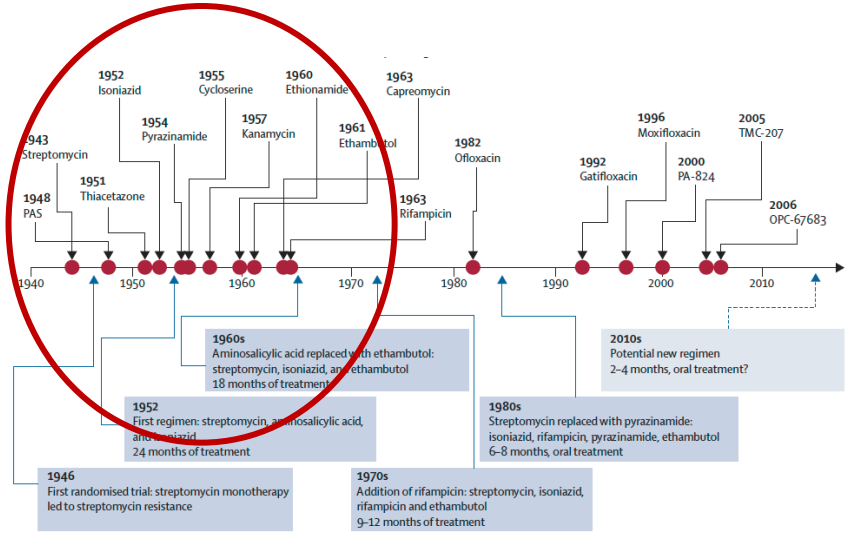


[a] 2012 is the first year for which WHO collected data about treatment outcomes for MDR/RR-TB.

Global TB Report, WHO 2024

TB and TB drugs pipeline – 2010

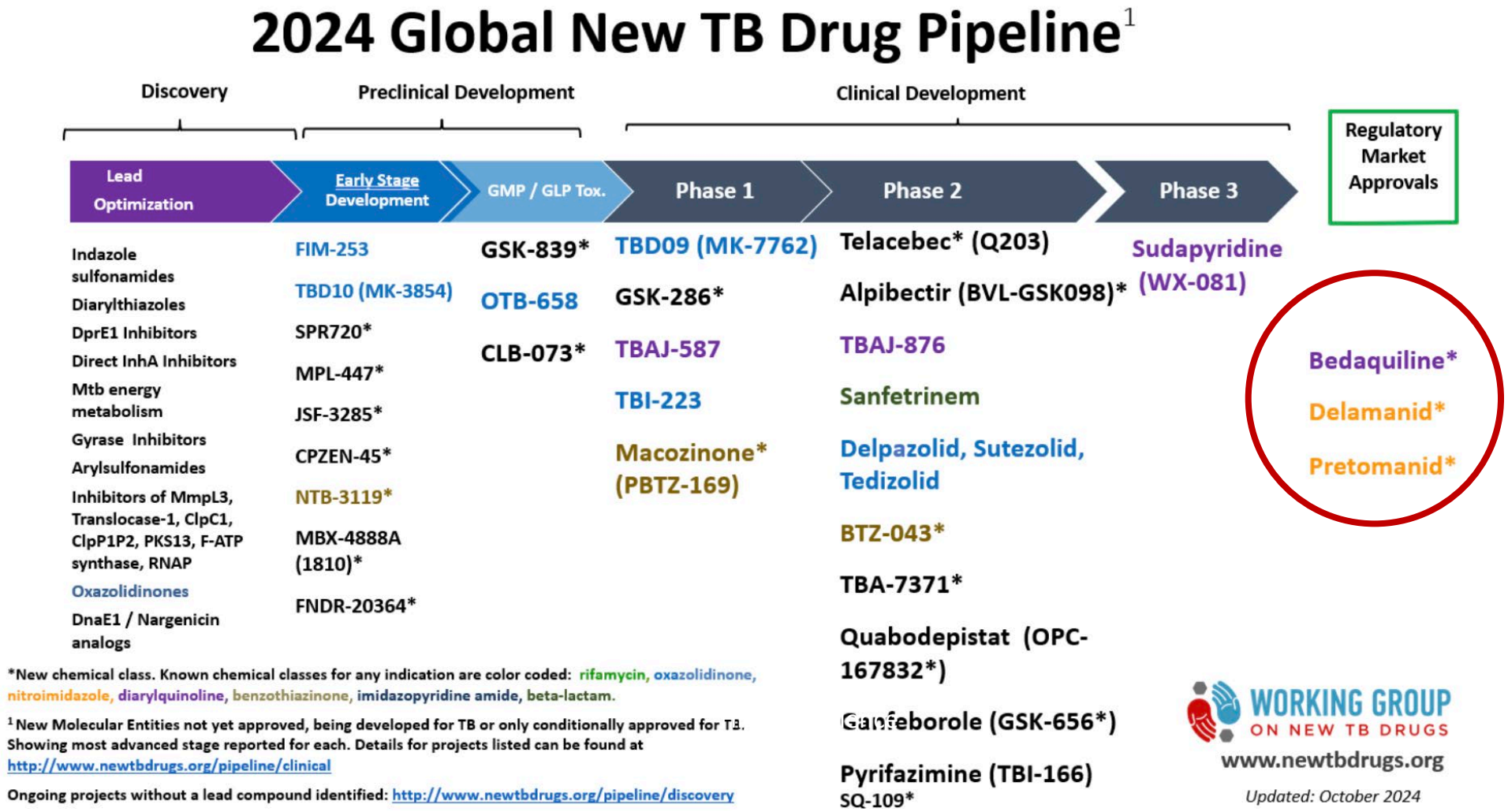




	Phase 1	Phase 2	Phase 3
Existing drugs redeveloped or repurposed for tuberculosis		Rifapentine Linezolid	Gatifloxacin Moxifloxacin
New drugs developed for tuberculosis	SQ-109 PNU-100480 AZD-5847	TMC-207 OPC-67683 PA-824	

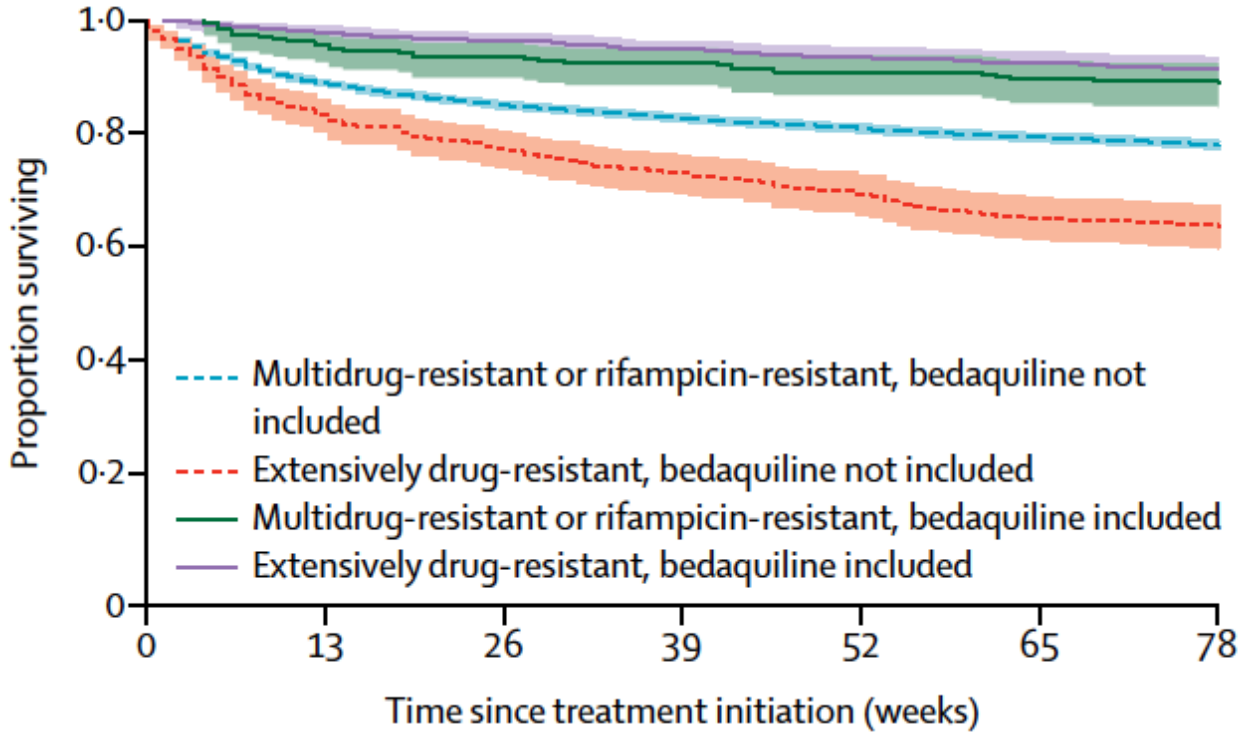
Gandhi et al, Lancet 2006
Ma et al, Lancet 2010

TB – drugs pipeline 2024



Impact of Bedaquiline in South Africa on TB Mortality 2015 - 2018

- BDQ first registered in 2012 by the FDA



MDR/RR TB: HR Mortality 0.35 95% CI 0.28 – 0,46

XDR TB: HR Mortality 0.25 95% CI 0.18 – 0,38

Schnippel et al, Lancet Resp Dis. 2018

Treatment of drug – resistant TB WHO Guidelines 2019/2020

Resistance	Regimen	Conditions	Duration
Shorter all oral BDQ regimen for RR/MDR-TB **(STREAM II)**	4 - 6 **BDQ**, LFX, hH, CFZ, PZA, E, ETH + 5 CFZ, LFX, E, PZA	- no exposure to SLD - FQ resistance excluded - not in extensive / cavitary disease	9 – 12 months
Shorter all oral BDQ regimen for RR/MDR-TB	2 LZD,4 - 6 **BDQ**,; LFX, hH, CFZ, PZA, E, 5 CFZ, LFX, E, PZA		9 – 12 months
Longer all oral BDQ regimen for RR/MDR-TB	min 4 effective drugs (3 group A + 1 group B) **BDQ** stopped after 6 months		18 – 20 months

Godall et al, Lancet 2022
Nunn et al, NEJM 2019
Menzies et al, Lancet 2018
WHO MDR- TB Guideline 2019

Treatment success rates in recent trials

Resistance	Trial	Duration	Success rate	Year
M/XDR- TB	NiX TB trial	6	90%	2020
MDR- TB	Stream II	9-12	79%	2021
M/XDR- TB	ZeNIX	6	89%	2022
MDR TB	**TB Practecal**	**6**	**89%**	**2022**
MDR TB	NEXT TB	9	78%	2023

Conradie et al, NEJM 2020
Conradie et al, NEJM 2021
Nyang`wa et al, NEJM 2022
Godall et al, Lancet 2022
Esmail et al, AJRCCM 2022

RR -TB Therapie for 6 months: TB PRACTECAL - Moxifloxacin, Pretomanid, Linezolid und Bedaquiline

	BPaLM n=151	BPaL n=126	BPaLC n=123	Standard of care n=152
Favorable. (%)	89	77	81	52
Unfavorable (%)	11	23	19	48
Recurrence (n)	0	3	1	
Deaths (n)	0	0	1	2
≥AE Grade III (%)	19	22	32	59

Linezolid 16 weeks 600 mg/ 8 weeks 300 mg

BPaLM: Hepatoxicity 4%, Anaemia 3%

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

Nyang`wa et al. NEJM 2022

Treatment of drug – resistant TB WHO Guidelines 2022

Resistance	Regimen	Conditions	Duration
Shorter all oral BDQ regimen for RR/MDR-TB **(STREAM)**	4 - 6 **BDQ**, LFX, hH, CFZ, PZA, E, ETH + 5 CFZ, LFX, E, PZA	- no exposure to SLD - FQ resistance excluded - not in extensive / cavitary disease	9 – 12 months
Shorter all oral BDQ regimen for RR/MDR-TB	2 LZD,4 - 6 **BDQ**,; LFX, hH, CFZ, PZA, E, 5 CFZ, LFX, E, PZA		9 – 12 months
Longer all oral BDQ regimen for RR/MDR-TB	min 4 effective drugs (3 group A + 1 group B) **BDQ** stopped after 6 months		18 – 20 months
Short regimen for RR/MDR-TB with Fluorquinolone resistance (ZeNIX)	**BDQ** + LZD + PA (Pretonamid)	- FQ - Resistenz	6 months
Short regimen for MDR-TB (TB Practecal)	**BDQ** + LZD + PA + MXF	- MDR-TB	6 months

BPaLM – also recommended in Switzerland since 2023

Conradie et al, NEJM 2021
Nyang`wa et al, NEJM 2022
WHO 2022

Treatment success rates in recent trials

Resistance	Trial	Duration	Success rate	Year
M/XDR- TB	NiX TB trial	6	90%	2020
MDR- TB	Stream II	9-12	79%	2021
M/XDR- TB	ZeNIX	6	89%	2022
MDR TB	TB Practecal	6	89%	2022
MDR TB	NEXT TB	9	78%	2023
MDR TB	**BEAT Tuberculosis**	**6**	**?**	**2024**
MDR TB	**END TB**	**9**	**85 - 91%**	**2023**

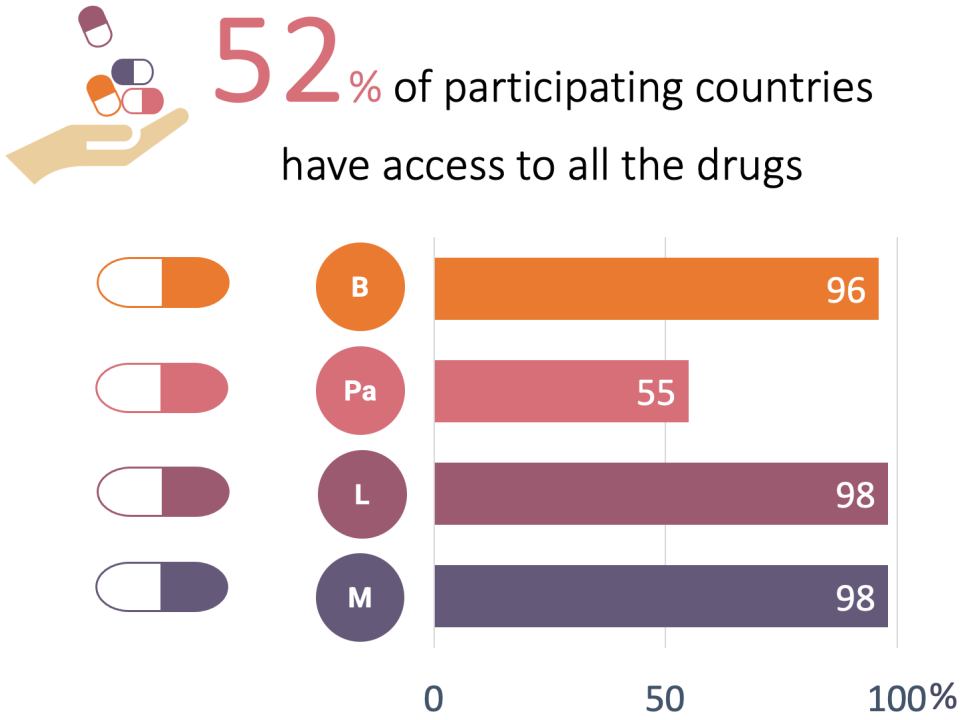
Conradie et al, NEJM 2020
Conradie et al, NEJM 2021
Nyang`wa et al, NEJM 2022
Godall et al, Lancet 2022
Esmail et al, AJRCCM 2022
Guglielmetti et al, medRxiv 2023
Conradie et al, abstract IJTLD 2022

Treatment of drug – resistant TB WHO Guidelines 2024

Resistance	Regimen	Conditions	Duration
9 months regimen for MDR- TB (endTB)	- **BDQ**, LZD, Mfx, PZA (89%) - **BDQ**, LZD, Lfx, CFZ, PZA (90%) - **BDQ**, DLM, LZD, Lfx. PZA (85%)	not recommended - DLM, Cfz, LZD, Lfx, PZA (79%)) - DLM, Cfz, Mfx, PZA (86%)	9 months
Short regimen for MDR-TB /pre XDR- TB (BEAT Tuberculosis)	- **BDQ**, DLM, LZD, LFx, CFZ	- BEAT TB trial: dropped Lfx or CFZ depending on resistance status	6 months

Guglielmetti et al, medRxiv 2023
Conradie et al, abstract IJTLD 2022
WHO rapid communication, 08/24

Access to BPaL(M) medicines in the WHO Europe region Nov. 2023



Günther et al, CMI 2024

Vision: PAN TB regimen – same treatment for all TB

PAN-TB Target Regimen Profile

Enable "Test and Treat" Paradigm

TRP Criteria	Hypothesis
Pan TB (No DST)	**Simple "test & treat":** Fewer patients lost to the system after Dx Decreases time from Dx to Tx → Less time to transmit (no waiting for DST or failure on HRZE)
Shorter: ⩽ 3mos	**Clear differentiation from SoC** Shorter → Improves Adherence → Improves Outcomes → Less transmission
Acceptable Safety Profile	**No baseline or ongoing safety monitoring. Enables Test & Treat.** Well tolerated → Improves Adherence → Improves Outcomes → Less Transmission
Simpler	**All Oral, Once daily** No DDIs to manage enables Test & Treat
Efficacy (NI to SoC)	**Short, forgiving regimen non-inferior to 6 months.** Minimize Efficacy – Effectiveness gap Forgiving regimen will minimize impact of non-adherence → Improve Outcome → Less Transmission
Affordable	**Low barrier to uptake → Impact**

3

Risks of the implementation of BPaLM

- Bedaquiline: long half life can cause exposure to single drug[5]
- Bedaquline: poor EBA[6]
- Bedaquline: raised MIC in Linage 4[2]
- Bedaquiline: slow cavitiy penetration, compared with MXF, LZD and Pretomanid[3]
- Bedaquiline: exposure with low concentrations can select for resistance mutations[4]
- Bedaquiline und Pretomanid: proven primary resistance
- Pretomanid: raised MIC in wildtype Lineage 1[1]

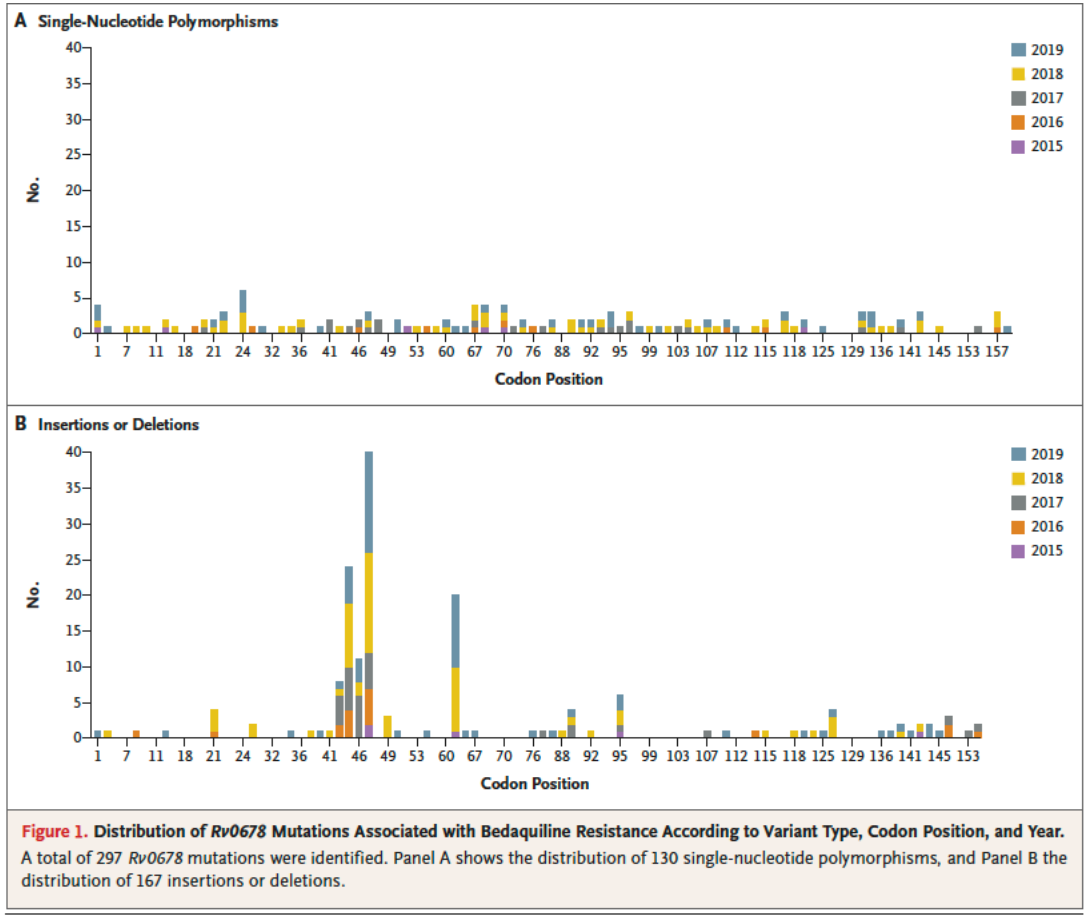


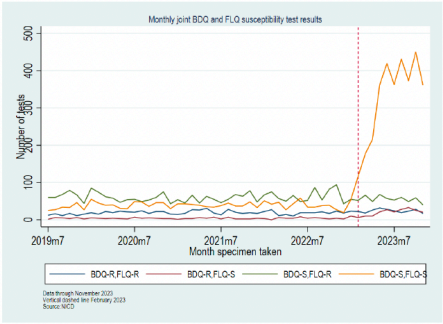
Figure 1. Distribution of *Rv0678* Mutations Associated with Bedaquiline Resistance According to Variant Type, Codon Position, and Year.
A total of 297 *Rv0678* mutations were identified. Panel A shows the distribution of 130 single-nucleotide polymorphisms, and Panel B the distribution of 167 insertions or deletions.

[1]Bateson et al, JAC 2022
[2]Rivere et al, AAC 2022
[3]Sarathy et al, ACS Inf Dis 2016
[4]Sonnenkalb et al, Lancet Microbe 2023
[5]De Vos et al, NEJM 2019
[6]Diacon et al, Lancet 2012
Omar et al, NEJM 2022

Emergence of Bedaquiline resistance in South Africa and Mocambique

South Africa:

National trends in BDQ-FLQ joint susceptibility



Month	BDQ-S FLQ-S	BDQ-S FLQ-R (Pre-XDR TB)	BDQ-R FLQ-S (not classified)	BDQ-R FLQ-R (XDR-TB)	All BDQ-R	Total tests
2023m3	177 (65.3%)	66 (24.4%)	10 (3.7%)	18 (6.6%)	28 (10.3%)	271
2023m4	216 (71.8%)	49 (16.3%)	10 (3.3%)	26 (8.6%)	36 (12.0%)	301
2023m5	362 (74.9%)	68 (14.1%)	21 (4.3%)	32 (6.6%)	53 (11.0%)	483
2023m6	419 (78.9%)	57 (10.7%)	27 (5.1%)	28 (5.3%)	55 (10.4%)	531
2023m7	363 (78.7%)	53 (11.5%)	21 (4.6%)	24 (5.2%)	45 (9.8%)	461
2023m8	431 (80.1%)	60 (11.2%)	28 (5.2%)	19 (3.5%)	47 (8.7%)	538
2023m9	373 (78.0%)	49 (10.3%)	33 (6.9%)	23 (4.8%)	56 (11.7%)	478
2023m10	450 (80.1%)	59 (10.5%)	25 (4.4%)	28 (5.0%)	53 (9.4%)	562
2023m11	361 (82.4%)	40 (9.1%)	20 (4.6%)	17 (3.9%)	37 (8.4%)	438
Total	**3152 (77.6%)**	**501 (12.3%)**	**195 (4.8%)**	**215 (5.3%)**	**410 (10.1%)**	**4063**

- Change in DR-TB reflex guidelines enabled identification of BDQ resistance amongst people with FLQ-S TB
- Prevalence of BDQ resistance between March and November 2023 was 10.1%
- In more recent months, the number of BDQ-R/FLQ-S tests exceeded BDQ-R/FLQ-R tests
- Test-level BDQ-R prevalence is, however, biased upwards because of repeat tests in those not responding to treatment and inclusion of provinces with lower coverage of BDQ reflex tests

Mocambique:

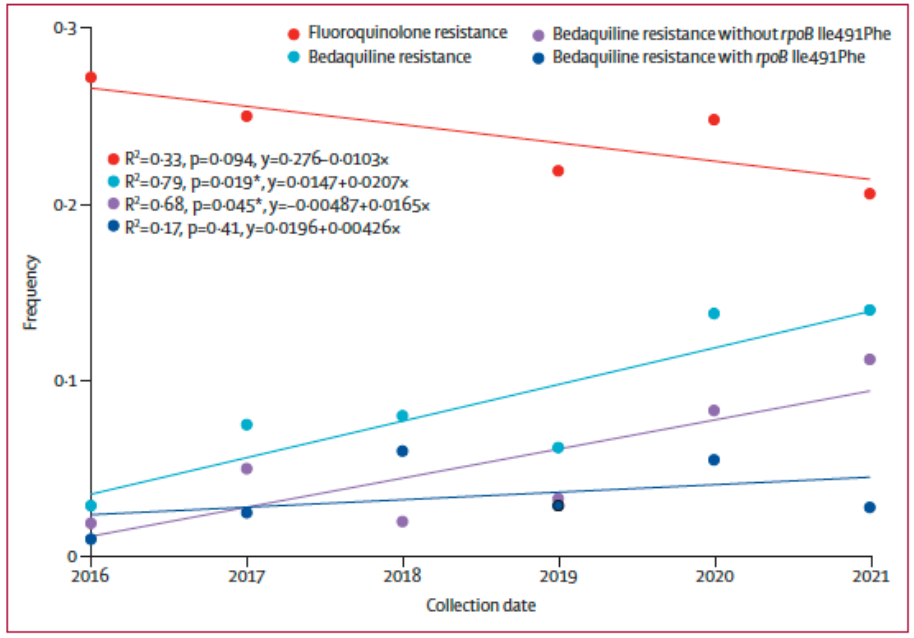


Figure 1: **Frequency of bedaquiline and fluoroquinolone resistance in *Mycobacterium tuberculosis* complex strains over time**
Linear regression analysis of correlation of bedaquiline and fluoroquinolone resistance frequency with the year of strain isolation, additionally stratified by presence or absence of the *rpoB* Ile491Phe mutation for bedaquiline. Frequencies of resistant strains were calculated over the period 2016–21.

Presentation World TB day 2024: Bedaquiline susceptibility surveillance using routine laboratory data, South Africa (July 2019 – November 2023), NICD South Africa
Barilar et al, Lancet Microbe 2024

Ongoing trials for DR- TB

Table 2
Recently completed and ongoing, unpublished trials on rifampicin-resistant tuberculosis treatment (excluding fluoroquinolone-resistant tuberculosis) (as of 6 July 2023)

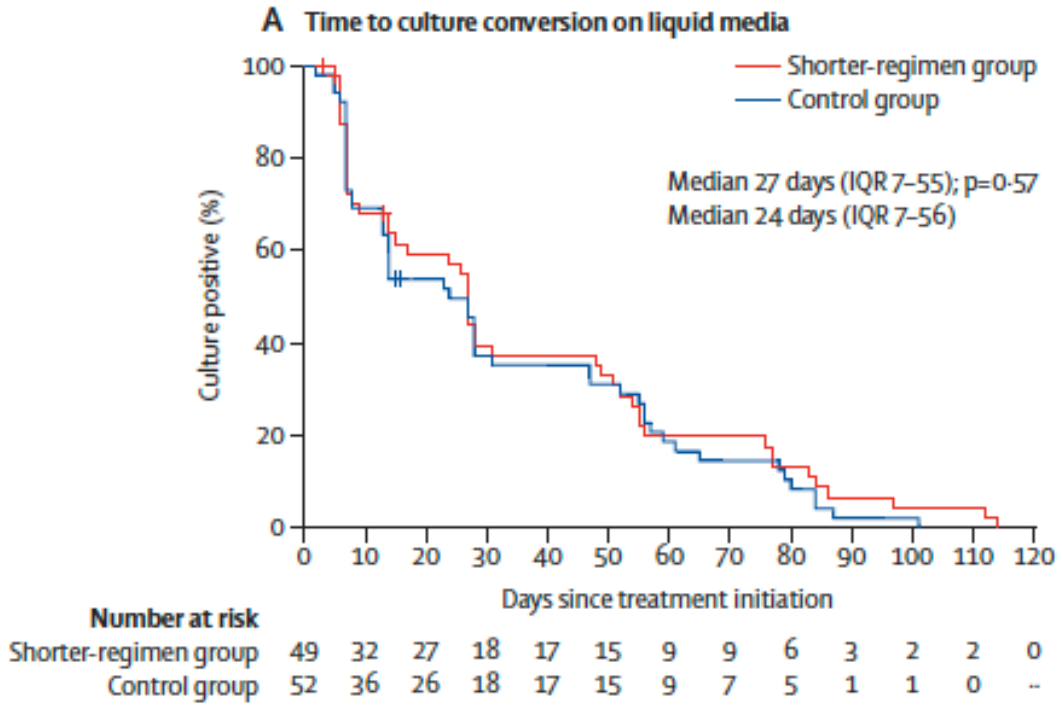
Trial	Phase	Control arm	Country	Experimental treatment regimen(s)	Treatment duration (mo)	Notes	Clinicaltrials.gov identifier
Recently completed trials							
OptiQ	II	No	Peru, South Africa	Lfx 11, 14, 17 or 20 mg/kg plus background regimen	6	750–1000 mg Lfx every day achieved target AUC/MIC	NCT01918397
SimpliciTB	II	Yes (only for DS-TB)	8 countries	Bdq, Pa, Z, Mfx	4	Not non-inferior to HRZE; no comparator for MDR-TB arm	NCT03338621
SUDOCU	II	No	South Africa, Tanzania	Sutezolid, Bdq, Dlm, Mfx	3	Regimen well tolerated	NCT03959566
TREAT-TB (India)	III	No	India	Bdq, Dlm, Lzd and Cfz	6–9	91% favourable outcomes	CTRI/2019/01/017310
Ongoing trials							
ACTG A5356	II	No	Multicountry	Bdq, Cfz, Dlm, and Lzd (different posologies)	6	TIW dosing of Lzd	NCT05007821
DECODE	II	No	South Africa, Tanzania	Delpazolid, Bdq, Dlm, Mfx	3	Dose-ranging and tolerability	NCT04550832
DRAMATIC	II	No	Multicountry	Lfx, Bdq, Lzd, Dlm, and Cfz	4–9	Duration-randomized clinical trial	NCT03828201
BEAT tuberculosis	III	Yes	South Africa	Bdq, Dlm, and Lzd, plus Lfx or Cfz	6	Experimental regimen adapted according to rapid molecular testing	NCT04062201
endTB [35]	III	Yes	Multicountry	Bdq, Mfx, Lzd, and Z; or Bdq, Cfz, Lfx, Lzd, and Z; or Bdq, Dlm, Lfx, Lzd, and Z; or Dlm, Cfz, Lfx, Lzd, and Z; or Dlm, Cfz, Mfx, and Z	9	Trial implementing Bayesian adaptive randomization	NCT02754765
TB-TRUST	III	Yes	China	Lfx, Lzd, Cs, and Z (or Cfz if resistant to Z)	6–9	No follow-up available	NCT03867136
TB-TRUST Plus	III	No	China	Bdq, Z, Lzd, Cs, Cfz	6–9	Regimen guided by Z susceptibility testing	NCT04717908
InDEX	IV	Yes	South Africa	Individualized regimens	NS	WGS-derived individualized regimen	NCT03237182
PROSPECT	IV	No	China	Cfz, Cs, Lfx, Lzd, and Pto; or Bdq, Cfz, Cs, Lfx, and Lzd	6 (first regimen), 9 (second regimen)	No follow-up available	NCT05306223
GRACE-TB	NA	Yes	China	Individualized regimens	NS	Individualized regimen guided by rapid molecular tests	NCT03604848
SMARTT	NA	Yes	South Africa	WGS-guided regimen	NS	Individualized regimen guided by rapid molecular tests	NCT05017324

Bdq, bedaquiline; Cfz, clofazimine; Cs, cycloserine; Dlm, delamanid; DS-TB, drug-susceptible tuberculosis; HRZE, isoniazid + rifampicin + pyrazinamide + ethambutol; Lfx, levofloxacin; Lzd, linezolid; MDR-TB, multidrug-resistant tuberculosis; Mfx, moxifloxacin; MIC, minimal inhibitory concentration; NS, not specified; NA, not applicable; Pa, pretomanid; Pto, prothionamide; TIW, three times weekly; WGS, whole genome sequencing; Z, pyrazinamide.

Motta et al, CMI 2024

The only RCT data on a BDQ free regimen, showing non - inferiority:

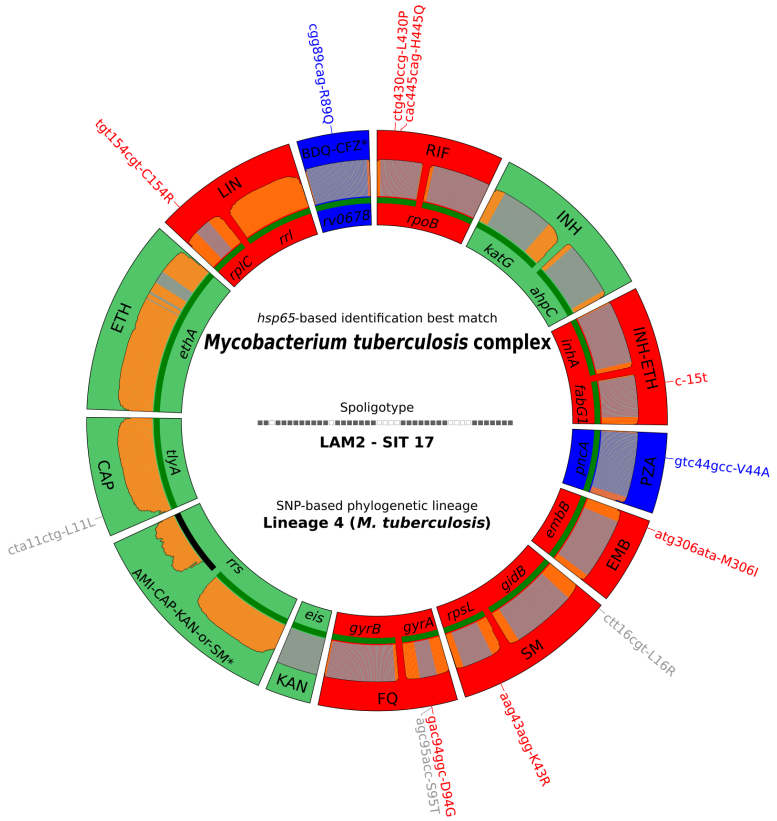
MDR END Trial - with 9 months Delamanid, Levofloxacin, Linezolid, Pyrazinamid vs. 18 – 24 Monate Standard of Care



	Short regimen	Standard of Care
Success after 24 months	75%	71%
Death	2%	3%
Failure	7%	12%
Grade 3 AE	36.7%	29.2%

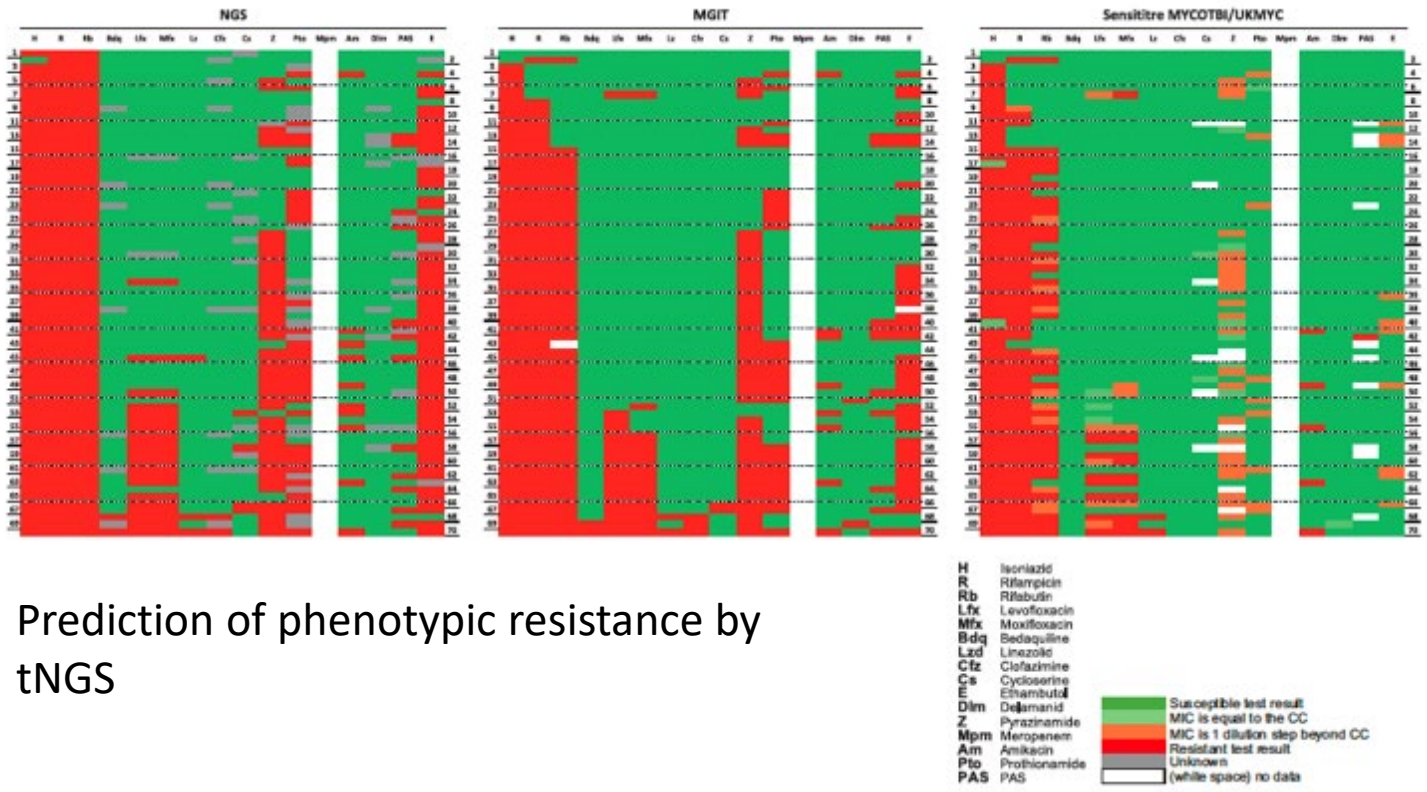
Mok et al., Lancet ID 2022

Back to the past…….. ???

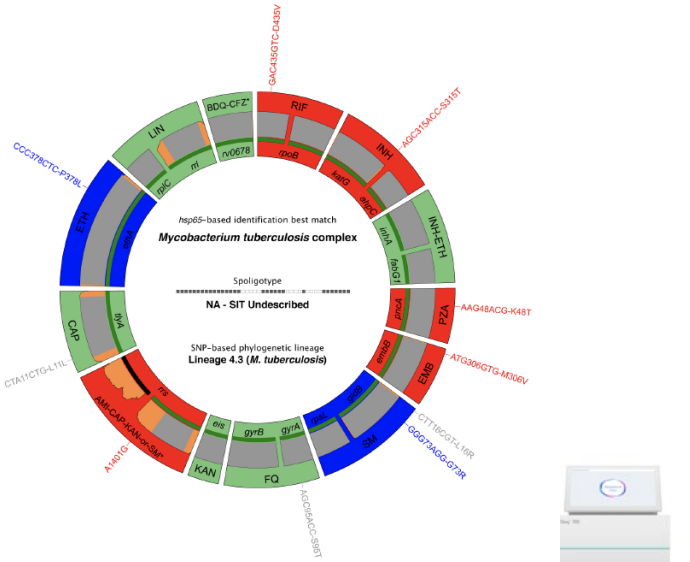


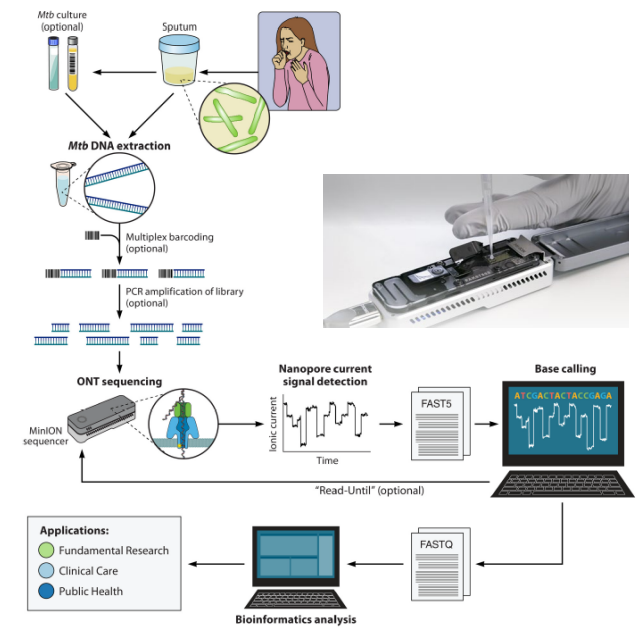
- toxic drugs (amikacin)
- iv. therapy (meropenem, amikacin)
- unknown treatment duration
- poor outcome
- high cost
- lots of human suffering
- ?? what to do with children and contacts….
- ?? extrapulmonary TB

Sequencing replaces (complements) phenotypic DST in some circumstances



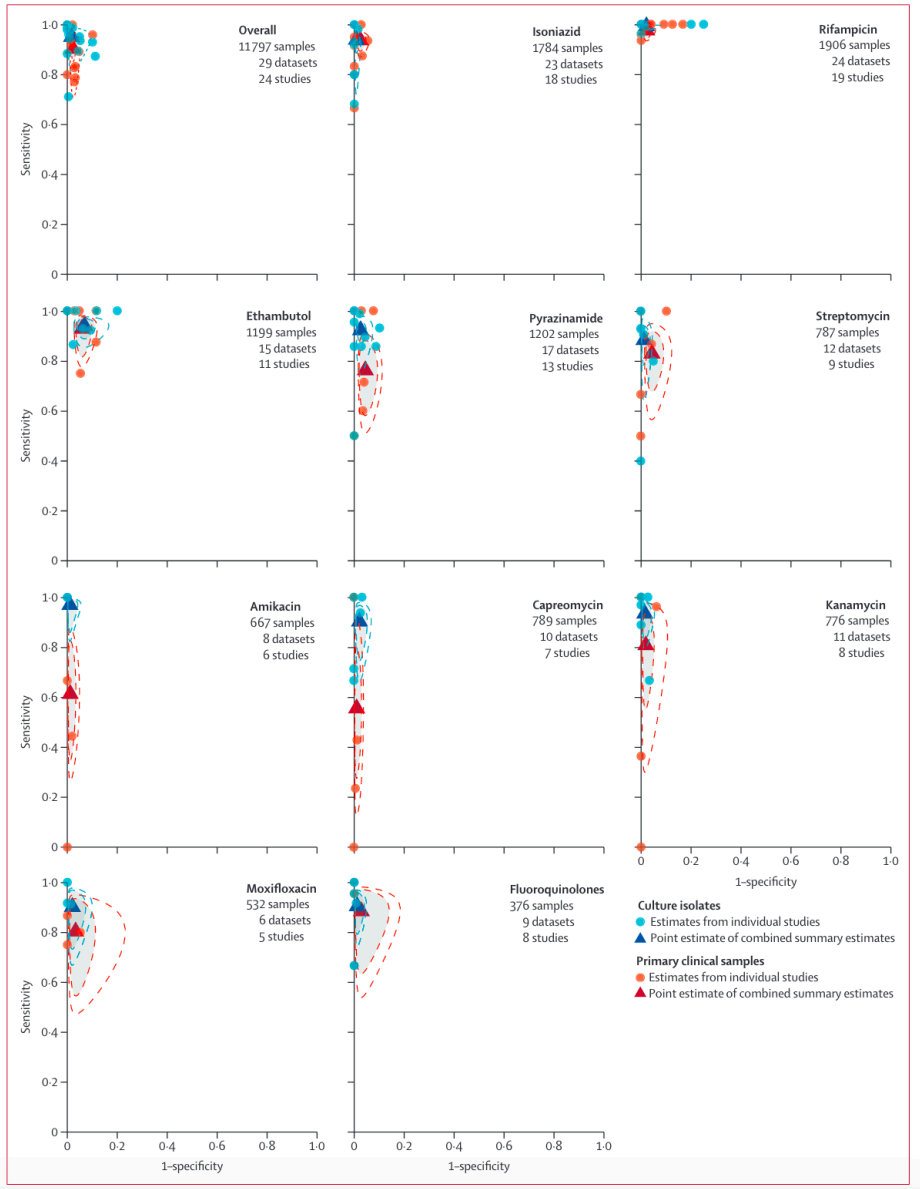
Prediction of phenotypic resistance by tNGS





Groppel et. al. CID 2021
Mehaan et al. , Nature Microbiology 2019

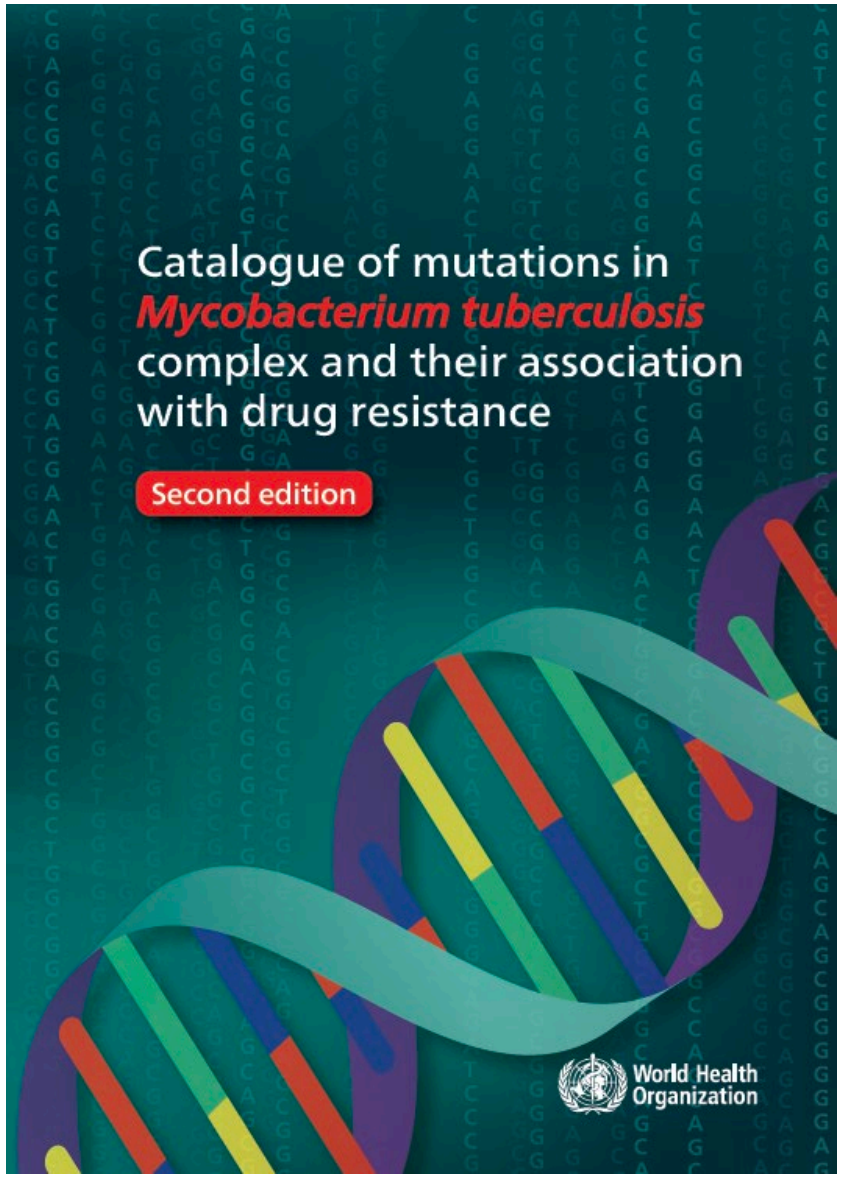
Diagnostic accuracy of tNGS



Bedaquiline	Phenotypic DST	Se: 67.9 (42.6–93.2)	3 (31)	Low
	Phenotypic DST	Sp: 97.0 (94.3–99.7)	4 (519)	High
Linezolid	Phenotypic DST	Se: 68.9 (38.7–99.1)	4 (31)	Low
	Phenotypic DST	Sp: 99.8 (99.6–100)	6 (1093)	High
Clofazimine	Phenotypic DST	Se: 70.4 (34.6–100)	4 (36)	Low
	Phenotypic DST	Sp: 96.3 (93.2–99.3)	6 (789)	High

Schwab et al, Lancet Inf Dis 2024
WHO Diagnostics Guideline 2024

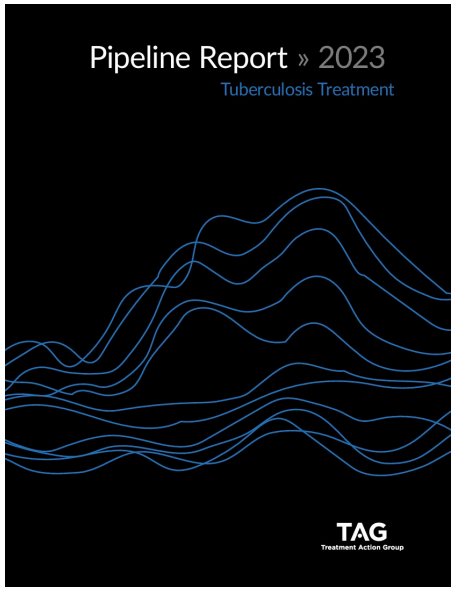
What do mutations mean?



Drug	Variant (common name)	MUT present_pheno S	MUT absent_pheno S	MUT present_pheno R	MUT absent_pheno R	SENSITIVITY	SPECIFICITY	PPV	NPV	PPV_95%CI_lo	PPV_95%CI_up	OR 95%CI	INITIAL CONFIDENCE GRADING	SUPPORTING DATASET	ADDITIONAL GRADING CRITERIA	FINAL CONFIDENCE GRADING
RIF	rpoB_S450L	74	24473	6536	3333	66.2%	99.7%	98.9%	98.6%	98.3%	98.9%	584.342	Assoc w R	ALL+WHO		1) Assoc w R
RIF	rpoB_D435V	9	24424	732	9117	7.4%	100.0%	98.8%	98.7%	97.6%	99.4%	236.417	Assoc w R	ALL+WHO		1) Assoc w R
RIF	rpoB_H445Y	4	24429	347	9502	3.5%	100.0%	98.9%	98.7%	96.7%	99.6%	392.067	Assoc w R	ALL+WHO		1) Assoc w R
RIF	rpoB_H445D	3	24430	288	9561	2.9%	100.0%	99.0%	98.9%	96.9%	99.8%	234.224	Assoc w R	ALL+WHO		1) Assoc w R
RIF	rpoB_D435Y	44	24389	162	9687	1.6%	99.8%	78.6%	58.9%	49.0%	58.3%	4.287	Assoc w R	ALL+WHO		1) Assoc w R
RIF	rpoB_S450W	5	24428	151	9698	1.5%	100.0%	96.8%	96.2%	91.4%	98.8%	63.979	Assoc w R	ALL+WHO		1) Assoc w R
RIF	rpoB_L452P	53	24380	121	9728	1.2%	99.8%	69.5%	59.5%	50.6%	68.0%	3.910	Assoc w R	ALL+WHO		1) Assoc w R
RIF	rpoB_H445L	8	24425	115	9734	1.2%	100.0%	93.5%	92.9%	86.5%	96.9%	32.934	Assoc w R	ALL+WHO		1) Assoc w R
RIF	rpoB_S450F	0	24433	112	9737	1.1%	100.0%	100.0%	100.0%	96.5%	100.0%	Inf	Assoc w R	ALL+WHO		1) Assoc w R
RIF	rpoB_L430P	103	24330	106	9743	1.1%	99.6%	50.7%	23.1%	16.3%	31.2%	0.806	Uncert. Sig.	ALL+WHO	Borderline	1) Assoc w R
RIF	rpoB_H445R	2	24431	79	9770	0.8%	100.0%	97.5%	97.0%	89.5%	99.6%	80.020	Assoc w R	ALL+WHO		1) Assoc w R
RIF	rpoB_V170F	0	24433	71	9778	0.7%	100.0%	100.0%	100.0%	90.0%	100.0%	Inf	Assoc w R	ALL+WHO		1) Assoc w R
RIF	rpoB_I491F	57	24376	54	9795	0.5%	99.8%	48.6%	44.1%	34.3%	54.3%	2.113	Assoc w R	ALL+WHO		1) Assoc w R
RIF	rpoB_H445N	39	24394	46	9803	0.5%	99.8%	54.1%	23.5%	12.8%	37.5%	0.786	Uncert. Sig.	ALL+WHO	Borderline	1) Assoc w R
RIF	rpoB_D435F	3	24430	39	9810	0.4%	100.0%	92.9%	92.1%	78.6%	98.3%	29.054	Assoc w R	ALL+WHO		1) Assoc w R
RIF	rpoB_H445C	3	24430	36	9813	0.4%	100.0%	92.3%	91.4%	76.9%	98.2%	26.555	Assoc w R	ALL+WHO		1) Assoc w R

WHO 2023

New drugs (targets) and new regimens needed



Folic Acid Metabolism
- p-Aminosalicylic Acid (PAS)

DNA Gyrase
- Fluoroquinolones - GyrA
- SPR-720 - GyrB

RNA Polymerase
- Rifamycins – Rifampin/Rifapentine

Cell Wall Synthesis (Mycolic Acids)
- Isoniazid
- Ethionamide
- Alpibectir (Ethionamide booster)

Ribosome (50S)
- Oxazolidinones
  - Linezolid, Sutezolid, TBI-223, MK-7762, Delpazolid, Tedizolid
- Macrolides/Ketolides

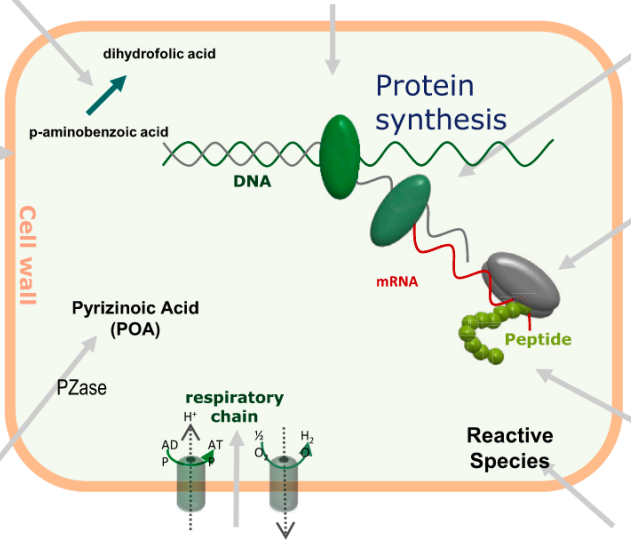
Cell Wall Synthesis (Peptidoglycan)
- Cycloserine
- Beta-lactams, Carbapenems
- Sanfetrinem

Ribosome (30S)
- Aminoglycosides
- Streptomycin
- Capreomycin
- Viomycin

Cell Wall Synthesis (Arabinogalactan)
- Ethambutol
- DprE1 Inhibitors
  - TBA-7371
  - Quabodepistat (OPC-167832)
  - BTZ-043 / PBTZ169

Amino acyl tRNA Synthetases
- Ganfeborole – LeuRS

Protein Degredation
- ClpP/ClpC



Proton Motive Force
- Pyrazinamide

Multiple Targets
- Nitroimidazoles
  - Pretomanid
  - Delamanid

Other Mechanisms
- GSK-286 - Cholesterol metabolism
- MmpL3
- Iron acquisition
- Fatty Acid Biosynthesis

ATP Synthesis
- Diarylquinolines - ATP Synthase
  - Bedaquiline
  - TBAJ-587
  - TBAJ-876
  - Sudapyridine
- Q203 – Cytochrome bc
- Pyrifazimine
- Clofazimine – NADH Dehydrogenase

Hoelscher et al, CMI 2024

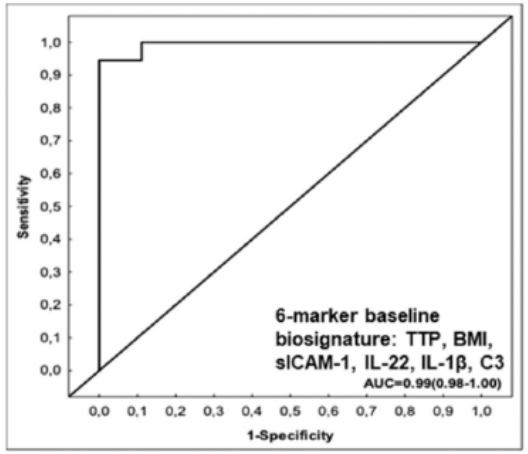
The bitter lesson…….

We cant introduce an new drug without phenotypic or genotypic drug resistance testing on population and individual level.

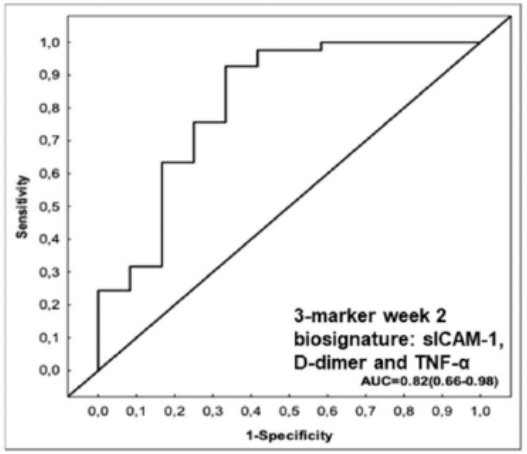
Summary

- New drugs allowed treatment shortening, better regimen tolerance and outcomes
- Bedaquiline and Linezolid are key drugs of new approved regimens, and resistance develops rapidly
- New drugs with new mechanisms in the pipeline
- Universal regime not promising, rather resistance appropriate individual treatment – using new diagnostic tools (i.e. sequencing)
- Evolution of pathogens does not respect our mistakes…..

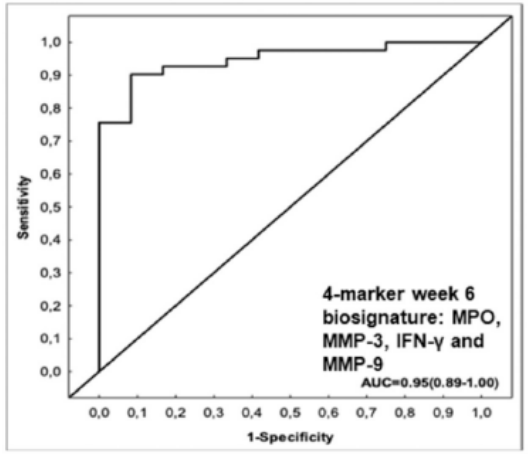
Biomarkers to predict optimal treatment duration



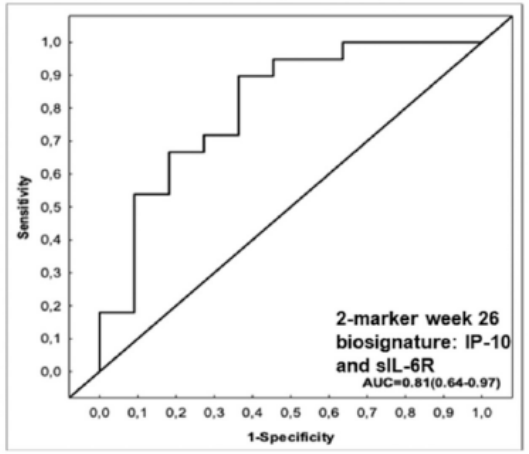
(A)



(B)



(C)



(D)

Mutahavsindi et al, J Infect 2024

Subklinische Tuberkulose – was ist ihre Bedeutung?

32. Tuberkulose-Symposium der LLS
2. Swiss Translational TB Forum

Klaus Reither

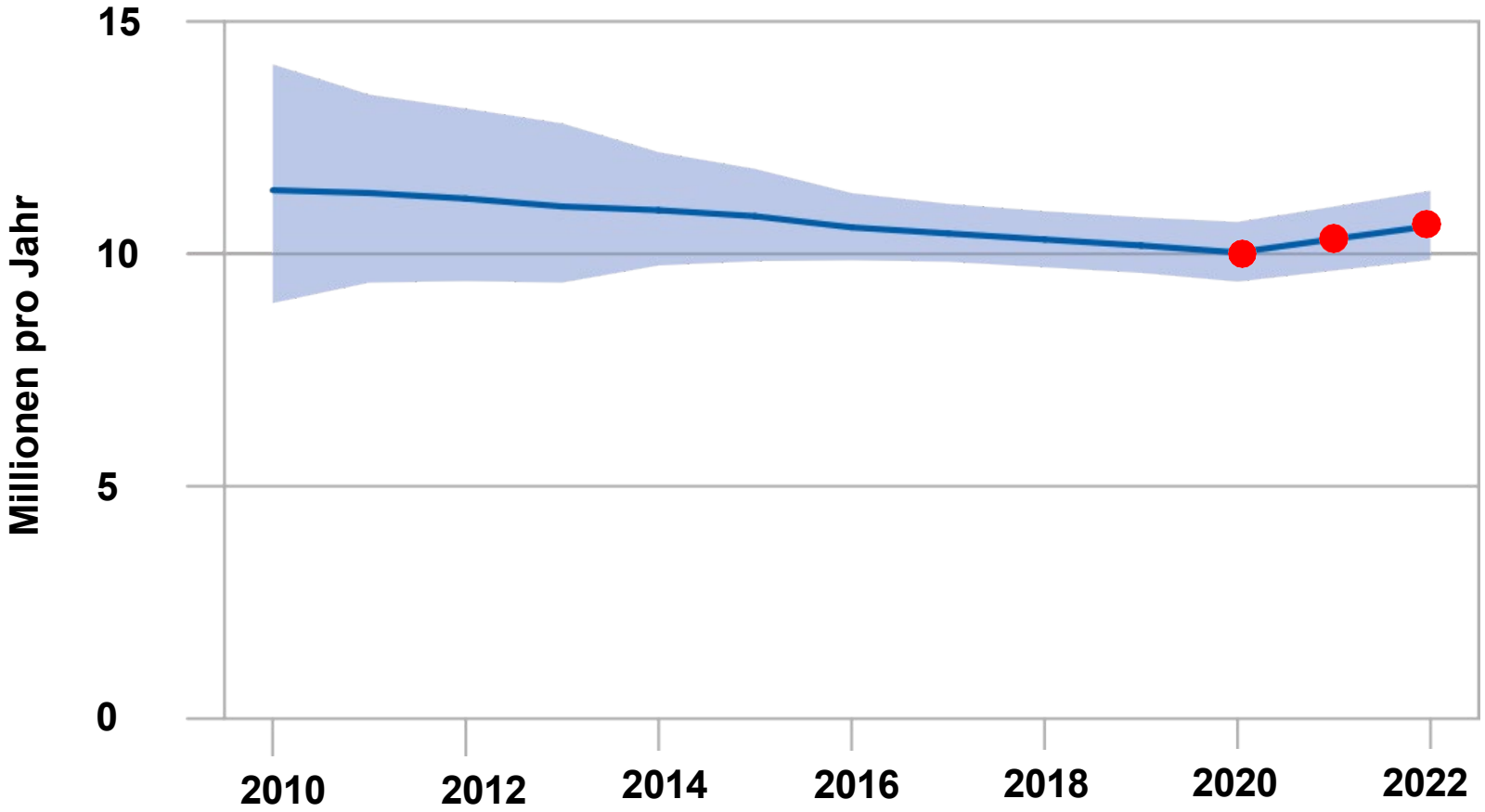
Head Clinical Research Unit, Swiss TPH

Agenda

- Tuberkulose – Krankheitsspektrum
- Subklinische Tuberkulose
  - Definition
  - Häufigkeit
  - Übertragung
  - Diagnose
  - Behandlung
  - Impfstoffentwicklung
- Eigenes Forschungsprojekt
- Zusammenfassung

Tuberkulose Inzidenz - weltweit

10.6 Millionen in 2022

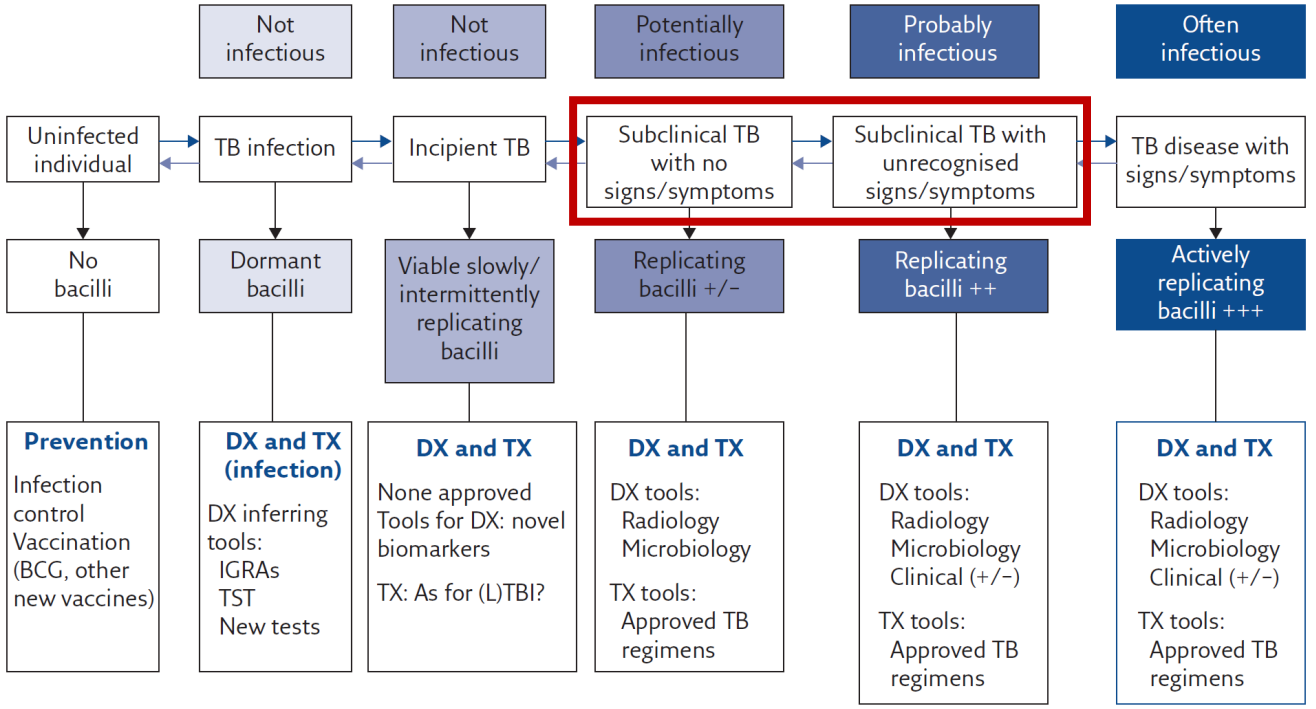


& die versteckte Bedrohung durch die subklinische Tuberkulose!

Shaded area shows 95% uncertainty interval

World Health Organization

Vom Eisberg zum dynamischen Krankheitsspektrum

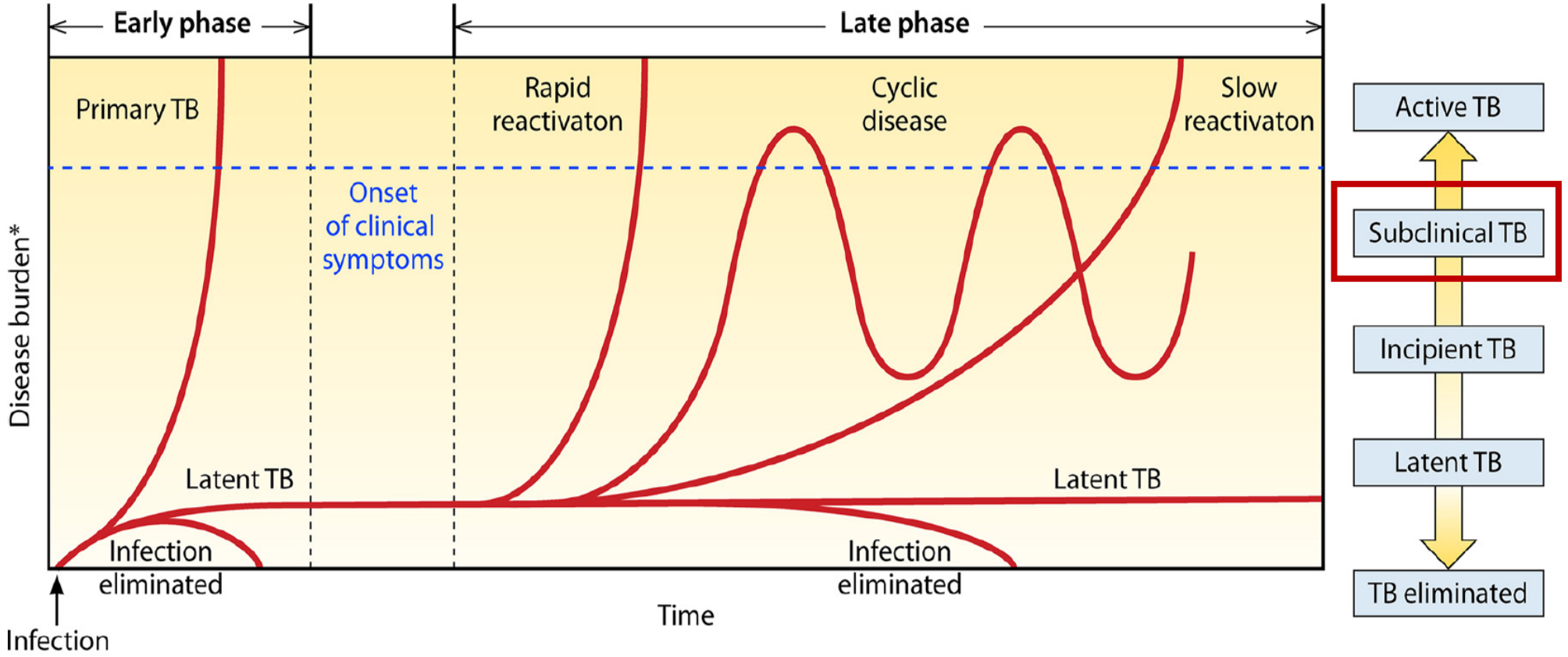


Das Lebenszeitrisiko für TB: ~10 %.
TB Infektion besteht lebenslang.

www.cdc.gov (modified)

Migliori et al Breathe 2021

Es gibt mittlerweile viele Modelle…



Drain et al Clin Microbiol Rev 2018

Was ist subklinische TB?

Gebräuchliche Definition: Subklinische TB

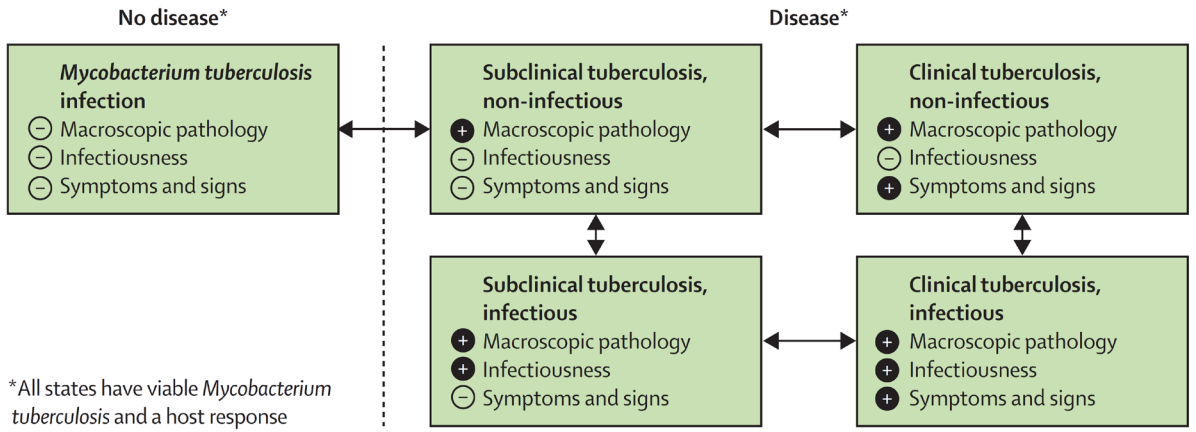
Durch lebensfähige *Mtb-Bakterien* verursachte Krankheit, die keine klinischen TB-bezogenen Symptome hervorruft, aber verschiedene Anomalien verursacht, die mit bestehenden *radiologischen (?)* oder mikrobiologischen Tests nachgewiesen werden können.

Escalante et al IJTLD 2023
Migliori et al Breathe 2021
Kendall et al Am J Respir Crit Care Med 2021
Drain et al Clin Microbiol Rev 2018

Was ist subklinische TB?

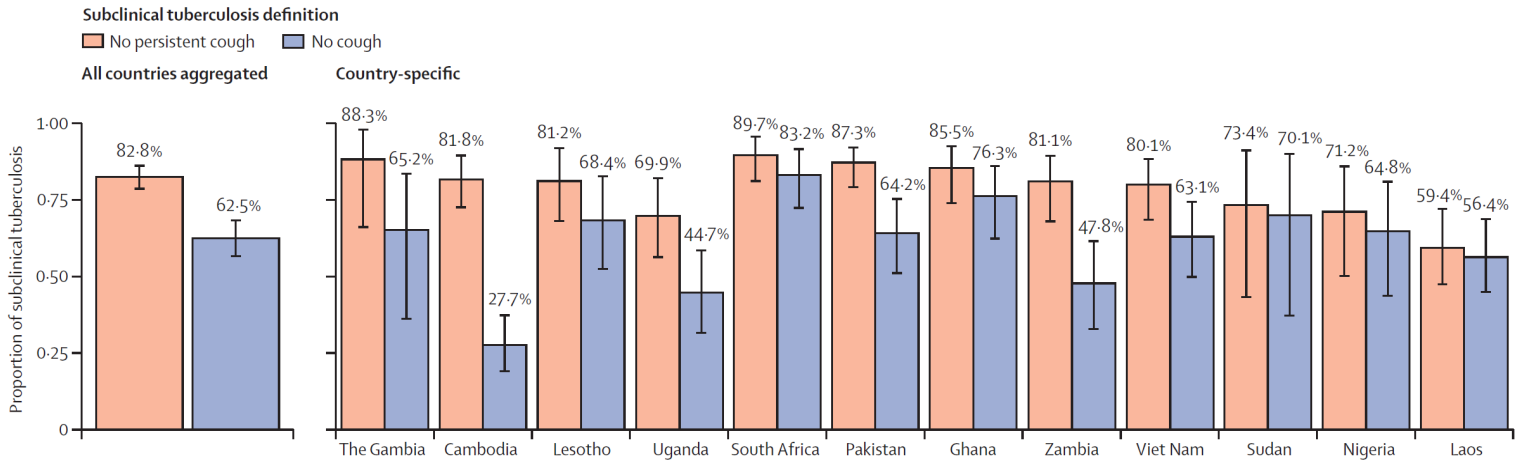
Delphi Consensus (International Consensus for Early TB, ICE-TB): Kriterien für Subklinische TB

- Nicht infektiöse versus infektiöse Subklinische TB
- Makroskopische Pathologie (z.B. Infiltration nach gescheiterter Eindämmung von *M. tuberculosis*)
- Symptome, wenn sie vorhanden sind, von der Person nicht erkannt oder nicht anerkannt werden oder nicht ausreichen, um die Person zu veranlassen, sich behandeln zu lassen (?).



Coussens et al.Lancet Respir Med 2024

Wie häufig ist subklinische TB? Teil I



82.8% (95% CI 78.6-86.6) keinen anhaltenden Husten (≥ 2 Wo)
62.5% (95% CI 56.6-68.7) keinen Husten
27.7% (95% CI 21.0-36.4) keine Symptome [in Untergruppe]

adjusted for false-negative chest x-rays and uninterpretable culture results.

Häufigkeit

Definitionen sind wichtig

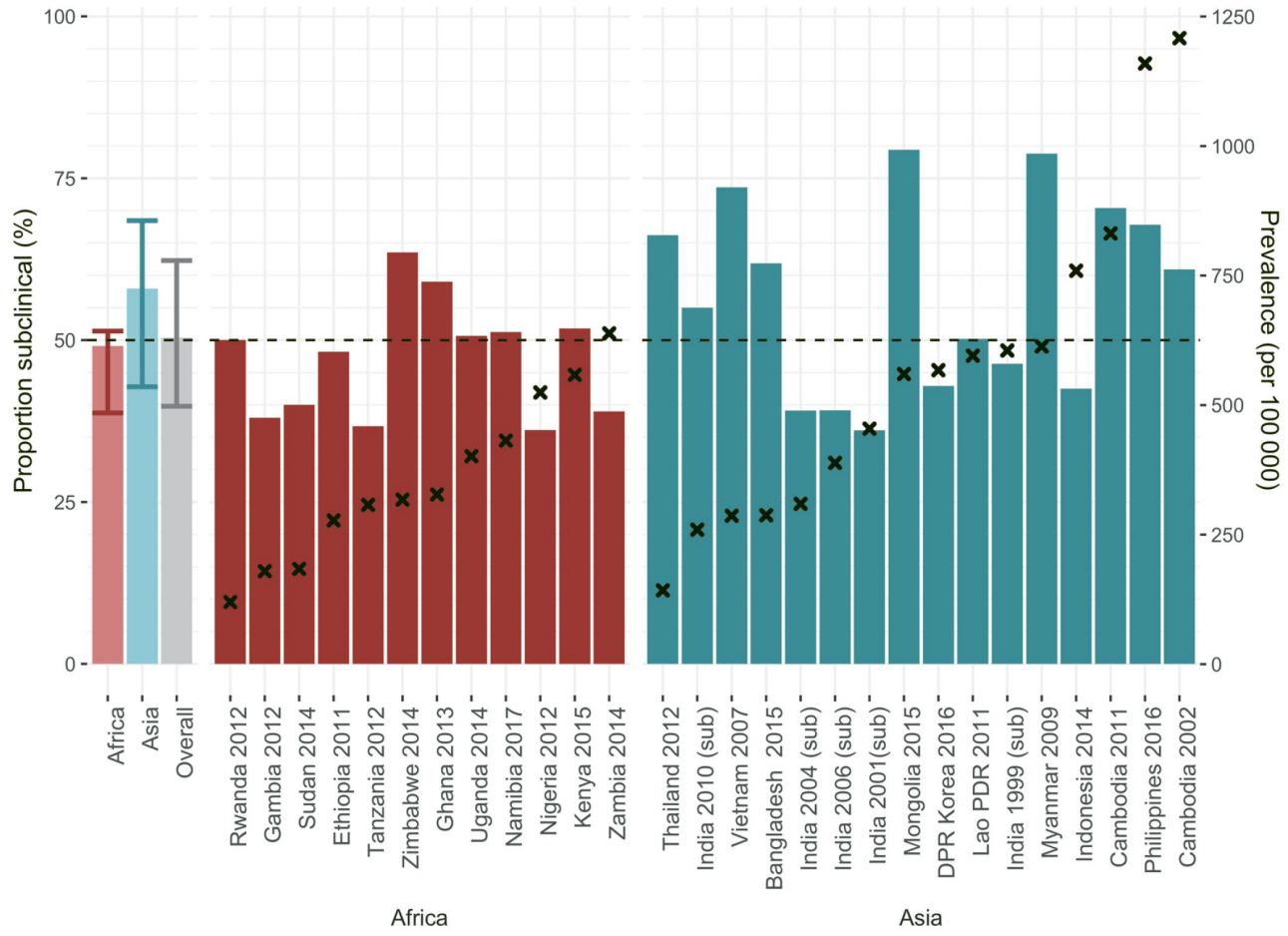
Prävalenzerhebungen

(12 prevalence surveys;
620682 Teilnehmer;
TB = Kultur+)

„In Asien und Afrika berichtet die **Mehrheit der Menschen mit noch nicht diagnostizierter Lungentuberkulose nicht über Husten**, unabhängig von dessen Dauer. “

Stuck et al Lancet Infect Dis 2021

Wie häufig ist subklinische TB? Teil II



Häufigkeit

Prävalenzerhebungen

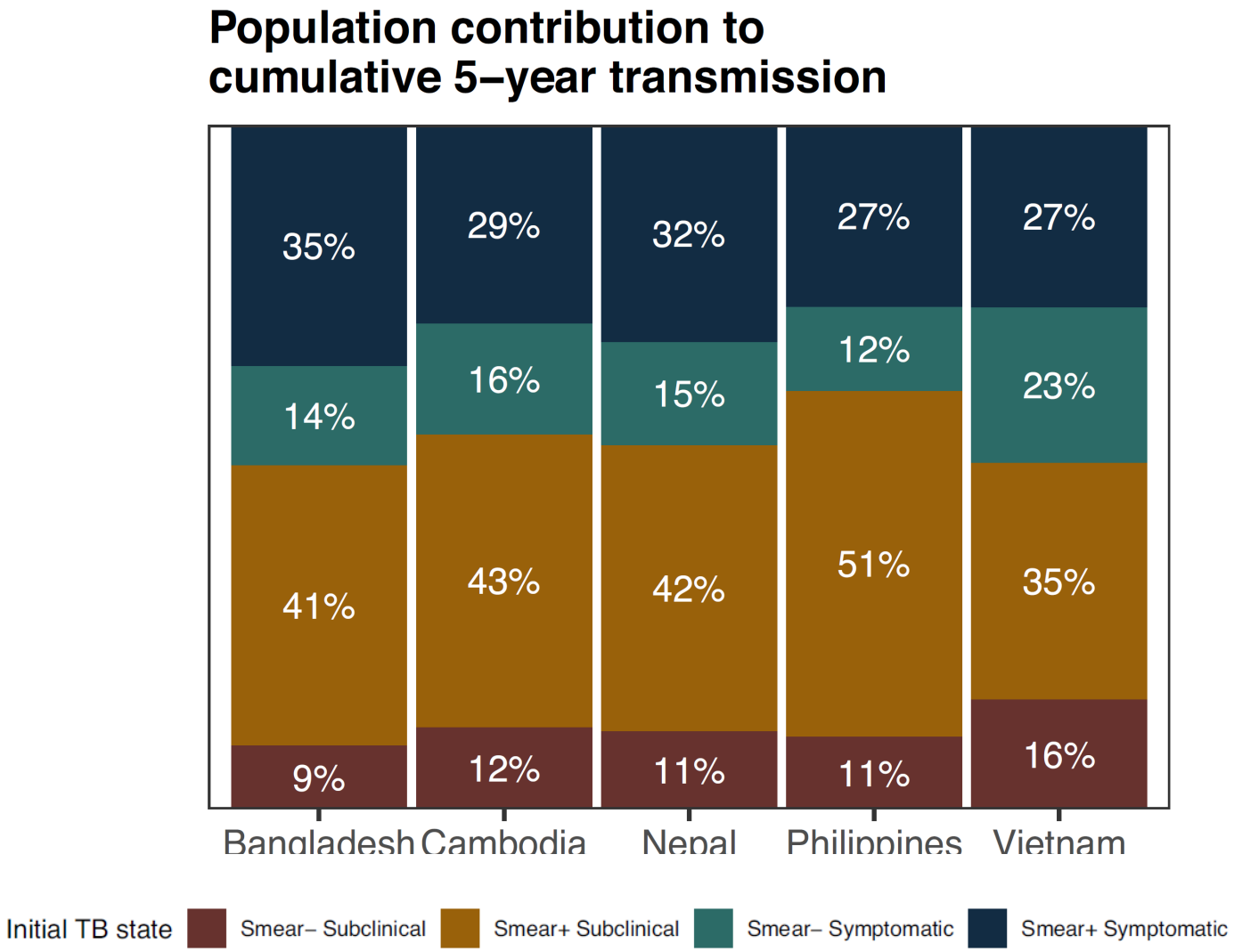
(28 prevalence surveys;
TB= positive Kultur oder PCR)

„Zwischen 36,1 % und 79,7 % (Median: **50,4 %**) der prävalenten bakteriologisch bestätigten TB waren **subklinisch***."

*Fehlen der survey-spezifischen Screening-Symptome

Frascella et al CID 2021

Trägt subklinische TB zur Transmission bei? Teil I



Übertragung

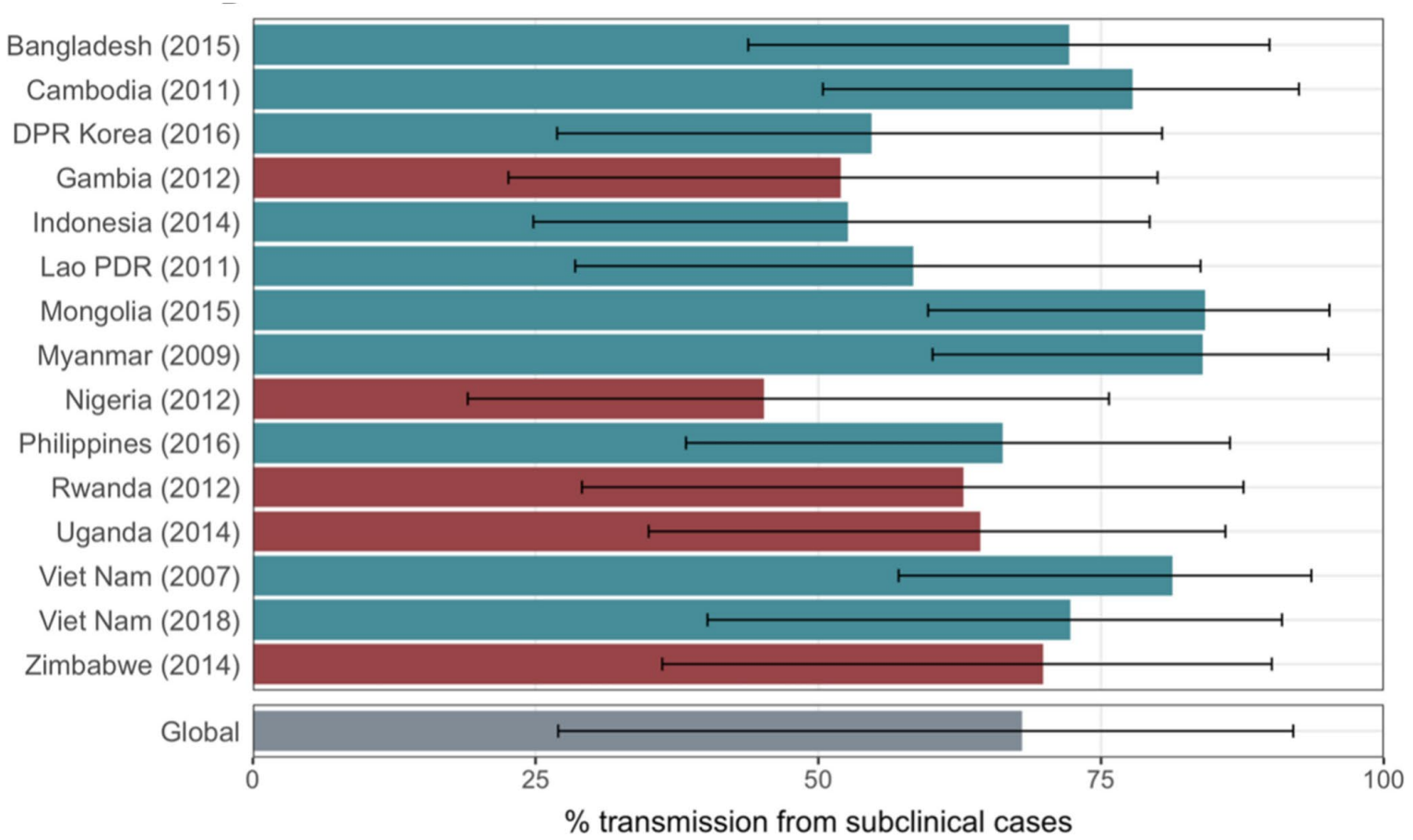
Bayesianische Modellierung

Kohorten und Prävalenzerhebungen aus fünf Ländern

„Obwohl sie nur 11 bis 19 % der prävalenten Erkrankungen ausmachte, war die **Sputum smear-positive subklinische TB für 35 bis 51 % der zukünftigen Übertragung verantwortlich**.“

Ryckman et al PNAS 2022

Trägt subklinische TB zur Transmission bei? Teil II



Übertragung

Analyse individueller Patienten-daten aus Prävalenzerhebungen

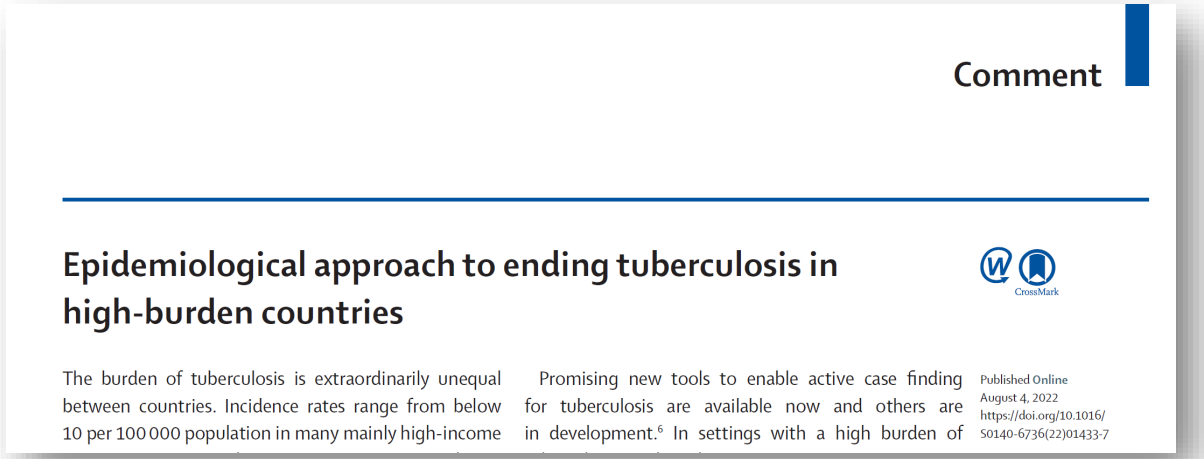
Modell: Schätzungen der Infektiosität basierend auf Prävalenzdaten der Haushaltskontakte von subklinischen und klinischen Indexfällen

„**Ca. 68 %** (27-92 %, 95 % prediction interval) der weltweiten Übertragung ist auf subklinische TB zurückzuführen sind.“

Emry et al Elife 2023

Was ist notwendig um subklinische TB zu diagnostizieren?

Symptom-unabhängiges Screening



Comment

Epidemiological approach to ending tuberculosis in high-burden countries

The burden of tuberculosis is extraordinarily unequal between countries. Incidence rates range from below 10 per 100 000 population in many mainly high-income

Promising new tools to enable active case finding for tuberculosis are available now and others are in development.[6] In settings with a high burden of

Published Online August 4, 2022 https://doi.org/10.1016/S0140-6736(22)01433-7

„…wesentliche Fortschritte auf dem Weg zur Beendigung der Tuberkulose … sind nur möglich, wenn man **sich auf die aktive Erkennung von Tuberkulosefällen in den Gemeinden mit Hilfe von symptom-unabhängigen Verfahren konzentriert, gefolgt von einer wirksamen Behandlung, um die endemische Übertragung zu stoppen**."

Marks et al Lancet 2022

Ziel:

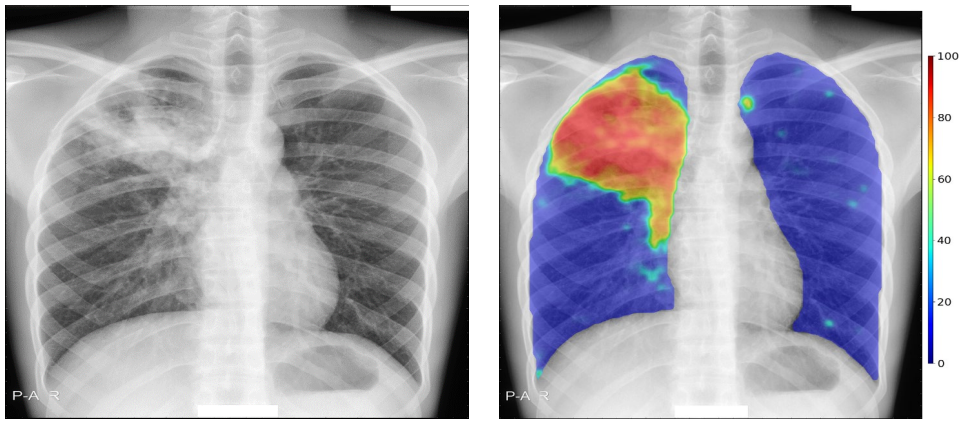
- Ansteckungsfähigkeit und Krankheitsübertragung↓
- frühzeitige Behandlung → schwere Krankheitsverläufe↓ → schwerer gesundheitliche Folgeschäden↓
- Finanzielle Folgen für den Einzelnen und auch für die Gemeinschaft↓

Mit welchen Methoden kann subklinische TB diagnostiziert werden?

2 Beispiele

Digitale Röntgenuntersuchung des Thorax

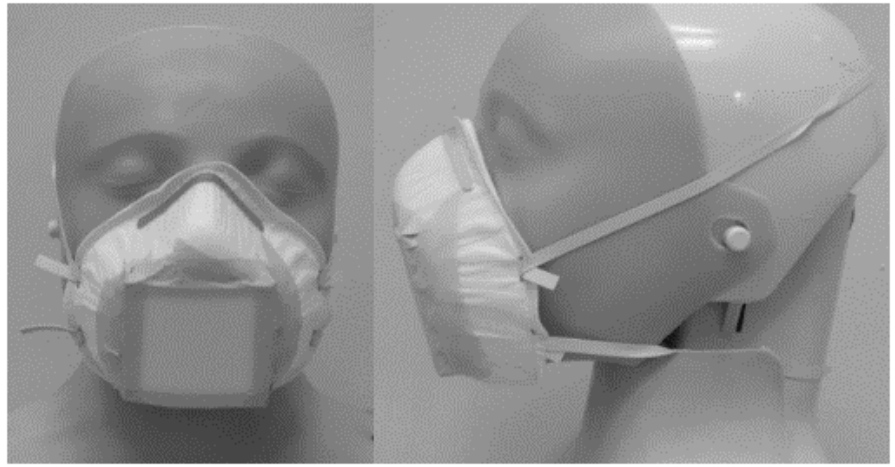
in Kombination mit:
Computergestützter Erkennung von Tuberkulose mit Hilfe KI-basierter Software (CAD)



Reither et al work in progress

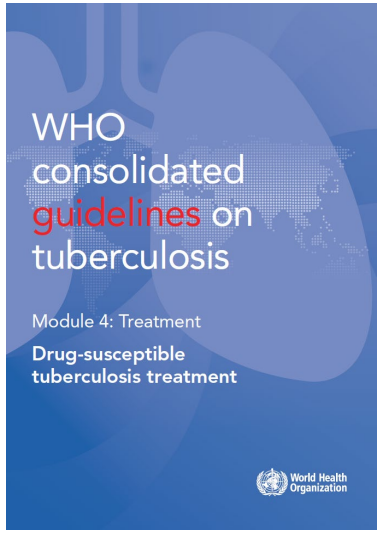
Aerosol-Erfassung durch Gesichtsmasken?

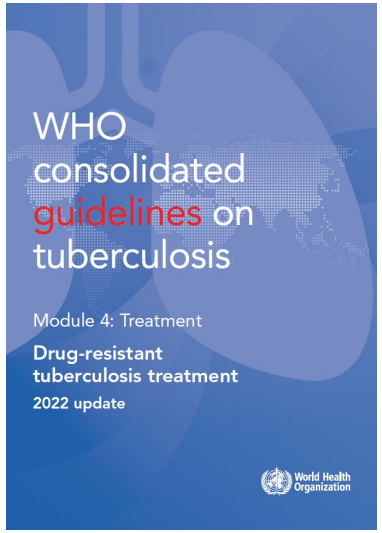
Initial sehr vielversprechend Ergebnisse konnten mit industriell gefertigten Masken nicht reproduziert werden

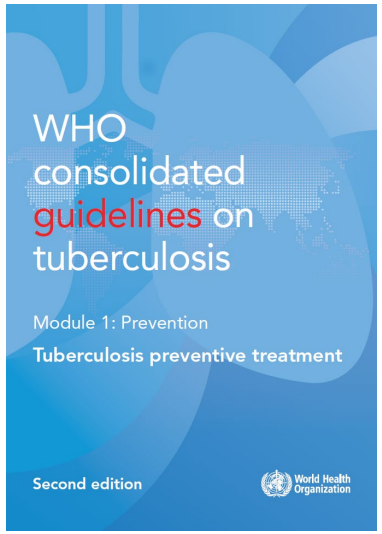


Williams et al Lancet Infect Dis 2020

Wie sollte subklinische TB behandelt werden?







Keine direkte Erwähnung der subklinischen TB in diesen Richtlinien

Aber: Bakteriologisch bestätigte TB → **Therapien für DS-TB oder DR-TB sollten begonnen werden**.

Meta-analyse (29 prevalence surveys, 71 andere Studien)

- Immer wurde Standardtherapie für subklinische TB gegeben.
- Behandlungserfolg bei Personen mit subklinischer und klinischer TB vergleichbar.

Teo et al Eur Respir Rev. 2024

Offene Frage

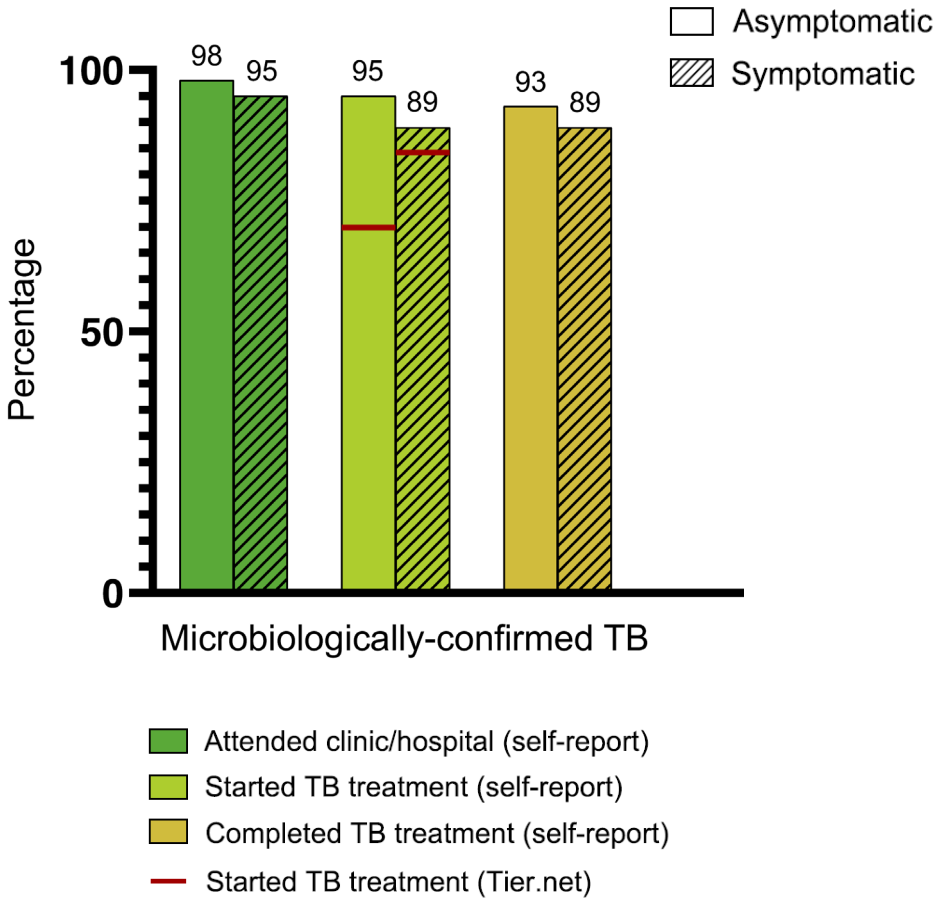
Ist eine **stratifizierte Therapie*** sinnvoll?

Subklinische und milde aktive TB	**'Hard-to-treat' aktive TB**
2PHMZ/2PHM (4mPM)	2HRZE/4HR (6mCat1)

* z.B. hohe Bazillenlast, Unterernährung, kürzlich durchgemachte TB, unkontrollierte HIV-Infektion

Imperial et al. Nat Med. 2018 Dorman et al. N Engl J Med. 2021

Wie akzeptieren Patienten mit subklinischer TB die Behandlung?

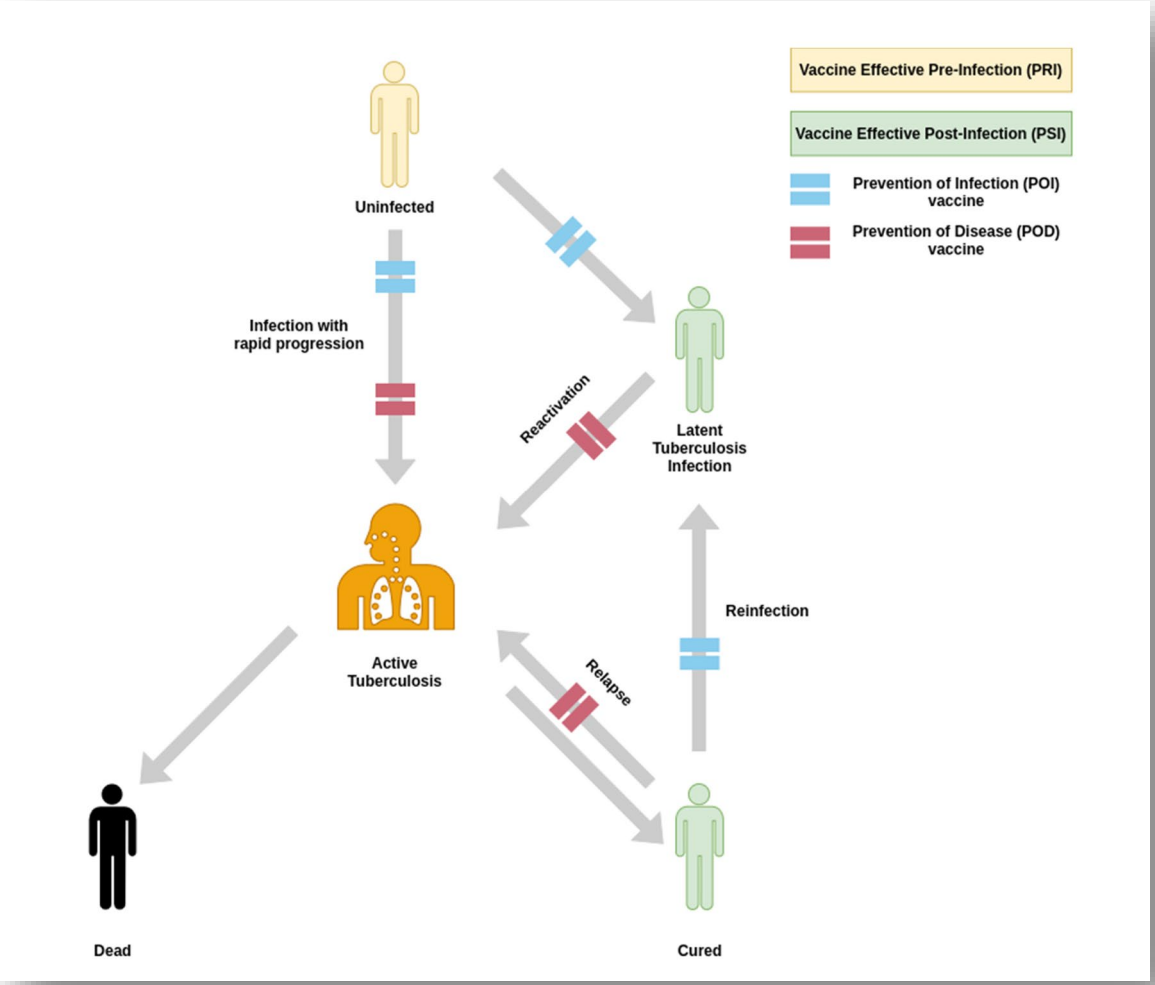


Vukuzazi-Studie

Gemeindebasierte Studie in Südafrika

- Hohe Raten von subklinischer TB.
- Symptomstatus oder HIV-Status hatten keinen Einfluss auf ‚linkage-to-care'.

Wie sollte subklinische TB in Impfstoffstudien berücksichtigt werden?

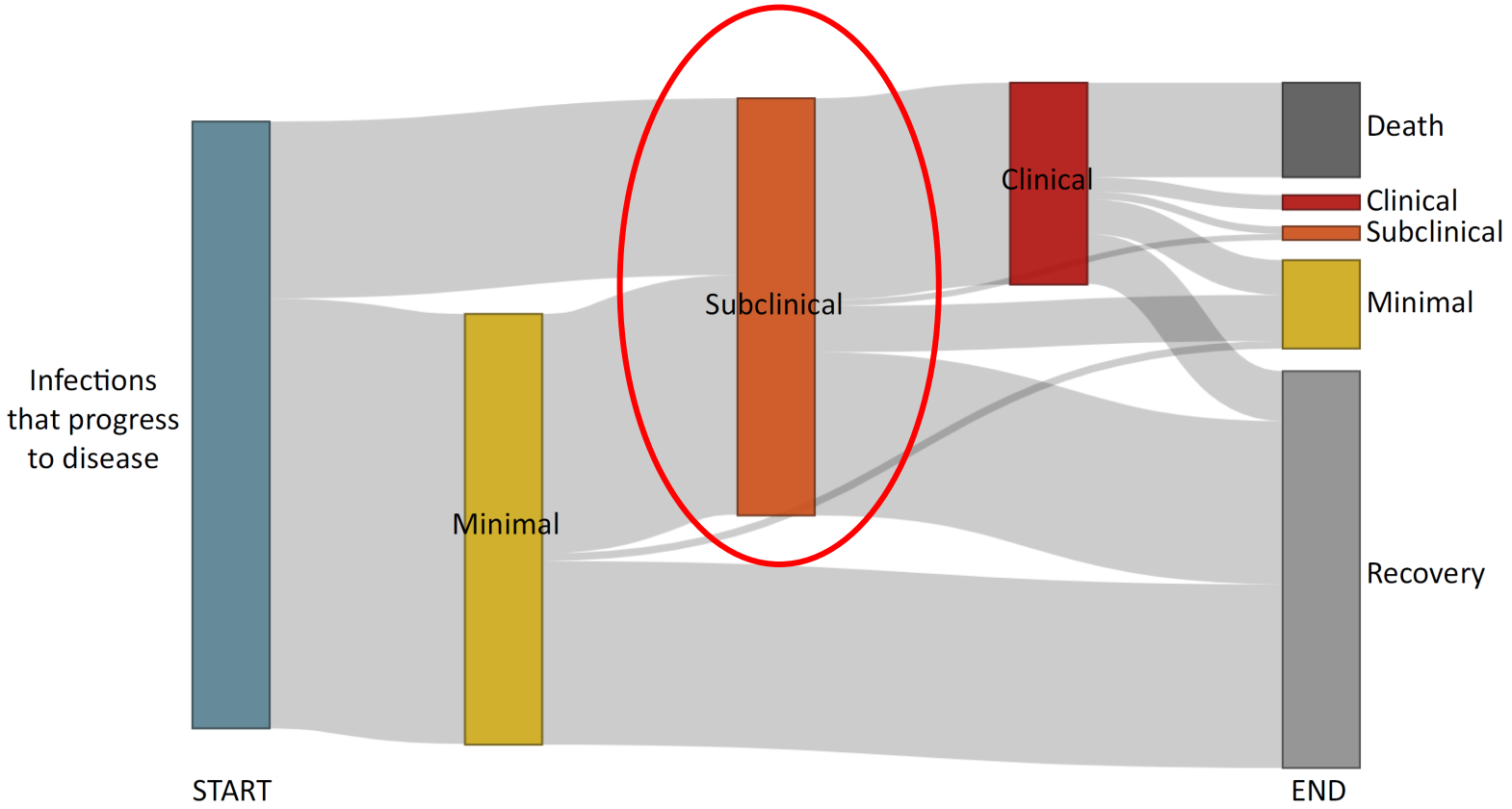


TB Impfstoffentwicklung

Spiegeln die bisherigen Konzepte zur Impfstoffentwicklung die dynamischen Verläufe der TB Infektion und Erkrankung wider?

Weerasuriya et al J Intern Med. 2020

Welche Verlaufswege gibt es nach einer *M. tuberculosis* Infektion?



Verlaufswege – 10 Jahre nach Infektion

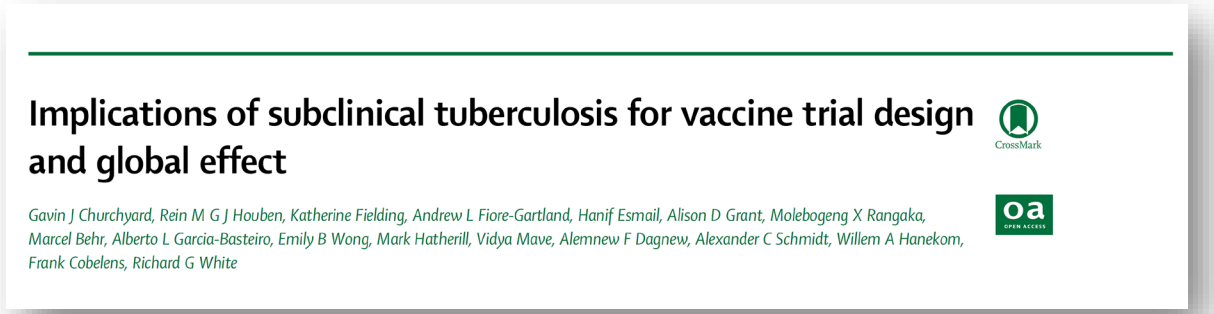
Bayesianische Modellierung

Historische TB Kohorten TST-neg. und Progression-/Regression-Studien

Heterogene Pfade durch das TB-Spektrum.

Horton et al PNAS 2023

Wie sollte subklinische TB in Impfstoffstudien berücksichtigt werden?



Implications of subclinical tuberculosis for vaccine trial design and global effect

Gavin J Churchyard, Rein M G J Houben, Katherine Fielding, Andrew L Fiore-Gartland, Hanif Esmail, Alison D Grant, Molebogeng X Rangaka, Marcel Behr, Alberto L Garcia-Basteiro, Emily B Wong, Mark Hatherill, Vidya Mave, Alemnew F Dagnew, Alexander C Schmidt, Willem A Hanekom, Frank Cobelens, Richard G White

TB Impfstoffentwicklung

- Prävention der **klinischen und der subklinischen TB** ist eine Priorität
- Die Einbeziehung der subklinischen TB als ‚**composite endpoint**‘:

  Stichprobenumfang ↓

  Dauer der Nachbeobachtung ↓

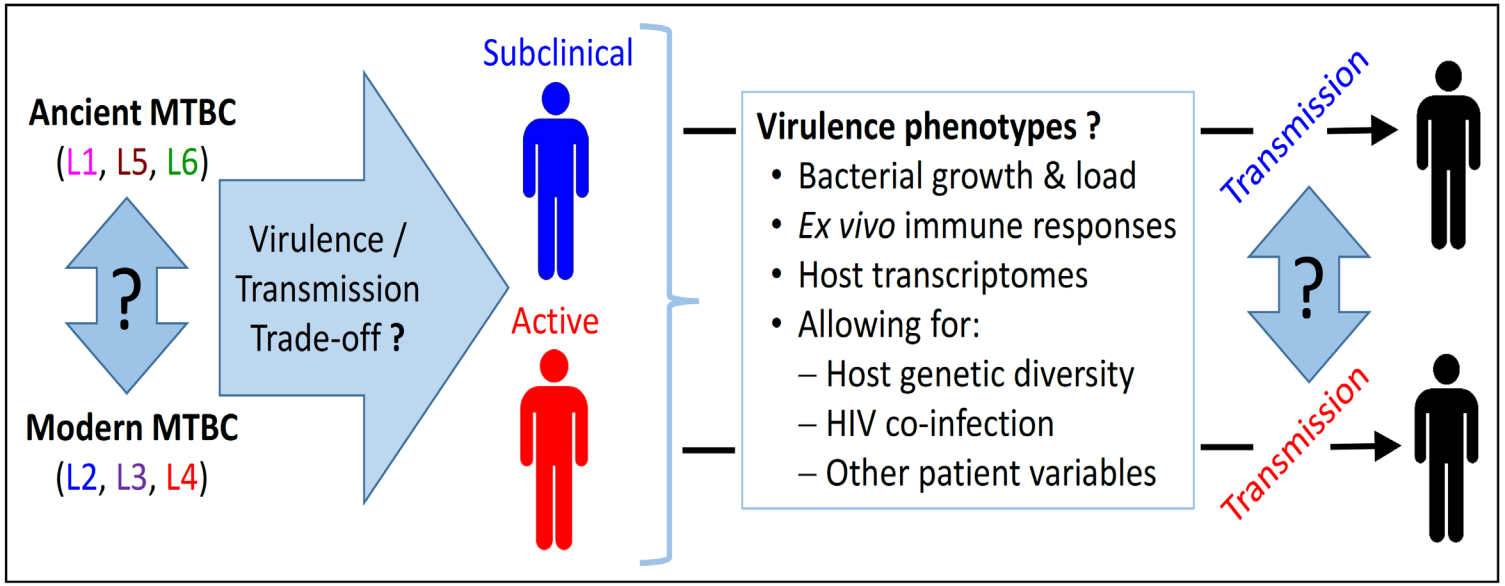
  Bewertbarkeit der Impfstoff-Wirksamkeit ✓✓
- Verschiedene Studiendesign-Varianten für POD Studien empfohlen

Unsere Forschung: Subklinische TB

Der Trade-Off zwischen Virulenz und Übertragung: Erforschung der biologischen Determinanten und epidemiologischen Konsequenzen der subklinischen Tuberkulose

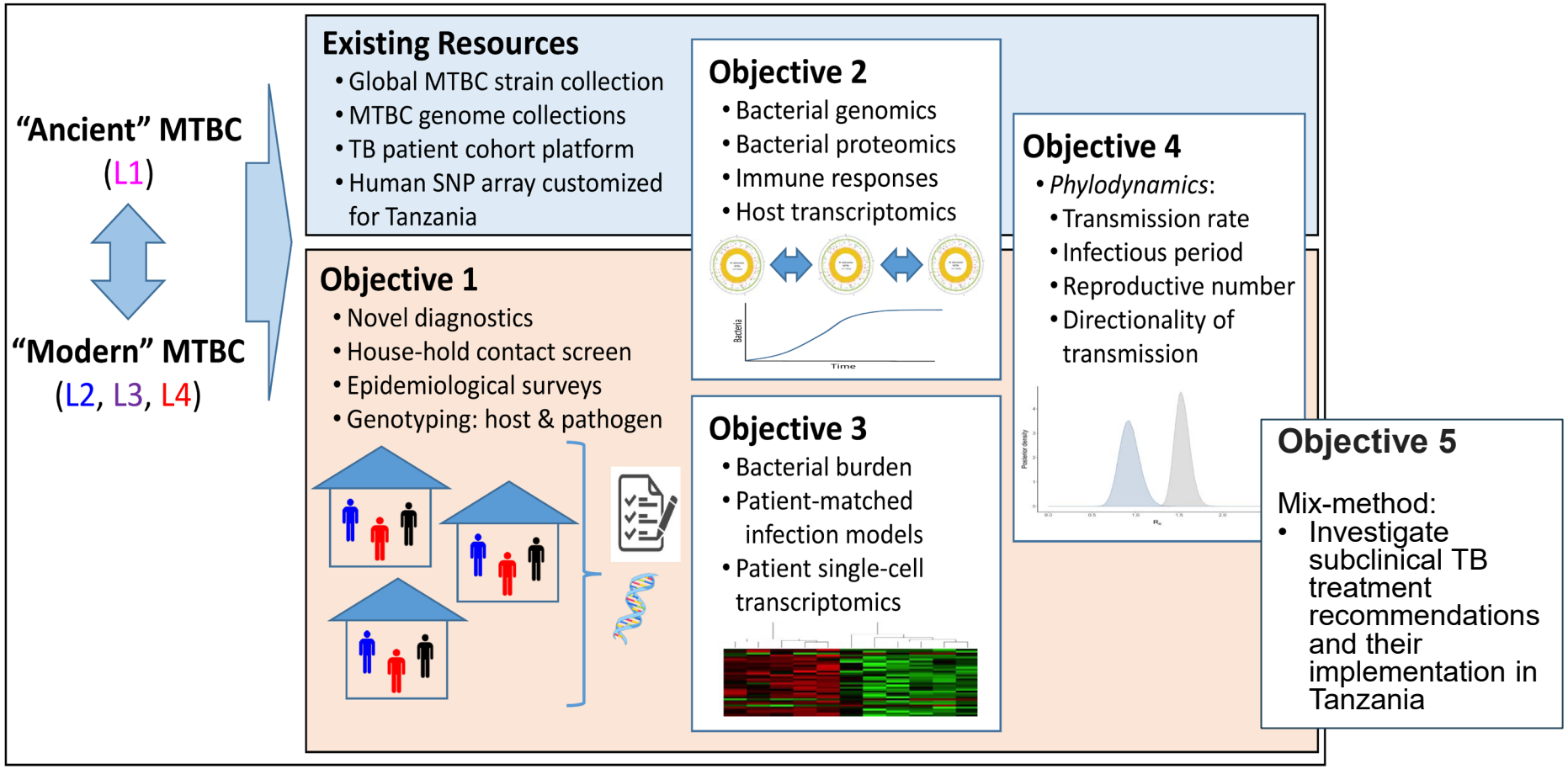
Hypothesen

- Subklinische TB ist eine evolutionäre Strategie, die für die **„alten“ MTBC-Linien** im Vergleich zu den virulenteren „modernen“ Linien charakteristisch ist.
- Die unterschiedlichen evolutionären Strategien der „alten“ und „modernen“ MTBC-Linien **spiegeln sich in molekularen und phänotypischen Unterschieden während der Wirt-Pathogen-Interaktion wider.**
- Subklinische TB **kann übertragen werden** und zu sekundären Fällen von aktiver oder subklinischer TB führen.



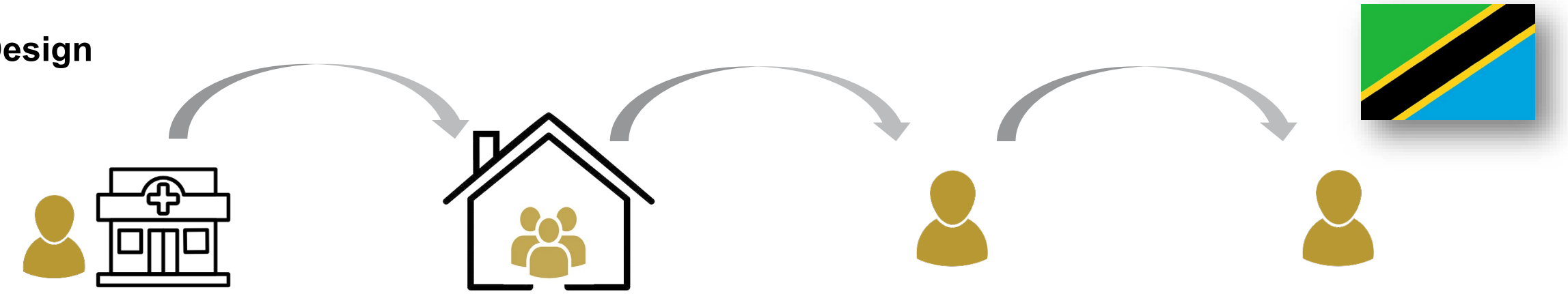
Der Trade-Off zwischen Virulenz und Übertragung: Erforschung der biologischen Determinanten und epidemiologischen Konsequenzen der subklinischen Tuberkulose

Zielsetzungen



Der Trade-Off zwischen Virulenz und Übertragung: Erforschung der biologischen Determinanten und epidemiologischen Konsequenzen der subklinischen Tuberkulose

Design



Index TB case	Household screening *interim analysis with 1,000 participants or 250 households **(oral consent only)**	Individual testing in positive households	6-m follow up of individuals from positive households
~3300	~10000	~1200	~1200
Sputum sample: liquid culture & IS6110 qPCR	Pooled sampling Tongue swaps & sputum samples: IS6110 qPCR*	Sputum sample: liquid culture & IS6110 qPCR, Tongue swaps: liquid culture	Sputum sample: liquid culture & IS6110 qPCR, Tongue swaps: liquid culture

Zu verschiedenen Zeitpunkten: PBMC für **immunologische Tests**, Blut für **transkriptomische Signaturen** des TB-Risikos und **genetische Wirtsmarker**, Blutbank

Swiss TPH

Partner

Swiss TPH

EPFL

ISO 9001: 2015 certified
IFAKARA HEALTH INSTITUTE
research | training | services

Swiss National Science Foundation

Zusammenfassung: Subklinische TB

1. Die grosse epidemiologische und klinische Bedeutung der subklinischen TB ist erst in den letzten Jahren deutlich geworden.

2. Eine standardisierte Definition der subklinischen TB ist dringend erforderlich.

3. Etwa jede zweite Person mit mikrobiologisch nachgewiesener TB hat eine subklinische Form.

4. Mathematische Modelle beschreiben ein hohes infektiöses Potenzial und einen heterogenen Verlauf der subklinischen TB.

5. Strategien zur TB-Erkennung müssen auch auf subklinische Fälle zugeschnitten sein, z.B. Fokus auf symptom-agnostische Screeningmethoden.

6. Die Behandlung der subklinische TB könnte durch einen stratifizierten Behandlungsansatz evtl. verbessert werden.

7. Impfstoffstudie sollten subklinische TB als Endpunkt mitberücksichtigen.

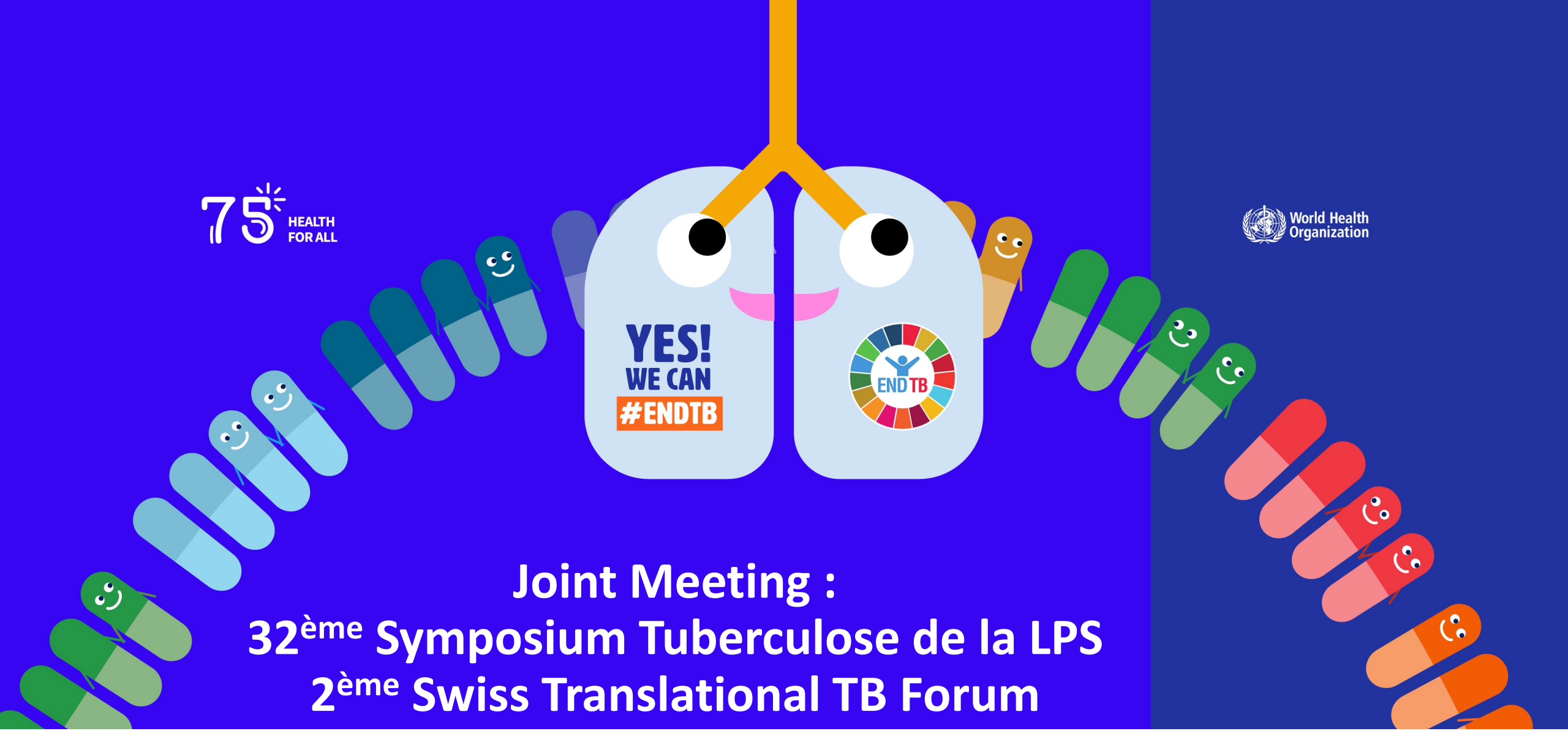
... vielen Dank für Ihre Aufmerksamkeit !

Joint TB-Meeting:
32. Tuberkulose-Symposium der LLS
2. Swiss Translational TB Forum

Pause bis 16.00 Uhr

Swiss Translational TB Forum

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA



Pause jusqu'à 16h00

Swiss Translational TB Forum

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA

Mit Unterstützung von
Avec le soutien de

QIAGEN

Diasorin

Swiss Translational
TB Forum

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA

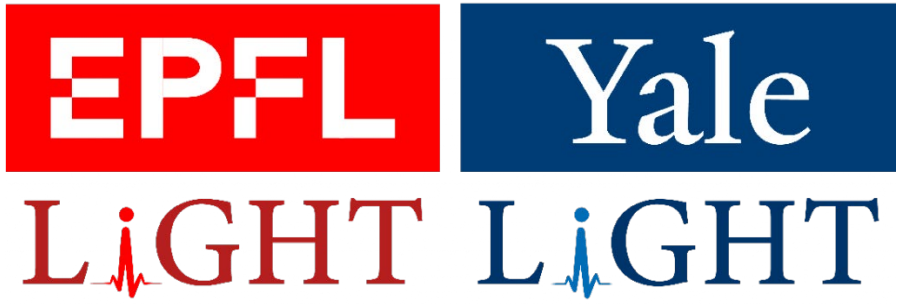
Künstliche Intelligenz in der TB-Diagnostik

Julia Wolleb, PhD
Annie Hartley, MD, PhD, MPH

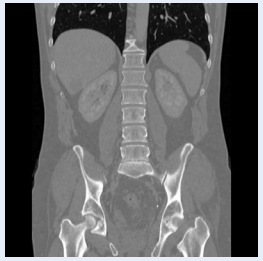
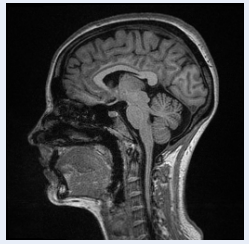
30. Oktober 2024

julia.wolleb@yale.edu

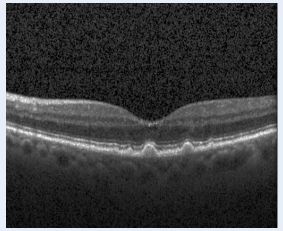
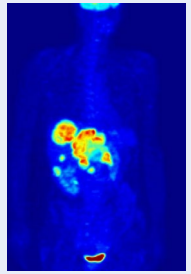
Laboratory for Intelligent Global Health & Humanitarian Response Technologies



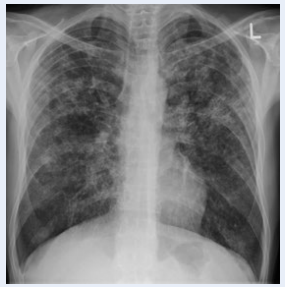
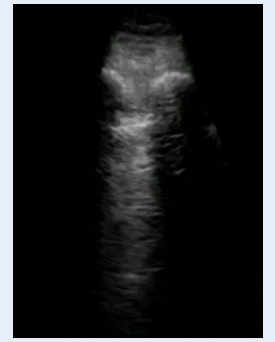
Motivation


Medizinische Bilder

Bilder in der TB-Diagnostik

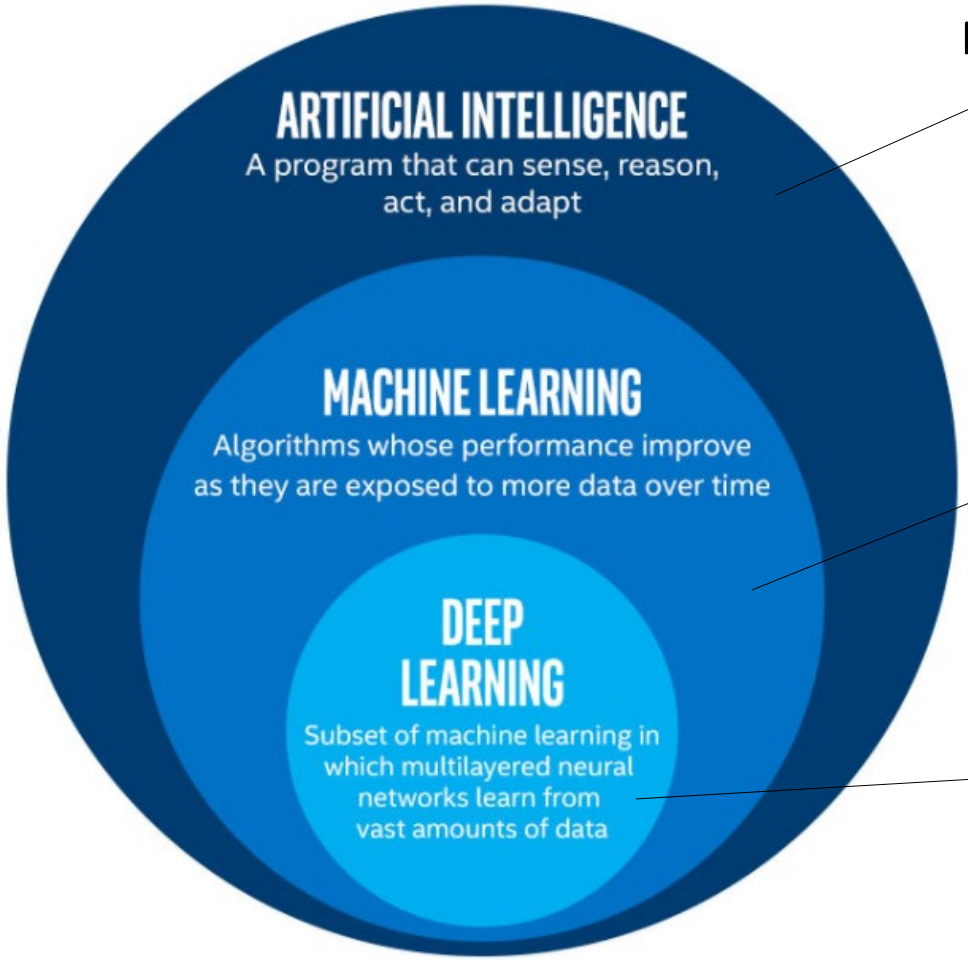
- Bilder sind eine wertvolle Informationsquelle
- Analyse ist zeitaufwändig und erfordert Expertenwissen → wir wollen diese Pipeline automatisieren, um medizinische Experten zu unterstützen

Inhalt:

- Kurze Einführung in Deep Learning für die Bildanalyse
- Deep learning in der TB-Diagnostik

EPFL Yale
LiGHT LiGHT

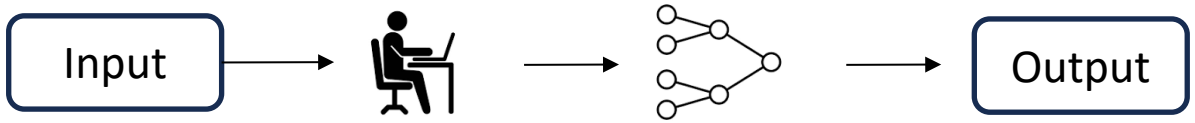
Viele Buzzwords…



Regelbasierte Systeme, Suchalgorithmen, ...

Von Menschen designtes Programm

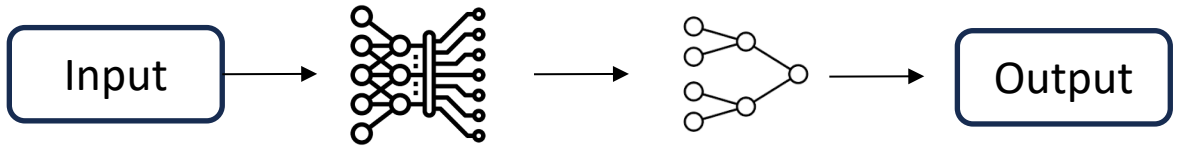
Support vector machines, decision trees, ...



Von Menschen gewählte Merkmale

Mapping von Merkmalen

Convolutional Neural Networks, Reinforcement Learning, ...



Automatisierte Extrahierung von Merkmalen

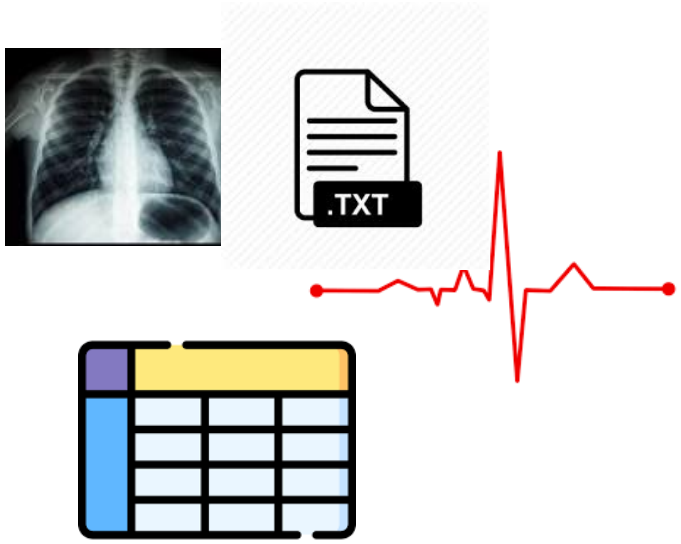
Mapping von Merkmalen

https://medium.com/swlh/artificial-intelligence-machine-learning-and-deep-learning-whats-the-real-difference-94fe7e528097

EPFL Yale LiGHT LiGHT

Was ist Deep Learning?

Input



Deep Neural Network «Black Box»

Verstellbare Knöpfe

Vorhersage

Welche Daten haben wir?

Wie wird das neuronale Netz designt und trainiert?

Welche Aufgabe wollen wir lösen?

Training von Neuronalen Netzen

Aufgabe: Wie alt ist die Person auf dem Bild?

Input x

Deep Neural Network

Vorhersage y

prognostiziertes Alter = y = 30

Echtes Label $\hat{y}$

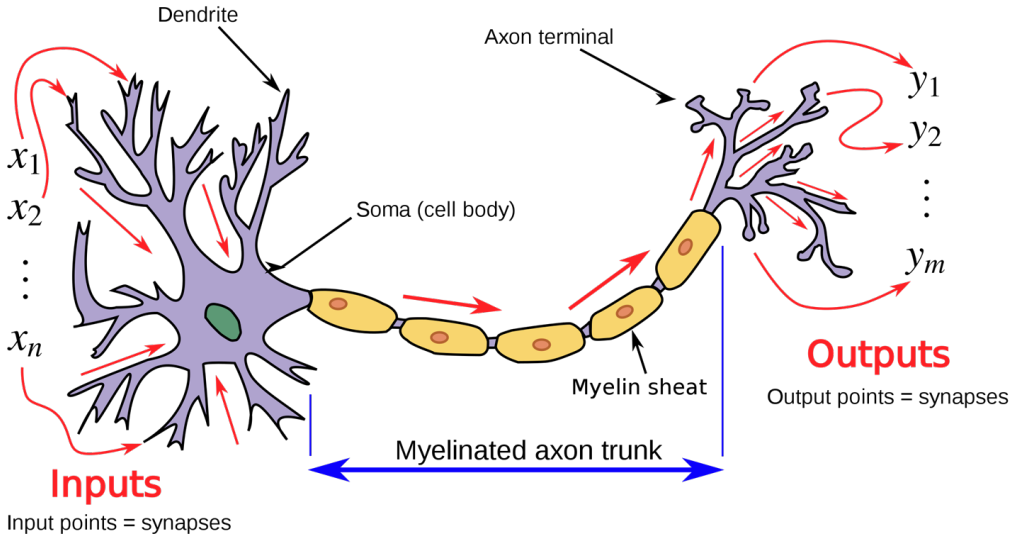
Echtes Alter = $\hat{y}$ = 34

Knöpfe neu einstellen

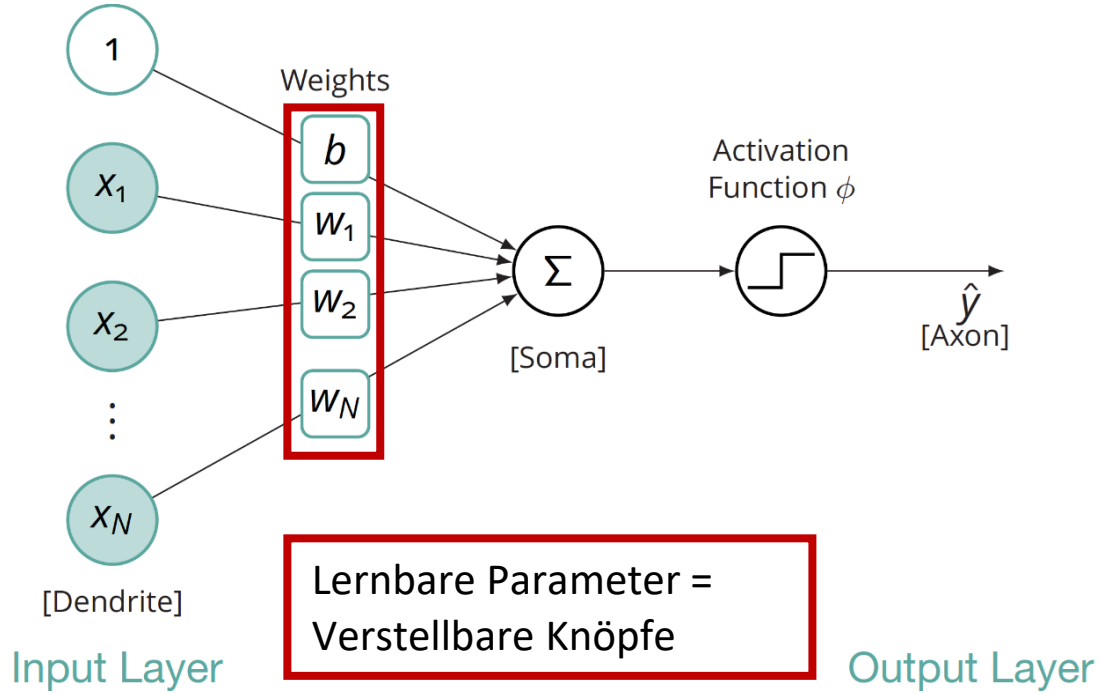
Loss: Wie gut stimmen $\hat{y}$ und y überein?

$34 - 30 = 4$

Was ist ein Künstliches Neuronales Netz?



Biologisches Neuron



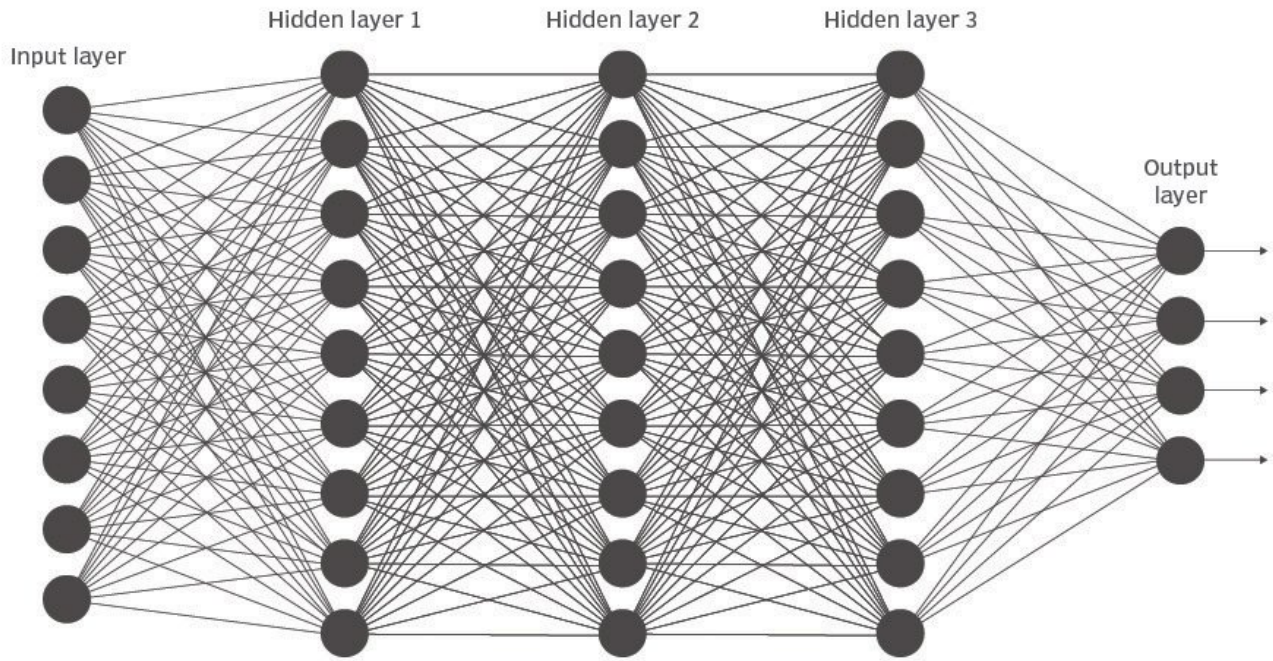
Mathematisches Neuron (Rosenblatt 1959)

https://commons.wikimedia.org/wiki/File:Neuron3.png#/media/File:Neuron3.svg

EPFL Yale LiGHT LiGHT

Deep Learning: Tiefe Neuronale Netze

Beim **Deep** Learning stapeln wir viele Ebenen von Neuronen:

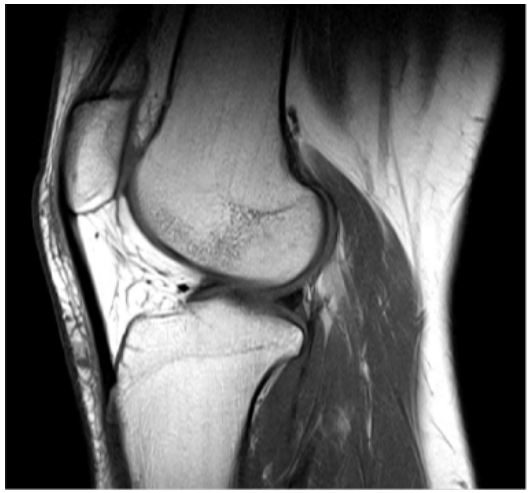


Dies führt zu Netzen mit Milliarden von Parametern.

Wir brauchen eine hohe Rechenleistung.

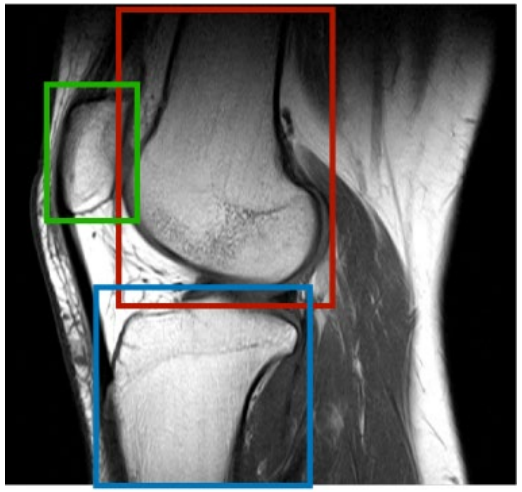
Aufgaben in der Medizinischen Bildanalyse

Klassifizierung



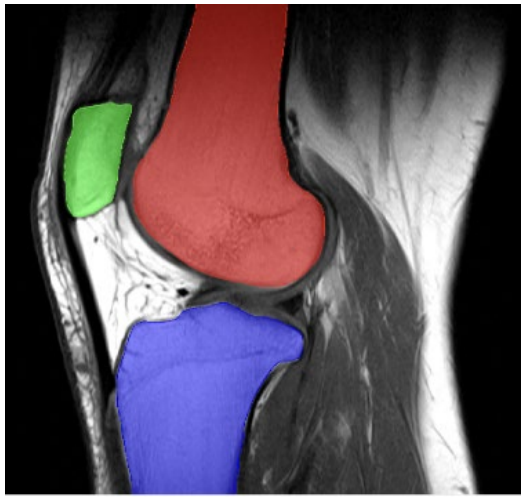
"Es ist ein Knie"

Objekterkennung



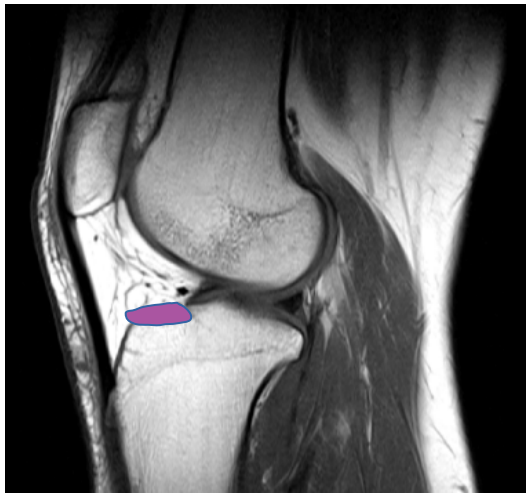
Femur + Tibia + Patella

Segmentierung



Femur + Tibia + Patella

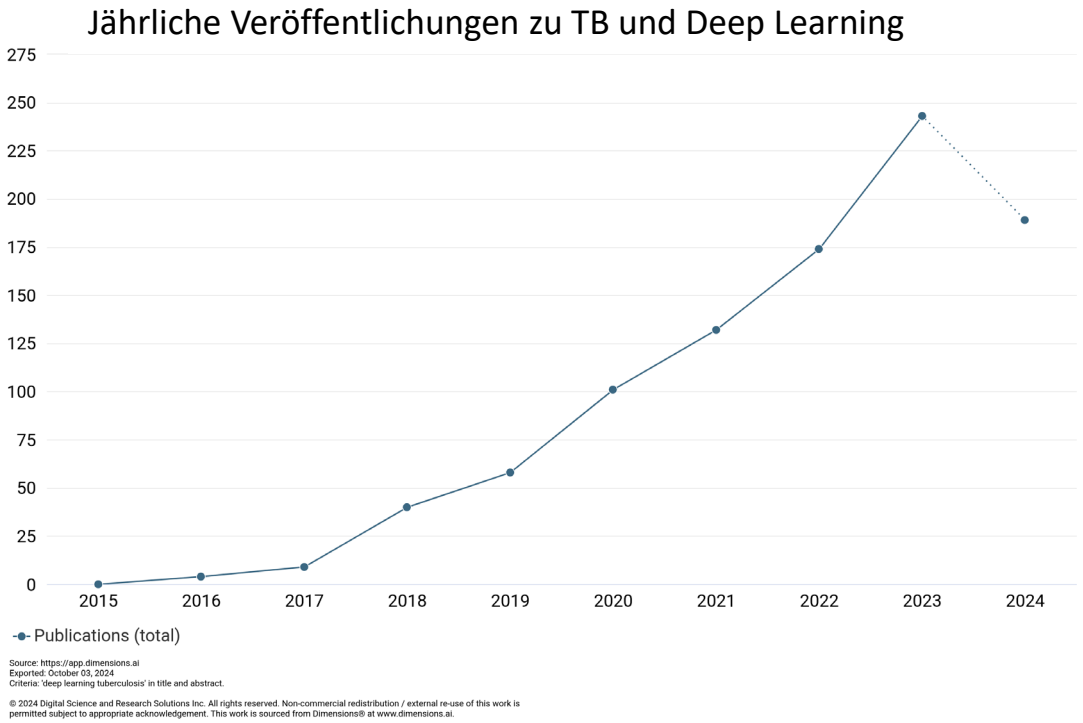
Entdeckung von Anomalien

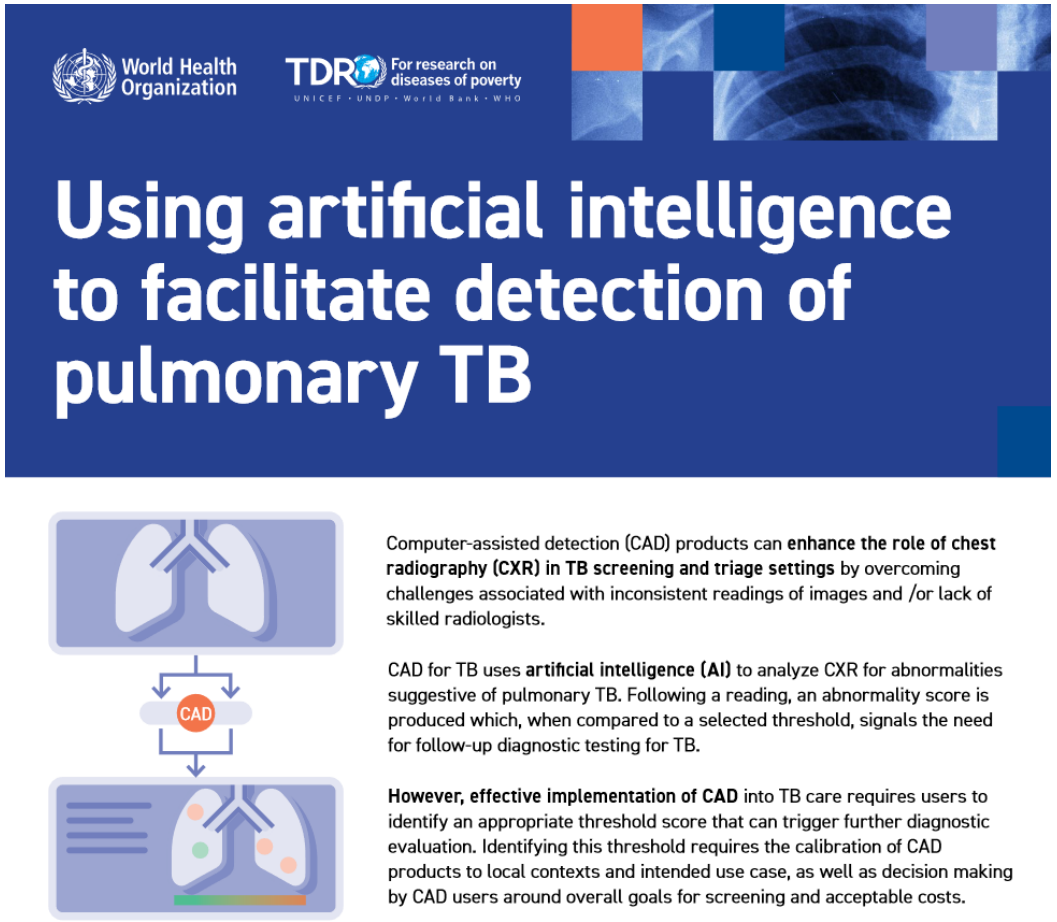


Pathologische Region

- Was sind mögliche Anwendungen in der Tuberkulose-Diagnostik?
- Wo kann Deep Learning die menschlichen Experten unterstützen?

TB-Diagnostik und Deep Learning

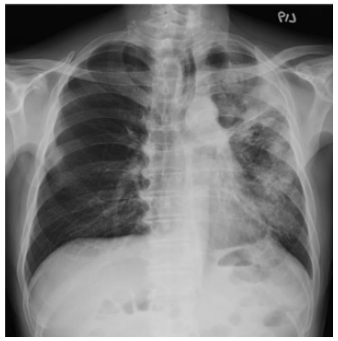




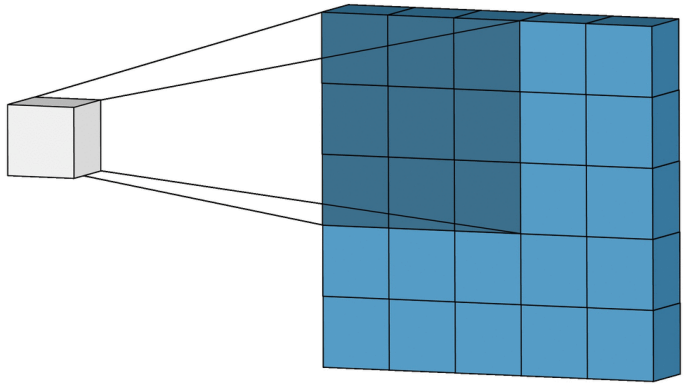
https://insightsimaging.springeropen.com/articles/10.1186/s13244-023-01395-9
https://journals.plos.org/globalpublichealth/article?id=10.1371/journal.pgph.0000800

EPFL Yale
LiGHT LiGHT

Deep Learning für TB Klassifizierung auf Röntgen-Thorax

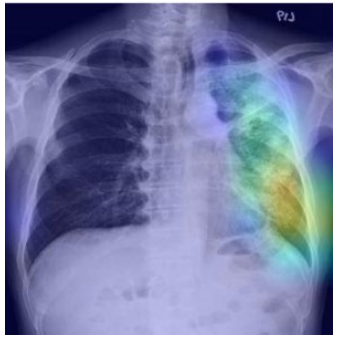


Input Bild



Convolutional neural network

Risiko Score für TB



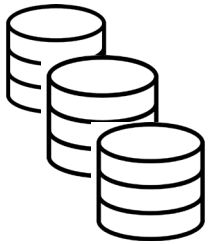
Class activation map für die Modellinterpretierbarkeit

T. Rahman *et al.*, "Reliable Tuberculosis Detection Using Chest X-Ray With Deep Learning, Segmentation and Visualization," in *IEEE Access*, vol. 8, pp. 191586-191601, 2020
Liu, CJ., Tsai, C.C., Kuo, LC. *et al.* A deep learning model using chest X-ray for identifying TB and NTM-LD patients: a cross-sectional study. *Insights Imaging* **14**, 67 (2023).

EPFL Yale LiGHT LiGHT

Einige Resultate

Um robuste Deep Learning Modelle zu trainieren, **benötigen wir große Datenmengen**



Grosse **öffentliche** Datensätze mit Röntgen-Thorax für TB Klassifizierung:

- PadChest (https://www.sciencedirect.com/science/article/abs/pii/S1361841520301614)
- NLM dataset (https://qims.amegroups.org/article/view/5132/6030)
- NIAID TB dataset (https://tbportals.niaid.nih.gov/download-data)
- Belarus dataset (B. P. Health. (2020). Belarus Tuberculosis Portal.)

…

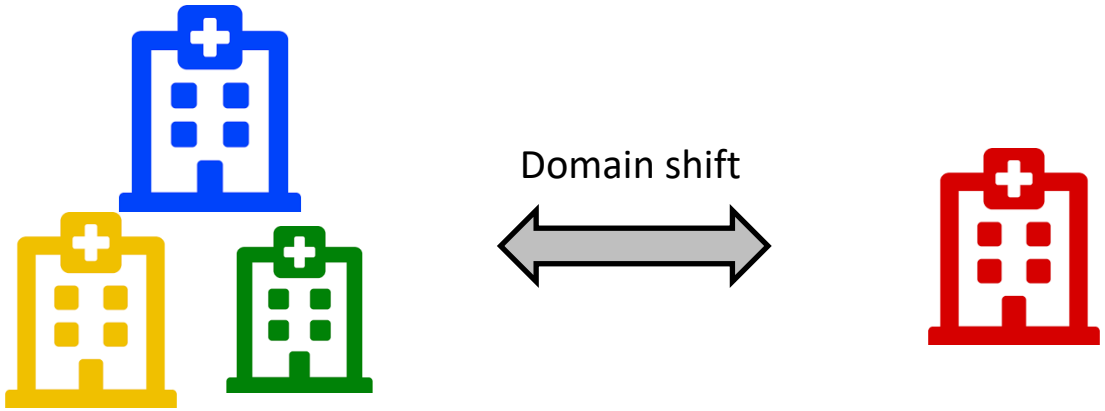
Author (year)	Methods	Dataset (image size)	Total number of images used (TB = Normal)	Accuracy (%)	AUC
Chia-Jung Liu et al. (2023). [9]	DenseNet	MIMIC + CheXpert	1500 (780 + 720)	66.5	81.3
Ahmed et al. (2023). [10]	Topo-CXR	Shenzhen CXR	662 (326 + 336)	89.5	93.6
Ahsan et al. (2019). [11]	VGG16	Montgomery + Shenzhen	800 (394 + 406)	81.25	NA
Devasia et al. (2022). [12]	ResNet50	Shenzhen + Montgomery County	3040	76.8	NA
Rajaraman et al. (2021). [13]	ResNet-BS	Montgomery + Shenzhen	800 (394 + 406)	92.30	96
Pattanasuwan et al. (2021). [14]	DenseNet	Montgomery, Shenzhen, and Bureau of tuberculosis	NA	91	95
Nijiati et al. (2021). [15]	TB-UNet	Local CXR data	2903 + 7994	85	NA
Present Work	**Self-Trained CNN**	**Tuberculosis (TB) Chest X-ray Cleaned Database**	**7000 (3500 + 3500)**	**96.57**	**0.99**

Sarawagi, Karan, et al. "Self-trained convolutional neural network (CNN) for tuberculosis diagnosis in medical imaging." *Cureus* 16.6 (2024).

EPFL Yale LiGHT LiGHT

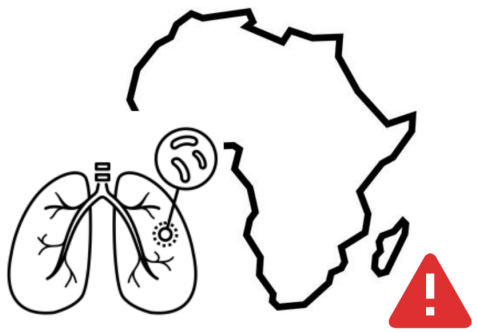
Herausforderung for TB Klassifizierung on CXR

Verschiebung der Datenverteilung zwischen verschiedenen Spitälern verschlechtert die Performance der Modelle.
Wir müssen Bias in den Daten entdecken und korrigieren.

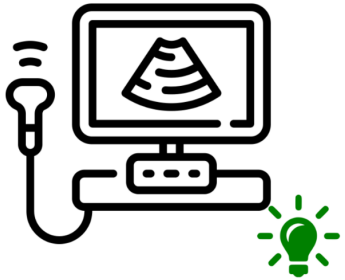


In ressourcenarmen Gebieten sind Röntgenaufnahmen nicht immer verfügbar → Lungenultraschall?

Lungenultraschall für TB Triage



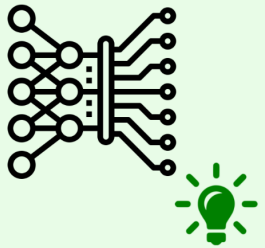
In Ländern mit niedrigem Einkommen klafft eine **diagnostische Lücke** im TB-Management



Lungen-Ultraschall hat das Potenzial, als kostengünstiges Triage-Instrument zur Früherkennung von TB zu dienen

Ein Hindernis für die Weiterentwicklung ist das **Fehlen standardisierter Protokolle für die Bildinterpretation** zum Nachweis TB-spezifischer Marker

ULTR-AI

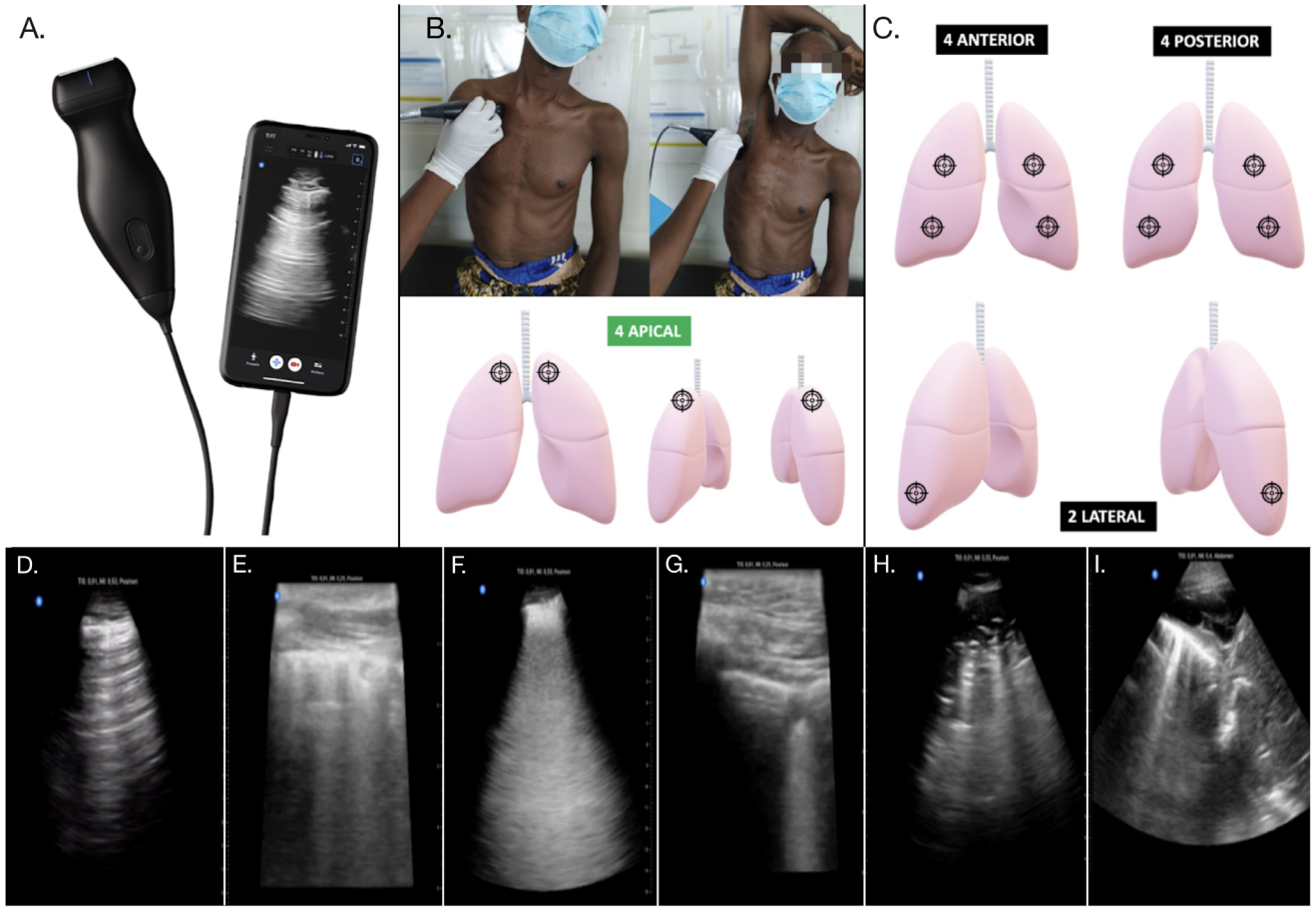


Wir schlagen **Deep-Learning-Modelle** für die automatische Interpretation von LUS-Bildern vor

Tuberkulose Triage Score

EPFL Yale LiGHT LiGHT

Datenerfassung

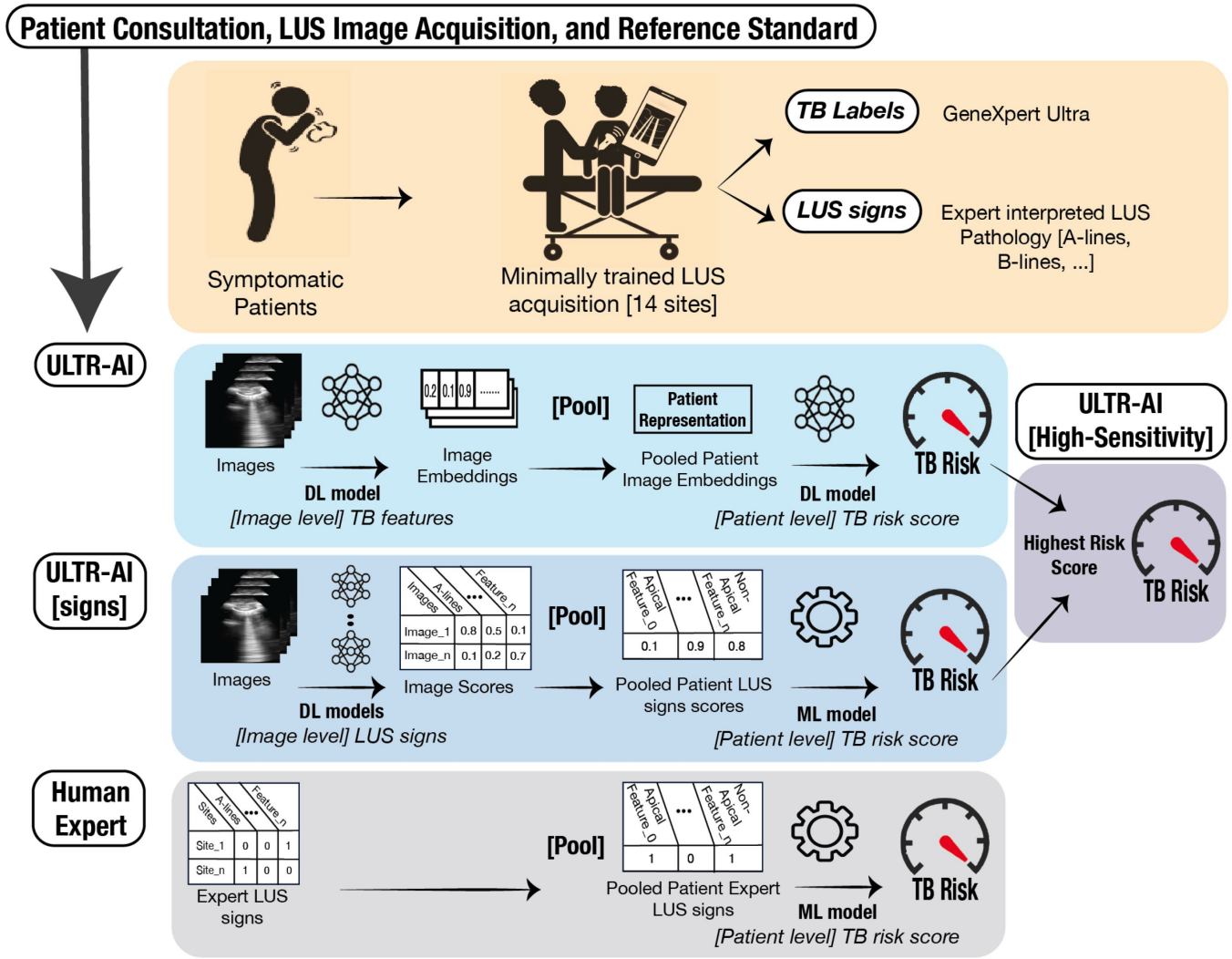


- **Ziel:** Point-of-care TB Triage mit minimaler Infrastruktur und Expertise
- **Standardisierstes** 14-Punkte LUS Erfassungsprotokoll, erhoben von medizinischem Personal mit minimalem POCUS Training
- 504 erwachsene Patienten mit Verdacht auf TB in Benin

Credits: Véronique Suttels

EPFL Yale
LiGHT LiGHT

Deep Learning für LUS Interpretation



Für das **Modelltraining** werden die LUS-Bilder von einem Expertengremium gelabelt.

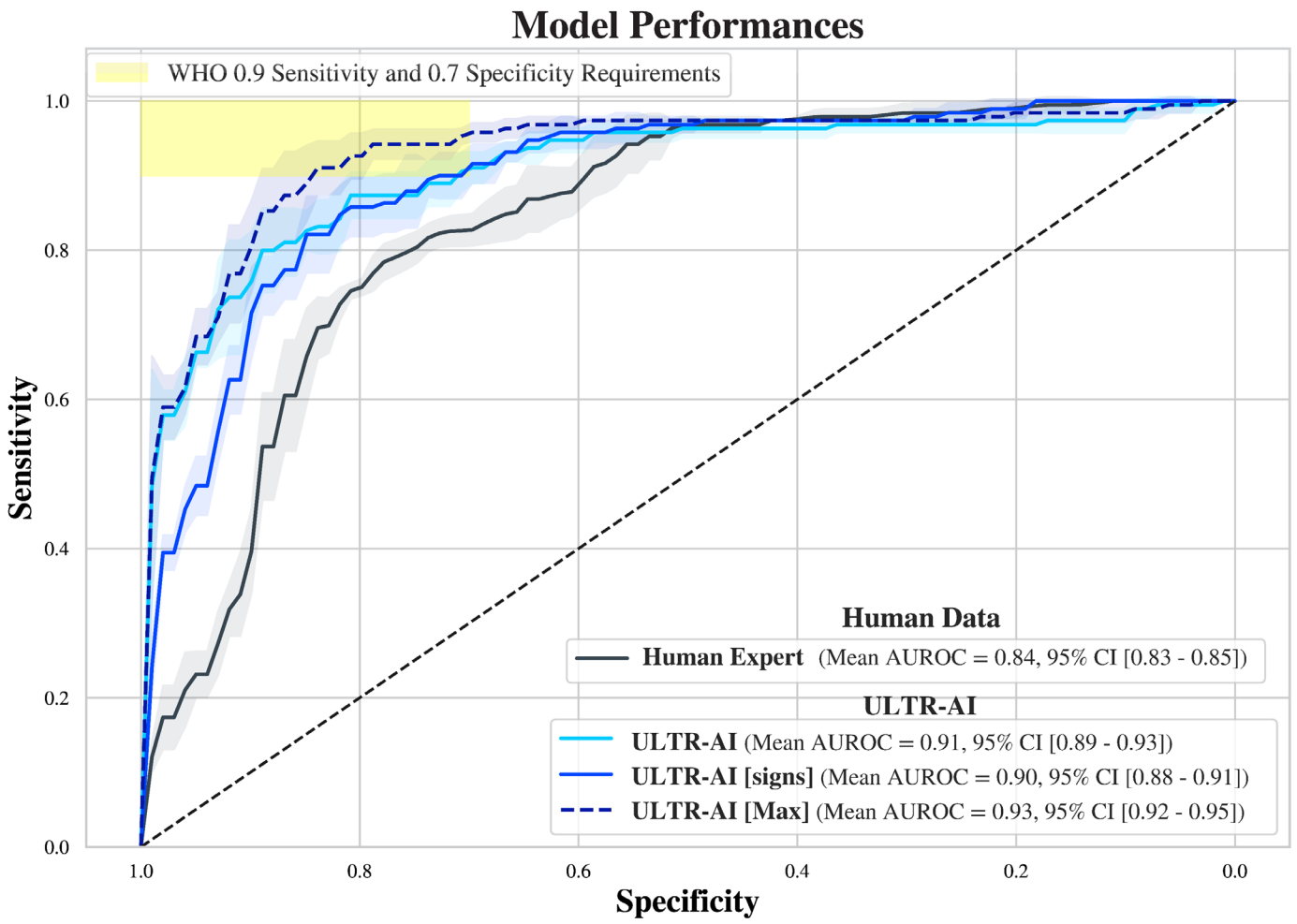
Ensemble von Deep-Learning-Modellen zur automatischen Vorhersage eines TB-Risikoscores

Vergleich mit der Bewertung von LUS-Artefakten, die von einem medizinischen Experten extrahiert wurden

Credits: Trevor Brokowski

EPFL Yale LiGHT LiGHT

Resultate



- Alle Versionen von ULTR-AI erreichten die von der WHO empfohlenen Anforderungen für TB Triagetests
- ULTR-AI hat das Potenzial, die TB Diagnostik zu dezentralisieren und die Triage für rechtzeitige Erkennung und Behandlung zu verbessern
- Studie wurde in einem einzelnen Referenzzentrum durchgeführt → wir müssen die Ergebnisse in anderen Bevölkerungsgruppen überprüfen

Take-home Botschaften

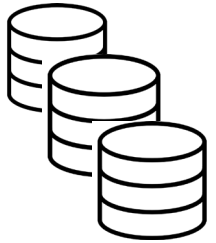
- KI hat das Potenzial, diagnostische Lücken im TB-Management zu schliessen:

✓ Wir wollen die Arbeit erleichtern,

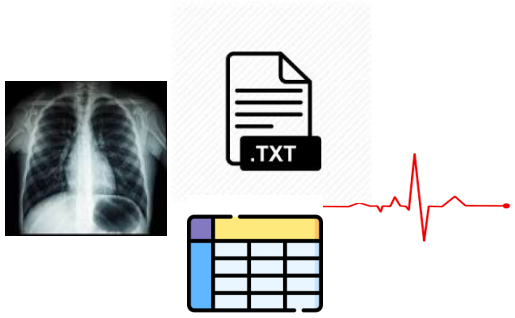
✓ dem Mangel an Experten entgegenwirken,

✓ die Gesundheitsversorgung kostengünstiger machen.

- **Ruf nach großen, interoperablen Datensätzen**, um den breiteren klinischen Nutzen und die Robustheit der Modelle in verschiedenen klinischen Settings zu bestätigen.



- Über Bilder hinausgehend: In **multi-modalen** Netzwerken können wir verschiedene Datenmodalitäten kombinieren.



- Weitere Ideen für Anwendungen?

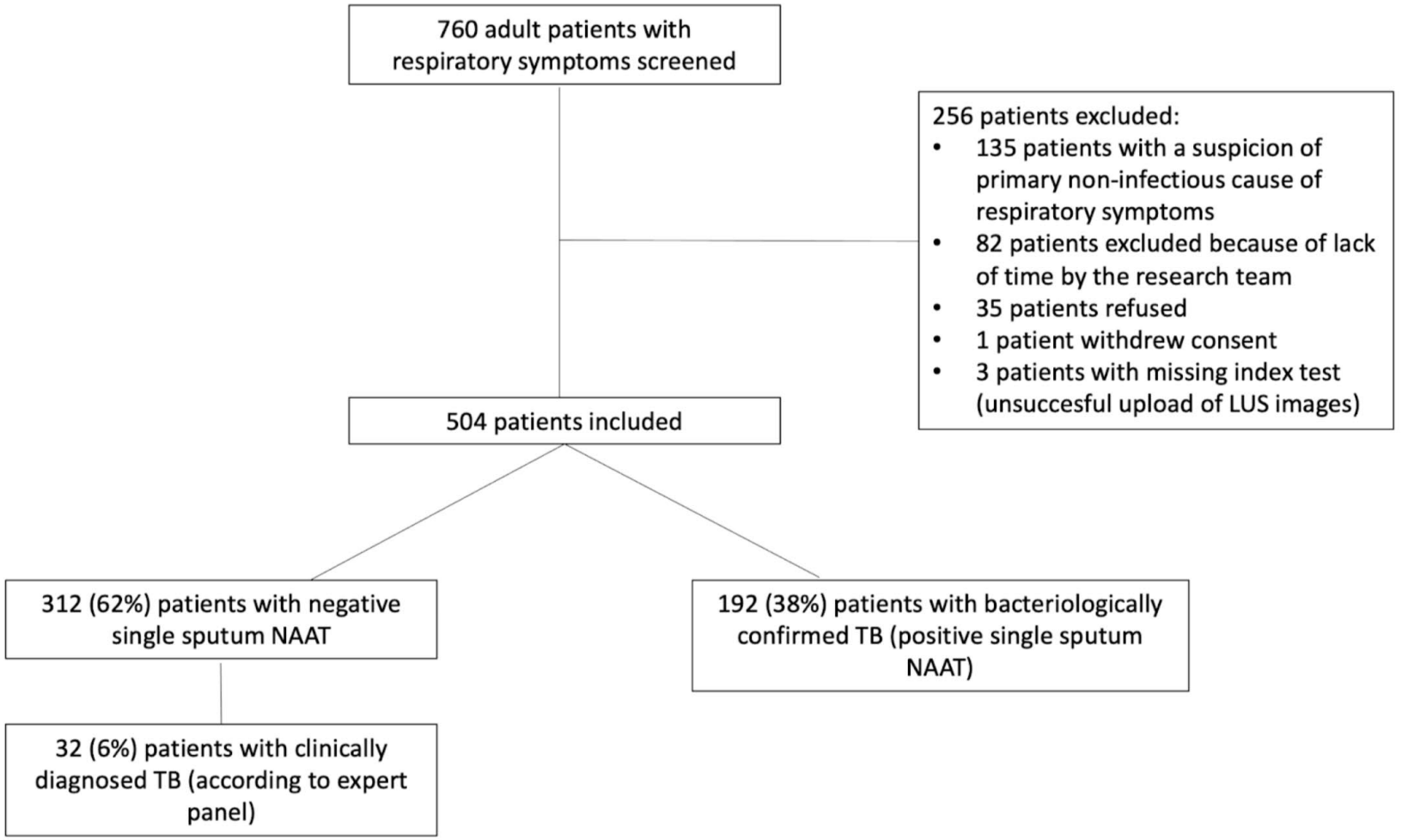
Fragen/Diskussion

julia.wolleb@yale.edu
https://www.yale-light.org/

Credits: Véronique Suttels *, Trevor Brokowski *, Prudence Ablo Wachinou, Aboudou Rasisou Hada, Jacques Daniel Du Toit, Arnauld Attannon Fiogbé, Brice Guendehou, Frederic Alovokpinhou, Elena Garcia, Thomas Brahier, Onya Opota, Jonathan Doenz, Julien Vignoud, Gildas Agodokpessi, Dissou Affolabi, Noemie Boillat-Blanco§, and Mary-Anne Hartley§

EPFL Yale
LIGHT LIGHT

Study Flow Chart



Summary of Patient Charateristics

	all (n=504)	TB+	TB- and TBc	p-value	More in TB+	More in TB- and TBc
Demography						
Patients N	504 (100)	192 (38)	312 (62)			
Male N(%)	308 (61)	151 (79)	157 (50)	<0.001	X	
Age (years); median (IQR)	40 (30-52)	36 (27-46)	45 (33-55)	<0.001	X	
Comorbidities						
Former TB N(%)	66 (13)	13 (7)	53 (17)	0.002		X
Diabetes	18 (4)	5 (3)	13 (4)	0.502		
Hypertension	66 (13)	5 (3)	61 (20)	<0.001		X
BMI >= 25 N(%)	72 (14)	4 (2)	68 (22)	<0.001		X
Co-infections						
Malaria positive N(%)	26 (5)	4 (2)	22 (7)	0.024		
COVID positive N(%)	59 (12)	17 (9)	42 (14)	0.149		
HIV positive N(%)	78 (15)	17 (9)	61 (20)	0.002		X
CD4 count; median (IQR)	92 (43-358)	76 (46-319)	100 (30-352)	0.927		
Symptoms						
Cough as main symptom N(%)	484 (97)	185 (97)	299 (97)	0.981		
Weigth loss N(%)	378 (75)	176 (93)	202 (66)	<0.001	X	
Hemoptysis N(%)	99 (20)	39 (21)	60 (20)	0.880		
Night sweats N(%)	189 (38)	105 (55)	84 (7)	<0.001	X	
Main symptom duration (days); median (IQR)	30 (14-90)	60 (30-90)	30 (14-75)	<0.001	X	
Signs						
BMI <18.5 N(%)	217 (43)	126 (66)	91 (30)	<0.001	X	
Temperature >38°C N(%)	18 (4)	12 (6)	6 (2)	0.022	X	
Temperature =<35°C N(%)	36 (7)	16 (8)	20 (7)	0.536		
Heart rate >100 bpm N(%)	207 (41)	116 (61)	91 (30)	<0.001	X	
Respiratory rate >=22 cpm N(%)	433 (86)	180 (95)	253 (82)	<0.001	X	
Systolic blood pressure <100 mmHg N(%)	89 (18)	52 (27)	37 (12)	<0.001	X	
SpO2 <95% N(%)	83 (16)	40 (21)	43 (14)	0.054		
GCS ≤ 14 N(%)	17 (3)	9 (5)	8 (3)	0.310		
Bad general state (>=4 on a 5-point scale) N(%)		46 (24)	56 (18)	0.137		
Blood formula						
Anemia (Hemoglobin <12 g/dL in female patients,; <13 g/dL in male patients) N(%)	167 (33)	66 (42)	101 (40	0.733		
MCV <80 fl N(%)	181 (36)	97 (51)	84 (27)	<0.001	X	
Platelets >450 G/L N(%)	123 (24)	78 (41)	45 (15)	<0.001	X	
Leukocytes >11 G/L N(%)	385 (76)	140 (74)	245 (80)	0.134		
Clinical evolution						
Follow-up day 7 completed	483 (96)	184 (96)	299 (96)	1		
Follow-up day 28 completed	465 (92)	178 (93)	287 (92)	0.882		
Hospitalized by day 7	86 (17)	37 (19)	49 (16)	0.377		
7-day mortality	9 (2)	4 (2)	5 (2)	0.967		
Hospitalized by day 28	90 (18)	39 (21)	51 (17)	0.327		
28-day mortality	15 (3)	7 (4)	8 (3)	0.680		

EPFL Yale
LiGHT LiGHT

Feature importance

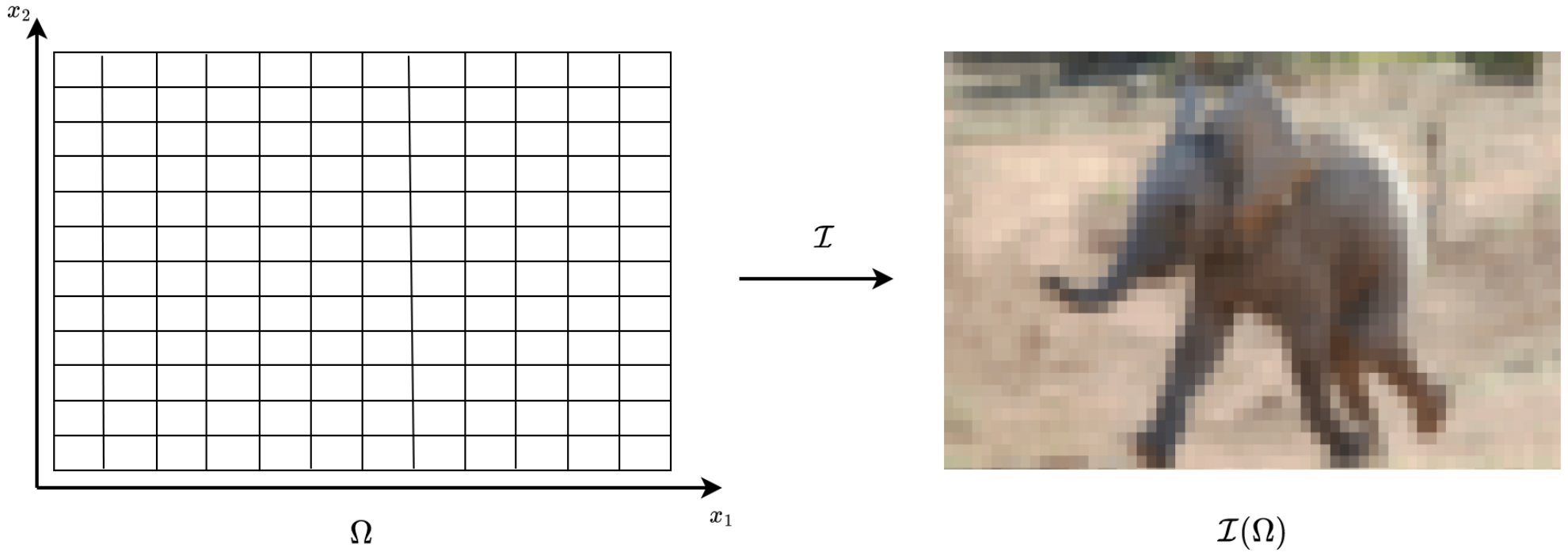
Lung ultrasound pattern and localisation	Prevalence n(%)		Univariate logistic regression			Human Expert (ML) with RFE
	TB+. (n=192)	TB- and TBc (n=312)	OR	95% CI	p-value	Feature importance
Any Non-Apical quadrant						
A-lines	167 (87)	303 (97)	0,20	[0.1, 0.4]	<0,001	0.06
B-lines	145 (76)	188 (60)	2,03	[1.4, 3.0]	<0,001	
Confluent B-lines	121 (63)	188 (60)	1,12	[0.8, 1.6]	0,536	0.02
Subpleural consolidations of <1cm or irregular/broken pleural lines	179 (94)	237 (76)	4,36	[2.3, 8.1]	<0,001	0.02
Consolidations ≥ 1cm	153 (80)	64 (21)	15,20	[9.7, 23.8]	<0,001	0.4
Pleural effusion	12 (6)	15 (5)	1,32	[0.6, 2.9]	0,486	
Any Apical Quadrant						
A-lines	108 (57)	288 (92)	0,11	[0.1, 0.2]	<0,001	0.04
B-lines	58 (30)	69 (22)	1,52	[1.0, 2.3]	0,043	0.04
Confluent B-lines	48 (25)	59 (19)	1,43	[0.9, 2.2]	0,105	0.01
Subpleural consolidations of <1cm or irregular/broken pleural lines	114 (60)	89 (29)	3,66	[2.5, 5.3]	<0,001	0.08
Consolidations ≥ 1cm	109 (57)	20 (6)	19,17	[11.2, 32.8]	<0,001	0.32
A-line pattern in all 4 apical quadrants	12 (6)	144 (46)	0,08	[0.0, 0.1]	<0,001	

What is an Image?

An image consists of pixels (in 2D) or voxels (in 3D) in a pixel space Ω.

The image is given by a function I, which maps every input pixel/voxel to a real number:

$$\mathrm{I}\colon \Omega \to \mathbb{R}$$



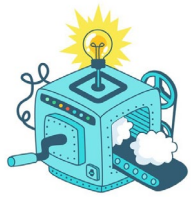
A First Example: Linear Regression

- In our dataset $D = \{(x_i, \hat{y}_i) \mid i = 1, \dots, n\}$, x_i is the input (for example drug dosage), $\hat{y}_i$ is the corresponding label (blood pressure).

- We **assume** a linear correlation. Therefore, we formulate our artificial neural network/machine as a linear equation:

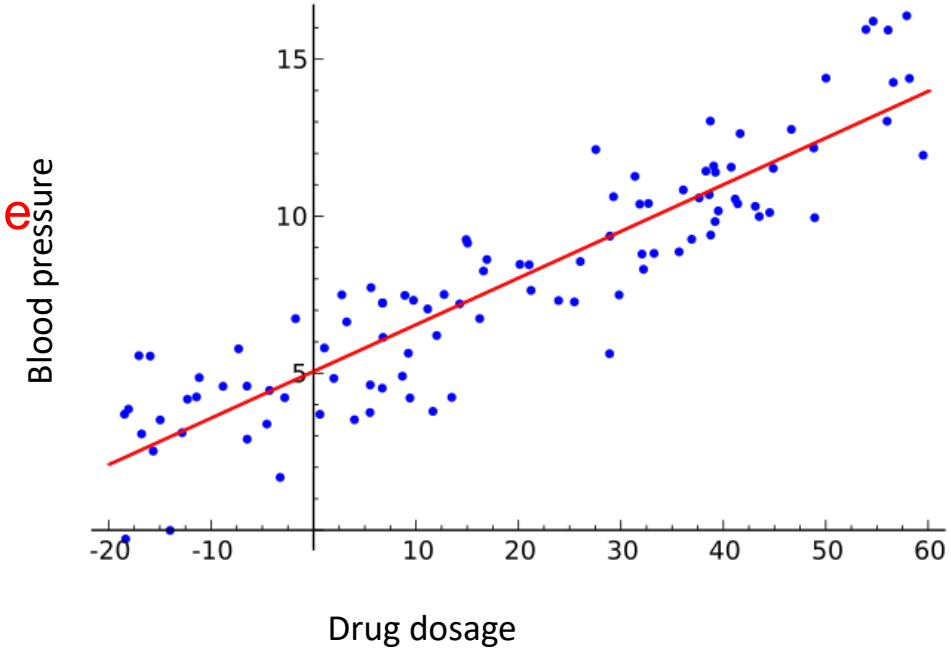
This is our machine

$$y = F_\theta(x) = wx + b$$



- In this case, the learnable parameterrs are $\theta = (w, b)$

- We want to find the ideal parameters $\theta^* = (w^*, b^*)$, such that the function $y = F_{\theta^*}(x) = w^* x + b^*$ matches the true datapoints $(x_i, \hat{y}_i)$ the best.



But We Deal with Images…

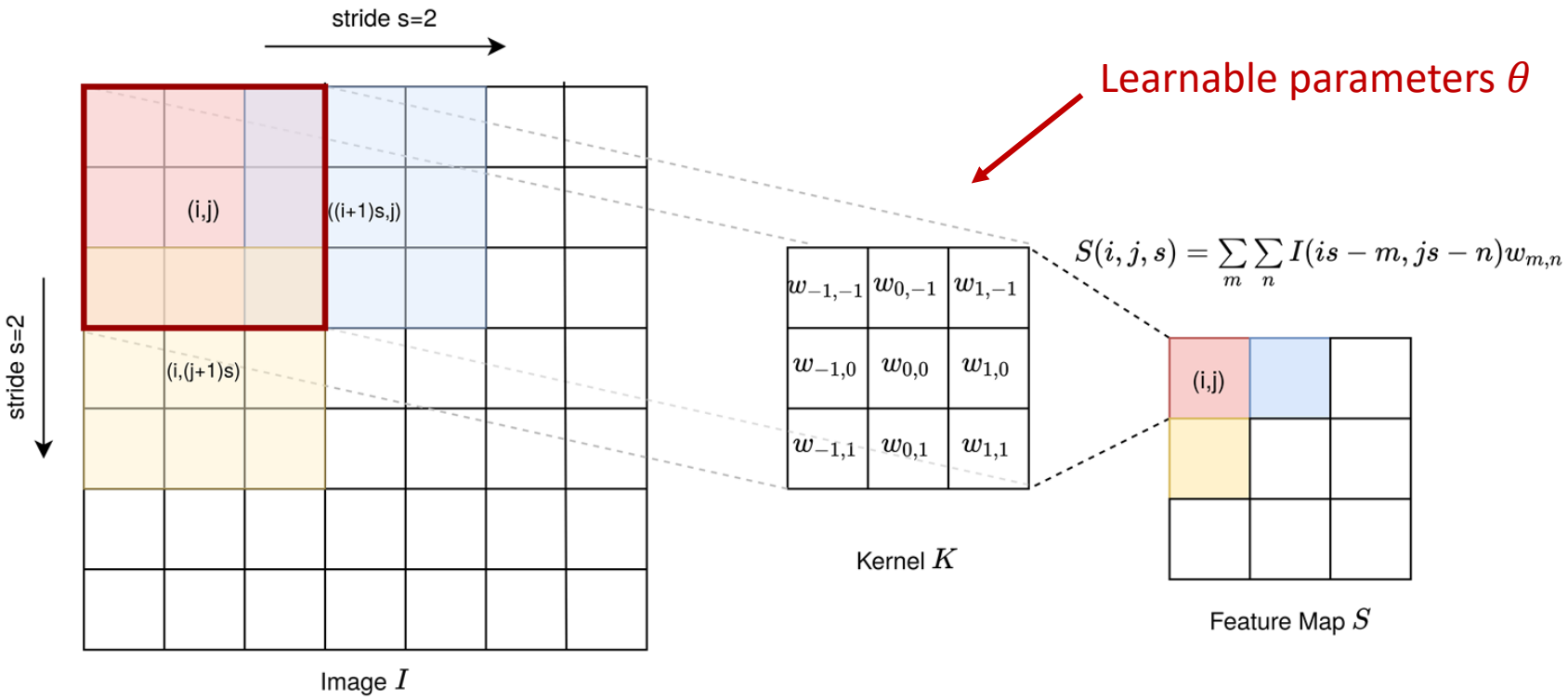
Perceptrons follow a linear equation and have a lot of learnable parameters for high-dimensional input
→ not optimal for images.

Does the image show an elephant?

Yes, it does not matter where.

For image analysis, we define the architecture of our artificial neural network differently. We look at convolutions….

What is a Convolution?



- The parameters w_{ij} of the kernel are learnable parameters of the model.
- Parameters are shared for the whole input image I.
- We learn equivariant representations with respect to translation.
- We have a relatively small number of weights → sparse connectivity.

A Gentle Introduction into Numerical Optimization

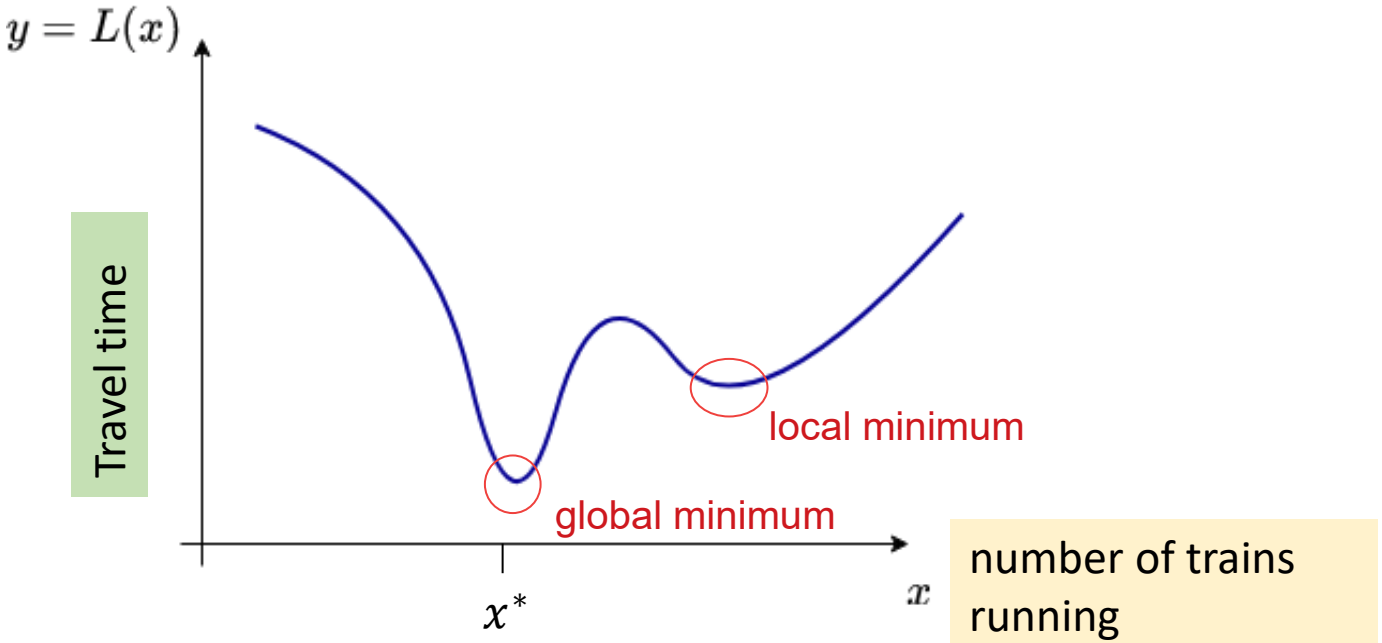
In a more mathematical setting:

We have an input space $\mathcal{X} = \{x_1, ..x_n\}$

And an output space $\mathcal{Y} = \{y_1, ..y_n\}$

We look at the cost function L that maps the pairs $L(x_i) = y_i \, \forall i \in \{1, ..., n\}$

We want to **minimize** this cost function $L : \mathcal{X} \rightarrow \mathcal{Y}$



How many trains do I need in Switzerland to minimize the total travel time?
With the cost function L, we measure the total travel time, given the number of trains x.

$$x^* = \underset{x}{\operatorname{argmin}}(L(x))$$

Gradient Descent

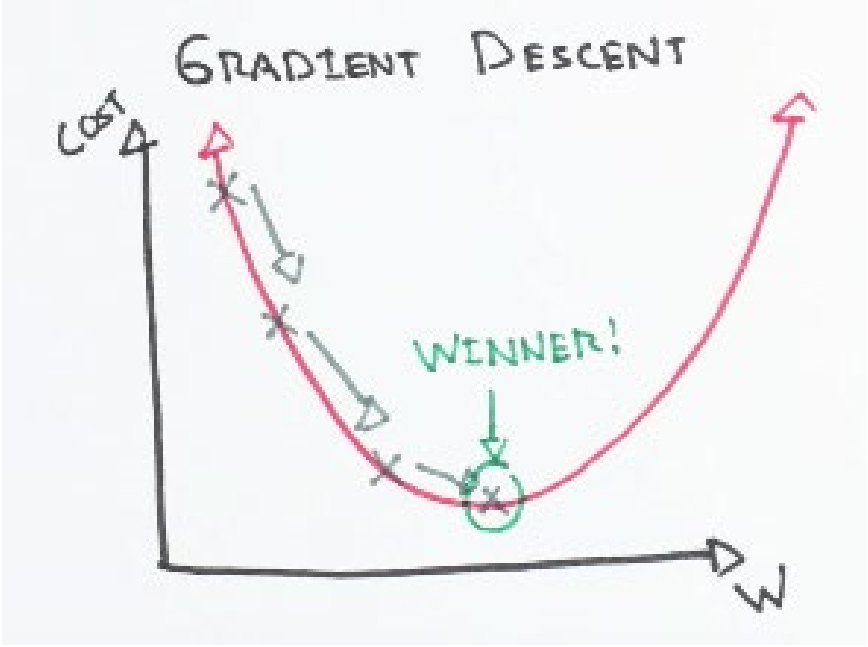
$$x^* = \underset{x}{\operatorname{argmin}}(L(x))$$

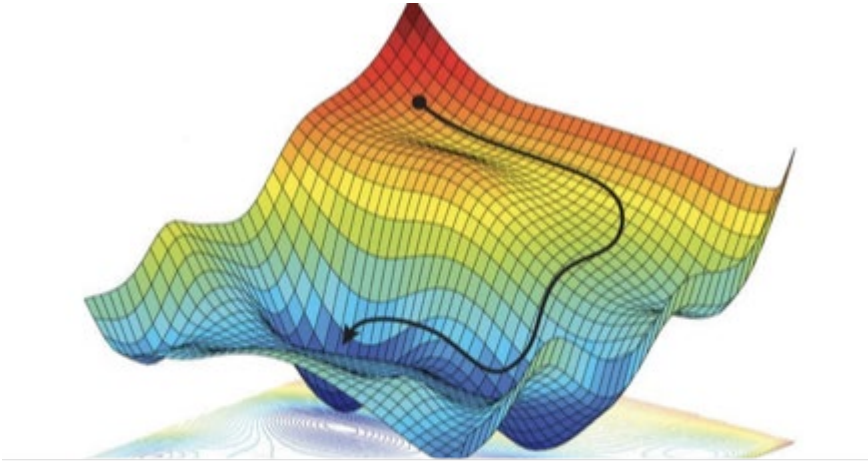
- We follow the negative gradient of L, which points toward the **steepest descent**.

- We make an update step with step size γ

$$\nabla L = (\frac{\partial L}{\partial x_1}, ..., \frac{\partial L}{\partial x_d})$$
$$(x_1^{i+1}, ..., x_d^{i+1}) = (x_1^i, ..., x_d^i) - \gamma \nabla L(x_1^i, ..., x_d^i)$$

- This is an iterative process.
- Does scale to higher-dimensional input spaces.





https://towardsdatascience.com/its-only-natural-an-excessively-deep-dive-into-natural-gradient-optimization-75d464b89dbb
https://ml-cheatsheet.readthedocs.io/en/latest/gradient_descent.html

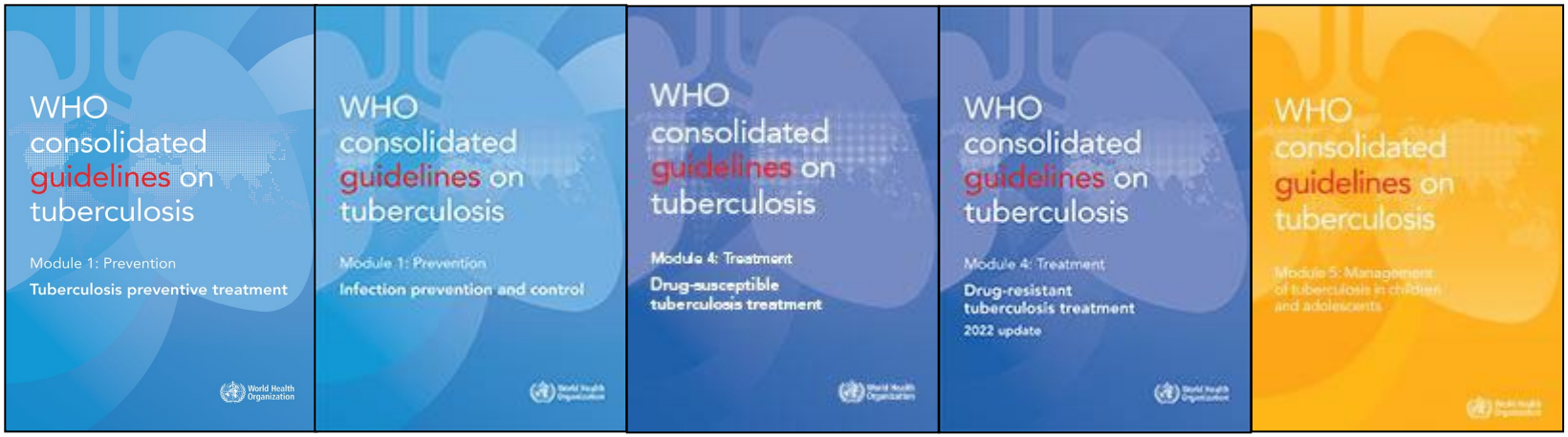
Access to TB medicines in 2024

32ème Symposium Tuberculose de la LPS
2ème Swiss Translational TB Forum

Bern, 30 October 2024

Christophe Perrin – TB advocacy pharmacist, MSF Access Campaign

WHO-recommended TB formulations: all are manufactured (except 2)



- Existing evidence supporting recommendations of shorter all oral DR-TB / DS-TB regimens as well as for TPT
- Already manufactured in quality-assured versions by at least one company:
  - ✓ DS-TB fixed dose combinations for adults & children + single medicines for DS-TB care
    - → *missing HPM, HPMZ fixed combinations*
  - ✓ single medicines to be combined for different types of resistances identified in people affected by DR-TB (*e.g.*, rifampicin, fluoroquinolones), including child-friendly formulations
  - ✓ TPT fixed dose combination + single medicines for TPT, including for child-friendly formulations

TB medicines not accessible to all people affected by TB / household contacts

- Access challenges in:
  - ✓ **LMICs** (mostly with high TB burden)

Kenya, October 2023

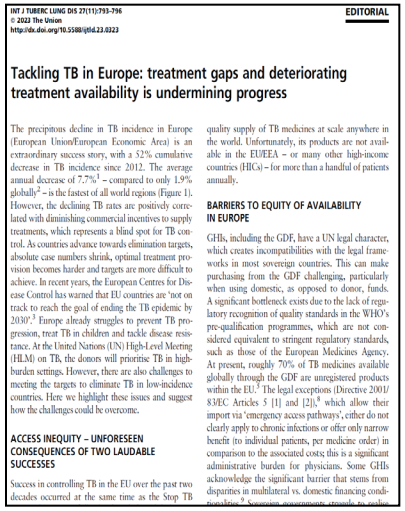
22/Sep/2023 https://thewire.in/health/will-the-un-high-level-meeting-address-indias-problem-of-tb-drugs-stock-out-situation

Unprecedented TB Drugs Stock-Out in India: Union Health Minister Skips UN High-Level Meet

'The Wire' spoke to several individuals across India, who are affected by the acute shortage of TB drugs in the country. The WHO has described this situation as 'worrying', while the state TB officials call it 'frustrating'.

Mumbai/New Delhi: As the high-level meeting on tuberculosis (TB) at the United Nations' headquarters begins on September 22, the stakeholders will need to address a pressing issue: that patients in India – which has the highest burden of drug-resistant tuberculosis (DR-TB) – are facing an acute shortage of the necessary medicines. This is forcing many to skip their doses, a choice strongly discouraged in any tuberculosis elimination programme.

  - ✓ **HICs** (mostly with low TB burden except in specific groups)


INT J TUBERC LUNG DIS 27(11):793–796
© 2023 The Union
http://dx.doi.org/10.5588/ijtld.23.0323

EDITORIAL

Tackling TB in Europe: treatment gaps and deteriorating treatment availability is undermining progress

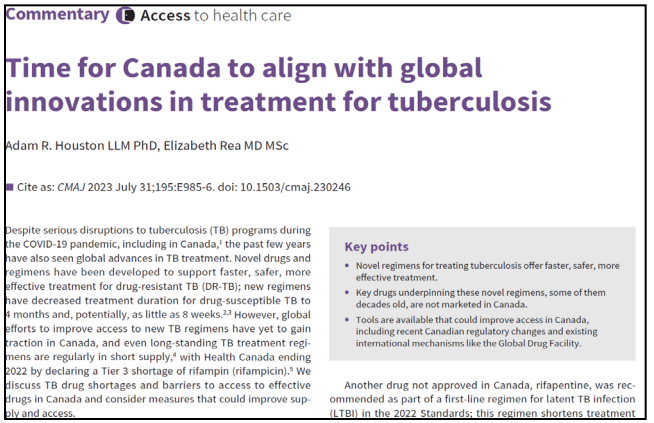
The precipitous decline in TB incidence in Europe (European Union/European Economic Area) is an extraordinary success story, with a 52% cumulative decrease in TB incidence since 2012. The average annual decrease of 7.7%[1] – compared to only 1.9% globally[2] – is the fastest of all world regions (Figure 1). However, the declining TB rates are positively correlated with diminishing commercial incentives to supply treatments, which represents a blind spot for TB control. As countries advance towards elimination targets, absolute case numbers shrink, optimal treatment provision becomes harder and targets are more difficult to achieve. In recent years, the European Centres for Disease Control has warned that EU countries are 'not on track to reach the goal of ending the TB epidemic by 2030'.[3] Europe already struggles to prevent TB progression, treat TB in children and tackle disease resistance. At the United Nations (UN) High-Level Meeting (HLM) on TB, the donors will prioritise TB in high-burden settings. However, there are also challenges to meeting the targets to eliminate TB in low-incidence countries. Here we highlight these issues and suggest how the challenges could be overcome.

ACCESS INEQUITY – UNFORESEEN CONSEQUENCES OF TWO LAUDABLE SUCCESSES

Success in controlling TB in the EU over the past two decades occurred at the same time as the Stop TB quality supply of TB medicines at scale anywhere in the world. Unfortunately, its products are not available in the EU/EEA – or many other high-income countries (HICs) – for more than a handful of patients annually.

BARRIERS TO EQUITY OF AVAILABILITY IN EUROPE

GHIs, including the GDF, have a UN legal character, which creates incompatibilities with the legal frameworks in most sovereign countries. This can make purchasing from the GDF challenging, particularly when using domestic, as opposed to donor, funds. A significant bottleneck exists due to the lack of regulatory recognition of quality standards in the WHO's pre-qualification programmes, which are not considered equivalent to stringent regulatory standards, such as those of the European Medicines Agency. At present, roughly 70% of TB medicines available globally through the GDF are unregistered products within the EU.[3] The legal exceptions (Directive 2001/83/EC Articles 5 [1] and [2]),[4] which allow their import via 'emergency access pathways', either do not clearly apply to chronic infections or offer only narrow benefit (to individual patients, per medicine order) in comparison to the associated costs; this is a significant administrative burden for physicians. Some GHIs acknowledge the significant barrier that stems from disparities in multilateral vs. domestic financing condi-


Commentary Access to health care

Time for Canada to align with global innovations in treatment for tuberculosis

Adam R. Houston LLM PhD, Elizabeth Rea MD MSc

Cite as: *CMAJ* 2023 July 31;195:E985-6. doi: 10.1503/cmaj.230246

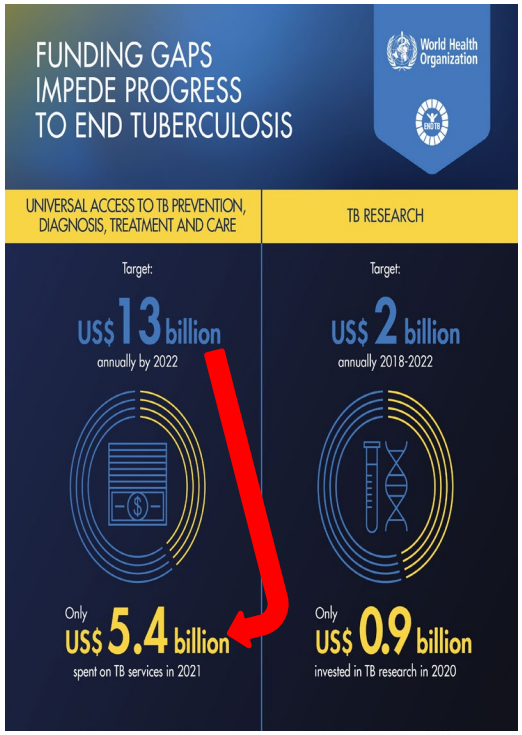
Despite serious disruptions to tuberculosis (TB) programs during the COVID-19 pandemic, including in Canada,[1] the past few years have also seen global advances in TB treatment. Novel drugs and regimens have been developed to support faster, safer, more effective treatment for drug-resistant TB (DR-TB); new regimens have decreased treatment duration for drug-susceptible TB to 4 months and, potentially, as little as 8 weeks.[2,3] However, global efforts to improve access to new TB regimens have yet to gain traction in Canada, and even long-standing TB treatment regimens are regularly in short supply,[4] with Health Canada ending 2022 by declaring a Tier 3 shortage of rifampin (rifampicin).[5] We discuss TB drug shortages and barriers to access to effective drugs in Canada and consider measures that could improve supply and access.

Key points

- Novel regimens for treating tuberculosis offer faster, safer, more effective treatment.
- Key drugs underpinning these novel regimens, some of them decades old, are not marketed in Canada.
- Tools are available that could improve access in Canada, including recent Canadian regulatory changes and existing international mechanisms like the Global Drug Facility.

Another drug not approved in Canada, rifapentine, was recommended as part of a first-line regimen for latent TB infection (LTBI) in the 2022 Standards; this regimen shortens treatment

https://doi.org/10.5588/ijtld.23.0323
https://openres.ersjournals.com/content/9/4/00730-2022
https://www.cmaj.ca/content/195/29/E985



https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022

LMICs

. Donor withdrawal + governments struggling to increase domestic funds to procure TB health products in contexts with countless health challenges

https://msfaccess.org/beware-global-fund-procurement-cliff

HICs

. Lack of awareness at MoH level regarding poor standards of TB care & extent of needs

. Too limited budget dedicated to TB health products procurement

Holding countries accountable to their commitments at UNHLM for TB, 22 Sept. 2023?

"Increase annual global TB fundings (excluding research) from current $5.4 billion to $22 billion annually by 2027 and $35 billion by 2030"

List of TB medicines required for optimal TB care

Drug Sensitive-TB

- **For adults:** rifampicin 150 mg, 300 mg, isoniazid 75 mg, pyrazinamide 400 mg, ethambutol 275 mg in **fixed dose combinations (2FDC, 3FDC, 4FDC)**
- **For children:** rifampicin 75 mg, isoniazid 50 mg, pyrazinamide 150 mg, in **dispersible fixed dose combinations (2FDC, 3FDC)** + ethambutol 100 mg **dispersible tablets**

Drug Resistant-TB

- **For adults:** bedaquiline 100 mg, pretomanid 200 mg, levofloxacin 250, 500 mg , moxifloxacin 400 mg, linezolid 600 mg, clofazimine 100 mg, cycloserine 250 mg, ethambutol 400 mg, delamanid 50 mg, pyrazinamide 400 & 500 mg, isoniazid 300 mg, ethionamide 250 mg, prothionamide 250 mg, amikacin, imipenem-cilastatin, meropenem, amoxiclav
- **For children:** bedaquiline 20 mg, levofloxacin 100 mg , moxifloxacin 100 mg, linezolid 150 mg, clofazimine 50 mg, cycloserine 125 mg, ethionamide 125 mg, delamanid 25 mg, pyrazinamide 150 mg, isoniazid 100 mg, ethambutol 100 mg All in **dispersible tablets or capsules** (cycloserine)

TB Preventive Treatment

- rifapentine 300 mg/isoniazid 300 mg in **FDC**
- rifapentine 300 mg, rifapentine 150 mg **dispersible tablets**
- rifampicine 75 mg, isoniazid 75 mg in **dispersible tablets**, **FDC**

A single disease, several challenges

. Most of generic companies of TB medicines are from India
. Their TB medicines are recommended by WHO Prequalification Program* that make them eligible for procurement and for accessing a broad range of countries (mainly LMICs)
. EU countries represent little interest due to low TB prevalence

- No regulatory dossiers filed for marketing authorizations in Western Europe

=> **key generic TB medicines are not registered in Western Europe**

. Innovators companies with new TB medicines have different price policies for LMICs and HICs, with often a global negotiated prices for a set of LMICs.

- unaffordable prices in the Western Europe (same for USA, Australia, etc...)
- 2 key new TB products are still patented in Western Europe limiting competition and entry of generic suppliers

* https://extranet.who.int/prequal/medicines/prequalified-lists

Registration of TB medicines in Western Europe

- **Existing registration** but old marketing authorisations (MA):
  - most single compounds for DS-TB in adults
  - repurposed medicines for DR-TB (*e.g.*, fluoroquinolones, linezolid)
- **Existing registration** for more recent MA with European Medicine Agency (EMA)
  - adult & child-friendly formulations for newer DR-TB medicines (bedaquiline full approval, pretomanid/delamanid conditional approvals)

- **No registration** due to limited demand and/or expensive regulatory fees and/or need for manufacturers to proceed with additional studies (*e.g.*, PK, stability, etc…) to match SRA* guidelines (even for WHO-prequalified TB medicines):
  - FDCs for DS-TB in adults
  - several generic medicines for DR-TB in adults (*e.g.*, cycloserin, ..)
  - most child-friendly formulations for DS-TB (both single compounds & FDCs) and for DR-TB
  - medicines for TPT (*i.e.*, rifapentine), both for adults and children

No regulatory reliance at EMA of WHO Prequalification Programme (while the opposite is true), either at the national level

*SRA = Stringent Regulatory Authority – EMA is a SRA

Prices of TB medicines in Western Europe

(some examples)

LMICs (mostly with high TB/DR-TB burden) via GDF*	HICs (mostly with low TB/DR-TB burden) such as EU countries
6-month course price for bedaquiline $122	6-month course price for bedaquiline Around $ 5.000 USD to $12.000
6-month course price for pretomanid $240	6-month course price for pretomanid $15 000
6-month course price for linezolid $31	6-month course price for linezolid Around $6200
BPaLM 6-month regimen cost $400	BPaLM 6-month regimen cost Up to $48.000

*https://www.stoptb.org/sites/default/files/2024.01.18_gdf_medicines_catalog_jan_2024.pdf

Swiss context

- Swiss Strategy on Antibiotic Resistance (StAR): could it cover newer/existing/old TB antibiotics?
  - Switzerland's National Action Plan (2024-2027)

  https://www.star.admin.ch/star/en/home/strategiestar/aktionsplan-star.html
  - Swiss Round Table on Antibiotics

  https://roundtableantibiotics.ch/en/downloads

- WHO EURO initiative since 2022

WORLD HEALTH ORGANIZATION
REGIONAL OFFICE FOR EUROPE

WELTGESUNDHEITSORGANISATION
REGIONALBÜRO FÜR EUROPA

ORGANISATION MONDIALE DE LA SANTI
BUREAU RÉGIONAL DE L'EUROPI

ВСЕМИРНАЯ ОРГАНИЗАЦИЯ ЗДРАВООХРАНЕНИ
ЕВРОПЕЙСКОЕ РЕГИОНАЛЬНОЕ БЮРО

Regional Meeting on Improving Access and Availability of Medicines for TB and DR-TB in Europe
Meeting Summary and Outcomes (June 2024)

Over one hundred and fifty attendees' (approximately half online and half in-person) from 23 countries, across two short-days, convened at the WHO Hub for Pandemic and Epidemic Intelligence in Berlin – for the first time since 2022 – to discuss the mounting challenges low-incidence EU/EEA countries are reporting in securing availability and access to anti-tuberculosis (TB) medicines.

➔ Hybride consultation in June 2024
➔ Survey soon to be circulated across Western European countries to better frame solutions enhancing access to older generic TB medicines and newer ones
➔ Next hybride consultation scheduled by Q1 2025
➔ WHO EURO contact: Dr Askar Yedilbayev yedilbayeva@who.int

Context
TB & WAR

Polish context

Average annual numbers of TB cases (pre-Covid)

Annual average	Ukraine	Poland	Total EU
TB	21000	5000	33000
DRTB	7000	50 (50% foreigners)	700

TB incidence UA 7 X > PL
DRTB/DSTB UA 30 X > PL

War consequences:

- **> 17 million UA border crossings since 02.2022**
- **> 2 million UA registered for Temporary Protection (currently 1 million)**
- **> 1 million UA since 2014.**

WHO TB estimation among 1.5 million UA refugees in PL

- **665 TB cases**
- **219 DRTB**

Polish context

Challenges – Access to DRTB treatment

Availability of the medicines

- 2 years treatment with injectables
- No clofazimine, cycloserine, pretomanid
- No paediatric presentation

Affordability of the medicines

- Bedaquiline 17k Euro
- Linezolid 1k Euro / month

Decentralised and fragmented system of TB care provision

- Each region different approach
- No national guidelines

Financial frame linked to hospitalisation

- Covering costs of medicines by bed occupancy quota

Stigma & Knowledge

- Isolation for the entire duration of treatment

Polish context

Achievements

- Impact on direct provision of care
  - 249 patients (100 DSTB, 149 DRTB)
  - Cross-border perspective on continuity of treatment & linkage to care - 10 countries.
  - Access to DRTB medicines (responsiveness and sustainability)
  - Capacity built

- Policies changes & Patient-centredness
  - From hospital based to Ambulatory care & new financial frame
  - Introduction of Patient support concept
  - Strengthening of governance /MOH & TB concilium
  - Introduction of new shorter regimens (BPaLM) & DRTB national recommendations

- Price reduction

- Time for 5 & TACTIC: Poland as EU perspective

- MSF visibility & role in catalysing awareness and partnership
  - TB EU working groups, WHO review report
  - UNHLM, WHA, UNION,
  - Comms & Conferences

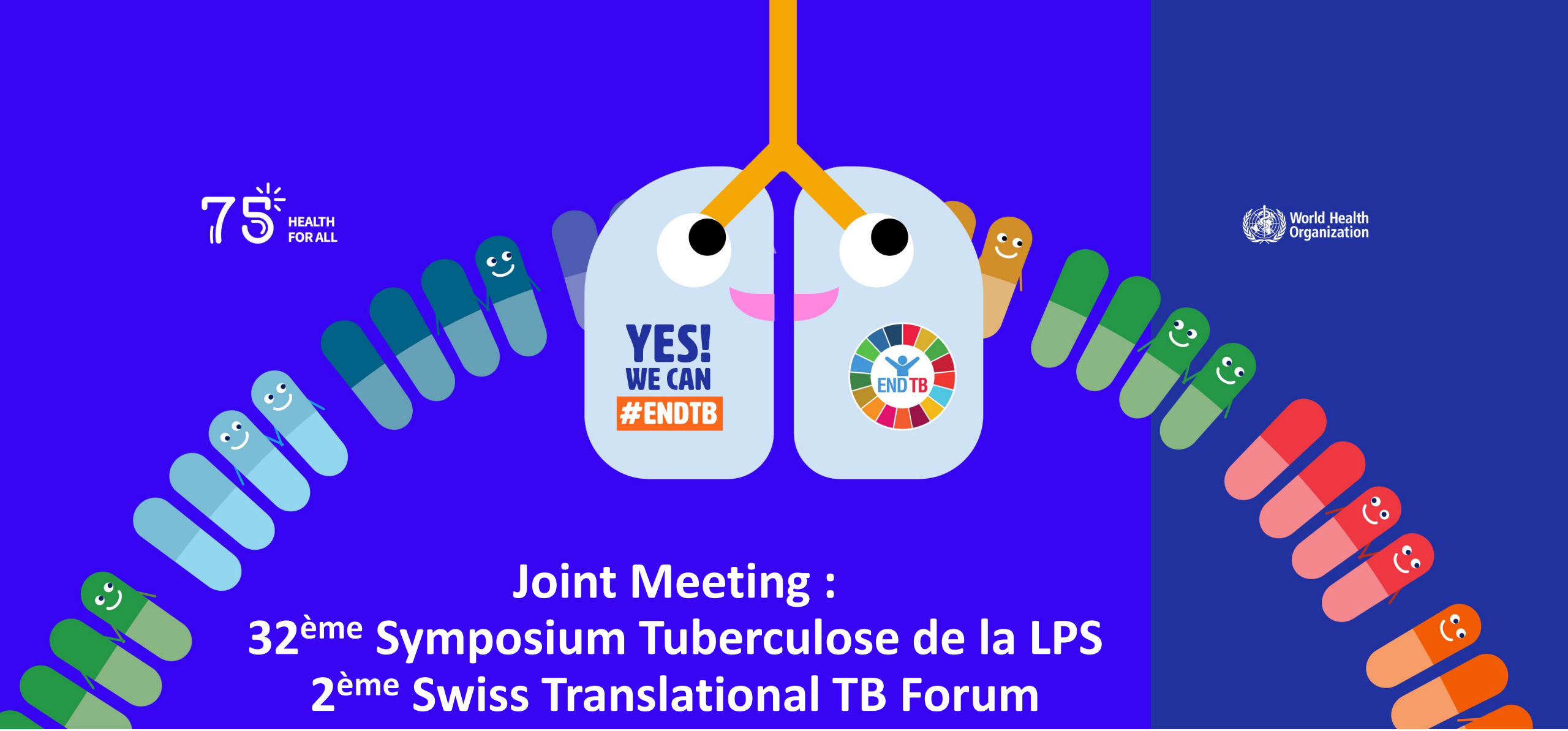
MERCI !

christophe.perrin@paris.msf.org

Ende | Herzlichen Dank!

Swiss Translational TB Forum

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA



Fin | Merci beaucoup !

Swiss Translational TB Forum

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA

Mit Unterstützung von
Avec le soutien de

QIAGEN

Diasorin

Swiss Translational
TB Forum

LUNGENLIGA SCHWEIZ
LIGUE PULMONAIRE SUISSE
LEGA POLMONARE SVIZZERA
LIA PULMUNARA SVIZRA