3 day training for Optima TB

Funding for the creation of these materials was provided by

Optima TB

Agenda - Day 1: Overview and introduction to Optima TB

Time	Session name and description
8.30	**Welcome and introduction to the workshop** • Welcome remarks • Introduction of participants and trainers • Participants to present their expectations • Presentation of objectives and confirm objective(s) for the training • Access to training materials
	RATIONALE FOR EFFICIENCY ANALYSIS
9.00	**Allocative efficiency analysis and an introduction to Optima TB** • Presentation • Questions and answers
10.30	**Break**
	EPIDEMIC AND ALLOCATIVE EFFICIENCY ANALYSIS IN OPTIMA
	Introduction to the Optima TB interface • Tour of the Optima TB interface • Brief demonstration of a complete Optima TB analysis
12.30	**Lunch**
13.30	**Training: Creating an Optima TB project and databook** • Creating and naming an Optima TB project • Managing Optima TB project files • Defining population groups • Guidelines for data entry in the Optima TB databook
14.00	**Practice: Create an Optima TB project and defining population groups**
14.30	**Collating data and populating the Optima TB databook** **Concept: Principles of data entry and model parameters**
15.15	**Practice: Uploading a completed Optima TB databook**
15.30	**Break**
16.00	**Optima TB model calibration** Steps for calibrating and what to look for in a calibration
16.30	**Practice: Calibrating a model**
17.10	**Interactive discussion of questions and ideas arising from Day 1**
17.25	**Evening exercise(s)/reading in preparation for Day 2** Review Optima TB databook Exploring sources for additional data to inform the model
17.30	**Closure of Day 3**

Agenda - Day 2: Getting to grips with Optima TB

Time	Session name and description
8.30	**Review of materials covered on Day 1, review questions, and plan for Day 2** Access to training materials
8.45	**Training: Defining programs and parameters**
9:10	**Practice: Defining programs and parameters**
9.30	**Concepts: Collating data to inform programs** • Data requirements, sources, and concerns Explore a demonstration examples
9.45	**Training: Defining cost functions**
10.00	**Practice: Defining cost functions**
10.30	**Break**
11.00	**Concept: Introduction to TB cascades** • Cascades for programmatic outcomes
11.30	**Practice: Working with cascades in Optima TB**
12.30	**Lunch**
13.30	**Training: Optima TB scenario analysis** • How to define scenarios • How to run scenario analyses, view, export, and interpret results
14.00	**Practice: Running Optima TB scenario analysis, viewing, exporting, and interpreting results**
14.30	**Concepts: Optima TB optimization analysis** • How mathematical optimization is achieved • Description of the Optima TB optimization algorithm • How does Optima TB incorporate constraints
15.00	**Training: Defining objectives and constraints in Optima TB** • How objectives, constraints, and time horizons are incorporated in Optima TB • Specifying settings in Optima TB to meet objectives and set constraints
15.30	**Break**
16.00	**Practice: Defining objectives and constraints in Optima TB** Consider objectives from the scope of work
16.45	**Practice: Performing optimization analysis using Optima TB** • Interpreting results • Understanding results with respect to objectives, time horizons, constraints, and cost functions
17.25	**Evening practical exercise: Complete a full country Optima TB analysis** • Work on an Optima TB epidemic and allocative efficiency analysis
17.30	**Closure of the day**

Agenda - Day 3: Completing an Optima TB analyses

Time	Session name and description
8.30	**Review of material covered on Day 2, review questions, and plan for Day 3** • Access to training materials
8.45	**Exercise: Complete a full country Optima TB analysis** • If complete, interpret findings and extract key messages and recommendations
10.30	**Break**
11.00	**Concepts: Interpreting analysis results and extracting key messages and recommendations** • Interpreting results from different types of analysis • Extracting key messages or lessons from the analysis • Structuring recommendations
11.20	**Practice: Structure key recommendations from an Optima TB analysis** • If full country Optima TB analysis is complete, use your results otherwise, use results from the demonstration project
11.40	**Concepts: Intervention modalities within an allocative efficiency analysis** • Example of intervention modalities Program interactions (additive, random, nested)
11.55	**Training: Intervention modalities** • Defining intervention modalities • Defining program interactions and how they work in Optima TB
12.10	**Practice: Conducting an analysis specifying interacting programs**
12.30	**Lunch**
	ADDITIONAL PRACTICE AND WAY FORWARD
13.30	**Practice: Open analysis practice and question period**
14.30	**Next steps in using tools for analytical applications**
15.00	**Concepts: Access to Optima TB and questions**
15.30	Participant reflection and feedback
16.00	Concluding remarks
16.30	**Plenary Closing Session**
17.30	**Workshop Closure**

Types of health system efficiencies

1. **Allocative inefficiency**: not distributing resources to the combination of programs that would yield maximum health impact using available resources
   a. **Pareto inefficiency**: health system could provide additional benefit to one person without disadvantaging another
   b. **Productive inefficiency**: not using an equally effective but lower cost intervention

2. **Social inefficiency**: when price mechanism does not take into account all costs and benefits associated with economic exchange (typically, price mechanism only take into account costs and benefits arising directly from production and consumption)

3. **Dynamic inefficiency**: no incentive to become technologically progressive, i.e. not using or investing in new products, production methods, services and/or service delivery modalities)

4. **'X' inefficiency**: no incentive for managers to maximize output (typically, uncompetitive markets)

Optima TB

What is allocative efficiency?

- The distribution of resources to a combination of programs, which will yield the largest possible effect for available resources.

- The right intervention being provided to the right people at the right place in a way that maximizes health outcomes for a given resource level.

Optima TB

How do you improve allocative efficiency?

- Mathematical models can be useful tools to identify the efficiencies in resource allocation
  - can address some of the limitations of cost-effective analysis.

- The Optima TB model, is an allocative efficiency tool that can be used to support decision making towards maximizing health outcomes, especially in settings with constrained budget.

Optima TB

OptimaTB

What is it?

How does it work?

How will it fit my needs?

Optima TB

What is Optima TB?

Effective interventions and service delivery

Optima TB aims to support countries to make the best possible investment **decisions**

Support demand for and **delivery of services** to the best feasible **standards:**

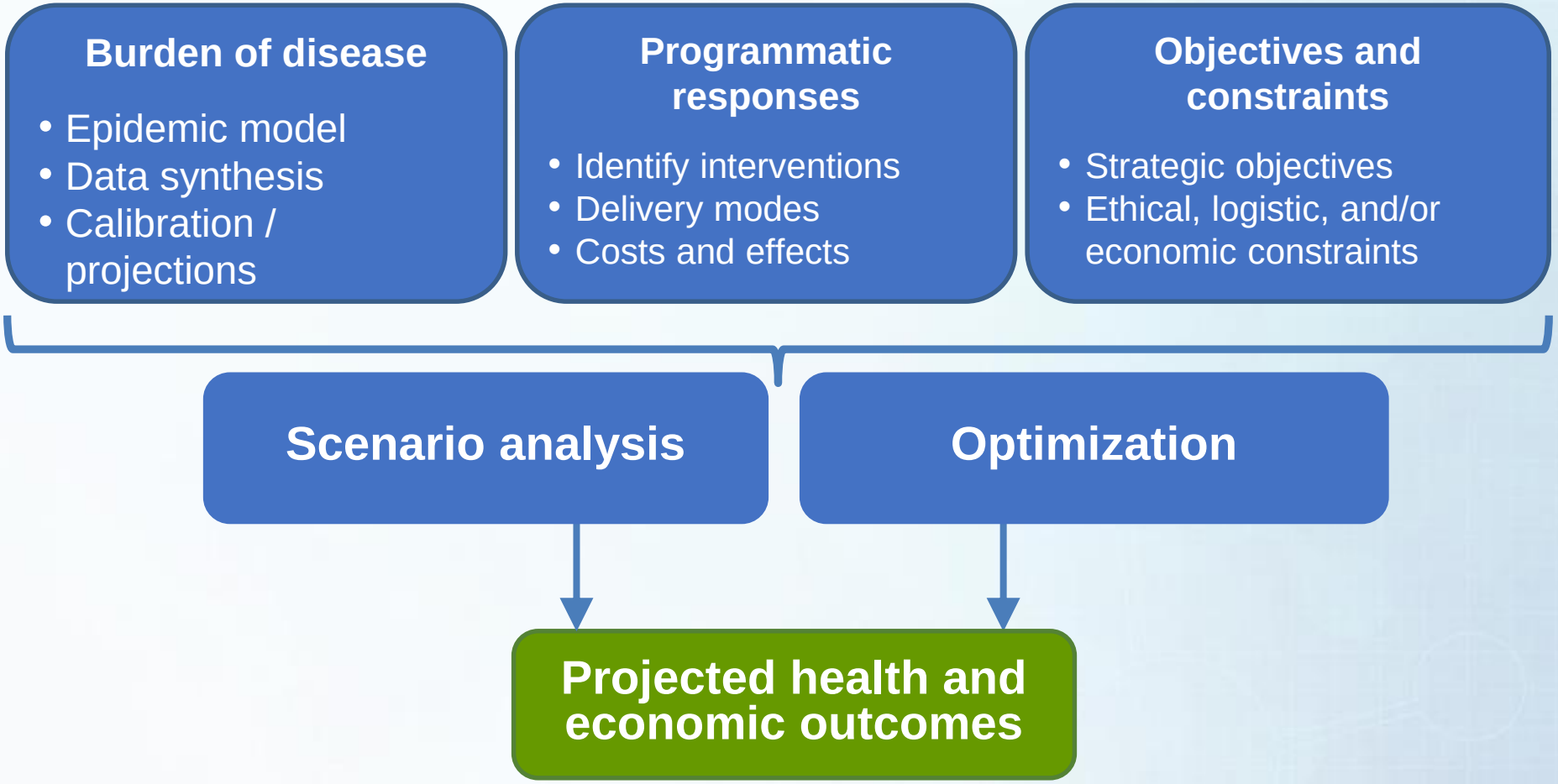
- for the right **people**
- in the right **places**
- at the right **time**
- in the right **ways**

For the greatest **tuberculosis** and **health impact**

While moving early and urgently to **institutionalize** and **sustain services**

Optima TB

The Optima approach



Optima TB

Using evidence from an **Optima TB** analysis to meet objectives

- What **impact** can be achieved if resources are optimally allocated?

- For example, how many:
    - existing and new TB **infections**
    - TB-related **deaths**

  can be averted?

Common objectives that can be addressed using by Optima TB

1. What will the projected TB epidemic look like under most recent funding?

2. What can be achieved through allocative efficiency gains?

3. What funding amount and allocation will be required to achieve the National Strategic Plan targets?

4. What is the expected future impact of different funding scenarios?

How does Optima TB work?

Optima TB is a model

Outcome: how many people can we safely fly in this plane?

How much further will this plane fly when spending is **optimized**?

Scenario analysis: what if we scaled up the size of wings?

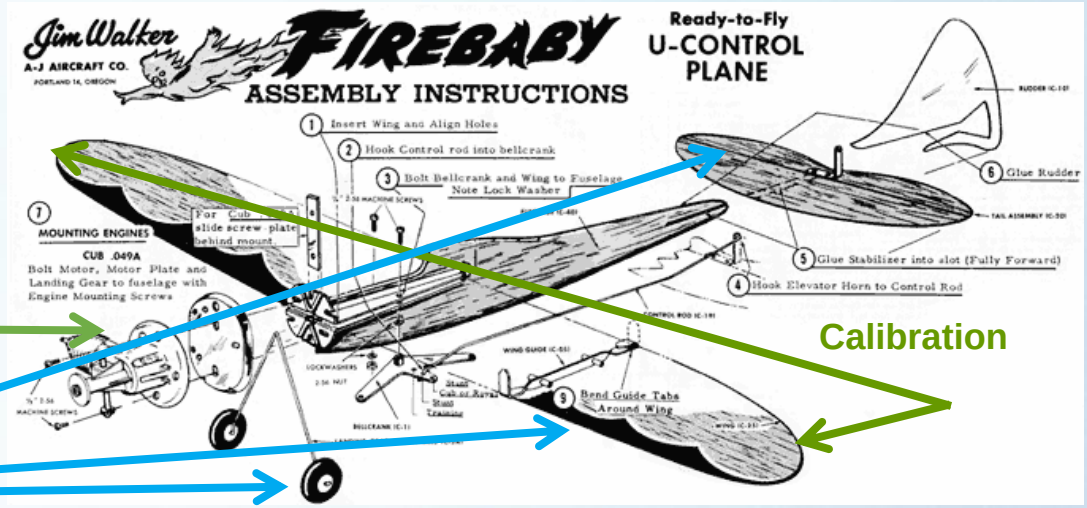
Populations: passenger groups

Programs: piloting, flight service, maintenance, etc.

Spending: part costs

Epidemic model

Optimization of $



Calibration

Epidemiological component

- Optima TB is a dynamic compartmental population-based model
- The population is divided into compartments based on:
  - age, risk-factors, comorbidities, location, etc.
  - health states (susceptible, infected (active or latent), vaccinated, recovered)
- At each point in time people can move between health states (i.e. model compartments)
- The Optima TB model includes default values related to disease. Default values assume:
  - No testing or treatment
  - No comorbidity
- Within a completed application, the model will be informed using country specific data.

Optima TB

Optima TB terminology

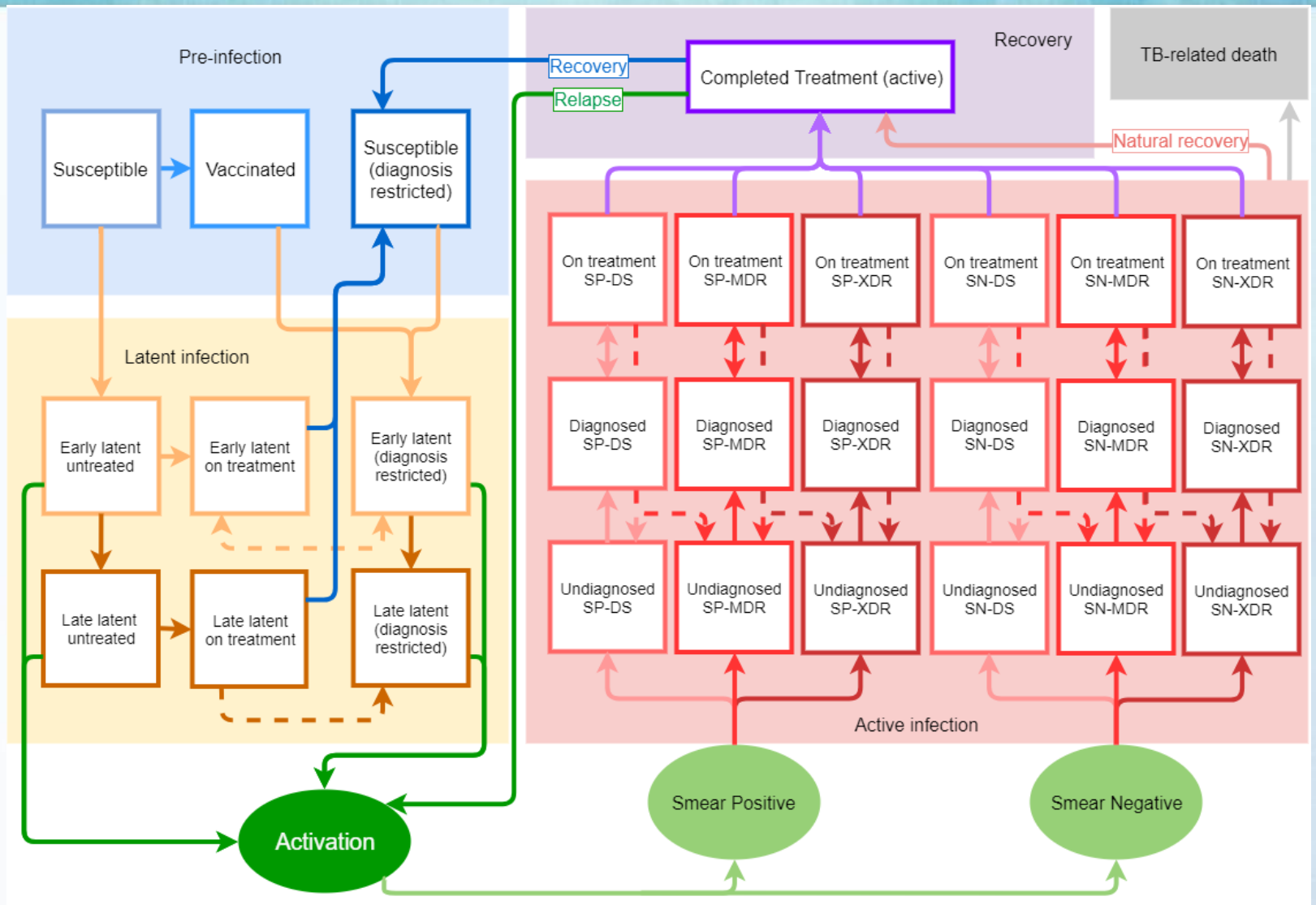
- Susceptible
- Latent TB
  - “Early” latent (infections within the last 5 years)
  - “Late” latent (older infections)
- Smear
  - SP = Smear positive
  - SN = Smear negative
- Strain
  - DS = Drug susceptible (or sensitive)
  - MDR = Multidrug resistant
  - XDR = Extensively drug resistant

Optima TB

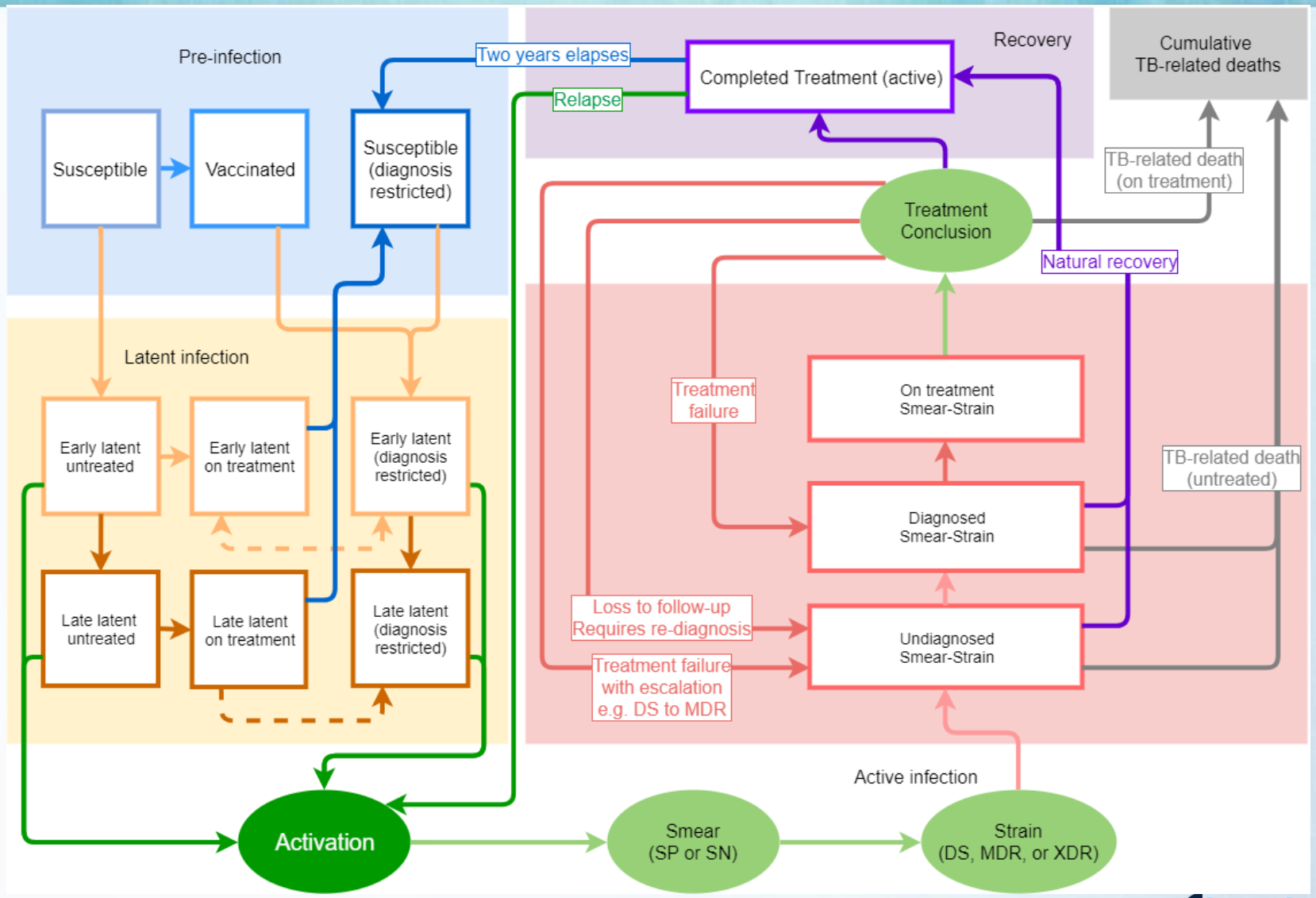
Optima TB terminology

- Compartment
  - Also known as a “stock”
  - Every person in the entire population should be in exactly one compartment at each point in time, e.g. 15-64 year olds with currently undiagnosed SP-DS TB
- Transition
  - Also known as “flow”
  - Every time step in the model, people have a chance to move from one compartment to another through a “transition”
  - Transitions can be based on average durations, probabilities, or proportions

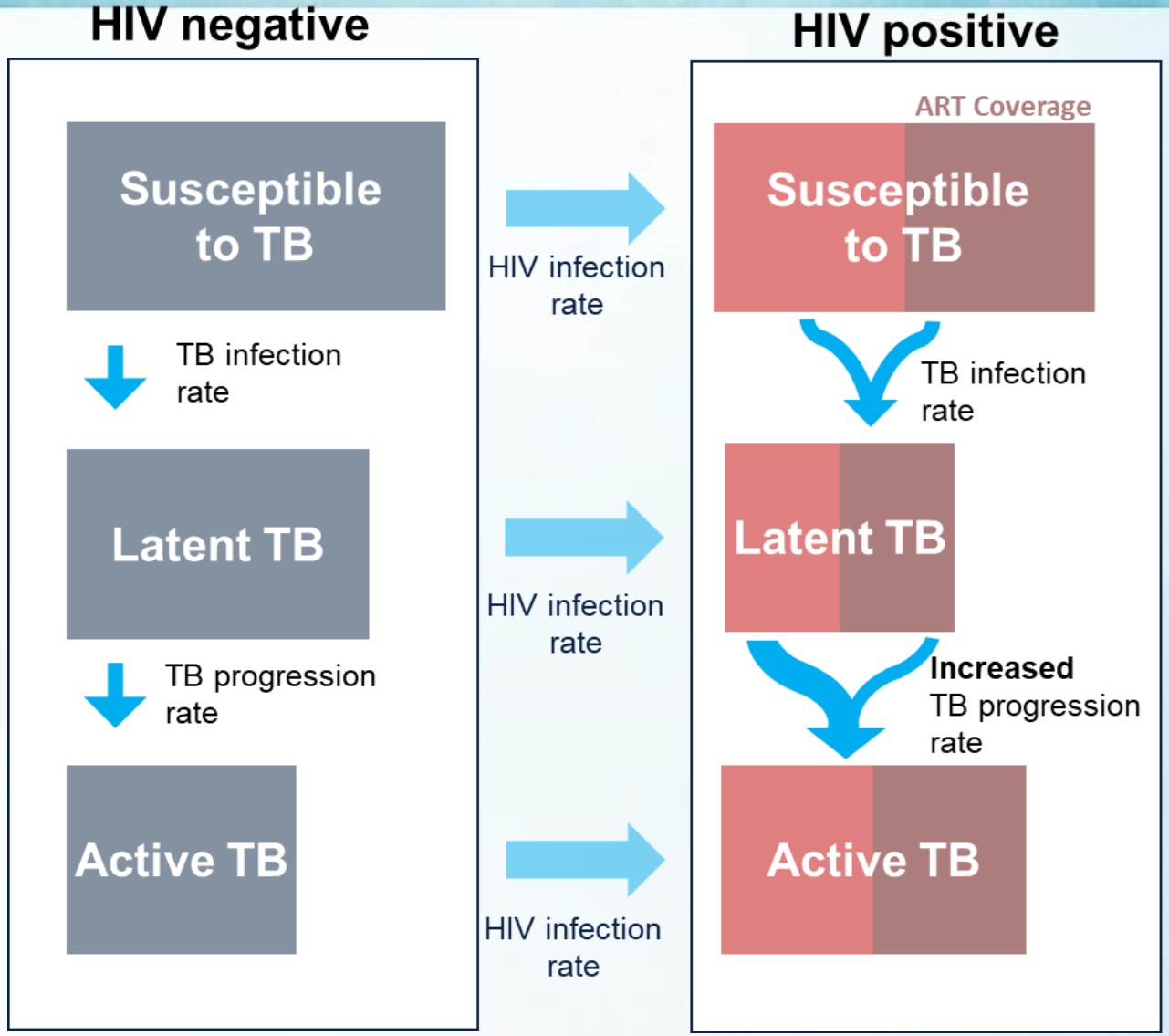
Optima TB disease model



Optima TB disease model with focus on treatment



Handling TB-HIV co-infection in the Optima TB model



Informing the TB epidemic component

Epidemic data is collated in an Optima TB databook (spreadsheet)

- Define populations
  - General populations by age and sex
  - Key populations
  - Coinfections and comorbidities

- Demographic data
  - Population size
  - Birth rate
  - Non-TB-related death rate
  - Transitions between population groups
  - Migration

Population groups, an example
Children aged 0-4 years
Children aged 5-14 years
Adults aged 15-64 years
Adults aged 65 years and older
Prisoners
Coinfected and comorbidities
People living with HIV (PLHIV)
Diabetics

Minimum epidemiological data requirements

- For each population group:
  - TB notifications by:
    - Drug-resistant strain
    - Smear status, if known
  - Number of treatment initiations
  - Treatment outcomes by cohort or year
- If available, estimates for:
  - Active TB prevalence*
  - Active TB incidence
  - Latent TB prevalence
  - TB-related deaths

Minimum data requirement:
3 years of recent annual data including the year program spending available

Example 1: 2010, 2012, 2016 (spending for 2016)

Example 2: 2015, 2016, 2017 (spending for 2017)

* Derived from estimates of incidence and average length of time to treatment initiation

Optima TB

Summary of data entry in the Optima TB databook

- Flexible for including populations of interest
- Requires setting-specific data and/or estimates
- Optima TB model contains disease-specific defaults

The more comprehensive, high-quality the data,
The more representative and informative output

Calibration

The Optima TB model is calibrated to reflect the TB epidemic in a given setting

Why is calibration necessary?

- **Calibration** is the process of adjusting model parameters to best match the observed TB epidemic

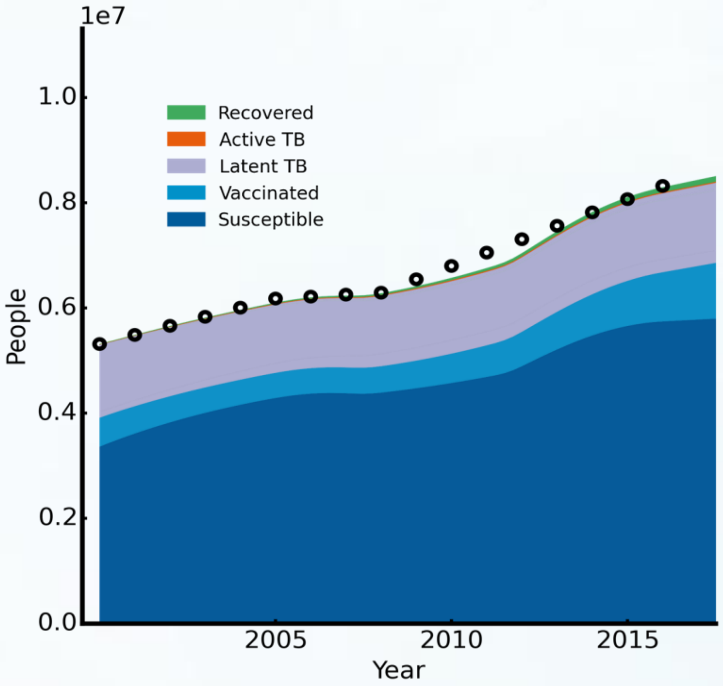
- Ideally
  - The model structure would perfectly reflect the real-world epidemic
  - All data and estimates would be consistent and comprehensive
  - Uncertainties and biases would be minimal

- In practice
  - The model makes simplifying assumptions (e.g., population homogeneity)
  - Epidemiological and behavioral data may not be consistent
  - There are uncertainties (especially for historical data) and biases

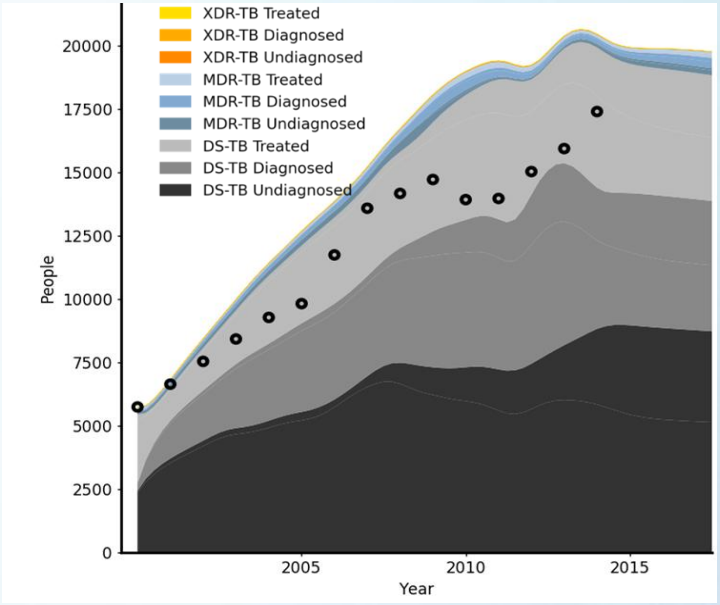
Optima TB

Epidemic outputs from the model calibration

Cross-section number of 15-64 HIV- population in each health state



Number of all active-TB (15-64 HIV-) infections by care-status



Why is the model predicting more cases of active TB than the data?

Optima TB

Review of assumptions and default values

Something missing from the model?

- Death rates could be slightly higher for people with TB
  - Adjust SP to SN ratio (higher mortality in SP)
- Latent infection rates could be slightly lower
  - Adjust population vulnerability factor
  - Adjust (other) population infectiousness factor(s)
- Progression from latent to active TB could be slightly lower for long term infections
  - Adjust late latent departure rate
- ...many other options

Which change is appropriate will depend on discussion and consultation – **every change should be justified**

Optima TB

TB program costs and coverage

Overview of TB programs

- Optima TB can accommodate programs that:
  - Directly target TB (i.e. diagnostic, treatment, prevention)
  - Less directly target TB (i.e. behavioral, awareness campaigns)
  - Do not directly target TB, these are included in the budget but not considered within the optimization (i.e. management)

- For each program, the minimum data requirements are:
  - Spending
  - Coverage (number of people reached)
  - Unit cost
  - Capacity constraints

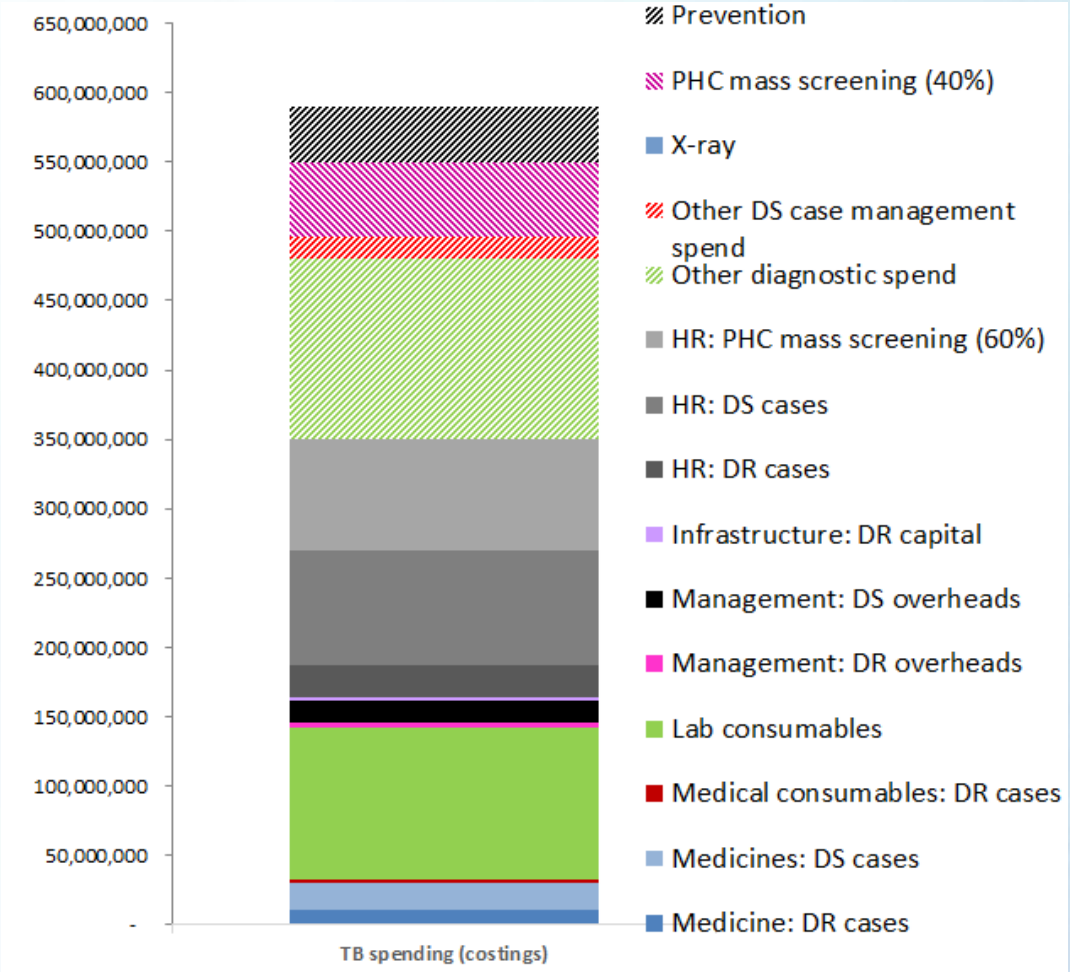
- TB programs not currently implemented, but planned for future implementation can be included in the Optima TB model

Optima TB

TB program spending

- Can be reported directly (top-down costing)
- Alternatively, can be reconstructed from unit costs and program coverage (bottom-up costing)
- Valuable to do both if possible

Example: total TB spending 590 million (2016)



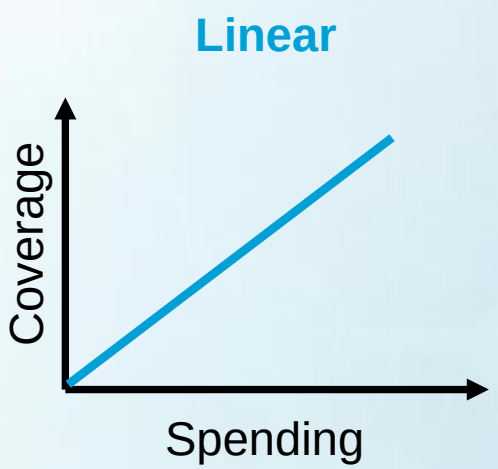
Optima TB

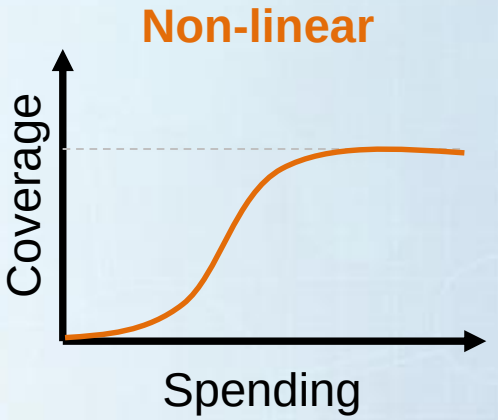
Cost functions

Cost functions relate program costs to population coverage and outcomes.

Cost-coverage curves

- Relates program spending to program coverage
- Cost-coverage curves can be:
  - **Linear**: slope represents a single unit cost, or
  - **Non-linear**: slope represent scale-up, stable implementation, and increasing effort in reaching additional people
- In the absence of data to inform non-linear cost-coverage curves, linear cost-coverage curves are assumed





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Reconciliation

- **Historical values are input directly** for treatment outcomes, number of cases diagnosed, etc
- **Future values are determined by spending** and program effectiveness for each program

- Example
  - Notified diagnoses in 2017 equal to **1000 people** (databook)
  - Program spending in 2017 only enough to **diagnose 800 people** (program book)
  - There is an inconsistency and there will be a sharp jump in the project output
- Reconciliation may require reviewing the databook and program book to determine which is accurate and ensuring they are aligned

Optima TB

Scenario Analysis

ASKING ‘WHAT IF?’

Overview of selected scenarios

- Scenario analysis allows examination of:
  - the epidemiological impact and cost implications of changing coverage levels and/or prevention, diagnosis, and treatment programs or modalities, and
  - the impact of varying budget levels.
- Specifically:
  - Changing rates (i.e. testing and treatment; proportion of MDR cases)
  - Changing coverage, or
  - Changing program budget
- Scenario analysis is **flexible** and can be tailored to address context **specific questions**
- May require: additional information, eg, reduced budget or target coverage level in scenario arm

Optima TB

Scenario example: impact of improved testing coverage

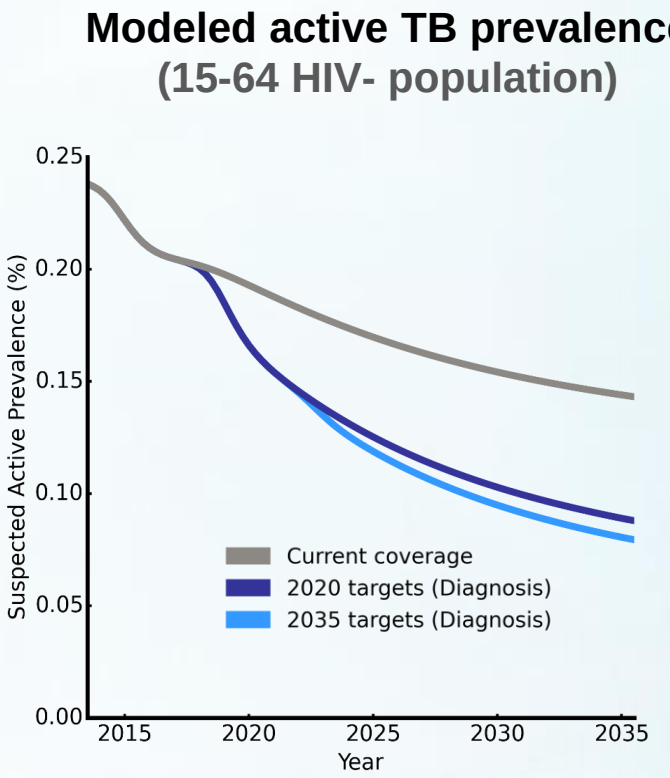
What is the projected impact of the TB epidemic if the 2020 and 2035 targets are achieved?

Scenario: Improved testing	Most recent conditions	2020 targets	End TB 2035 targets
Case diagnosis for DS-TB among HIV negative population	67%	90%	95%
Case diagnosis for MDR-TB among HIV negative population	67%	90%	95%
Case diagnosis for XDR-TB among HIV negative population	67%	90%	95%

Optima TB

Scenario example: impact of improved testing coverage

- If testing targets were achieved, it is estimated that there would be a reduction in active TB cases



Scenario possibilities

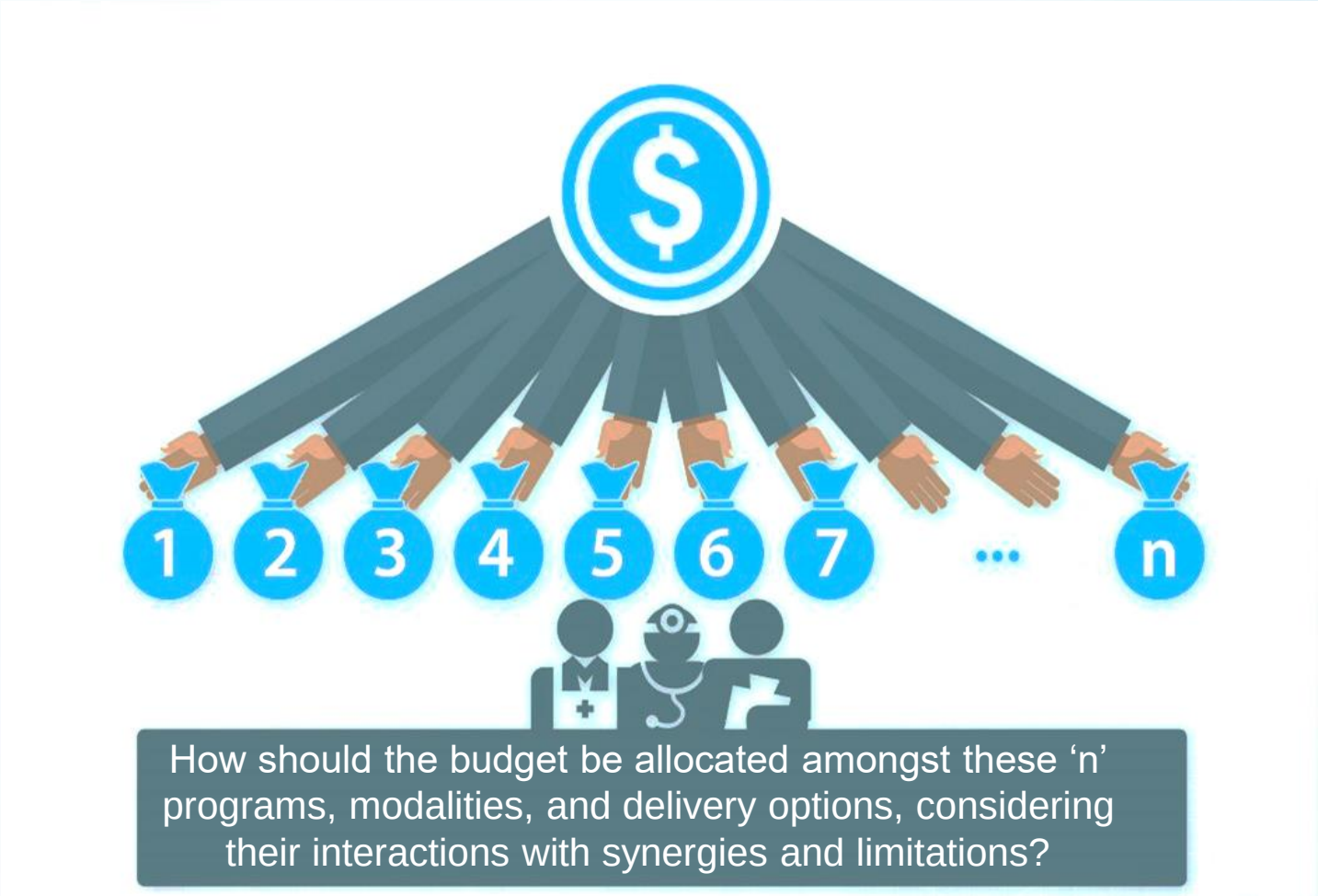
- The website offers the most commonly used “budget” scenario where funding allocations for different programs are varied.
- What other scenario questions would you want to explore?

Optimization analysis

OPTIMIZING RESOURCE ALLOCATION

Optima TB

Optimizing resource allocation: What does it mean?



Optimal allocation redistributes budgets to the most efficient, targeted programs

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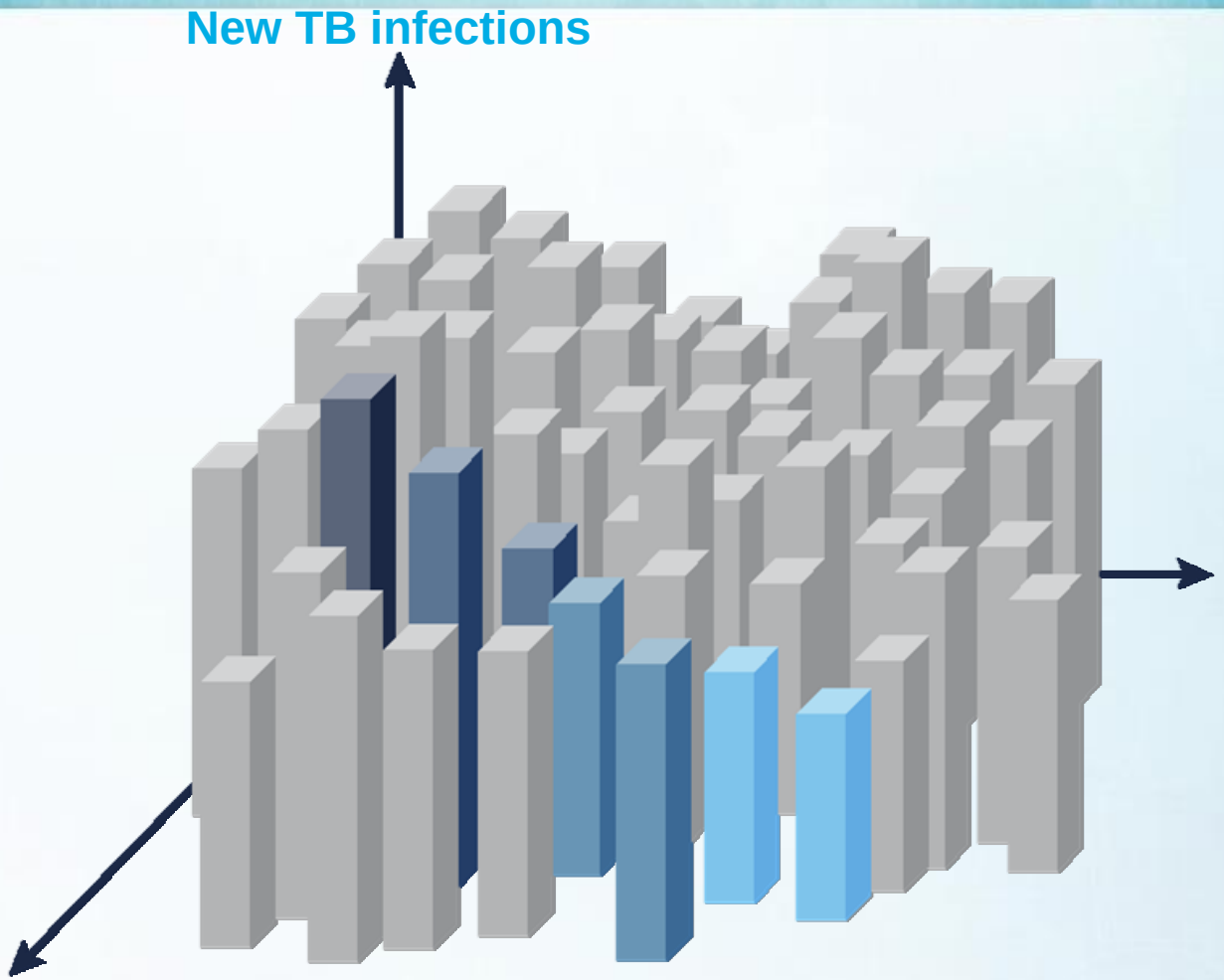
Optimization between just two programs



An efficient Adaptive Stochastic Descent algorithm is applied

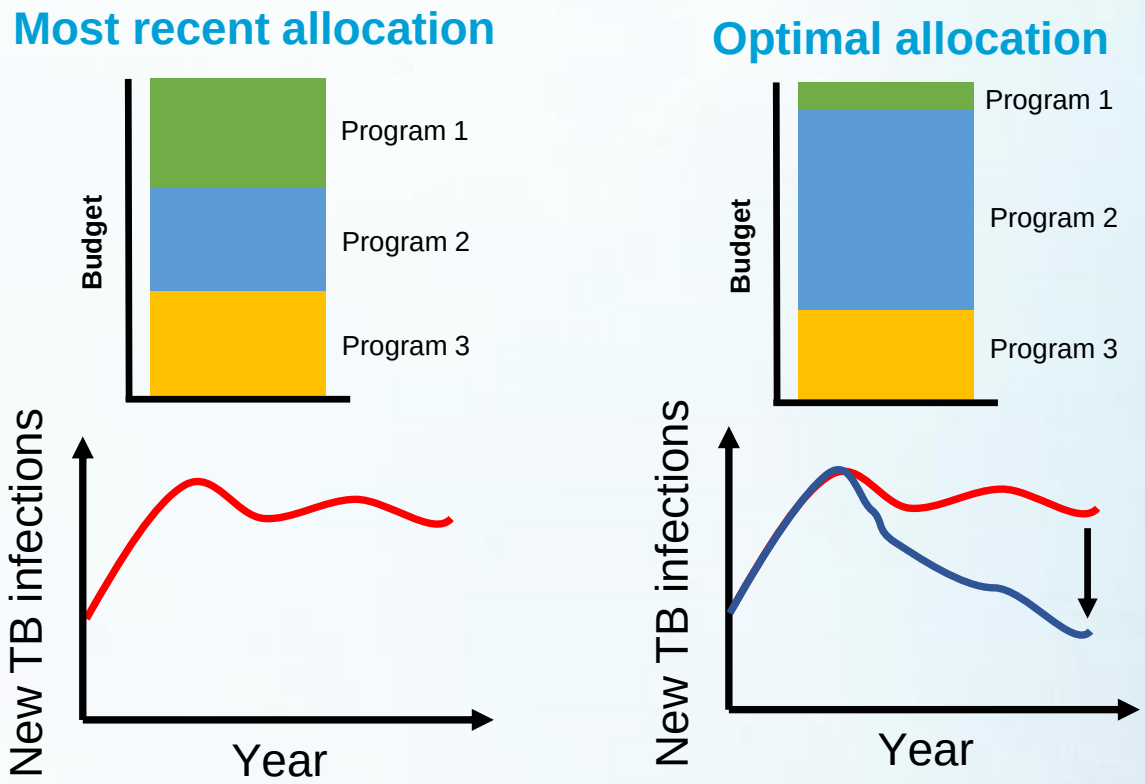
Adaptive: learns probabilities and step sizes
Stochastic: chooses next parameter to vary at random
Descent: only accepts downhill steps

Optima TB

Kerr et al. 2018

Optimizing resource allocation: What does it do?

Optimal allocation redistributes budget to the most cost-effective combination of programs



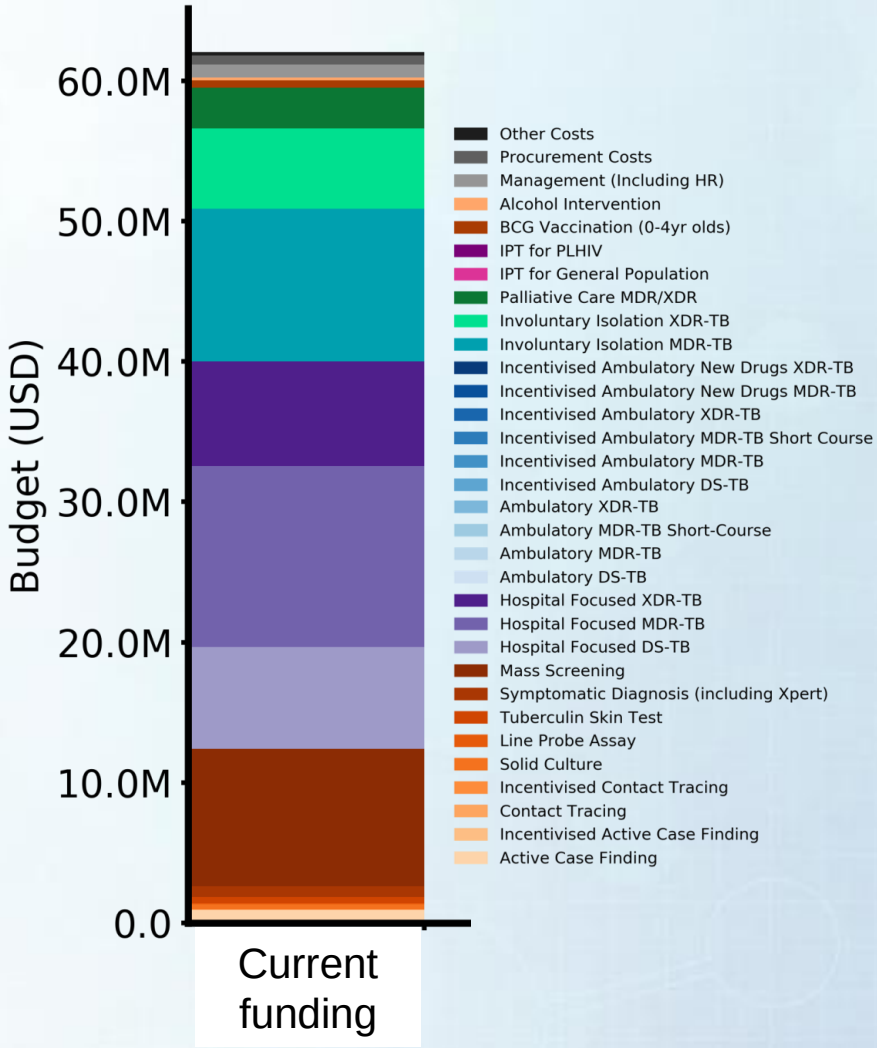
Optimization aims to identify the best combination of investment in programs to minimize new TB infections and/or TB-related deaths

Optima TB

Example from Belarus - Optimizing allocation

- Most recent funding (2015): ~$61M
- Could a different allocation of the 2015 budget:
  - Avert more new infections?
  - Further reduce prevalence?
  - Prevent additional TB deaths?
  - Decrease the number of MDR/XDR cases?
- Movement towards 2020 and 2035 targets

Objective can be to minimize infections or deaths, or both

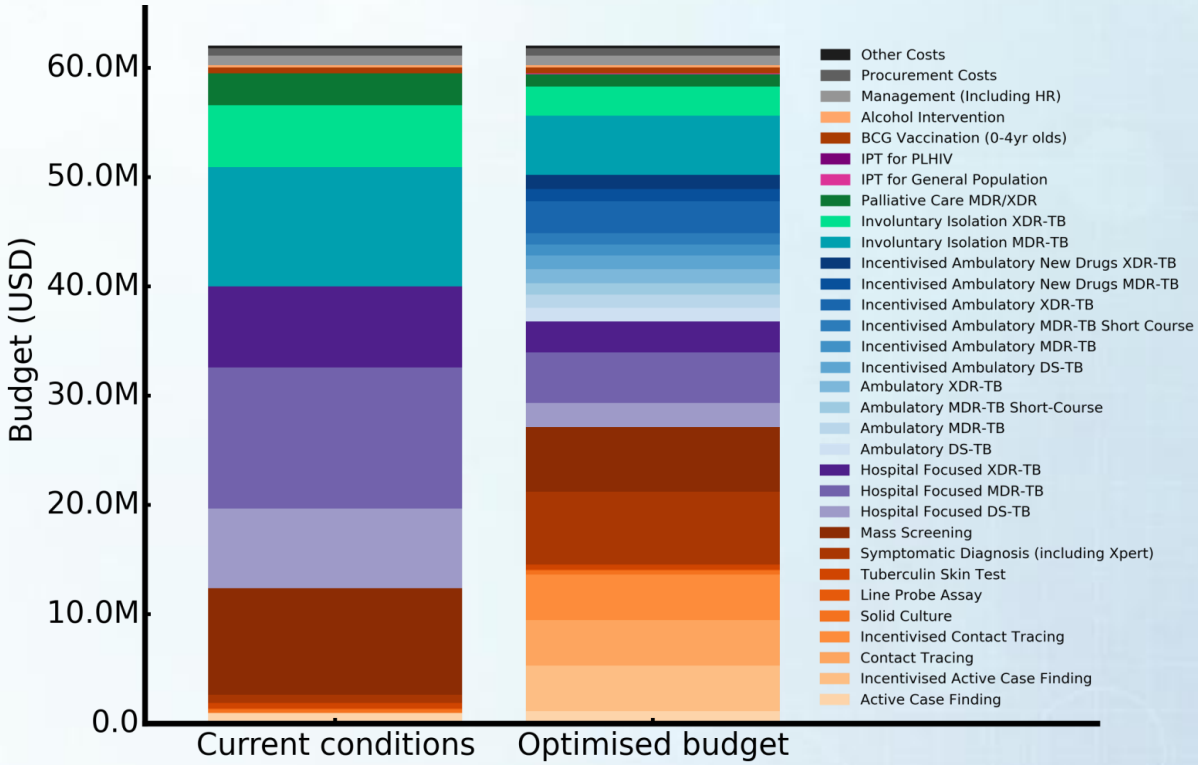


Optima TB

Example from Belarus - Optimizing allocation

Optimized budget allocation to minimize TB infection and TB-related deaths:

- Doubles the budget for testing programs, with a marked shift towards **active case finding** and **contact tracing** while reducing mass screening
- Shifts funding from hospital-based to **ambulatory treatment modalities**



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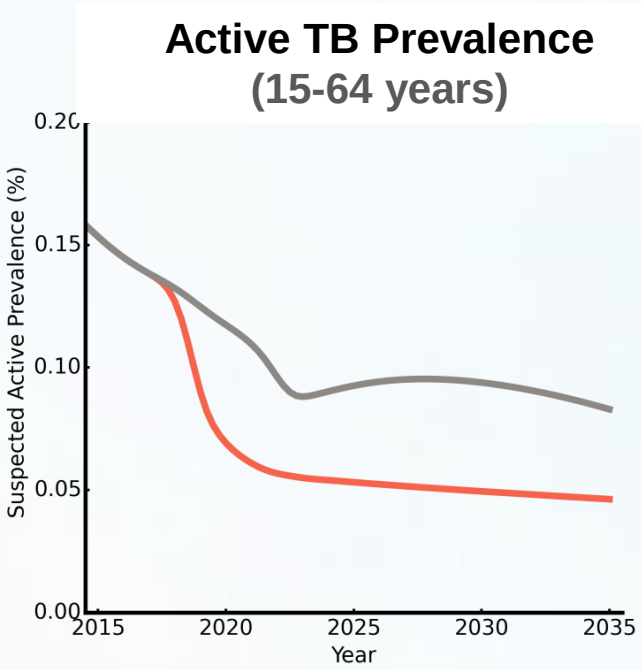
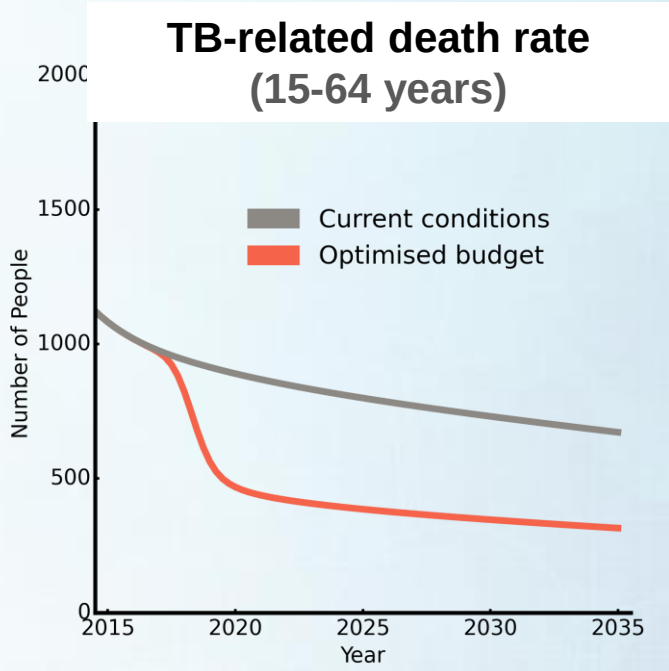
Example from Belarus - impact of optimized budget on the general population

The annual budget is assumed to be constant at $590 million until 2035

An optimized budget allocation could result in a:

- Relative reduction of adult TB prevalence by 45% in comparison to current funding, to 0.05% of the adult population by 2035
- Reduction of TB-Deaths by 60% relative to the most recent funding allocation, and 70% of 2015 levels, by 2035





How will Optima TB fit my needs?

GROUP DISCUSSION

QUESTIONS?

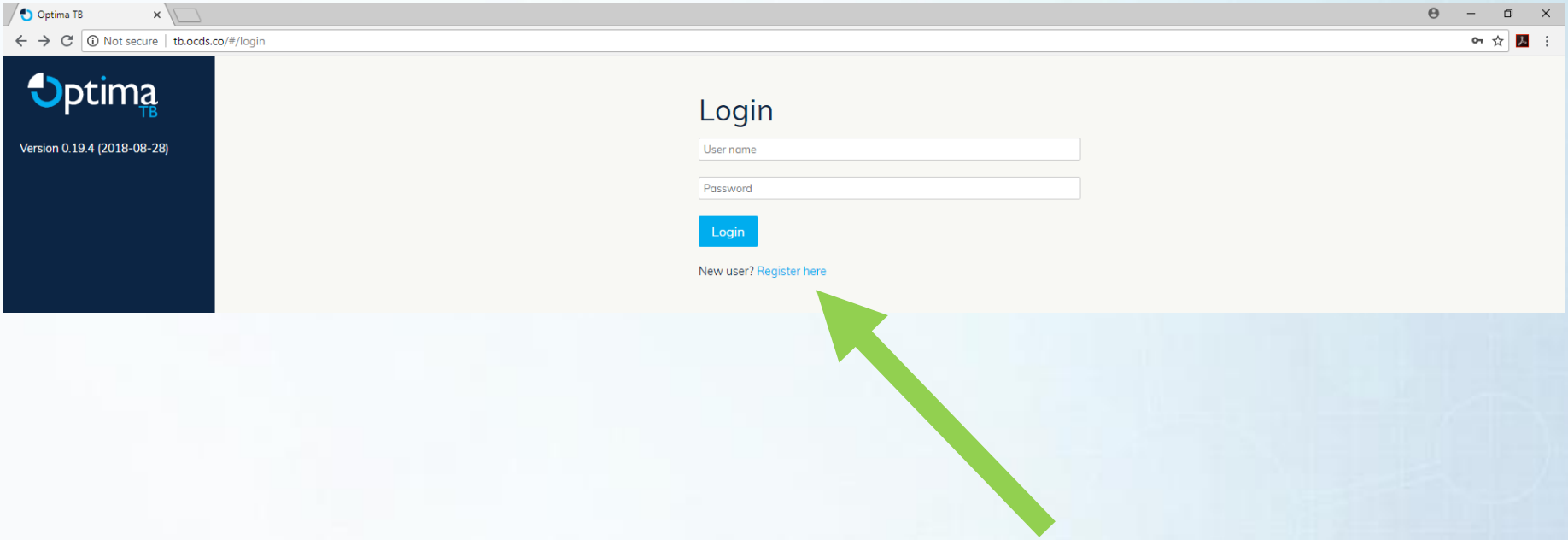
Introduction to the Optima TB interface

Creating a new Optima TB project

Register for your free Optima TB account

In your web browser (e.g. Chrome, Internet Explorer) go to:

tb.ocds.co



QUESTIONS?

Collating data and populating the Optima TB databook

Determining populations for Optima TB analysis

- Populations can be further broken down into smaller groups to better reflect the epidemic.
- Important to consider the availability of data for subpopulations before including them in the analysis

Population groups, an example
Children aged 0-4 years
Children aged 5-14 years
Adults aged 15-64 years
Adults aged 65 years and older
Prisoners
Coinfected and comorbidities
People living with HIV (PLHIV)
Diabetics

Optima TB

Exercise: Creating a new project

From the Projects page select Create new project

Years for data entry should reflect

- The first year from which you want to model the epidemic (default 2000)
- The last year for which you may wish to enter data (we recommend allowing for future years for easy updates)

For this training, it is recommended to pick just two populations such as “General population” and “PLHIV” or a different most significant key population.

Optima TB

Optima TB databook indicators

Data are entered into the databook, an Microsoft Excel spreadsheet, which is then uploaded into the Optima TB model.

Enter data in the following sheets:

1. Population definitions
2. Demographics
3. Notifications
4. Treatment outcomes
5. Latent treatment
6. Initialization estimates
7. New infections proportions
8. Optional data

Additional sheets (shaded in grey) have default values and usually do not need to be modified:

- Infection Susceptibility
- Untreated TB Progression Rates
- Interactions
- Transfers

Entering data in the Optima TB databook

Blue cells = input data required

Red cells = ignored

Number of vaccinations administered	Units	Constant		2000	2001	2002
0-4	Number	100000	OR	90000	95000	99000
5-14	Number		OR			
15-64	Number		OR			
65+	Number		OR			
Prisoners	Number		OR			
LTBI treatment initiations total	**Units**	**Constant**		**2000**	**2001**	**2002**
0-4	Number	0	OR			
5-14	Number	0	OR			
15-64	Number	0	OR			
65+	Number	0	OR			
Prisoners	Number	0	OR			

Non-shaded cells= structural (do not edit)

Grey cells = default values

“Constant” value vs annual data

- Data can be entered either with a single value in the “constant” column

OR, alternatively,

- One or more values in the annual data columns

Every row needs to have *at least* one value either in the constant column or in the annual data columns

A constant value is the same as entering that value for all individual years, and should generally be used if you need to make an assumption with limited data.

Considerations when entering data

- Data cannot be entered into the white cells
  - Unless a tag '#ignore' is entered into the first column for a row in which additional data is entered.
- Input data for the model versus calibration data
- Optima will **automatically interpolate missing data**
  - First entered data point is used for all previous years
  - Data values are interpolated linearly between every two entered data points
  - Last entered data point is used for all years thereafter
- "Constants" are ignored if any annual data points are entered for that parameter

Optima TB

Data units

- **Proportions:** these values should be interpreted as a proportion of outcomes that are grouped together and should sum to 1
  - such as the proportions of people who have different treatment outcomes.
- **Probability:** this refers to an annual probability of an outcome occurring at least once during that year,
  - such as the annual probability that latent TB progresses to active TB.
- **Number**: input values will be used directly for annual totals
  - such as the number of people initiating treatment in a given year.
- **N.A.**: relative multipliers that don't have any units
  - such as the relative risk of being infected with TB for someone with vaccination compared to someone without vaccination

Optima TB

2. Demographics

- Demographics data include:
  - Population size
    - avoid double-counting across population groups, verify total population size
  - Number of births
  - Non-TB deaths
  - Data on migration

- Data input units are specified for each, and may include options in the dropdown menu

- Exclude TB-related deaths from non-TB death rate

Optima TB

Probabilities Example

- Death rates may be entered as a probability instead of a number
- Non-TB death rate = crude death rate – estimated TB death rate

A “Non-TB death rate” of 0.04 would mean that each person in that population has a 4% chance of death due to non-TB related causes each year.

Optima TB

3. Notifications

- Clinical numbers of TB diagnoses and new treatment initiations
  - Should include best estimates of actual diagnoses and treatments if reporting is not comprehensive
- Notification data must be broken down by smear status, drug resistance and population
  - Where data is not available in this format, some judgements will have to be made
- Treatment initiation data must be broken down by drug resistance strain and population
  - If outcomes differ by smear status, then this can be calibrated later via the website

Optima TB

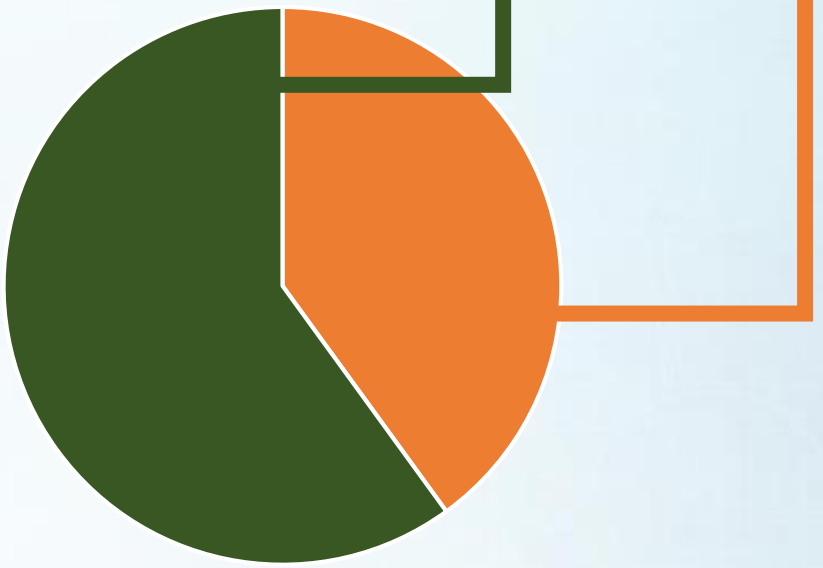
4. Treatment outcomes

- Should be entered using cohort data if available (most accurate to least):
  - Cohort data for people **concluding** treatment in the specified year
  - Cohort data for people **initiating** treatment in the specified year
  - Annual reported number of each outcome, adjusted so that the proportions add to 1
  - Best estimates using other sources
    - Treatment modality reported efficacy
    - Local expertise
    - Regional values

Optima TB

Proportions example: Population to Smear status

New active infections: proportion of population that are SP	Units	Constant		2000	2001
General population	Proportion		OR	0.6	0.55
Prisoners	Proportion		OR	0.7	0.65
New active infections: proportion of population that are SN	**Units**	**Constant**		**2000**	**2001**
General population	Proportion		OR	0.4	0.45
Prisoners	Proportion		OR	0.3	0.35



Proportion of the general population that are smear positive/smear negative

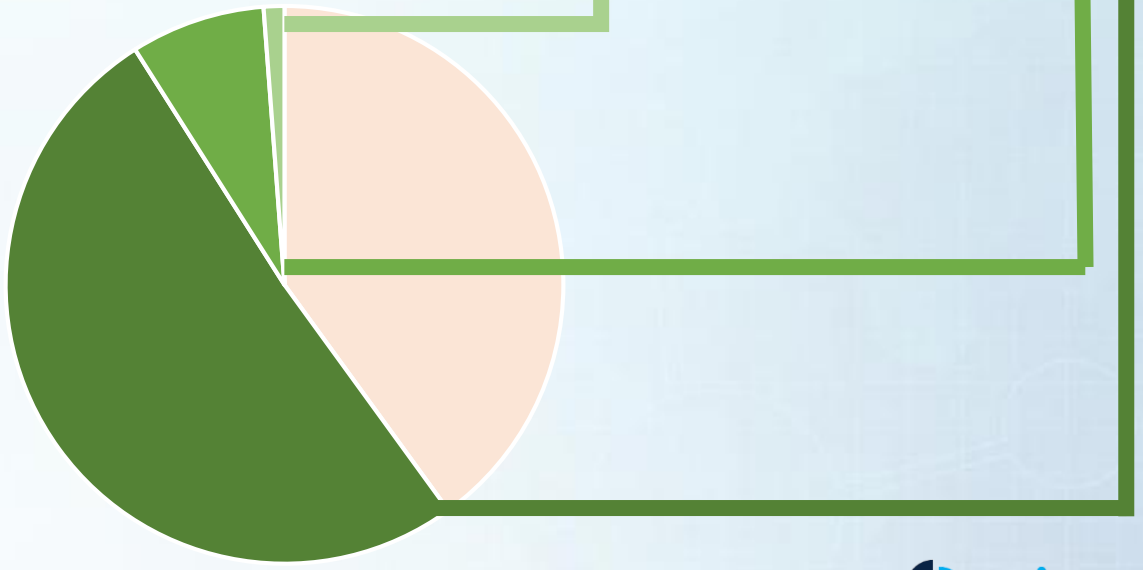
Total = 0.6 + 0.4 = 1

Proportions example: Smear status to drug resistance

New SP infections: proportion of population that are SP-DS	Units	Constant		2000
General population	Proportion		OR	0.85
Prisoners	Proportion		OR	0.8
New SP infections: proportion of population that are SP-MDR	**Units**	**Constant**		**2000**
General population	Proportion		OR	0.13
Prisoners	Proportion		OR	0.18
New SP infections: proportion of population that are SP-XDR	**Units**	**Constant**		**2000**
General population	Proportion		OR	0.02
Prisoners	Proportion		OR	0.02

Proportion of the SP general population that are DS/MDR/XDR

Total = 0.85 + 0.13 + 0.02 = 1



5. Treatment of latent TB infections (LTBI)

- The number of annual BCG vaccinations for each year should be input here

- Default values of zero for LTBI treatment can be updated if LTBI treatment program exists

Optima TB

6. Initialization estimates

- Initialization (start point) estimates are required to initiate model (e.g. in year 2000)

- At least one value is mandatory for the latent and active prevalence
  - other estimates will improve the initialization

- Population sizes is duplicated here, to enable initialization
  - Can be adjusted during calibration, without changing actual data

Optima TB

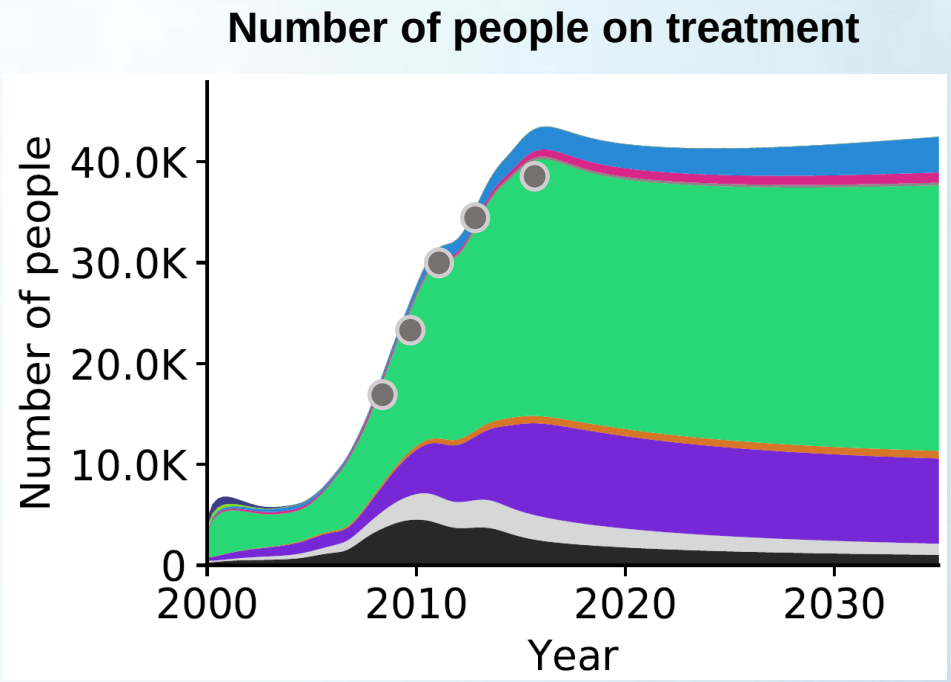
7. New infections proportions

- Proportional breakdowns by smear status and drug resistance input here
  - calculated using notification data
- Example: In 2017 for population ages 5-14, there were **1500 Smear positive (SP)** notifications and **750 smear negative (SN)** notifications.
  - SP proportion of new active infections: 1500/(1500+750)
    - **SP proportion = 0.67**
  - SN proportion of new active infections: 750/(1500+750)
    - **SN proportion = 0.33**
- In contexts where there is incomplete notification data, estimates here can be used to disaggregate notification data
  - Some smoothing may be necessary to ensure data is consistent and reasonable.

Optima TB

8. Optional data

- Optional, are **not model inputs**
  - Used to plot known values against model outputs
- Values here are point estimates e.g. the number on treatment as of January 1 each year, rather than the total over the entire year



Documenting data sources

- Documenting data sources is important. Comments should be added to cells, outlining:
  - **Source**: a reference for the data
  - **Notes**: highlighting the quality of the data (such as sample size or confidence bounds), and any assumptions and/or calculations.

- Example
  - **Source**: Paper, Author, Year: value A
    Report, Author, Year: value B
  - **Notes**: Paper was a very small study in one town of the country, used Value B from Report as this was a national study on a large cohort.

Optima TB

QUESTIONS?

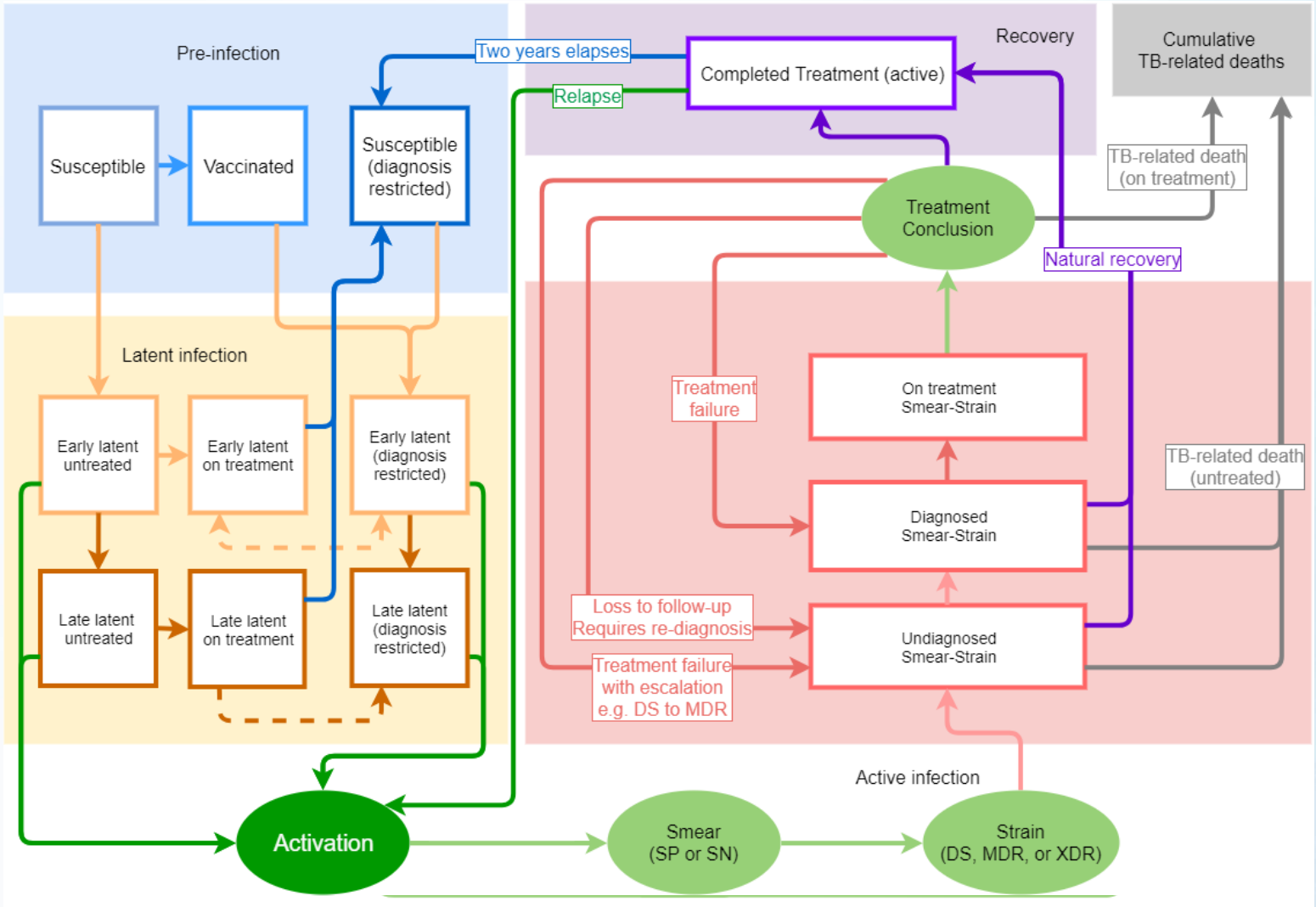
Optima TB

Considerations when entering data

- Data cannot be entered into the white cells
  - Unless a tag '#ignore' is entered into the first column for a row in which additional data is entered.
- Input data for the model versus calibration data
- Optima will **automatically interpolate missing data**
  - First entered data point is used for all previous years
  - Data values are interpolated linearly between every two entered data points
  - Last entered data point is used for all years thereafter
- "Constants" are ignored if any annual data points are entered for that parameter

Optima TB

To review: the Optima TB model schema



Optima TB model calibration

The calibration process

1. Enter data, estimates, and assumptions where necessary in the Optima TB databook

2. Determine if data is reasonable and identify values that are the most reliable

3. Certain data values may need adjustment to ensure consistency

4. Calibrate additional parameters to ensure model outputs match the most reliable data

5. Review initialization estimates
   - to ensure the model starting point is stable in subsequent years

1. Inputs used to calibrate the model

- All data entered in the databook can be iteratively adjusted if necessary

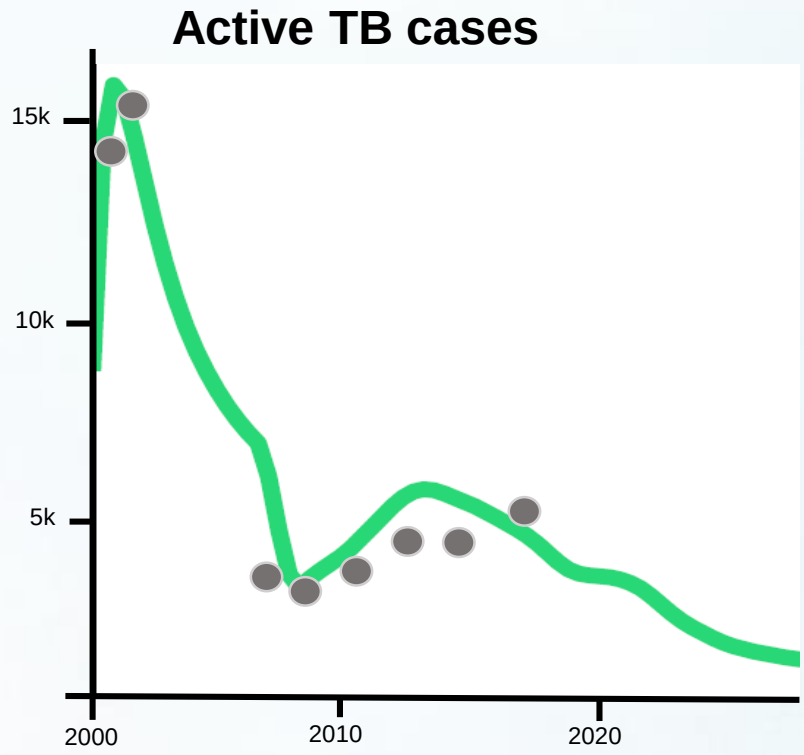
- In practice, the most reliable data or estimates are, in order:
  - Population sizes
  - TB notifications
  - Treatment outcomes
  - Prevalence estimates (latent and active)
  - Estimates for new cases of TB, TB-related deaths, etc. (typically from *another model*)
  - Starting year estimates of number of people with latent, active, treated, and recovered TB

Optima TB

2. Are data inputs reasonable?

- Data from different sources may not be consistent
- Methodologies, sites, etc. can change from year to year

- For example, are these trends realistic?



Calibration: first step, fit to demographic data

- Annual population size and birth rate data are very reliable.
- Ageing rates, non-TB-related death rates, migration rates are less reliable data inputs and may need to be adjusted to ensure population sizes each year are well matched.
- The model should first be calibrated to population size related data before calibrating to other epidemiological data/estimates.

3. Are data values consistent?

- Even if data seem reasonable, they may not be consistent
- Within a single epidemiological measure
  - E.g. data points may be from different cities and neither accurately portrays national trends
- Across different epidemiological measures
  - E.g. very high incidence and very low prevalence are unlikely to be true at the same time
- In cases like this, data sources and methodologies or meta-data must be scrutinized to determine which data points are most representative.

Optima TB

4. Key parameters for calibrating the Optima TB model

Primary parameters for calibration

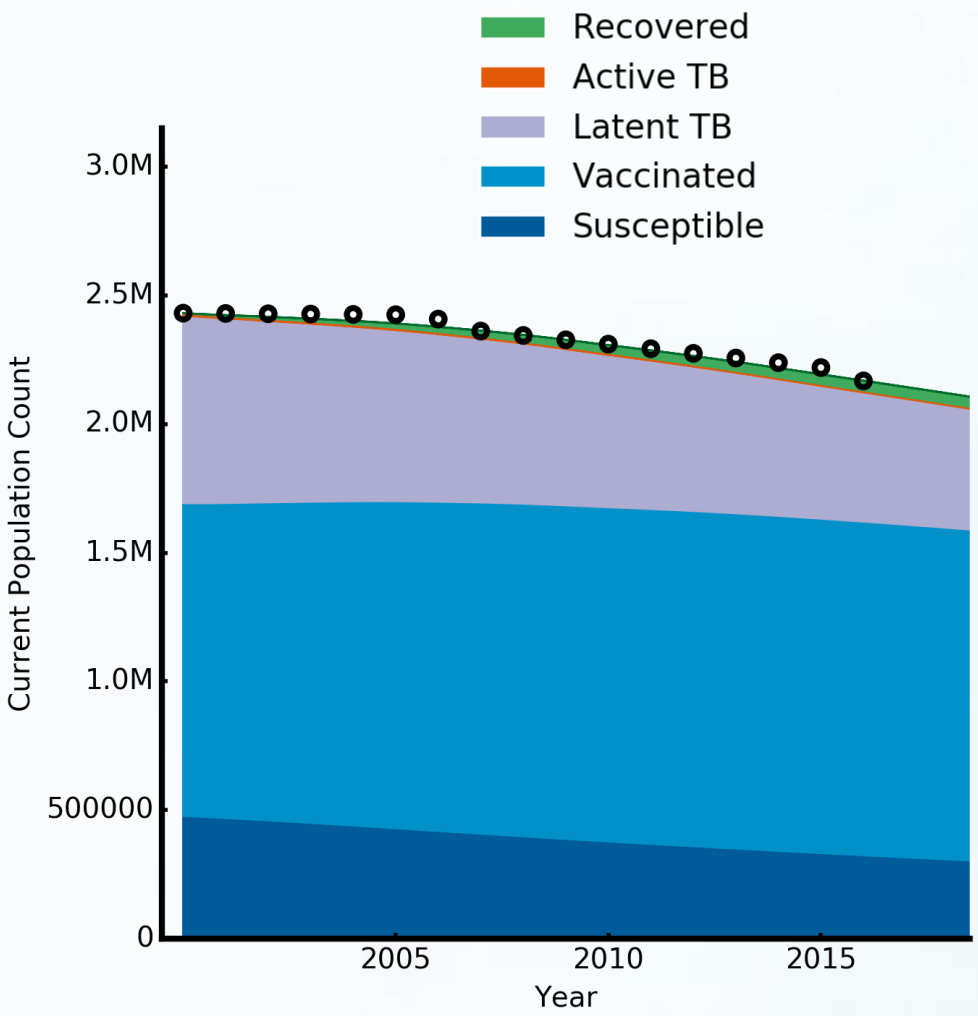
1. Parameters affecting new latent TB infections
   a. Relative infectiousness (the main force of infection parameter)
2. Parameters affecting progression to active TB
   a. Early latency activation rate
   b. Late latency activation rate
   c. Relapse rate

Secondary parameters for calibration

4. Natural TB recovery rates
5. TB escalation rates
6. TB-related death rates

Optima TB

5. Review starting year estimates



- Should be relatively smooth in first few years, may need to adjust initialization estimates for
  - Latent TB
  - Active TB
  - Treatment
  - Vaccination
  - Recovered (previously infection)

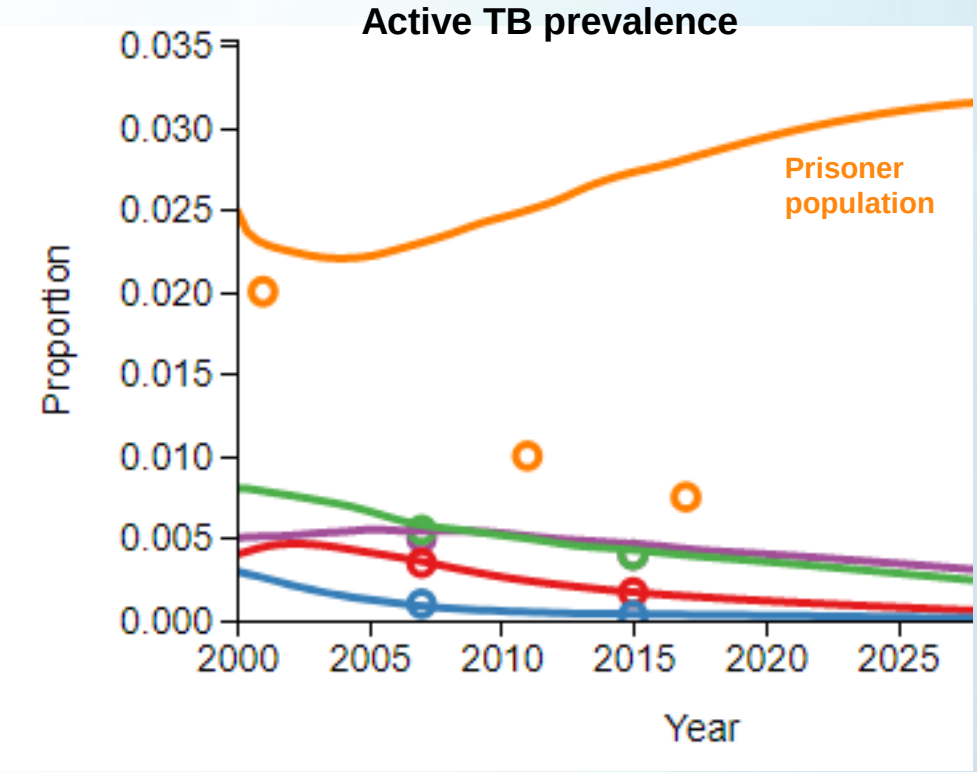
Recap on calibration

- When **calibrating** the model, you may choose to pay more attention to some data points than others
- If you need to adjust a calibration parameter too much (e.g. infectiousness of 100) to get a good calibration fit, it may be an indication of an issue with data inputs.
- Optima will **automatically interpolate to fill in missing data**

Optima TB

Calibration example 1: Active TB

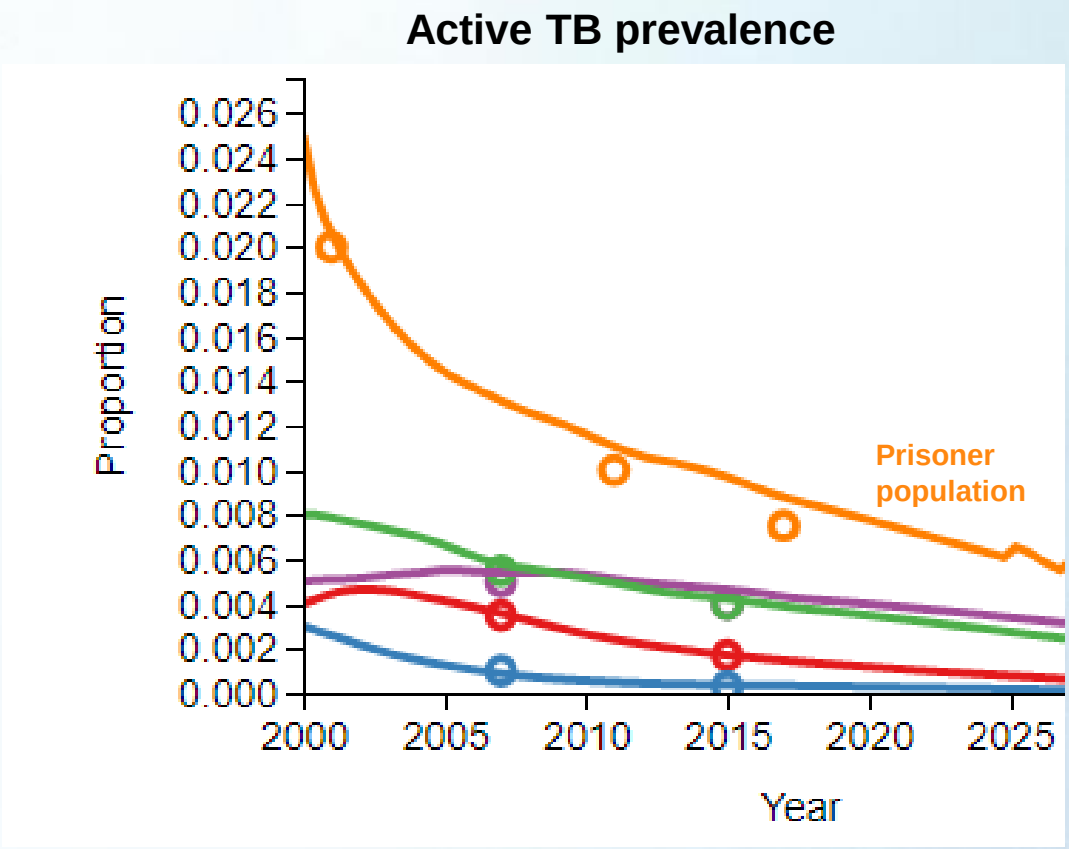
- Does the model output seem like a good fit for the prisoner population prevalence values?
- What parameters could you adjust to reduce Active TB prevalence in prisoners?



Calibration example 1: Active TB

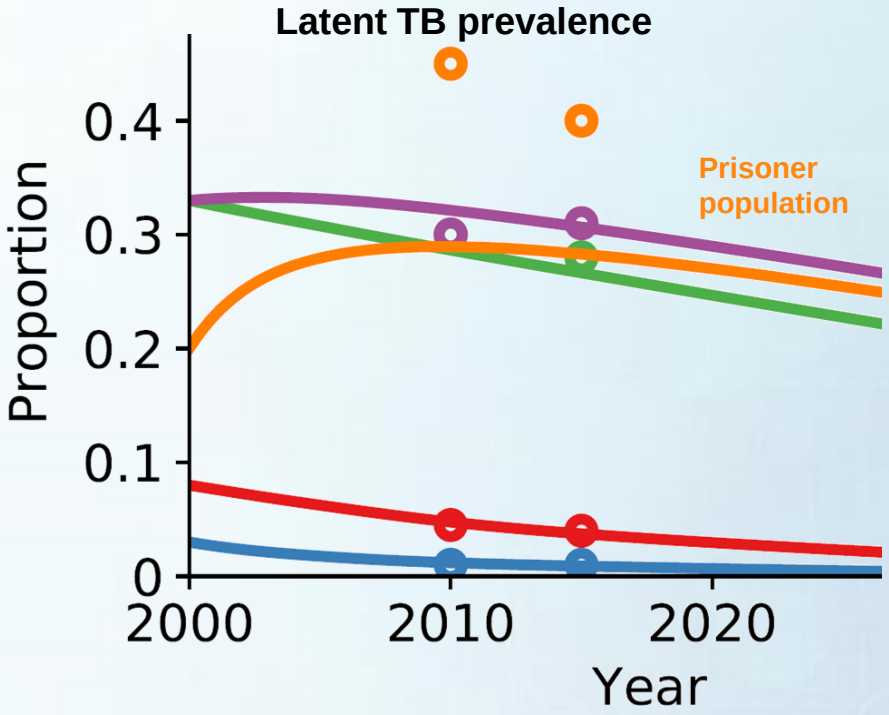
- Reduce **late latency departure rate** from 0.01 to 0.003

- Other parameters that could be adjusted:
  - Early latency activation rate
  - Relapse rate



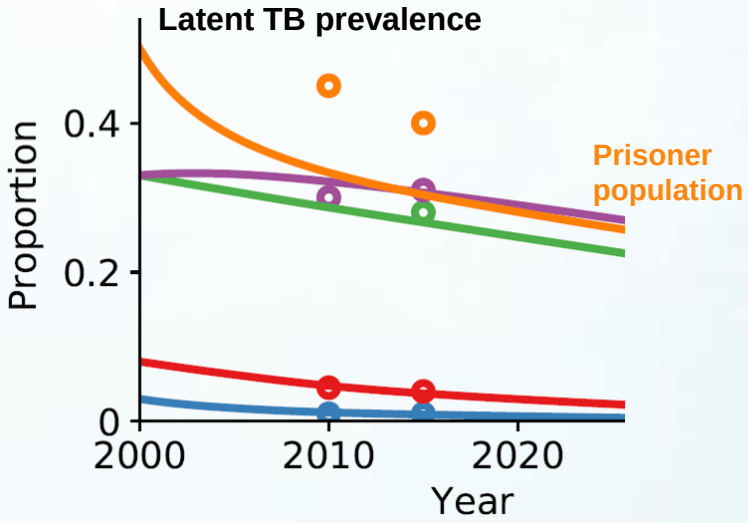
Calibration example 2: Latent TB

- Does the model output seem like a good fit for the prisoner population latent TB prevalence values?
- What parameters could you adjust to reduce latent TB prevalence in prisoners?

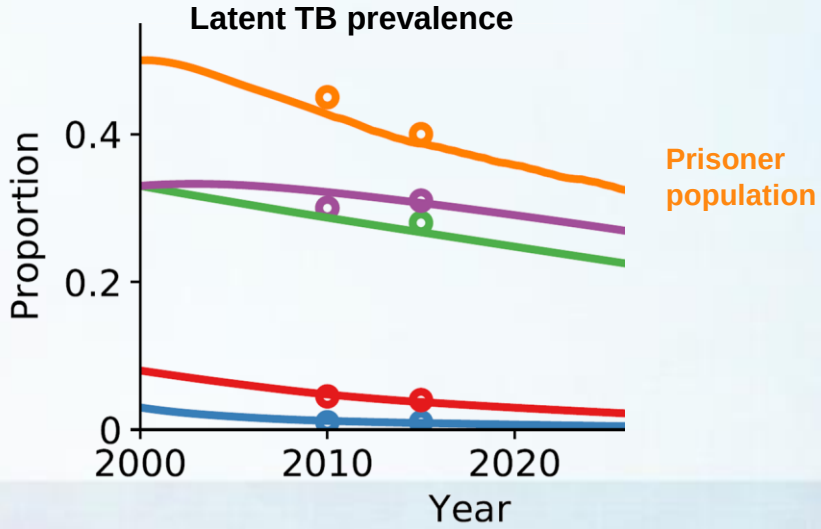


Calibration example 2: Latent TB

1. Increase **Initialization proportion of the population with latent TB** to 0.5



2. Increase **SP-DS infectiousness** to 10



Exercise

- Improve the calibration for your project

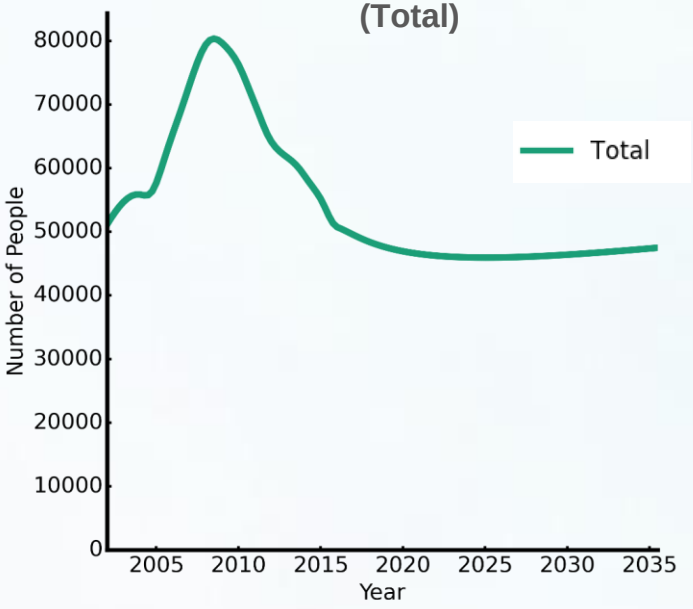
QUESTIONS?

Epidemic outputs from the model calibration

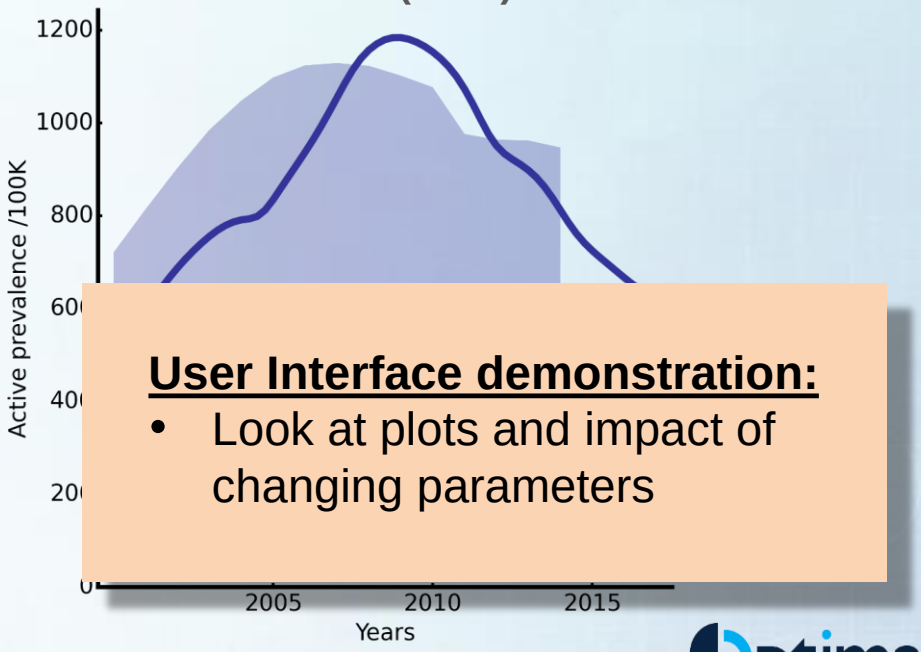
Trends and projections for incidence, prevalence, TB-related deaths, and other metrics

- Examine trends and projected values
- Compare against known data or estimates

Modeled number of all new TB infections*



Modeled prevalence of all TB infections*



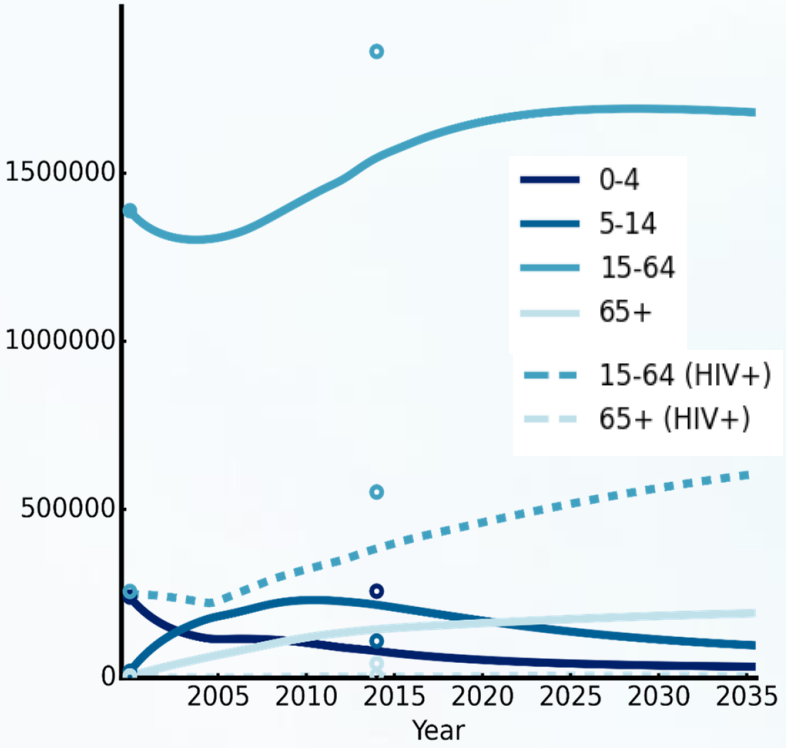
User Interface demonstration:

- Look at plots and impact of changing parameters

Modelled trends and projections for unreported metrics

Since the burden of latent TB is not clinically measured or known, Optima TB uses disease mechanics and active TB notifications to estimate the burden of latent TB

Modeled number of latent TB cases



O Data (based on Houben et al., 2016)

- In this example, latent TB infections are projected to increase among
  - Adults 15-64 years (HIV negative)
  - Adults 15-64 years (HIV positive)
- Resulting in increased latent TB infections among those 65 years and older as a result

Defining programs and parameters

Optima TB

Overview of TB programs

- Optima TB can accommodate programs that:
  - Directly target TB (i.e. diagnostic, treatment, prevention)
  - Less directly target TB (i.e. behavioral, awareness campaigns)
  - Do not target (non-targeted), are included in the budget but whose budget is kept constant in the optimization (i.e. management)
- For each program, require values for:
  - Coverage (number of people reached)
  - Unit cost
  - Spending
  - Impact on disease
- Program component can include programs not currently implemented, but may be included in future

Optima TB

Selecting programs for analysis

- Considerations for including programs in the analysis:
  - Does the program play an important role in the overall epidemic response?
  - Is there data on program coverage?
  - Is there past expenditure data?
  - Is there evidence to indicate the effect that the intervention has on rates of flow between model compartments?

- Important to keep the number of programs manageable, for the resulting analysis to be robust.
  - You can also add prospective or planned programs to this to be included in the analysis.

Optima TB

Example of programs

Prevention, screening and case finding programs	Treatment programs
Bacillus Calmette-Guérin (BCG) vaccination	DS-TB regimen
Contact tracing of drug sensitive (DS)-TB cases/isoniazid preventive therapy (IPT)	Old multidrug-resistant (MDR)-TB regimen
Contact tracing of DR-TB cases/IPT	Old MDR regimen with Bedaquiline (BDQ)
Mass screening at primary healthcare (PHC)	New MDR-TB regimens (including short-course)
Enhanced mass screening at PHC	Old extensively drug-resistant (XDR)-TB regimen
Screening outreach in high-risk areas	New XDR-TB regimen with BDQ
Active case finding among HIV populations	
Passive case finding across all populations	

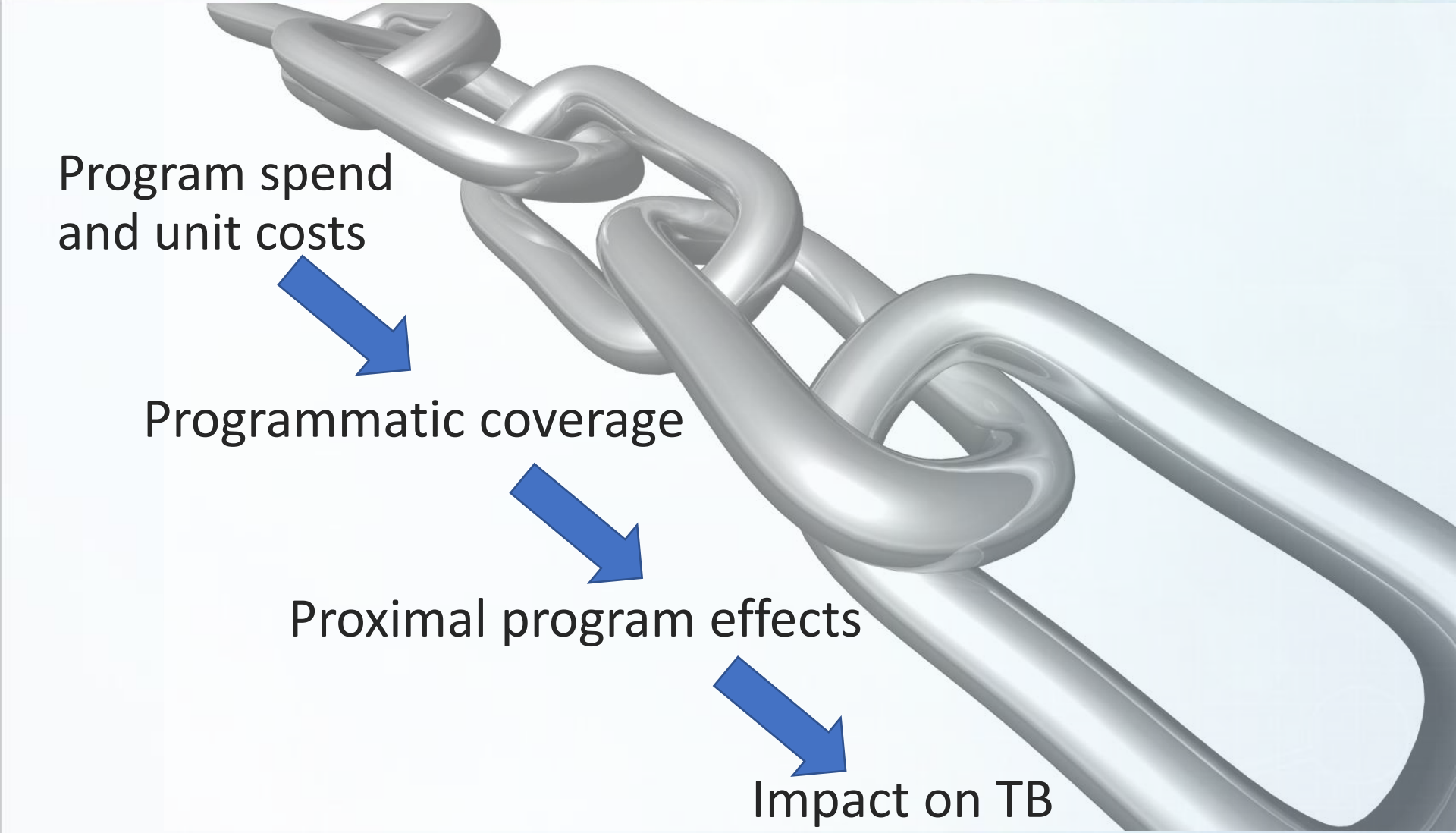
Optima TB

Exercise: review demo project program book

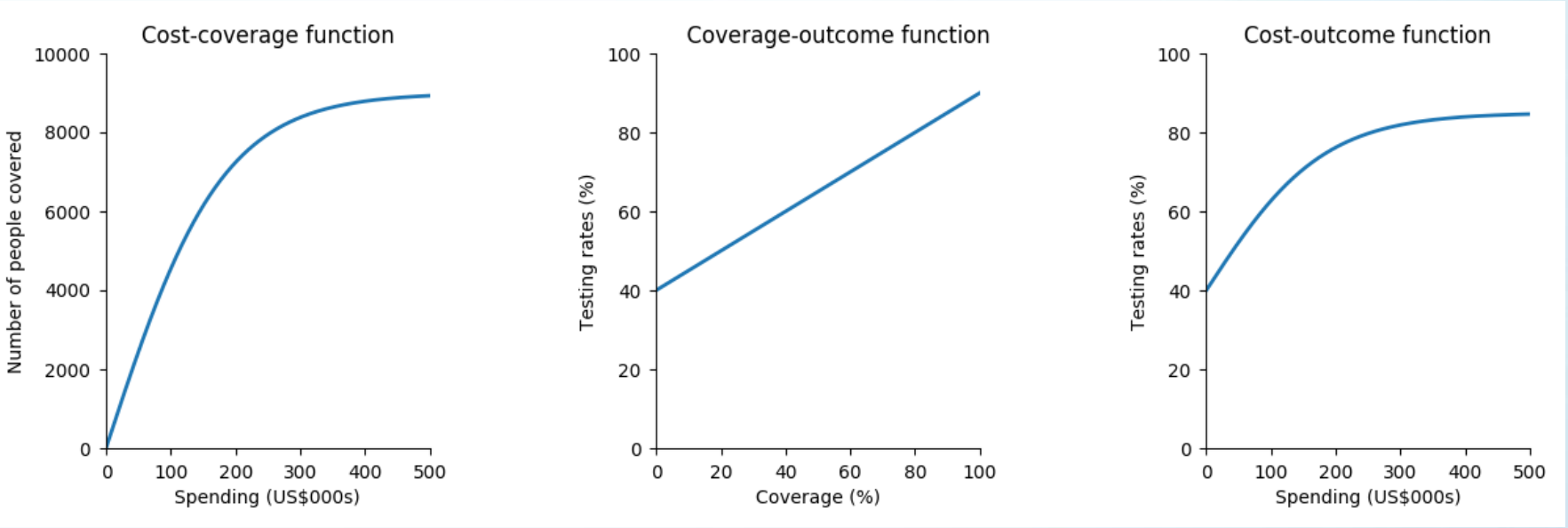
1. Program targeting
   - **Who** does the program apply to?
   - Specify by populations and by compartments
2. Spending data
   - **How many** people does the program cover?
   - Specify by total spending, unit cost, and coverage
   - How many people could the program cover if scaled up?
   - Specify by capacity constraints and saturation
3. Program effects
   - **What impact does the program have** on each person covered?
   - Specify by what value the *parameter* should have for a person who is not covered by any programs, and what value if they are covered by each program
   - Specify how programs interact

Optima TB

How are interventions modelled?



Program spending → coverage → outcomes



- Cost-coverage function: based on the average cost of program delivery (measured at current coverage levels) and information on capacity constraints
- Coverage-outcome function: based on the outcome under no public investments and an assumed maximal outcome

Exercise: create a new program book

- Select appropriate programs from the default program list
- Select a limited list with no more than two different treatment modalities for each strain

Optima TB

Program targeting in Optima TB

- For each program modeled, targets must be specified:
  - **Targeted populations**: the populations impacted by this program
    - For example, a program for testing and treatment in prisons would only be targeted at prisoners.
  - **Targeted model compartments**: if a particular program is targeted to a compartment this should be specified
    - For example, a testing program is typically targeted to the “undiagnosed” compartment

Spending data for programs

- **Total spend**
  - Annual program spending for any years
- **Unit cost**
  - Includes all costs for one person to receive service for a given program (e.g., cost per person initiating treatment, cost per person diagnosed, cost per vaccine administered)
- **Capacity constraints**
  - Maximum number of people that could be covered by this program (e.g. number of hospital beds)
- **Saturation** (demand constraint)
  - The largest possible proportion of the target compartment(s) that could be covered by a program in a given year
- **Coverage**
  - Number of people covered by a program in recent years (for cost function plotting purposes only, coverage is not used by the model)

Optima TB

Cost functions: requirements and data sources

Data requirements

1. Cost: total spending and unit costs

   Data sources

   - Global Health Unit Cost Repository (once populated for TB)
   - Country reports
   - Other (e.g. World TB reports)

2. Coverage: number of people reached under:

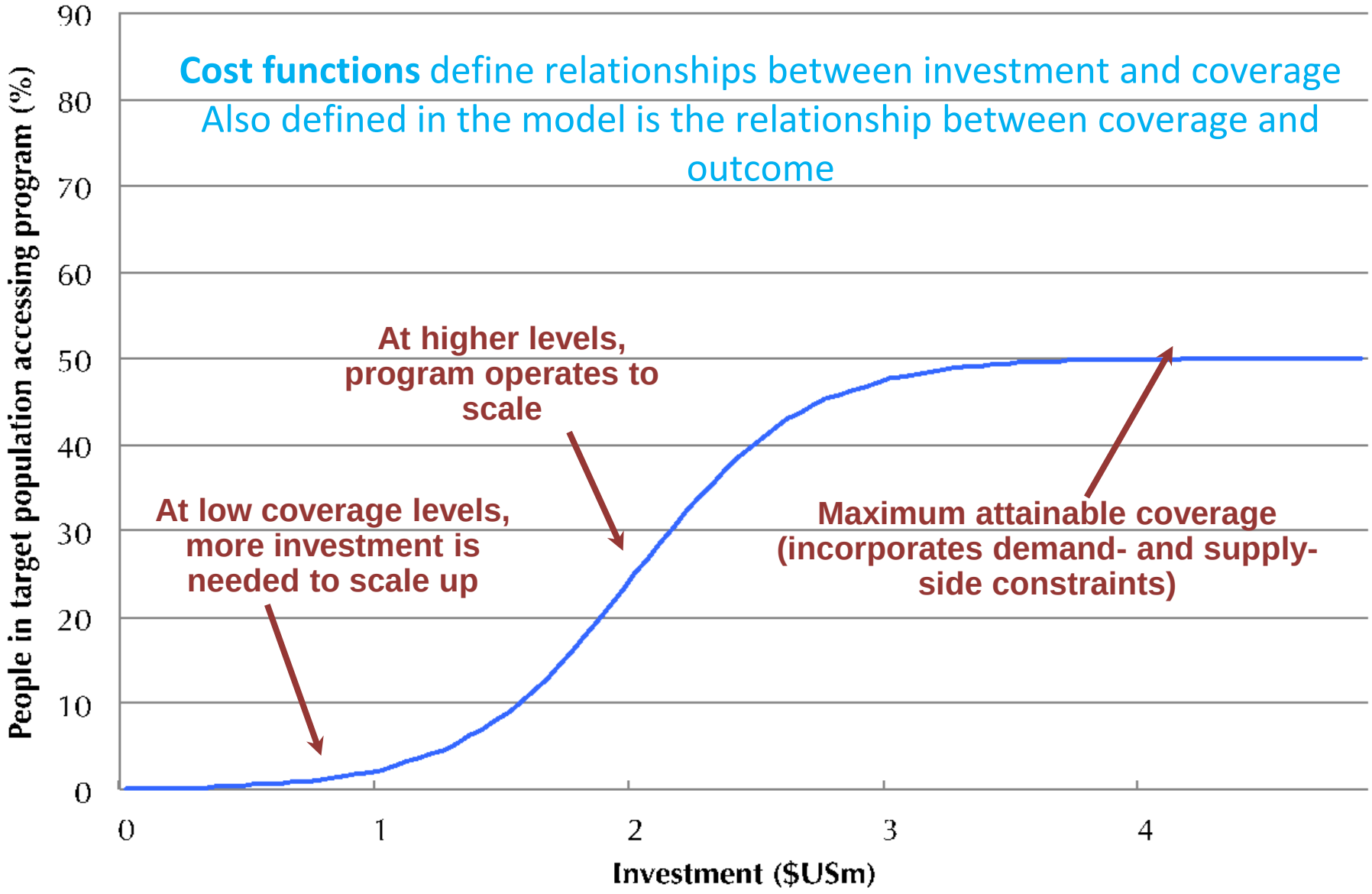
   a. See program book

   Data sources

   - National TB program reports

Optima TB

Modeling targeted TB programs

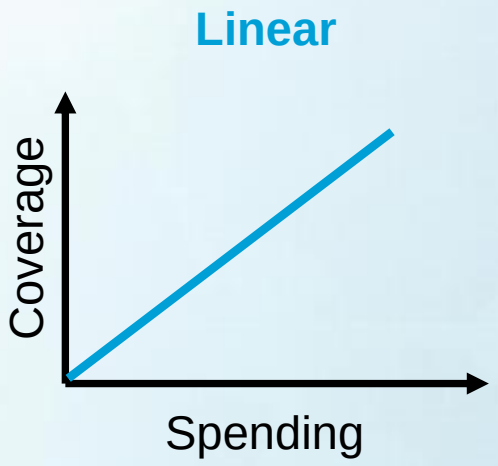


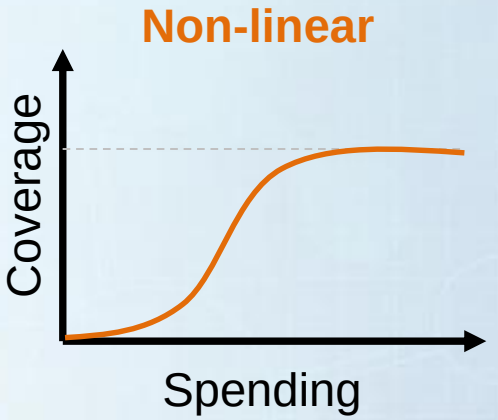
Cost functions

Cost functions relate program costs to population coverage and outcomes.

Cost-coverage curves

- Relates program spending to program coverage
- Cost-coverage curves can be:
  - **Linear**: slope represents a single unit cost, or
  - **Non-linear**: slope represent scale-up, stable implementation, and increasing effort in reaching additional people
- In the absence of data to inform non-linear cost-coverage curves, **linear** cost-coverage curves are assumed





Optima TB

Examples of TB diagnostic programs

Passive case finding	Assumption		2016	2017
Total spend		OR	700,000	600,000
Unit cost	1000	OR		
Capacity		OR		
Saturation	0.25	OR		
Coverage		OR	700	600

Contact tracing	Assumption		2016	2017
Total spend		OR	160,000	240,000
Unit cost	2000	OR		
Capacity		OR		
Saturation	0.5	OR		
Coverage		OR	80	120

Support will be provided for completing the Optima TB program book

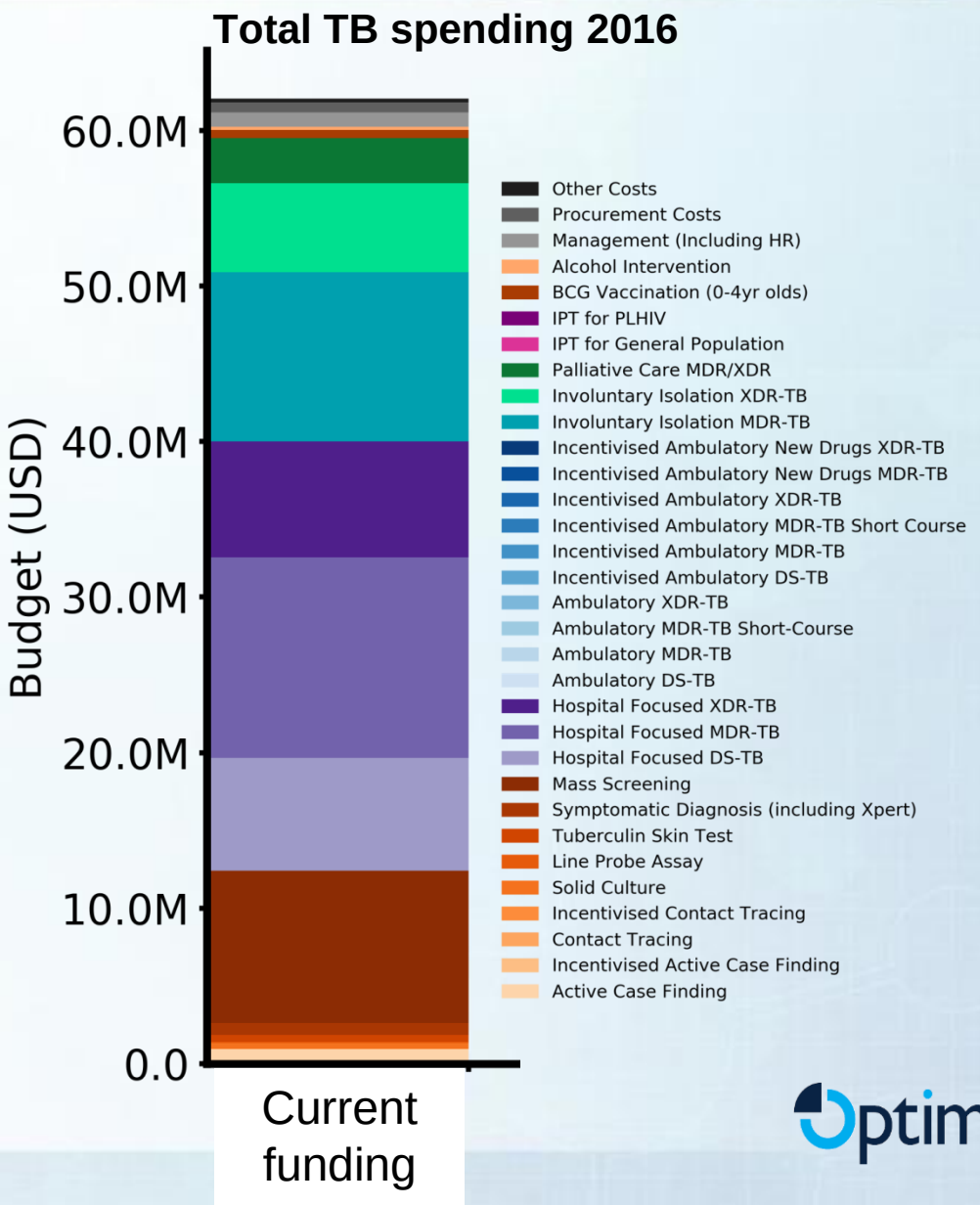
SP-DS annual probability of diagnosis	Baseline value	Coverage interaction	Impact interaction		BCG	PCF	ACF
Children 0-4	0	Additive	Best			0.96	0.96
Children 5-14	0	Additive	Best			0.96	0.96
Adults 15-64	0	Additive	Best			0.96	0.96
Adults 65+	0	Additive	Best			0.96	0.96
Prisoners	0	Additive	Best			0.96	0.96

Optima TB

TB program spending

- Can be reported directly (top-down costing)
- Alternatively, can be reconstructed from unit costs and program coverage (bottom-up costing)

- **Example: TB spending**
- Total national TB spending was 61 million in 2016



Recap: TB programs

- Programs can include:
  - Testing
  - Treatment
  - Prevention
  - Fixed or overhead costs (non-targeted programs not considered in the optimization)
- All programs require spending and unit cost data, and coverage data is recommended to ensure consistency
- New programs can be included that are yet to be implemented
- Programs with epidemiological impact also require data on:
  - Effectiveness of screening (for screening programs)
  - Adherence to treatment (for treatment programs)
- Spending can be reported directly from country or generated from unit costs multiplied by coverage

Optima TB

QUESTIONS?

Cost Functions

Effect of programs on the TB response

To model the effect of TB programs on the epidemic, the first step is to relate changes in program **spending** to changes in program **coverage**, and changes in program **coverage** on **outcome** using **cost functions**.

Optima TB

Notes

- Suggested **currency** (for consistency): USD
- **Any** currency can be used, however consistently use the same currency throughout the entire project
- Model does *not apply* inflation or discounting
  - These adjustments to spending output can be made *outside* the model
- Typically includes transportation, personnel, and other overhead costs per person

Definitions of cost

- **Unit** cost
  - total program cost divided by the number of people covered
  - Total cost/number of people covered
  - E.g. $100/10 = unit cost of $10

- **Marginal** cost
  - cost of covering one more person

- Costs typically should include all costs such as HR, management, personnel that **would not otherwise be incurred** if the program did not exist.

Optima TB

Defining unit cost in Optima TB

- Unit cost is the **cost per person** in the **target population(s)** who is **covered by the intervention**, in order to achieve the listed outcome of the intervention for that person.

- BCG vaccination
  - Target population is susceptible 0-4 year olds
  - Unit cost is cost per susceptible 0-4 year old who is given a vaccination
  - Program effect is that one person receives a vaccination

- Diagnosis through passive case finding
  - Target population (can be) all undiagnosed people with any smear/strain combination
  - Unit cost is cost per undiagnosed person with any smear/strain combination who is tested
  - Program effect (can be) that 0.87 people are diagnosed based on the false negative rate of 0.13

- Possible to define testing programs in different ways

Optima TB

Calculating unit costs: **Top down calculation**

Takes overall expenditures for a program and then allocates costs using formulae.

- Example:
  - Program budget = $1million
  - Number of people *diagnosed* = 100
  - Estimated false negative rate in testing: 13%
  - Number of people *covered* = 100*(1/0.87) = 115
  - **Unit cost = $1m/115 = $8,700**

Optima TB

TB program costing

- Unit costs should include all costing components for one person to receive service for a particular TB program
  - This includes transportation, personnel, and other overhead costs per person

- **For diagnostic programs**
- Testing program interventions
  - E.g. 'symptomatic diagnosis' includes:
    - Screening costs
    - Chest X-ray
    - GeneXpert
    - 2x sputum smear microscopies
    - 2x culture test, or 1x culture and 1x line probe assay (LPA)
- Effectiveness of program reflected in 'detection probability':
  - Yield (of all people screened, how many cases identified)
  - Test sensitivity (how many true positives)

Optima TB

TB program costing (continued)

- Unit costs should include all costs for one person to receive a given TB program service
  - This includes transportation, personnel, and other overhead costs

For treatment programs:

Cost for person to complete an entire treatment course

- Typically includes:
  - In-patient and out-patient costs
  - Drug costs
  - Other measures, including modality related costs
- Measures included:
  - Adherence
  - Efficacy
  - Duration

Optima TB

Treatment cost components

		Costs of care	Other costs		Total non-drug costs	Drug costs	Total costs	
Modality	**Treatment regimen group**	**Total**	**Food packages**	**Incentives**		**Full course**	**Full course**	**Annualized**
Current practice								
Hospital-based	DS treatment	2491.52	63		2,555	55	**2,610**	2609.7
Hospital-based	MDR	10170.43	205		10,376	3,782	**14,158**	8612.8
Hospital-based	XDR	12646.19	237		12,883	7,600	**20,483**	10383.8
Involuntary isolation	MDR	17700.00	0		17,700	3,782	**21,482**	13068.4
Involuntary isolation	XDR	21240.00	0		21,240	7,600	**28,840**	14620.3
Alternative modalities								
Standard ambulatory	DS treatment	1735.40	87		1,823	55	**1,878**	1877.8
Standard ambulatory	MDR - long	6121.77	292		6,414	3,782	**10,196**	6202.7
Standard ambulatory	MDR - short	3370.36	150		3,520	1,000	**4,520**	4520.5
Standard ambulatory	XDR	7493.35	348		7,841	7,600	**15,441**	7827.7
Incentivized ambulatory	DS treatment	1735.40	87	338	2,160	55	**2,215**	2215.4
Incentivized ambulatory	MDR - long	6121.77	292	1129	7,543	3,782	**11,325**	6889.2
Incentivized ambulatory	MDR - short	3370.36	150	580	4,100	1,000	**5,100**	5100.0
Incentivized ambulatory	XDR	7493.35	348	1342	9,183	7,600	**16,783**	8508.0

*Compared to Schnipple et al., 2012 for inpatient/MDR-TB costs, Cox et al., 2015 for outpatient costs, Guthrie et al., 2015 for patient management costs and Aurum Institute, 2016; Pooran et al., 2013 for other monitoring costs

Optima TB

Variable unit costs

- Relationships between costs and coverage are generally nonlinear, because costs change depending on the level at which the program is operating

- Optima allows users to **specify** programs with costs that vary depending on coverage

- We expect **increasing marginal costs** as programs **expand coverage** to increasingly hard to reach populations (saturation)

Calculating unit costs: **Bottom up calculation**

Uses detailed activity and program component costs at the service level to estimate unit costs.

- Estimated active prevalence in population = 1%
- Number of people needed to be screened to screen one person with TB = 100
- Cost per screening = $10
- Estimated cost per person with TB who is screened = $1000
- Cost per diagnostic test A = $40
- Cost per diagnostic test B = $300
- Proportion of people with TB who need each test = 90%, 20% (some need both)
- Average unit cost per person = 90% * $40 + 20% * $300 = $96
- **Unit cost = $1096**

- See unit cost calculation guide

Components	Cost	Number	Sensitivity	Specificity
Symptom screening	4.02	227,552		
Xray screening	4.56	151,701		

Modalities	Cost per screening event (EUR)				Coverage & outcome				Total cost (EUR)	Cost per person diagnosed
	Symptom screening	Xray screening	Other	Total	Total screened	Diagnosed	Yield (%)	Share of total	Total	
Contact tracing	4.02	3.04		7.06	23,047	277	1.2%	6.5%	162,703	588
Active case finding	4.02	3.04		7.06	36,672	348	1.0%	8.2%	258,891	743
Active case finding - NGO outreach risk pop	4.02	3.04	5.00	12.06	10,000	95	1.0%	2.2%	120,596	1,269
Passive case finding	4.02	3.04		7.06	157,832	3,515	2.2%	83.0%	1,114,233	317

Optima TB

Target compartments effect unit cost

Unit cost per latent treatment course = $1000

- Mass screening and treatment
  - Target compartments = Susceptible, Vaccinated, Early latent, Late latent
  - Unit cost = $1000
  - Effect = people with latent TB initiate treatment for latent TB

- Contact tracing
  - Target compartment = Early latent TB
  - On average, 50% of people treated have latent TB
  - Unit cost = $1000 / 0.5 = $2000
  - Effect = people with latent TB initiate treatment for latent TB

Optima TB

Understanding the target populations

- Exercise
  - Review the program targeting tab in the program book
  - Review the program effects tab in the program book
  - Complete the unit cost entry for each program

Optima TB

QUESTIONS?

Introduction to TB cascades

Optima TB

Context: Measurements of programmatic outcomes

Effective program delivery and **how to measure:**

- Dominant theme in health and development (also Paris Declaration on Aid Effectiveness, Accra Agenda for Action)
- Focus on **results** and how they can be achieved **most efficiently**

Multitude of systems in operation to collect/aggregate program results

In theory, these data are intended to enable organizations to **assess implementation:**

- which strategies and programs are effective
- identify elements of programs associated with better results
- demonstrate accountability to external stakeholders
- make decisions about allocating further funding

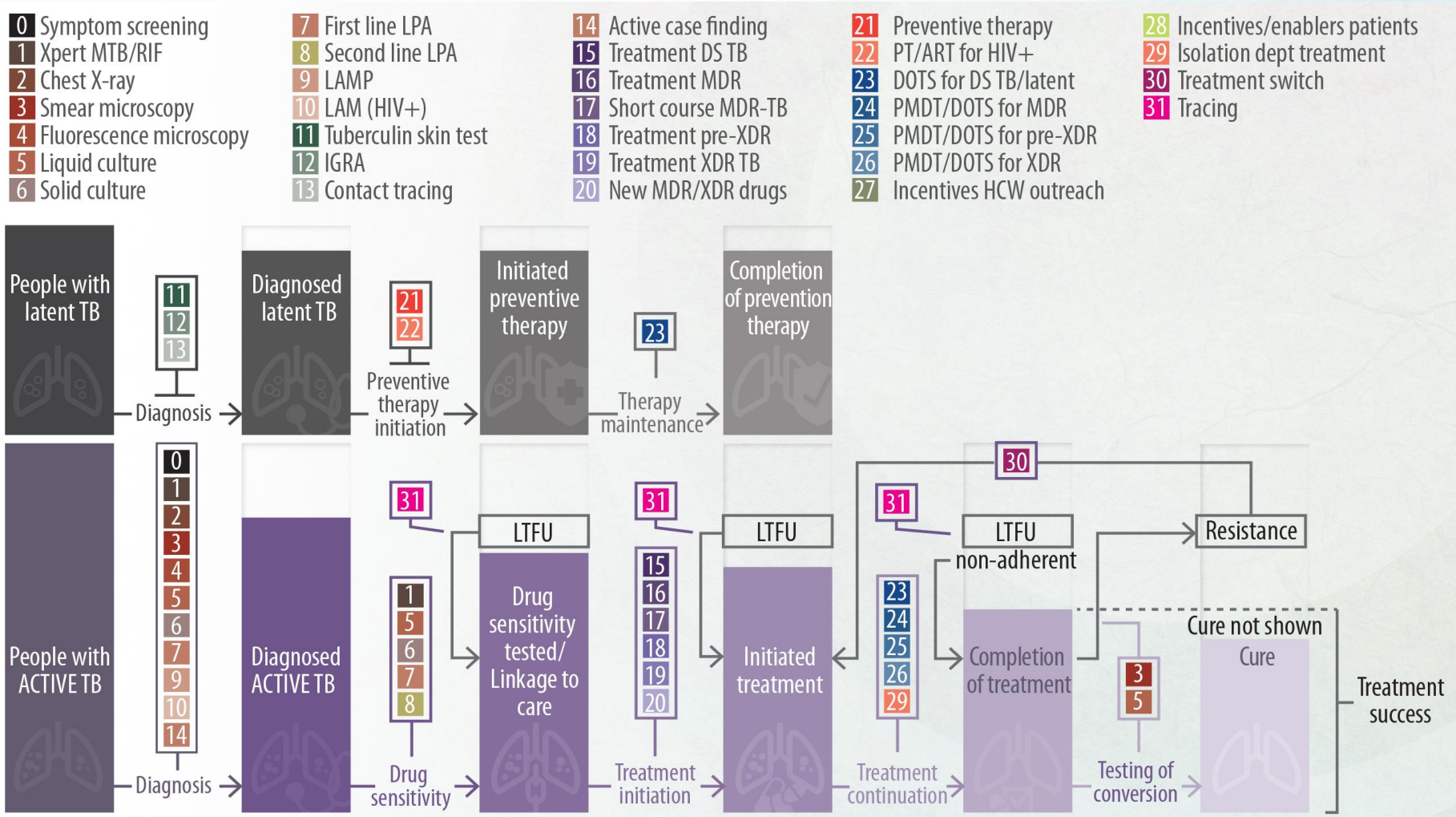
In practice, there is **a disconnect between the data being collected and the methods available for analyzing them.**

Why “Cascades”?

- Many service delivery processes composed of sequence of actions to happen (“cascade”)
- Cascade concept used to characterize **steps of engagement** involved in linking people into program/service
- Completion of cascade stages central to improved service delivery and health outcomes
  - Success at each stage increases the possible success at the next stage
- Critical to identify effective approaches to **improve results at each step** in cascade
- Must remediate big **breakpoints** in cascade—where biggest improvements can be made

Questions we ask

TB Implementation Cascade



TB implementation cascade in your context

- The TB cascade will be very context specific
- Certain modalities will be specific to certain cascade stages
- Not all modalities make sense or are available in all contexts
  - For example fluorescence microscopy
- Context specific modalities can be input into Optima as programs affecting steps in the cascade

Optima TB

TB implementation cascade in your context

Exercise: think through:

- What modalities are used or are planned on being used in your context?
- What data is available for cascade stages and how was this data derived?
  - For example, How is latent TB follow-up calculated?
- What evidence is there to inform the effectiveness of different modalities affecting steps across the cascade?
  - How effective is DOTS (Directly Observed Treatment, Short Course) in your context?
  - Are there peer-reviewed literature, reports, abstracts from your setting which measure program effectiveness?
  - If not from your setting, then from a comparable context(s)?

Optima TB

QUESTIONS?

Optima TB scenario analysis

Scenario analysis in Optima TB

Scenario analysis can be used to:

- Explore the impact of past spending, future anticipated increased or decrease spending
- Compare the impact of theoretical changes to the epidemic
- Compare the impact of different program assumptions
- Compare different model assumptions
- Many other factors can be examined using scenario analysis

Budget and coverage scenarios

- Specify spending or coverage amounts for each program within the scenario (compared to baseline ”business as usual”

- Results can be used to inform **strategic planning objectives and policy questions**

Optima TB

Examples of scenario questions

Scenario analysis allows exploration of the epidemiological impact and cost implications of changing coverage levels and/or prevention, diagnosis, and treatment modalities:

- **Scenario 1** explores the epidemiological impact of increasing coverage to meet national and global targets
- **Scenario 2** explores the potential cost savings of shifting from inpatient to outpatient modalities
- **Scenario 3** explores the impact of enhanced XDR-TB treatment and coverage

Optima TB

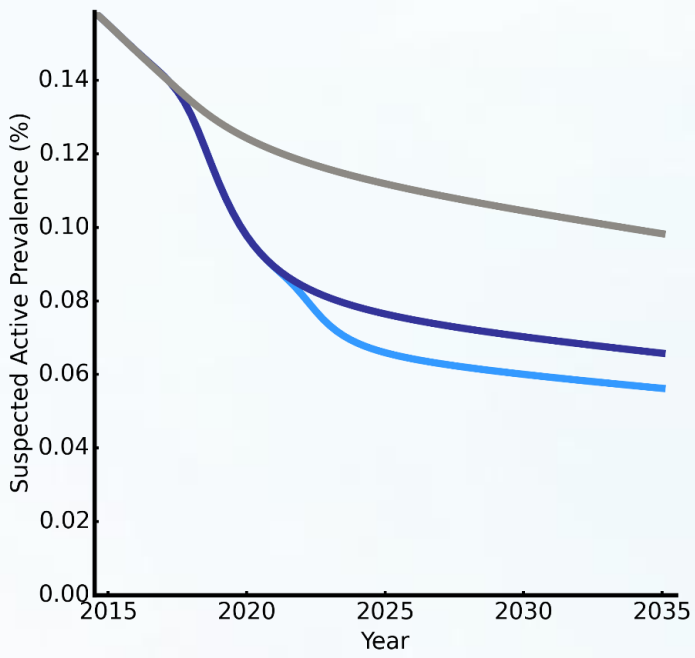
Scenario 1: Scaling up coverage to meet targets

	Most recent coverage	2020 NSP targets and global milestones*	2035 global End TB targets**
Proportion of all DS-TB diagnosed	76%	90%	95%
Proportion of all MDR-TB diagnosed and initiated on treatment	76%	90%	95%
Proportion of all XDR-TB diagnosed and initiated on treatment	76%	90%	95%
Proportion of DS-TB patients successfully completing treatment	87%	95%	98%
Proportion of MDR-TB patients successfully completing treatment	52%	75%	90%
Proportion of XDR-TB patients successfully completing treatment	38%	60%	80%
Timeframe for change to occur		**2017-2020*	***2021-2035*
Time frame for tracking impact:		**2017-2035*	***2017-2035*

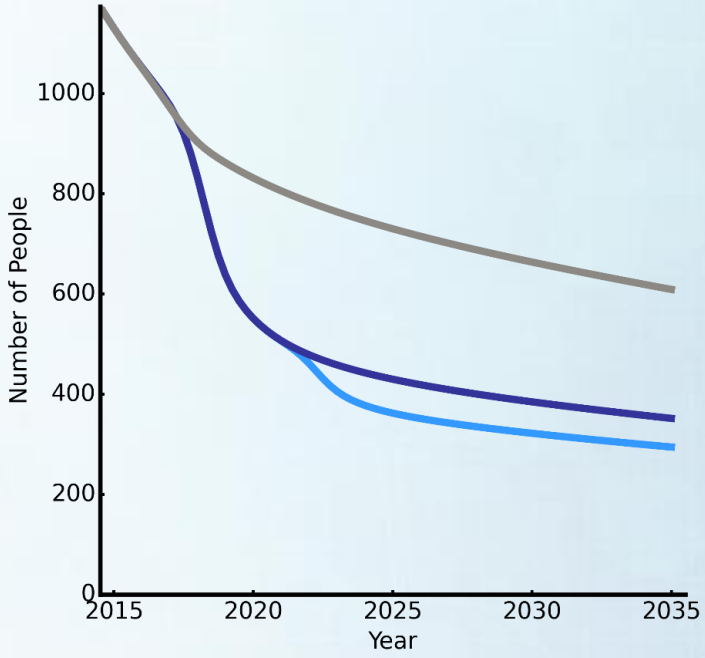
Optima TB

Achieving national and global diagnosis and treatment coverage targets reduces active TB cases and deaths (Scenario 1)

Estimated prevalence of active TB cases
(15-64 years)



Annual rate of TB-related deaths
(15-64 years)



Current coverage
NSP target and Global Milestones for 2020
End-TB targets for 2035

Optima TB

Impact from meeting coverage targets

Compared with most recent conditions:

- Scaling up to meet **2020** national targets and global milestones, it was project there could be an additional:
  - 40% fewer active TB infections
  - almost 30% fewer TB-related deaths

- Scaling up to meet **2035** global End TB targets;
  - Reduces active infections by 52% compared with most recent coverage
  - Averts 53% of projected deaths

- Scaling up to meet national and global goals will decrease the TB death rate relative to most recent coverage among PLHIV. However, persistently high death rates in this population remain a challenge.

Optima TB

Scenario 2: Shifting from inpatient to outpatient modalities

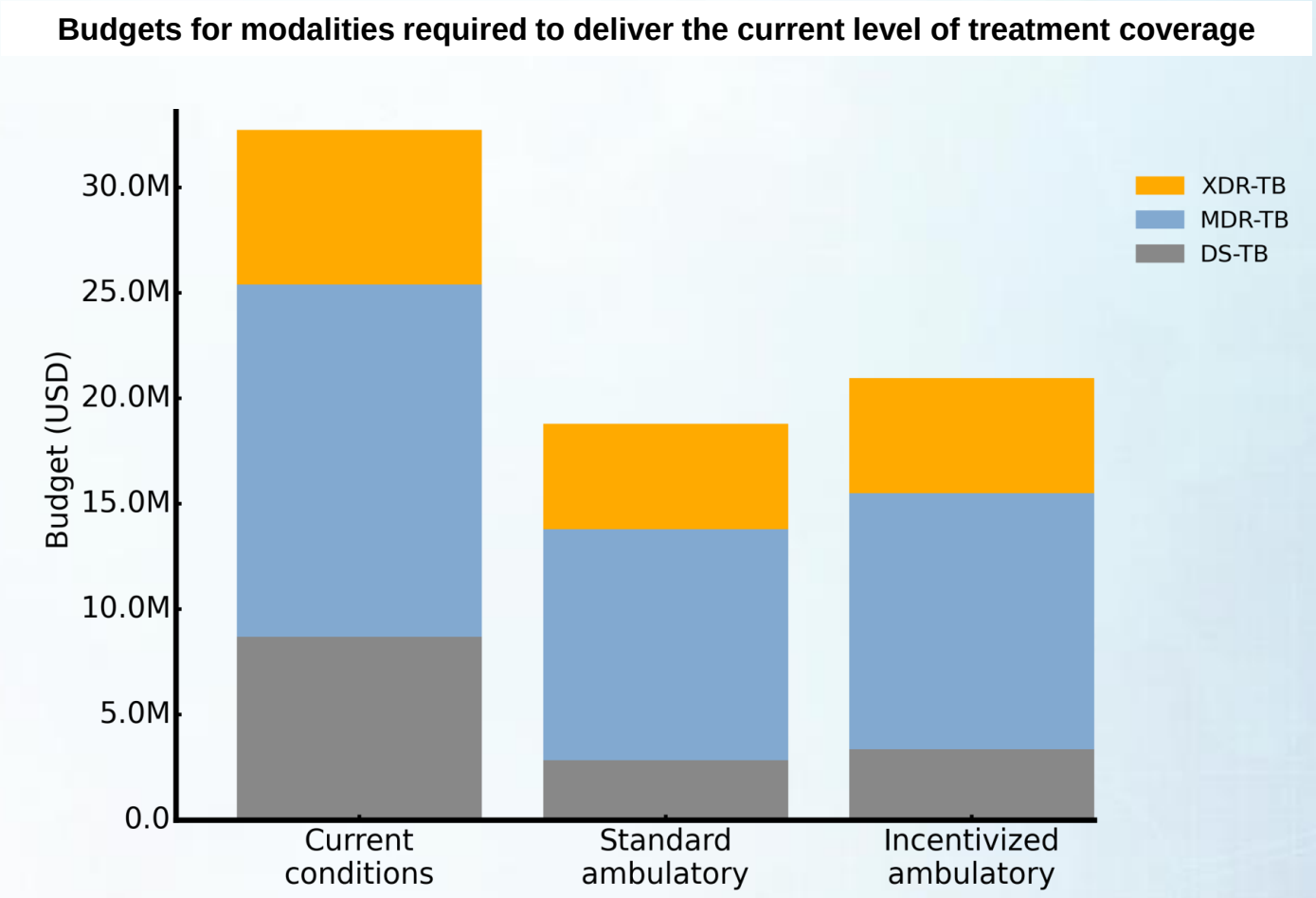
Program parameters:

- Decrease in the number of inpatient and outpatient days for ambulatory care, informed by the country and WHO recommendations
- Relative changes in treatment success rates depending on a given treatment modality are derived from literature (Bassili et al., 2013, Nguyen, 2016)

		Current (Hospital-based)	Standard ambulatory	Incentivized ambulatory
Total days	DS treatment	180	180	180
	MDR-long	600	600	600
	MDR-short	-	315	315
	XDR	720	720	720
Number of outpatient days	DS treatment	120	166	166
	MDR-long	390	555	555
	MDR-short	-	285	285
	XDR	450	660	660
Number of inpatient days	DS treatment	60	14	14
	MDR-long	210	45	45
	MDR-short	-	30	30
	XDR	270	60	60
Relative increase in treatment success rate	All (DS, MDR-long, MDR-short, XDR)	Standard (baseline)	No change	16%

Optima TB

Shifting modalities reduces spending but maintains effectiveness



Scenario 3: Enhanced XDR-TB regimens and coverage

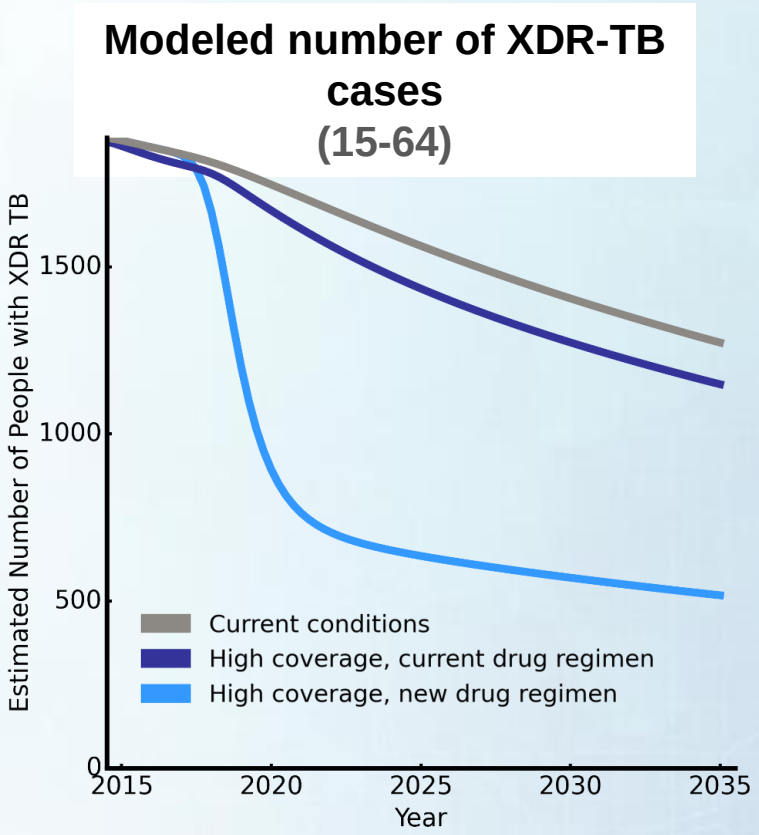
- XDR-TB has lower diagnosis and successfully completed treatment rates than other drug-resistant forms of TB
- New alternative XDR drug regimens are available and have higher success rates (linezolid, clofazimine, bedaquiline)
- Examine whether to minimize XDR, effort should be on identifying XDR cases alone, or whether new drug regimens would help?

	2015 conditions	Increased coverage of 2015 XDR drug-regimen	Increased coverage of new XDR drug-regimen
Percent of XDR-cases correctly diagnosed	56%	90%	90%
Percent initiated on treatment	85%	97%	97%
Percent of XDR-TB cases treated with 2015 regimen	100%	100%	
Percent of XDR-TB cases treated with new drug regimen			100%
Treatment failure rate and loss to follow-up, with 2015 regimen	62%	62%	
Treatment failure rate and loss to follow-up, with new regimen			40%
Treatment success rate, current regimen	38%	38%	
Treatment success rate, new drug regimen			60%
**Timeframe for tracking impact: 2017-2035*			

Optima TB

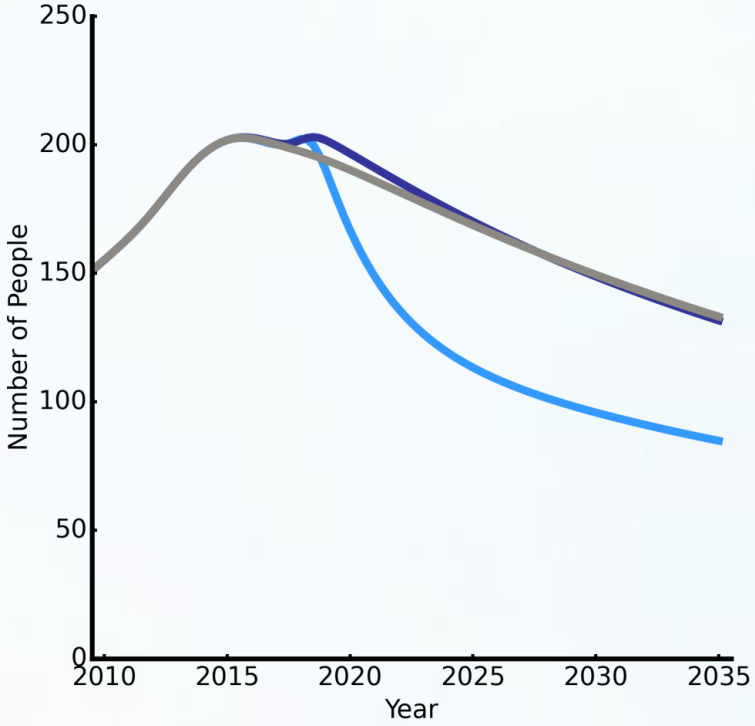
Enhancing XDR treatment regimens and coverage reduces prevalence

- The provision and increased coverage of new XDR drugs reduces the prevalence of XDR cases by 65%
- Increased coverage through the correct diagnosis of XDR cases and increase linkage to care is important
- Higher treatment success rate of new drug regimen contributes to reducing the number of XDR cases
- XDR treatment requires sustained support beyond most recent NSP funding period to make an impact by 2035

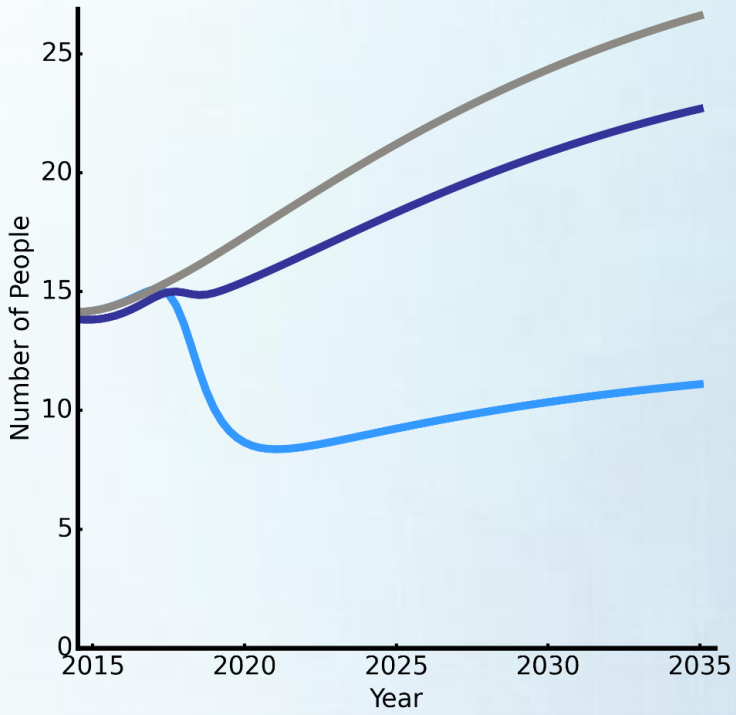


XDR-TB-related deaths averted by drug regimen (Scenario 3)

Annual number of XDR-related TB deaths
(15-64 years)



Annual number of XDR-related TB deaths
(PLHIV)

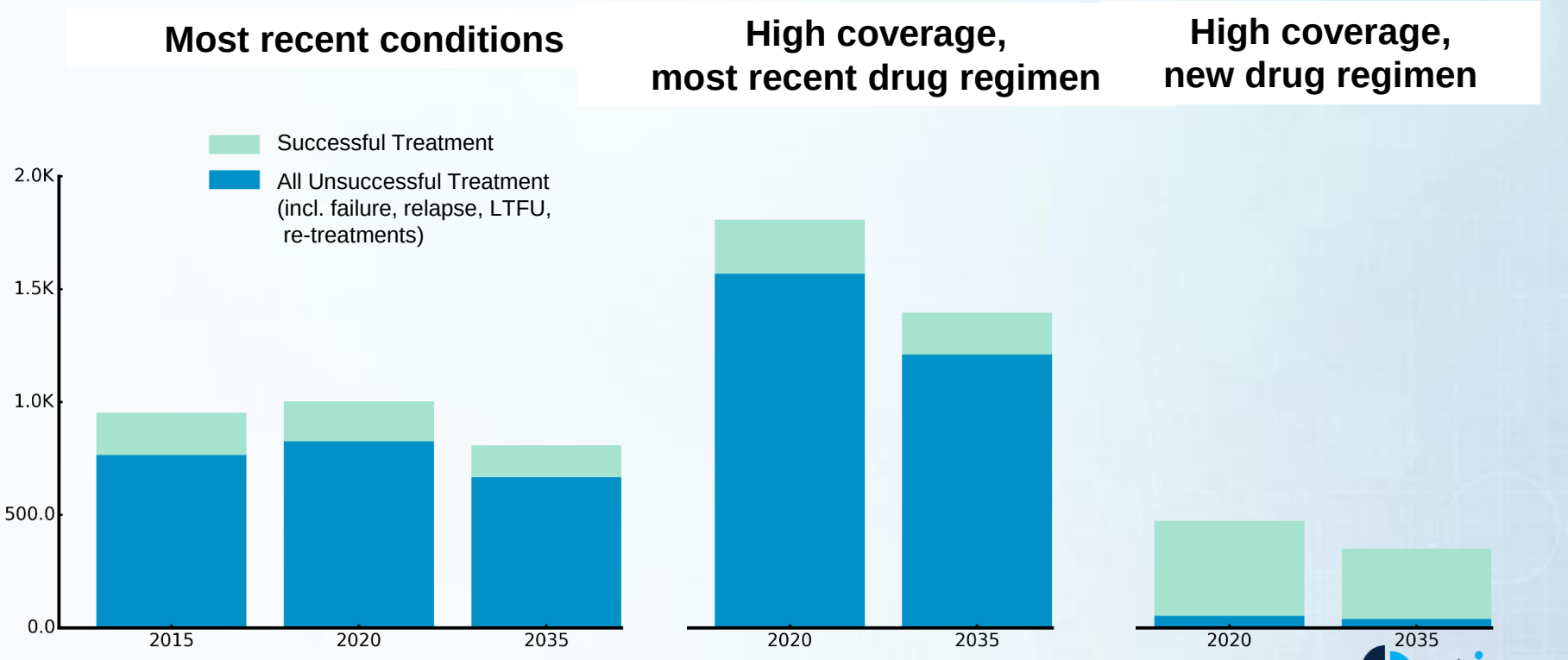


Current conditions
High coverage, current drug regimen
High coverage, new drug regimen

Optima TB

Treatment initiation, completion, and failure (Scenario 3)

- Increased coverage and new drug-regimens significantly improve treatment initiation and completion
- New drug-regimens result in the highest treatment completion rates
- Patients covered by new drug-regimens are less likely to relapse or undergo re-treatment, ultimately decreasing the number of treatments initiated



Scenario 3: Findings

- The improved provision of MDR/XDR drug-regimens is recommended by the 2017 GLC report (Gurbanova, 2017)
- The GLC report states a need for 400 additional regimens for MDR-TB patients, which include new and repurposed drugs (e.g. Bedaquiline, Linezolid, Clofazimine), to meet demand in 2017-2018 – and an extra 250 courses to cover patients previously treated with XDR-TB (Gurbanova, 2017)
- New drug-regimens, consisting of new and repurposed drugs, can improve treatment outcomes:
  - **Linezolid** results in significantly higher rates of sputum-smear conversion and overall treatment success for MDR-TB (Sotgiu et al. 2012).
  - **Clofazimine** and **Bedaquiline** demonstrated promising outcomes for XDR-TB treatment despite the need for more evidence (Gualano et al., 2016)
- Bedaquiline is currently funded by the Global Fund to fight AIDS, Tuberculosis and Malaria. The scale-up and sustained provision of effective treatment regimens will require financial and political commitment from the national government

Optima TB

Recap: Scenarios

- Scenarios help estimate the impact of:
  - Changing rates (i.e. testing and treatment; proportion of MDR cases)
  - Changing coverage, or
  - Changing program budget
- Scenarios are **flexible** and can be tailored to address **context specific questions**
- Require: additional information, specific to scenarios

Optima TB

QUESTIONS?

Optima TB optimization analysis

Optimizing resource allocation to best meet objectives

How should the budget be allocated amongst these ‘n’ programs, modalities, and delivery options, considering their interactions with synergies and limitations?

Optima TB

Wanting to achieve maximum impact

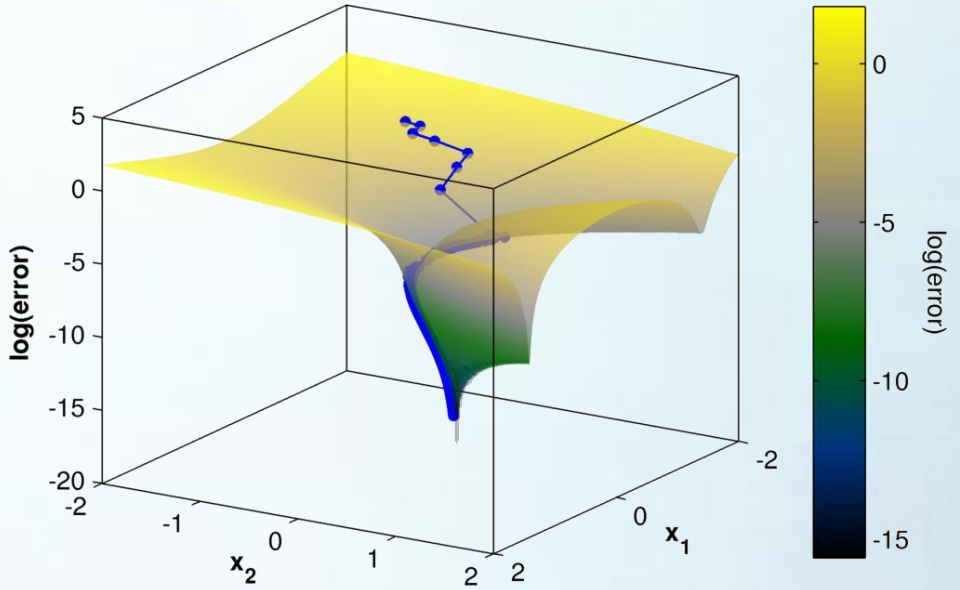
- National strategic plans often have multiple objectives to be achieved before the end of the strategy timeframe
  - For example:
    - 60% reduction in TB incidence by 2022 (compared with most recent levels)
    - 50% reduction in TB-related deaths by 2020 (compared with most recent levels)
    - Attain universal treatment coverage by 2035
  - Simultaneously get as close as possible to all national strategic plan targets with the funding available

Theory of optimization

Aim: For a given amount of money, what's the best outcome we can achieve?

"Best" could mean:

- Fewest infections
- Fewest deaths
- Lowest costs
- All of the above

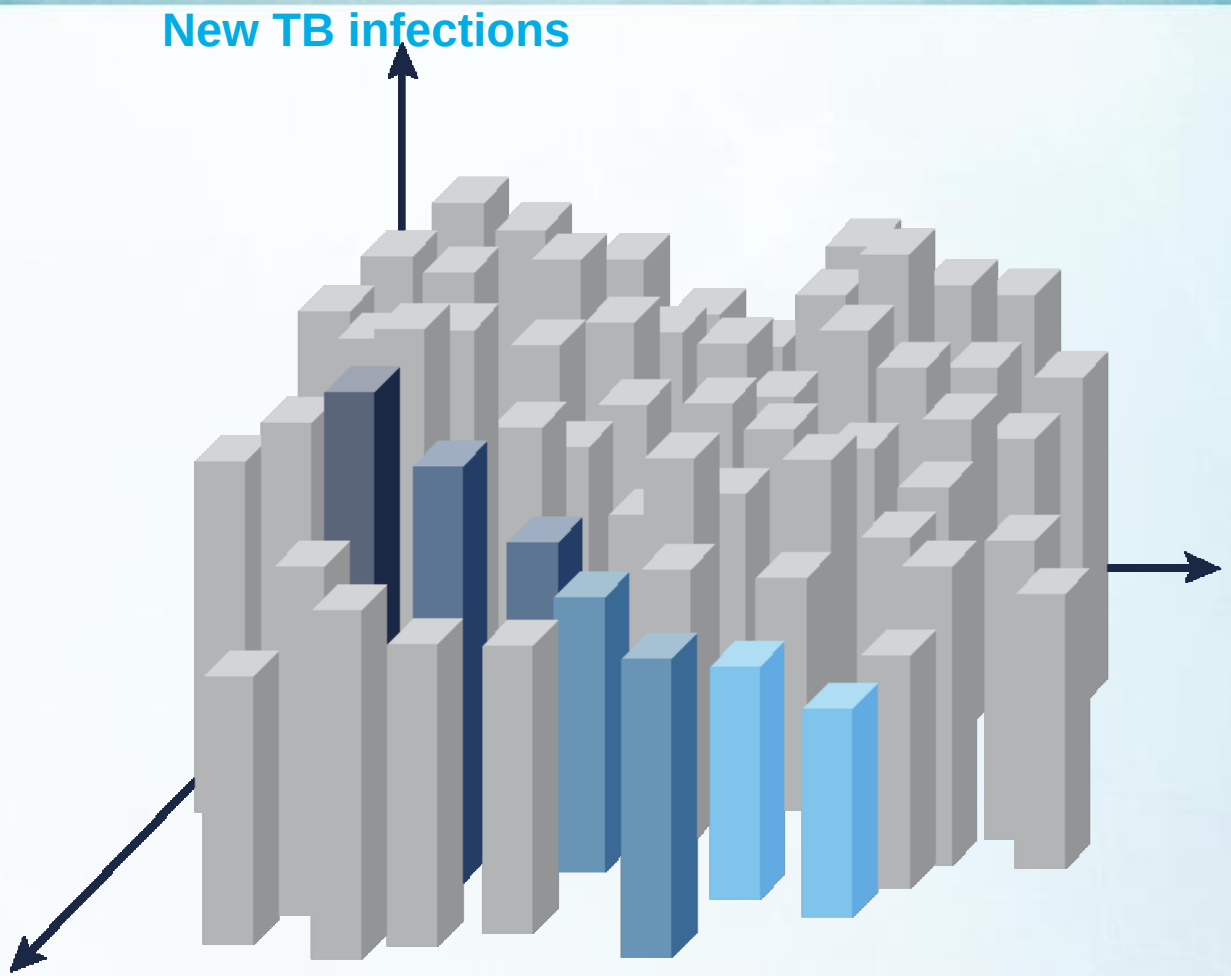


Formally:

For resource vector $\mathbf{R}$ such that $\sum \mathbf{R} = \text{const.}$ and outcome $O = f(\mathbf{R})$, find $\mathbf{R}$ that minimizes O.

Optima TB

Optimization between just two programs



An efficient Adaptive Stochastic Descent algorithm is applied

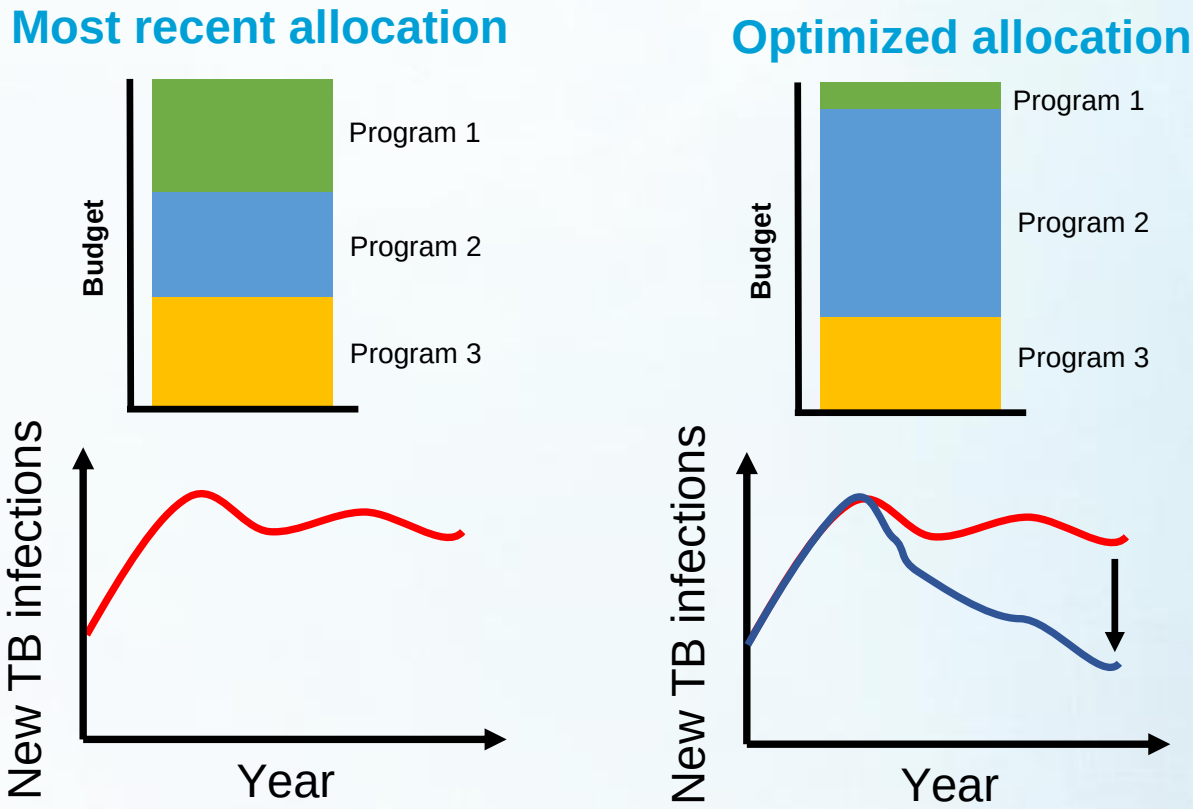
Adaptive: learns probabilities and step sizes
Stochastic: chooses next parameter to vary at random
Descent: only accepts downhill steps

Kerr et al. 2018

Optima TB

Optimizing resource allocation: What does it do?

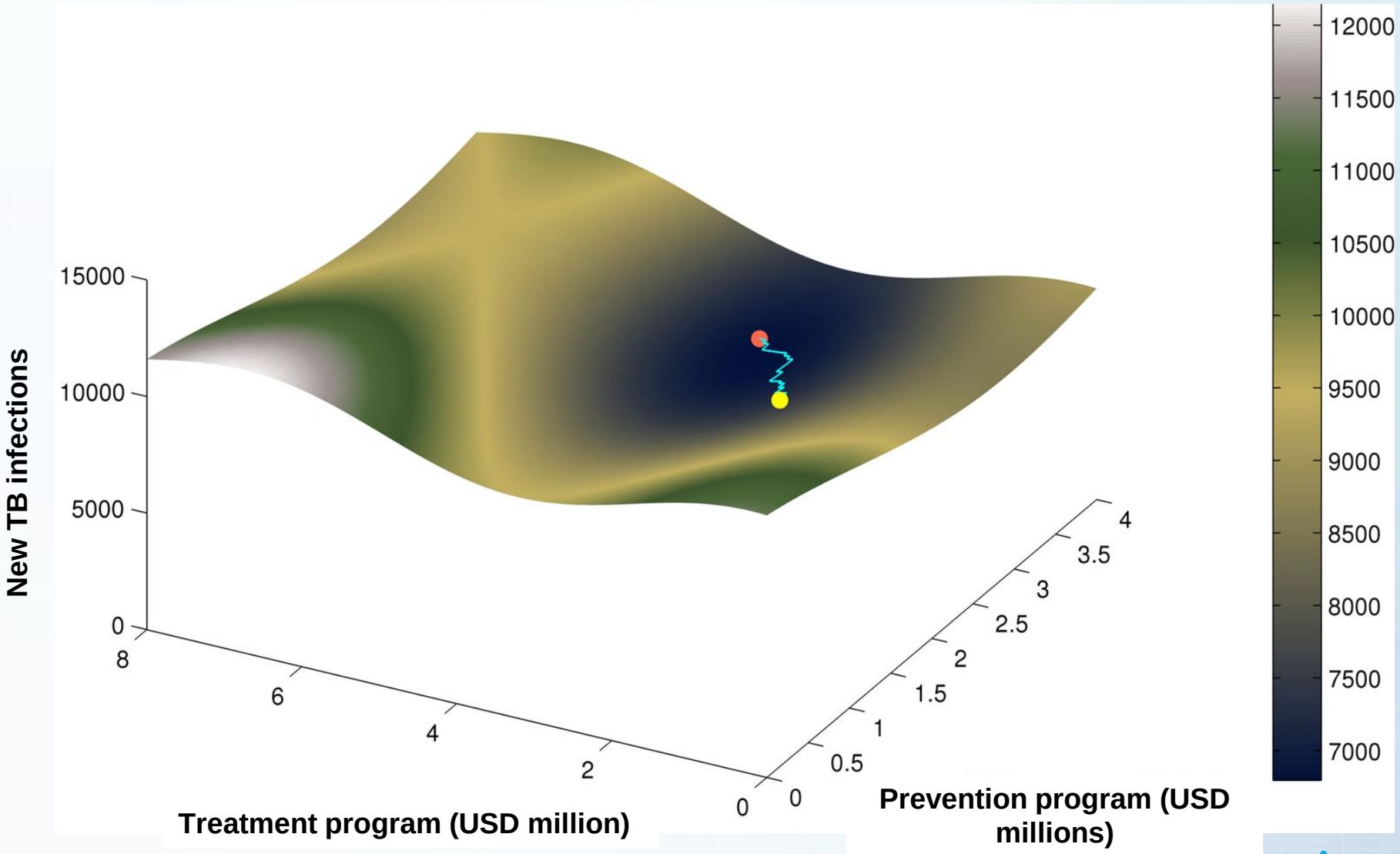
Optimized allocation redistributes budget across the most cost-effective combination of programs



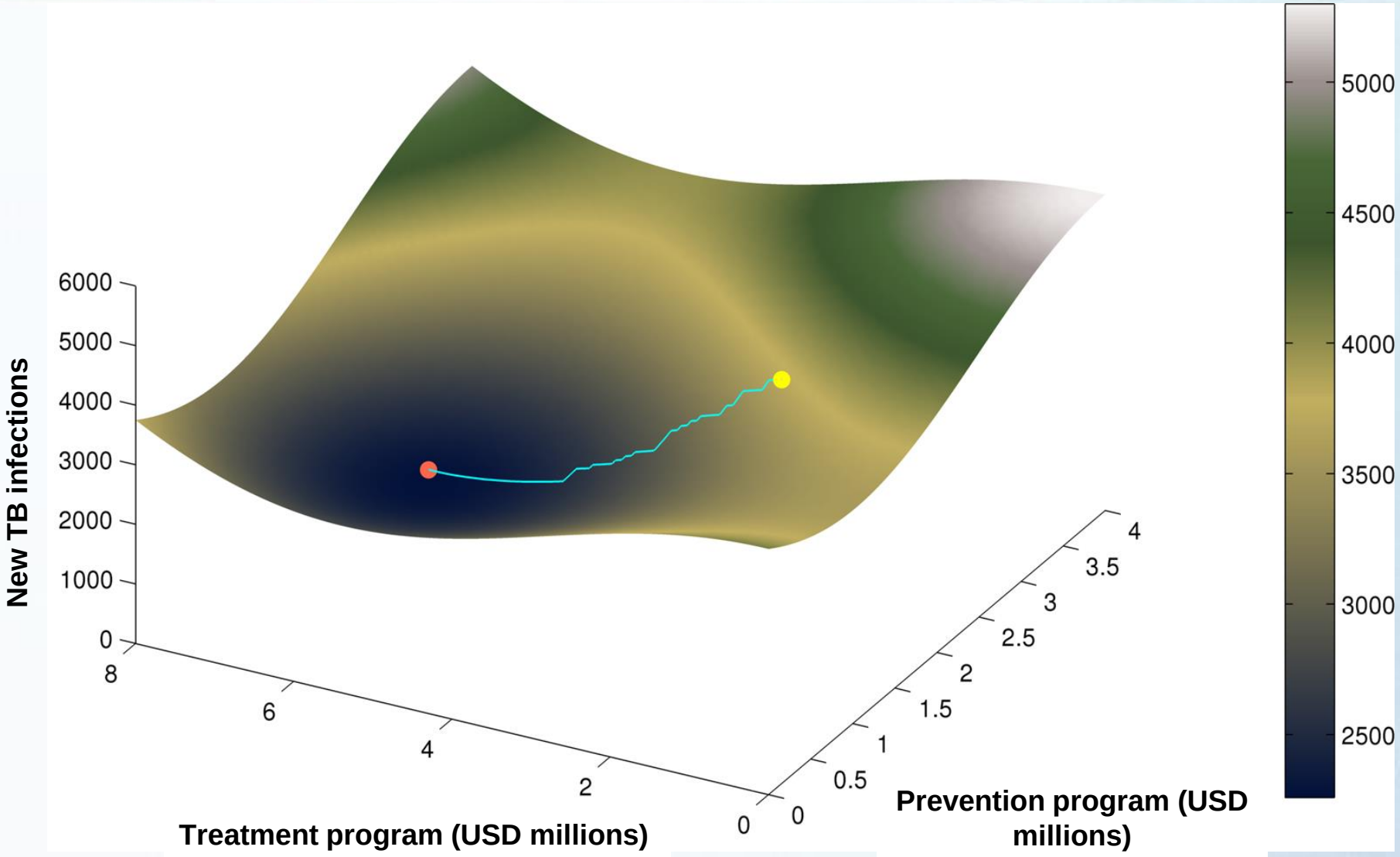
Optimization aims to identify the best combination of investment in programs to minimize new TB infections and/or TB-related deaths

Optima TB

Different allocation lead to a certain result

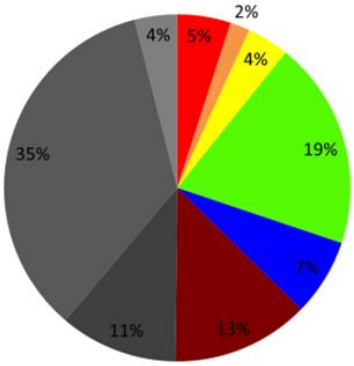


Different allocation leads to different results

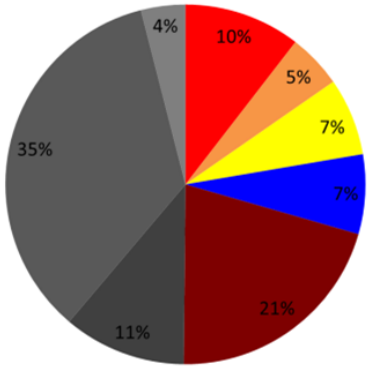


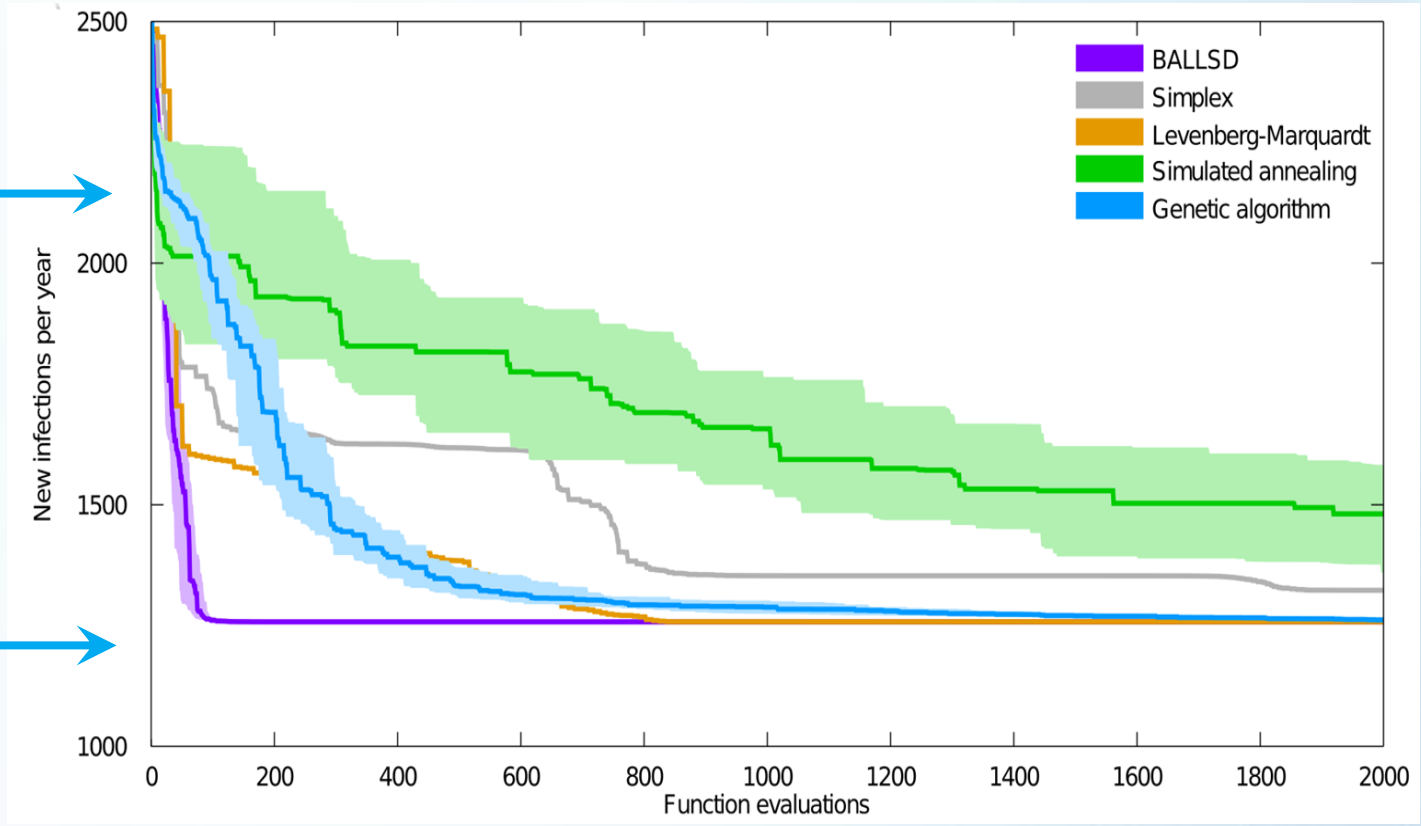
Comparing optimization algorithms

Most recent



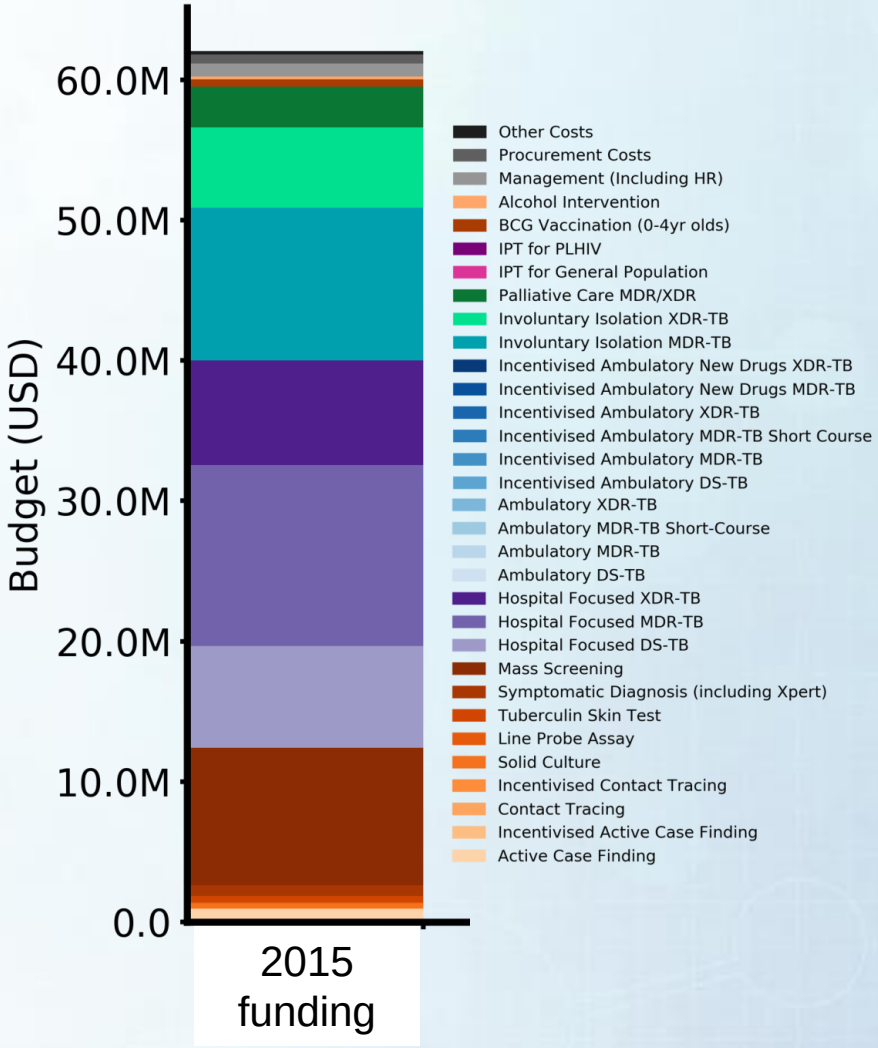
Optimized





Impact of optimized budget allocation

- 2015 funding $61 million
- Could a different budget allocation:
  - Avert more new infections?
  - Prevent additional TB deaths?
  - Decrease the number of MDR/XDR-TB cases?
  - Bring us closer to 2020 and 2035 targets?



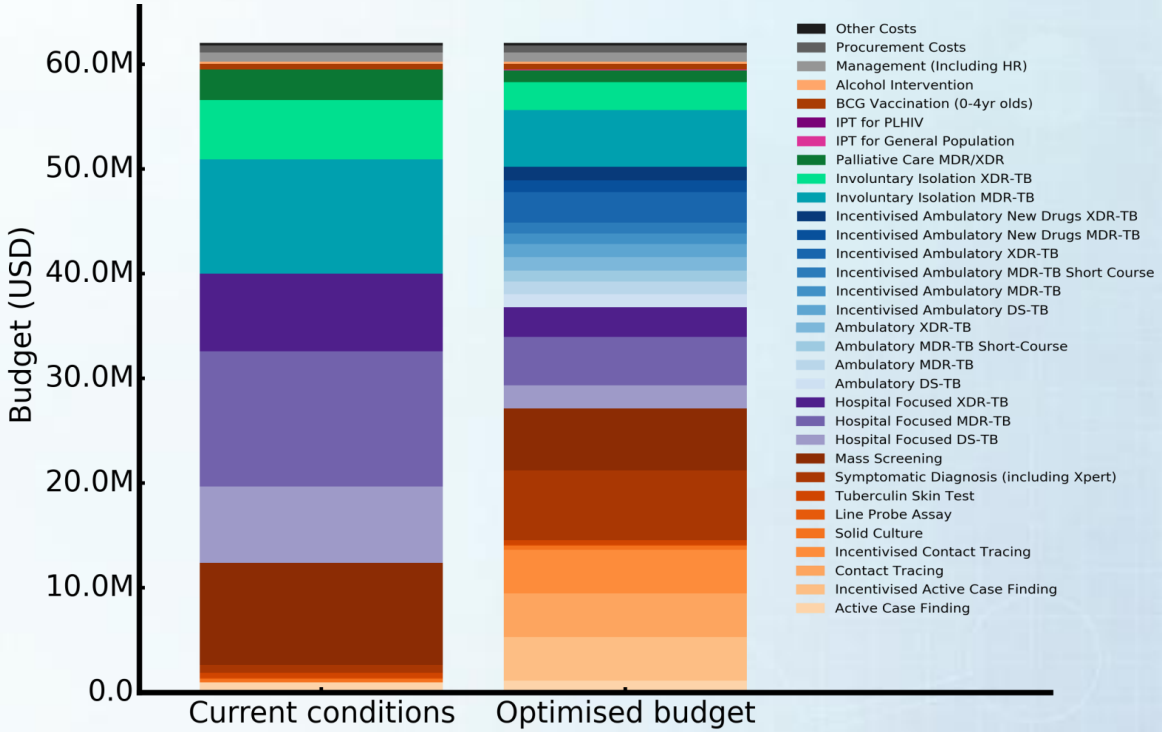
Optima TB

Optimizing TB program funding allocations

After identifying the initial starting budget, targets and constraints, the most recent budget allocation is optimized

To reduce incidence, prevalence and TB-related deaths, **an optimized budget allocation:**

- **Doubles the budget for testing programs**, with a marked shift towards active case finding and contact tracing while reducing mass screening
- Shifts funding from hospital-based to ambulatory treatment modalities

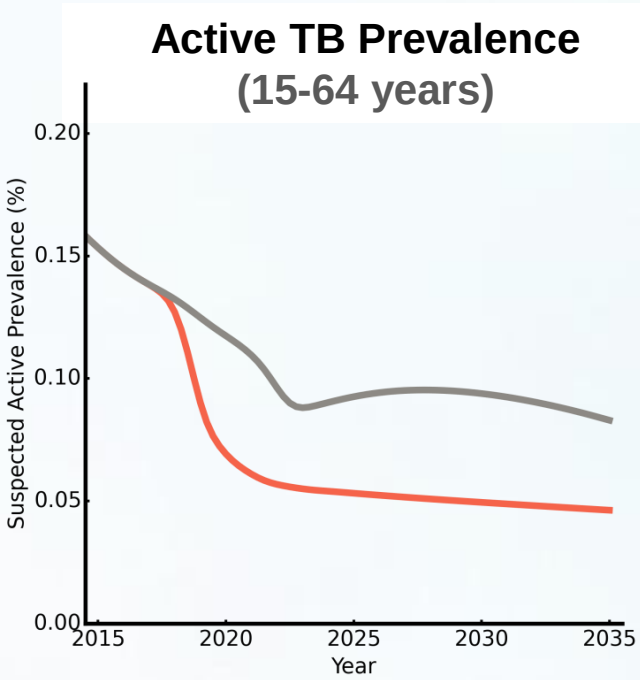


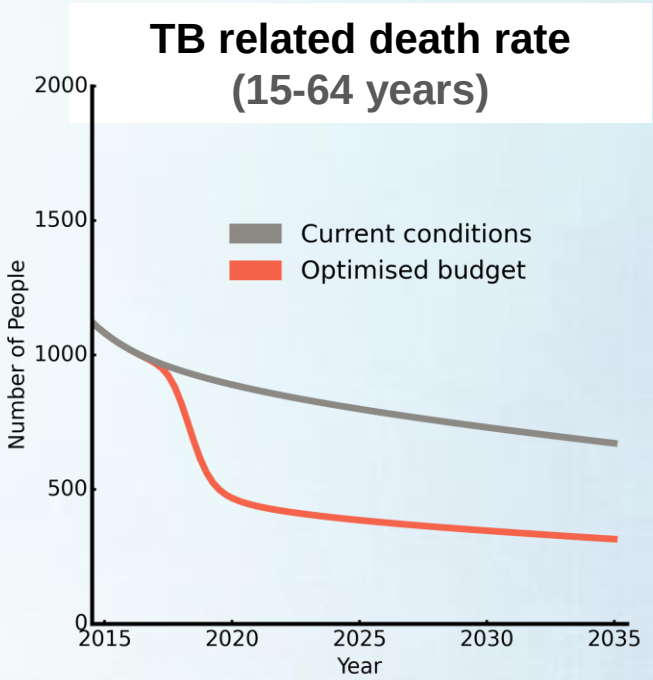
Optima TB

Impact of optimized budget: general population

With the optimized budget, we can compare its impact against the most recent conditions overall

- Among the general population An optimized budget allocation could:
  - Reduce adult TB prevalence by 45% to 0.05% by 2035 in comparison to most recent funding
  - Reduce TB-Deaths by 60% in comparison to most recent funding, and 70% of 2015 levels, by 2035





Recap: optimization

- **Optimization** uses mathematical algorithm to identify combination of programs that will have maximal impact
- Impact can be defined for **one or multiple targets**, such as
  - Reducing infections
  - Reducing number of active cases
  - Among one or many populations
- **Constraints** and **implementation limits** are included and should be defined
- **Compare optimization for multiple targets** to identify consistent trends
- Use optimized budget to **compare progress towards goals**

Optima TB

QUESTIONS?

Defining objectives and constraints in Optima TB

Objectives: achieving maximum impact

- Optimizations can be set to identify budget allocation to:
  - minimize **new active TB infections**
  - minimize **TB-related deaths**

- Weighting between infections and deaths can be specified, e.g. 5 to 1 deaths to infections.

- Other objectives can be set depending on context

- **Different objectives will result in different budget optimizations**

Optima TB

Recommendation: single objective to ease interpretation

- Recommend selecting a single objective with multiple outcomes
  - Identify allocation to minimize **active TB incidence**
  - Identify allocation to minimize **TB deaths**
  - Identify allocation to minimize **DALYs**
  - Identify allocation to minimize **active DS/MDR/XDR TB prevalence**

- Highlight or present the optimal allocation for a single objective for a single outcome, e.g. by 2035 reduce TB incidence by 90% compared with 2010

Optima TB

Time horizons matter

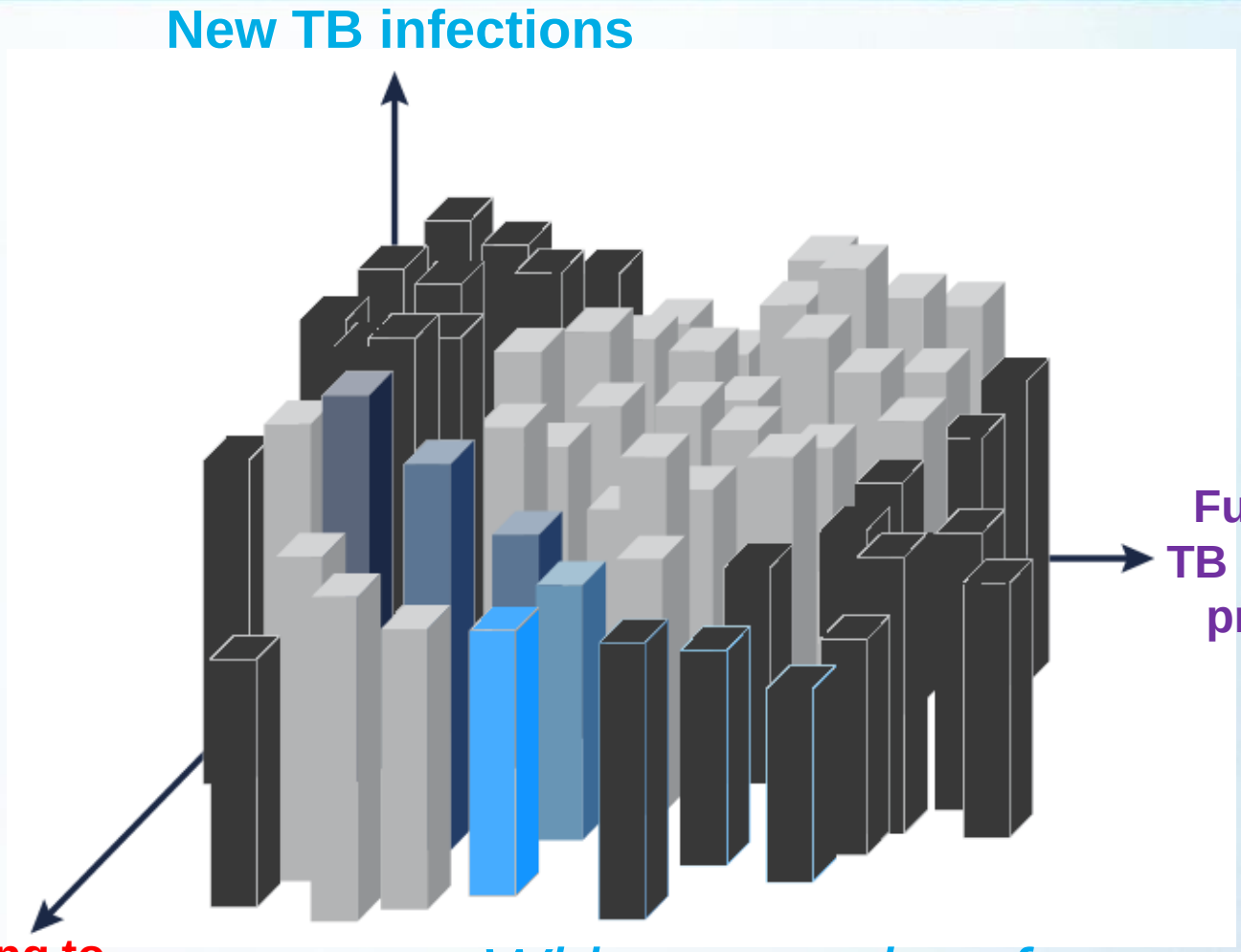
Optimal allocations can sometimes be very different over different time horizons:

- If the objective is to minimize TB-related deaths by **2020** → may prioritize funding to immediately scale-up treatment programs
- If the objective is to minimize TB-related deaths by **2035** → may also prioritize programs that prevent new TB infection

How to balance short-term with long-term impacts is an important decision in setting objectives.

Optima TB

Constraints: ethical, economic, logistic, political



With constraints for treatment

Optima TB

Constraints are important, but should be limited

- If all commonly requested constraints were incorporated, there would be limited or no change in funding allocation
  - Little to no change towards achieving the objective

- Recommendations
  - Analyses be as unconstrained as possible
  - No one on treatment be removed from treatment
  - Add constraints around funding mechanisms
    - Donor-based program targeting policies
  - Reasonable scale-up/down periods (with allowance for as large changes as possible)

Optima TB

Constraints for reallocating program funding

Minimum and maximum spending constraints can be included in the optimization process

	Min % of most recent budget	Max % of most recent budget
BCG Vaccination	100%	100%
Testing: TST, LPA and solid culture tests	100%	100%
Mass screening (including X-ray)	50%	70%
Active case finding: key populations	100%	120%
Hospital-based treatments for DS, MDR-TB and XDR-TB	30%	50%
Palliative care	40%	40%
Involuntary isolation for MDR-TB and XDR-TB	20%	50%

Optima TB

Reallocating from most recent to optimized budgets

Scaling up programs can often not be implemented immediately, especially for large increases.
The optimization process allows for this, by limiting the amount of scale up or down per year.

- To reflect the reality of program implementation, changes in program funding between most recent and target funding levels were capped at either
  - a maximum of 30% per year, for existing programs
  - a maximum of 15M (equivalent to around US$1M), for new programs for the first year, and 30% in subsequent years

  until the target level for the program funding was reached

Optima TB

Limitations of Optima TB analysis

- Analysis does not determine the implementation efficiency of programs
  - Additional implementation efficiencies, such as reductions in drug prices, could result in different resource allocations
  - Scenarios can be used in Optima TB to explore the effect of different implementation efficiencies where significant uncertainty exists
- Effects outside the TB endpoints are not modelled
  - non-health benefits, human rights, ethical, employment and psychosocial impacts are not considered
- Analysis results are only as reliable as the data and assumptions used to generate them

Optima TB

QUESTIONS?

Interpreting analysis results and extracting key messages and recommendations

How and why key findings differ between analyses

- Optimization results and recommendations will differ depending on:
  1. Type of TB epidemic
     - Which key populations are affected?
  2. Time horizon, e.g., 2018-2020, 2018-2030, 2018-2035
  3. Budget level
  4. Programs
     - Parameters which get influenced by particular programs
     - Unit costs
     - Cost function values, e.g., saturation, outcome in the absence of or under maximum coverage of programs

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Case study – the TB epidemic in Belarus

- Background: “Belarus has a **contracting TB epidemic** with increasing drug-resistance and MDR-TB challenges: 37% of new cases and 69% of re-treated cases are MDR-TB”

- Epidemic characteristics:
  - Highly affecting men, 75% of incident TB cases are among males
  - Exceptionally high levels of drug-resistance
  - Large variation in treatment outcomes

Source: WHO TB epidemic profile 2016

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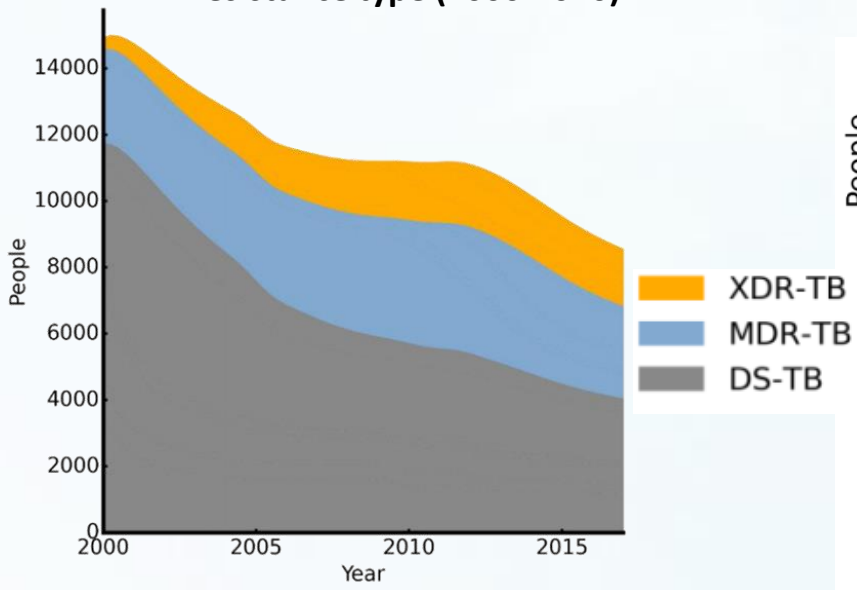
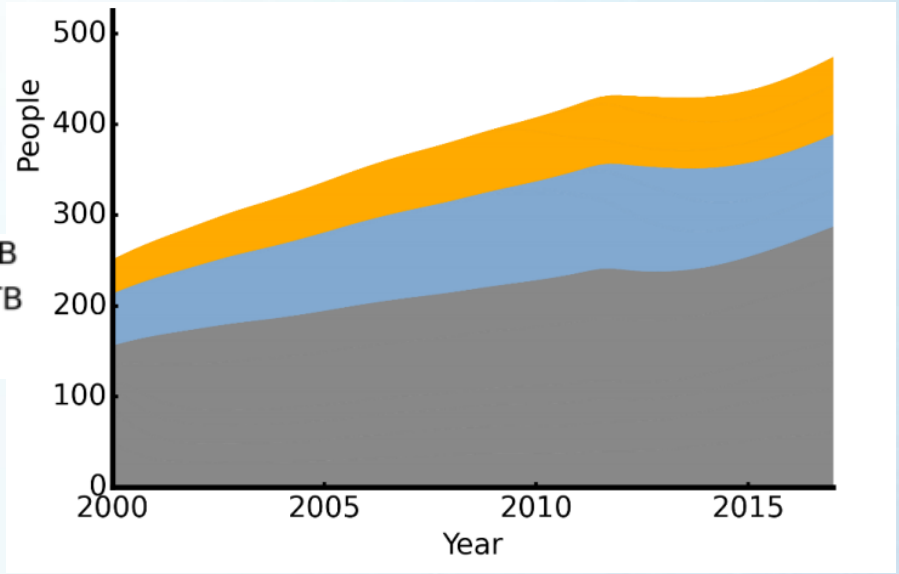
Epidemic trends estimated by Optima TB in Belarus

Trends in the estimated number of people aged 15-64 with active TB in Belarus by drug-resistance type (2000-2016)

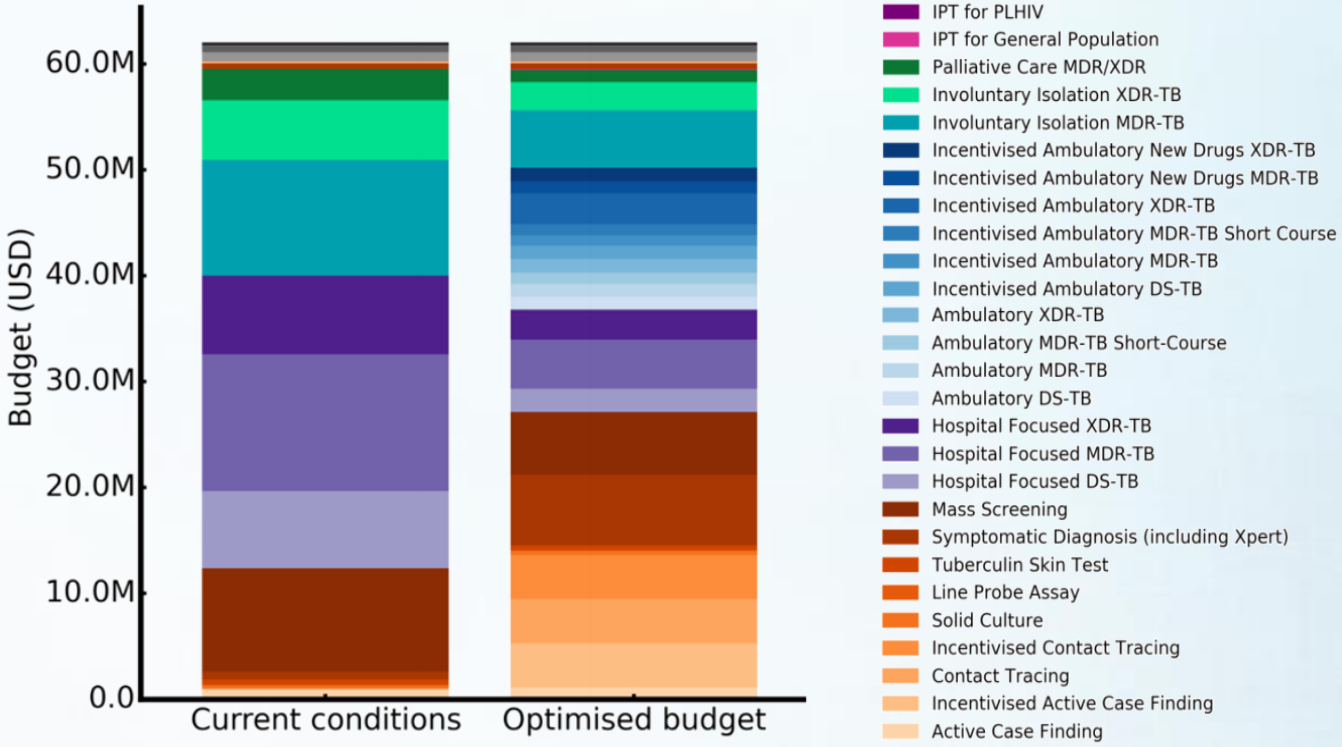


People living with HIV who have active TB by drug-resistance strain



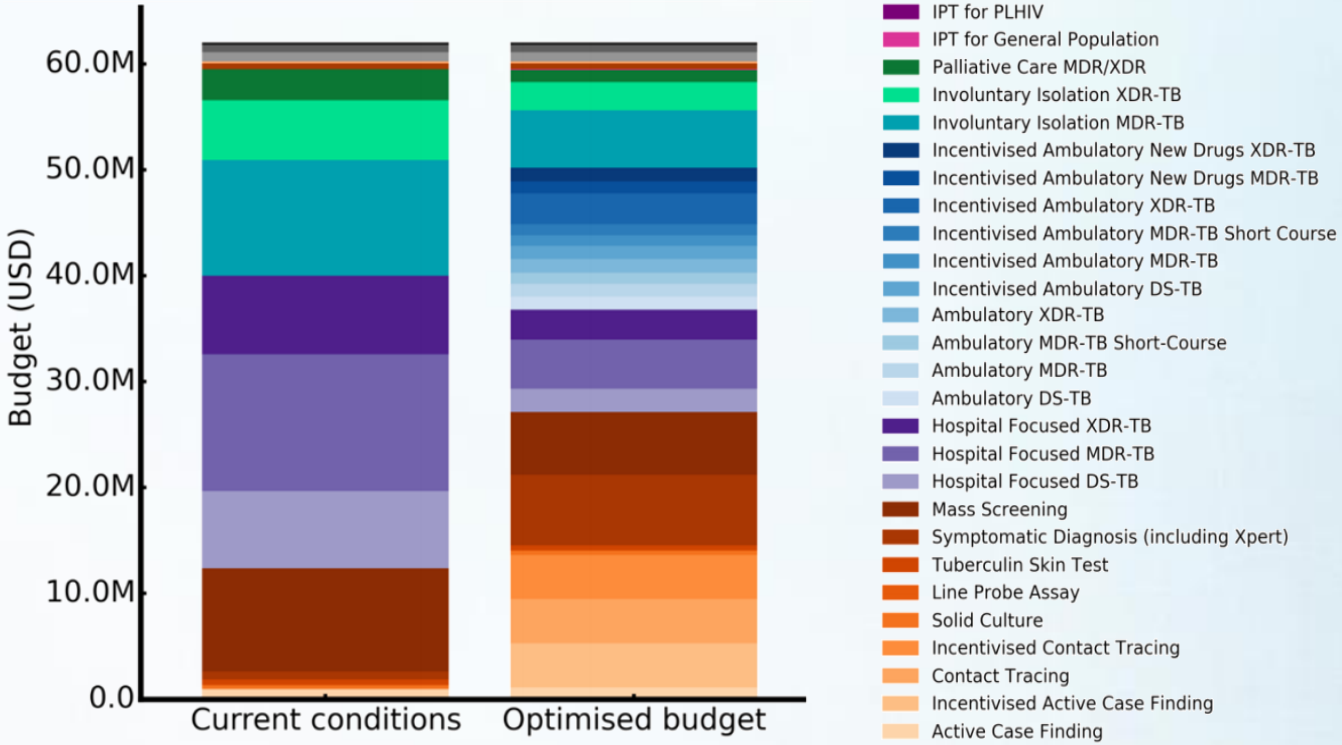
Key findings – optimization in Belarus

- Reallocation of 2015 funds show an **increase** in funding of:
  - Enhanced /incentivized contact tracing and active case finding among key populations
  - Incentivized ambulatory care
  - New TB drug regimens
  - Rapid-molecular testing



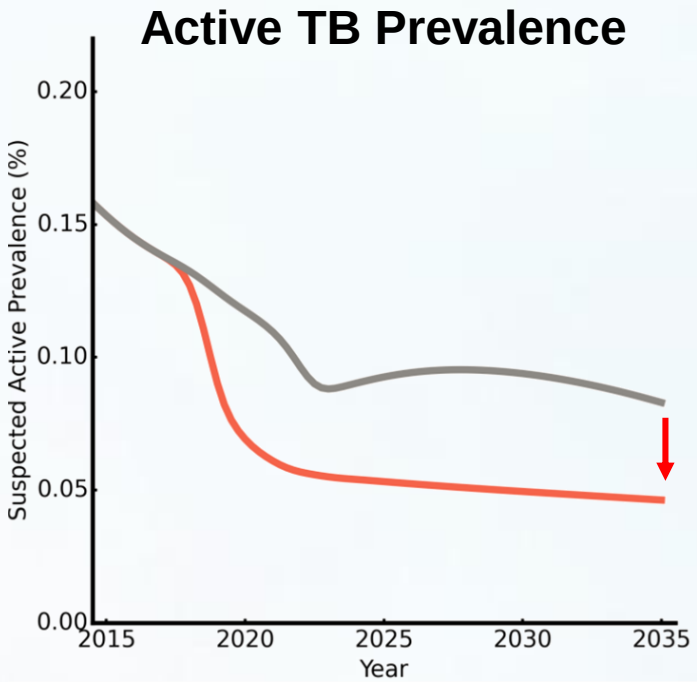
Key findings – optimization of 2015 TB funding in Belarus

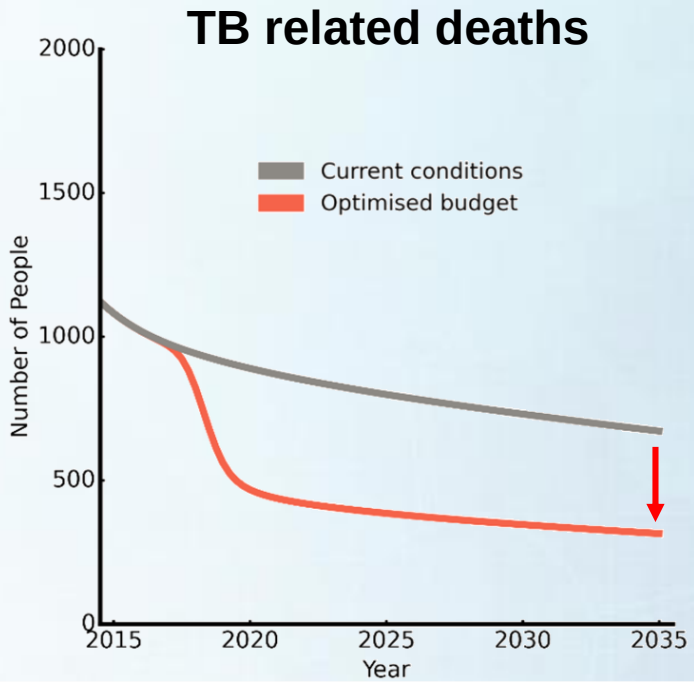
- Reallocation of 2015 funds show a **decrease** in funding of:
  - Hospital based treatment modalities
  - Mass screening
  - Involuntary isolation
  - Palliative care



Epidemiological outcomes for general population (aged 15-64) for Belarus 2015-2035

- The same budget for TB-related activities in 2015 could achieve the following by 2035:
  - Reduce prevalence in the general adult population by up to 45%
  - Reduce the total number of TB deaths by up to 60%
  - Reduce TB incidence among PLHIV by up to 45% and TB prevalence among PLHIV by up to 30%.





Key findings

- Transition from hospital-focused to ambulatory treatment modalities reduce the costs and free funding for effective treatment strategies.
  - High and long hospitalization is the primary cost driver of the TB response in Belarus.

- More targeted screening approaches could increase diagnostic yield.
  - Mass screening of entire adult population is expensive for the number of cases identified
  - Targeted screening (PLHIV, Prisoners) and contact tracing, would be more effective

Optima TB

Understanding the Outputs/Results

1. **Consider the limitations**
   - Data gaps and assumptions?
   - Simplifications?
   - Covering up important heterogeneities?
   - Effects of time horizons?
2. **What might drive the results?**
   - Can a simple deterministic sensitivity analysis be done (scenario type)?
3. **Capturing current?**
   - Do the results describe the current situation, or use historical data – how might it affect conclusions?
   - Is there a need for re-analysis, maybe because policy has moved on, or new data has come out?
4. **Representativeness**
   - For a setting, population, area

Review Model Outputs and other Results obtained

1. **What findings** - review, from the descriptive to the analytical/modelling outputs – sometimes a large amount of different types of results
   - Simple descriptive findings might be as valuable as model outputs
   - Order findings by research question/objective – most important results?
   - Useful "by-products" - assessment of guidelines, benchmarking, unit cost

2. **Do findings hold up** - review and consider them carefully
   - Plausibility - Do they make epidemiological sense? Match understanding of what interventions work and their effects? Concur with any findings from comparable studies or real-world experiences?
   - Are any results sensitive for dissemination? E.g. potentially undermining an important program, or clash with political reality?

3. **Are findings supported** by solid data?
   - Disclaimers need?

Documentation and Reporting

Important: Express the **uncertainty** of modelled estimates

- Describe model-related and data related limitations

- Follow a clear sequence
  - Description of outputs (Results section)
  - Interpretation and contextualisation of these findings (Discussion)
  - Drawing policy-relevant lessons on how HIIV response can be improved (Recommendations)

- **Lack of clarity minimises the usefulness of the results**
- For policy-makers in deciding which allocative changes to make
- For implementers to change practice

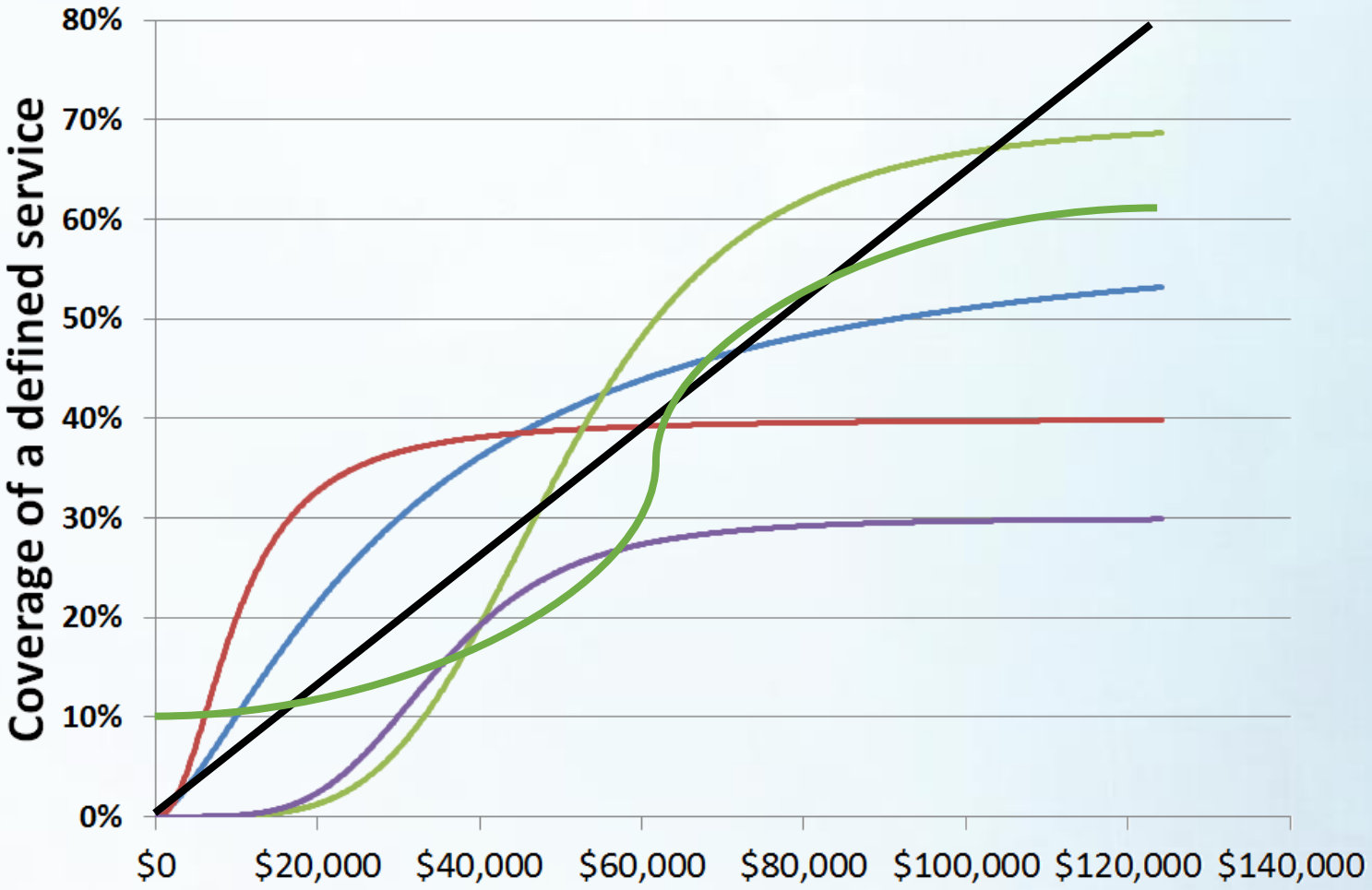
Considerations when interpreting results

- Ensure results seem reasonable
  - This may also require reviewing model inputs, as results are only as reliable as model input and assumptions used
- Again different objectives, time horizons and budget levels will lead to different results
- All model projections are subject to uncertainty
  - Estimates are indicative of trends rather than exact values
- Consider implication of recommendations
  - May be ethical, economic, and political considerations
  - Feasibility

QUESTIONS?

Intervention modalities within an allocative efficiency analysis

Cost functions for each program, intervention, or intervention modality



Each program/intervention/modality has it's **own cost-coverage and coverage-outcome** curve

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Interactions between programs/modalities

- For each program/modality:
  - Define **cost-coverage** and **coverage-outcome** relationships
    - **Coverage** is % of population reached (or number of people)
    - **Outcome** described as relationship mapping
      - "Change in outcome per person" for
      - "Change in coverage per person
        - e.g., for every person reached by a testing program, their chance of being tested is x%
- Map vector of anticipated spending to outcomes
  - $[\$_0, \$_1, \ldots, \$_N] \rightarrow [Out_0, Out_1, \ldots, Out_N]$
- For allocative efficiency assessment, ideally want to map to single outcome: $[\$_0, \$_1, \ldots, \$_N] \rightarrow Out_X$

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Spending on different programs/modalities related to coverage

$[\$_0, \$_1, \ldots, \$_N] \rightarrow [C_0, C_1, \ldots, C_N]$ ($ relates to coverage)

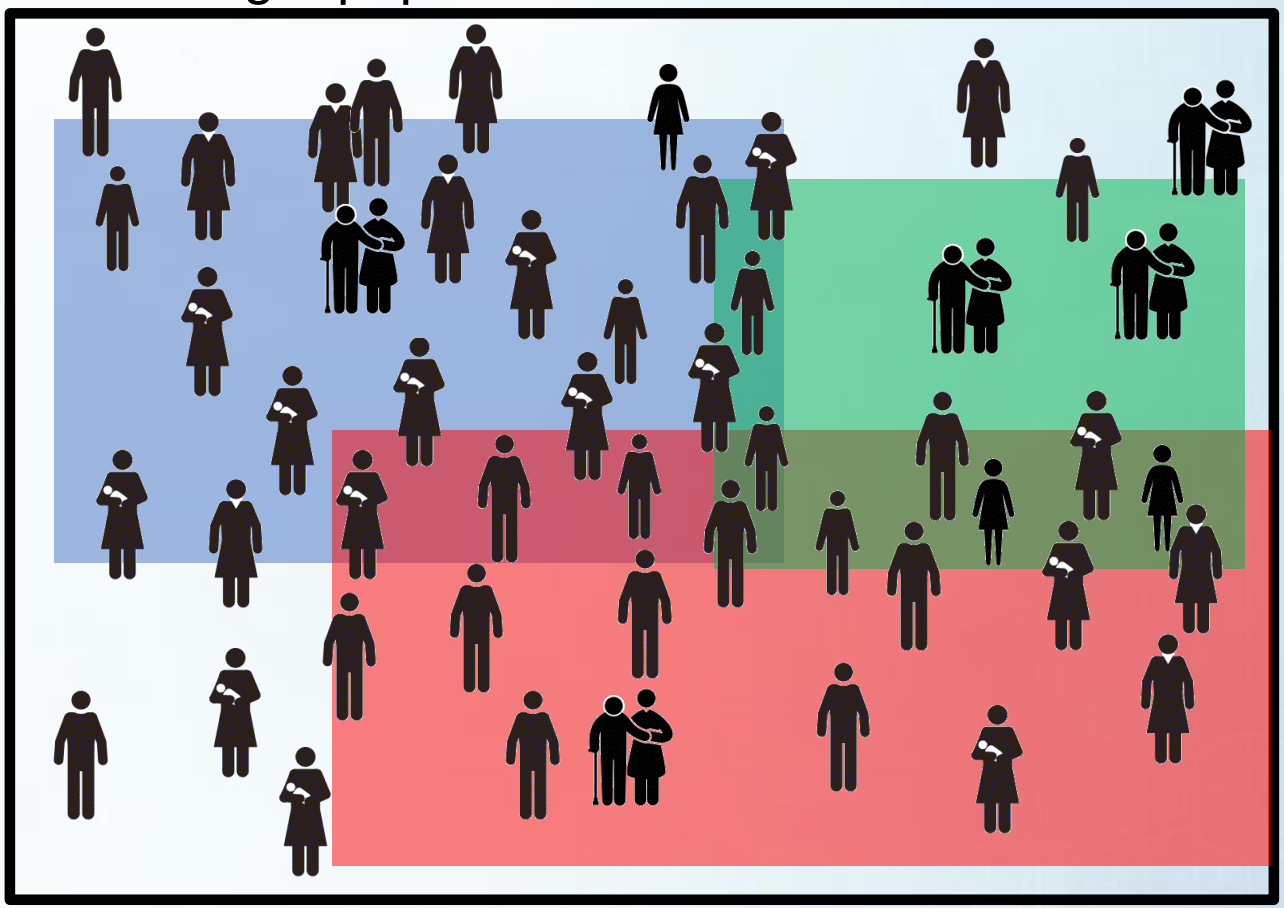
Entire target population

Coverage reached by program X for $\$_X$

program 1

program 2

program 3



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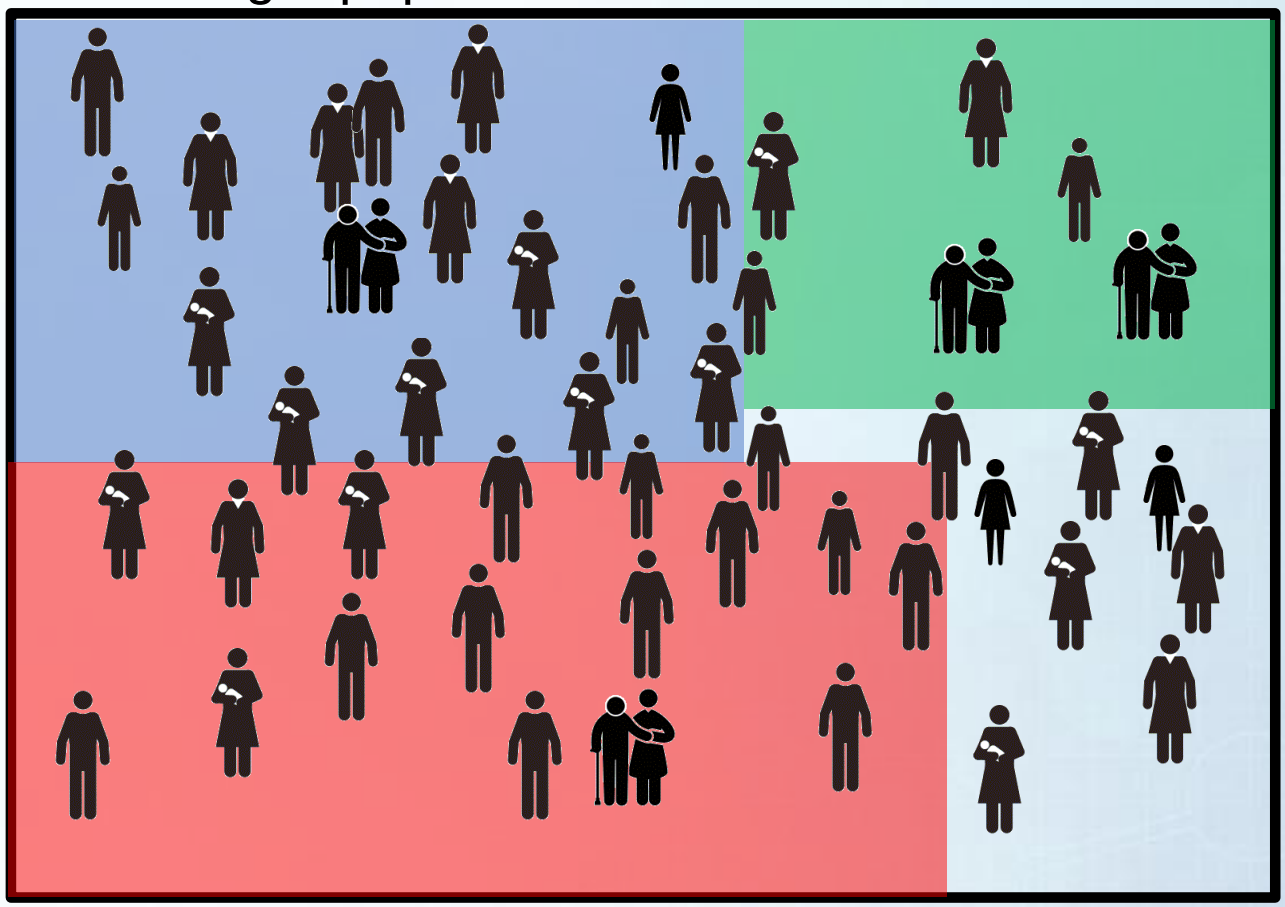
For every parameter, there is a type of program interaction

Option 1: **additive** (optional) program interaction

Coverage reached by program X for $\$_X$

- program 1
- program 2
- program 3

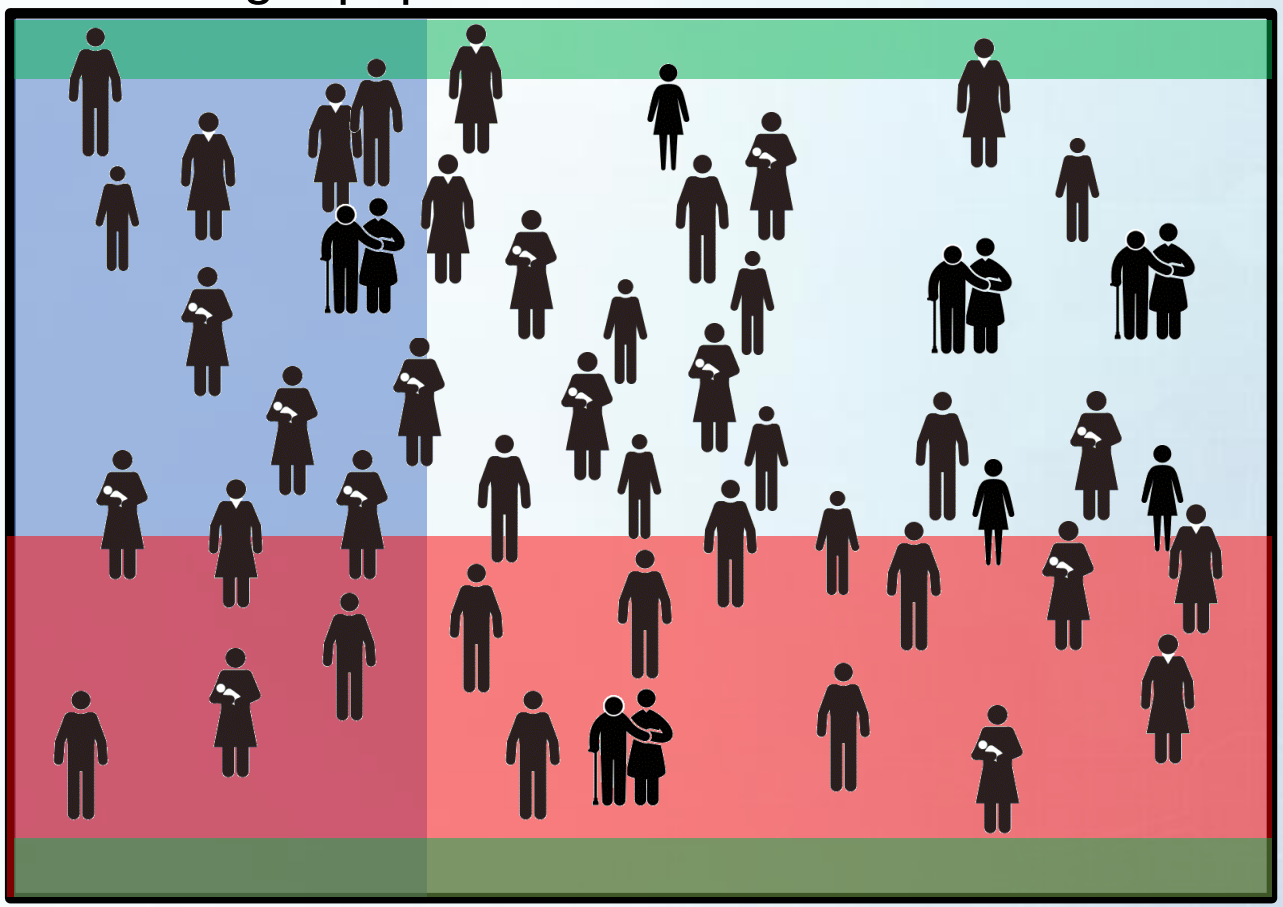
Entire target population



For every parameter, there is a type of program interaction

Option 2: **random** (default)

Entire target population



Coverage reached by program X for $\$_X$

program 1

program 2

program 3

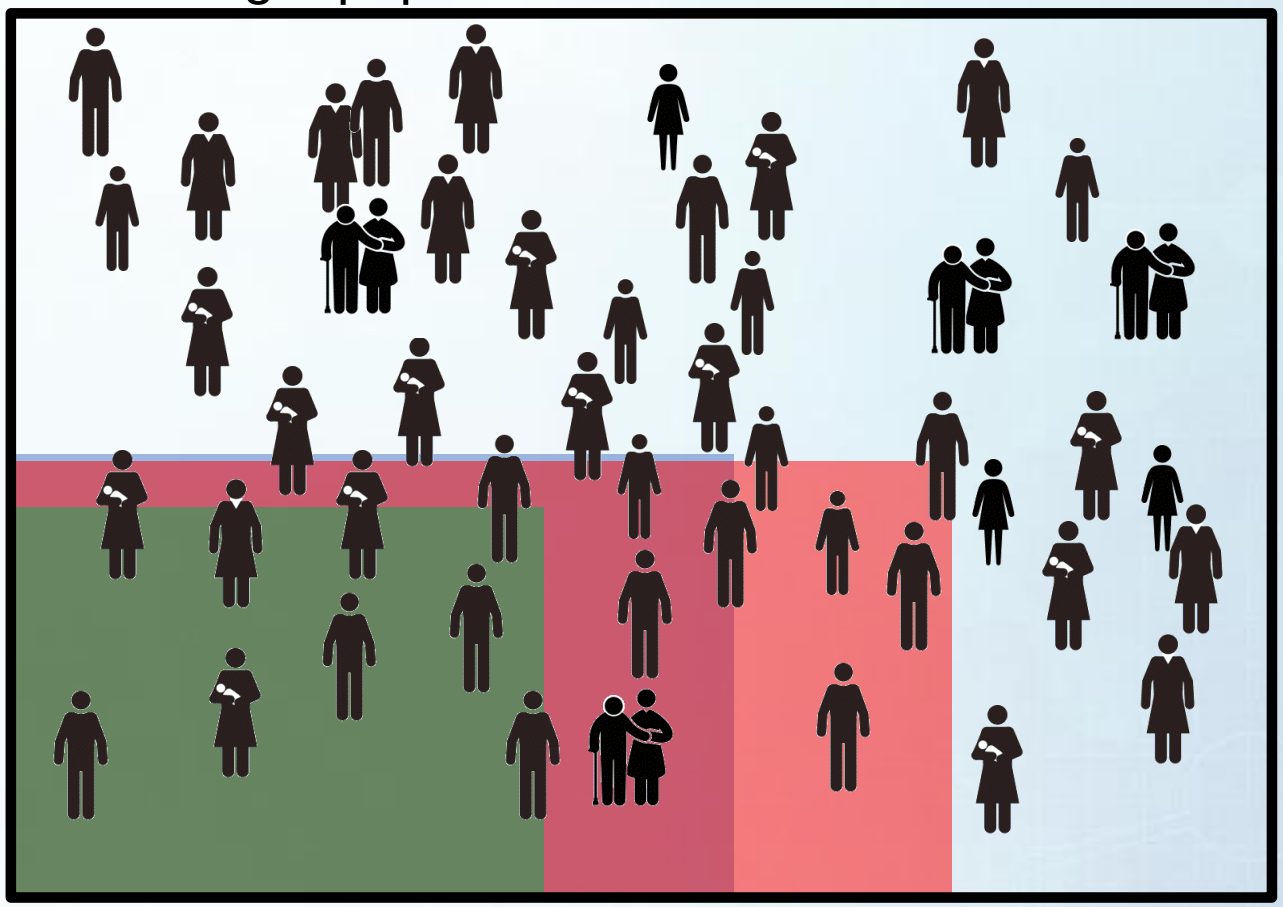
For every parameter, there is a type of program interaction

Option 3: **nested** (optional)

Coverage reached by program X for $\$_X$

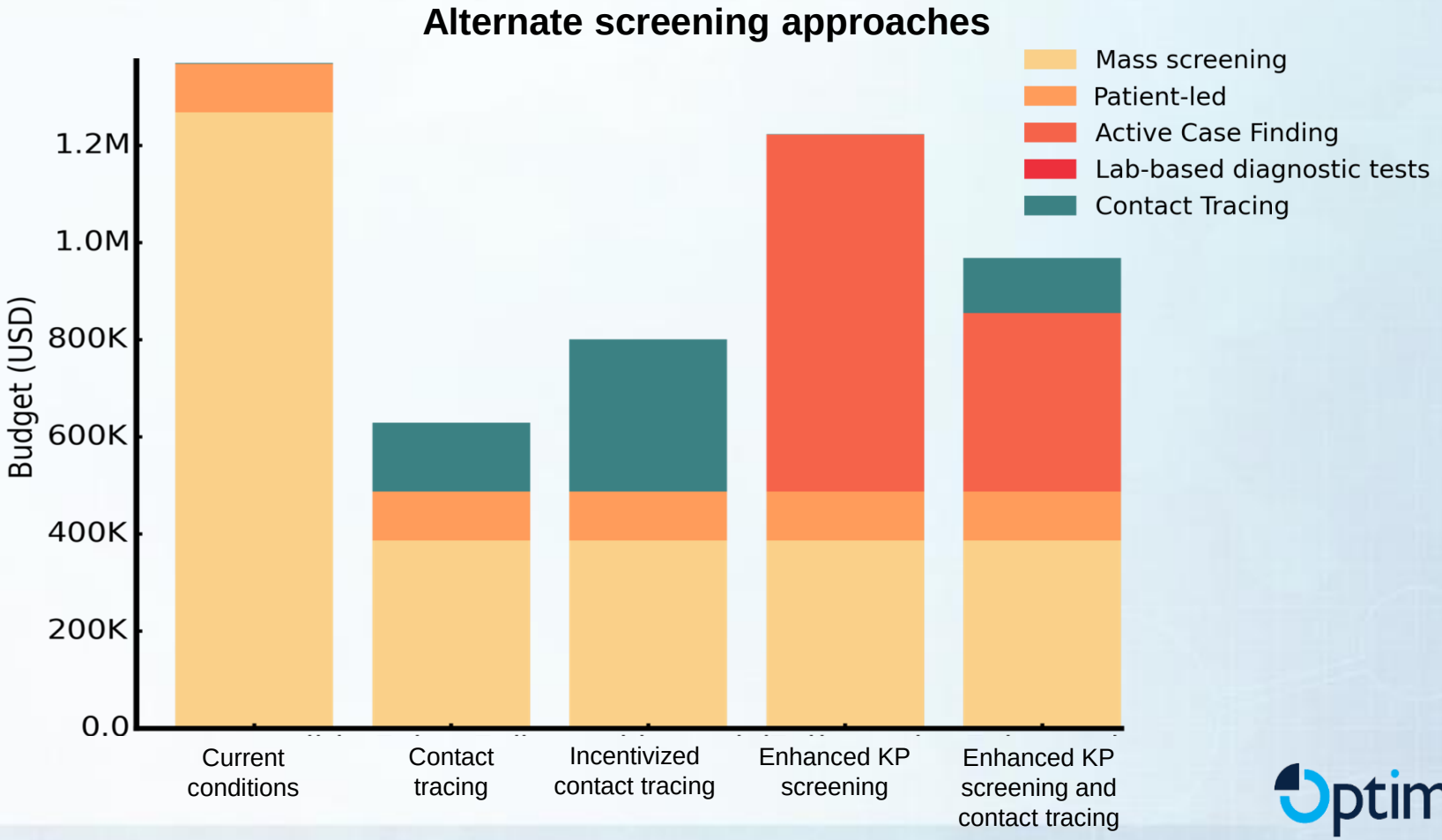
- program 1
- program 2
- program 3

Entire target population



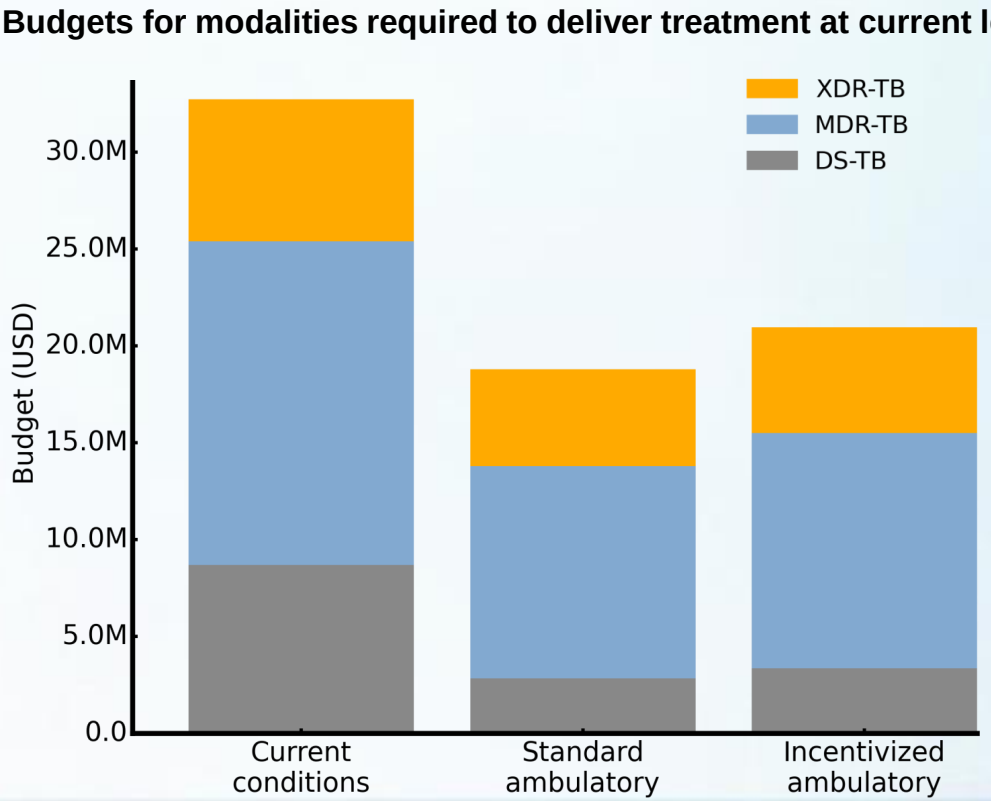
Belarus case study 1 - modelling different screening approaches

- By moving from mass screening to contact tracing and active case finding, **the same number of TB cases** could be identified **with a significantly smaller budget**



Belarus case study 2- shifting from inpatient to outpatient care modalities

- Program parameters:
  - Decrease in the number of inpatient and outpatient days for ambulatory care, informed by the country and WHO recommendations
  - Relative changes in treatment success rates depending on a given treatment modality are derived from literature (Bassili et al., 2013, Nguyen, 2016)



QUESTIONS?

Steps for Optima TB modelling

1. Access: login and logout, user guides, training documentation, help (**info@ocds.co**)
2. Projects: create a new project and define populations
3. Data: create project & download databook
   a. Enter data in spreadsheet: ensure completeness, model needs *at least one* data *or* assumption value for each population for: population size, prevalence, behaviour, etc.)
4. Upload complete spreadsheet to project
5. Calibration
   a. Automatic calibration
   b. Manual calibration: adjust as necessary
6. Download a program book, define programs and enter costs and coverage data
7. Cost functions
   a. Define cost functions
   b. Define outcome functions
8. Analyses
   a. Scenario
   b. Optimization
9. Interpret results, generate slides and report, disseminate results
10. In future: update model project and re-run results in consultation with Optima team

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