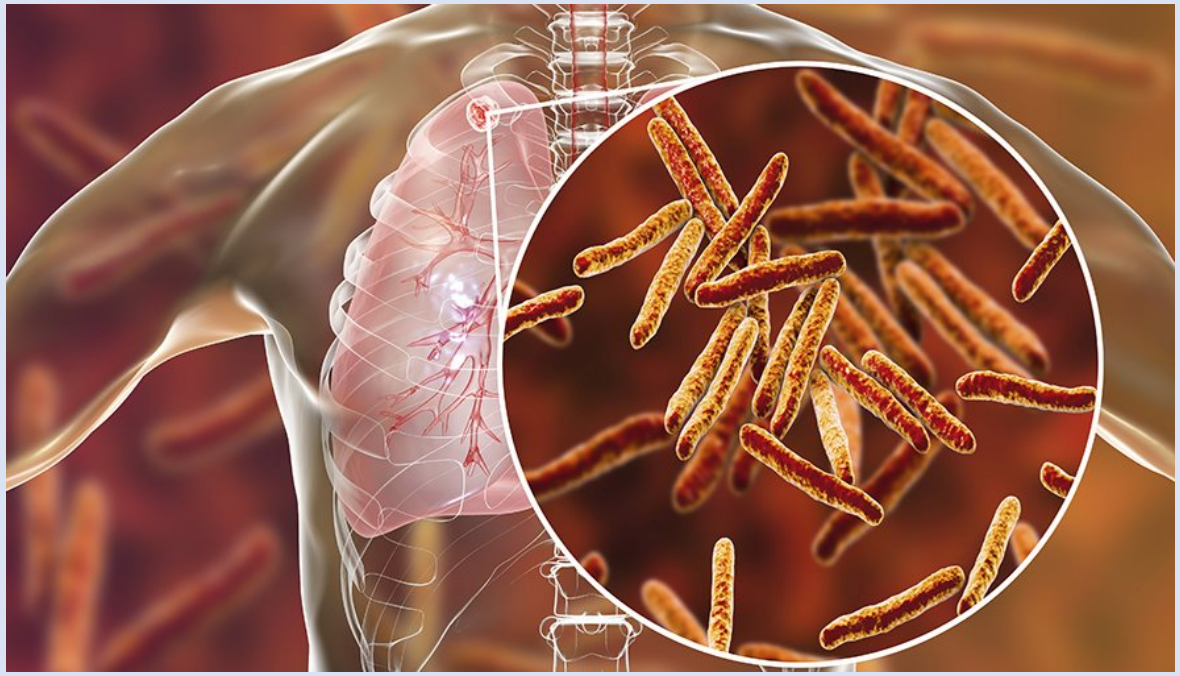
July 20, 2023

# Progressing towards tuberculosis elimination: An ounce or a pound of prevention



**JONATHON CAMPBELL**
Assistant Professor
McGill University & McGill International TB Centre

*McGill University is on land which has long served as a site of meeting and exchange amongst Indigenous peoples, including the Haudenosaunee and Anishinaabeg nations. I acknowledge and thank the diverse Indigenous peoples whose presence marks this territory on which peoples of the world now gather.*

McGill | Faculty of Medicine | Faculté de médecine

Centre international de TB McGill | McGill International TB Centre
A PAHO/WHO Collaborating Centre for Tuberculosis Research

jonathon.campbell@mcgill.ca
@JCampbellMcGill

# Disclosures

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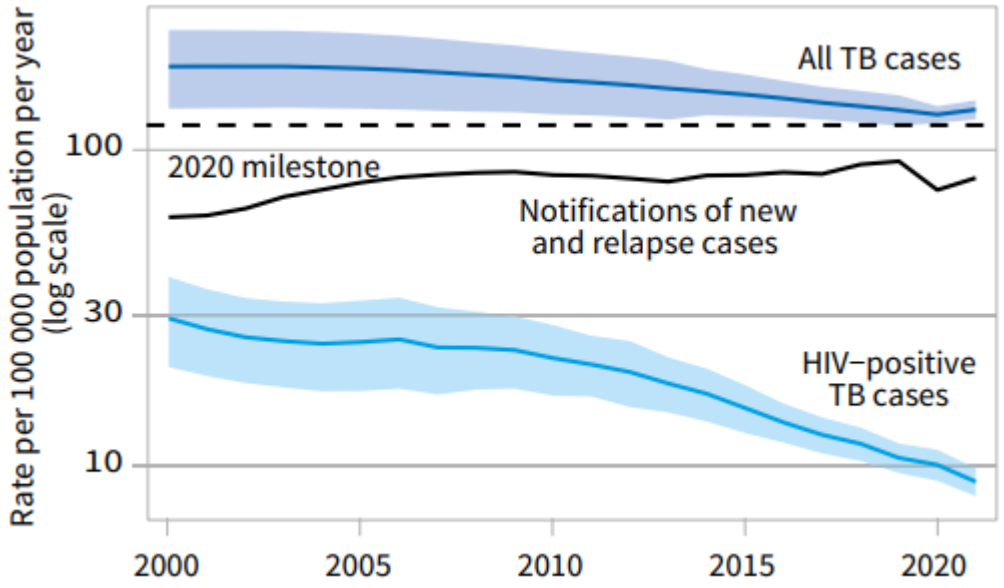
- I have received consulting fees from WHO, World Bank, and COVID-19 Immunity Task Force (Canada)—unrelated to this presentation.

- I hold research funding from CIHR, FRQS, National Sanitarium Association (Canada), McGill University Health Centre Foundation, and WHO.

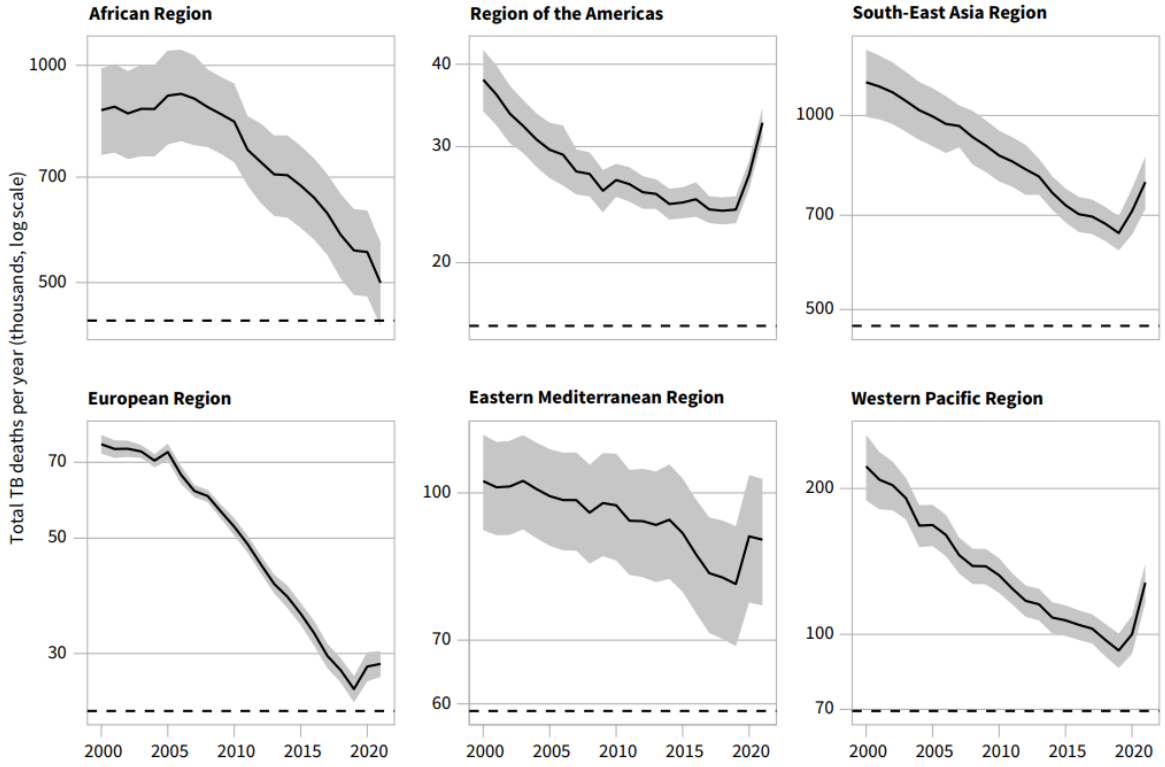
jonathon.campbell@mcgill.ca
@JCampbellMcGill

# Motivation

## TB Incidence Rate, 2000-2021



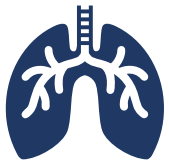

## TB Deaths by WHO Region, 2000-2021




WHO Global TB Report 2022

jonathon.campbell@mcgill.ca
@JCampbellMcGill

# (Some) Downstream consequences of tuberculosis disease



Tuberculosis-associated disability is common—best data available for respiratory disability.

- In a large systematic review and meta-analysis, 1 in 4 people surviving tuberculosis reported breathlessness (MRC dyspnoea score 3-5) and 3 in 5 had abnormal spirometry.
- A modeling study estimated an additional 0.03 DALYs per year attributable to post-tuberculosis respiratory consequences among survivors.

People with TB and their families and caregivers face catastrophic costs.

- 47% (95% CI: 34% to 59%) of TB-affected households face catastrophic costs; the number is nearly double for those affected by drug-resistant TB.
- Data in high-income settings scarce, but a study in the Netherlands suggests 1 in 4 people with TB lost their jobs.
- Disability caused by tuberculosis may keep people out of the workforce for years.

Taylor J, et al. *eClinMed*. 2023
WHO. 2022
Menzies N, et al. *Lancet GH*. 2021
Meghji J, et al. *Thorax*. 2021

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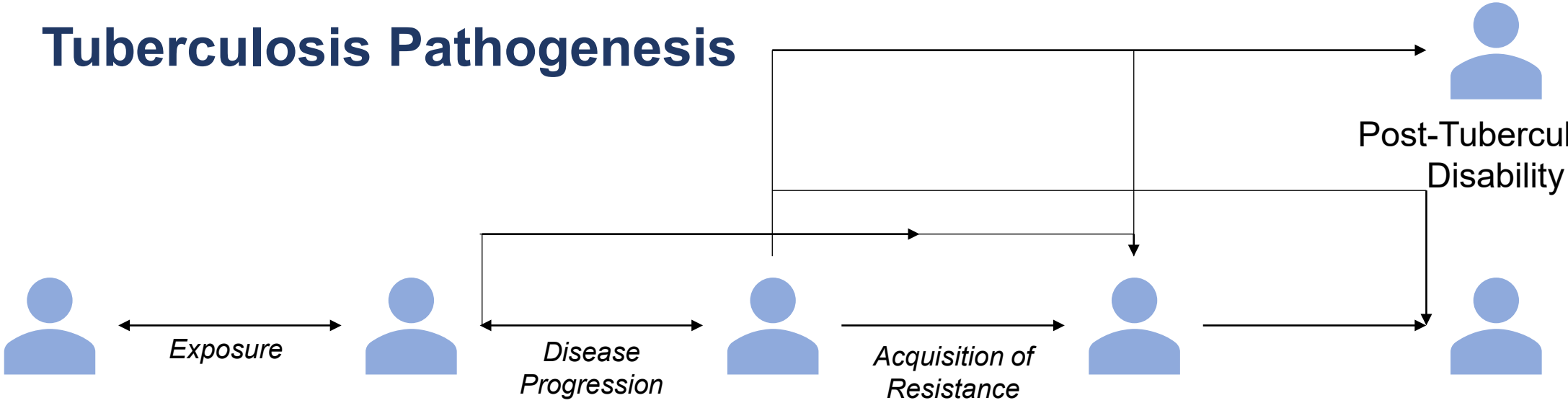
@JCampbellMcGill

# Tuberculosis Pathogenesis



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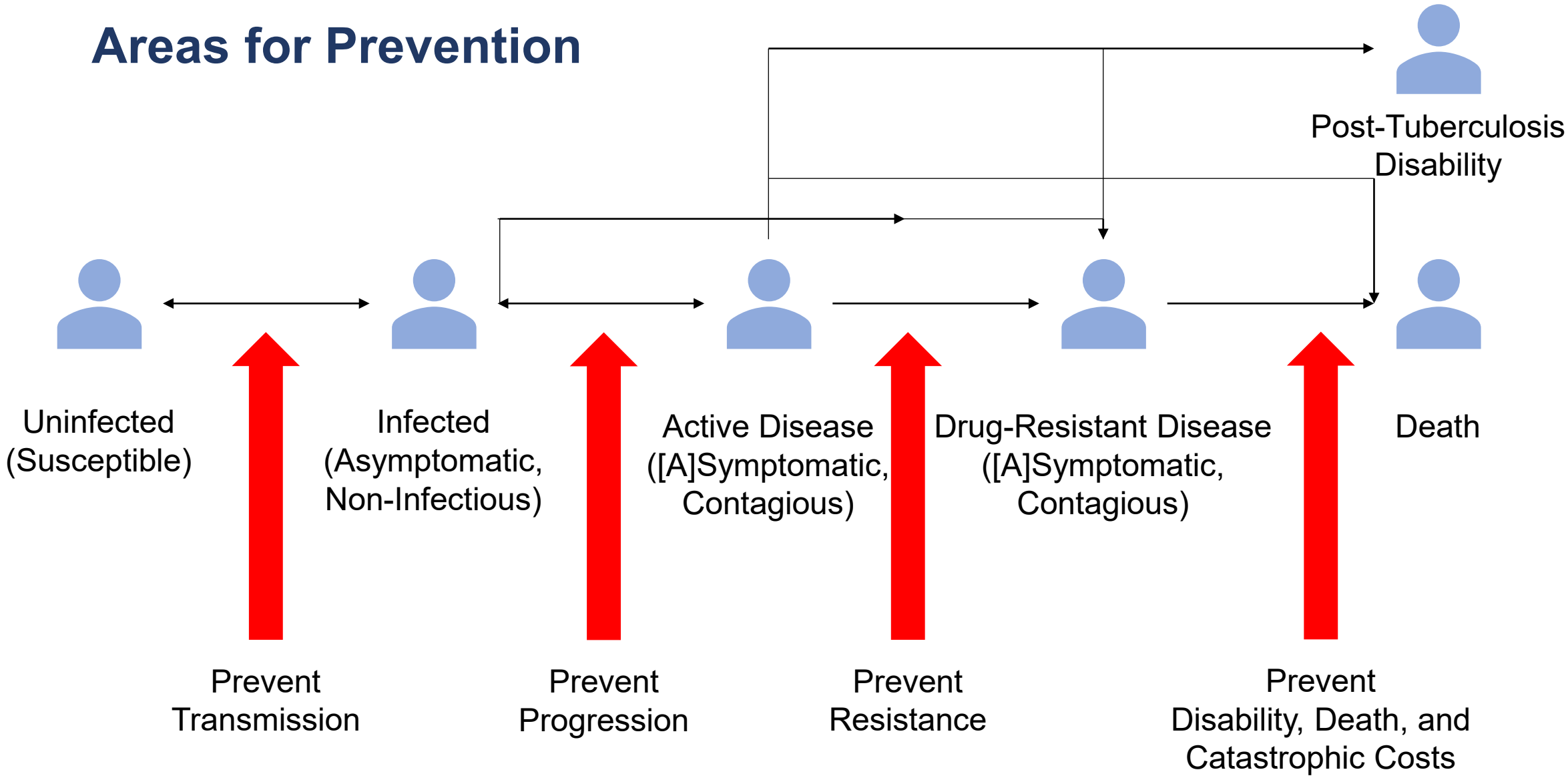
# Areas for Prevention



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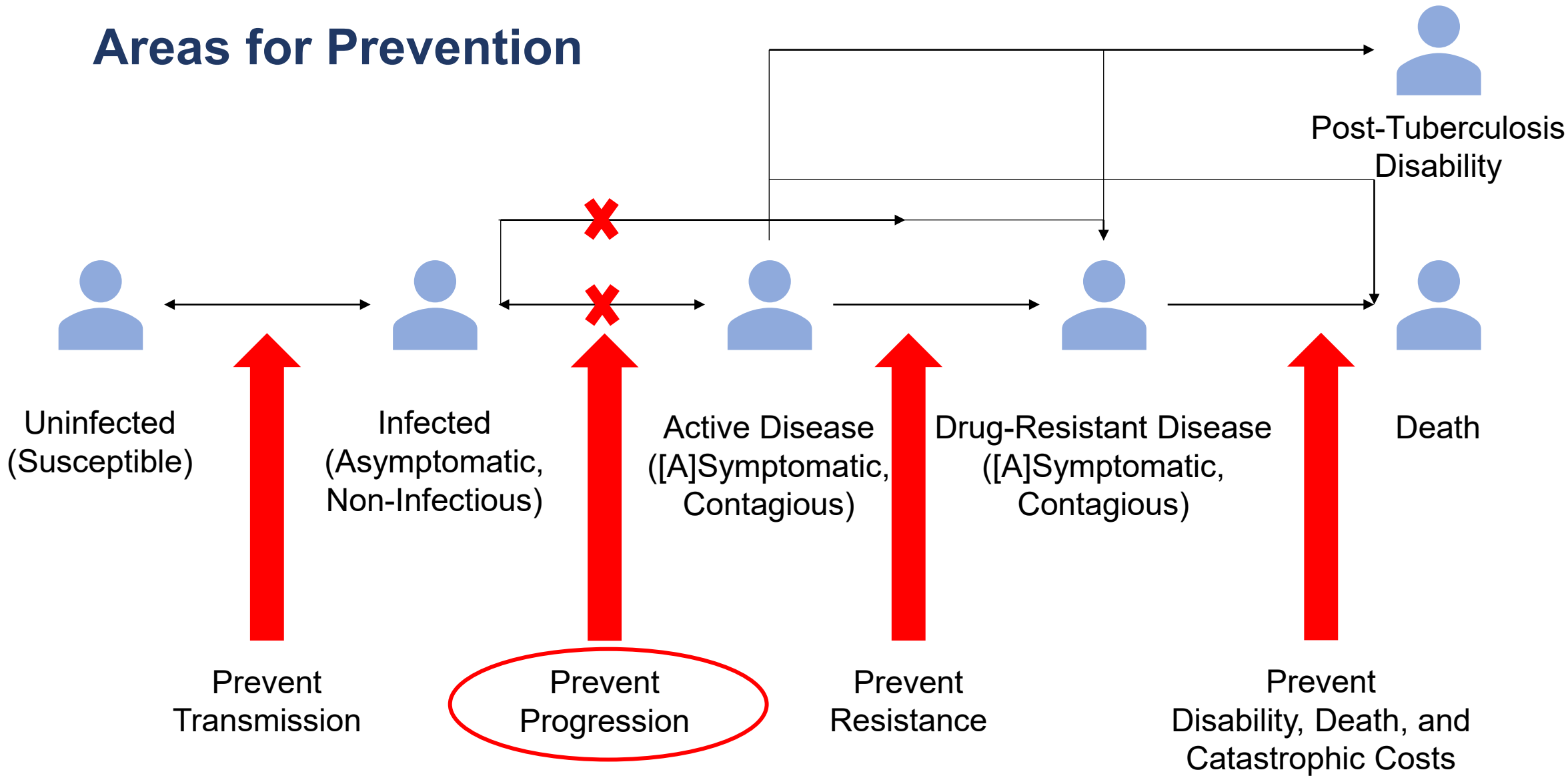
# Areas for Prevention



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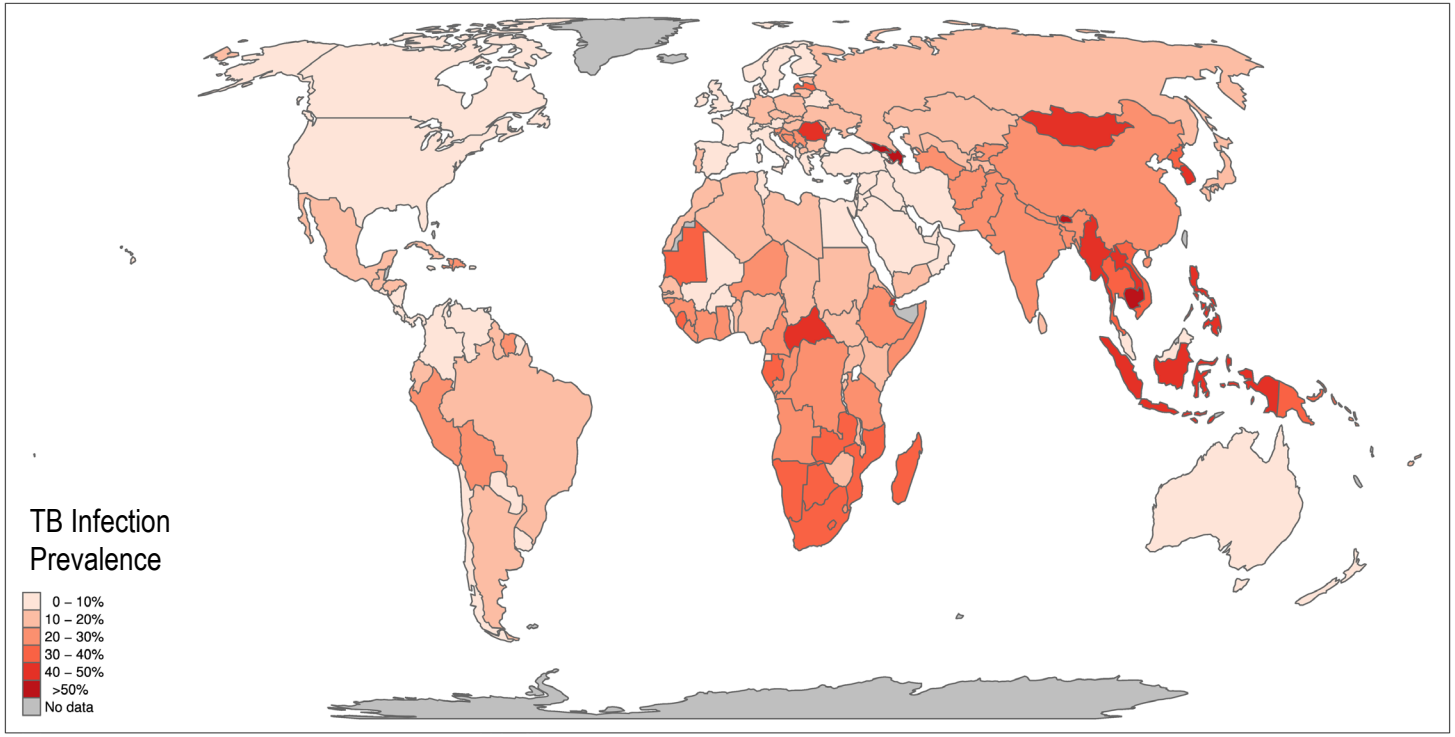
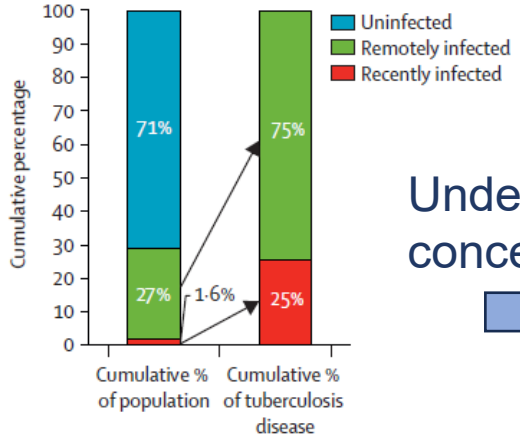
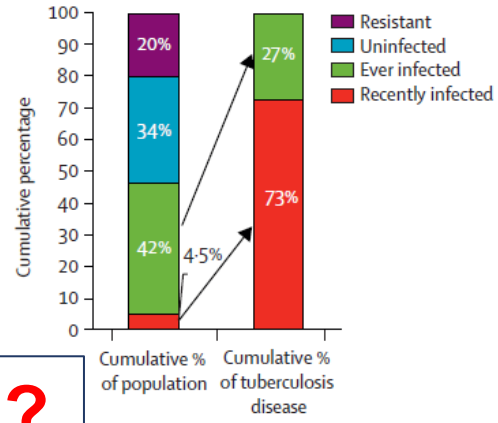
# Around 1.7 Billion People Have (or Have Had) TB Infection Globally




Under an adjusted conceptualization




**Does this change global priorities for prevention?**

Houben & Dodd. *PLoS Med.* 2016
Dowdy & Behr. *Lancet ID*. 2022

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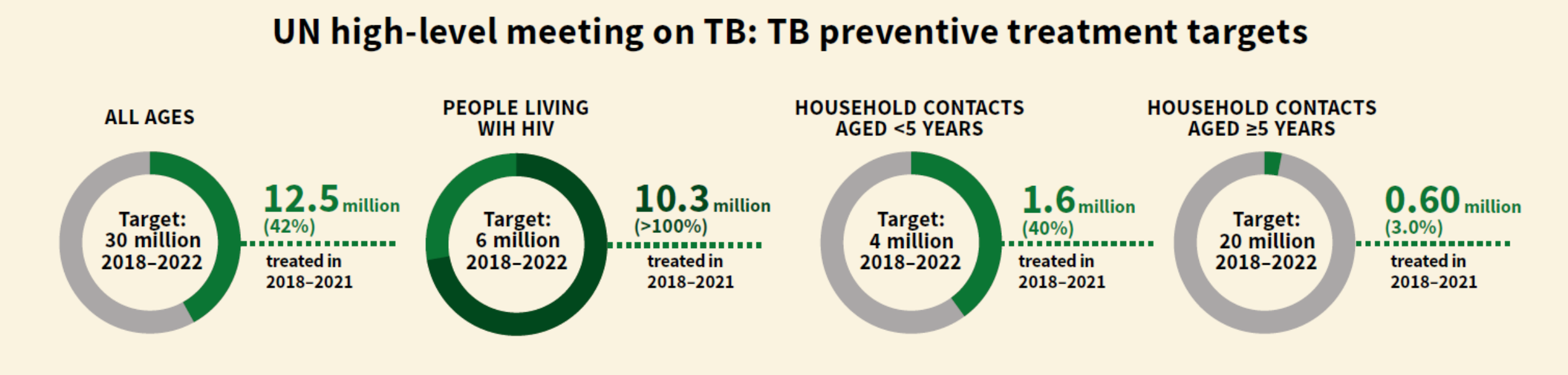
# Current TB Prevention Priorities

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jonathon.campbell@mcgill.ca
@JCampbellMcGill

# Costs of Managing Tuberculosis

- Treatment of tuberculosis infection is **significantly** cheaper than treatment of tuberculosis disease—including disease NOT requiring any hospitalization.

| Country | Cost of 6/9H | Cost of DS-TB (no hospitalization) | Ratio |
|---|---|---|---|
| Canada | $795 | $5400 | 6.8 |
| USA | $511 | $3300 | 6.5 |
| Ghana | $40 | $131 | 3.3 |
| Kenya | $40 | $148 | 3.7 |

All costs in USD; costs vary due to differences in care and follow-up

Campbell JR, et al. *Emerg ID*. 2022
Vesga J, … Campbell JR. *In prep*.
Adusi Poku Y, et al. *In prep.*
Shepardson D, et al. *IJTLD*. 2013

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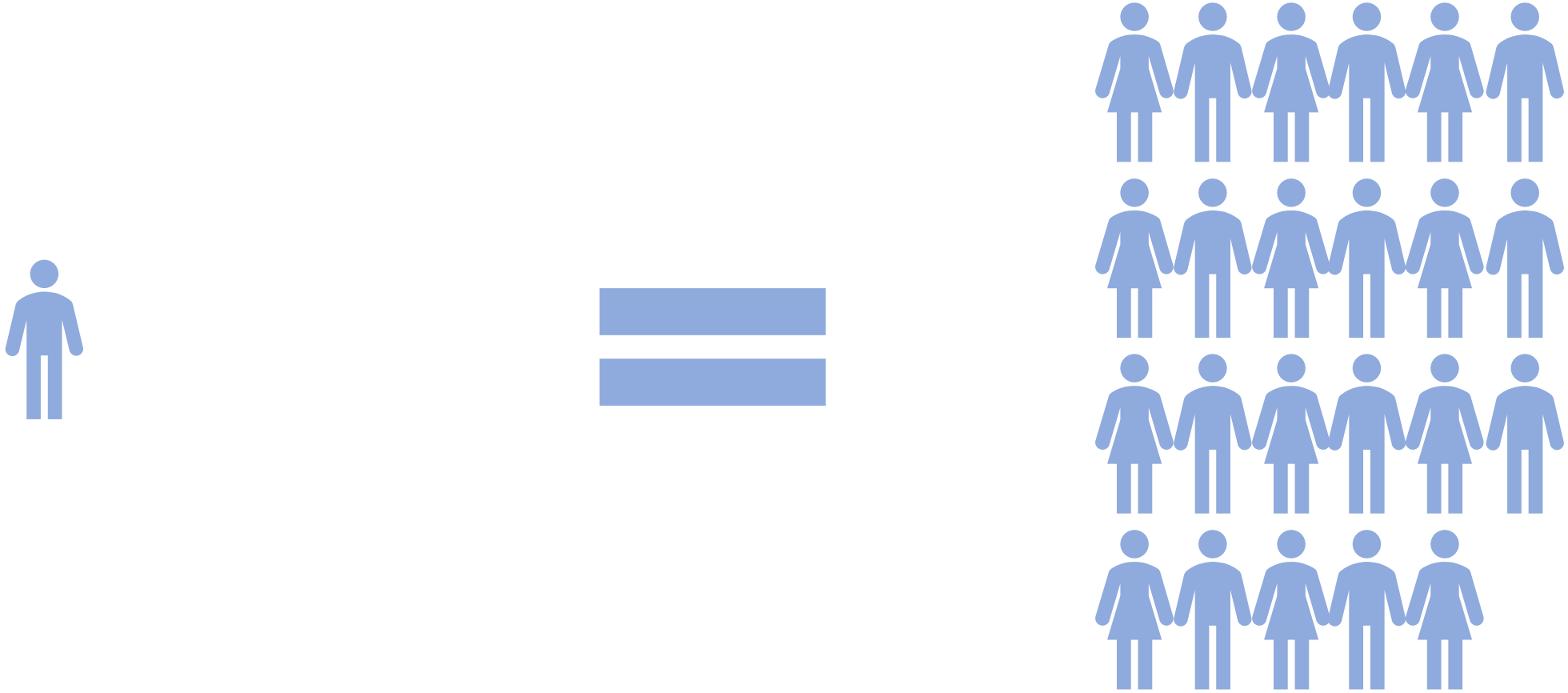
@JCampbellMcGill

# If you consider hospitalization costs for DS-TB in Canada…



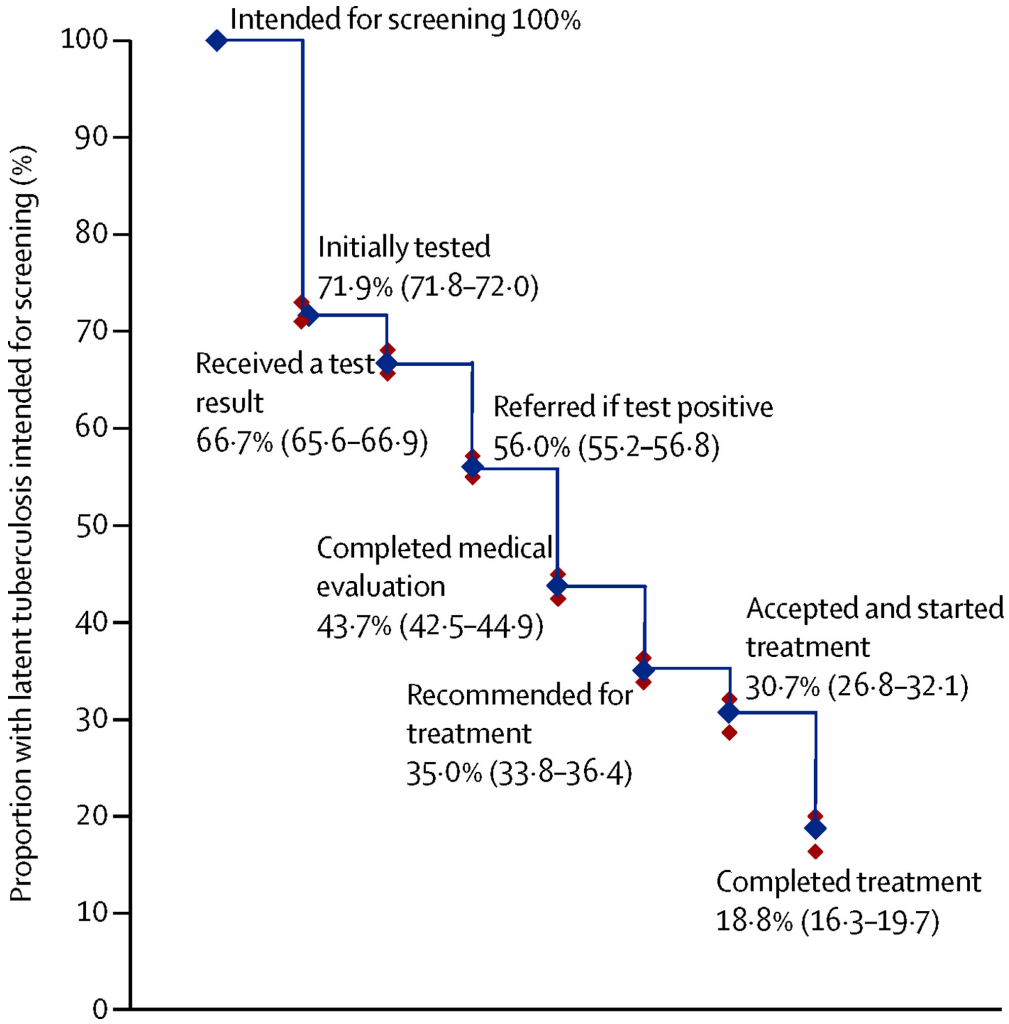
**Providing TPT with four months of rifampicin to 23 people is the SAME PRICE as providing TB disease treatment to 1 person**

Campbell JR, et al. *Emerg ID*. 2022

jonathon.campbell@mcgill.ca
@JCampbellMcGill

# The catch is we have imperfect tools and care

- TB infection diagnosis is based on immune reactivity to TB antigens.
  - Current tests CANNOT distinguish infection from disease, so should be supplemented with ADDITIONAL tests to rule out disease.
  - Sensitivity for (*current or previous*) infection is high (80-90%) but drops substantially among immunocompromised persons.
  - TB infection tests have VERY POOR positive predictive value for development of TB disease.




Alsdurf et al. *Lancet Inf Dis*. 2016

jonathon.campbell@mcgill.ca
@JCampbellMcGill

# With ~~great power~~ imperfect tools comes great responsibility

- Necessary to balance the **RISKS** associated with TB preventive treatment with its **BENEFITS**

| TUBERCULOSIS PREVENTIVE TREATMENT | |
|---|---|
| **RISKS** | **BENEFITS** |
| • Medication side effects<br>• Serious (maybe fatal) adverse events<br>• Psychological impacts of diagnosis and treatment<br>• Costs of treatment (time off work, travel) | Reduced risk of tuberculosis disease and its consequences<br>• Transmission<br>• Hospitalization, adverse events<br>• Catastrophic costs<br>• Psychological and social impacts<br>• Tuberculosis-associated disability<br>• Death from TB and increased risk post-TB |

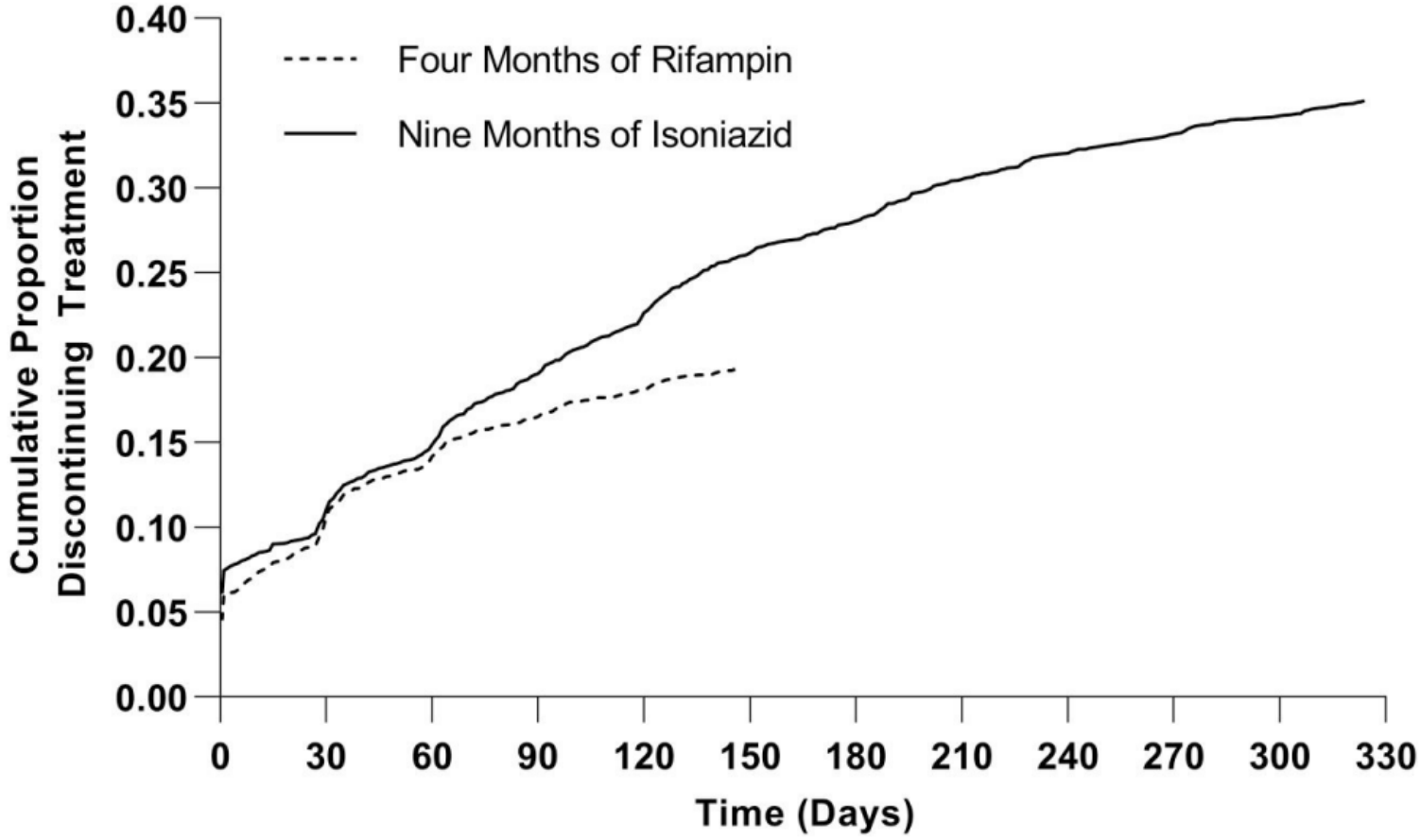
- With imperfect tests… an individual who may never develop TB disease may absorb all the risk associated with treatment without any of the potential benefits.

*table non-exhaustive

jonathon.campbell@mcgill.ca
@JCampbellMcGill

# TPT regimens are effective, but poorly completed

- Completing TPT regimens ensures those treated receive the full benefits of treatment.
- In general, mono-isoniazid regimens are completed ~60-70% of the time, while rifamycin-based regimens are completed ~70-80% of the time.
  - Completion is linked to duration… but not fully explained by it.




Allard-Gray A, et al. *Clin Infect Dis*. 2023

jonathon.campbell@mcgill.ca
@JCampbellMcGill

# Behavioral predictors of TPT discontinuation

- While patient and clinical characteristics have been inconsistently associated with premature discontinuation of TPT, we hypothesized patient behaviors early in treatment may better identify those at risk of discontinuation.

- We investigated this using data from two multicentre, international, randomized controlled trials comparing 9-months isoniazid to 4-months rifampin among 6859 participants.

- We evaluated 4 behaviors at the first-month and second-month follow-up visit and their impact on subsequent treatment discontinuation

| | |
|---|---|
| Self-reported medication intolerance (i.e., side-effects not meeting criteria for adverse events) | Participant decision to reschedule their follow-up appointment |
| Participant forgetting to bring their medication bottle to the appointment | Participant not taking at least 80% of their medication between appointments |

Allard-Gray A, et al. *Clin Infect Dis*. 2023

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@JCampbellMcGill

# Participant behaviors predicted discontinuation

| Number of Behavioral Factors Present at Visit | Discontinuation Between First and Second Month Visit vs. Attending Second Month Visit | | Discontinuation After Second Month Visit but Before Completing Treatment vs. Completing Treatment Ever | |
|---|---|---|---|---|
| | n/N | Adjusted odds ratio (95% CI) | n/N | Adjusted odds ratio (95% CI) |
| 0 | 85/3738 (2.3%) | 1.0 (reference) | 343/3155 (10.9%) | 1.0 (reference) |
| 1 | 119/1155 (10.7%) | 4.9 (3.6 to 6.7) | 191/1289 (14.8%) | 1.8 (1.4 to 2.2) |
| 2 | 98/330 (29.7%) | 18.6 (13.3 to 26.1) | 120/395 (30.4%) | 4.7 (3.6 to 6.2) |
| 3 or 4 | 24/37 (64.9%) | 79.4 (38.2 to 165.0) | 37/95 (38.9%) | 7.4 (4.6 to 11.9) |

- Presence of at least 2 factors should prompt discussion with patient and potential intervention

Allard-Gray A, et al. *Clin Infect Dis*. 2023

jonathon.campbell@mcgill.ca
@JCampbellMcGill

# TPT regimens are also not without risks

- In the same trials comparing rifampin and isoniazid, we evaluated the most common adverse events with each regimen and the age-related and co-morbidity-related risks of adverse events.

| Rifampin (n=3280) | Isoniazid (n=3205) |
|---|---|
| **Rash**<br>• **Any: 25 (0.8%)**<br>• **Severe: 6 (0.2%)** | **Hepatotoxicity**<br>• **Any: 83 (2.6%)**<br>• **Severe: 65 (2%)** |
| GI Intolerance<br>• Any: 13 (0.4%)<br>• Severe: 3 (0.1%) | GI Intolerance<br>• Any: 16 (0.5%)<br>• Severe: 1 (0.03%) |
| Hepatotoxicity<br>• Any: 12 (0.4%)<br>• Severe: 11 (0.3%) | Rash<br>• Any: 13 (0.4%)<br>• Severe: 2 (0.1%) |
| Hematologic<br>• Any: 8 (0.2%)<br>• Severe: 6 (0.2%) | Dizziness<br>• Any: 7 (0.2%)<br>• Severe: 2 (0.1%) |

Campbell JR, et al. *Lancet ID*. 2020

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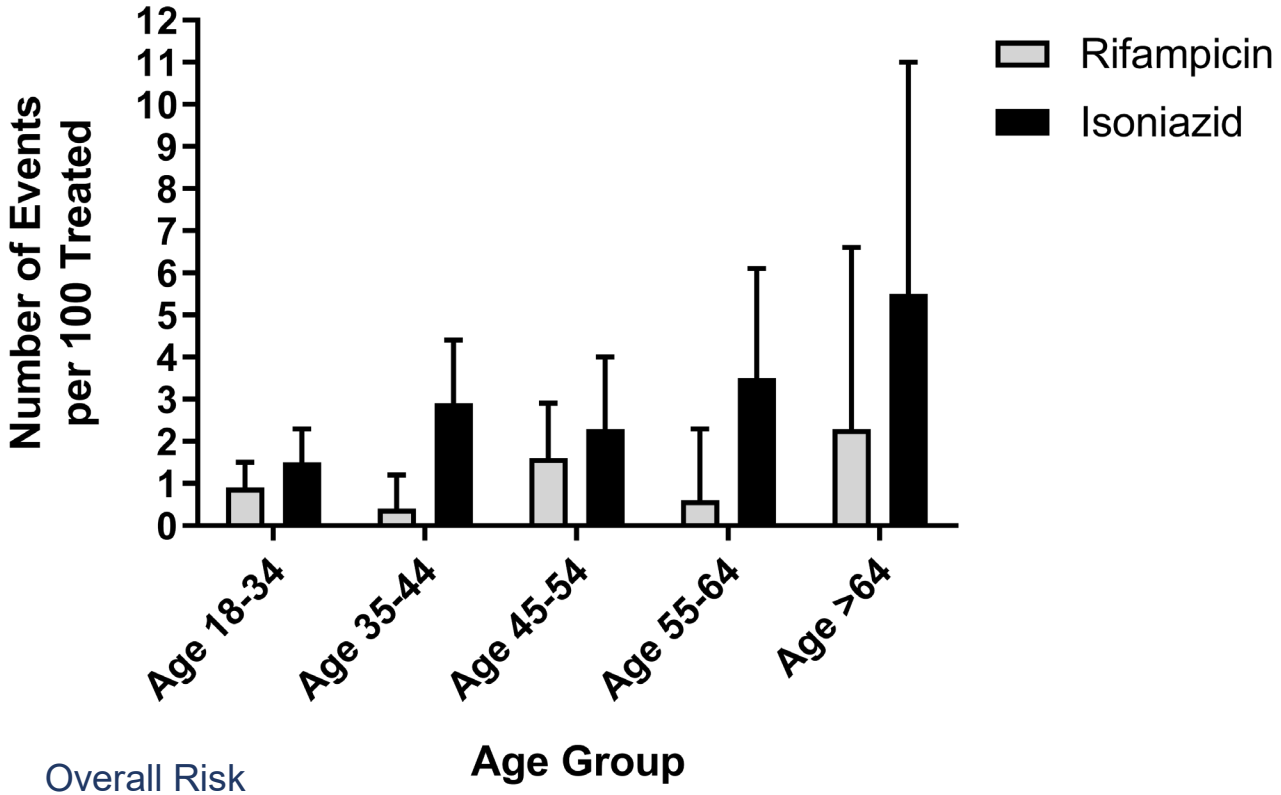
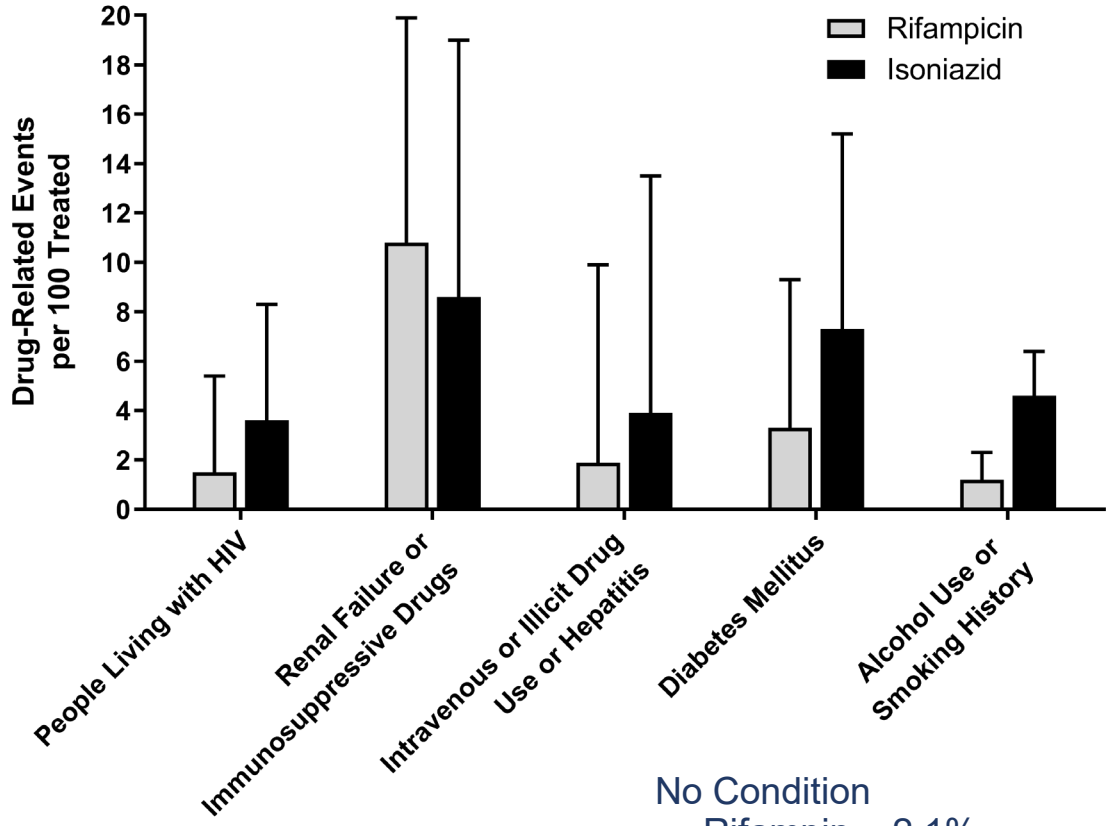
# Adverse event risk age-related with isoniazid, but not rifampin




Overall Risk
- Rifampin = 2.1%
- Isoniazid = 4.1%




No Condition
- Rifampin = 2.1%
- Isoniazid = 3.7%

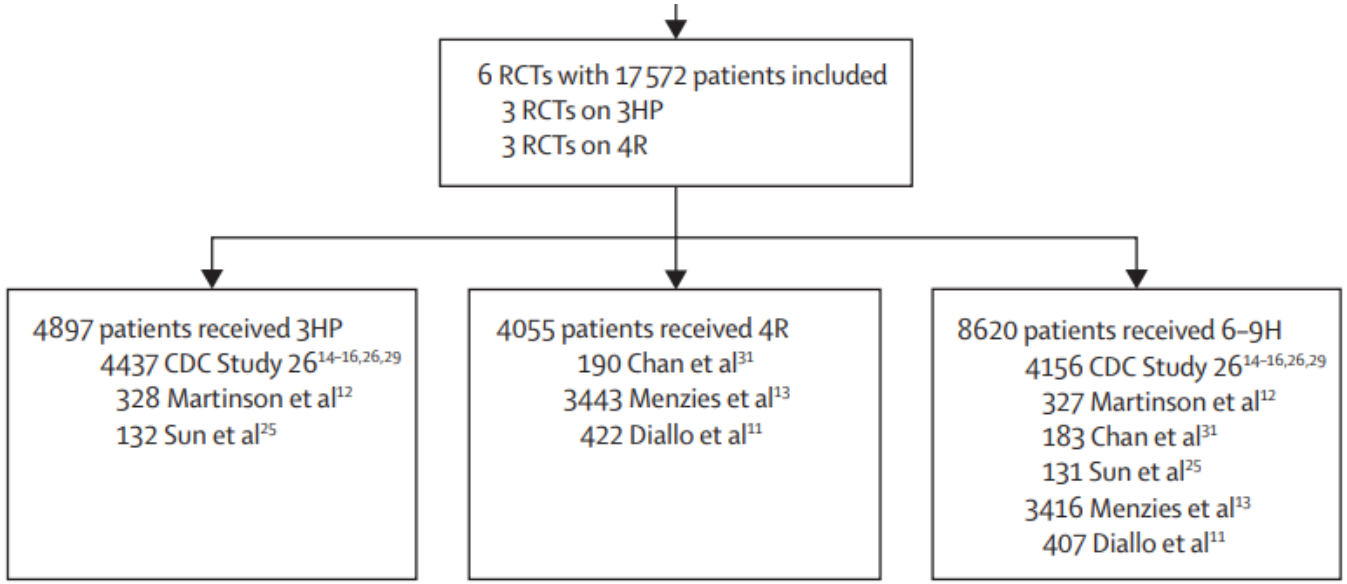
Campbell JR, et al. *Lancet ID*. 2020
Campbell JR, et al. *Clin Infect Dis*. 2021

jonathon.campbell@mcgill.ca
@JCampbellMcGill

# How about the “new” kid on the block?

- The landmark clinical trial comparing 3HP to 9INH suggested much lower risk of hepatotoxicity with 3HP (0.4% vs. 2.7%), but those receiving 3HP were **more likely** to permanently discontinue their medication due to an adverse event (4.9% vs. 3.7%).

- We did a network meta-analysis of clinical trials comparing mono-isoniazid regimens to 4-months rifampin or 3HP to determine differences in **safety** and **completion** for 4-months of rifampin vs. 3HP.




Sterling TR, et al. *NEJM*. 2011.
Winters N, et al. *Lancet Resp Med*. 2023

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# 3HP better completed than 4R… but there's a catch

| | Completing intervention (3HP or 4R) | Completing comparator (6–9H) | Adjusted risk ratio (95% CI)* | Adjusted risk difference (95% CI)* |
|---|---|---|---|---|
| **3HP vs 6–9H, direct individual patient data meta-analysis** | | | | |
| CDC Study 26[14-16,26,29] | 3545/4437 (79·9%) | 2609/4156 (62·8%) | .. | .. |
| Martinson et al[12] | 300/328 (91·5%) | 143/327 (43·7%) | .. | .. |
| Sun et al[25] | 118/132 (89·4%) | 104/131 (79·4%) | .. | .. |
| Total | 3963/4897 (80·9%) | 2856/4614 (61·9%) | 1·30 (1·24–1·37) | 0·19 (0·17–0·21) |
| **4R vs 6–9H, direct individual patient data meta-analysis** | | | | |
| Menzies et al[13] | 2476/3443 (71·9%) | 1965/3416 (57·5%) | .. | .. |
| Diallo et al[11] | 352/422 (83·4%) | 305/407 (74·9%) | .. | .. |
| Total | 2828/3865 (73·2%) | 2270/3823 (59·4%) | 1·23 (1·17–1·30) | 0·14 (0·12–0·16) |
| **3HP vs 4R, individual patient data network meta-analysis** | | | | |
| All studies | .. | .. | 1·06 (1·02–1·10)† | 0·05 (0·02–0·07)† |
| 9H only‡ | .. | .. | 1·02 (0·98–1·07)† | 0·03 (0·00–0·06)† |

| | Intervention (3HP or 4R) | Comparator (6–9H) | Adjusted risk ratio (95% CI)* | Adjusted risk difference (95% CI)* |
|---|---|---|---|---|
| **Any treatment-related adverse event that led to permanent drug discontinuation†** | | | | |
| 3HP vs 6–9H, direct individual patient data meta-analysis | | | | |
| CDC Study 26[14-16,26,29] | 247/4343 (5·7%) | 170/4066 (4·2%) | .. | .. |
| Martinson et al[12] | 0/328 | 2/326 (0·6%) | .. | .. |
| Sun et al[25] | 12/132 (9·1%) | 7/131 (5·3%) | .. | .. |
| Total | 259/4803 (5·4%) | 179/4523 (4·0%) | 1·37 (1·13 to 1·66) | 0·01 (0·01 to 0·02) |
| 4R vs 6–9H, direct individual patient data meta-analysis | | | | |
| Chan et al[31] | 2/190 (1·1%) | 13/183 (7·1%) | .. | .. |
| Menzies et al[13] | 68/3281 (2·1%) | 131/3231 (4·1%) | .. | .. |
| Diallo et al[11] | 0/420 | 0/397 | .. | .. |
| Total | 70/3891 (1·8%) | 144/3811 (3·8%) | 0·48 (0·36 to 0·63) | −0·02 (−0·03 to −0·01) |
| 3HP vs 4R, individual patient data network meta-analysis | | | | |
| All studies | .. | .. | 2·86 (2·12 to 4·21)‡ | 0·03 (0·02 to 0·05)‡ |

- When considering only grade 3-4 adverse events, the adjusted risk difference was **0.02 (0.01 to 0.03).**

Winters N, et al. *Lancet Resp Med*. 2023

jonathon.campbell@mcgill.ca
@JCampbellMcGill

# Target TPT to those at highest risk of disease (ie, most likely to benefit)

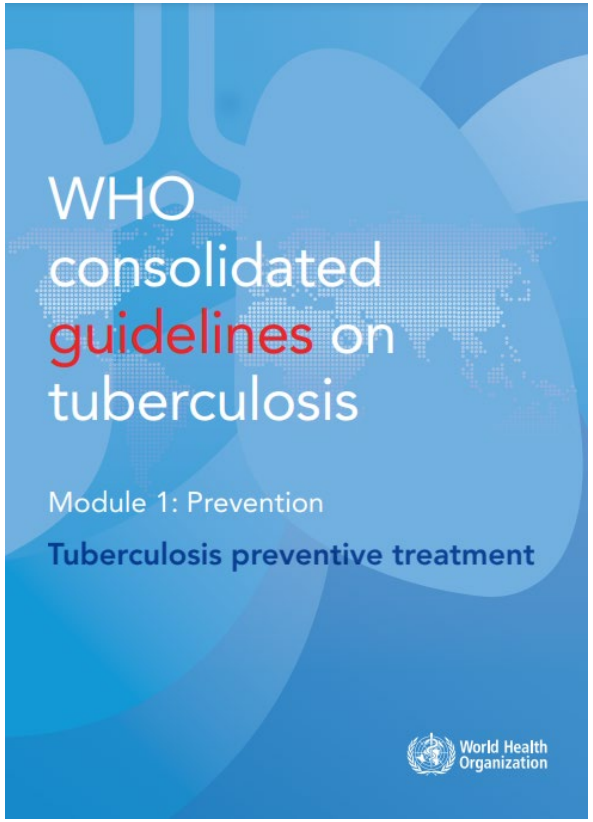
- We typically had defined “high-risk” based on incidence of TB disease in “groups” with vs. without specific “risk factors”

- This is problematic as it conflates two very different phenomena:

    1. The risk of being infected with tuberculosis—influenced by local epidemiology, immunocompetency, transmission dynamics, and patient history

    2. The risk of progressing from infection to disease—influenced by time since infection and immunocompetency.

- WHO TB Prevention guidelines list 24 (!) “at-risk” groups, but absolute risks of developing disease are absent.



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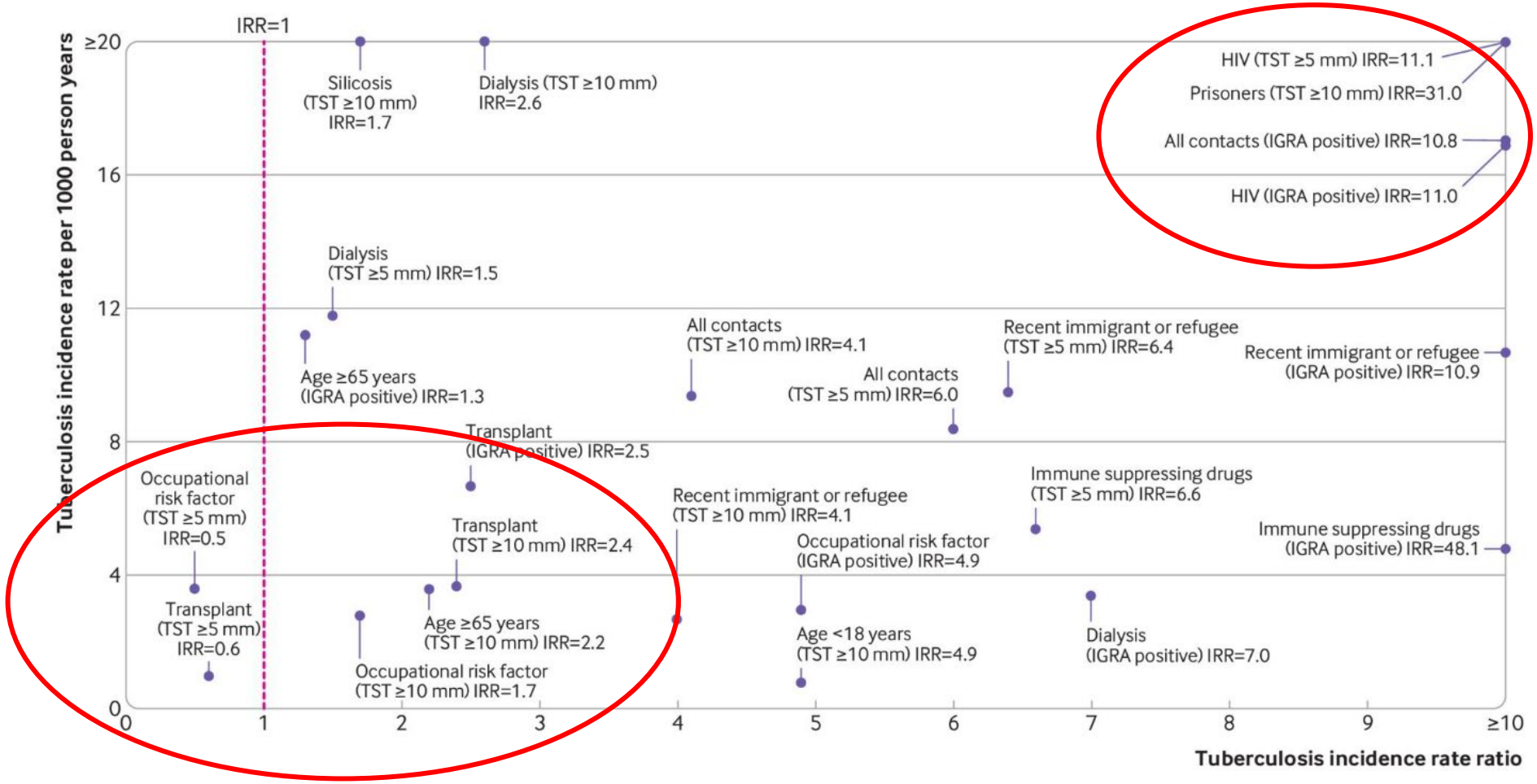
# Risk of tuberculosis disease appears elevated in many groups

- We estimated absolute risk of progressing to tuberculosis disease in a systematic review and meta-analysis of 122 studies and 116,197 people with a positive TST/IGRA who did NOT receive treatment.
- In studies who followed those with negative tests, we estimated incidence rate ratios




Campbell JR, Winters N, Menzies D. *BMJ*. 2020

jonathon.campbell@mcgill.ca
@JCampbellMcGill

# Absolute risk of tuberculosis disease after a positive TST/IGRA

| Risk Factor | Annual Risk of TB Disease for the First 2-3 Years After Testing-Positive |
|---|---|
| **VERY HIGH RISK** | |
| People Living with HIV | 1.7% to 2.7% |
| Child or Adolescent (<18y) Tuberculosis Contact | 2.9% to 14.6% |
| Adult (≥18y) Tuberculosis Contact | 0.8% to 3.7% |
| Silicosis | 3.7% |
| **HIGH RISK** | |
| Stage 4 or 5 Chronic Kidney Disease with or Without Dialysis | 0.3% to 1.2% |
| Transplant Recipients (solid organ or hematopoietic) | 0.1% to 0.7% |
| Fibronodular Disease | 0.2% to 0.6% |
| Receiving Immunosuppressing Drugs (e.g., tumour necrosis factor α inhibitors or steroids) | 0.5% |
| Cancer (lung, sarcoma, leukaemia, lymphoma, or gastrointestinal) | 0.1% to 0.4% |
| **MODERATE RISK** | |
| Granuloma on Chest X-Ray | 0.1% |
| Diabetes | 0.1% to 0.2% |
| Heavy Alcohol Use (at least 3 drinks/day) | 0.1% to 0.2% |
| Heavy Tobacco Cigarette Smoker (at least 1 pack/day) | 0.1% |
| **LOW RISK** | |
| General, Adult Population with No Known Risk Factor | 0.03% |

Campbell JR, Winters N, Menzies D. *BMJ*. 2020
Gupta RK, et al. *Nat Med*. 2020.
Zhou G, et al. *Lancet ID*. 2020.
Martinez L, et al. *Lancet*. 2020.
Campbell JR, et al. *Can J Respir Crit Care Sleep Med*. 2022.

jonathon.campbell@mcgill.ca
@JCampbellMcGill

# What if we scaled TPT to all PLHIV and HHC?

- We did a modeling study looking the impact and cost-effectiveness of scaling TPT to all PLHIV newly initiating ART and all HHC in Brazil and South Africa beginning in 2020 and then sustained through to 2035.
  - We compared the current standard of care, scale-up of 6INH, scale-up of a regimen mimicking 3HP ("minimal"), and scale-up of a universally acceptable regimen ("optimal").

| Parameter | 6H | Minimal | Optimal |
|---|---|---|---|
| **Regimen attributes** | | | |
| Regimen duration (months) | 6 | 3 | 1 |
| Efficacy | 70% | 70% | 100% |
| Rifampicin-resistance barrier | 100% | 95% | 100% |
| Regimen forgiveness* | 25% | 50% | 80% |
| Treatment completion | 70% | 80% | 90% |

*Regimen forgiveness, defined as the proportion who receive full benefit among persons who complete between 50% and 100% of treatment.

Nsengiyumva NP,* Campbell JR,* et al. *PLoS Med.* 2022
Vesga J, et al. *BMC Med.* 2022

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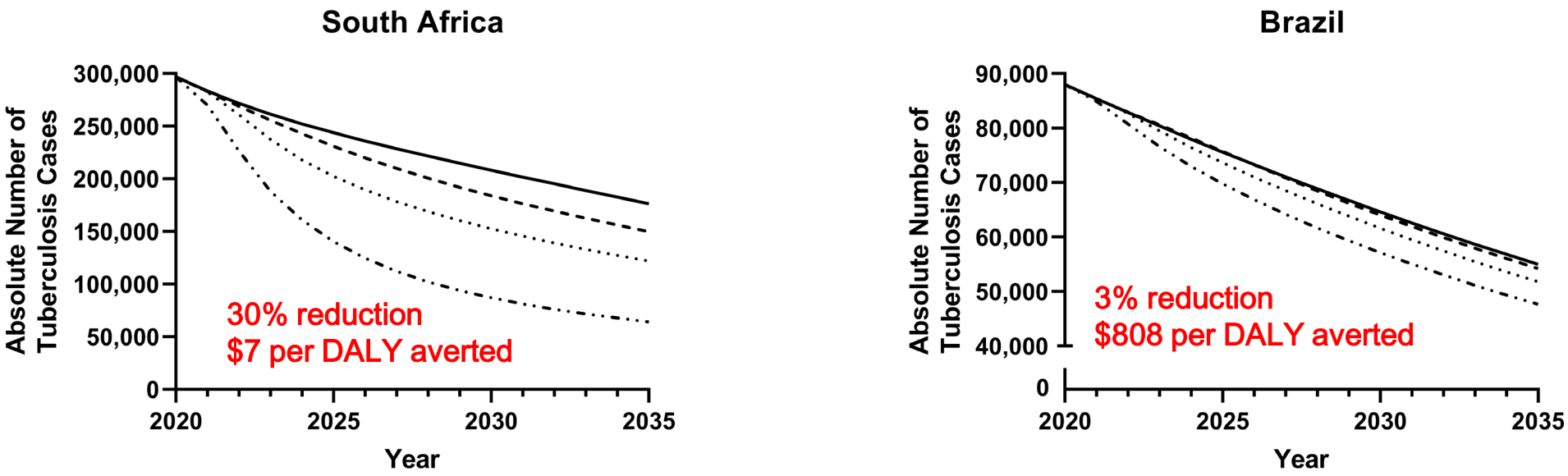
# Benefits of scaling TPT vary by TB epidemiology




— Current Trend

- - - Scale-up Isoniazid Preventive Treatment

···· Scale-up Rifamycin-Based Preventive Treatment

- · · Scale-up Universally Acceptable Preventive Treatment

Nsengiyumva NP,* Campbell JR,* et al. *PLoS Med.* 2022
Vesga J, et al. *BMC Med.* 2022

jonathon.campbell@mcgill.ca
@JCampbellMcGill

# Moving beyond PLHIV and HHC

- In many low-incidence, high-income countries, tuberculosis is concentrated among people born outside the country.
  - The vast majority of tuberculosis in this group occurs among people with no known history of tuberculosis contact.

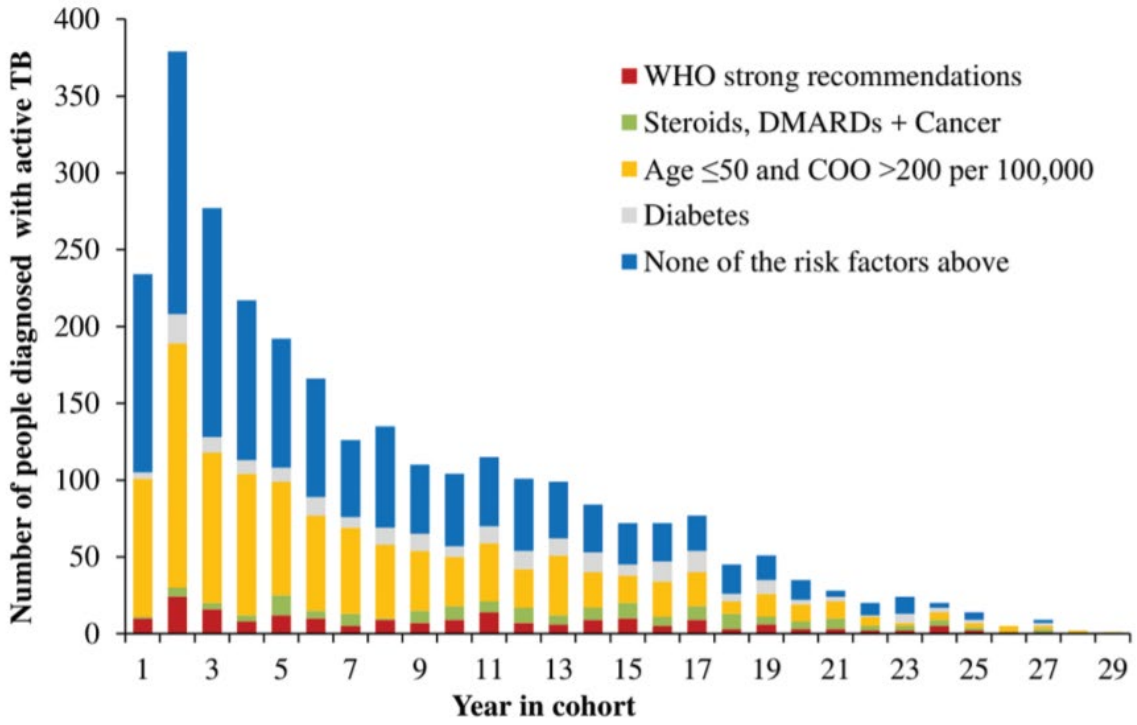
- In Canada, the estimated prevalence of tuberculosis infection (as measured by a TST/IGRA) among people born outside of Canada is 22% (95% UR 19% to 28%).
  - Of all people with tuberculosis infection in Canada, only 1 in 440 were likely to have acquired infection in the previous two years*
    - When considering only those newly arriving, the number is 1 in 39.

**Given risk of disease is low—even among those newly arriving—how should we target screening and what would be the potential impact?**

Jordan A, et al. *Under Revision*.

jonathon.campbell@mcgill.ca
@JCampbellMcGill

# Targeting TB infection screening and treatment to those with risk factors




| Population to Screen | Percent of Population to Screen and Treat | Percent of TB Prevented |
|---|---|---|
| HIV, contacts, TNF-alpha, dialysis, transplant, silicosis | 1.5% | 4.2% |
| Add: steroids, DMARDS, cancer | 3.8% | 8.3% |
| Add: People immigrating from very high incidence country under 50 years of age | 24.6% | 42.4% |
| Add: diabetes | 30.5% | 49.4% |

- Strategies become increasingly inefficient as you add additional groups and risk-benefit considerations become increasingly important

Ronald LA, et al. *Clin Infect Dis*. 2019

jonathon.campbell@mcgill.ca
@JCampbellMcGill

# Concluding thoughts

- Providing tuberculosis preventive treatment to only the highest risk groups can have a major impact on TB epidemiology outside of any other TB-related intervention in some settings, but its impact is significantly more limited in others.

- Moving beyond the highest risk groups for TB preventive treatment will be necessary in many contexts, but for these populations, risks of TB are likely to be lower, while risks of adverse events with current therapy might be higher.

- We need to better quantify the **risks** associated with developing tuberculosis disease, as well as better support those receiving TPT, so they complete treatment and receive the **benefits**.
  - Doing this in parallel with other TB-related interventions and the development of improved diagnostics and treatments, should **motivate the scale-up of an underutilized and effective intervention to prevent tuberculosis disease**.

jonathon.campbell@mcgill.ca
@JCampbellMcGill

# Thank you for your attention

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