From TSTin3D to TSTin4D:
Why do we need Risk-Benefit Analyses?
When can we stop?

Webinar Curry TB Center, UCSF 18 June 2025

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Disclosures

Dr Menzies Receives salary support as a Canada Research Chair (Tier 1)

And operating grants from CDC (TBTC) and CIHR and WHO.

Dr Menzies, will present on Investigational use of high dose rifampin, rifapentine, levofloxacin for TPT

Background TSTin3D (2011 version)

- Estimated the risk of progressing to TB. Considered 3 “Dimensions”:
  - TB Infection Test result (size of TST reaction)
  - Positive Predictive value of the test
  - Epidemiological and clinical risk factors
- Did not estimate: mortality and disability after TB disease
  - Considered TPT adverse events (but not benefits)
- Only for 9H (last update 2011)
- Website originally designed for providers only

Old Version (TST in 3D)

The Online TST/IGRA Interpreter
Version 3.0

English

The following tool estimates the risk of active tuberculosis for an individual with a tuberculin skin test reaction of ≥5mm, based on his/her clinical profile. It is intended for adults tested with standard tuberculin (5 TU PPDS, or 2 TU RT-23) and/or a commercial Interferon Gamma release assay (IGRA).

Enter

Français

L'outil suivant évalue le risque de développer une tuberculose active chez une personne ayant eu une réaction au test cutané à la tuberculine de ≥5mm selon son profil clinique. L'outil a été conçu pour une utilisation chez une population adulte soumise au test tuberculine standard (5 TU PPDS ou 2 TU RT-23) et/ou les tests de libération d'interféron-gamma (TLIG(IGRA)).

Entrez

Calculator | About | Disclaimer | References | Links

The Online TST/IGRA Interpreter
Version 3.0

The following tool estimates the risk of active tuberculosis for an individual with a tuberculin skin test reaction of ≥5mm, based on his/her clinical profile. It is intended for adults tested with standard tuberculin (5 TU PPDS, or 2 TU RT-23) and/or a commercial Interferon Gamma release assay (IGRA). For more details about the algorithm used, go to the About page. The current version of the algorithm contains modifications of the original version, which was detailed in a paper by Menzies, et al. (2008). For further information see references, or contact dick.menzies@mcgill.ca

Results

Once you have completed the form, click on "Submit" and your results will show up in this space.

For inquiries, and suggestions please contact dick.menzies@mcgill.ca.

Please select the best response for each field:

TST Size: Select...

IGRA Result: IGRA Not Done

Age: Select...

Age at immigration (if person immigrated to a low TB incidence country): N/A

Country of birth: Select...

BCG status: Select...
For more info, visit: BCG World Atlas.

Recent contact with active TB: No Contact

Please select all the conditions that currently apply to the patient:
(If none of these conditions apply, please leave boxes unchecked)

- ☐ AIDS
- ☐ Abnormal chest x-ray: fibronodular disease
- ☐ Chronic renal failure requiring hemodialysis
- ☐ Diabetes Mellitus (all types)
- ☐ Recent TB infection (TST conversion ≤ 2 years ago)
- ☐ Silicosis
- ☐ Tumor Necrosis Factor (TNF)-alpha inhibitors(e.g. Infliximab/Etanercept)
- ☐ Young age when infected (0-4 years)
- ☐ Abnormal chest x-ray: granuloma
- ☐ Carcinoma of head and neck
- ☐ Cigarette smoker(>1 pack/day)
- ☐ HIV infection
- ☐ Transplantation (requiring immune-suppressant therapy)
- ☐ Treatment with glucocorticoids
- ☐ Underweight (< 90 per cent ideal body weight or a body mass index (BMI) ≤ 20)

Submit

The new TST in 4D

- **Estimates the absolute TB risk plus TB related mortality & Disability. And reduction in risk with TPT – 4 regimens**
  - 1st Dimension: Risk groups (20 risk groups)
  - 2nd Dimension: treatment (4 TPT regimens vs none)
  - 3rd Dimension: age group (4 age groups)
  - 4th Dimension: TBI test results (three categories)

Methods for the calculations (the ‘back end’)

- State-transition Markov microsimulation model with a probabilistic sensitivity analysis
- Time horizon: 20 year
- Four treatments: None, 9H, 3HP, 4R and 3HR
- Four age groups: 18 to 34, 35 to 49, 50-64, +65
- Input parameters: Utilities and probabilities from published literature
- Outcomes: quality-adjusted life years (QALYs), risk of developing TB disease, developing severe respiratory disability after TB treatment, and dying from TB. Plus reduction of these risks, and adverse events with TPT

Populations (Risk groups – each divided into 4 age groups)

- **General Population (healthy, no risk factors)**
- Casual Contact
- **Recent immigration (tested within 5 years after arrival)**
- Health Care Workers
- **Close Contact**
- Abnormal chest x-ray - fibronodular disease
- Abnormal chest x-ray – granuloma
- Cigarette smoker (at least 1 pack/day)
- Steroids
- Diabetes Mellitus
- Chronic kidney disease on dialysis
- **Person with HIV on ART**
- **Receiving TNF alfa inhibitors**
- Carcinoma: Head and Neck
- Carcinoma: Lung
- Hodgkin’s Lymphoma
- Non-Hodgkin’s Lymphoma
- Transplant liver: requiring immunosuppressants
- Transplant kidney: requiring immunosuppressants
- Silicosis

Results: The 1st dimension

Patient aged 18 to 34 with TST ≥10 mm:

Effect of:

- Risk group

Results: The 1st and 2nd dimensions

Patient aged 18 to 34 with TST ≥10 mm:

Effect of:

- Risk group
- TB Preventive Treatment (TPT)

Results: The 3rd dimension

Effect of Age on benefits of TPT

Results: The 4th dimension

Patient aged 18 to 34

Influence of type of TB infection test on TB risks

In words: what's the risk if IGRA positive vs TST pos

From cohort studies that have tested groups with TST and IGRA

A total of three studies identified in 2020 systematic review plus a recent large TBESC study in USA

Incidence rate ratios of TB disease in untreated persons:

QFT+/TST10+ Range from 1.33 to 1.57 for QFT/TST10+

Slightly higher for Tspot/TST10+

This is a modest effect, compared to IRR for HIV or close contact vs no risk factors

Discordant tests – what's the risk

A common clinical scenario (and question)

- Positive TST – and an IGRA is done.
- If IGRA is positive – is the risk higher?
- If IGRA is negative – is the risk lower? How much lower?

From earlier systematic review (Campbell, BMJ, 2020)

- Six studies identified: All in contacts, Initially tested, not treated, Followed for TB disease.
- Incidence rate ratio (IRR) of Discordant/TST pos or Concordant/TST pos

Discordant tests – what's the risk

Rate TST Pos = 1.24 per 100 PY

Rate TST+/IGRA- = 0.66 per 100 PY

Rate TST+/IGRA+ = 2.74 per 100 PY

Relative to risk if TST is 10+mm

IRR = 0.53 if TST Pos & IGRA negative

IRR = 2.21 if TST Pos & IGRA positive.

And… **Relative to risk if IGRA is positive:** *(very few studies and numbers)*

IRR = 0.65 if TST Neg & IGRA positive

These will be incorporated in revision planned soon

Discordant TST/IGRA – 2 examples

- 20 year old nursing student. Born in Canada. TST 13mm. No known TB exposure, some travel but only a few weeks. No medical illnesses. Takes no meds. CXR is Normal.
  - Interpretation: Risk of TB disease is LOW. (VERY LOW). Treat?
  - IGRA is done – and is negative: Risk is now about half what it was before IGRA was done.
  - Half of VERY LOW is ? Treat??

- Patient # 2: 50 year old nurse. Born in Canada. TST 13mm. Works in ER. Had a TST a year ago and this was negative. Had probable TB exposure in ER 2 months ago. Has diabetes and mild renal impairment. No symptoms. CXR is normal
  - Interpretation: Risk of TB disease is ?? Treat?
  - IGRA is done and is negative: Risk is about half
  - Still.... Half of moderate to high is still considerable....Treat?

Methods for the New Website (the “front-end”)

- Qualitative study – patients and providers
  - Semi-structured interview/survey guide
  - One-on-one ‘interviews’/usability surveys

- Interviewed a total of 30 participants
  - 15 patients
  - 15 health care providers

- What they liked/didn’t like about current TSTin3D
- What they wanted from a new decision aid
- Looked at choices and examples
- (**https://www.tstin4d.com**)

Recent Immigrant – no TPT

1. Input Your Information

What is your age

40

What is the size of your TST (Skin Test)

≥10mm

What is your IGRA result (Blood Test)

Not Done

Please Check All That Applies Below:

- Habits
- TB Exposure
  - Casual Contact
  - Close Contact
  - Recent Immigration (within the past 5 years)
  - Occupational Risk (Healthcare Worker)
- Cancer
- Immune-Compromised
- Immunosuppressive Treatment
- TB-related Chest X-Ray findings

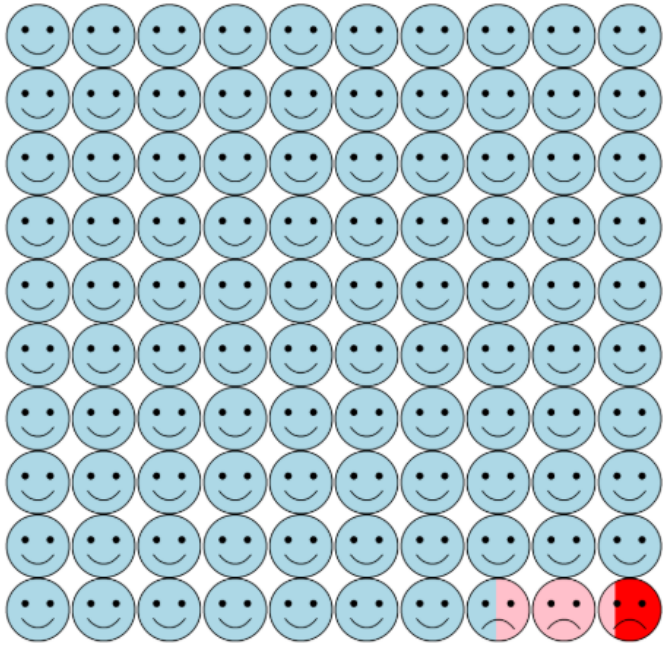
Uncheck All Selection

2. Your TB Risk (Over the Next 20 Years)

Healthcare Provider | Patient

FAQ

What is the risk of TB disease in the next 20 years without treatment? Out of 100 persons with the risk factors selected:



97.5% Will not develop TB disease with or without treatment

2.5% will develop TB disease without treatment

0.8% will develop TB disease and TB-related long-term disability or death without treatment

3. Input Preventive Treatment

Select one of the following treatment options:

- (●) No Treatment
- ( ) 4 months of daily rifampin (4R)
- ( ) 9 months of daily isoniazid (9H)
- ( ) 3 months of once-weekly isoniazid plus rifapentine (3HP)
- ( ) 3 months of daily isoniazid plus rifampin (3HR)

For drug interactions, see Medscape Drug Interaction Checker

4. Summary of your TB Risk

Without Treatment

- Your risk of TB disease without treatment in the next 20 years: 2.5%
- Your risk of disability and death from TB disease without treatment in the next 20 years: 0.8%

Download Patient Handout

Recent Immigrant – 4R

1. Input Your Information

What is your age

40

What is the size of your TST (Skin Test)

≥10mm

What is your IGRA result (Blood Test)

Not Done

Please Check All That Applies Below:

- Habits
- TB Exposure
  - Casual Contact
  - Close Contact
  - Recent Immigration (within the past 5 years)
  - Occupational Risk (Healthcare Worker)
- Cancer
- Immune-Compromised
- Immunosuppressive Treatment
- TB-related Chest X-Ray findings

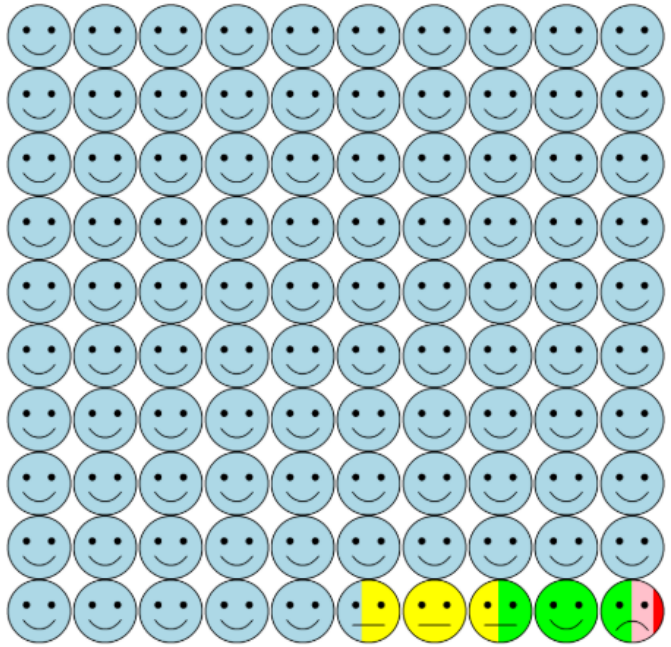
Uncheck All Selection

2. Your TB Risk (Over the Next 20 Years)

Healthcare Provider | Patient

FAQ

What is the risk of TB disease in the next 20 years if I recommend treatment (accounting for people who don't take it)? Out of 100 persons with the risk factors selected:



97.5% Will not develop TB disease with or without treatment

2.1% Had an adverse event that led to stopping therapy

2.0% of those prescribed therapy will prevent TB disease (accounting for overall completion rates)

0.5% of those prescribed therapy will develop TB disease despite treatment (this also accounts for possible non-adherence)

0.2% of those prescribed therapy will develop TB disease and TB-related long-term disability or death despite treatment (accounting for overall completion rates)"

3. Input Preventive Treatment

Select one of the following treatment options:

- ○ No Treatment
- ◉ 4 months of daily rifampin (4R)
- ○ 9 months of daily isoniazid (9H)
- ○ 3 months of once-weekly isoniazid plus rifapentine (3HP)
- ○ 3 months of daily isoniazid plus rifampin (3HR)

For drug interactions, see Medscape Drug Interaction Checker

4. Summary of your TB Risk

Without Treatment

- Your risk of TB disease without treatment in the next 20 years: 2.5%
- Your risk of disability and death from TB disease without treatment in the next 20 years: 0.8%

With Treatment 4 months of daily rifampin (4R)

Accounting for possible non-adherence:

- Your risk of developing TB disease in the next 20 years despite taking treatment: 0.5% (reduced by 2.0%)
- Your risk of developing long-term disability and death despite taking treatment: 0.1%
- Your risk of having an adverse event from the treatment (leading to treatment discontinuation): 2.1%

Download Patient Handout

Close contacts– no TPT

1. Input Your Information

What is your age

40

What is the size of your TST (Skin Test)

≥10mm

What is your IGRA result (Blood Test)

Not Done

Please Check All That Applies Below:

- Habits
- TB Exposure
  - Casual Contact
  - Close Contact
  - Recent Immigration (within the past 5 years)
  - Occupational Risk (Healthcare Worker)
- Cancer
- Immune-Compromised
- Immunosuppressive Treatment
- TB-related Chest X-Ray findings

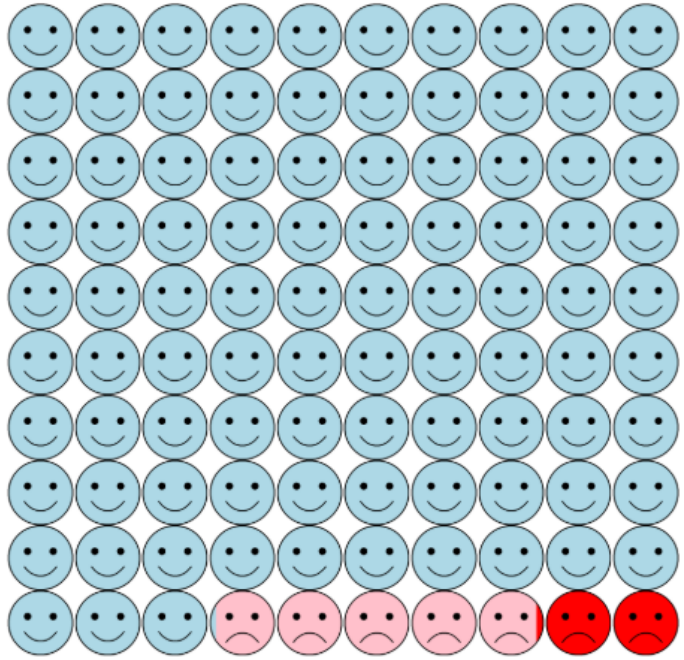
Uncheck All Selection

2. Your TB Risk (Over the Next 20 Years)

Healthcare Provider | Patient

FAQ

What is the risk of TB disease in the next 20 years without treatment? Out of 100 persons with the risk factors selected:



93.0% Will not develop TB disease with or without treatment

7.0% will develop TB disease without treatment

2.1% will develop TB disease and TB-related long-term disability or death without treatment

3. Input Preventive Treatment

Select one of the following treatment options:

- (●) No Treatment
- ( ) 4 months of daily rifampin (4R)
- ( ) 9 months of daily isoniazid (9H)
- ( ) 3 months of once-weekly isoniazid plus rifapentine (3HP)
- ( ) 3 months of daily isoniazid plus rifampin (3HR)

For drug interactions, see Medscape Drug Interaction Checker

4. Summary of your TB Risk

Without Treatment

- Your risk of TB disease without treatment in the next 20 years: 7.0%
- Your risk of disability and death from TB disease without treatment in the next 20 years: 2.1%

Download Patient Handout

Close contacts– 4R

1. Input Your Information

What is your age

40

What is the size of your TST (Skin Test)

≥10mm

What is your IGRA result (Blood Test)

Not Done

Please Check All That Applies Below:

- Habits
- TB Exposure
  - Casual Contact
  - Close Contact
  - Recent Immigration (within the past 5 years)
  - Occupational Risk (Healthcare Worker)
- Cancer
- Immune-Compromised
- Immunosuppressive Treatment
- TB-related Chest X-Ray findings

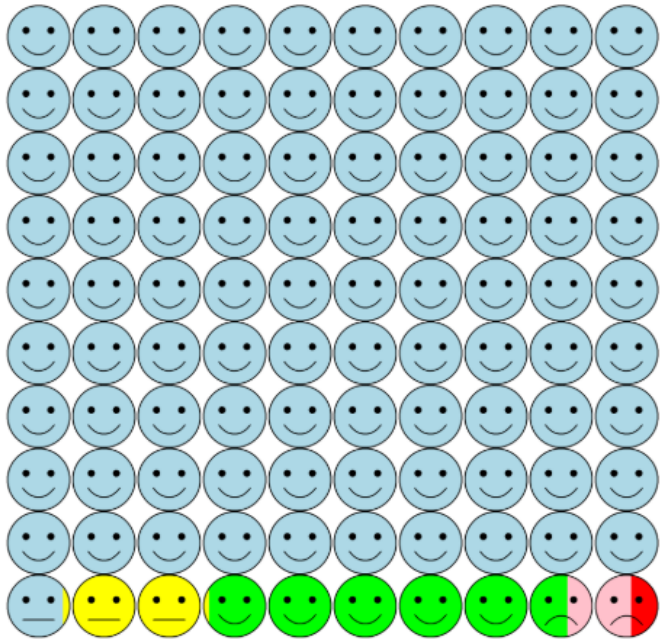
Uncheck All Selection

2. Your TB Risk (Over the Next 20 Years)

Healthcare Provider | Patient

FAQ

What is the risk of TB disease in the next 20 years if I recommend treatment (accounting for people who don't take it)? Out of 100 persons with the risk factors selected:



93.0% Will not develop TB disease with or without treatment

2.1% Had an adverse event that led to stopping therapy

5.6% of those prescribed therapy will prevent TB disease (accounting for overall completion rates)

1.4% of those prescribed therapy will develop TB disease despite treatment (this also accounts for possible non-adherence)

0.4% of those prescribed therapy will develop TB disease and TB-related long-term disability or death despite treatment (accounting for overall completion rates)"

3. Input Preventive Treatment

Select one of the following treatment options:

- ○ No Treatment
- ◉ 4 months of daily rifampin (4R)
- ○ 9 months of daily isoniazid (9H)
- ○ 3 months of once-weekly isoniazid plus rifapentine (3HP)
- ○ 3 months of daily isoniazid plus rifampin (3HR)

For drug interactions, see Medscape Drug Interaction Checker

4. Summary of your TB Risk

Without Treatment

- Your risk of TB disease without treatment in the next 20 years: 7.0%
- Your risk of disability and death from TB disease without treatment in the next 20 years: 2.1%

With Treatment 4 months of daily rifampin (4R)

Accounting for possible non-adherence:

- Your risk of developing TB disease in the next 20 years despite taking treatment: 1.4% (reduced by 5.6%)
- Your risk of developing long-term disability and death despite taking treatment: 0.4%
- Your risk of having an adverse event from the treatment (leading to treatment discontinuation): 2.1%

Download Patient Handout

TNF alfa inhibitors – no TPT

1. Input Your Information

What is your age

40

What is the size of your TST (Skin Test)

≥10mm

What is your IGRA result (Blood Test)

Not Done

Please Check All That Applies Below:

- Habits
- TB Exposure
- Cancer
- Immune-Compromised
- Immunosuppressive Treatment
  - Steroids, at least 10mg of prednisone daily (or equivalent)
  - TNF-alpha Inhibitors
- TB-related Chest X-Ray findings

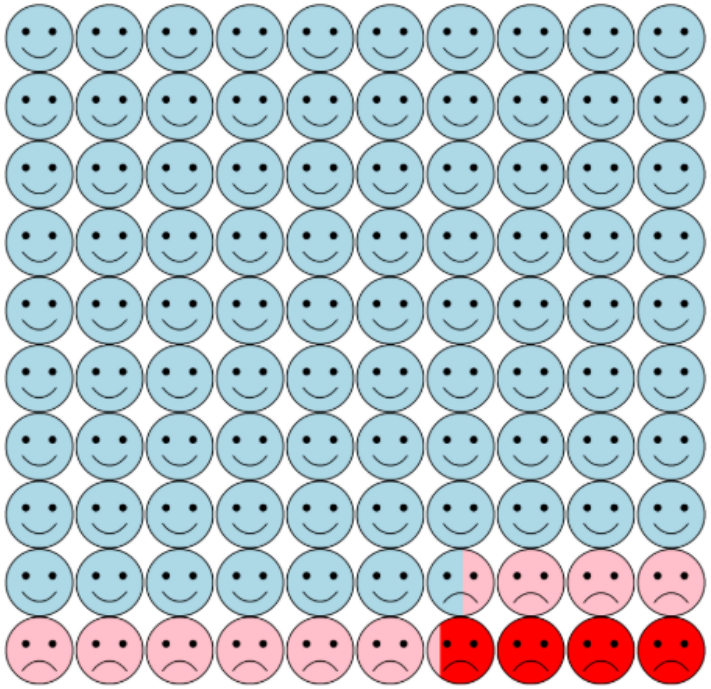
Uncheck All Selection

2. Your TB Risk (Over the Next 20 Years)

Healthcare Provider | Patient

FAQ

What is the risk of TB disease in the next 20 years without treatment? Out of 100 persons with the risk factors selected:



86.5% Will not develop TB disease with or without treatment

13.5% will develop TB disease without treatment

3.8% will develop TB disease and TB-related long-term disability or death without treatment

3. Input Preventive Treatment

Select one of the following treatment options:

- (●) No Treatment
- ( ) 4 months of daily rifampin (4R)
- ( ) 9 months of daily isoniazid (9H)
- ( ) 3 months of once-weekly isoniazid plus rifapentine (3HP)
- ( ) 3 months of daily isoniazid plus rifampin (3HR)

For drug interactions, see Medscape Drug Interaction Checker

4. Summary of your TB Risk

Without Treatment

- Your risk of TB disease without treatment in the next 20 years: 13.5%
- Your risk of disability and death from TB disease without treatment in the next 20 years: 3.8%

Download Patient Handout

TNF alfa inhibitors – 4R

1. Input Your Information

What is your age

40

What is the size of your TST (Skin Test)

≥10mm

What is your IGRA result (Blood Test)

Not Done

Please Check All That Applies Below:

- Habits
- TB Exposure
- Cancer
- Immune-Compromised
- Immunosuppressive Treatment
  - Steroids, at least 10mg of prednisone daily (or equivalent)
  - TNF-alpha Inhibitors
- TB-related Chest X-Ray findings

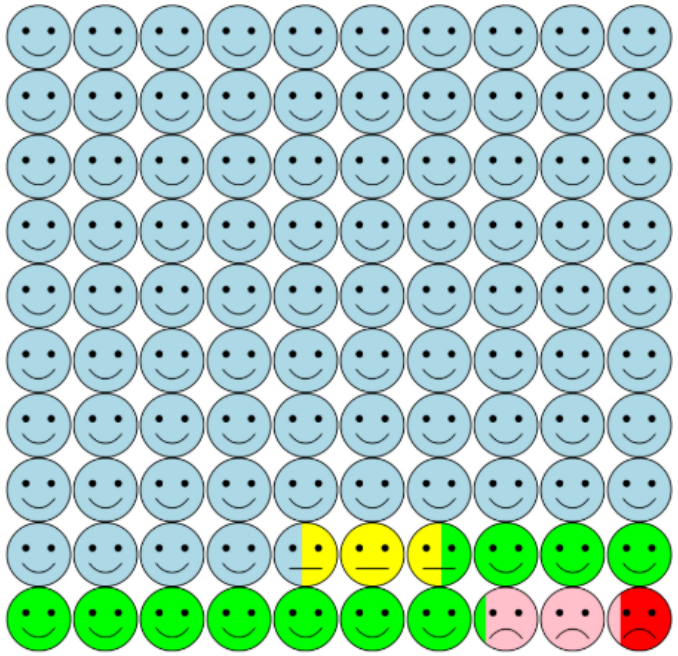
Uncheck All Selection

2. Your TB Risk (Over the Next 20 Years)

Healthcare Provider | Patient

FAQ

What is the risk of TB disease in the next 20 years if I recommend treatment (accounting for people who don't take it)? Out of 100 persons with the risk factors selected:



86.5% Will not develop TB disease with or without treatment

2.1% Had an adverse event that led to stopping therapy

10.6% of those prescribed therapy will prevent TB disease (accounting for overall completion rates)

2.8% of those prescribed therapy will develop TB disease despite treatment (this also accounts for possible non-adherence)

0.8% of those prescribed therapy will develop TB disease and TB-related long-term disability or death despite treatment (accounting for overall completion rates)"

3. Input Preventive Treatment

Select one of the following treatment options:

- ○ No Treatment
- ◉ 4 months of daily rifampin (4R)
- ○ 9 months of daily isoniazid (9H)
- ○ 3 months of once-weekly isoniazid plus rifapentine (3HP)
- ○ 3 months of daily isoniazid plus rifampin (3HR)

For drug interactions, see Medscape Drug Interaction Checker

4. Summary of your TB Risk

Without Treatment

- Your risk of TB disease without treatment in the next 20 years: 13.5%
- Your risk of disability and death from TB disease without treatment in the next 20 years: 3.8%

With Treatment 4 months of daily rifampin (4R)

Accounting for possible non-adherence:

- Your risk of developing TB disease in the next 20 years despite taking treatment: 2.8% (reduced by 10.6%)
- Your risk of developing long-term disability and death despite taking treatment: 0.8%
- Your risk of having an adverse event from the treatment (leading to treatment discontinuation): 2.1%

Download Patient Handout

Handout for Patients

- Can be downloaded
- and printed
- Provides patient education
- Plus individual results
- And major AE with TPT

TSTin4D Website Results and Patient Information

What is the Tuberculin Skin Test (TST) and the IGRA?

The tuberculin skin test (TST) or an Interferon-Gamma Release Assay (IGRA) whole-blood test are used to see whether an individual has been infected with tuberculosis (TB) bacteria.

What is TB infection and TB disease?

Tuberculosis (TB) infection *can occur when an individual has been exposed to someone with TB disease. People can be infected with TB bacteria without knowing they are exposed. When someone has TB infection, the TB germs are dormant (sleeping), so they do not feel sick. They can remain healthy for years without any symptoms or signs of illness. Infected individuals are not contagious during this time, meaning they cannot pass the TB infection to others. Most people will never get sick at all, because their immune systems are strong enough to control and contain the TB bacteria.*

TB Disease*: However, in some people the TB bacteria can develop into TB disease. This occurs when the TB bacteria become active in the body, resulting in the person becoming ill. There is a higher chance of this occurring in people who have other medical conditions (their immune system is weakened), but in some people there is no obvious reason why TB disease develops. A person who has TB disease feels sick with cough, fever, weight loss, and other symptoms. TB disease can cause disability and even death. It is also often contagious, meaning the TB can spread to others. Thus, TB disease must be treated.*

Tuberculosis Preventive Treatment

To avoid the complications of TB disease, tuberculosis preventive treatment (TPT) is offered to individuals with TB infection (tested positive for the TST or the IGRA) and have no symptoms or signs of TB disease. TPT reduces the chances that TB infection will progress to TB disease in the future. If taken properly, it can also prevent the spread of TB disease to others. However, as with any medication, TPT can have side effects. The potential side effects of the TPT regimen your doctor has recommended are listed below.

Your TSTin4D Results

Date: 27, February, 2025

TST Size: 10mm IGRA: Not Done

Age: 40

Primary risk factors entered:
- Recent Immigration

Without treatment, your current risk of developing TB disease in the next 20 years is: 2.5%

With 4R treatment, (if you take every dose) your risk of developing disease is reduced to 0.3% (reduced by 2.2%)

The risk of side effects that can lead to stopping 4R treatment is 2.1%

Side effects of (regimen selected)

More common, but usually mild:
-Discolouration of urine, feces, and/or tears
-Stomach upset, nausea
-Drug-drug interactions (can be serious if not monitored or recognized)

Less common, but potentially serious:
-Rash, hypersensitivity, or other allergic symptoms
-Hepatotoxicity (rare; ~3 per 1,000 persons treated)

FAQs

- For Patients
- For providers
- A growing list!

X

Frequenty Asked Questions

Healthcare Provider | Patient

What is new for the TSTin3D? And why are you calling it TSTin4D?

TSTin4D is the new, updated version of TSTin3D. This version shifts the focus of the calculator from likelihood of having infection, including probabilities of false positive results, to the risk of developing TB disease and reduction of that risk by TB preventive treatment. 1) We have incorporated probability of disability and death due to TB disease. 2) We have estimated risks and benefits of four different TB preventive treatment (TPT) regimens that are in common use. 3) The new calculator now includes a figure to help illustrate risk for individuals who prefer a visual presentation of risks and benefits (in addition to the 'numbers'). 4) The calculator has a "Patient Handout" feature that provides a summary of TSTin4D results plus explains the basics of TB infection and TB preventive treatment in layman's terms for individuals to take home.

Why is it called TSTin4D or IGRAin4D?

This calculator estimates risk based on the following 4 major determinants: First Dimension: Risk factors for developing TB disease, including factors indicative of recent infection, and factors increasing risk due to immune compromise. This, by far, is the most important determinant of risk of TB disease. Second Dimension: The TB infection test – IGRA or TST and if TST the size of TST (5-9mm, and 10mm or larger). This dimension has the least impact on important patient outcomes. Third Dimension: Age of the patient – this is an important determinant of the risks and benefits of TB preventive therapy. Fourth Dimension: Impact of TB preventive treatment (or treatment of TB infection) on TB incidence and related disability and death. Four regimens are considered; these are recommended by WHO, and currently are in common use in Canada or the US. The differences in risks and benefits between regimens are determined mainly by the probabilities of adverse events and completion – taken from published studies.

How is risk of TB disease being estimated?

The risk of disease is taken from published cohort studies. Results of these studies were synthesized in several systematic reviews which estimated cumulative risk of disease in persons with the listed risk factors. Most of these studies included persons with BCG vaccination; hence, the results account for prior BCG vaccination.

Coming soon

- Discordant test results (e.g. IGRA-/TST >10)
- Update FAQs
- French version

- Comments and suggestions welcome!!

Why do we need a calculator?

- Consider the following scenario…..

Why do we need a Risk calculator: A scenario

- You have a sore throat and fever. You feel BAD.
- You are worried (Its not any ordinary sore throat)
- You go to a Walk-in clinic
- After waiting NN hours, the MD sees you.
- MD looks at your throat. Says “Hmmmmm”
- You are MORE worried

scenario (2)

- The doctor says – “There is a 10% chance this could be Strep Throat. But that is still serious enough. You should take antibiotics”
- You are a little skeptical. You ask “How long do I take it? Will it work?”
- MD: “Good questions. This treatment last 1 month. It is 90% effective if you take every dose.”
- You: “Is it safe”
- MD “Glad you asked. You will need to come back after 2 weeks for a check-up and some blood tests to make sure there are no side effects with the treatment”
- You are now VERY worried

What is wrong with this scenario??

The diagnosis – only 10% certainty of the condition

- For TB prevention – current tests identify people with similar, **or lower** probability of TB disease

The treatment duration

- The most successful treatments for infectious diseases involve one single dose
- Steady increase in conditions treated in this way
- For TB prevention – one month sounds FANTASTIC

The safety

- The rate of serious adverse events (enough to warrant follow-up) with most antibiotics is 3-10 per 100,000 treatment courses
- For TB prevention = rate of serious AE is 3-25 per 1000 (ie 100 times more frequent)

The monitoring

- Have you ever had antibiotics and the MD wanted to see you mid-way? And do blood tests?
- For TB prevention – this is normal

To get rid of these calculators – what's missing??

- Diagnosis – test that accurately identifies persons who will develop disease
- Efficacy – need to have effective TPT
- Safer treatment – rates of AE like other antibiotics
- Shorter treatment – 2weeks? Single shot?
- Monitoring – none needed routinely during treatment
  - No baseline labs
  - This emphasizes the need for SAFE regimens

Comparison of hepatotoxicity risk among antimicrobial agents

Drug	Hepatotoxicity incidence per 100,000 courses	Comments
Amox-clav *	1-17	Generally benign
Telithromycin *	17	Withdrawn from the market
Levofloxacin *	0.02	
Trovofloxacin *	6	Withdrawn from the market

- *Andrade R, Tulkens PM. J Antimicrob Chemother 2011; 66: 141-6*
- *Slide courtesy Bill Burman*

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Rifampin	70	Annals Intern Med 2008; 149: 694
Isoniazid	380	Annals Intern Med 2008; 149: 694
Pyrazinamide	430	Ann Intern Med 2002; 137: 640-7

- ** Andrade R, Tulkens PM. J Antimicrob Chemother 2011; 66: 141-6*
- *Slide courtesy Bill Burman*

Updated systematic review of Adverse events with TPT

(L. Melnychuk and others, CID 2023)

- 175 studies, 277 cohorts, 186,281 patients
- Received 8 different TPT regimens
- 4R: 28 cohorts, 11,200 people,
  - No deaths, 0.6% severe AE (Grade 3-4); 2.9% drug DC
- 3HP: 37 cohorts, 16,800 people
  - 1 death; 3.6% severe AE; 8.2% drug DC
- 6-9 INH: 132 cohorts, 110,000 people
  - 12 deaths; 2.7% severe AE; 4.1% drug DC

Network Meta-Analysis using Individual Patient Data – 4R vs 3HP

(N Winters et al, Lancet Resp 2023)

- Pooled data from 6 RCTs with 17,572 patients
  - 3 RCT 3HP vs 6-9H; and 3 RCT 4R vs 9H. All 3HP was directly observed.
  - Individual patient records obtained from authors
    - Allows better matching/adjustment for confounding
- Completion: 5% better with 3HP (2%, 7%)
- Treatment related Adverse Events with drug DC
  - All grades: 3% worse with 3HP (2%, 5%)
  - Severe (Grade3-4): 2% worse with 3HP (1%, 3%)
- The Bottom Line: 4R is the safest of current TPT
  - BUT, Safety of 4R is still far from ideal

Future TPT options:

- FOOD
- 6Lfx
- 1HP
- 1B
- 2R20
- 6wP
- 1LP

Future TPT

Bold new concept !! FOOD!!

Tested in an RCT (RCT) in 2015-2023 in India. Published in the Lancet in 2023.

24,000 household contacts, mainly children. Food baskets distributed to households for 6 months.

50-60% reduction in the incidence of active TB in the following 2 years (rates similar to the 6INH regimen).

Very safe. No adverse effects. Several other benefits.

Recommended in 2024 by the WHO.

Efficacy uncertain for Canada and US. (In India, the majority of household contacts were malnourished.)

Highlights the importance of assessing and addressing social determinants..

Ultra-short regimen: 1 month INH & Rifapentine (1HP)

(Swindells et al NEJM 2019)

Study sponsored by AIDS Clinical Trials Group.

3,000 HIV infected adults. Median CD4=490-500. 20% TST positive. Remainder – Residents of high TB incidence countries (>100/100,000).

9INH, and 1HP – Both daily and self-administered.

Completion rates: 90% (9INH) and 97% (1HP).

TB rates: 1HP non-inferior to 9H.

Adverse events: High (17%) although drugs stopped in 2%. Rate of AE with 1HP same as 9INH (not better).

Conditionally recommended for HIV-positive patients by the WHO.

Needs more evidence – but several studies are ongoing.

2R20 (2 months double dose Rifampin)

Ruslami et al, Lancet Resp Jan 2024

Clinical trial with 450 people on 4R10 vs. 450 people on 2R20.

No difference in terms of Grade 3-4 adverse events

No difference in the percentage who stopped medications due to AE

Excellent exposure (3 times higher than 4R10)

Preclinical study (mice) at McGill

Similar results with 2R20 and 4R10

Promising – we will continue to pursue

Current Trials of novel TPT regimens

- 6 weeks Daily Rifapentine (6wP)
- 1 month Daily Levofloxacin & Rifapentine (1LP)
- 1 months daily Bedaquiline (1B)
- Novel Diarylquinolines (Bedaquiline like)

6 weeks daily rifapentine (6wP)

Based on mouse model data that 600mg RPT Daily for 6 weeks appeared adequate for efficacy.

TBTC trial (Canada, US, Benin, Haiti, S Africa and Vietnam).

Primary outcome: Efficacy for TB prevention

Secondary: Safety – analyzed after 1150 enrolled

Total of 3400 participants. Randomized 1:1 to 6wP or Control (4R or 3HP or 3HR).

Enrolment to date: 1120 (Expected completion 2029).

Future TPT Options:

1 month Bedaquiline (1B)

Tested on animals only to date

An RCT is starting soon (BREACH) **(safety & tolerability)**

Bedaquiline has been used in thousands of patients with multidrug-resistant tuberculosis. Safety appears to be very good.

Options de traitement préventif de la TB (à venir) :

SSTARLET: Shorter & Safer: Phase 2 RCT

Safety, tolerability, completion, acceptability, pharmacokinetics, and cost assessment

8 Canadian sites: Montreal (Chest, and Sacre Coeur), Ottawa, Toronto, Winnipeg, Calgary, Edmonton, and Vancouver.

4 international sites: Benin, Brazil, Indonesia, and Vietnam

1800 total enrolment planned

3 experimental regimens:

2 months of daily double doses of RIF (2R20)

1 month of daily levofloxacin and rifapentine (1LP)

Later (when 700 enrolled): 1 month of bedaquiline or another.

Current enrolment: 1

Conclusions (1)

- Individual risk factors drives TB progression, and other TB related outcomes

- TPT all regimens: reduced TB disease, post-TB disability and TB mortality, improved QALYs
  - 4R and 3HP higher benefits
  - Older groups have surprisingly high QALYs gained (due to high risk TB death)
  - **In low-risk populations: Little benefit from TPT**

- Positive IGRAs associated with higher risk of progressing to TB disease compared to those with TST>10mm or TST≥5mm.
  - But in high-risk groups, TB incidence is high with any pos. TB Infection test.
  - And in lower-risk populations, the risk was low with any positive TBI test.

Conclusions (2)

- Current TPT of 3-4 months: Good efficacy, reasonable safety

- New TPT – shorter and shorter
  - **Obsession over duration should not blind us to need for SAFETY**
  - Safe regimens would eliminate need for all follow-up and all testing
  - 1 month regimens (or less) would also allow one visit to dispense drugs
- Several promising regimens:
  - 1HP – best known, and most advanced in RCT
  - 2R20 – promising in humans and mice
  - 6wP – promising in mice. RCT well underway
  - 1B – promising in mice. Stalled in human trials
  - 1LP – promising in mice. Starting RCT.
  - But studies needed – in mice and humans

Acknowledgements

for www.TSTin4D.com

- Mayara Bastos – all the modelling work
- Harsimren Sidhu (qualitative study)
- Zhe Tian (website design)
- Jonathon R Campbell
- Placide Nsengiyumva
- James Johnston
- Kevin Schwartzman

For sharing slides

- Bill Burman, Jon Campbell

Questions/Comments?

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