Tuberculosis and Biologic Therapy

What 25 systematic reviews tell us about screening and prevention before biologics and JAK inhibitors

Anti-TNF | JAK inhibitors | PD-1/PD-L1 inhibitors | Interleukin inhibitors

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THE QUESTION

Does the screening model we built for anti-TNF agents work for everything else?

1

Our screening model was born with anti-TNF agents

Screening for TB infection with TST or IGRA before starting a biologic is recommended (TBNET consensus, 2010).

2

The therapeutic arsenal has changed

Interleukin inhibitors, JAK inhibitors and immune checkpoint inhibitors are now prescribed at scale.

3

Evidence on newer agents is scattered

Data on JAK and checkpoint inhibitors are limited and fragmented — differential risk stratification is missing.

Fernandes Alves R, Hilário C, Barros Ferreira N, et al. TB risk during treatment with biological agents and Janus kinase inhibitors: an umbrella review. Int J Tuberc Lung Dis 2026;30(6):244–254.

MECHANISMS

Each class interferes with a different step in containing M. tuberculosis

Anti-TNF

TNF-α is essential for granuloma maintenance; blocking it compromises granuloma integrity.

JAK inhibitors

Intracellular blockade of signalling by multiple cytokines.

Granuloma containment of infection

Interleukin inhibitors

IL-6, IL-17, IL-23: selective modulation of the immune response.

PD-1/PD-L1 inhibitors

Immune stimulation: disrupting the PD-1 axis can paradoxically worsen TB.

Fernandes Alves R, Hilário C, Barros Ferreira N, et al. TB risk during treatment with biological agents and Janus kinase inhibitors: an umbrella review. Int J Tuberc Lung Dis 2026;30(6):244–254. Cavalcanti YV, et al. Pulm Med 2012; Barber DL, et al. Sci Transl Med 2019.

STATE OF THE ART

We knew a lot about anti-TNF agents — and little about everything else

What we already knew

- Anti-TNF agents raise TB risk two- to fourfold.
- Screening with TST or IGRA is recommended before starting a biologic.
- A recent narrative review (autoimmune arthritis): highest risk with anti-TNF monoclonals; intermediate with JAK inhibitors and IL-6R blockers; low with IL-17/23 antagonists, abatacept, rituximab and apremilast.

What was missing

- Limited, fragmented data on JAK and checkpoint inhibitors.
- Evidence scattered across specialties, with no comparison between classes.
- No second-order synthesis to stratify risk by class and guide screening and prevention.

Cantini F, et al. J Rheumatol Suppl 2014; Solovic I, et al. Eur Respir J 2010; Picchianti-Diamanti A, et al. Front Immunol 2025; Cantini F, et al. Expert Opin Drug Saf 2020; Bae S, et al. J Immunother Cancer 2021.

METHODS

An umbrella review: synthesising systematic reviews, not primary studies

Umbrella review

1 synthesis

Systematic reviews ± meta-analysis

25 included

Aim

To systematically assess TB risk associated with biologic therapies and small molecules, identify differences between classes and inform risk-based screening.

Methodological standards

- Reported according to the PRIOR statement
- Protocol registered in PROSPERO (CRD42024497515)
- Risk of bias assessed with ROBIS

METHODS

Criteria designed to isolate the effect of the drug

Search

- PubMed, Web of Science, Scopus, Cochrane Library
- From inception to 27 May 2025
- No date or language restrictions; manual and citation searching

Eligibility

- Adults (>18 years) on anti-TNF, interleukin, checkpoint or JAK inhibitors
- Excluded: other major risk factors (HIV, prolonged corticosteroids)
- Comparator: general population or non-biologic therapy

Outcomes

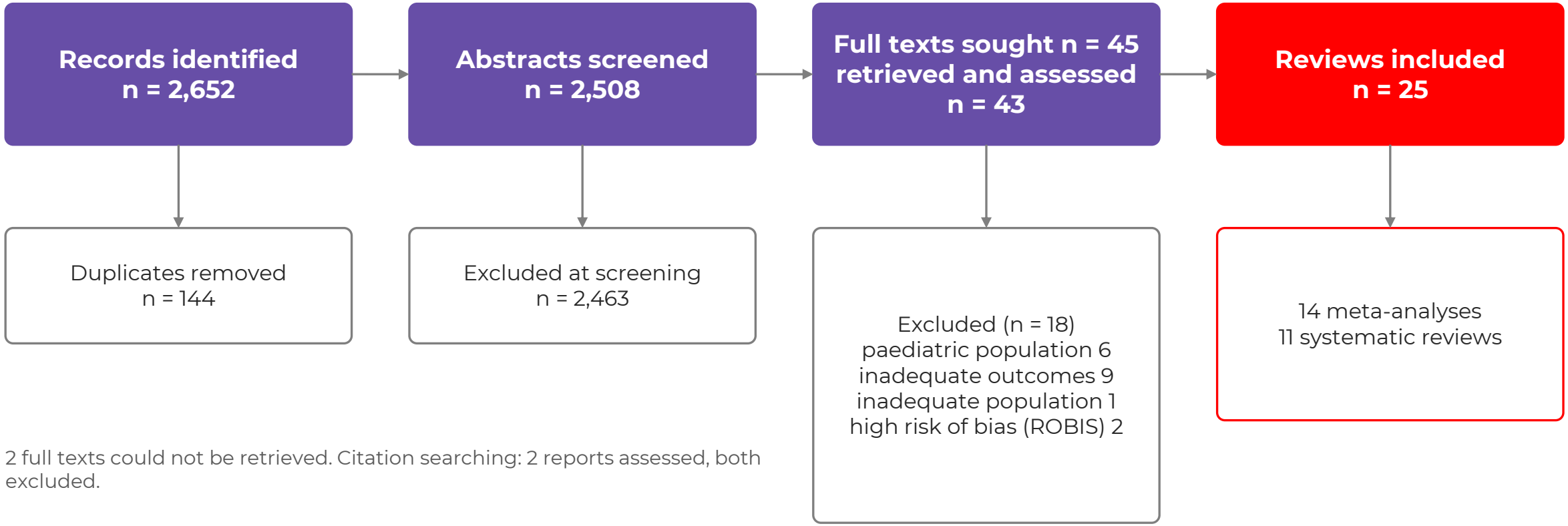
- Primary: TB risk/incidence
- Secondary: TB type, time to onset, prognosis, mortality

Process

- Independent selection and extraction, in duplicate
- ROBIS by two reviewers
- Descriptive synthesis by class: heterogeneity precluded meta-analysis

SELECTION

From 2,652 records to 25 systematic reviews



2 full texts could not be retrieved. Citation searching: 2 reports assessed, both excluded.

CHARACTERISTICS

Broad evidence, but heavily weighted towards anti-TNF agents

25

reviews: 14 meta-analyses and 11 systematic reviews

2006–2023

publication years of the reviews

1970–2021

period covered by primary studies, mostly observational

13 / 25

reviews on anti-TNF agents; only 3 on checkpoint inhibitors

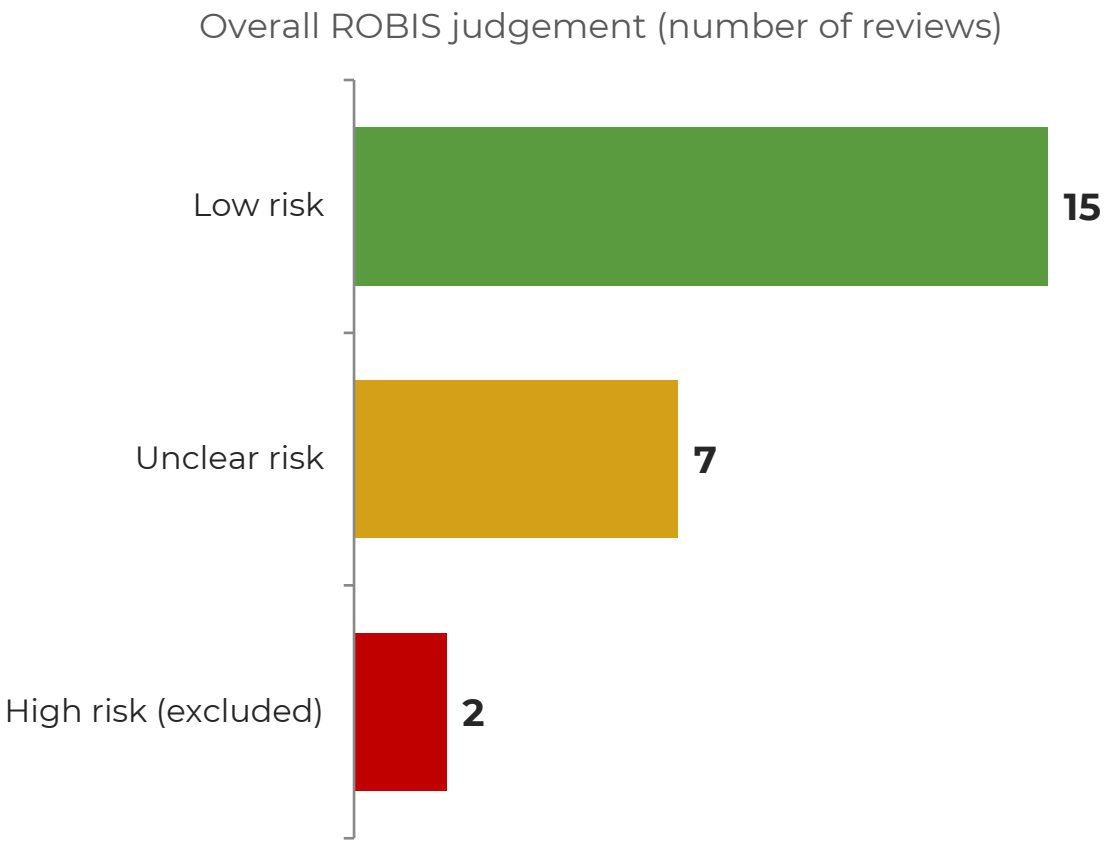
Underlying conditions

Rheumatoid arthritis · psoriatic arthritis · ankylosing spondylitis and spondyloarthritis · inflammatory bowel disease · psoriasis · cancer (mainly lung) · myeloproliferative neoplasms

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QUALITY

Overall acceptable methodological quality, with known weaknesses



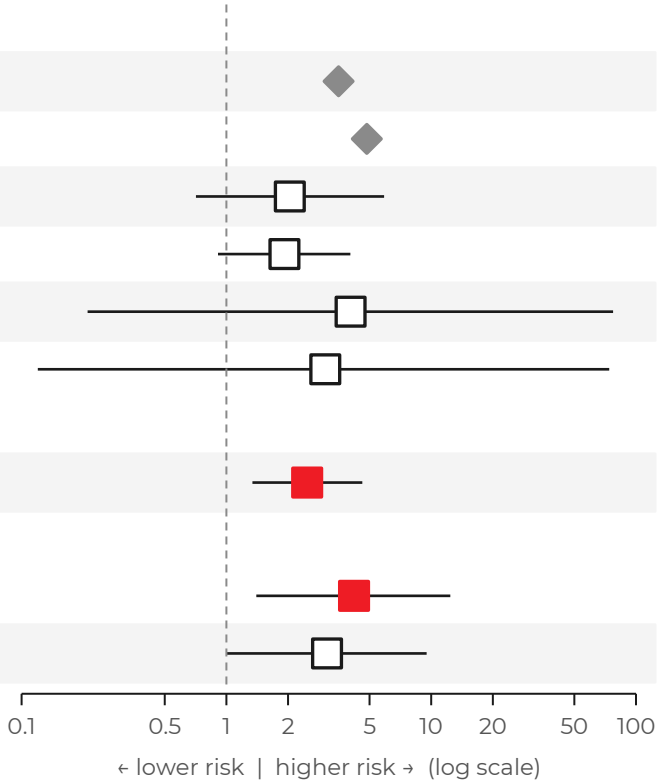
Main weaknesses

- Potential publication bias
- Inconsistent data extraction methods
- No grading of certainty of evidence (GRADE) in most
- Many reviews focused on general safety, not TB — incidence probably underestimated

ANTI-TNF · HIGH RISK

Anti-TNF agents: every relative estimate points to higher risk

Review	Population	Estimate (95% CI)
ANTI-TNF VS PLACEBO / CONTROL		
Minozzi 2016	RA, PsA, AS · 78 RCTs	OR 3.53 †
Cao 2018	Crohn's disease · 23 RCTs	OR 4.85 †
Bonovas 2016	IBD · 49 RCTs	OR 2.04 (0.71–5.89)
Souto 2014	Immune-mediated · RCTs	OR 1.92 (0.91–4.03)
Piovani et al.	Elderly IBD · lower-RoB study ‡	RR 4.04 (0.21–77.3)
Singh et al.	RA · golimumab · 4 studies	RR 3.04 (0.12–74.01)
ANTI-TNF VS OTHER BIOLOGICS		
Queiroz 2022	RA · 31 studies	RR 2.48 (1.34–4.61)
MONOCLONAL ANTIBODY VS ETANERCEPT (REFERENCE)		
Goh 2013	RA · adalimumab	IRR 4.2 (1.4–12.4)
Goh 2013	RA · infliximab	IRR 3.1 (1.0–9.5)



No pooled relative estimate — not plottable

Vassilopoulos
PsA, 3,425 pts: 5 TB cases among 17 opportunistic infections

Snast
78 cases: 47% disseminated; 51% within 6 months (ADA 41%, IFX 38%, ETN 12%)

Baronnet 2011
RA: risk ×2–4 with anti-TNF; 9.3–449/100,000 PY; 60% extrapulmonary

Ramiro
12–35/100,000 person-years

Man 2021
7 cases (2 adalimumab, 2 infliximab)

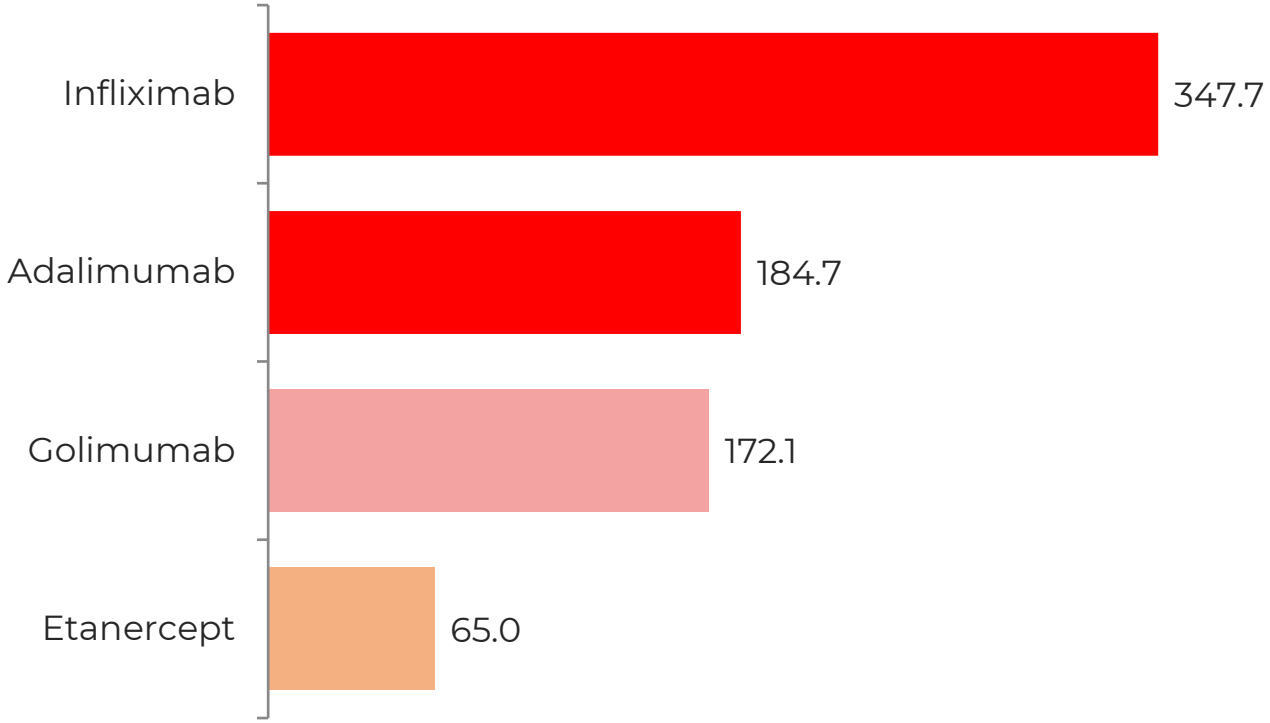
Gartlehner
Time to diagnosis: IFX ~3 vs ETN ~11.5 months

Lorenzetti
Combination OR 54 (5.3–288) vs monotherapy OR 4 → combination slide

ANTI-TNF · HIGH RISK

Risk concentrates in monoclonal antibodies; etanercept carries less — but is not exempt

TB incidence per 100,000 patient-years (long-term extension studies, Souto 2014)



Golimumab: consistently fewer cases across studies, though less widely used.

Etanercept as reference

Adalimumab IRR 4.2 (1.4–12.4)
Infliximab IRR 3.1 (1.0–9.5)

British Biologics Register data (Goh 2013)

Why?

A soluble receptor, not an antibody: less TNF-α neutralisation within granulomatous tissue.

Lower risk ≠ no risk

TB still occurs on etanercept: 12% of cases in Snast. "Generally considered safer but still poses a risk for TB."

Certolizumab not shown: 474.2 per 100,000 patient-years in Souto, from 10 cases in 1,275 patients, no CI reported; described in the review as close to infliximab and adalimumab, with conflicting evidence. Fernandes Alves R, Hilário C, Barros Ferreira N, et al. TB risk during treatment with biological agents and Janus kinase inhibitors: an umbrella review. Int J Tuberc Lung Dis 2026;30(6):244–254. Souto A, et al. Rheumatology 2014; Goh L, et al. Rev Bras Reumatol 2013; Fallahi-Sichani M, et al. J Immunol 2012.

ANTI-TNF · HIGH RISK

Most anti-TNF TB appears in the first months — but timing varies by drug

When does TB appear? 78 cases (Snast)



33%

within 3 months of starting treatment

51%

within 6 months of starting treatment

Time to TB by drug

Drug	Range of onset (Baronnet)	Median (Gartlehner)
Infliximab	3–12 months	~3 months
Etanercept	8–13 months	~11.5 months
Adalimumab	12–18.5 months	not reported

Gartlehner medians come from a single study (infliximab) and a single abstract (etanercept).

Reading: early onset supports reactivation as the key mechanism, so screening before starting is decisive. But late cases occur, particularly with adalimumab — vigilance cannot stop at six months.

Fernandes Alves R, Hilário C, Barros Ferreira N, et al. TB risk during treatment with biological agents and Janus kinase inhibitors: an umbrella review. Int J Tuberc Lung Dis 2026;30(6):244–254. Snast I, et al. Am J Clin Dermatol 2019; Baronnet L, et al. Joint Bone Spine 2011; Gartlehner G, et al. J Rheumatol 2006.

ANTI-TNF · HIGH RISK

Combining immunosuppressants with anti-TNF therapy concentrates the risk

Anti-TNF monotherapy

OR 4

95% CI 0.2–15.7

Anti-TNF + immunosuppressant

OR 54

95% CI 5.3–288

10,010 patients in RCTs · 26 TB cases, 24 in combination therapy arms
Time to TB: 6 to 54 weeks. Only 26 cases and very wide intervals: the magnitude is highly uncertain, but the signal points towards combination therapy.

Fernandes Alves R, Hilário C, Barros Ferreira N, et al. TB risk during treatment with biological agents and Janus kinase inhibitors: an umbrella review. Int J Tuberc Lung Dis 2026;30(6):244–254. Lorenzetti R, et al. Ann Med 2014.

INTERLEUKIN INHIBITORS · LOW RISK

IL-17 and IL-23: no active TB — in screened and treated populations

Review	Exposure	TB outcome	What qualifies the result
Fowler 2020	23 trials (secukinumab, ixekizumab, brodalumab): secukinumab 7,355 patients (16,226.9 PY + 96,054 post-marketing); ixekizumab 5,730 (13,479 PY)	**0 active or reactivated TB**	*TB infection treated 4 weeks before start; no IGRA conversions*
Wu 2023	45 placebo-controlled RCTs + 27 extension studies; 25,496 and 17,591 patients (psoriasis, psoriatic arthritis)	**0 active or reactivated TB**	*Isolated TB infection detections during follow-up*
Man 2021	63 RCTs; 8,490 biologic or targeted therapy allocations	**0 with IL-17 or IL-23 inhibitors**	*All 7 cases on anti-TNF agents, in moderate-to-high burden areas*
Naik 2017	7 RCTs of IL-17 and IL-12/23 inhibitors (secukinumab, ixekizumab, brodalumab, ustekinumab); 1,718 treated, 840 placebo	**0 in all arms**	

Why these zeros come with conditions

Fowler's authors conclude IL-17 blockade does not increase reactivation risk "given proper screening and prophylaxis". Many studies included only screened and prophylaxed patients: the real-world risk in high-endemic settings remains uncertain.

Fernandes Alves R, Hilário C, Barros Ferreira N, et al. TB risk during treatment with biological agents and Janus kinase inhibitors: an umbrella review. Int J Tuberc Lung Dis 2026;30(6):244–254. Fowler E, et al. JEADV 2020; Wu S, et al. Front Immunol 2023; Man S, et al. Front Pharmacol 2021; Naik GS, et al. Dermatology 2017.

IL-6 blockade

Review	Exposure	TB outcome	What qualifies the result
Campbell 2021	47,205 tocilizumab safety reports; 19 cohorts (~80,000 PY)	**135 TB events (0.9% of infections)**	
Souto 2014	All biologics and tofacitinib: 100 RCTs (~75,000 participants) + 63 extension studies (80,774 PY); tocilizumab-specific exposure not reported in the review	**0 in placebo-controlled phases; 75.6/100,000 PY in extensions (95% CI 36.1–129.5)**	*Mostly pulmonary, also extrapulmonary; onset 4 weeks to 5 years; no untreated comparators* *Same analysis: infliximab 347.7, etanercept 65.0 per 100,000 PY*

Additional evidence — outside the umbrella review

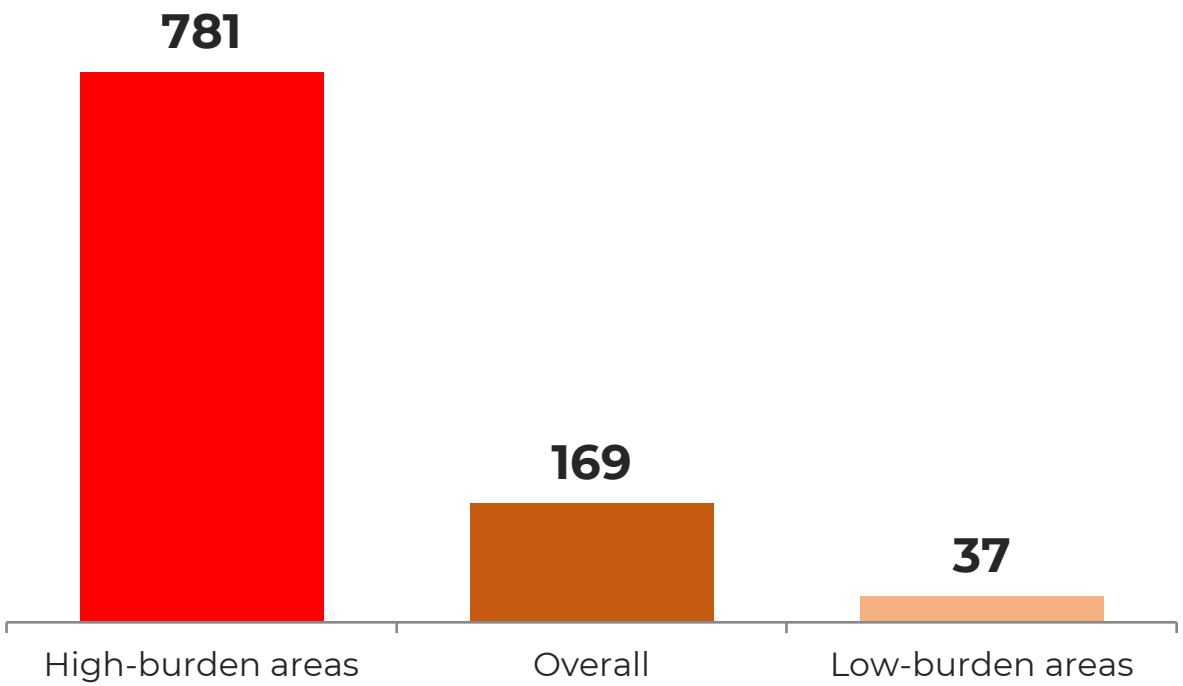
A multi-ancestry Mendelian randomisation study (IL6R variants as proxies for IL-6 inhibition) found reduced classical IL-6 signalling associated with lower odds of TB disease.

Fernandes Alves R, Hilário C, Barros Ferreira N, et al. TB risk during treatment with biological agents and Janus kinase inhibitors: an umbrella review. Int J Tuberc Lung Dis 2026;30(6):244–254. Campbell C, et al. Front Med 2021; Souto A, et al. Rheumatology 2014; Hamilton F, et al. Lancet Microbe 2025;6(1):100922.

JAK INHIBITORS · VARIABLE RISK

Tofacitinib: risk comparable to anti-TNF monoclonals, and concentrated in high-burden settings

TB incidence with tofacitinib per 100,000 (Souto 2014)



Cantini 2020 · rheumatoid arthritis

- 79 TB cases in 28,099 tofacitinib-treated patients (0.28%)
- Mostly in intermediate/high TB burden countries; one case from a low-burden region (USA)
- 82% of cases on the high dose (10 mg BID) — exposure by dose not reported

Why trials missed it

No TB was reported in RCTs, "likely due to limited exposure time". The authors stress strict TB prevention, especially in endemic areas.

Fernandes Alves R, Hilário C, Barros Ferreira N, et al. TB risk during treatment with biological agents and Janus kinase inhibitors: an umbrella review. Int J Tuberc Lung Dis 2026;30(6):244–254. Cantini F, et al. Expert Opin Drug Saf 2020; Souto A, et al. Rheumatology 2014.

JAK INHIBITORS · VARIABLE RISK

Other JAK inhibitors: limited exposure, geographically focused signals

Drug	TB cases / exposed	Details	Review's reading
Baricitinib	**10 / 4,310 (0.23%)**	All from high-burden areas, at 4 mg/day; one QFT-negative, two indeterminate (one with prophylaxis, one without)	*"Risk is low but geographically focused, highlighting screening needs"*
Upadacitinib	**0 / 3,437**	No TB disease reported	*Data limited by smaller samples and shorter follow-up*
Filgotinib	**0 / 1,326**	No TB disease reported	*Data limited by smaller samples and shorter follow-up*
Ruxolitinib	**0 / 1,144 in the phase IV JUMP trial; ≥10 case reports**	Case reports: median diagnosis 4.5 months (range 1–51); 40% mortality; pulmonary, disseminated and lymph node TB	*"Thorough baseline screening and surveillance are needed"*

Reading: zero cases with upadacitinib and filgotinib reflect limited follow-up, not demonstrated safety; ruxolitinib shows that no cases in a trial is not the same as no risk.

Fernandes Alves R, Hilário C, Barros Ferreira N, et al. TB risk during treatment with biological agents and Janus kinase inhibitors: an umbrella review. Int J Tuberc Lung Dis 2026;30(6):244–254. Cantini F, et al. Expert Opin Drug Saf 2020; Lussana F, et al. Am J Hematol 2018.

PD-1/PD-L1 INHIBITORS

Checkpoint inhibitors: TB is frequent in treated patients — the drug effect is uncertain

What the reviews show

~2,000

TB cases per 100,000 treated patients (Liu)

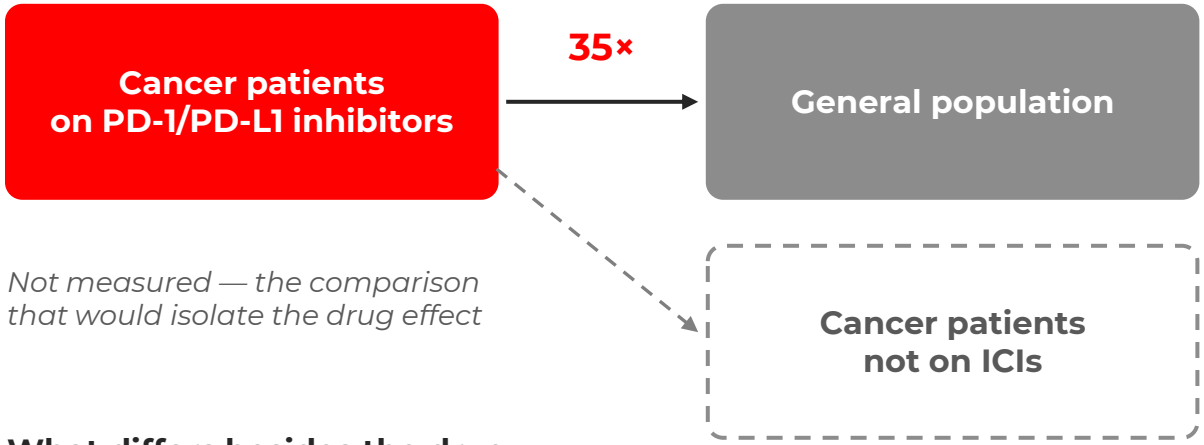
Zaemes: 16 cases · median diagnosis 6.3 months

Liu: 35 cases · symptom onset 120 days · 77% pulmonary

He: 53 lung cancer patients · median diagnosis 3 months

~85% of cases on nivolumab or pembrolizumab

The comparison behind "35-fold"



What differs besides the drug

- Underlying malignancy
- Prior immunosuppression
- Corticosteroids
- Comorbidities

Fernandes Alves R, Hilário C, Barros Ferreira N, et al. TB risk during treatment with biological agents and Janus kinase inhibitors: an umbrella review. Int J Tuberc Lung Dis 2026;30(6):244–254. Zaemes J, Kim C. Eur J Cancer 2020; Liu K, et al. Front Immunol 2022; He Y, et al. J Clin Pharmacol 2023.

PD-1/PD-L1 INHIBITORS · POTENTIALLY HIGH RISK

Checkpoint inhibitors

Review	TB cases	Time to TB	Presentation
Zaemes 2020	16, all on PD-1/PD-L1 inhibitors (nivolumab 10, pembrolizumab 6)	**Median diagnosis 6.3 months (1–24)**	Extrapulmonary single cases: pericardium, bone, liver, GI tract
Liu 2022	35 in 27 ICI studies (pembrolizumab 16, nivolumab 15, durvalumab 3, avelumab 1)	**Median symptom onset 120 days (22–730)**	Pulmonary 77%, extrapulmonary 17%, mixed 6%
He 2023	53 lung cancer patients in 25 studies; 92% on PD-1 inhibitors	**Median diagnosis 3 months (IQR 1.3–7.9)**	Pulmonary 21 cases; extrapulmonary 8 (17%)

~2,000

per 100,000: a 35-fold increased TB risk vs the general population (Liu). Observational comparison in cancer patients, not a causal drug effect.

~85%

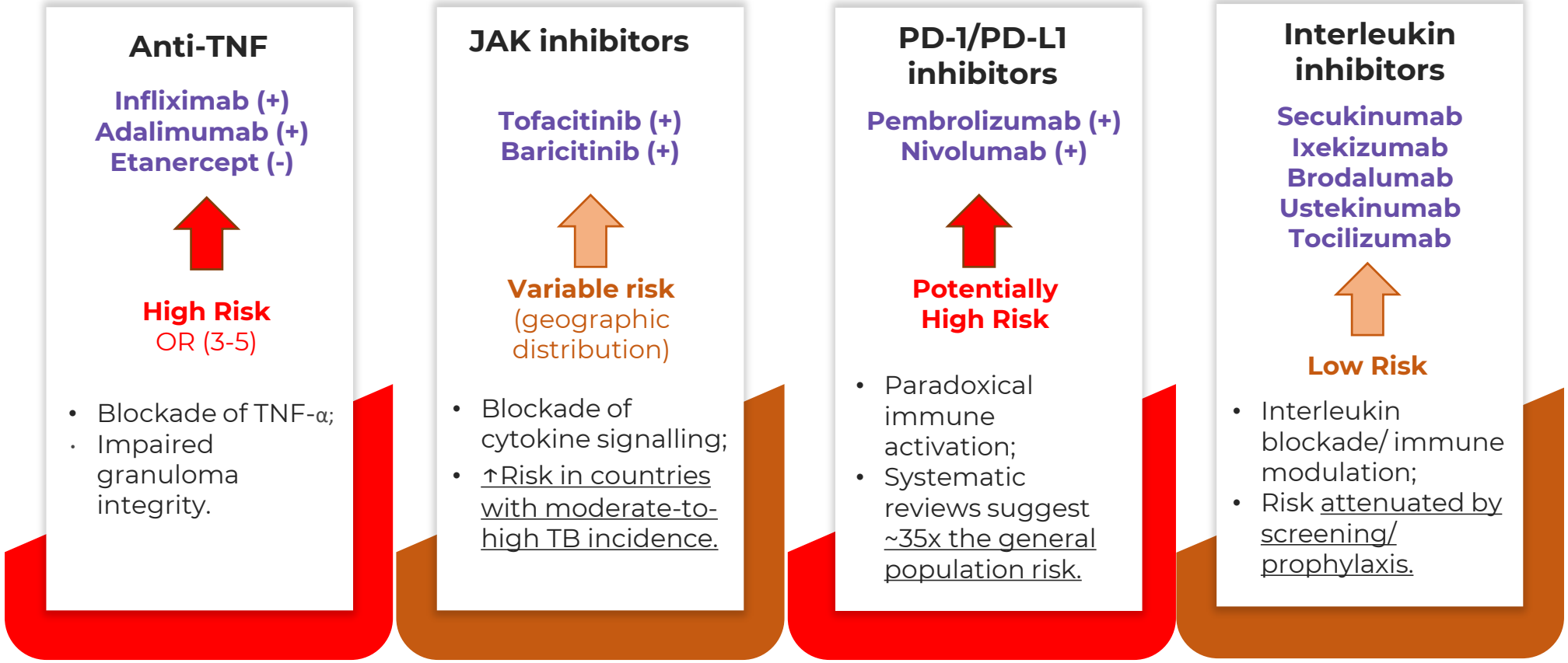
of ICI-associated TB with nivolumab (n=47) and pembrolizumab (n=45). Others: durvalumab 7; camrelizumab, sintilimab, sugemalimab, tislelizumab 2 each; avelumab 1.

Time to onset by drug

Nivolumab 2.96–7.75 months
Pembrolizumab 2.3–8.25 months
Durvalumab ~13 months
Sugemalimab ~22.7 months

SYNTHESIS

TB risk is a gradient across classes, not a single category



LIMITATIONS

What this evidence does not allow us to claim

Heterogeneity

Different effect measures, designs and outcomes: a meta-analysis would give false precision.

Zero-event studies and overlap

Frequent trials with no cases and primary studies shared across reviews.

Imbalance between classes

13 of 25 reviews on anti-TNF agents: evidence for other classes is sparse.

Screened and treated populations

Especially for interleukin inhibitors: real-world risk may be underestimated.

Geographic bias

More prescribing and screening in high-income countries; data from high-burden settings are lacking.

TB as a secondary outcome

Reviews focused on general safety: probable under-reporting.

SCREENING

How to screen: risk-stratified before starting, clinical vigilance during treatment

1 Baseline screening

Comprehensive: risk assessment, symptoms, IGRA and/or TST, chest radiograph

Anti-TNF, JAK: all patients, any setting

IL-6: especially in intermediate/high incidence

IL-17/23, other lower-risk agents, checkpoint inhibitors: risk-adapted

2 Preventive strategy

TB infection: start preventive therapy before the immunomodulator

Completion not required: start after a short lead-in, guided by urgency, agent and patient

TB disease: complete treatment first, unless the underlying disease is urgent

Screening should not delay urgent therapy

3 Monitoring

Clinical: symptoms and exposure at every visit; patient education

Repeat IGRA/TST: previously negative with new or ongoing exposure

Intermediate/high incidence, long-term high-risk agents: consider periodic reassessment

4 Individualised care

Higher progression risk: endemic residence, immunosuppressive conditions, diabetes, occupational or ongoing exposure

An international consensus on TB screening and prevention in patients receiving biologics and targeted immunomodulators is being finalised for submission.

FINAL COMMENT

The question is no longer whether to screen,

but whom, how, and for how long.

What the evidence still lacks

- Longitudinal pharmacovigilance in endemic regions
- Uniform, high-quality research with standardised criteria to stratify TB risk by biologic class
- Tailored surveillance strategies and predictive tools