Farmaci antitubercolari

1882
Robert Koch scopre il *M. tuberculosis*

1900
Il 12% di tutti i decessi causato da tubercolosi
La maggior parte degli adulti nelle grandi città europee è infettato dal *M. tuberculosis*

1905
Robert Koch viene insignito del Nobel per la Fisiologia e Medicina

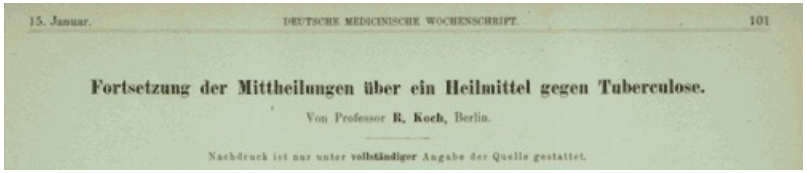
1944, 20 novembre
Viene testata nell'uomo la streptomicina (Selman Waksman, premio Nobel nel 1952)

1998
Sequenziato il genoma del *M. tuberculosis*

Oggi
- 30% della popolazione mondiale infetto da *M. tuberculosis*
- 8,8 milioni di nuovi casi ogni anno
- 1,6 milioni di decessi/anno
- 4000 casi/anno in Italia
- 9 morti/settimana in Italia
- 15 milioni di persone con coinfezione HIV e TBC
- 50 milioni di persone infettate con *M. tuberculosis* multiresistente

1880 | 1900 | 1920 | 1940 | 1960 | 1980 | 2000 | 2020

1890-91
La tubercolina viene utilizzata a scopo terapeutico e diagnostico



15. Januar. DEUTSCHE MEDICINISCHE WOCHENSCHRIFT. 101

Fortsetzung der Mittheilungen über ein Heilmittel gegen Tuberculose.

Von Professor R. Koch, Berlin.

Nachdruck ist nur unter vollständiger Angabe der Quelle gestattet.

1921
Vaccino attenuato (Albert Calmette e Camille Guerin)

1947
Primi ceppi di *M. tuberculosis* resistenti alla streptomicina

1949
Acido p-aminosalicilico

1952
Isoniazide

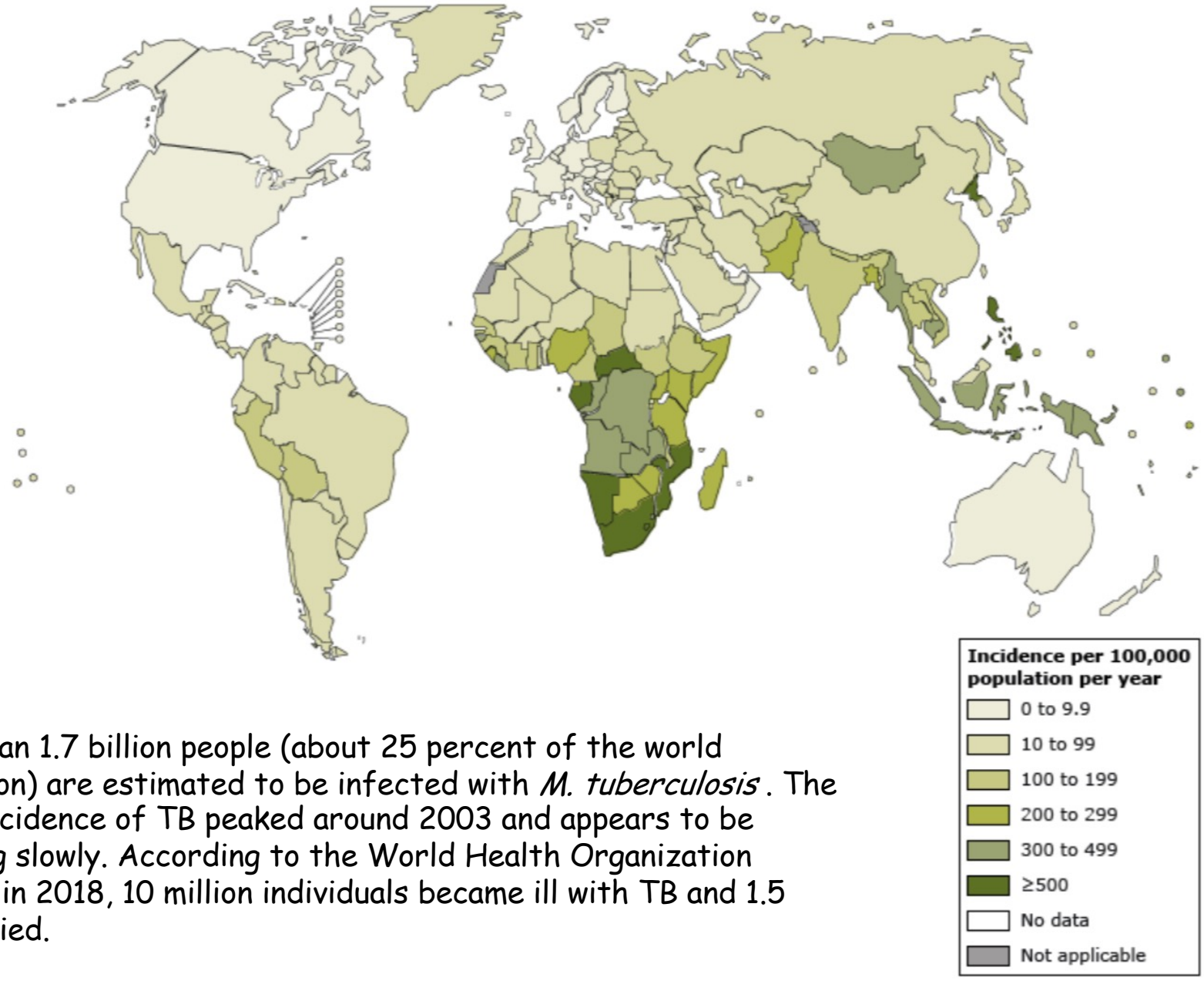
1954
Pirazinamide

1962
Etambutolo

1963
Rifampicina

1993
L'Organizzazione Mondiale della Sanità dichiara la tubercolosi emergenza globale

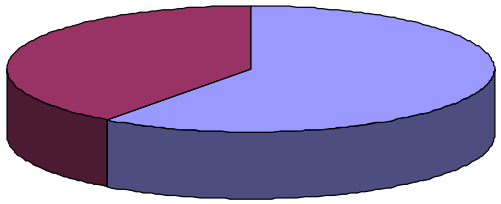
Estimated tuberculosis incidence rates, by country, 2018



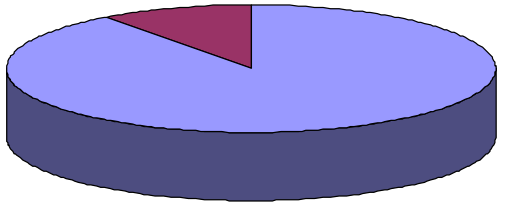
More than 1.7 billion people (about 25 percent of the world population) are estimated to be infected with *M. tuberculosis* . The global incidence of TB peaked around 2003 and appears to be declining slowly. According to the World Health Organization (WHO), in 2018, 10 million individuals became ill with TB and 1.5 million died.

Qual'è lo scopo della terapia antitubercolare?

- Curare il paziente
  - Il 60% dei pazienti con tubercolosi attiva muore se non viene trattato

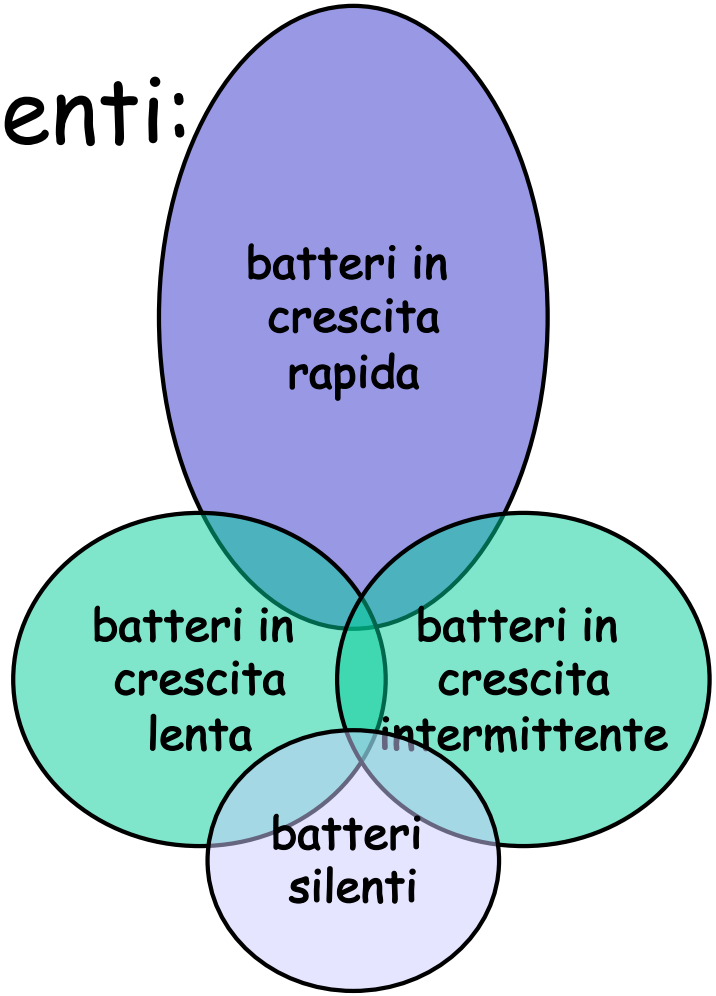


  - Il 90% dei pazienti trattati guarisce



- Minimizzare la trasmissione del *Mycobacterium tuberculosis*

- **La terapia della TBC è sempre una terapia di combinazione (nelle lesioni cavitarie 10^9-10^{10} bacilli)**
- Frequenza di ceppi resistenti:
  - all'isoniazide: 10^{-6}
  - alla rifampicina: 10^{-8}
  - all'etambutolo: 10^{-5}
  - alla streptomicina: 10^{-6}
- **È una terapia cronica**



Farmaci antitubercolari

Farmaci di prima scelta

Isoniazide (Nicizina®…)

Rifampicina (Rifadin®)

Pirazinamide (Piraldina®)

Etambutolo (Etapiam®…)

(Rifabutina, Mycobutin®)

Farmaci di seconda scelta

Moxifloxacina

Streptomicina

Acido p-aminosalicilico

Amikacina o kanamicina

Levofloxacina

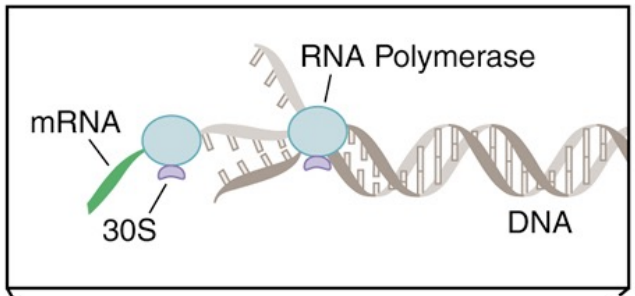
(Capreomicina)

(Etionamide)

(Cicloserina)

(Gatifloxacina)

Meccanismi d'azione dei farmaci antitubercolari



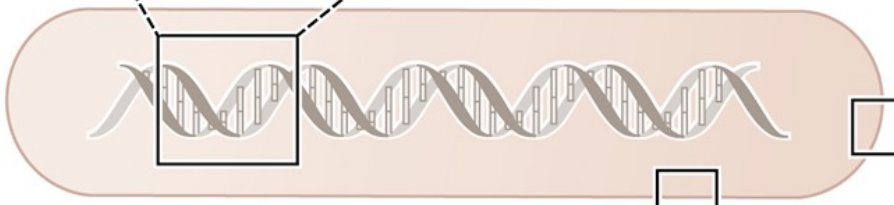
Approved Drugs

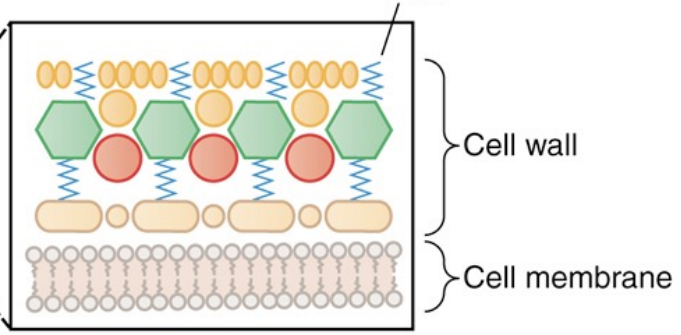
Fluoroquinolone:
inhibits DNA synthesis and supercoiling by targeting topoisomerase

Rifamycin:
inhibits RNA synthesis by targeting RNA polymerase

Streptomycin:
inhibits protein synthesis by targeting the 30S ribosomal subunit

Macrolides:
target 23S ribosomal RNA, inhibiting peptidyl transferase

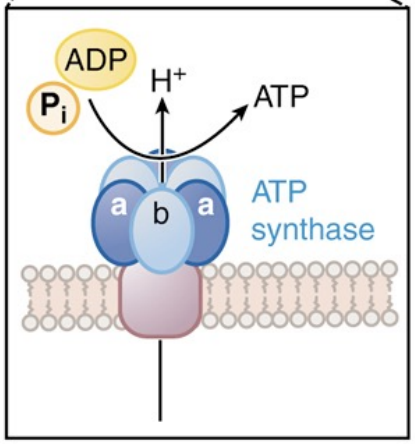




Isoniazid and Ethionamide:
inhibit mycolic acid synthesis

Ethambutol:
inhibits cell wall synthesis

Pyrazinamide:
inhibits cell membrane synthesis

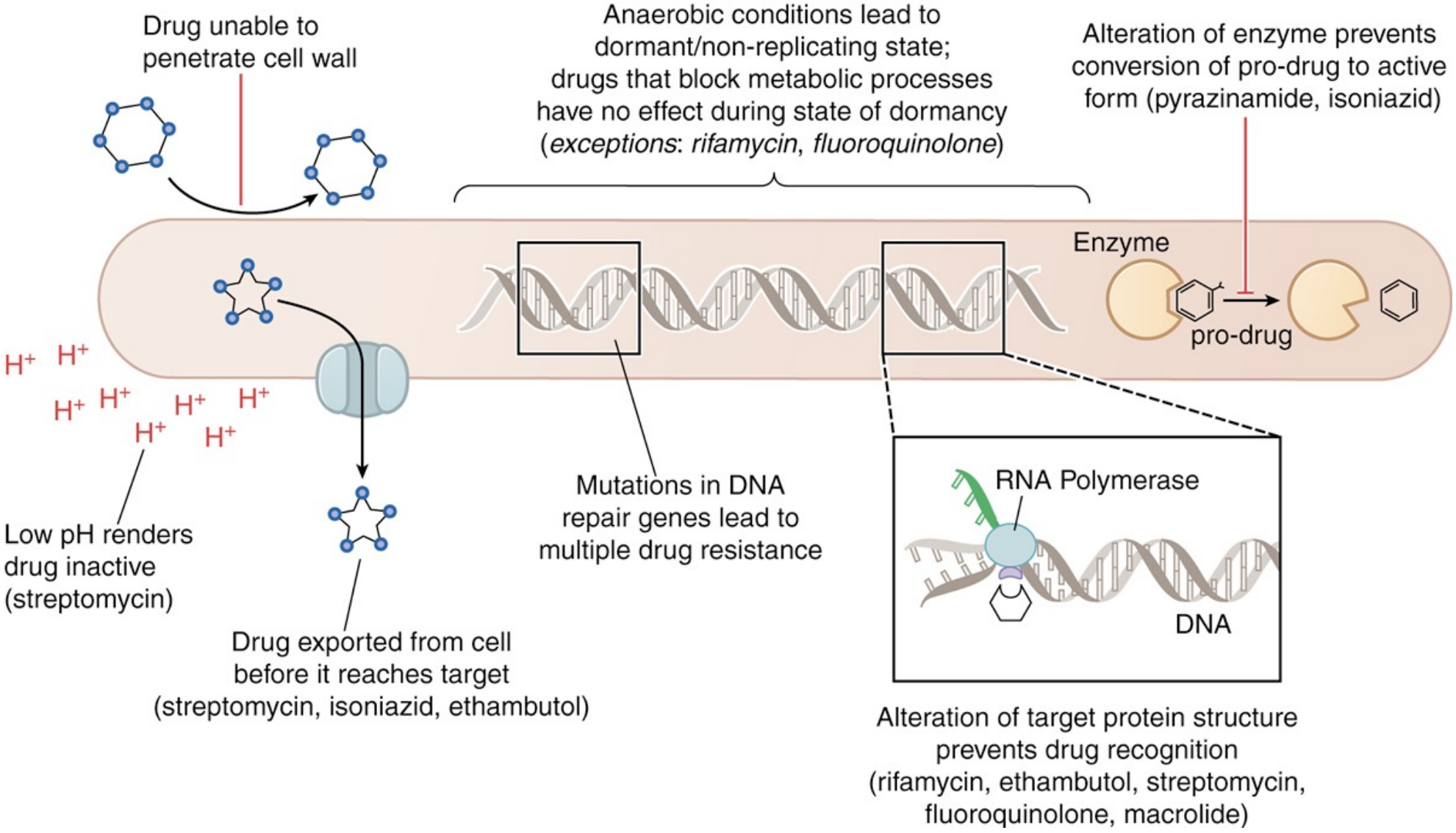


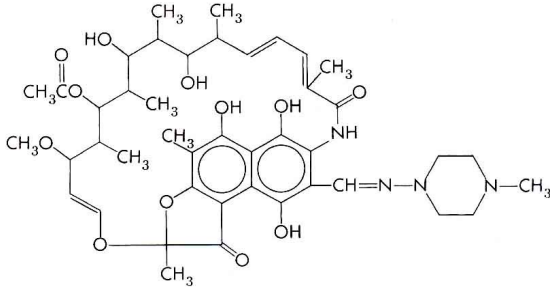
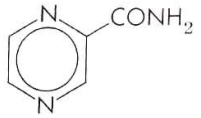
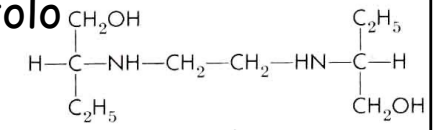
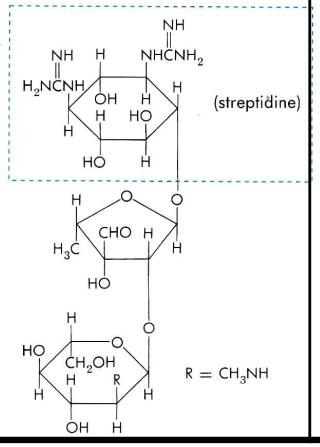
Experimental Drugs

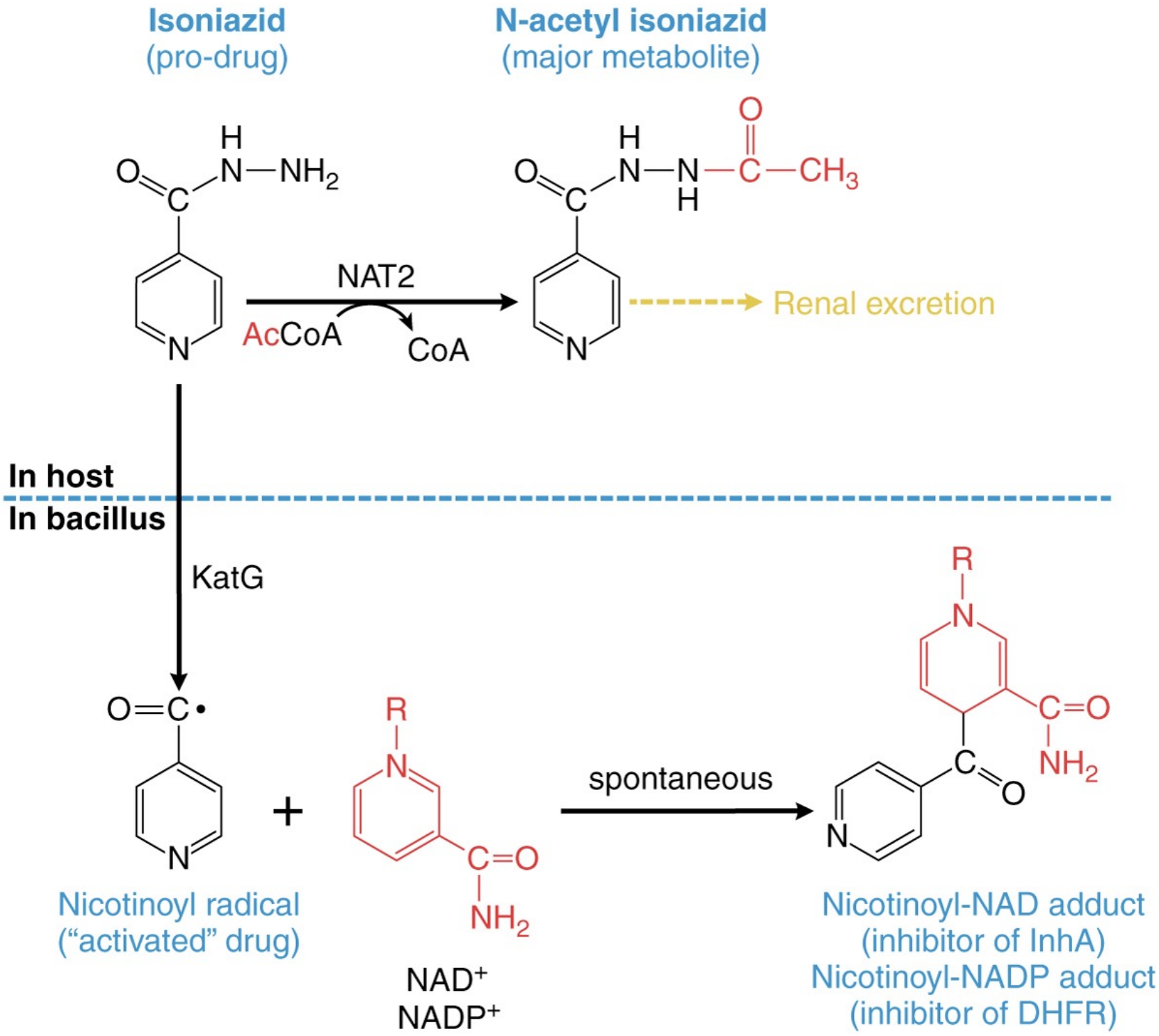
TMC-207 (R207910, TMC):
inhibits ATP synthase

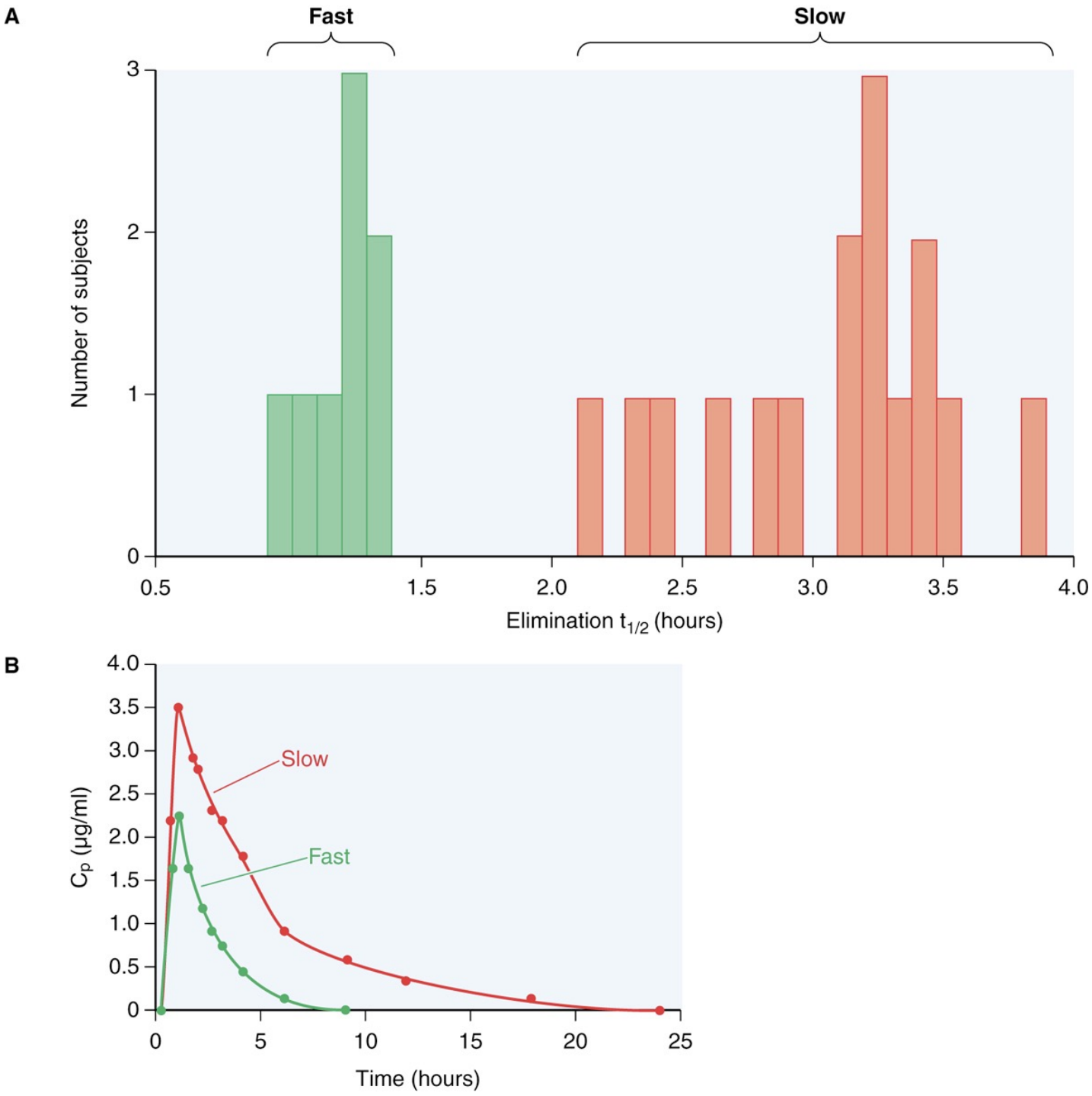
PA-824:
inhibits mycolic acid and protein biosynthesis; possibly acts via generation of toxic radicals

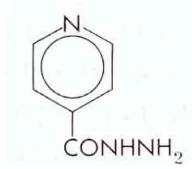
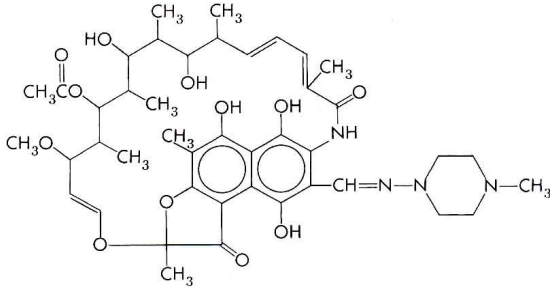
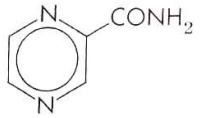
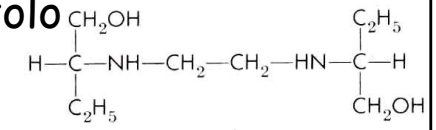
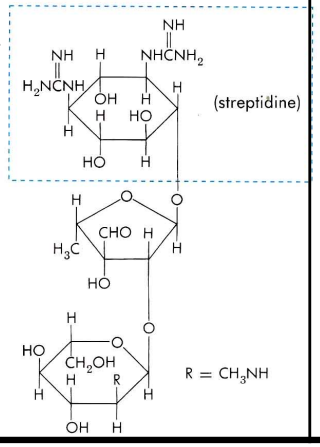
Meccanismi di resistenza ai farmaci antitubercolari



Farmaco	Assorbimento orale	Distribuzione	$t\frac{1}{2}$ (h)	Escrezione	Dose (mg/kg)
Isoniazide 	Ottimo	Eccellente	1-5	Epatica acetilazione	5
Rifampicina 	Ottimo	Eccellente	2-5	Epatica ⇩ metaboliti deacetilati attivi	10
Pirazinamide 	Ottimo	Eccellente	9-10	Epatica	15 – 30
Etambutolo 	Buono	Buona	3-4	$\frac{3}{4}$ renale	15 - 25
Streptomicina 	Nullo	Discreta	2-3	Renale	15


Isoniazid
(pro-drug)
N-acetyl isoniazid
(major metabolite)
NAT2
AcCoA
CoA
Renal excretion
In host
In bacillus
KatG
Nicotinoyl radical
("activated" drug)
NAD+
NADP+
spontaneous
Nicotinoyl-NAD adduct
(inhibitor of InhA)
Nicotinoyl-NADP adduct
(inhibitor of DHFR)


A
Fast
Slow
Number of subjects
0
1
2
3
0.5
1.5
2.0
2.5
3.0
3.5
4.0
Elimination $t_{1/2}$ (hours)
B
C_p (µg/ml)
0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Slow
Fast
0
5
10
15
20
25
Time (hours)

Farmaco	Assorbimento orale	Distribuzione	$t\frac{1}{2}$ (h)	Escrezione	Dose (mg/kg)
Isoniazide 	Ottimo	Eccellente	1-5	Epatica acetilazione	5
Rifampicina 	Ottimo	Eccellente	2-5	Epatica ⇓ metaboliti deacetilati attivi	10
Pirazinamide 	Ottimo	Eccellente	9-10	Epatica	15 – 30
Etambutolo 	Buono	Buona	3-4	$\frac{3}{4}$ renale	15 - 25
Streptomicina 	Nullo	Discreta	2-3	Renale	15

Effetti collaterali

Farmaco	Effetto collaterale	Segni e sintomi
Tutti	Allergia	Rash cutanei
Isoniazide, Pirazinamide, Rifampicina	Epatite	Alterazione dei test di funzionalità epatica Anoressia, malessere, nausea, vomito, ittero..
Isoniazide	Neuropatie periferiche	Parestesie, prevenibili con piridossina (15-50 mg/die)
	Alterazioni di SNC	Euforia, amnesie, perdita dell'autocontrollo, psicosi

Effetti collaterali

Farmaco	Effetto collaterale	Segni e sintomi
Rifampicina		Colora di rosso arancio urine, feci, saliva, lacrime e sudore
Pirazinamide Etambutolo	Disturbi gastroenterici Iperuricemia	Disturbi gastrici, vomito, perdita di appetito Dolori articolari Gotta (rara)
Etambutolo	Neurite ottica	Ridotta acuità visiva Alterata visione dei colori
Streptomicina	Danni acustici e vestibolari Danni renali	Disturbi dell'equilibrio Sordità, tinnito Alterazione dei test di funzionalità renale

Farmaco	Interazioni farmacologiche
Rifamicine •**Rifampicina** •Rifabutina •Rifapentina	rifampicina Ridotti livelli plasmatici di contraccettivi orali, warfarin, prednisone, sulfaniluree, inibitori delle proteasi, teofillina, metadone…

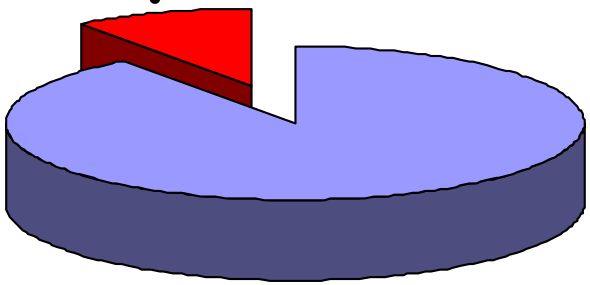
Table 3. Percentage by Which Rifampin and Rifabutin Lower the AUC of PIs and NNRTIs*

	Indinavir	Nelfinavir Mesylate	Saquinavir Mesylate	Amprenavir	Ritonavir	Ritonavir and Lopinavir	Efavirenz	Nevirapine	Delavirdine Mesylate
Rifampin	89	82	84	82	35	75	25	37	96
Rifabutin	32	32	40	15	0	0	0	16	80

*Data adapted from previously published guidelines.[25] AUC indicates area under the concentration-time curve; PI, protease inhibitor; and NNRTI, nonnucleoside reverse transcriptase inhibitor.

	Metabolita **Metaboliti**
Isoniazide	Inibisce il metabolismo della fenitoina

Cause di insuccesso terapeutico



- Scarsa aderenza alla terapia
  - Utilizzare la terapia più sicura ed efficace per il minor tempo possibile
  - Educare il paziente
  - Controllare l'assunzione regolare dei farmaci, se necessario ricorrendo alla DOT
- Resistenza
  - Utilizzare più farmaci a cui il micobatterio è sensibile
  - Non aggiungere mai un solo farmaco se la terapia non funziona

Terapia della TBC (non MDR)

- La terapia iniziale include 3-4 farmaci (2 mesi)
  - Isoniazide 5 mg/kg die (+ piridossina)
  - Rifampicina 10 mg/kg/die
  - Pirazinamide 15-30 mg/kg/die
  - (Etambutolo 15-25 mg/kg/die)
- La terapia viene quindi aggiustata quando a conoscenza dei test di sensibilità, e continuata per altri 4 – 7 mesi (isoniazide 5 mg/kg/die + rifampicina 10 mg/kg/die)

KEY CLINICAL POINTS

LATENT TUBERCULOSIS INFECTION

- Prevention of progression from latent tuberculosis infection (LTBI) to tuberculosis disease is an important individual and public health goal.
- Adults and children should be screened for risk factors for *Mycobacterium tuberculosis* exposure and for risk factors for progression to tuberculosis disease. Persons who screen positive should be tested for *M. tuberculosis* infection, preferably with the use of an interferon-γ release assay. Persons who test positive for *M. tuberculosis* infection should be assessed for tuberculosis disease.
- Persons with LTBI who are at increased risk for progression to tuberculosis disease generally should be treated for LTBI and followed until treatment is completed.
- Preferred LTBI treatment regimens include 3 months of once-weekly rifapentine plus isoniazid, 4 months of once-daily rifampin, or 3 months of once-daily isoniazid plus rifampin. Isoniazid administered once daily for 6 or 9 months is an alternative.
- Risk factors for hepatotoxic effects and drug–drug interactions should be considered when the LTBI treatment regimen is selected.

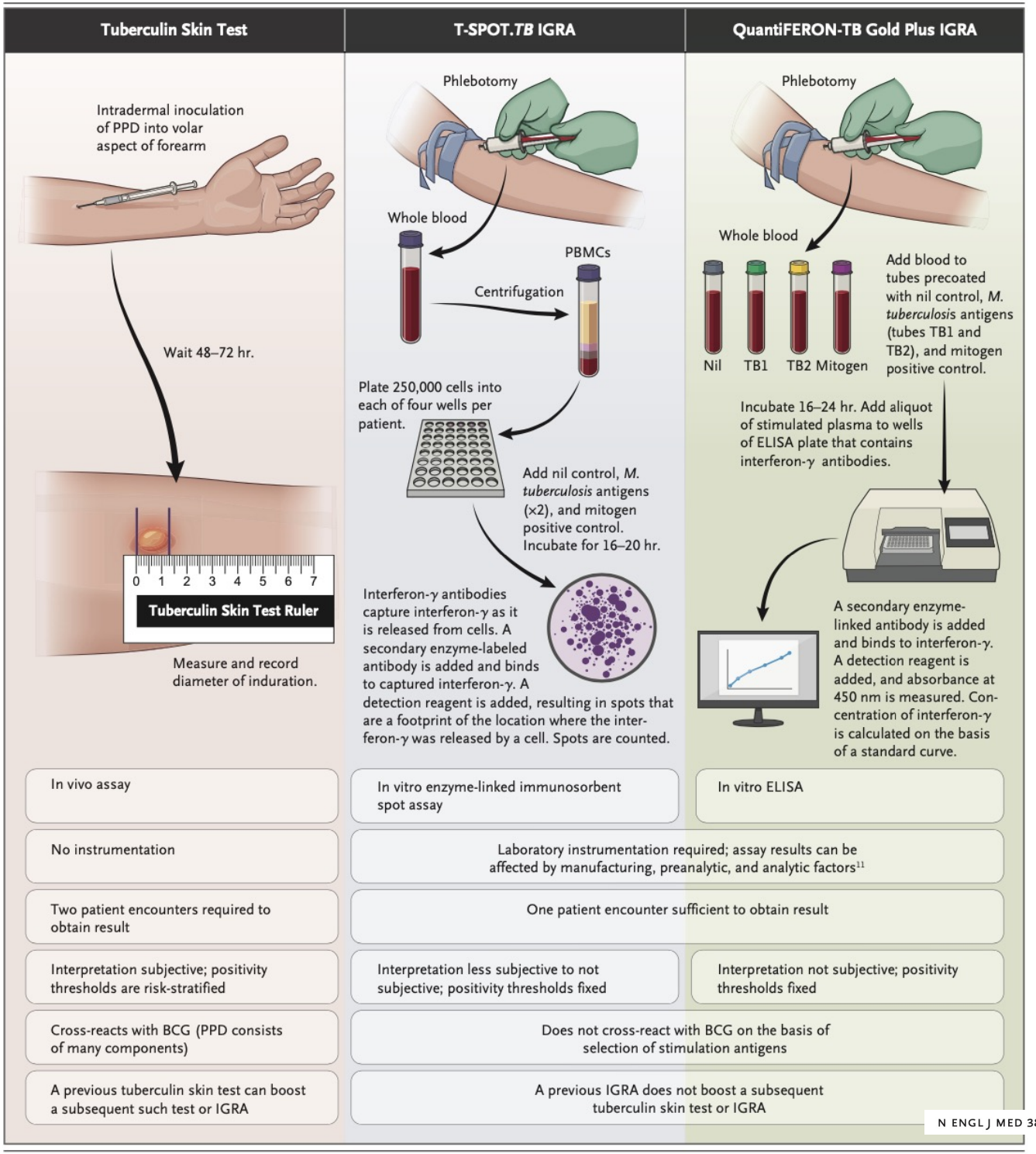

Tuberculin Skin Test
T-SPOT.TB IGRA
QuantiFERON-TB Gold Plus IGRA
Intradermal inoculation of PPD into volar aspect of forearm
Wait 48–72 hr.
0 1 2 3 4 5 6 7
Tuberculin Skin Test Ruler
Measure and record diameter of induration.
Phlebotomy
Whole blood
PBMCs
Centrifugation
Plate 250,000 cells into each of four wells per patient.
Add nil control, M. tuberculosis antigens (×2), and mitogen positive control. Incubate for 16–20 hr.
Interferon-γ antibodies capture interferon-γ as it is released from cells. A secondary enzyme-labeled antibody is added and binds to captured interferon-γ. A detection reagent is added, resulting in spots that are a footprint of the location where the interferon-γ was released by a cell. Spots are counted.
Phlebotomy
Whole blood
Nil
TB1
TB2
Mitogen
Add blood to tubes precoated with nil control, M. tuberculosis antigens (tubes TB1 and TB2), and mitogen positive control.
Incubate 16–24 hr. Add aliquot of stimulated plasma to wells of ELISA plate that contains interferon-γ antibodies.
A secondary enzyme-linked antibody is added and binds to interferon-γ. A detection reagent is added, and absorbance at 450 nm is measured. Concentration of interferon-γ is calculated on the basis of a standard curve.
In vivo assay
In vitro enzyme-linked immunosorbent spot assay
In vitro ELISA
No instrumentation
Laboratory instrumentation required; assay results can be affected by manufacturing, preanalytic, and analytic factors[11]
Two patient encounters required to obtain result
One patient encounter sufficient to obtain result
Interpretation subjective; positivity thresholds are risk-stratified
Interpretation less subjective to not subjective; positivity thresholds fixed
Interpretation not subjective; positivity thresholds fixed
Cross-reacts with BCG (PPD consists of many components)
Does not cross-react with BCG on the basis of selection of stimulation antigens
A previous tuberculin skin test can boost a subsequent such test or IGRA
A previous IGRA does not boost a subsequent tuberculin skin test or IGRA

Table 1. Risk-Based Approach for Latent Tuberculosis Infection (LTBI) Testing and Treatment.*

Findings Based on History	Recommended Action
Any of the following high-priority risk factors†: Household or other close contact with someone with infectious active tuberculosis disease‡ Birth, residence, or prolonged travel (>1 mo) in a setting in which tuberculosis disease is common (most countries in Africa, Asia, Eastern Europe, Latin America, and the Pacific Islands)§ Other circumstances based on local epidemiology (e.g., corrections facilities and homeless shelters)§ Immunosuppression (HIV infection or current or planned immunosuppression with the use of a TNF-α antagonist, glucocorticoids equivalent to prednisone at a dose of 2 mg per kilogram of body weight per day or 15 mg per day for ≥1 mo, or other immunosuppressing medications)‡	Testing for *M. tuberculosis* infection should be performed. If LTBI is present, LTBI treatment is recommended unless there are medical contraindications or clinically significant drug–drug interactions that cannot be mitigated.
Any of the following biologic factors that confer generally modest increased risk of progression to active tuberculosis disease if *M. tuberculosis* infection is present§: diabetes mellitus; chronic kidney disease; leukemia or lymphoma; cancer of the head or neck; chronic malabsorption, gastrectomy, or intestinal bypass; a body-mass index (the weight in kilograms divided by the square of the height in meters) of ≤20; silicosis; current or former smoking status; or an age of ≤5 yr¶	In the absence of epidemiologic risk factors (as noted above) for tuberculosis exposure, testing for *M. tuberculosis* infection is generally not recommended. However, if LTBI is present, LTBI treatment is recommended unless there are medical contraindications or clinically significant drug–drug interactions that cannot be mitigated.
No epidemiologic risk factors for tuberculosis exposure and no host risk factors for progression to active tuberculosis disease if *M. tuberculosis* infection is present	Testing for *M. tuberculosis* infection is not recommended.

* This table is based on recommendations from the National Society of Tuberculosis Clinicians.[6] HIV denotes human immunodeficiency virus, and TNF-α tumor necrosis factor α.

† Tuberculin skin test (TST) results are interpreted at the listed positivity thresholds on the basis of epidemiologic or host risk and to improve test positive and negative predictive values. Interferon-γ release assays currently have absolute thresholds for positivity without incorporation of host or epidemiologic risk.

‡ The TST positivity threshold is 5 mm or more.

§ The TST positivity threshold is 10 mm or more.

¶ Children 5 years of age or younger are at high risk for rapid progression to active tuberculosis disease after infection, and severe forms of tuberculosis (including disseminated and central nervous system tuberculosis) are more likely to develop in such children than in older children or in adults.

Table 2. Dose, Frequency, and Prescribing Information for Recommended Regimens for Treatment of LTBI.*

Priority and Regimen†	Dose for Adults and Children ≥12 Yr of Age[37,38]	Additional Prescribing Information‡
Preferred		
Isoniazid plus rifapentine once weekly for 3 mo (12 doses)§	Isoniazid: 15 mg/kg/dose rounded up to nearest 50 or 100 mg; maximum dose, 900 mg Rifapentine: 750 mg per dose if weight is 32.1–49.9 kg; 900 mg per dose if weight is ≥50 kg; maximum dose, 900 mg	Administration: taking with high-fat foods increases rifapentine absorption and is recommended. Avoid concomitant aluminum-containing antacids and foods with high monoamine content. Adverse reactions: possible hypersensitivity reaction (3.8%), rash (0.8%), hepatotoxic effects (0.4%).[26] Hypersensitivity reactions can include hypotension, bronchospasm, angioedema, conjunctivitis, and urticaria. Drug–drug interactions: rifapentine causes reductions in plasma concentrations of certain drugs, including warfarin, apixaban, rivaroxaban, dabigatran, hormonal contraceptives, levothyroxine, methadone, and many HIV antiretroviral drugs. The effect of once-weekly rifapentine appears to be less than that of daily rifampin, but data are limited. For interactions with isoniazid, see below.
Rifampin once daily for 4 mo	10 mg/kg/day; maximum daily dose, 600 mg	Administration: taking on an empty stomach is preferable, if side effects are acceptable. Adverse reactions: hepatotoxic effects (0.3%), rash or other allergy (0.2%), hematologic toxic effects (0.2%), unacceptable GI adverse events (0.1%).[31] Drug–drug interactions: as for rifapentine, above.
Isoniazid plus rifampin once daily for 3 mo	Isoniazid: 5 mg/kg/day; maximum daily dose, 300 mg Rifampin: 10 mg/kg/day; maximum daily dose, 600 mg	Administration: taking on an empty stomach is preferable, if side effects are acceptable. Avoid concomitant aluminum-containing antacids and foods with high monoamine content. Adverse reactions: limited published data; hepatotoxic effects (1–6%), rash (1–8%), unacceptable GI adverse events (0–6%).[35] Isoniazid can cause peripheral neuropathy that can be mitigated by pyridoxine (25–50 mg/day).¶ Drug–drug interactions: as for rifapentine (above) and isoniazid (below).
Alternative		
Isoniazid once daily for 6 mo‖**	5 mg/kg/day; maximum daily dose, 300 mg	Administration: taking on an empty stomach is preferable, if side effects are acceptable. Avoid concomitant aluminum-containing antacids and foods with high monoamine content. Adverse reactions: hepatotoxic effects (2–3%), rash (0.6%), possible hypersensitivity (0.5%).[26,31,34] Isoniazid can cause peripheral neuropathy that can be mitigated by pyridoxine (25–50 mg/day).¶ Drug–drug interactions: Isoniazid can increase the serum concentrations of carbamazepine, phenytoin, warfarin, disulfiram, and others. Isoniazid can decrease the serum concentrations of itraconazole and ketoconazole.
Isoniazid once daily for 9 mo‖††	Same as above	Same as above

* GI denotes gastrointestinal.

† With respect to priority, "preferred" indicates excellent side-effect profile and efficacy, shorter treatment duration, and higher completion rates than longer regimens and therefore higher effectiveness; "alternative" indicates good efficacy but lower completion rates than shorter regimens and therefore lower effectiveness. The guidelines for regimens do not apply in circumstances in which there is evidence that the infecting strain of *M. tuberculosis* is resistant to both isoniazid and rifampin.

‡ An online resources for up-to-date information about drug–drug interactions is the Medscape Drug Interaction Checker: https://reference.medscape.com/drug-interactionchecker. Information about possible interactions between tuberculosis drugs and HIV drugs is available at https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv.

§ A regimen of once-weekly isoniazid plus rifapentine is not recommended for use in pregnant persons or those who anticipate becoming pregnant during the treatment period because its safety in these populations has not been adequately studied.

¶ Pyridoxine is recommended for persons with preexisting neuropathy or neuropathy risk factors such as diabetes or HIV infection.

‖ Isoniazid may also be administered twice weekly by directly observed therapy for 6 or 9 months, at a dose of 15 mg per kilogram per dose for adults.

** Once-daily isoniazid is strongly recommended for HIV-negative adults who are unable to take a preferred regimen. For persons living with HIV infection, either 6 or 9 months of isoniazid can be used.

†† The recommendation for a 9-month regimen emerged after a reanalysis of data showed that increased protection was obtained with 9 to 10 months of treatment; clinical-trial data are lacking that directly compare 9 months of isoniazid with other durations.[39,40]