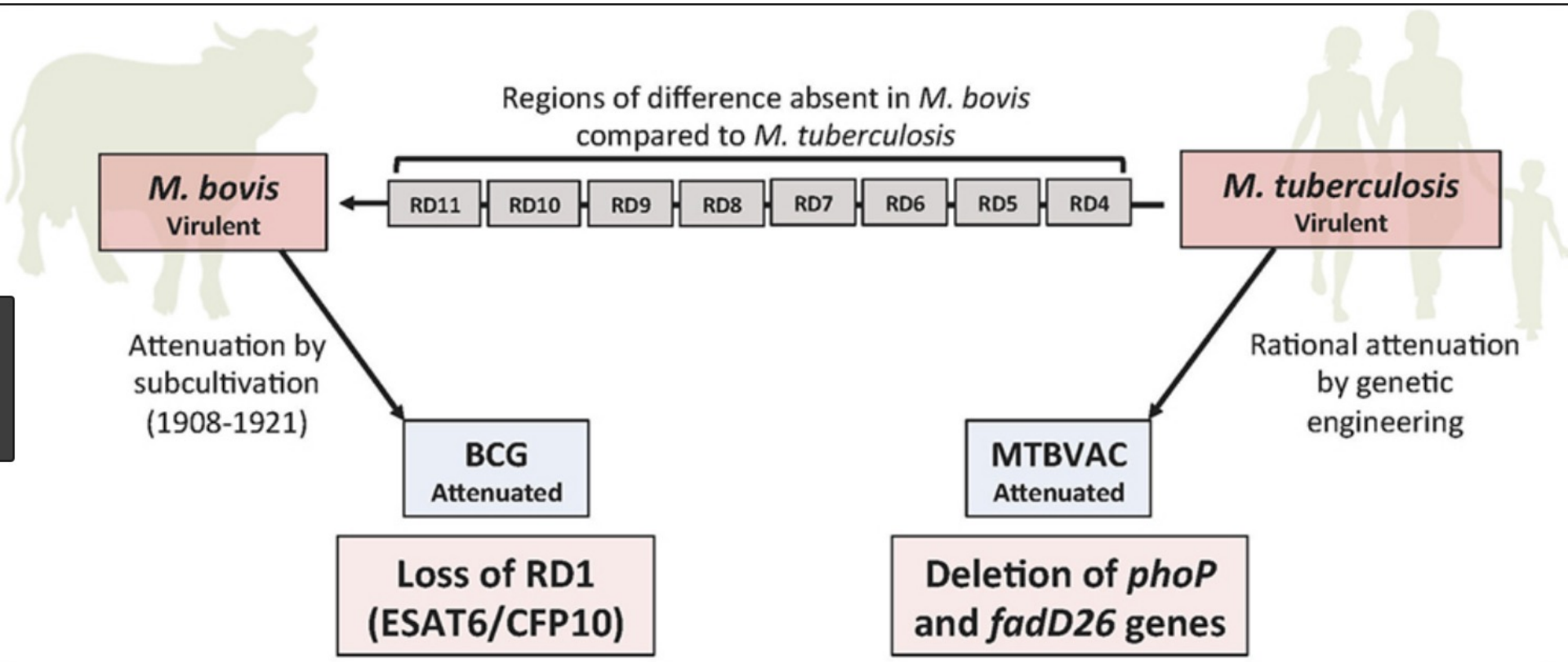
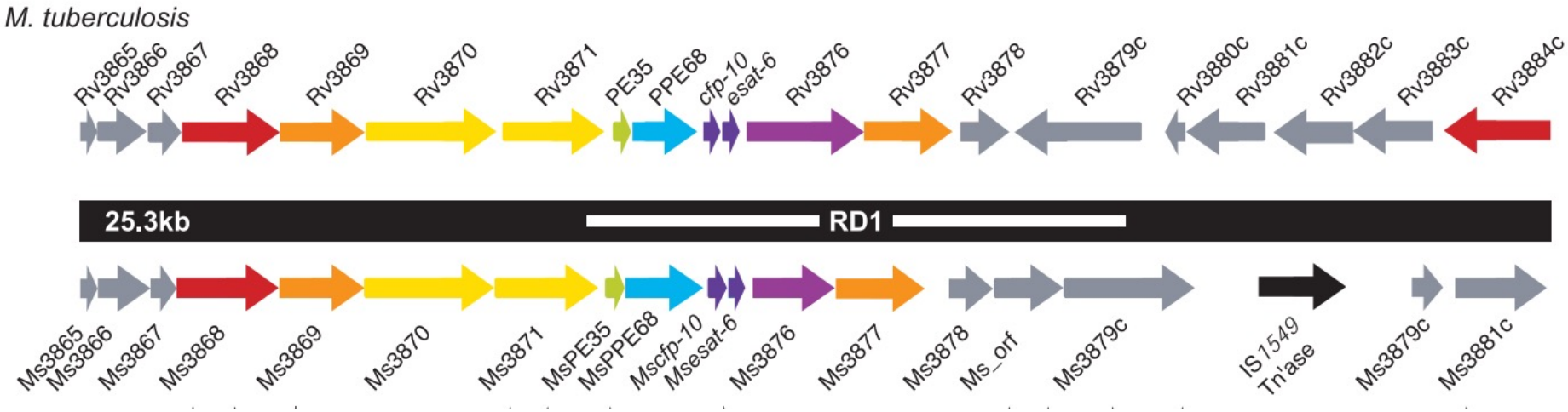
BCG and TB vaccines

Calmette and Guerin

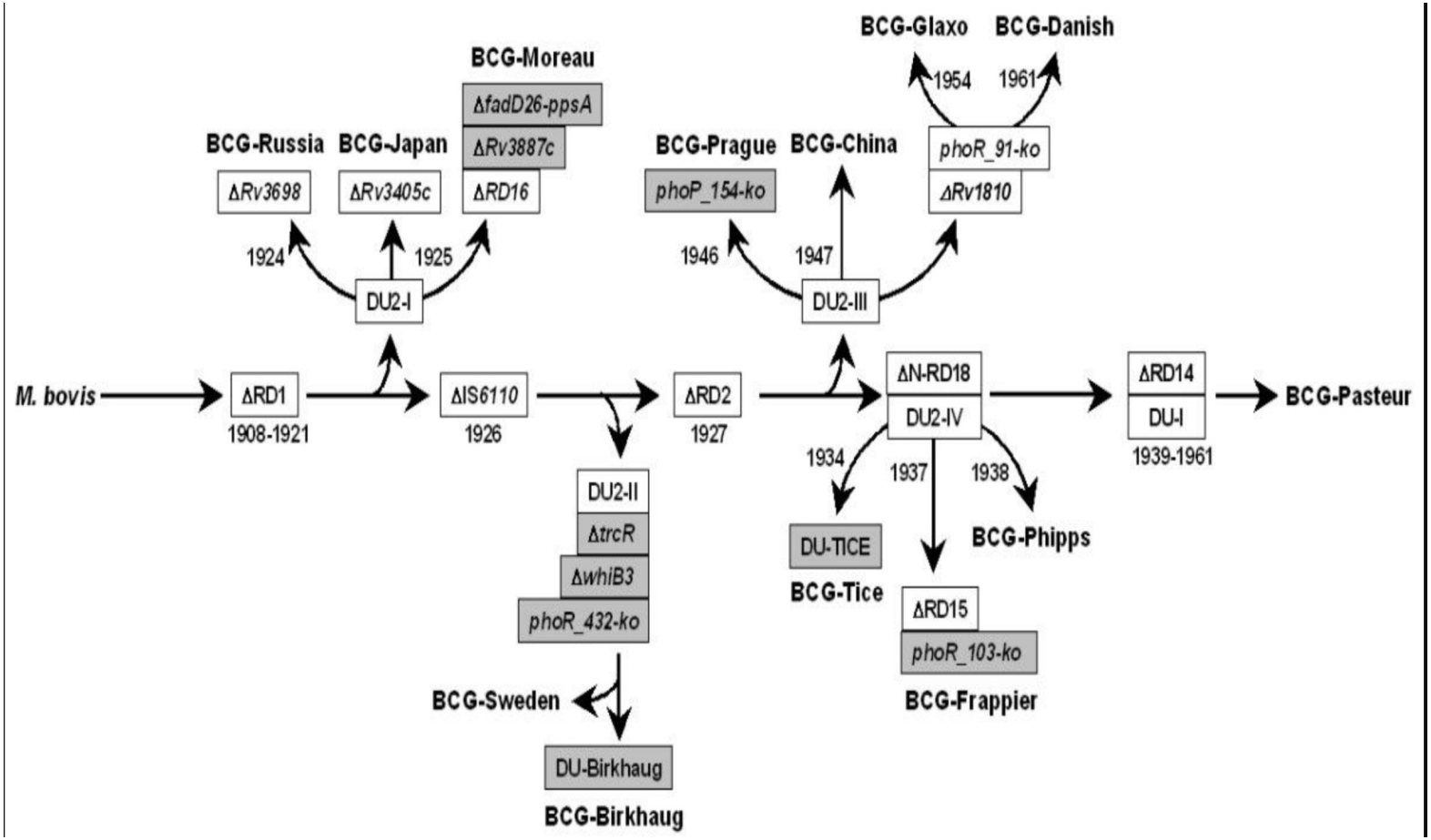
Development of BCG

- Started with M. bovis
- Passaged q 3 weeks on glycerin and ox blood from 1906 to 1917
- Strain found to be attenuated in animal models including guinea pigs, rabbits, cows and horses.
- First human experiment in newborn in Paris

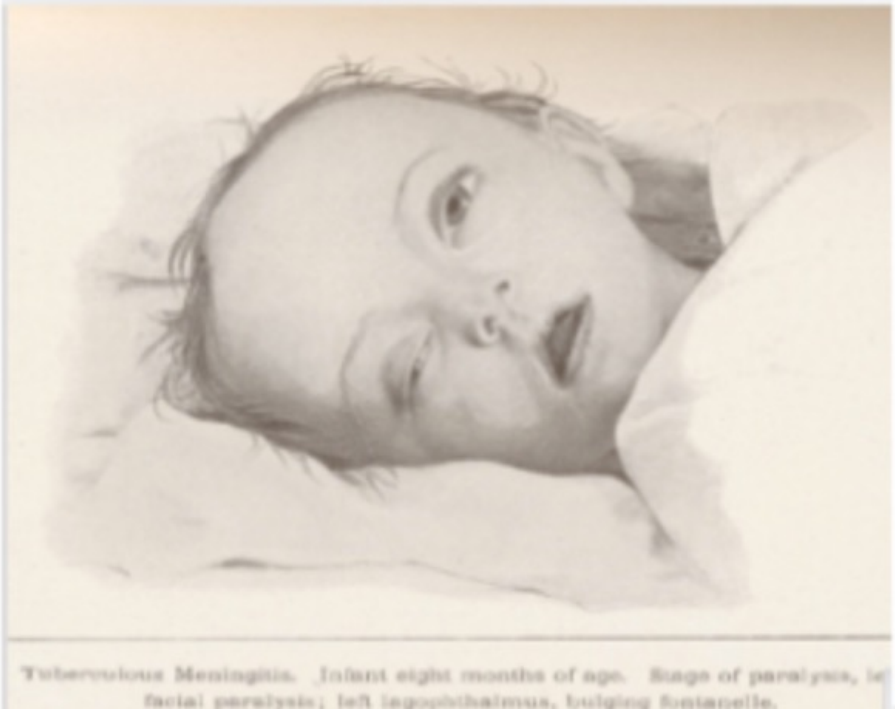

Regions of difference absent in M. bovis compared to M. tuberculosis
M. bovis Virulent
RD11
RD10
RD9
RD8
RD7
RD6
RD5
RD4
M. tuberculosis Virulent
Attenuation by subcultivation (1908-1921)
Rational attenuation by genetic engineering
BCG Attenuated
MTBVAC Attenuated
Loss of RD1 (ESAT6/CFP10)
Deletion of phoP and fadD26 genes


M. tuberculosis
Rv3865
Rv3866
Rv3867
Rv3868
Rv3869
Rv3870
Rv3871
PE35
PPE68
cfp-10
esat-6
Rv3876
Rv3877
Rv3878
Rv3879c
Rv3880c
Rv3881c
Rv3882c
Rv3883c
Rv3884c
25.3kb
RD1
Ms3865
Ms3866
Ms3867
Ms3868
Ms3869
Ms3870
Ms3871
MsPE35
MsPPE68
Mscfp-10
Msesat-6
Ms3876
Ms3877
Ms3878
Ms_orf
Ms3879c
IS1549 Tnase
Ms3879c
Ms3881c

Sequential loss of genes



1929: Lubeck tragedy



Tuberculous Meningitis. Infant eight months of age. Stage of paralysis, le
facial paralysis; left exophthalmus, bulging fontanelle.

1929

Tuberculosis: Lübeck Disaster

A disaster caused by BCG struck the German city of Lübeck. During 1929 and 1930, 72 babies died from tuberculosis out of 252 vaccinated. Many other infants were made ill as a result of vaccination. The vaccine used was later found to have been contaminated with a human tuberculosis strain being studied in same lab.

1946: UNICEF founded

- Unicef responded to abrupt increase in TB rates in Europe after WWII with BCG campaign undertaken with Scandinavian countries.
- By early 1950s, WHO expanded BCG campaign to other high burden countries.
- Initially restricted to people who were skin test negative but later expanded to all.

Early BCG trials: MRC

- Used Copenhagen strain BCG and vole bacillus vaccine
- 54239 TST negative participants aged 14-15 in 1950 in Great Britain
- Followed for 20 years
- 84% efficacy in years 1-5
- Declining efficacy over time
- Average of 77% per year

Early BCG trials: PHS US

- 1950s in two Southern counties, one in Alabama and one in Georgia.
- Used Tice BCG
- 64136 residents of all ages of which non-reactors were randomized to vaccine and no vaccine.
- 14% reduction in TB in vaccinated group.
- Almost all reduction occurred in first 4 years.
- Least effective in African Americans.

How to explain discrepancy

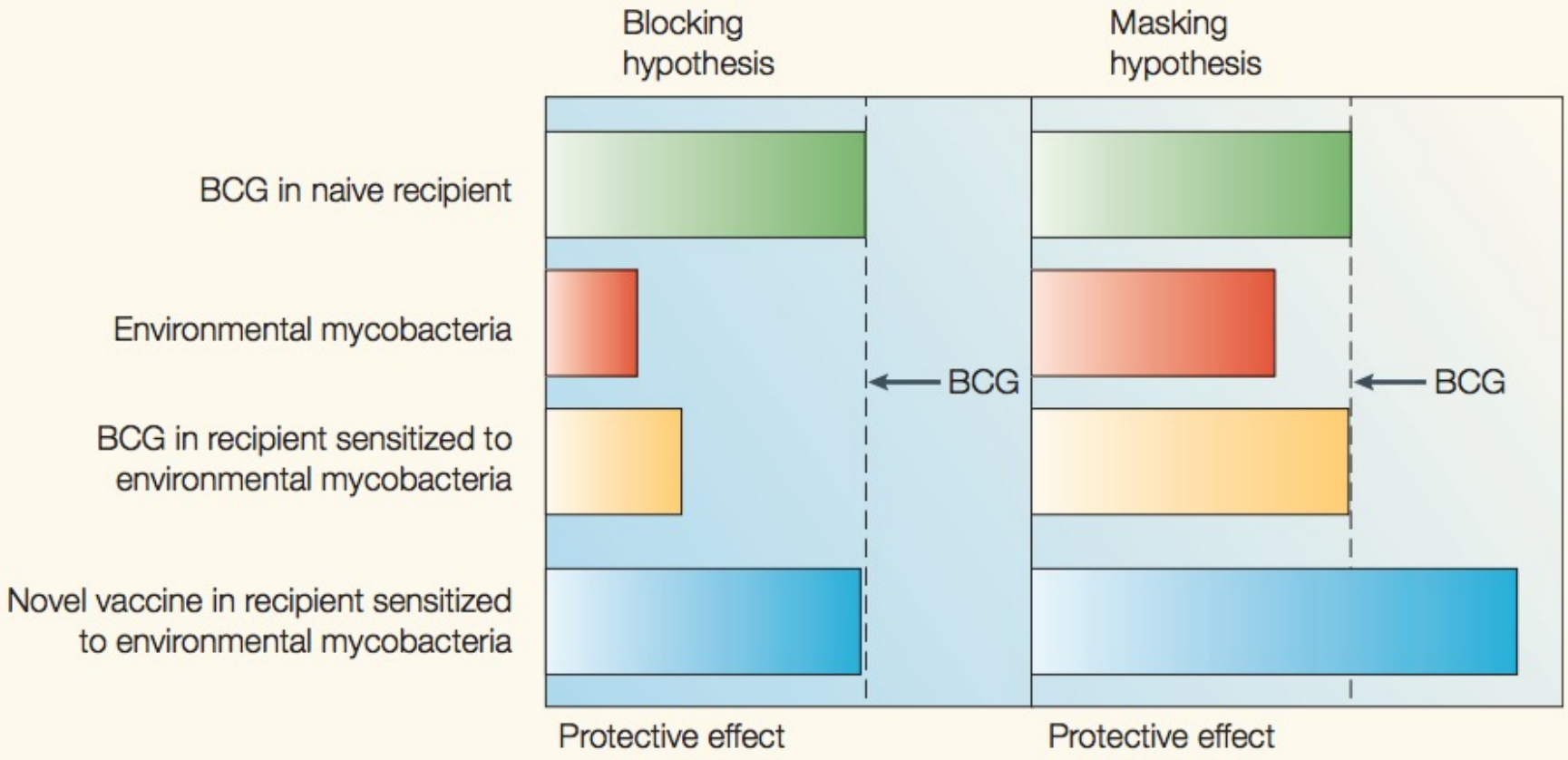
- Different BCGs?
  - Multiple types of BCG created from different attenuation procedures.
  - Different immunogenicity
- Environmental mycobacteria
  - Blocking of BCG
  - Masking of BCG

Blocking Hypothesis

- Prior sensitization to non-tuberculous mycobacteria blocks BCG dissemination by inducing an immune response to antigens that are cross-reactive with BCG antigens
- BCG replication required for sustained immune response.
- Partial immunity from environmentals not adequate protection against virulent TB.

Masking hypothesis

- Prior exposure to environmental mycobacteria provides similar protection to BCG and additional protection from BCG is therefore limited.
- In support of this, M avium isolated from soil from S. India provided 20-90% protection from TB and subsequent BCG added no benefit in GPs.


Blocking hypothesis
Masking hypothesis
BCG in naive recipient
Environmental mycobacteria
BCG in recipient sensitized to environmental mycobacteria
Novel vaccine in recipient sensitized to environmental mycobacteria
BCG
BCG
Protective effect
Protective effect

Chingelput trial

- Started in 1968 to differentiate the two hypotheses. (but Northern India arm got dropped).
- Compared French (Pasteur) and Danish (Statens Serum) strains at two doses
- Included 281,161 of which 109873 TST -.
- 15 year follow up.
- Small benefit in children (25%), none in adults.

Overall efficacy

Source, y	Population		Cases of TB			TB Death		
	BCG	No BCG	BCG	No BCG	RR	BCG	No BCG	RR
Aronson,[23] 1948†	123	139	4	11	0.41	0	4	0.14
Ferguson and Simes,[40] 1949	306	303	6	29	0.20	2	9	0.22
Rosenthal et al,[42] 1960‡	231	220	3	11	0.26	0	4	0.12
Hart and Sutherland,[41] 1977	13 598	12 867	62	248	0.24	...	...	...
Frimodt-Moller et al,[45] 1973	5069	5808	33	47	0.80	...	...	...
Stein and Aronson,[44] 1953	1541	1451	180	372	0.46	...	...	...
Vandiviere et al,[43] 1973	2545	629	8	10	0.20	...	...	...
Madras,[15] 1980§	88 391	88 391	505	499	1.01	...	...	...
Coetzee and Berjak,[39] 1968‖	7499	7277	29	45	0.63	...	...	...
Rosenthal et al,[49] 1961¶	1716	1665	17	65	0.25	1	6	0.16
Comstock et al,[47] 1974	50 634	27 338	186	141	0.71	8	12	0.36
Comstock and Webster,[48] 1969#	2498	2341	5	3	1.56	...	...	...
Comstock et al,[46] 1976#	16 913	17 854	27	29	0.98	...	...	...
Aronson et al,[51] 1958**	1541	1451	...	...	...	13	68	0.18
Levine and Sackett,[50] 1948††	566	528	...	...	...	8	8	0.93
Overall RR (95% confidence interval)				0.49 (0.34-0.70)			0.29 (0.16-0.53)	

Colditz, 1994

Updated Meta-analysis

- Reviewed 132 studies
- Confirms heterogeneity with efficacy ranging from 0 to 78%.
- Declining efficacy over time but protection remains at 10 years.
- Subsequent efficacy could not be estimated due to loss to follow up.
- Efficacy increased with distance from equator but not with strain.
- Efficacy high in young children

Latitude

- Is latitude a proxy for environmental mycobacterial exposure?
- Vitamin D exposure?
- SES?
- Seasonality?
- Maternal exposures? (TB, helminths)

- Note: Comparison of response of neonates in UK and Malawi shows weaker IF-gamma response in Malawi.

Other issues

- Protection from progression or infection?
- Non-specific immunity

- Route of administration
- Timing of administration
- Trained immunity

Protection

- BCG traditionally considered to protect against disease progression.
- Difficult to assess since BCG affects measurable outcome of infection (TST).
- Intro of IGRA shows that BCG also reduces infection risk.

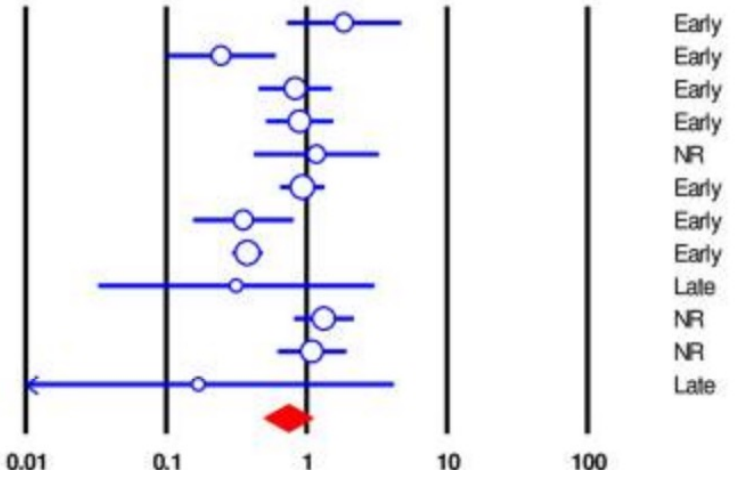
Non-Specific immunity

- Mortality benefit in young children
  - Infants vaccinated at birth have .5-.7 X reduction in mortality compared to unvaccinated kids in 38 studies, esp in low BW infants. Not due to reduced tb risk. Same benefit not observed in recent Danish study.

Protection from childhood leukemia?

BCG vaccination

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Vaccinated / Total: Leukemia	Vaccinated / Total: Non-leukemia	
Dockerty JD/1999	1.84	0.72	4.71	0.20	8 / 120	11 / 295	Early
Nishi M/1989	0.25	0.10	0.60	0.00	48 / 63	117 / 126	Early
Salonen T/1976	0.83	0.46	1.51	0.54	348 / 373	352 / 373	Early
Von Kries R/2000	0.89	0.51	1.54	0.68	107 / 129	273 / 323	Early
MacArthur AC/2007	1.17	0.42	3.27	0.76	8 / 376	7 / 385	NR
Mallol-Mesnard N/ 2007	0.93	0.65	1.34	0.71	624 / 672	1309 / 1403	Early
Crispen RG/1976	0.35	0.16	0.81	0.01	6 / 112	85350 / 620114	Early
Davignon L/1971	0.38	0.30	0.48	0.00	96 / 287	1092400 / 1917000	Early
Sutherland I/1982	0.32	0.03	3.03	0.32	1 / 4	13598 / 26465	Late
Mathe/1974	1.32	0.81	2.16	0.26	76 / 130	67 / 130	NR
Petridou/1997	1.09	0.62	1.91	0.76	22 / 153	40 / 300	NR
Comstock GW/1975	0.17	0.01	4.17	0.28	0 / 1	5524 / 8340	Late
	0.73	0.50	1.08	0.12			



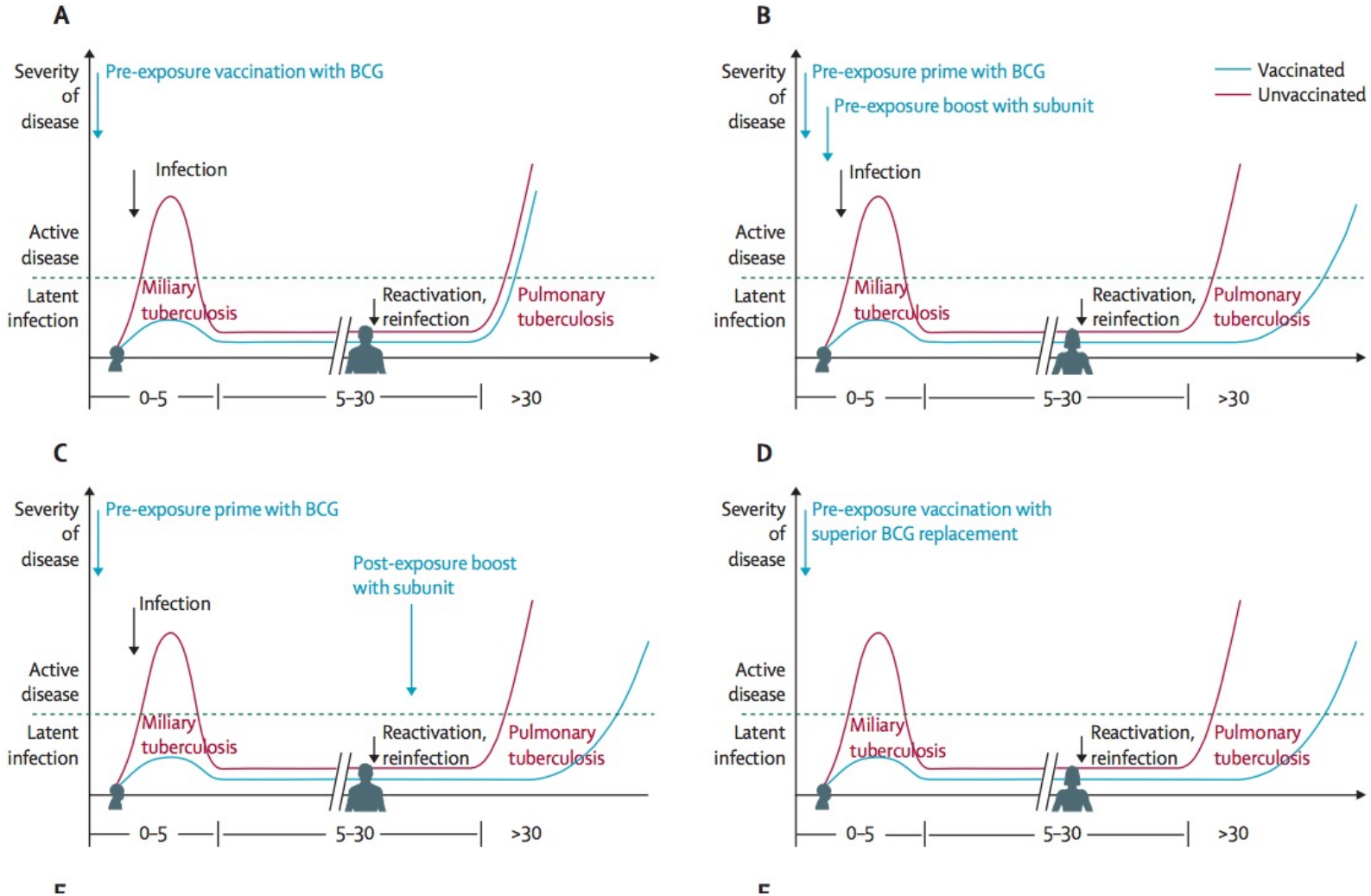
Bladder Cancer

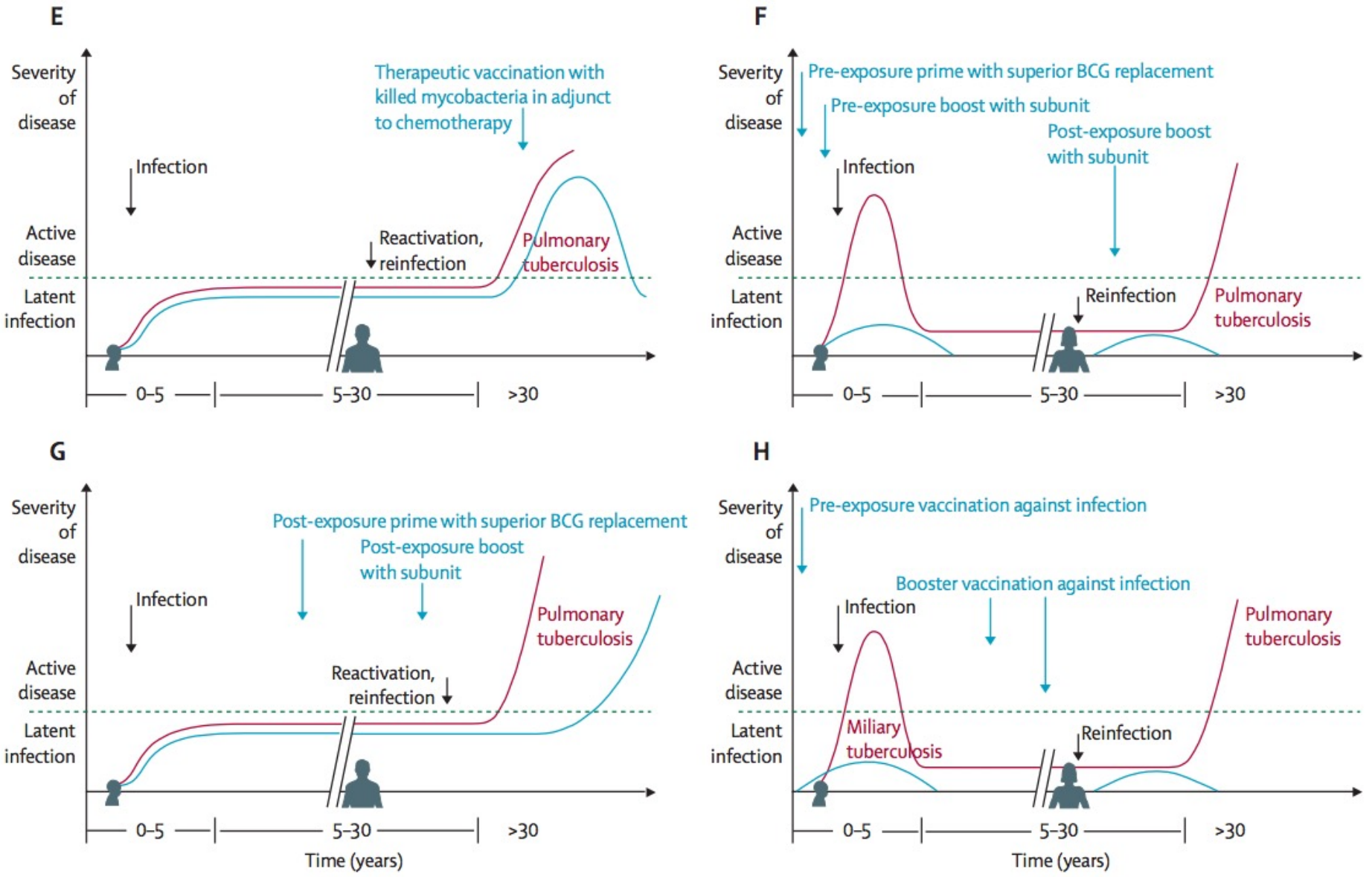
- BCG irrigation of bladder standard treatment for non-invasive bladder cancer.
- Studies show complex immune responses including upregulation of T-regs which may interfere with long term suppression.

Other vaccines: Types

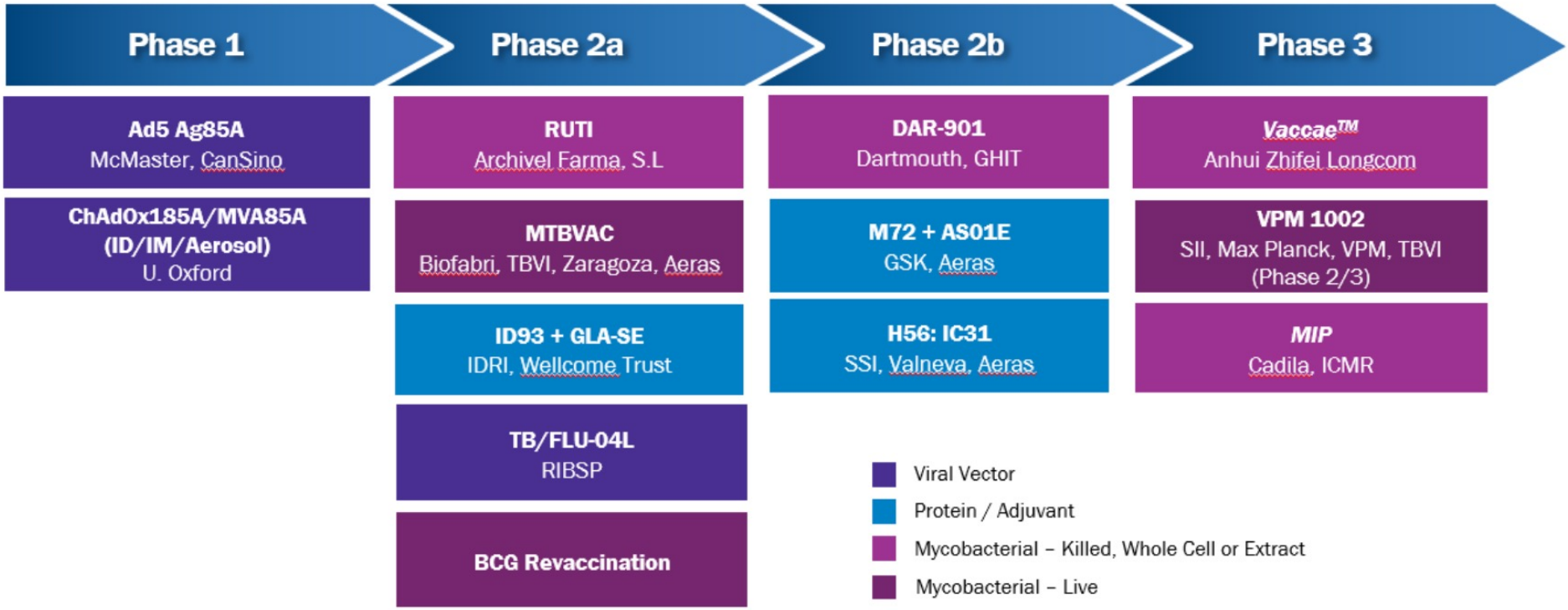
- Live attenuated
- Inactivated, killed
- Subunit/conjugate
- Toxoid
- DNA

Proposed TB vaccination strategies




E
Severity of disease
Therapeutic vaccination with killed mycobacteria in adjunct to chemotherapy
Infection
Active disease
Reactivation, reinfection
Pulmonary tuberculosis
Latent infection
0–5
5–30
>30
F
Severity of disease
Pre-exposure prime with superior BCG replacement
Pre-exposure boost with subunit
Post-exposure boost with subunit
Infection
Active disease
Reinfection
Pulmonary tuberculosis
Latent infection
0–5
5–30
>30
G
Severity of disease
Post-exposure prime with superior BCG replacement
Post-exposure boost with subunit
Infection
Pulmonary tuberculosis
Active disease
Reactivation, reinfection
Latent infection
0–5
5–30
>30
Time (years)
H
Severity of disease
Pre-exposure vaccination against infection
Booster vaccination against infection
Infection
Pulmonary tuberculosis
Active disease
Miliary tuberculosis
Reinfection
Latent infection
0–5
5–30
>30
Time (years)

Global Clinical Pipeline



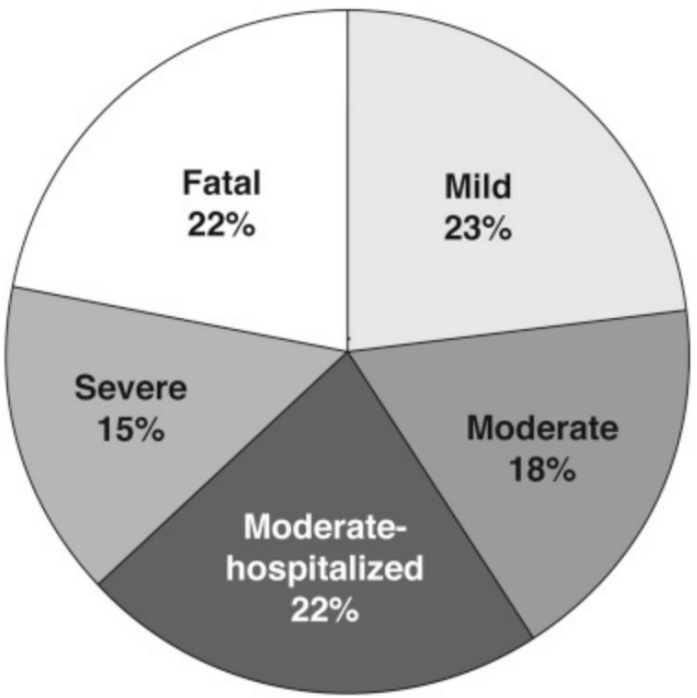
New vaccine trials

- 3 candidate vaccines showed no or limited effect (M. obuense, Ag85 in vaccinia, new subunit vaccine).
- But recent trial in NEJM of M72/ASO1-E showed 54% efficacy in previously BCG vaccinated adults with stronger benefit in participants over 25.

But many cases are under-reported.

Drug induced liver injury network reports 60 cases between 20014 and 2013, of whom 13 died or had liver transplant. Only one case had been counted by CDC. Many had not been stopped following existing ATS guidelines.

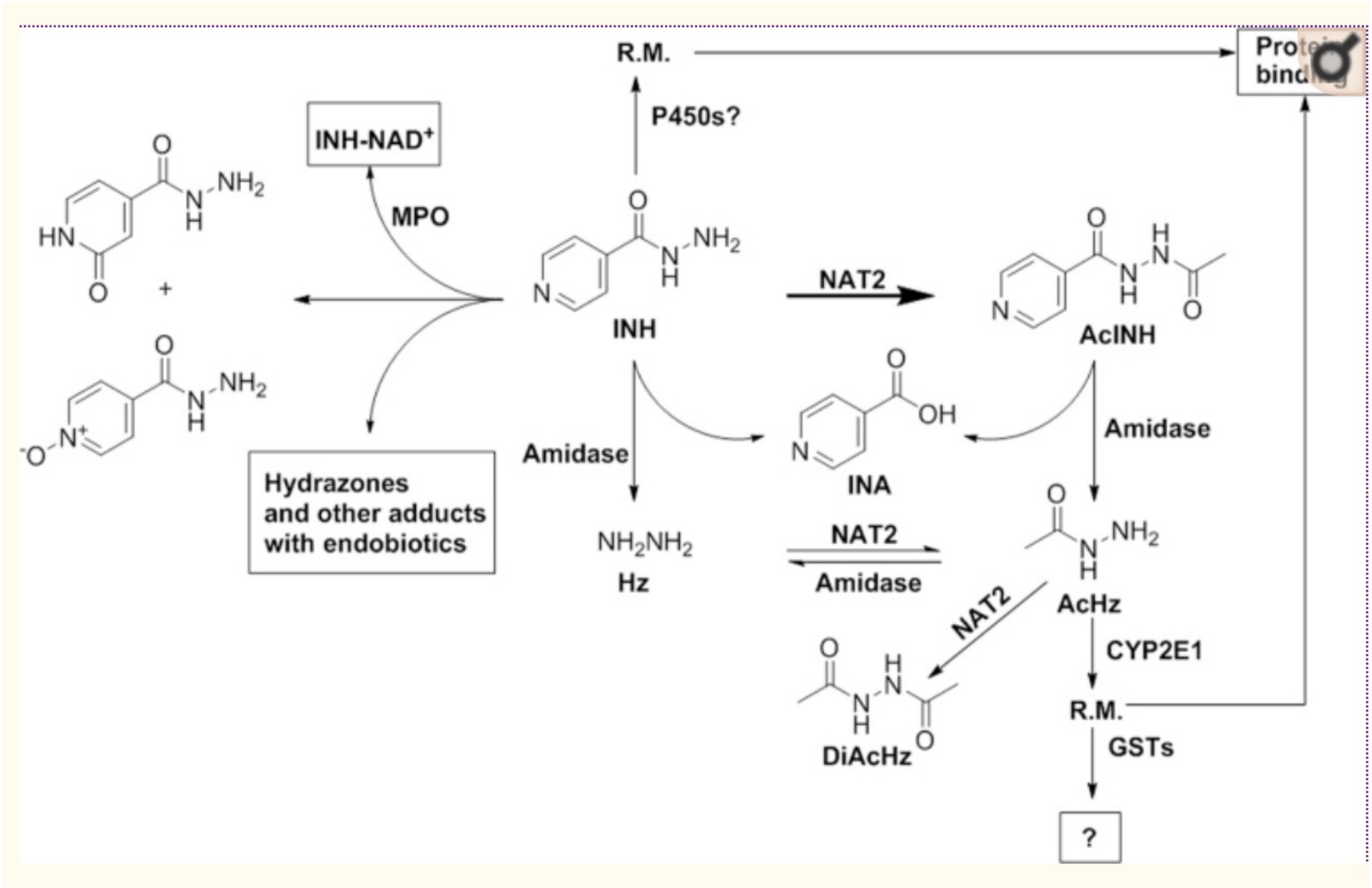
Female pattern persist but not racial pattern.



Under-reporting and Poor Adherence to Monitoring Guidelines for Severe Cases of Isoniazid Hepatotoxicity

Paul H. Hayashi, MD, MPH,[1] Robert J. Fontana, MD,[2] Naga P. Chalasani, MD,[3] Andrew A. Stolz, MD,[4] Jay A. Talwalker, MD,[5] Victor J. Navarro, MD,[6] William M. Lee, MD,[7] Timothy J. Davern, MD,[8] David E. Kleiner, MD, PhD,[9] Jiezhun Gu, PhD,[10] and Jay H. Hoofnagle, MD[11], for the U.S. DILIN Investigators

Acetylator status: unclear associations



INH and alcohol

- Alcohol
  - Potentiates liver injury with INH uses
  - Evokes and “intolerance” response similar to but by a different mechanism than disulfiram.

Target populations

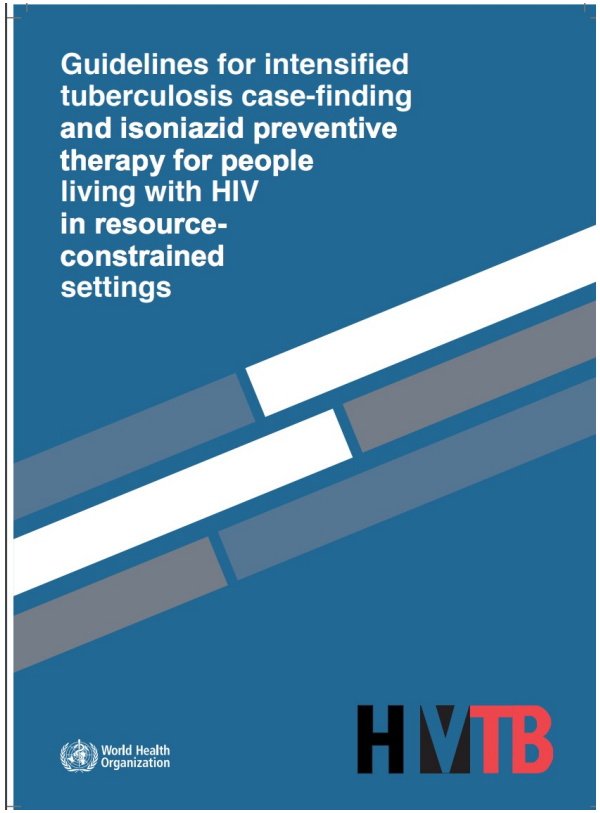
- HHCs
- HIV infected patients
- Other high risk groups: homeless, imprisoned, RA patients on T-cell suppressing drugs, DM?

- Policy issue: do people need to be TST/IGRA positive to be started?

Risk of TB in HHCs

- Ranges from 1-5% per year after exposure depending on age and previous infection status.
- In our study, IPT reduced risk by 70% in all age groups.
- Most often recommended for <5s, in some cases <15 or 19.

HIV


Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings
World Health Organization
HIV TB

Why not treat all infected people?

- Impractical if 1/3 world infected
- As risk declines, trade-off with hepatotoxicity less favorable.
- Frequent false positives with TST (BCG, atypicals)
- Cost of IGRA, monitoring of treatment, etc.