12th Annual Conference IUATLD-NAR

- Dr. Kenneth G. Castro has no financial relationship with companies who have provided support to this meeting that suggests a personal conflict of interest in relations to the planning for the above captioned CME Event.

IUATLD North America Region Meeting

San Diego, California

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How Can New Tools Strengthen TB Elimination & Global TB Control?

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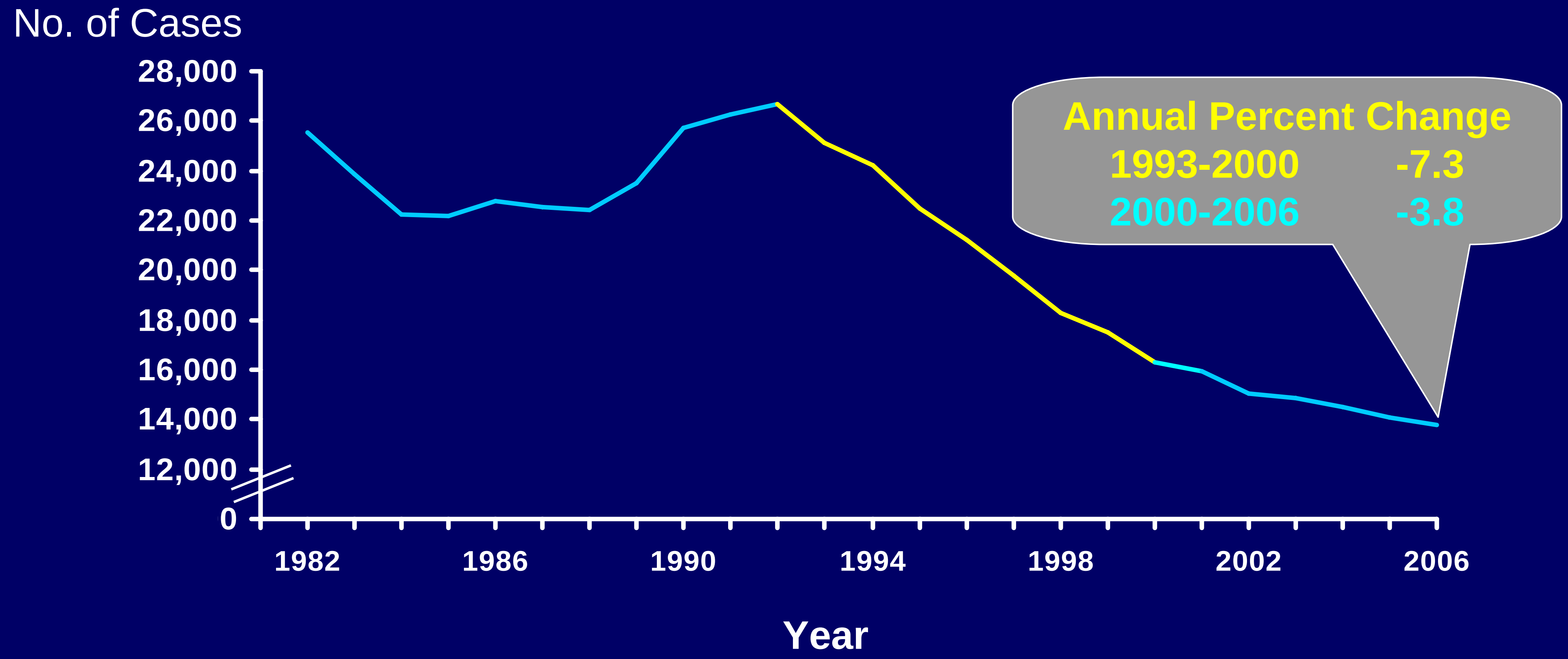
Coordinating Center for Infectious Diseases

Outline: Focus on U.S. Experience

- Post-resurgence trends
- Challenges (epidemiologic and technical)
- Mathematical model as tool
- Role of new tools
- Vision of future

Reported TB Cases*
United States, 1982–2006



TB Elimination Challenges in the U.S.

- Maintain support for core activities
- Retain expertise as cases decrease
- Respond promptly to outbreaks/clusters
- Identify and target interventions to high risk groups (address health disparities)
- Focus efforts on foreign-born & global TB
- Invest in development of new tools

Technical Challenges in TB

- Rapid, reliable diagnostic tests
  - Latent TB
  - Paucibacillary disease
  - Drug resistance
- Safe & effective SHORT course chemotherapy
- Safe & effective drugs for MDR and XDR TB
- Anti-TB drug–antiviral drug interactions
- Immune reconstitution reactions
- Safe & effective vaccine(s)

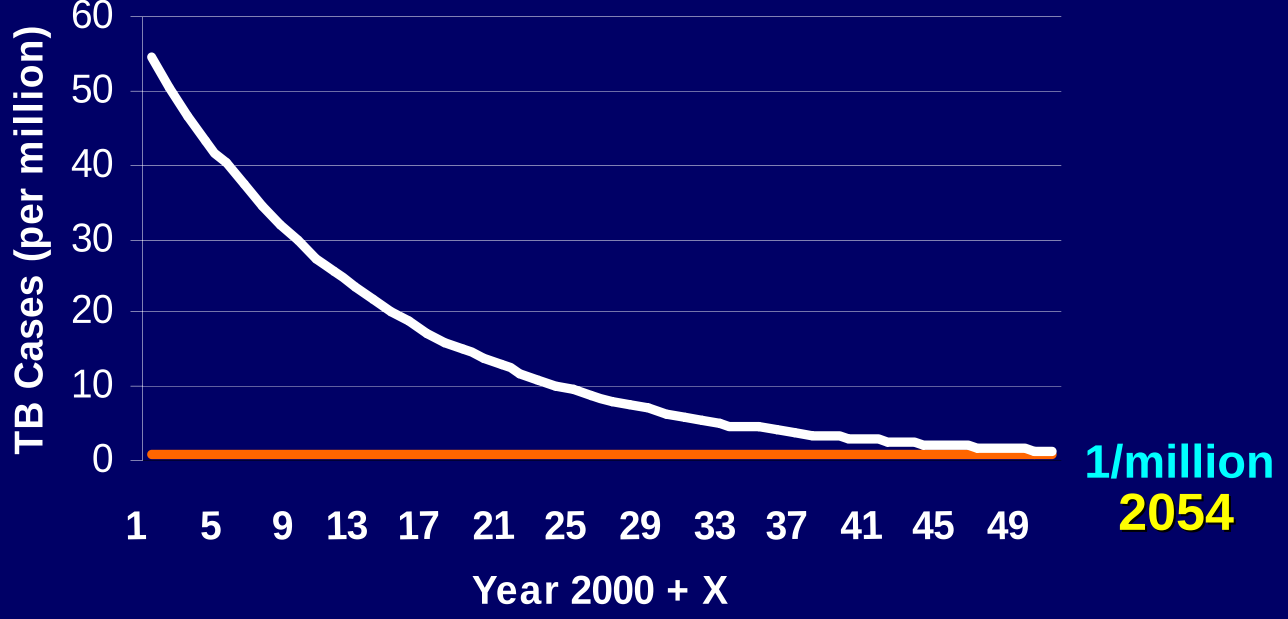
Technical Tools for TB Control

Mathematical Models as Tools

- TB transmission models as tools to understand and predict the consequences of interventions
- Strength of models – evaluate RELATIVE impact of interventions

TB 1993-2000 Incidence Trend Model*
2001-2050 Projection

F_T = 90%	F_V = 0 %
F_L = 65%	E = 0 %
Reproductive number:	0.225
Incidence reduction rate:	7.6%

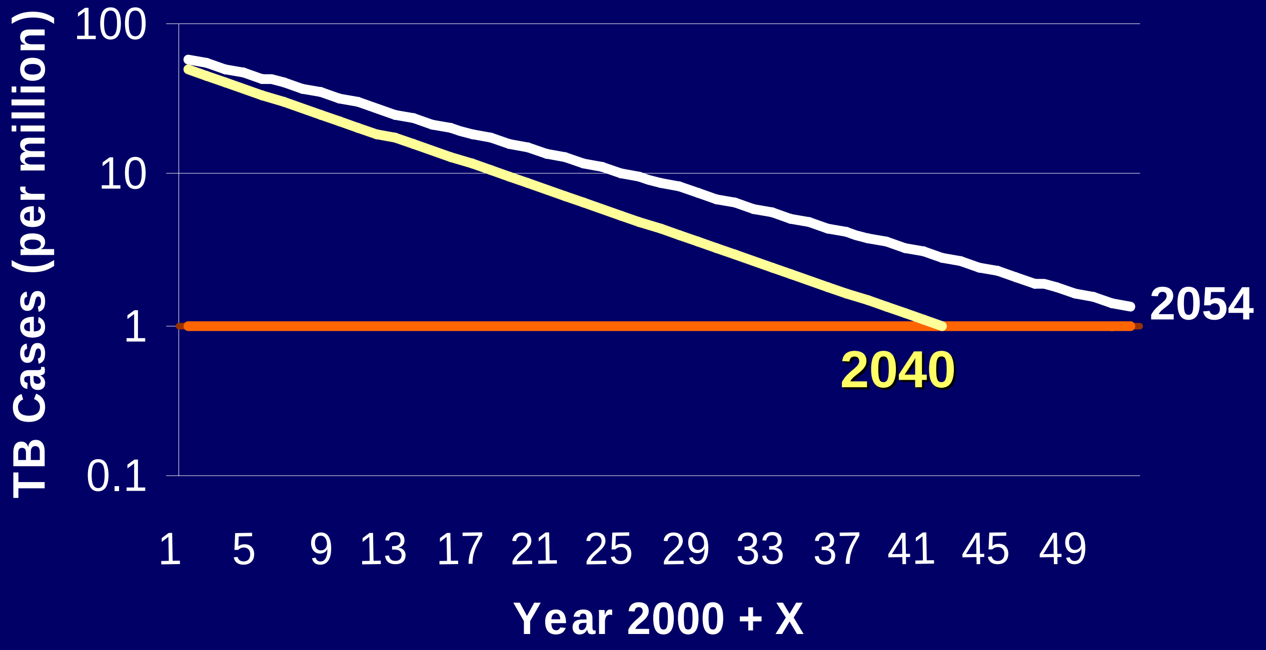


* Adaptation of model developed by Blower et al.

TB 1993-2000 Incidence 2001-2050 Projections

F_T = 90% → 95% F_V = 0 %
F_L = 65% E = 0 %

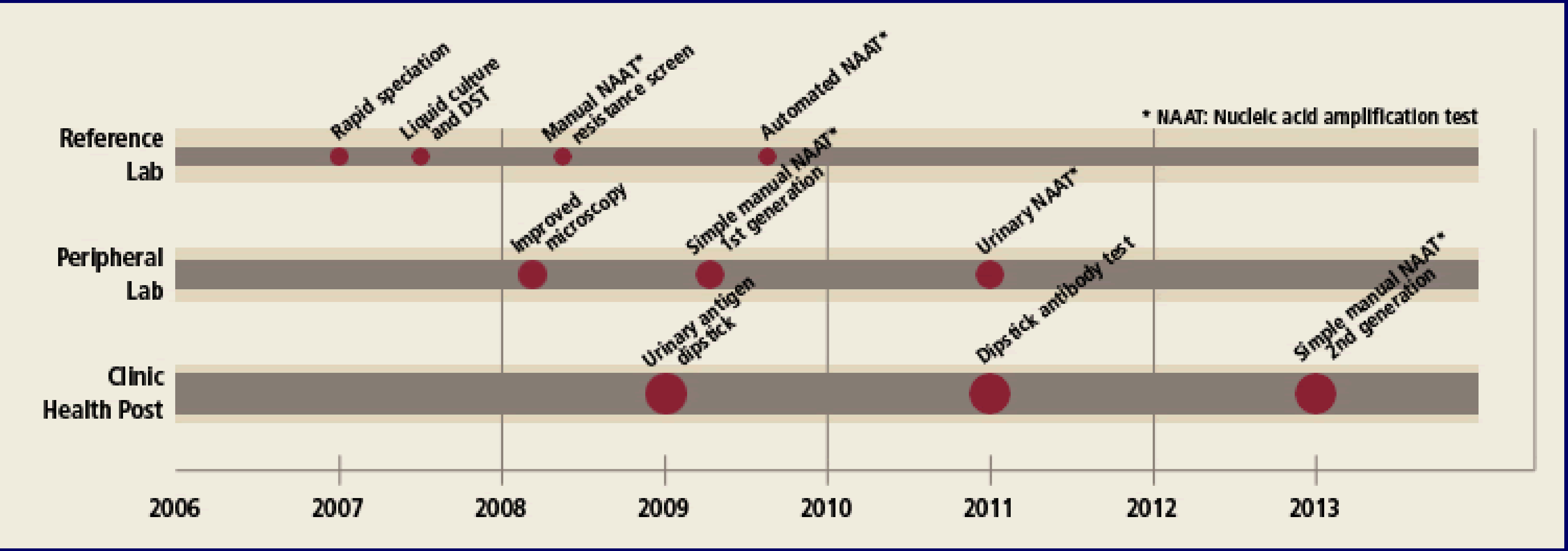
Reproductive number: 0.225 → 0.112
Incidence reduction rate: 7.6% → 9.8%



Gain: 14 yrs

CDC

TB Diagnostics Product Pipeline



FIND
FOUNDATION FOR INNOVATIVE NEW DIAGNOSTICS

Examples of Rapid Drug Resistance Methods

Test	GenoType® MTBDR	INNO-LiPA Rif.TB
Company	Hain Lifescience	Innogenetics
M. tuberculosis detection	Yes	Yes
Detection RMP resistance	Yes	Yes
Detection INH resistance	Yes	No
Strip Assay	Yes	Yes
DNA basis: PCR	Yes	Yes
Direct assay	No	Yes (modified version)
RMP resistance:*rpo*B gene	Yes	Yes
INH resistance:*kat*G gene	Yes	No

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

TB Clinical Development Pipeline

Compound	Development Stage	Sponsor / Coordinator
Gatifloxacin	Phase III	EC / OFLOTUB Consortium; IRD*; WHO TDR°; Lupin Ltd.
Moxifloxacin	Phase II / III	Bayer; TB Alliance; CDC♦; University College of London; Johns Hopkins University
Diarylquinoline TMC207	Early Bactericidal Activity	Johnson & Johnson (Tibotec)
Nitroimidazo-oxazole OPC-67683	Early Bactericidal Activity	Otsuka Pharmaceutical Co., Ltd.
Nitroimidazole PA-824	Phase I	TB Alliance
Pyrrole LL-3858	Phase I	Lupin Ltd.

Novel compounds, highlighted in blue boxes, are active against MDR/XDR TB

* Institut de Recherche pour le Developement
° World Health Organization, Tropical Disease Research
♦ Centers for Disease Control and Prevention

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

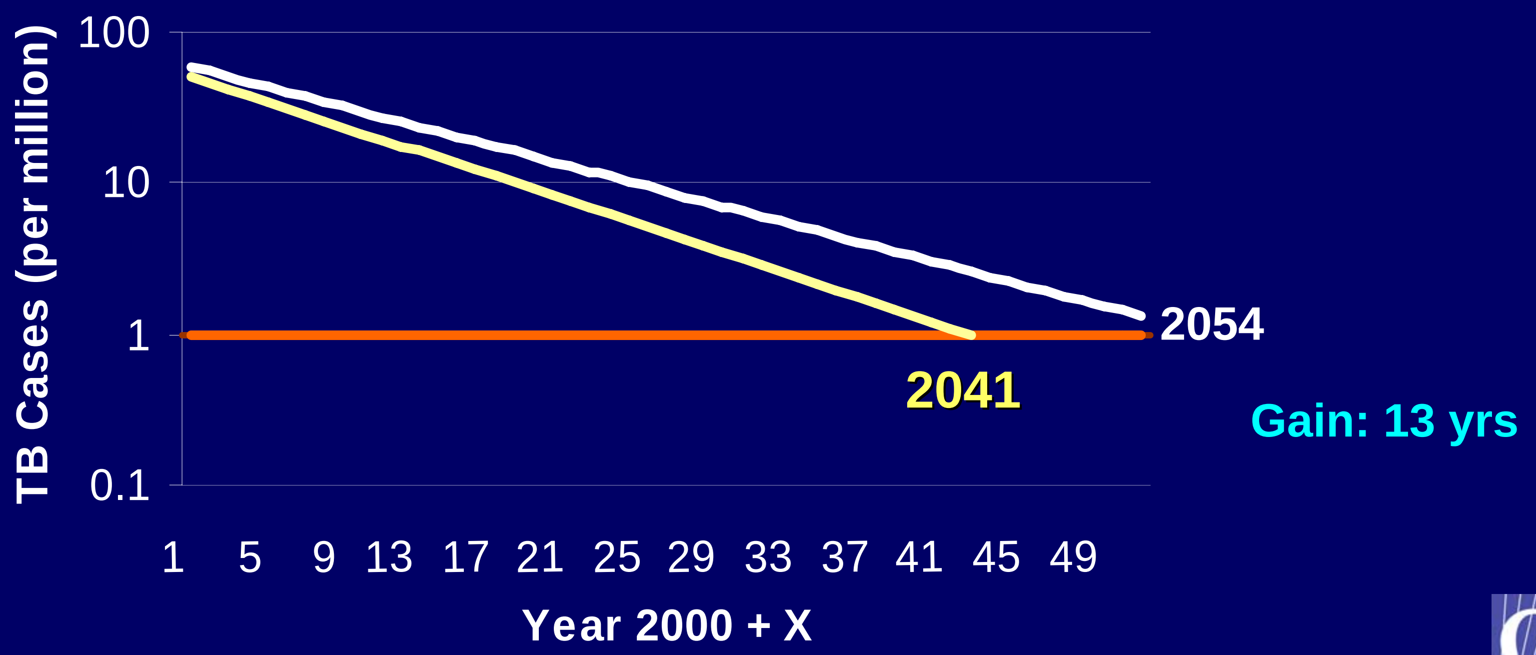
Portfolio (Partners)

- **Mycobacterial gyrase inhibitors (GSK)**
- **Pleuromutilins: inhibit bacterial protein synthesis (GSK)**
- **Multifunctional molecules (Cumbre)**
- **InhA inhibitors (GSK)**
- **Riminophenazines: inhibit energy metabolism (Institute Materia Medica)**
- **Malate synthase inhibitors: isocitrate lyase (GSK)**
- **Phenotypic screening (U Illinois)**

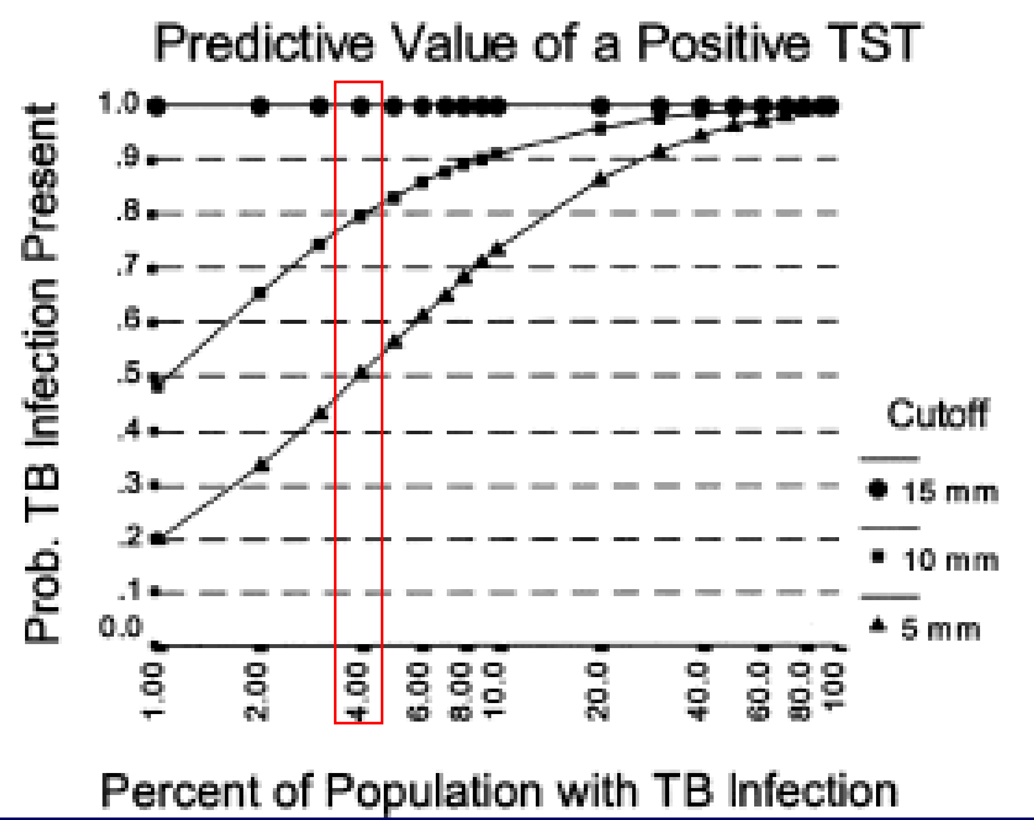
TB 1993-2000 Incidence
2001-2050 Projections

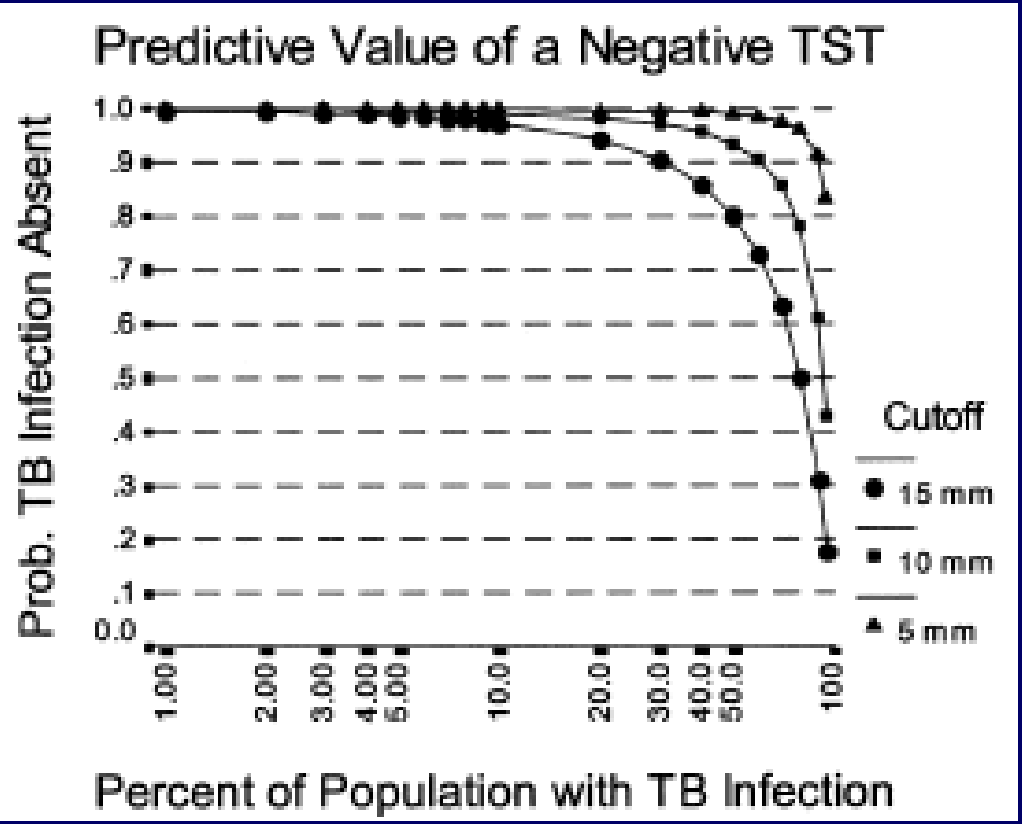
F_T = 90% F_V = 0 %
F_L = 65% → 90% E = 0 %

Reproductive number: 0.225 → 0.120
Incidence reduction rate: 7.6% → 9.6%



Predictive Value Of Tuberculin Skin Test, As Function of Population Prevalence of TB Infection



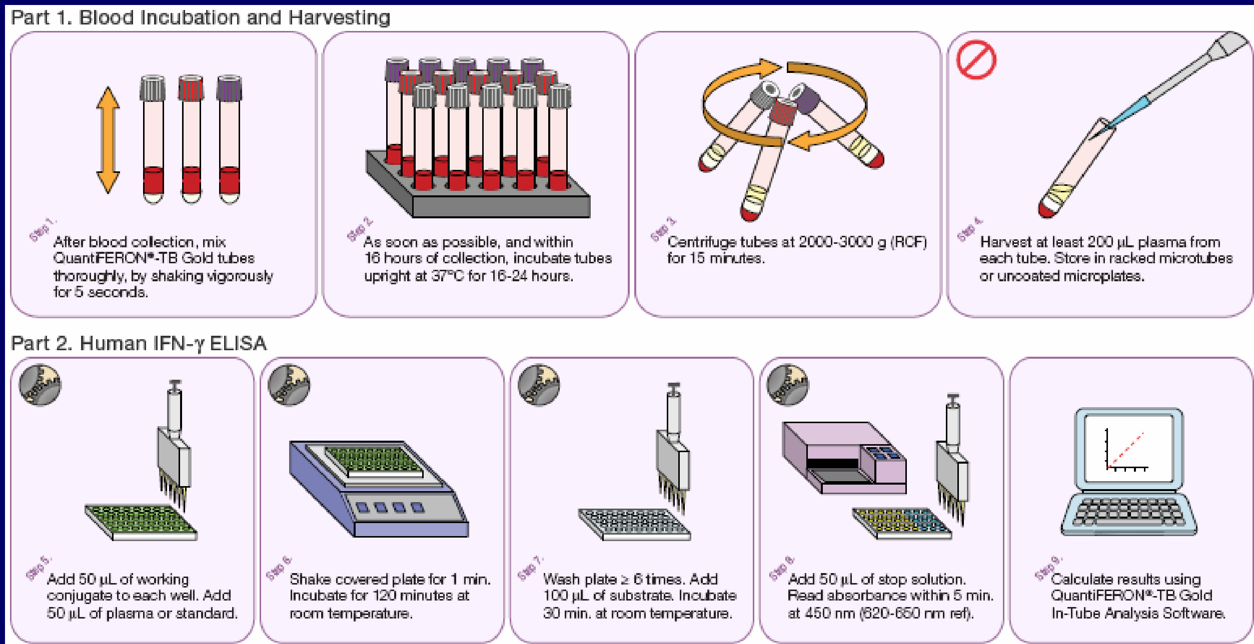


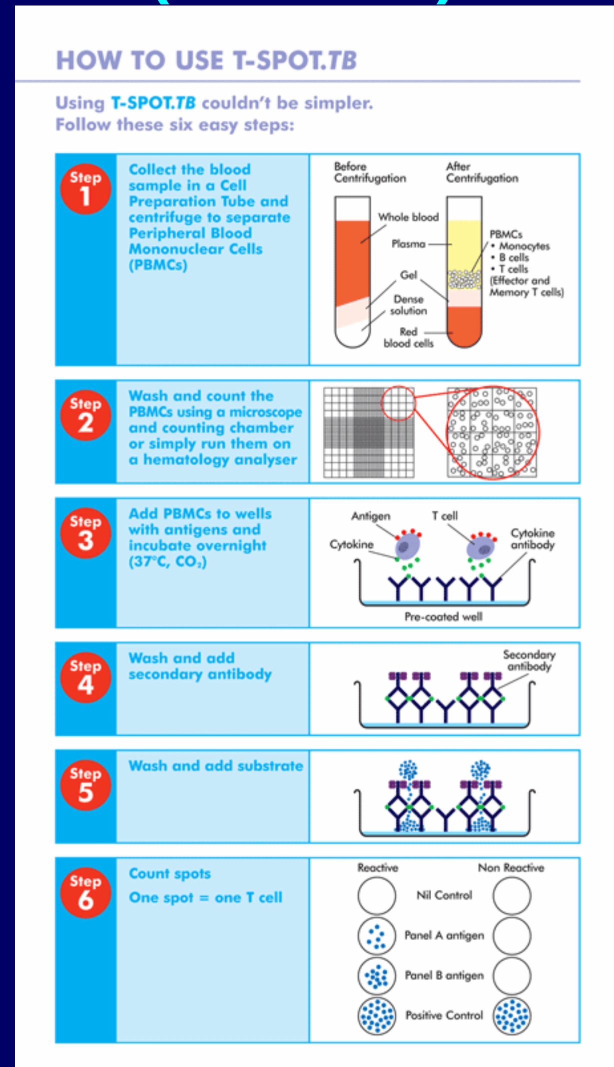
Lee E, Holzman RS. Evolution and current use of the tuberculin test. *Clin Inf Dis* 2002;34:365-70

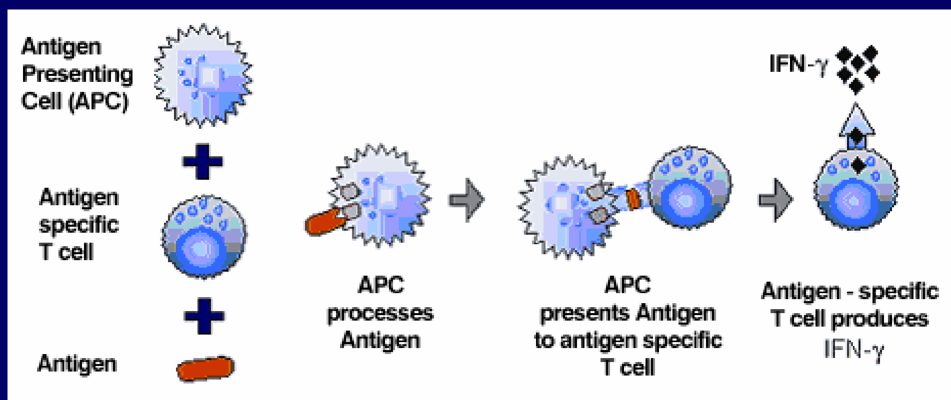
Interferon Gamma Release Assays (IGRA)

Quantiferon-Gold In Tube Assay

T SPOT–TB Test (ELISPOT)







Positive Predictive Value
Assays used separately

	Assay 1 Sens 95.5% Spec 99.5%	Assay 2 Sens 95.5% Spec 99.9%
Prevalence	PPV	PPV
0.1%	16.05%	48.87%
4.0%	88.84%	97.55%

Positive Predictive Value

Assays used sequentially

	Assay 1 Sens 95.5% Spec 99.5%	Assay 2 Sens 95.5% Spec 99.9%
Prevalence	**PPV**	**PPV**
0.1%	16.05%	99.46%
4.0%	88.84%	99.99%

Evaluating the Efficacy of Short Treatment for Latent TB Infection

TB Trials Consortium
Study 26

3 mo INH+RPT
Once/week (12 doses)

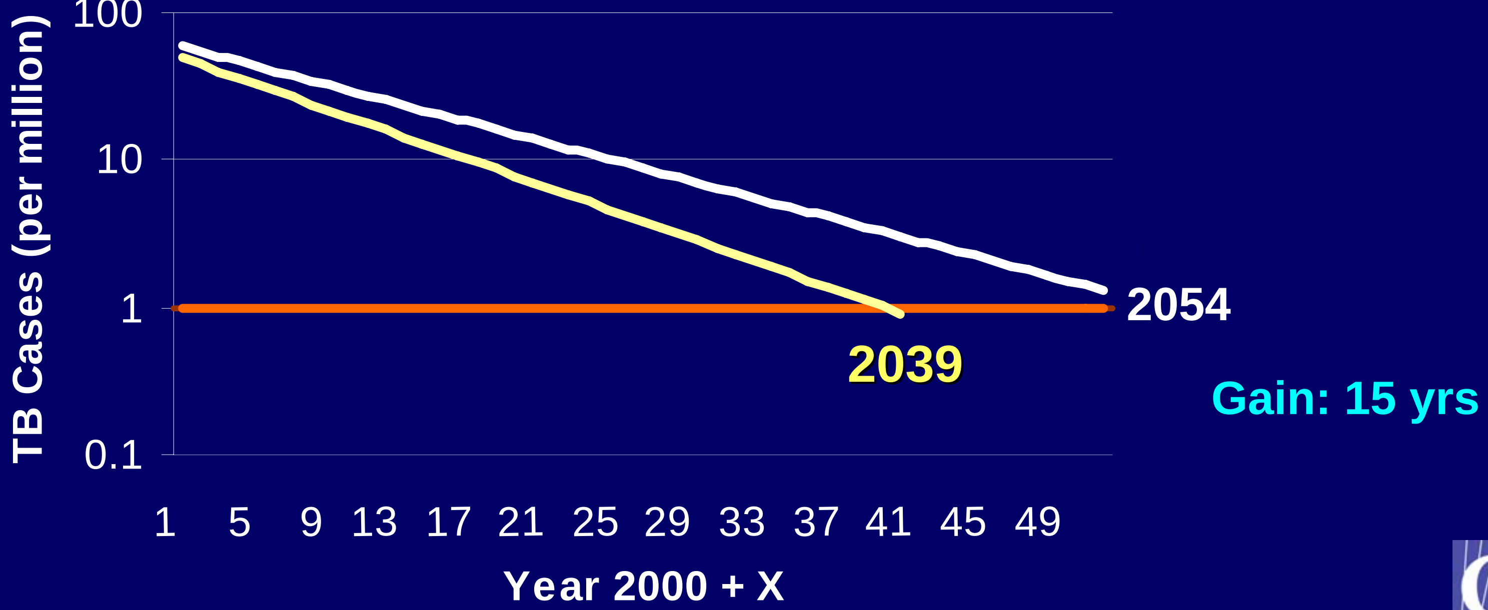
9 mo INH
Daily (270-300 doses)

8,056 persons (100% sample) enrolled as of Feb 15, 2008

TB 1993-2000 Incidence
2001-2050 Projections

F_T = 90% F_V = 0% → 75%
F_L = 65%   E = 0% → 75%

Reproductive number: 0.225 → 0.098
Incidence reduction rate: 7.6% → 10.2%



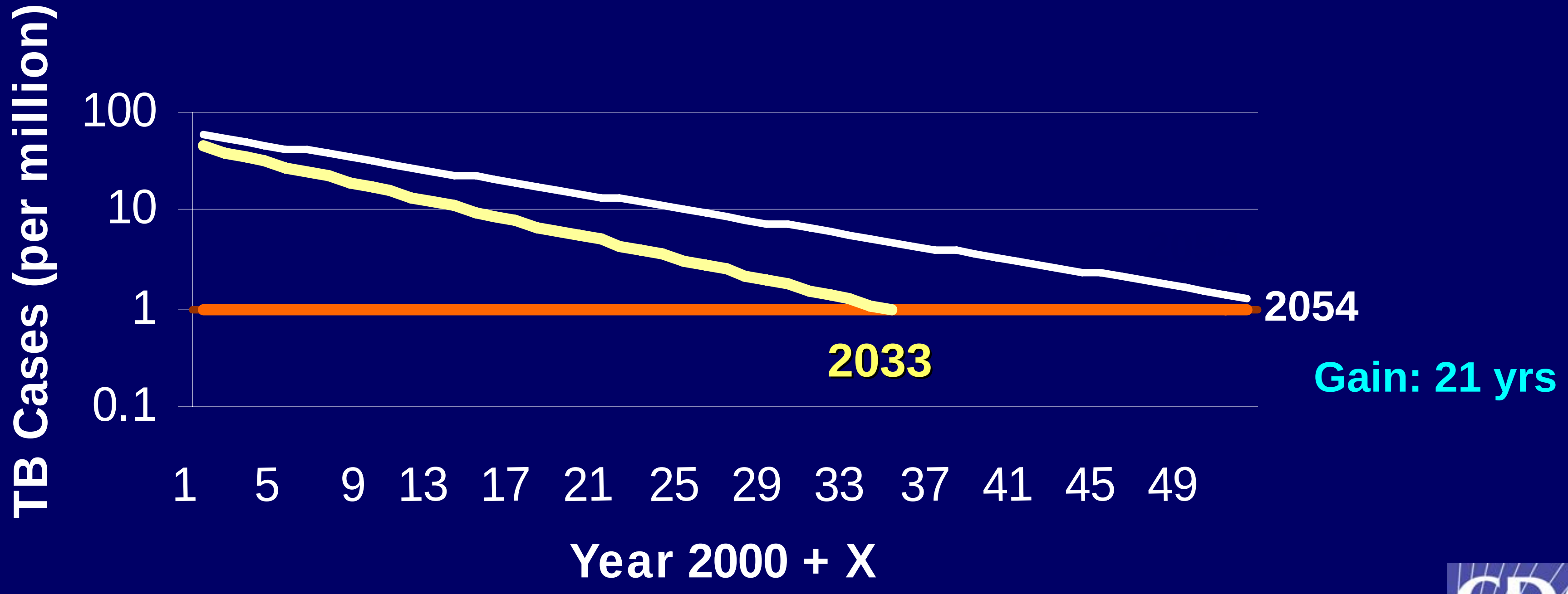
Aeras' TB Vaccine Candidates Under Development

Vaccine	Source	Stage	Description
AERAS-406 rBCG	Aeras	Phase I Q1 2008	Recombinant BCG which over-expresses antigens 85A, 85B, 10.4, Rv3407, 40 DosR proteins and pro-apoptotic endosome escape
AERAS-402 / Crucell Ad35	Crucell / Aeras	Phase I	Recombinant adenovirus 35 expressing antigens 85A, 85B and 10.4 to boost AERAS-406 rBCG
Oxford MVA85A	Oxford	Phase IIa	Recombinant vaccinia vectored, expressing high levels of CD4+ T cells
AERAS-X05 *Shigella*	Aeras	Phase I Q2 2008	Mtb antigens delivered by oral Shigella RNA capsid system to boost rBCG in infants and as a booster for adolescents given BCG at birth
GSK M72	GSK / Aeras	Phase I	Fusion molecule comprised of a protein from the PPE family (Rv1196), combined with an inactive serine protease Rv0125 to boost BCG
HyVac 4 / AERAS-404	SSI / Intercell Aeras	Phase I Q4 2007	Recombinant Mtb antigens 85B and 10.4 combined with adjuvant IC31 to boost BCG

TB 1993-2000 Incidence
2001-2050 Projections

F_T = 90% → 95% | **F_V = 0%**
F_L = 65% → 90% | **E = 0%**

Reproductive number:	**0.225 → 0.120**
Incidence reduction rate:	**7.6% → 11.6%**



TB 1993-2000 Incidence
2001-2050 Projections

F_T = 90% → 95%

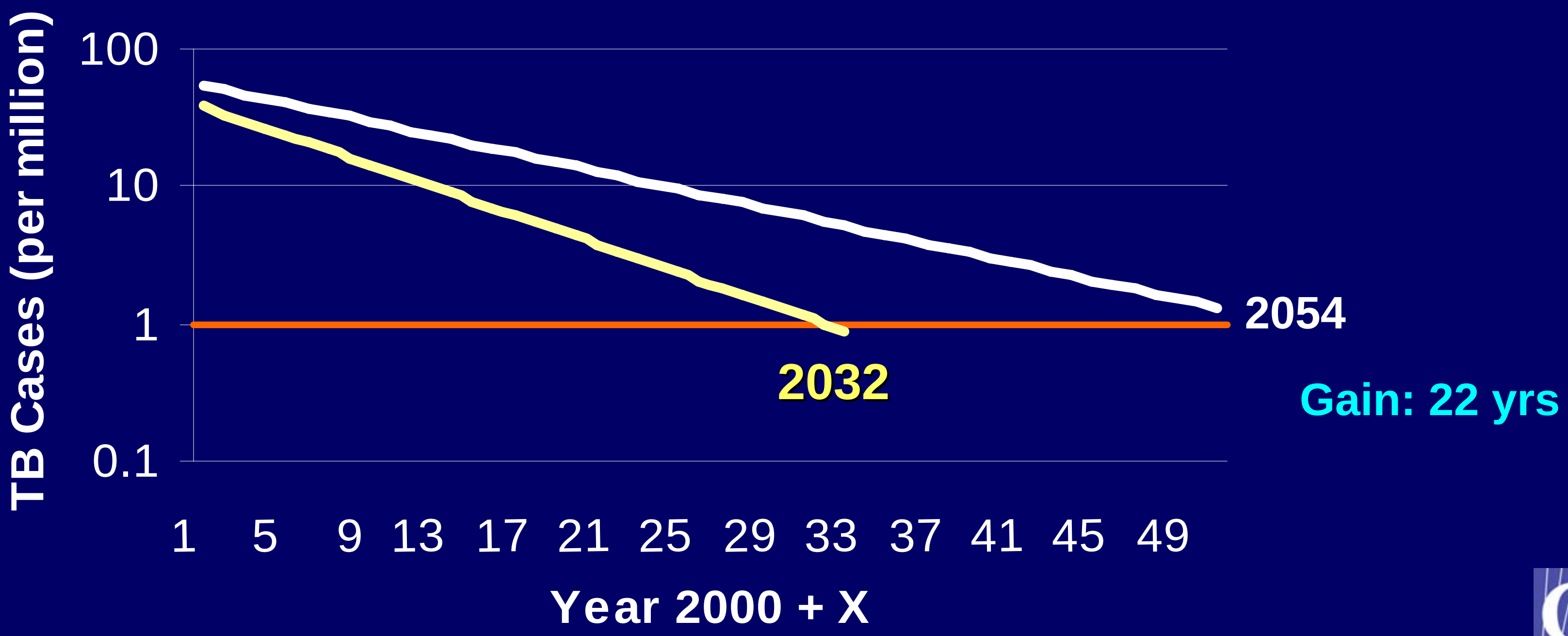
F_L = 65%

F_V = 0% → 75%

E = 0% → 75%

Reproductive number: 0.225 → 0.049

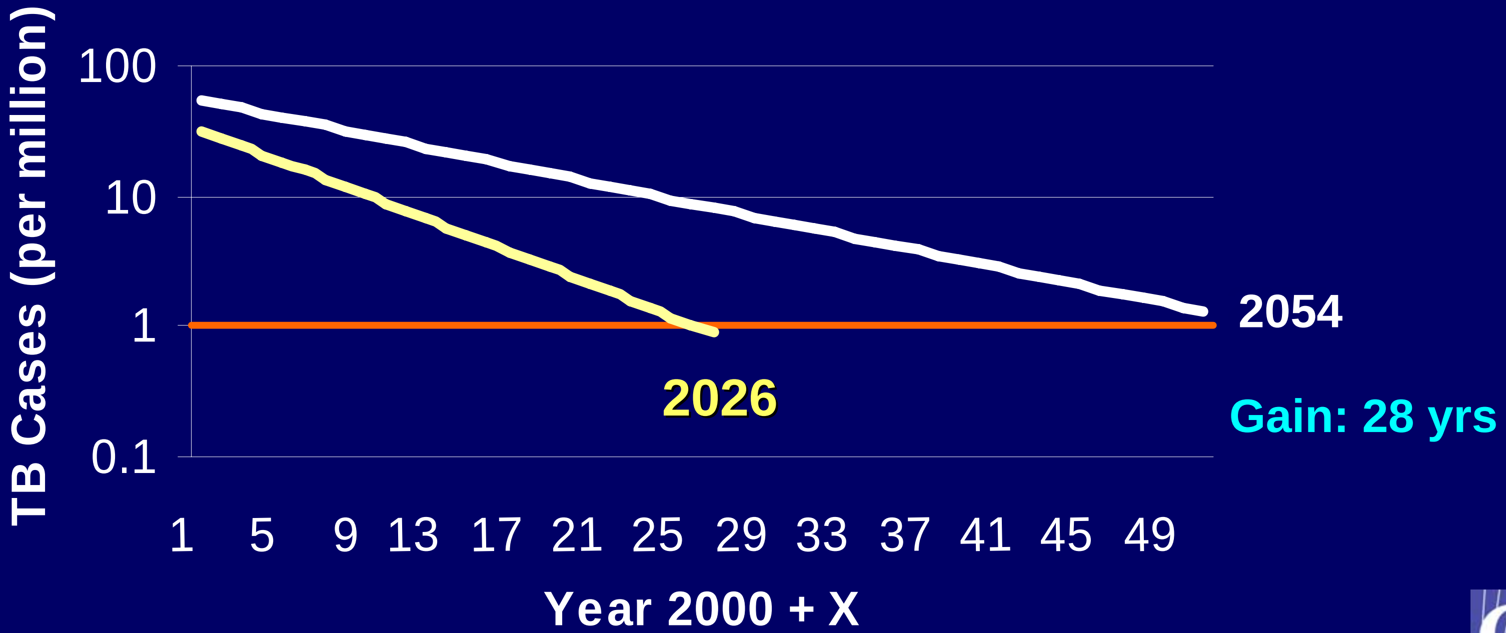
Incidence reduction rate: 7.6% → 12.1%



TB 1993-2000 Incidence 2001-2050 Projections

F_T = 90% → 95%	F_V = 0% → 90%
F_L = 65%	E = 0% → 90%

Reproductive number:	0.225 → 0.021
Incidence reduction rate:	7.6% → 14.3%



Modeling Summary: Role of New Tools

- Similar impact for new tools which achieve
  - small increase in TB cases effectively treated
  - mod. increase in LTBI cases effectively treated
  - vaccine with 75% coverage & efficacy

- Caveats (more work needed)
  - Average rate of decline in TB incidence being updated
  - Average rates of decline differ by U.S. born and non-U.S. born

Vision of Future TB Interventions

1. Accurate blood assays for *M.tuberculosis*
2. Rapid (48–72 hours), reliable DST
3. 2–3 month curative regimens well tolerated, relapses < 3%, with options for M/XDR TB
4. Safe and effective vaccine(s) for uninfected and/or latently infected in U.S. and globally
5. Public-Private partnerships
6. Affected communities “at the table”
7. Limited AIIR* facilities for exceptional cases

* Airborne infections isolation rooms

In a globalized world, given the high burden of TB in other countries--as well as the rise of drug-resistant strains--is it really possible to eliminate TB in the US?

"The success of any disease eradication initiative depends strongly on the level of societal and political commitment, with a key role for the World Health Assembly. Eradication and ongoing programmes constitute potentially complementary approaches to public health. Elimination and eradication are the ultimate goals of public health, evolving naturally from disease control. The basic question is whether these goals are to be achieved in the present or some future generation."

Dowdle WR. Bull WHO. 1998;76 Suppl 2:22-25

Acknowledgements

- J Courval, C Rose, J Becerra
- TB medical officers & program consultants
- TB controllers
- Stop TB USA
- Global Stop TB Partnership
- Patients and affected communities