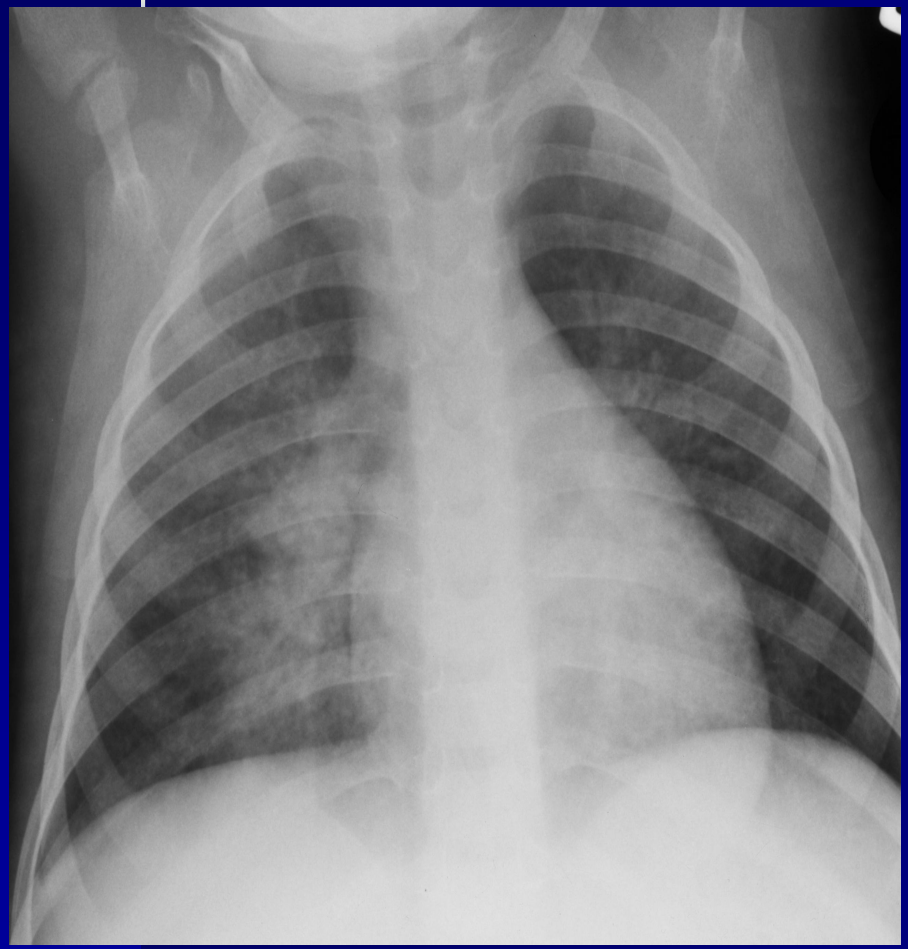
Childhood TB (and the mother-child dyad)



- **Chairs:** Mark Cotton and Lisa Nelson
- **Rapporteur**: Soumya Swaminathan

Speakers

- Anneke Hesseling
- Philippa Musoke
- Amita Gupta
- Jerald Sadoff

Over 2 million paediatric HIV infections in 2007

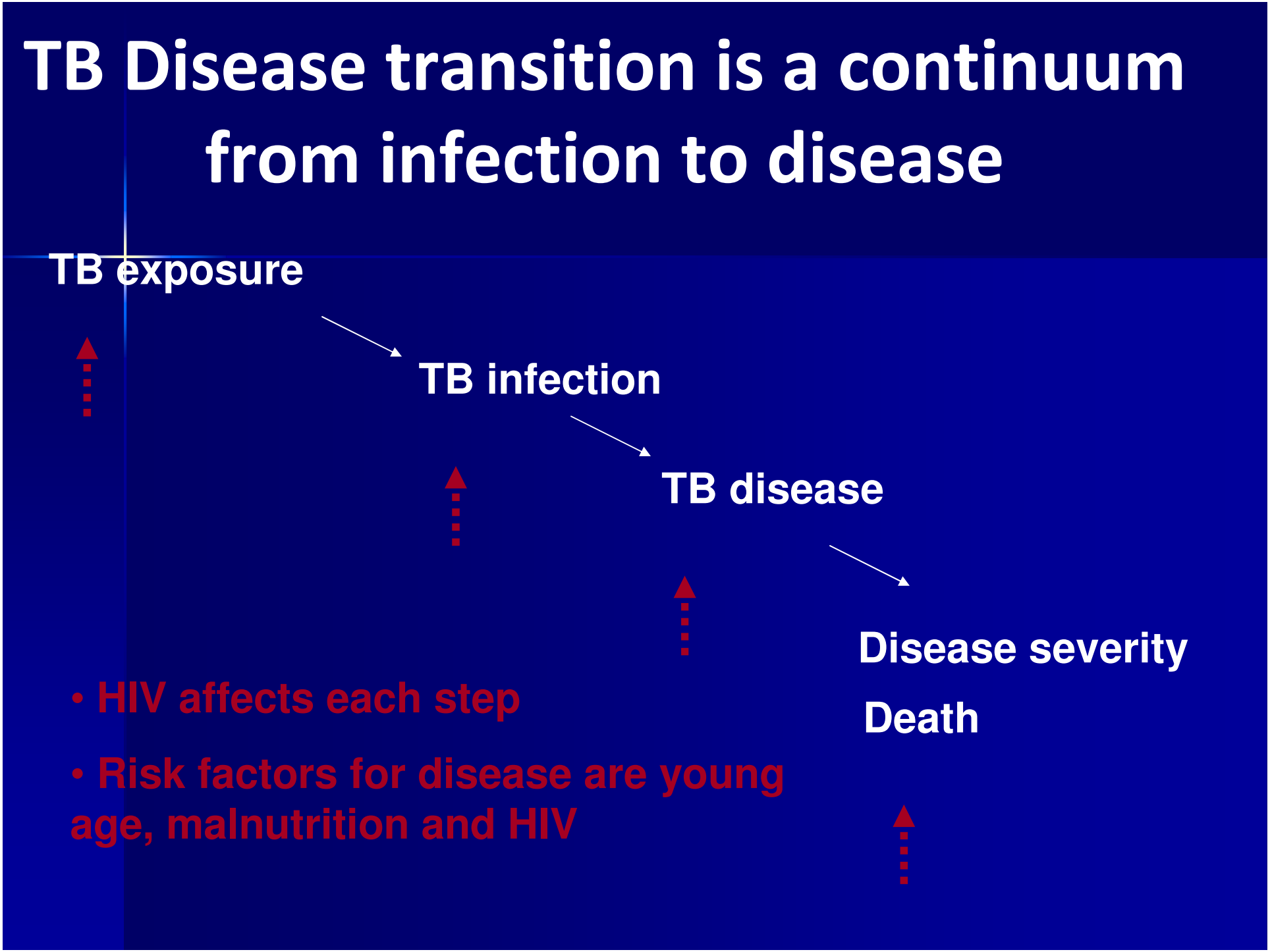
Over 1,500 new pediatric infections a day in Africa

www.who.int

WHO ESTIMATED TB CASES BY AGE, 2006

Country	Total Cases	Cases in Children < 15	% in Children
Myanmar	78,489	8,007	10.2
Nigeria	261,404	32,310	12.4
Pakistan	244,736	61,905	25.3
The Philippines	230,217	12,167	5.3
Russian Fed.	183,373	7,778	4.2
South Africa	220,486	35,449	16.1
Thailand	85,928	2,317	2.7
Uganda	75,250	12,099	16.1
Tanzania	117,489	18,890	16.1
Viet Nam	143,023	7,559	5.3
Zimbabwe	76,296	12,267	16.1
Total	6,678,188	630,722	9.4

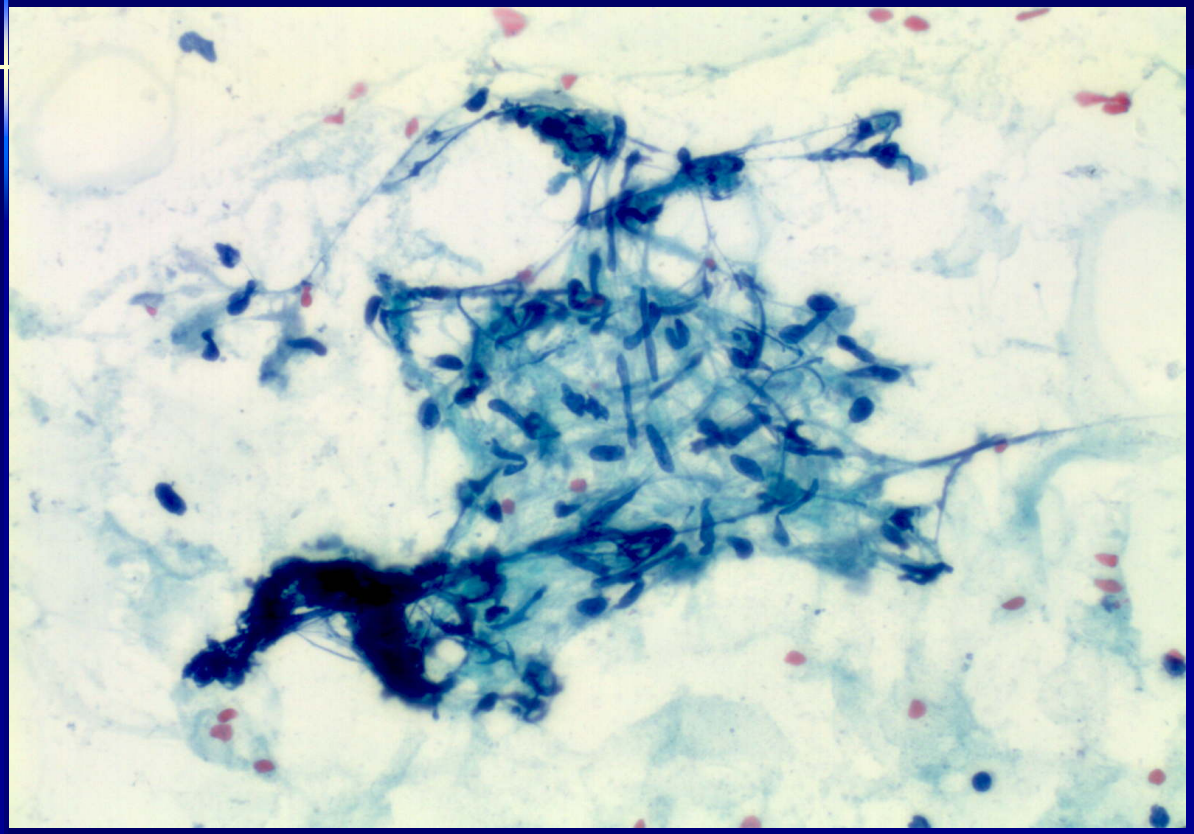
TB Disease transition is a continuum from infection to disease



Diagnostic Challenges

- Symptom-based diagnosis has low sensitivity in HIV
- Atypical presentation
- Chest radiographs: LIP mimics miliary TB
- Liquid media vs. solid media yield: addition of growth supplements reduces time to detection
- In general, bacteriologic yield correlates with disease severity
- Need to be creative about getting the organism from various specimens
- 1 induced sputum = 3 gastric aspirates
- Other techniques – N/P aspirate, string test
- Fine needle aspiration useful, under-utilized technique

FNA AND MYCOBACTERIAL INFECTION



Well formed granuloma

Michelow, Cytopathology. 2008

Newer Diagnostic Tests

- ELISpot assay (RD1 antigens) had a sensitivity of 73% compared to 36% for TST among HIV-infected children with active TB, not affected by age or malnutrition
- More sensitive in detecting infection but does not differentiate from active disease
- Urinary LAM ? Performs better in adult HIV+
- Point of care test ideal, will need respiratory specimen?
- None of the newer techniques eg line probe assays or NAAT tests have been evaluated

Isoniazid Preventive Therapy

- SA trial showed reduction in TB AND all-cause mortality with IPT in young children
- Reasons for mortality impact unclear ? Effect of co-trimoxazole
- IPT given after exposure seems to be more effective than primary prophylaxis
- Maybe cost-effective to target children in households with HIV or TB
- National programs include IPT for children <5 yr but implementation lacking

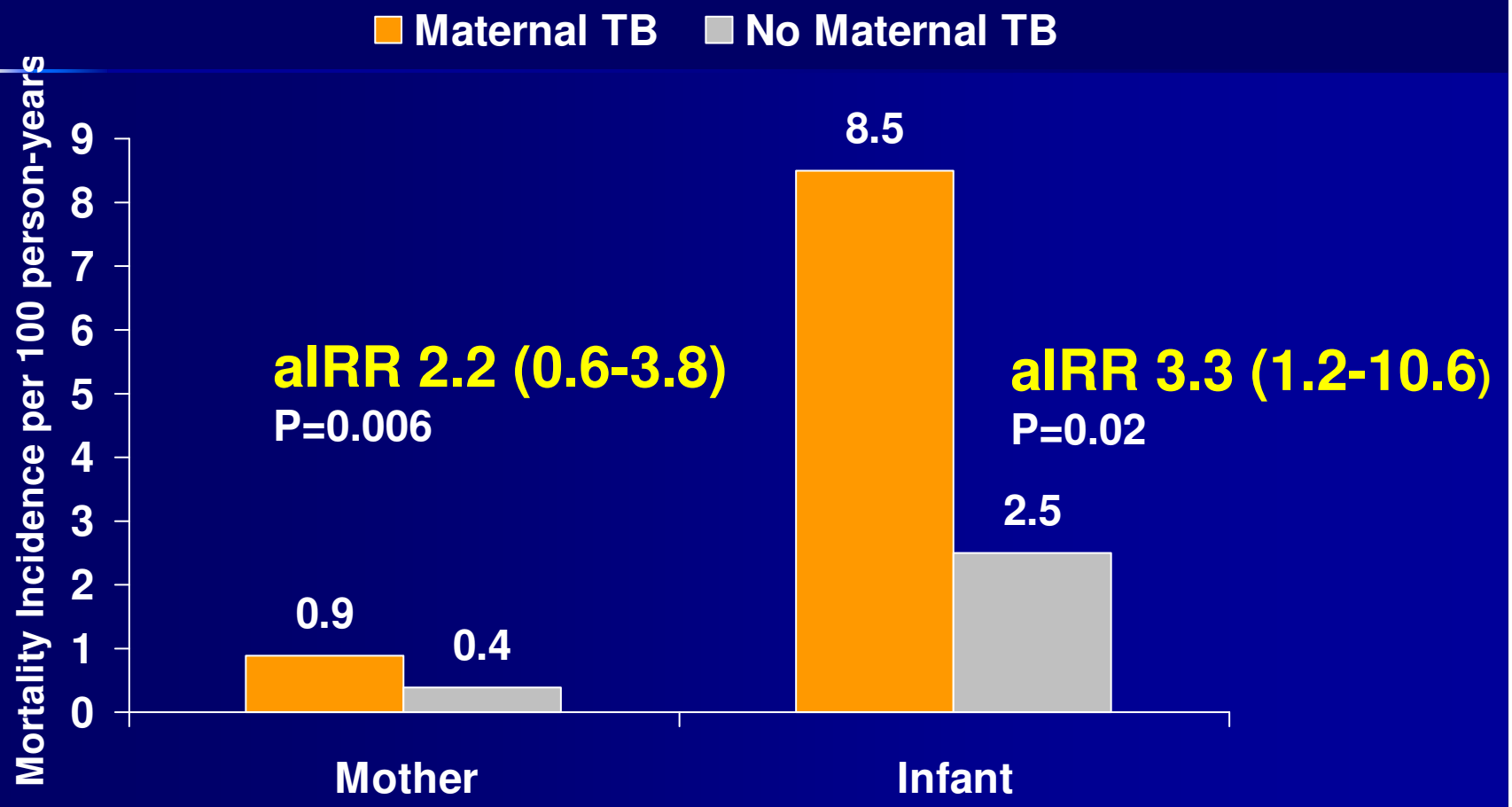
Summary

- High risk of TB infection and disease in HIV-infected children
- Diagnostic challenges due to co-morbidities, immune suppression
- Bacteriological confirmation: novel collection methods
- Infection vs. active disease
- Novel diagnostic tools needed relevant to paucibacillary disease and immune suppression

TB and HIV in women

- TB is the most common HIV-1 related illness and cause of mortality in women of reproductive age in Asia and Africa
- HIV and TB are independent risk factors for maternal mortality
  - TB-associated deaths in Zambia increased from 0% in 1970s to 14% in 1997
- Upto 15% of maternal deaths due to HIV/TB
- Postpartum TB higher in women with lower CD4 counts, higher VL, positive TST

Adjusted maternal and infant mortality rates within first year post-partum by maternal TB status



Maternal mortality adjusted for CD4, log viral load, hemoglobin, age, educational status. Infant mortality adjusted for HIV PCR status, preterm birth (<38 weeks), birth weight and maternal factors as above.

Maternal TB/HIV important risk factor for pediatric TB and mortality

- Estimated TB rate
  - 10 times higher in HIV-exposed uninfected children
  - 30 times higher in HIV-infected children < 5 y
  - Extremely high rates in HIV+ infants ≤12 mo

TB Transmission can occur in-utero, intra-partum and postpartum

HIV transmission higher from women with active TB

INH safety in pregnancy and post-partum

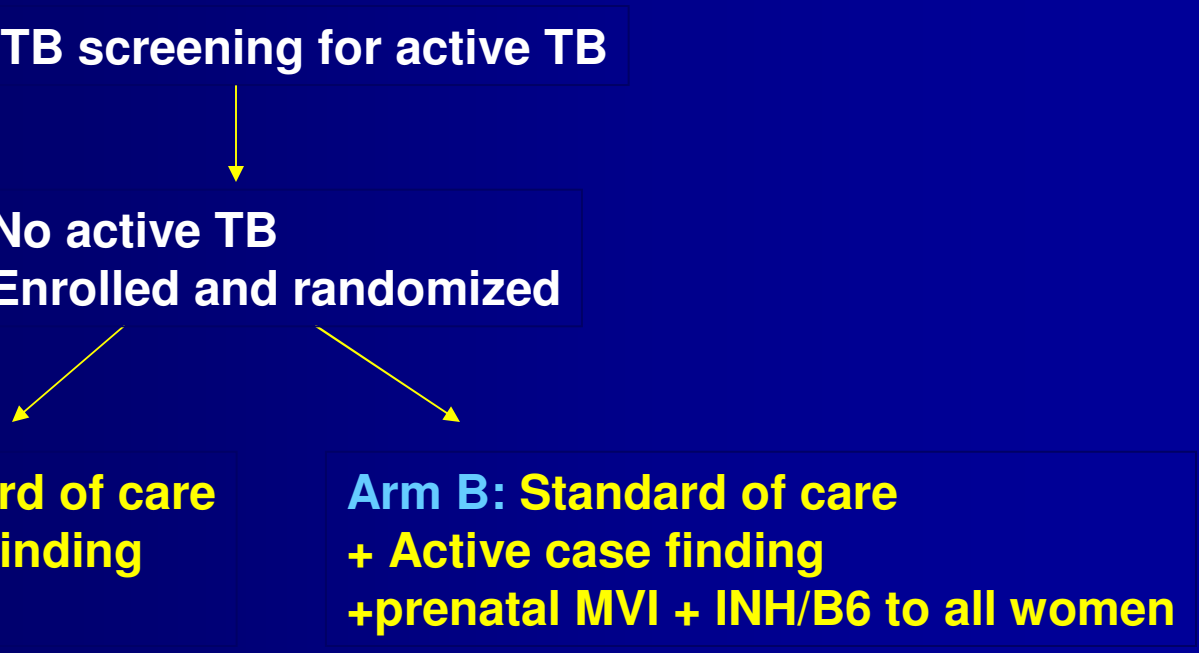
- Not teratogenic
- Hepatotoxicity
  - **Abnormal liver enzymes :1-25%**
  - **Symptomatic liver disease 5.2 per 1000 patients in a study where 20,838 given INH for 12 mo.**
  - **Risk factors age, alcohol, underlying liver disease including chronic Hep B**
  - **Hepatoxicity when combined with HAART in pregnancy unknown**
- Breastmilk: safe. Concentration 1% upto 20%
- Generally safe in children
- Most first line drugs safe in pregnancy except aminoglycosides and quinolones

Ongoing and planned studies

- CDC-BOTUSA study- Botswana
- TB/PMTCT Study- Soweto
- TB APPRISE- IMPAACT multicountry Africa/India
- TB in pregnancy outcomes study- Soweto
- Pk studies of TB/HIV drugs in pregnancy- South Africa and IMPAACT

TB APPRISE: IMPAACT P1078 with TBTC scientific input

- Randomized trial to assess safety and efficacy of INH initiated in antepartum to reduce maternal TB incidence and infant mortality



Sample size n=1600, plan 144 week follow-up

TB APPRISE: IMPAACT P1078

- 1 endpoint: time to incident TB in mother, rate of hepatoxicity
- Maternal
  - TB prevalence in diverse ANC settings
  - INH Completion rates
  - Examine acetylator status and risk of hepatotoxicity
  - Predictive value of IGRAs in pregnancy and postpartum
  - INH resistance among culture confirmed cases
- Infant
  - TB-free survival
  - Assess impact on infant immune response to BCG
  - IGRA responses
- Cost-effectiveness

Botswana IPT Trial 2004-2009

Randomized Double-Blind Placebo Controlled Trial
2,000 participants- 1,000 per study arm

- To measure how much TB there is among **all** pregnant women.
- To study the health of infants born to mothers with TB and/or HIV
- To determine how best to implement TB screening in the PMTCT Clinics.

Unanswered questions: research opportunities

- What are the best strategies for screening for latent TB in TB/HIV endemic areas?
  - Role of TST, IGRAs, sputum, CXR?
- What are the best detection strategies for active TB in high risk pregnant women?
- What are the safety, tolerability, PK and drug interactions of new promising TB drugs in pregnant and nursing women?

Questions with Implications for maternal and child care

- Can detection and treatment of TB in mother have impact on mother and child health?
- Safety and efficacy of IPT in mother (antenatal or postnatal)
- Young infants in close contact with mother – kangaroo care ⇑ survival, also ? ⇑ TB
- What is the best time to initiate IPT for child? Diagnosis of TB in young infant an issue

Factors Impacting Drug Levels in Children

- Age and maturation of metabolic enzyme pathways have major impact; younger children metabolize drugs faster
- Appropriate dose of drug: mg/sqm BSA
- Malnutrition: some evidence that stunting/wasting affect drug metabolism
- Genetic polymorphism in enzymes eg Cyp2B6, Cyp3A4, NAT

What ARV to start ?

- HIV infected child co-infected with TB
  - If on NVP based HAART need a higher dose to maintain adequate NVP levels
    - However can switch to ABC
  - If on EFV based HAART can continue on same drug and dose
  - If on a PI, doubling the PI dose is not beneficial in increasing the PI levels while on Rifampicin
  - The best regimen if child needs a PI is not yet clear and needs further study

ATT and ART Drug Interactions

- Rifampicin inducer of Cyp 450 enzymes
- Reduces NVP levels by 40-50%, EFZ by 20% and protease inhibitors by >80%

<u>Strategies</u>

Increase dose of NVP (by 30%?)

What are alternatives in children < 3yrs as EFZ cannot be used

Doubling of Lop/r dose did not help

- **Use of newer classes of ARVs eg raltegravir needs to be investigated**

When to start TB treatment and ideal regimen

- As soon as possible in the severely immunosuppressed children (2- 8 weeks) or other criteria?
- Recent data suggest currently used doses of anti-TB drugs (H, E, R) inadequate
- In advanced HIV, malabsorption may occur
- Lack of evidence for daily/intermittent dosage
- Rifabutin: studies to determine dose, efficacy and pediatric formulations required

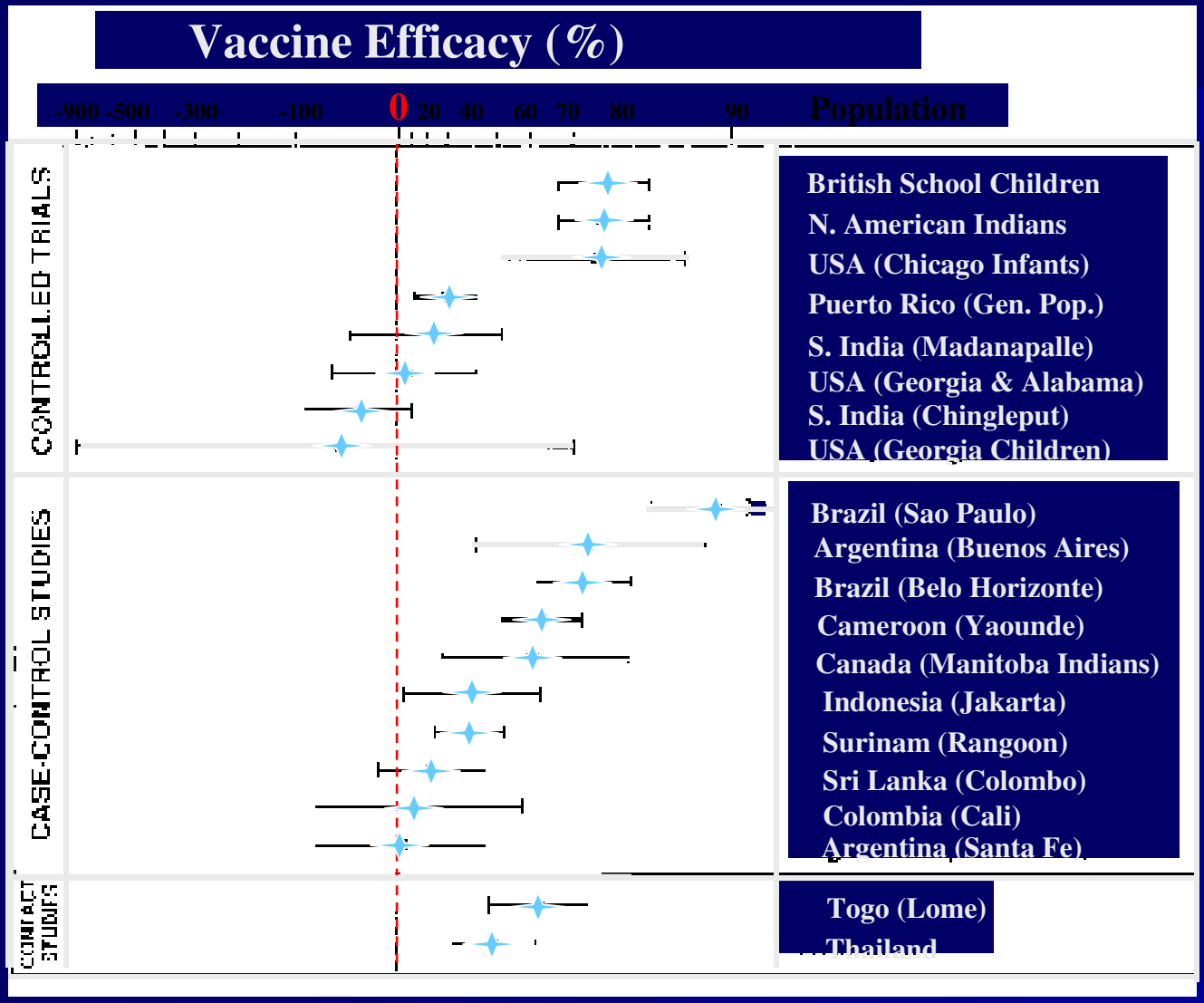
Issues and Research Questions

For TB therapeutic trials in children, what should be the inclusion criteria?

- Only bacteriologically confirmed OR
- All children diagnosed and started on ATT

Will have implications for pharmacokinetic studies as diseased children may respond/metabolize drugs differently than non-diseased children

Variable Efficacy of BCG vs. Pulmonary TB



BCG – The Dilemma

- BCG protects against disseminated and CNS TB in children (efficacy ~ 75%)
- In high HIV prevalence areas:

  - BCG IRIS rate of 10-15% in ARV roll-out programs

  - Disseminated BCG disease ~ 1% with high case fatality (needs high index suspicion, GA, Bct, BM, PCR)
- WHO revised guidelines may not be practical and feasible

Efficacy of BCG vs. Disseminated TB

	Publication date	Efficacy (%, 95% CI)
Tuberculous meningitis		
Buenos Aires, Argentina	1988	98% (70 to 100)
Bahia, Brazil	1991	91% (78 to 97)
São Paulo, Brazil	1990/93	87% (72 to 94)
São Paulo, Brazil	1990/93	92% (65 to 98)
Belo Horizonte, Brazil	1988	81% (47 to 93)
Belo Horizonte, Brazil	1988	65% (17 to 86)
Yangon, Burma	1987	52% (13 to 73)
Nagpur, India	1996	87% (70 to 94)
Chennai, India	1996	77% (63 to 86)
Delhi, India	1996	64% (30 to 81)
Delhi, India	1989	84% (69 to 97)
Lucknow, India	1999	47% (-6 to 74)
Papua New Guinea*	1980	58% (-36 to 87)
Delhi, India	1993	56% (-49 to 87)

	Publication date	Efficacy (%, 95% CI)
Miliary tuberculosis		
Buenos Aires, Argentina	1988	78% (28 to 93)
Yangon, Burma	1987	80% (45 to 92)
Papua New Guinea*	1980	70% (0 to 91)
Djakarta, Indonesia	1983	75% (5 to 94)

Summary Efficacy
Miliary Tuberculosis 77% (58 to 87)

Summary Efficacy
Tuberculous Meningitis 73% (67 to 79)

Trunz, Fine, Dye.

The Lancet 2006; **367**:1173-1180

Prime –Boost Regimen for Infants

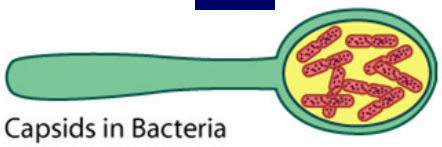
rBCG

Recombinant BCG

Newborn

Protein with Adjuvant

Viral Vector



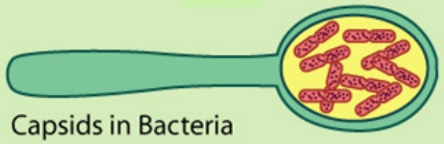
Capsids in Bacteria

IM or as an aerosol

10 -14 Weeks

Protein with Adjuvant

Viral Vector



Capsids in Bacteria

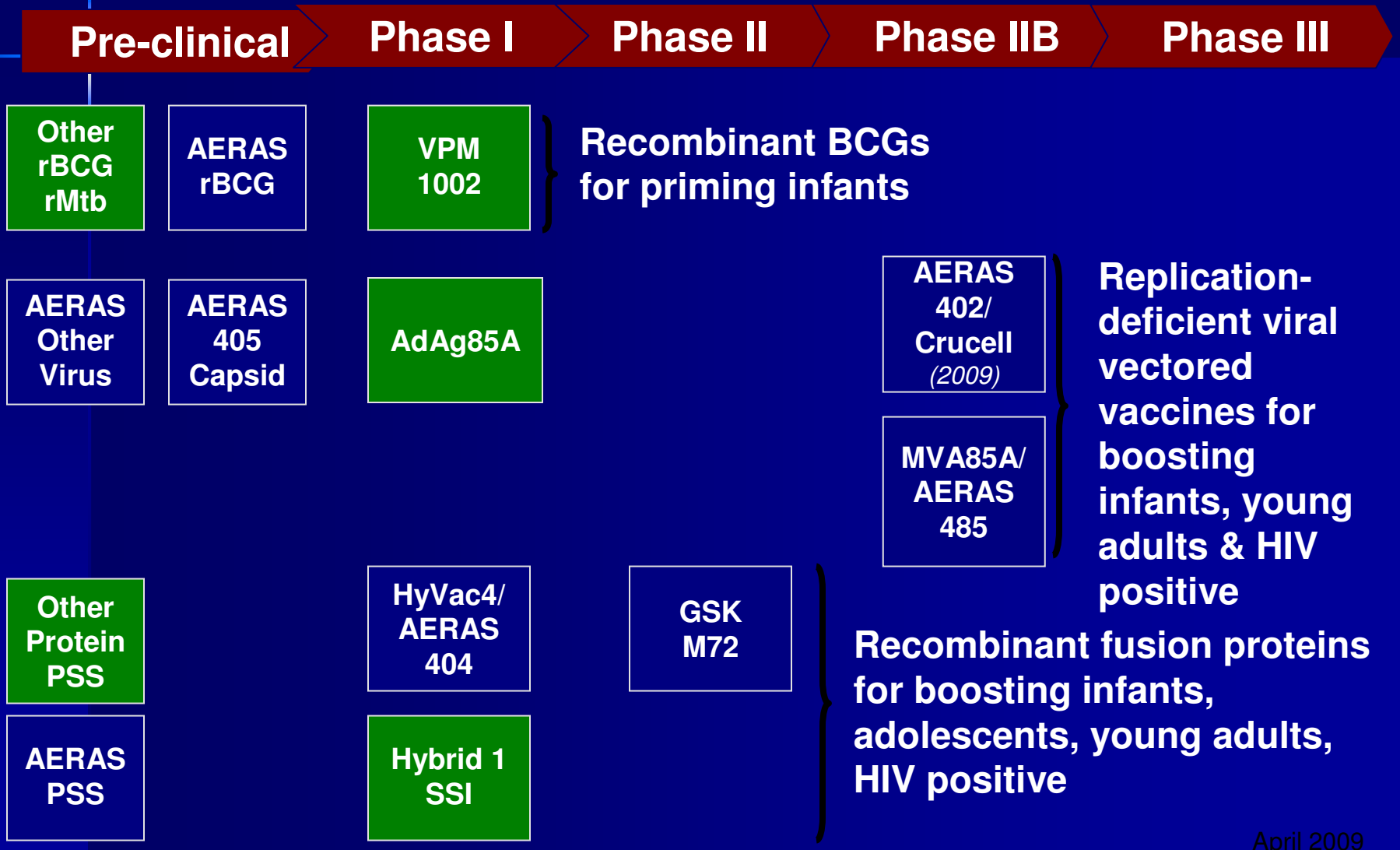
Capsids in bacteria orally or as an aerosol

14- 24 Weeks

Safer, More Effective Infant TB Vaccines

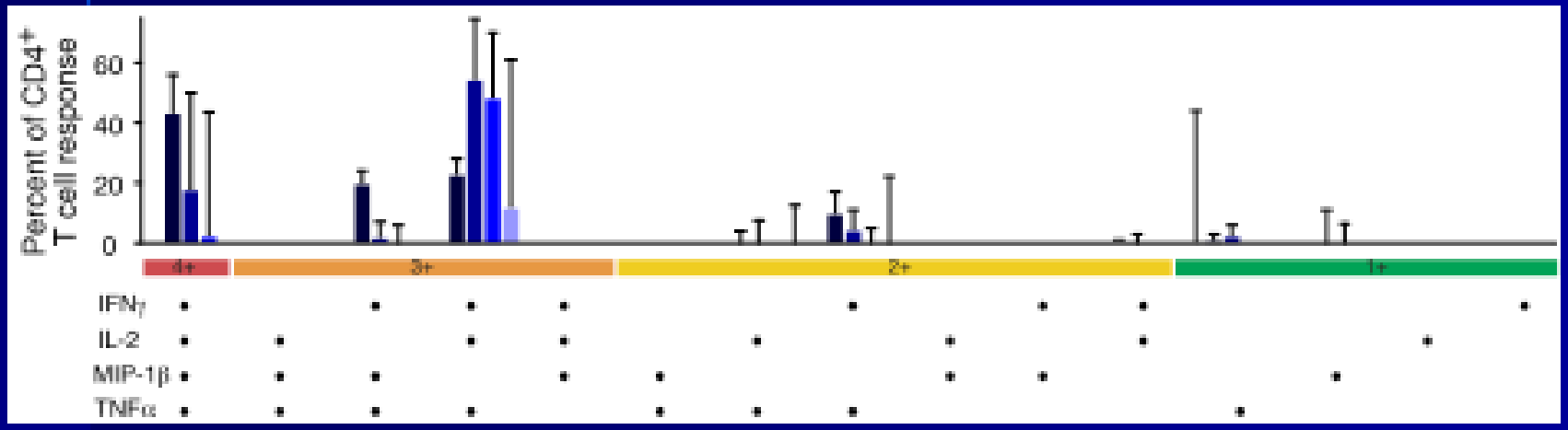
- Develop a safer BCG that is more potent
  - Endosomal membrane perforation increases safety through greater access to organism
    - Lysteriolysin or Perfringolysin expression
  - Over-expression of key proteins increases potency and ability to prime for booster
- Safe booster vaccines
  - Proteins with adjuvants safe for use in children
  - Non-replicating viral vectors

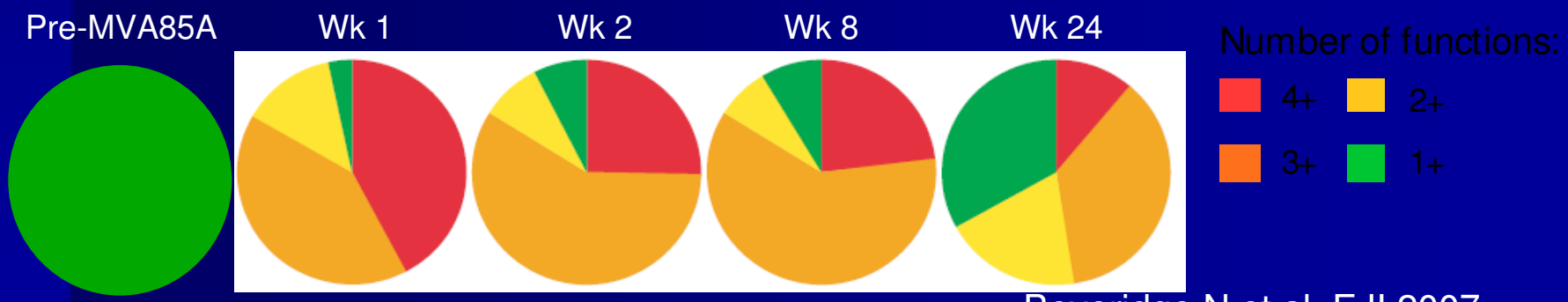
Current TB Vaccine Pipeline



April 2009

MVA85A/AERAS-485 induced antigen specific CD4+ T cells are highly polyfunctional





Beveridge N et al, EJI 2007

Vaccine Efficacy Trials

- **MVA85A/AERAS-485**
  - First efficacy trial of a new TB vaccine in infants in more than 80 years (proof of principle)
  - 2,800 infants – 90% power for 60% efficacy compared to BCG
  - In collaboration with SATVI, Oxford-Emergent Tuberculosis Consortium (OETC) and Wellcome Trust
- **AERAS-402/Crucell Ad35**
  - Planned multicenter study including SATVI (South Africa), Makerere University (Uganda), KEMRI/CDC (Kenya), Manhiça Health Research Centre (Mozambique)
  - In collaboration with EDCTP and Crucell
- **GSK M72** to be tested late 2010
- **AERAS-rBCG** to be tested in infant Phase III non-inferiority trial vs BCG in 2011

Safety & Proof of Principle in HIV+ Individuals

- AERAS-402/Crucell Ad35 to be tested this year in S. Africa and possibly other sites for safety & efficacy
- MVA85A/AERAS-485 in HIV+ subjects in 2010 (Aeras & EDCTP sponsorship)
- Establish safety and efficacy in HIV infected adults prior to testing in HIV positive infants

Summary

- Three Aeras rBCG vaccines in preparation for the clinic and intended to be safe and immunogenic in HIV + infants
- Recombinant protein + adjuvant and non-replicating viral vectored TB vaccines thus far appear safe and immunogenic as boosters in HIV + individuals
- Proof of concept studies underway in infants and about to start in HIV+ adults
- New TB vaccines for HIV + infants 2014-16

Priority Research Areas

- Development of better diagnostic tests for TB
- Establishing safe and effective anti-TB drug dosage and regimens in children – can we shorten treatment further?
- Strategies to overcome drug interactions between ARVs and ATT
- Maternal interventions to reduce risk in children
- Safe and effective vaccine for TB that can be used in HIV+ and HIV-

Challenges in Community

- Role of BCG with earlier initiation of HAART in infants?
- Integrated approach (IMCI, EPI, TB and HIV) to disease prevention and control
- Deliver care at primary health care level
- Approach the family as a whole esp mother
- Targeted screening of children in households with TB/HIV
- High index of suspicion → over-treatment
- No child should die of TB