MEETING OF THE WHO STEERING COMMITTEE ON NEW DELIVERY SYSTEMS

An overview of Aerosol Immunization

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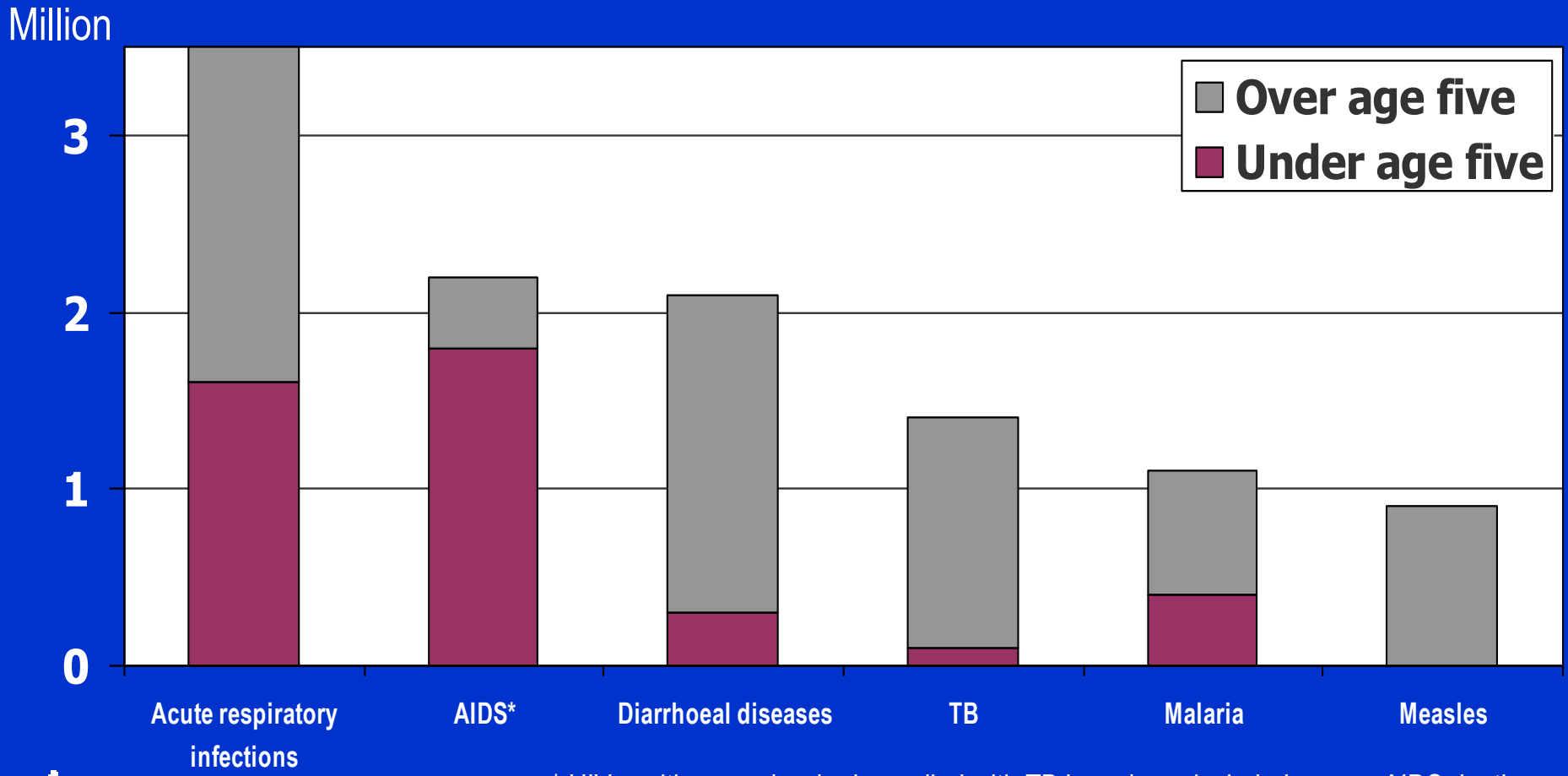
Leading infectious killers

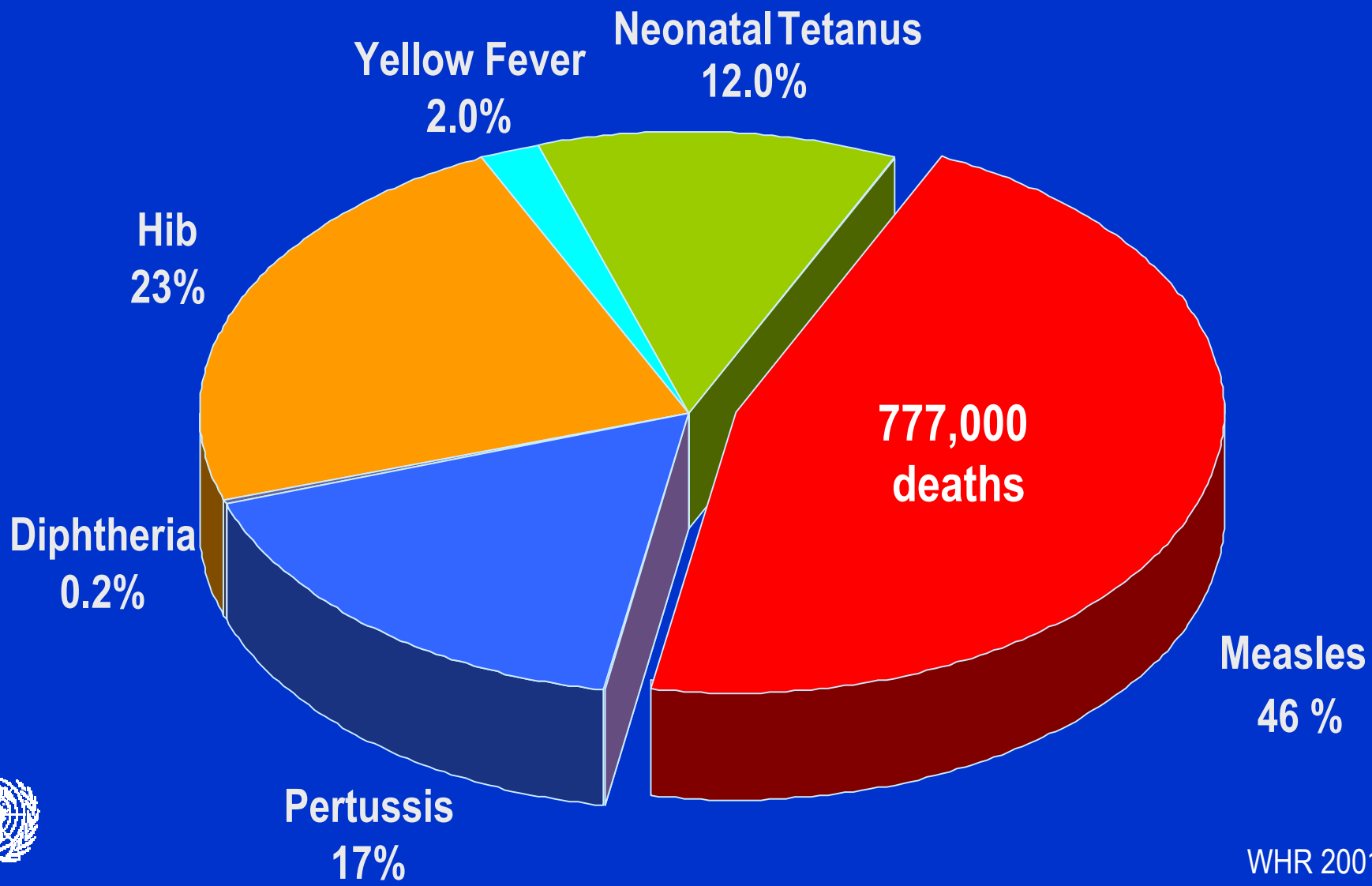
Six high-burden diseases cause 90% of total deaths



* HIV positive people who have died with TB have been included among AIDS deaths

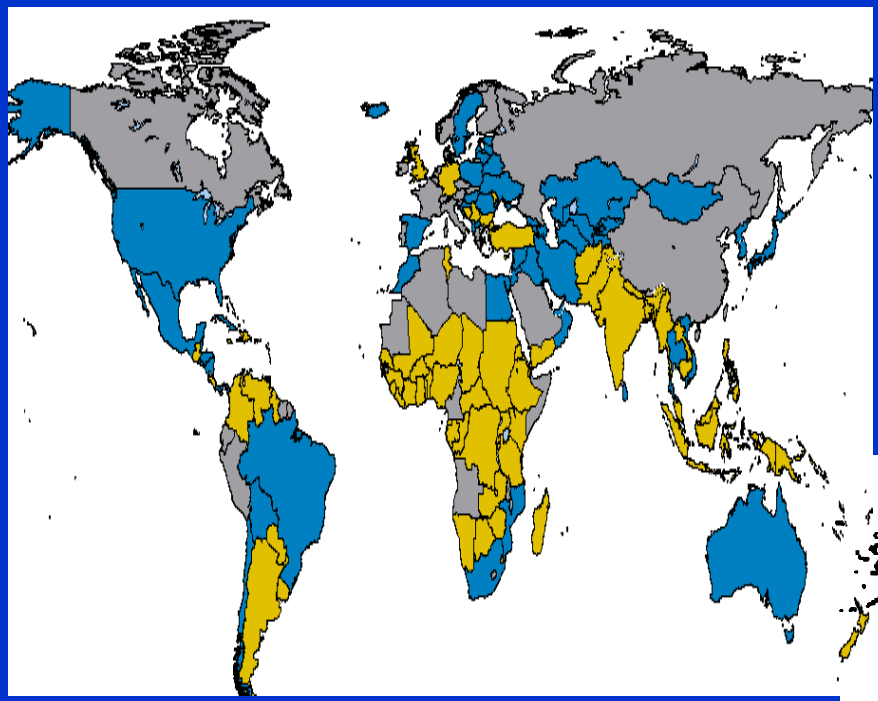
Source: Communicable Diseases/WHO-CDS, 1999

Causes of 1.7 million vaccine-preventable deaths among children < 15 years, 2000



WHR 2001

Countries reporting measles routine coverage > 90%, 2000

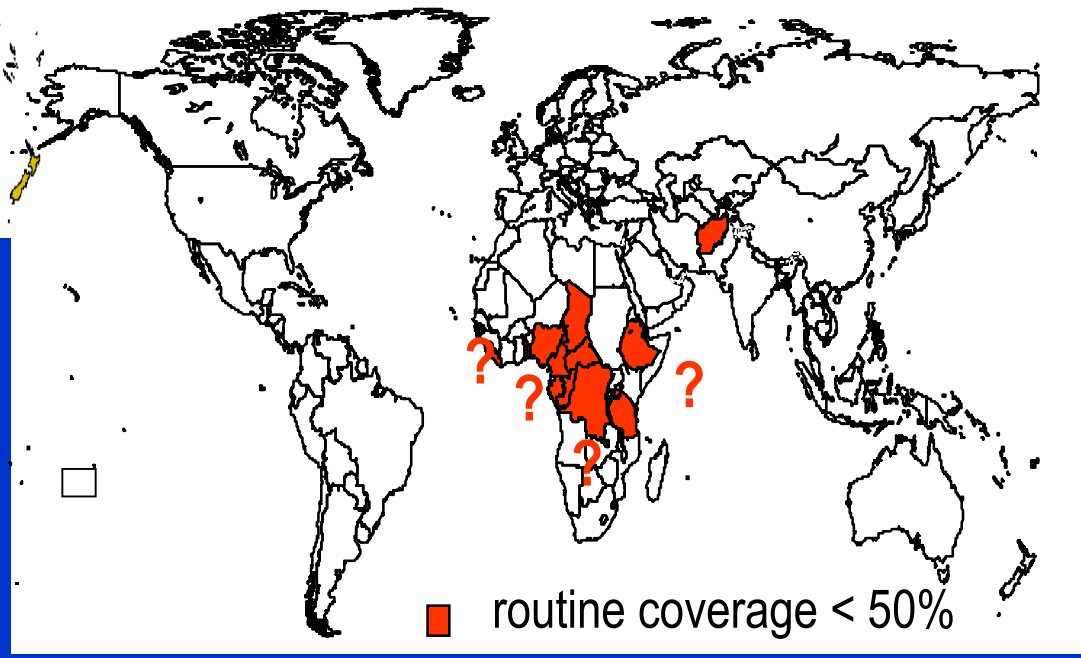


≥ 90% *(74 countries or 35%)*

< 90% *(81 countries or 38%)*

No data *(59 countries or 27%)*

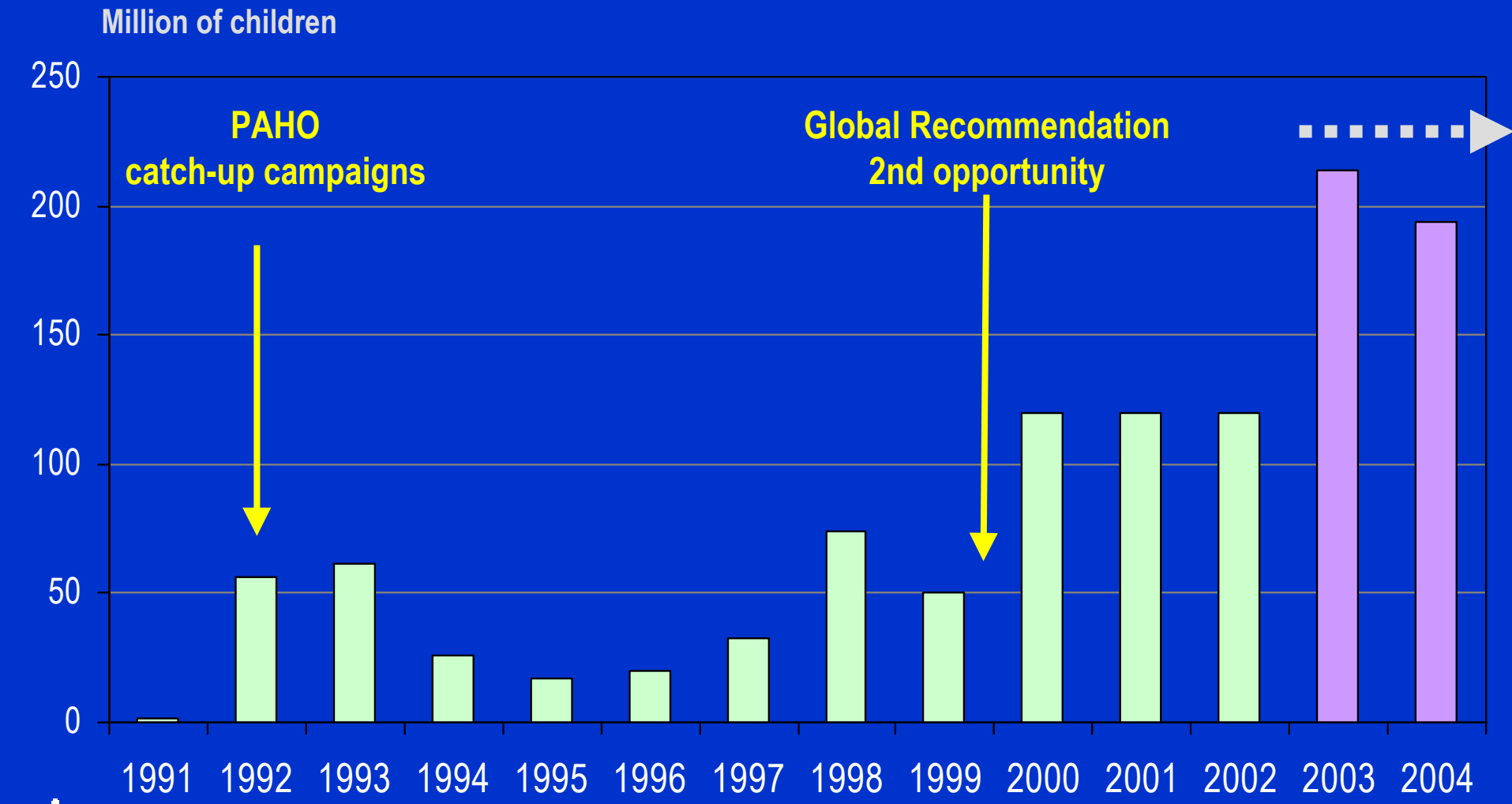
Countries reporting measles coverage < 50%, 2000



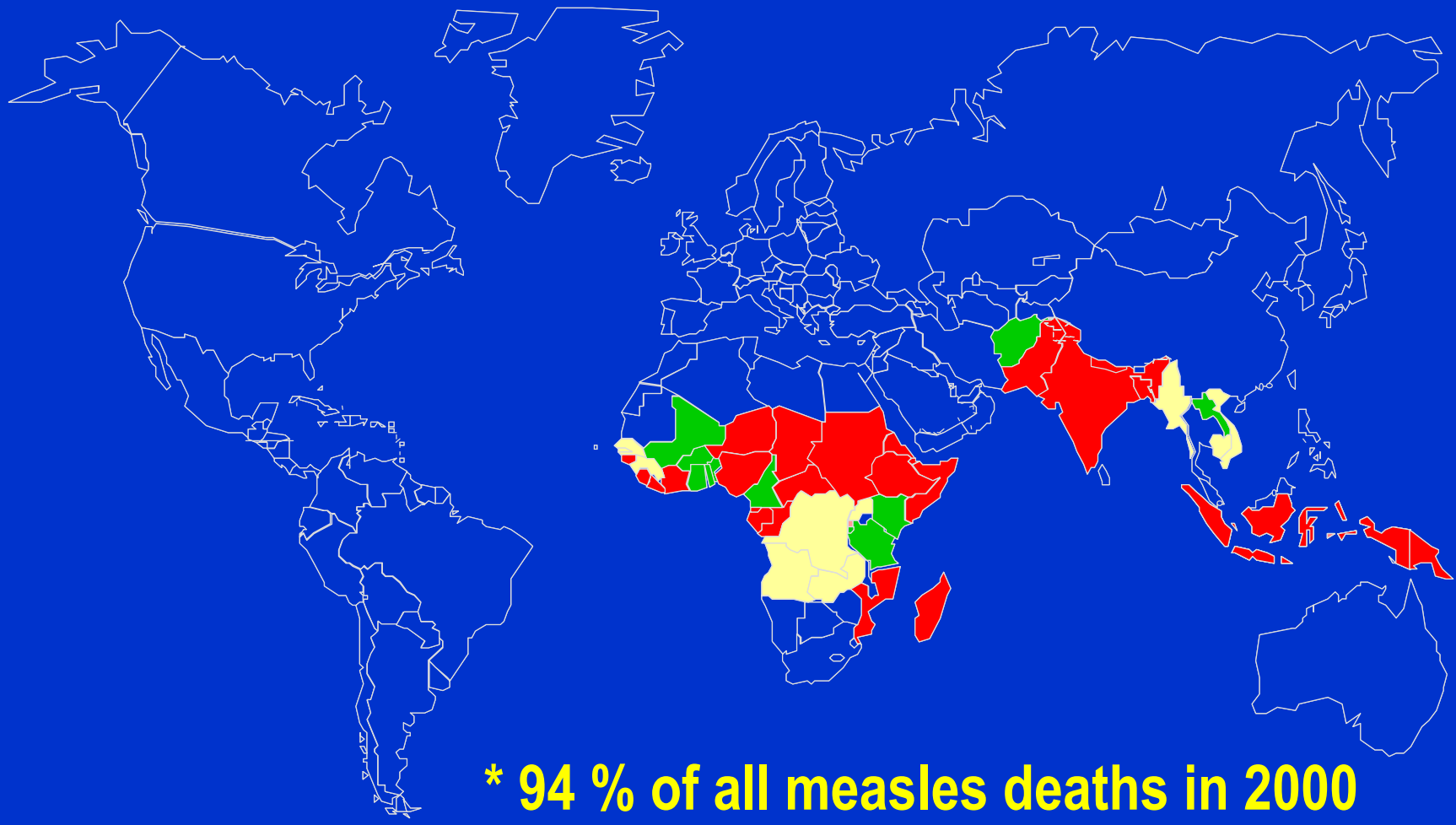
18 countries, approx 12 million children < 1 yr

Source: WHO/UNICEF joint reporting form, 2000 & WHO country information, 2001

Number of children targeted (and planned) during measles mass campaigns 1991-2004



Status of implementation in measles priority countries*, 2002



* 94 % of all measles deaths in 2000

- Nation-wide second opportunity 2002 (11)
- Partial implementation of second opportunity 2002 (10)
- No second opportunity 2002 (26)

Can we improve measles immunization ?

THE CURRENT VACCINE IS EXCELLENT !!!

Over 40 years since it was licensed

- excellent **safety** record
- proved **effectiveness** when recommended strategies are implemented:
  - prevents disease, reduces mortality
  - interrupts transmission
- good **heat stability** before reconstitution
- low **cost**
  - approx US $ 0.26 (vaccine & safety equipment)
  - approx US $ 0.8 (per child immunized - campaigns)

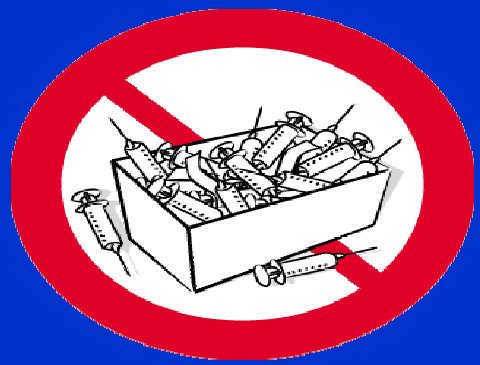
Why do we work on measles aerosol immunization ?

- In some countries the availability of **trained personnel** to administer **injections safely** is limited

- There are concerns over **inadequate safe injection practices**

Reuse of equipment

Unsafe collection



Unsafe disposal

These problems are more critical during mass campaigns when millions of doses of vaccine are administered.

Measles aerosol immunization

SAFE ☑ no serious AEFIs, fewer AEFIs than SC route

IMMUNOGENIC ☑ induced >80% response among infants < 9 months of age

☑ 86-100% response in studies (1961-2000) among > 9 months & school-aged children

EFFECTIVE ☑ lower attack rate (outbreak Mexico 1988-90):
- immunized with aerosol *(0.8%)*
- immunized with s-c *(14%)*
- unvaccinated group *(26%)*

Measles aerosol immunization

COLD CHAIN ☑ no additional requirements or guidelines

EASY TO ADMINISTER ☑ could be administered by non-health personnel, with limited training

ADDITIONAL COST BENEFITS

- ☑ cost probably low, devices cost US $ 100 - 200
- ☑ decrease in vaccine demand (i.e. up to 5 times more children vaccinated using same amount of vaccine)
- ☑ elimination of syringe and needle costs,
- ☑ savings in disposal & waste management

Measles aerosol immunization

New route administration = New product

Safety Issues

- Assessment of safety and efficacy under GP conditions
- Safety concerns
  - Live virus to the brain through cribiform plate
  - Children with asthma
  - HIV, immunocompromised children

Regulatory Issues

- Each vaccine manufacturer needs to re-license their product for aerosol route
- Failure of device or its registration
- Rumours, liability

New delivery systems
Aerosol Immunization

➡ Jet nebulizers

- ☑ evaluated in humans with good results
- ☑ portable with rechargeable batteries
- ☑ successfully used in mass campaigns
- ☑ low cost (approx US$ 70-100)
- ☑ can be used by trained non health staff
- ☒ loss of virus potency of some strains
- ☒ dosage not precisely known
- ☒ concerns about safety
- ☐ basic & modern model to be licensed
- ☐ additional pre-clinical trials in progress

New delivery systems
Aerosol Immunization

➡ Ultrasonic nebulizer

- ☑ portable
- ☑ rechargeable batteries
- ☑ cost approx US $ 200-300
- ☑ can deliver up to 100 doses/hour
- ☑ more suitable for campaigns
- ☑ trials in animals in progress
- ☒ not yet tested in humans
- ☐ licensing in process

Measles Aerosol Project

GOAL:

To develop & license at least one method (vaccine & delivery device) for respiratory delivery of currently licensed measles vaccines

- a **measles vaccine** that is cheap, safer and easier than percutaneous administration
- at least **three devices** for aerosol administration of reconstituted vaccine tested
- if feasible, a **dry powder** method will enter the initial studies

Measles Aerosol Priority & Partnerships

- ☑ WHO has given high priority to the **Measles Aerosol Project**
- ☑ **Partnership consolidated between American Red Cross, CDC, & WHO**
- ☑ This project has received financial support from the **Gates Foundation**

Product Development Group (PDG) for measles aerosol vaccine

To advise WHO to:

- identify critical licensure steps
- define clinical trial strategies & assist in protocol design
- identify sites for clinical trials
- ensure adequate implementation, monitoring & documentation of good practice

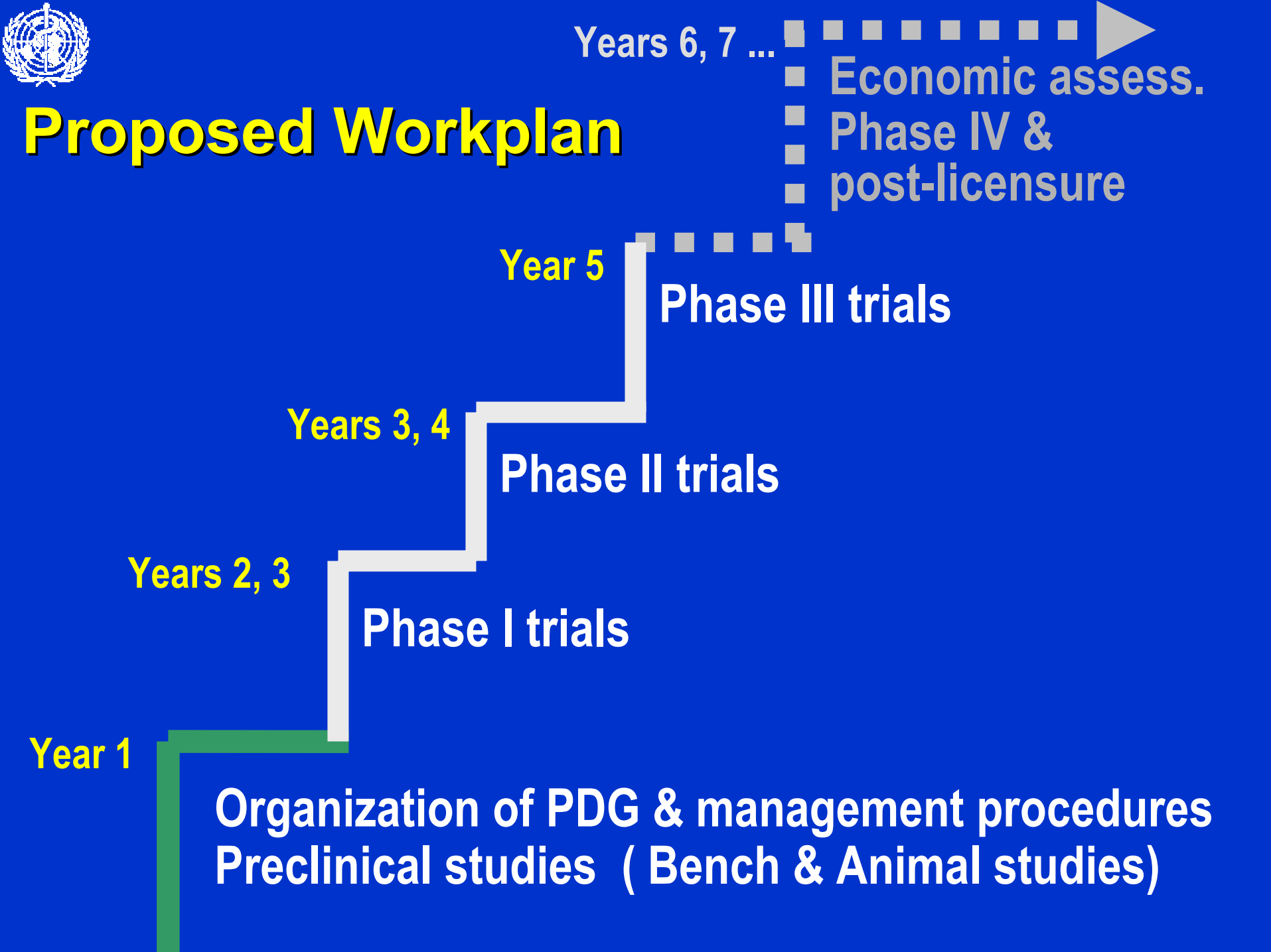
Key members of the PDG include researchers & representatives of NRAs working in close collaboration with interested manufacturers

Product profile

- Target success criteria: measles vaccine and device licensed for aerosol vaccination

- Studies needed: Preclinical and phase I-III trials
- Target population: 12 -59 m (routine)
  1 to 18 years (campaigns)
- Vaccine: Currently licensed vaccine
  same formulation and presentation
- Dose: to be determined (standard titre or lower)
- Devices: at least 3 prototypes to be tested

Proposed Workplan



Devices: bench tests

- Potency testing
- Particle size distribution
- Performance consistency testing
  - Standardisation of methods to measure dose
  - Dose volume consistency
  - Time to administer required dose
  - particle size distribution consistency
- Pulmonary distribution
- Suitability & performance under field conditions
- Studies on potential device contamination

Animal studies : vaccine & devices

- Selection of appropriate animal models
- Need to assess excipients alone
- Distribution through Respiratory Tract
- Safety - criteria & methods; healthy/immune-suppressed
- Local tolerance
- Respiratory effects; CNS effects
- SIV model will be needed

Clinical: phase I trials

- Age groups - adults; school-aged-children, toddlers
- Screen for pre-vaccination seronegatives or low seropositives; stratify by antibody status pre-vaccination
- Exclude special risk groups in phase I trials
- 12-18 months safety follow-up

Clinical: Phase II trials

- Age groups : 1-15 years
- Assess response in naïve & primed individuals
- Dose-ranging studies important
- Controlled design with blinding as much as possible.
- Intensive follow-up at least 6 months, longer term follow-up continued for at least 2 years
- Exclude high risk groups

Clinical: Phase II trials, cont.

Main Outcomes:

- Acceptability of methods
- Serology Abs: prevaccine & 1 month after
- Key marker: Measles neutralising Antibody
- Safety in first 4 weeks
- Virus shedding;
- Secondary infection risk; administrator safety
- Lung function & atopy status after 6 months
- CNS concerns?

Clinical: Phase IIb / phase III

- Evaluation in a campaign setting
- Cluster randomised trial
- Evaluate impact on measles incidence
- Large-scale passive AEFI surveillance
- Serology & active safety evaluation in sub-sample
- Compare cost-effectiveness

Preparation for post-licensure evaluation

- Identify sites for detailed post-marketing surveillance of impact & safety
- Establish surveillance systems to get baseline data
- Look for funding for post-marketing surveillance
- Establish sites for demonstration projects

Fast-tracking

2002

- Project developed & funding secured ☑
- Managerial procedures established ☑
- Ethical & regulatory pathways outlined ☑
- Preparation of sites for clinical trials ☑
- Criteria for devices evaluation developed ☑
- Bench studies ongoing ☑
- Animal studies ongoing ☑

2003

- WHO RFPs for Phase I & II studies ☐
- Start of Phase I studies ☐
- Protocols for phase II studies ☐

In summary

- Measles continues to be a **major childhood killer** in developing countries
- Countries and their partners have given high priority to **reducing measles mortality**
- Measles aerosol immunization could **contribute to ongoing & future disease control efforts**
- WHO/IVR has given especial focus to the **Measles Aerosol Project**

Dr. Sabin at the National Institutes of Health, Ca. mid-1980's

"Mass immunization of almost of all susceptible children in a short period of time, has the potential of rapidly eliminating measles as a public health problem. Immunization by ***inhalation of aerosolized measles vaccine*** *provides a procedure that could make such a mass programme possible, especially in parts of the world where measles continues to be a serious problem…"*

Albert Sabin, JAMA 1983