JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

# Priorities for Measles Control and Research

Initiative for Vaccine Research
Global Vaccine Research Forum

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# Acknowledgements

**Measles Landscape Analysis for the Bill and Melinda Gates Foundation - 2008**

Felicity Cutts, Rehan Hafiz, Susan Hahné, Hector Izurieta, Violaine Mitchell, Mary Ramsay, and Bo Stenson.

# Measles Control and Elimination Goals

Measles mortality reduction

Regional elimination

Global eradication

# Mortality Reduction

Will the successful reduction of measles mortality lead to complacency and the resurgence of measles?

# Global Reductions in Measles Mortality 2000-2008 and the Risk of Measles Resurgence

Further progress towards reaching the goal of reducing mortality by 90% is curtailed by two key factors:

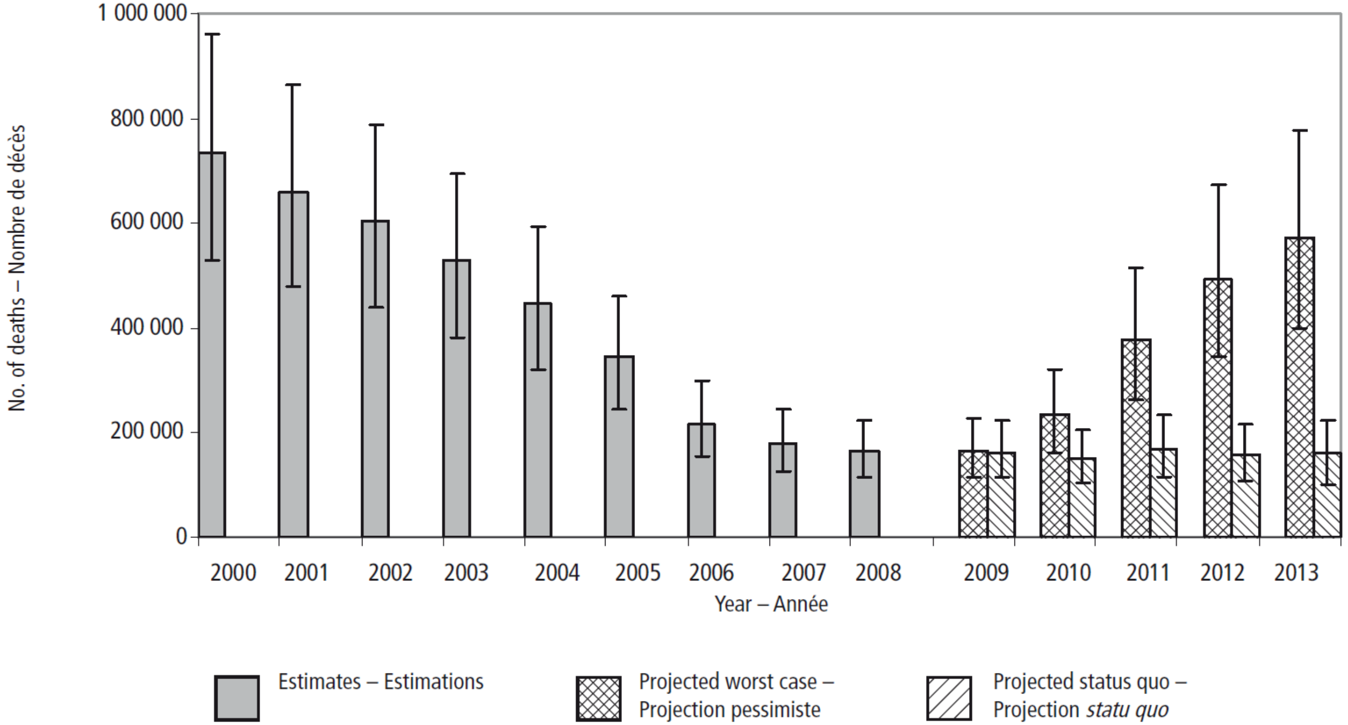
1. The strategy for accelerating the reduction of measles mortality has not been implemented in India.

2. Political and financial commitments to measles control in many of the remaining 46 countries with the highest burden has been declining.

Weekly Epidemiol Rec December 4, 2009:84:509-516.

# Global Reductions in Measles Mortality 2000-2008 and the Risk of Measles Resurgence

Fig. 1 **Estimated number of measles deaths worldwide, 2000–2008[a] and projections of possible resurgence in measles deaths worldwide, 2009–2013 (see text for description of worst-case and status quo scenarios and the 47 priority countries)**
Fig. 1 **Nombre estimé de décès annuels par rougeole dans le monde, 2000-2008[a] et projections indiquant une résurgence possible des décès par rougeole dans le monde, 2009-2013. (Pour la description des scénarios pessimistes et du *statu quo* et les 47 pays prioritaires, se reporter au texte.)**




Source: WHO. – Source: OMS.

[a] Lines indicate uncertainty bounds based on Monte Carlo stimulations that account for uncertainty in key input variables (that is, vaccination coverage and case-fatality ratios). – Les lignes indiquent les limites d'incertitude d'après les simulations de Monte-Carlo qui tiennent compte de l'incertitude des variables importantes (à savoir couverture vaccinale et taux de létalité)

# WHO/UNICEF Measles Mortality Reduction Plan 2006-2010

1. Achieve and maintain high coverage of 2 doses of measles-containing vaccine delivered either through routine services or supplementary immunization activities

2. Implement effective laboratory-supported disease surveillance

3. Provide appropriate clinical management for measles cases.

Measles mortality reduction and regional elimination strategic plan 2001–2005. Geneva, World Health Organization and UNICEF, 2001.

# Routine 1st Dose of Measles Vaccine

| WHO Region | % coverage with 1st dose of MCV - 2000 | % coverage with 1st dose of MCV - 2008 |
|---|---|---|
| African | 56 | 73 |
| Americas | 92 | 93 |
| Eastern Mediterranean | 72 | 83 |
| European | 91 | 94 |
| South East Asia | 61 | 75 |
| Western Pacific | 85 | 93 |
| Total | 72 | 83 |
| 47 Priority Countries | 58 | 74 |

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# Challenges and Priorities

## Routine First Dose

Improve routine vaccine coverage, particularly in Africa and South East Asia

58% of missed children reside in 6 populous countries

India, Nigeria, China, DRC, Pakistan and Ethiopia

Assess impact of measles control activities on health systems using case studies[1]

Assess potential synergies with rubella and polio planning and activities[1]

[1]Gates Measles Landscape Analysis

# Second Opportunity for Measles Vaccination

2nd opportunity provided in 46 of 47 priority countries during 2000-2008, with exception of India

16 priority countries (34%) conducted SIAs in 2008

Measles SIAs were combined with other child survival interventions in 13 countries

- oral polio vaccine
- insecticide-treated bednets
- de-worming
- tetanus toxoid vaccination

# Challenges and Priorities
## Second Opportunity

Operational issues:

- optimal interval between SIAs
- when and how to transition from SIAs to routine 2nd dose
- optimal age of routine 2nd dose

Impact of other interventions linked to SIAs

Measles-containing vaccines market supply study[1]

[1]Gates Measles Landscape Analysis

# Surveillance

Case-based surveillance with laboratory confirmation

90% of WHO Member States had implemented case-based surveillance in 2008

WHO measles and rubella laboratory network provided quality-controlled testing for 95% of member States in 2008

# Challenges and Priorities
## Surveillance

Need for point-of-care diagnostic test for measles and rubella

Reconsideration of methods to estimate measles mortality

Evaluation of surveillance indicators

Validate vaccine coverage figures and identify within-country low coverage areas[1]

Develop lifetime immunization records or registries[1]

[1]Gates Measles Landscape Analysis

# Case Management

## Vitamin A and Measles Mortality

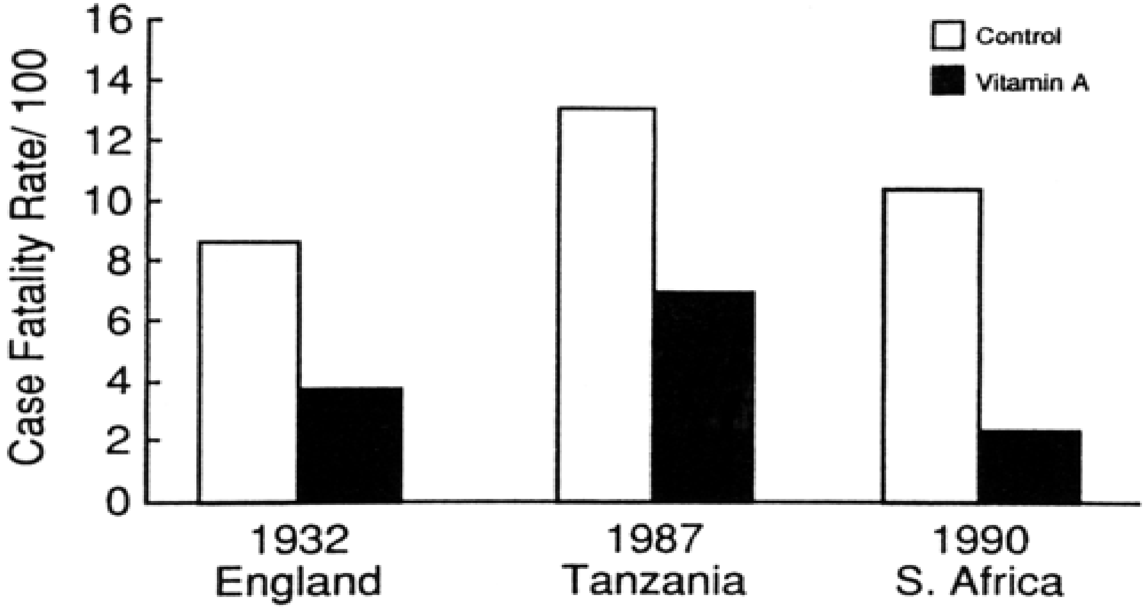



**Fig. 2–17.** Measles case-fatality rates among hospitalized patients randomized to receive high-dose vitamin A (cod liver oil in the London trial) compared with those of their controls. Vitamin A supplementation reduced mortality by ~ 50% in all three trials.[92,93,94]

Sommer and West. Vitamin A Deficiency. 1996.

# Challenges and Priorities
## Case Management

Increase use of vitamin A for case management of measles

Optimal use of antibiotics for measles

*Cochrane Database Systematic Review 2008*: "This review suggests a beneficial effect of antibiotics in preventing complications such as pneumonia, purulent otitis media and tonsillitis in children with measles. On the basis of this review, it is not possible to give definitive guidelines on the type of antibiotic, duration, or the day of initiation. Use of penicillin or co-trimoxazole may be considered. There is a need to generate more evidence by well planned RCTs to answer these questions."

Antiviral agents

# Elimination and Eradication

# Biological Feasibility of Eradication

1. Humans are the sole pathogen reservoir
2. Accurate diagnostic tests exist
3. Effective intervention is available

Interruption of transmission in large geographical areas for prolonged periods supports feasibility of eradication.

# Are Humans the Only Reservoir for Measles Virus?

- Non-human primates can be infected with measles virus
- Evidence of prior measles virus infection in free-ranging populations of non-human primates
  - One quarter of 47 rhesus macaques in southern India
  - One-third of 15 wild macaques in Indonesia
  - Presumed human-to-animal transmission
- The high infectivity of measles virus, and not viral tropism, precludes establishment of a non-human reservoir

# Challenges and Priorities

## Persistent Infection and Prolonged Virus Shedding

Persistent infection

- Subacute sclerosing panencephalitis

Prolonged virus shedding

- HIV infected and immunocompromised persons
- Vaccine virus

Sustained subclinical shedding of measles virus

# Are There Accurate Diagnostic Tests for Measles?

- IgM enzyme immunoassays
  - Plasma
  - Dried blood spots
  - Oral fluid
- Virus isolation
- Virus RNA detection by RT-PCR

# Challenges and Priorities
## Diagnostic Tests

False negative tests due to low IgM levels during first three days of rash

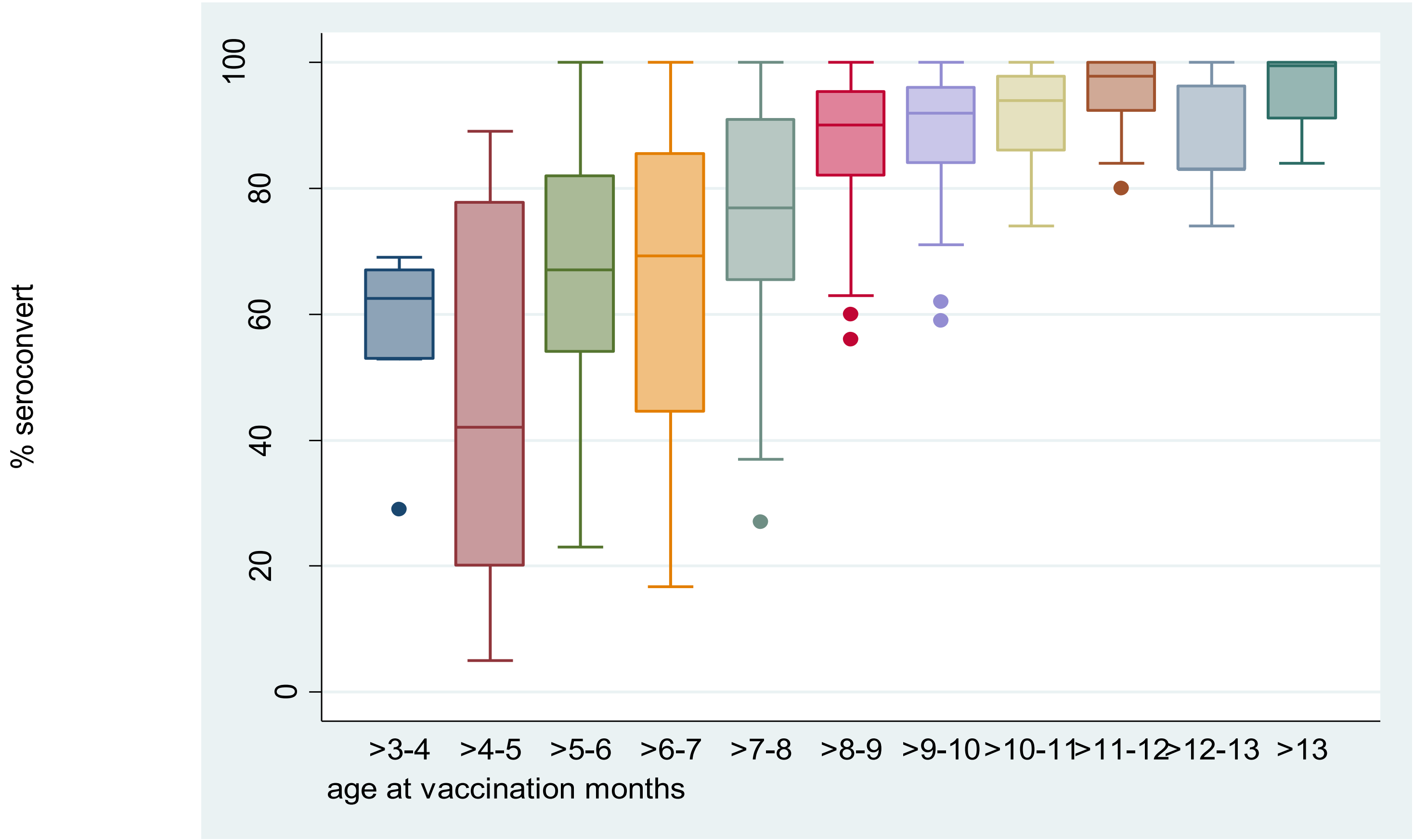
False positive tests due to cross reacting antibodies

Infrequent testing of asymptomatic cases

Need to transport samples to central laboratory

# Do We Have an Effective Intervention?

## Proportion of Children Who Seroconvert After Measles Vaccination, by Age



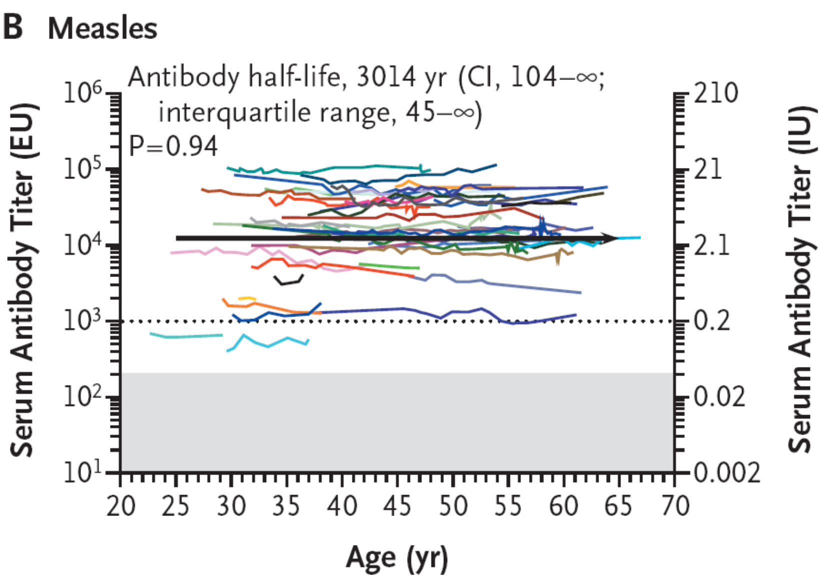

Susana Scott

Summary of 65 published studies

# Do We Have an Effective Intervention?

## Waning Immunity

**Wild-type measles virus infection**




N Engl J Med 2007;357:1903-15.

**Measles vaccination**

1. 56 persons from the US
2. Measles vaccine study 1971
3. 26-33 years after vaccination
4. 100% measles Ab by PRN
5. 92% PRN ≥120 mIU/mL

J Infect Dis 2004;189:S123-130.

# Challenges and Priorities
## Effective Intervention

Ideal measles vaccine:

- Inexpensive
- Heat stable
- Single dose (induces long-lasting immune protection)
- Non-parenteral
- Immunogenic in young infants
- Safe in immunocompromised persons

Evolution of wild-type measles viruses away from vaccine-induced protective immune responses

# Challenges to Eradication

Challenges to achieving high levels of vaccine coverage

Challenges to achieving high levels of population immunity

Challenges to sustained measles eradication

# Challenges to Achieving High Levels of Measles Vaccine Coverage

Sustainability of current measles mortality reduction strategies

Conflict and political instability

Population growth and demographic changes

Public perceptions of vaccine safety

# Challenges to Achieving High Levels of Population Immunity

Waning immunity

Heterogeneities in vaccination and clustering of susceptibles

HIV pandemic

# Implications of the HIV Pandemic for Measles Control

## Measles

Unusual and severe clinical manifestations

Prolonged measles virus shedding

## Measles Vaccination

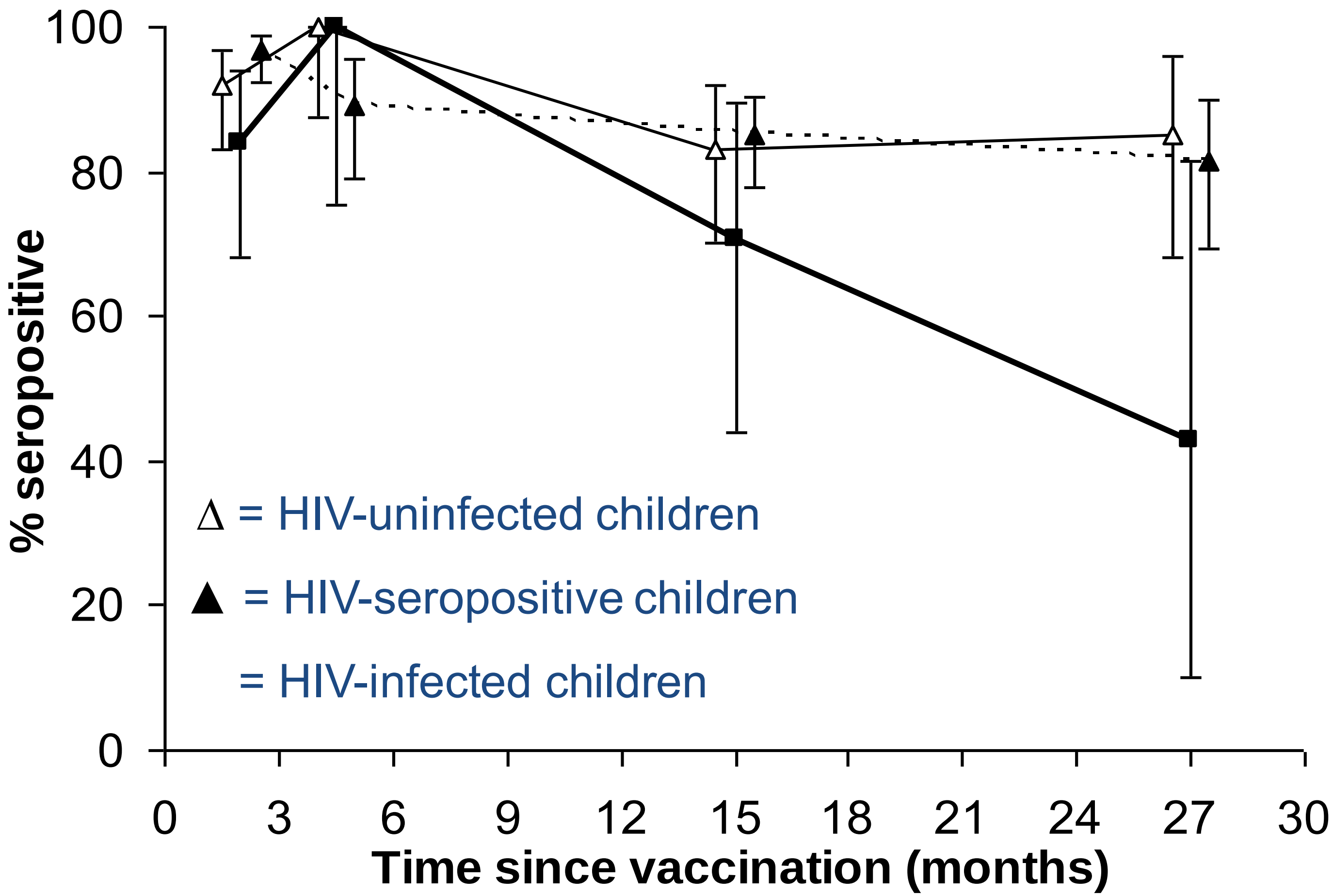
Lower titers of maternal antibodies

1° and 2° measles vaccine failure

Higher rate of severe adverse events

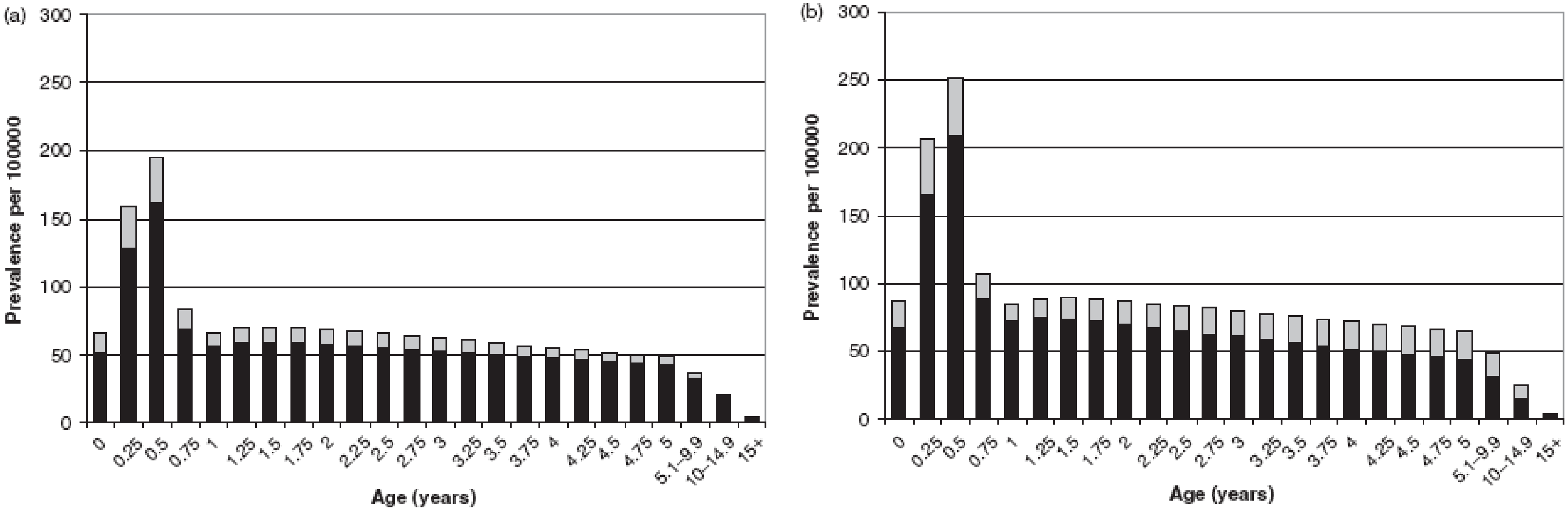
Impact of antiretroviral therapy

# Waning Vaccine-Induced Immunity




J Infect Dis 2007;196:347-55.

# Predicted Impact of HIV-1 Infection and Antiretroviral Therapy on Measles




Measles Cases by Age

Without Antiretroviral Therapy

Measles Cases by Age

With Antiretroviral Therapy

Int J Epidemiol 2008; 37:356-67.

# Challenges to Sustaining Measles Eradication

## Measles Virus as an Agent of Bioterrorism

High infectivity of measles virus is a characteristic suitable to a biothreat agent.

High levels of measles vaccination coverage would protect many from the deliberate use of measles virus.

Measles vaccine virus can be used as a vector to deliver genes derived from other pathogens.

Genetic engineering of a measles virus strain that was not neutralized by antibodies induced by the current measles vaccines would likely have reduced infectivity.