Measles

William Moss, MD, MPH
Johns Hopkins University
Objectives

- Different goals of measles control
- Virologic and clinical aspects of measles
- Basic epidemiology of measles virus
- Strategies for control
- Obstacles to control
- Eradication
Goals

- Measles control
  - Reduce measles mortality
  - Reduce measles incidence (number of cases)
- Measles elimination
  - Stop indigenous transmission in a region
- Measles eradication
  - Stop global transmission
What Do We Need to Know About?

- Measles and measles virus
- The epidemiology of measles
- Measles control strategies
- Measles control programs
- Obstacles to measles control
Section A

Background
Measles Virus

- Family: *Paramyxoviridae*
  - Genus: *Morbillivirus*
- Sensitive to UV light and heat
- Antigenically stable
- Major proteins
  - Hemagglutinin (H): receptor binding protein
  - Fusion (F): membrane fusion and virus entry
  - Nucleoprotein (N): most variable genetically
Measles Virus Budding from Cell
Phylogenetic Tree

- **Ruminants**
  - Rinderpest virus
  - Peste des petits ruminants virus

- **Carnivores**
  - Phocid distemper virus
  - Canine distemper virus

- **Primates**
  - Measles virus

- **Cetaceans**
  - Dolphin morbillivirus
  - Porpoise morbillivirus

Ancestral Virus
Clinical Features of Measles

Measles Rash

Source: CDC PHIL
Measles Conjunctivitis and Coryza
### Complications of Measles Virus

<table>
<thead>
<tr>
<th>Equivalent of the rash on other epithelial surfaces produced:</th>
<th>External rash:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Conjunctivitis</td>
<td>Normal rash develops</td>
</tr>
<tr>
<td>• Sore mouth</td>
<td>▼</td>
</tr>
<tr>
<td>• Laryngitis</td>
<td>Rash darkens to a deep red and violet color</td>
</tr>
<tr>
<td>• Bronchopneumonia</td>
<td>▼</td>
</tr>
<tr>
<td>• Enteritis, diarrhea</td>
<td>Desquamation (amount depends on the extent of the rash’s darkening)</td>
</tr>
</tbody>
</table>

*The possible association between the severity of measles rash and the manifestation of the disease in epithelial surfaces*
Example of Desquamating Rash

Photo Source: William Moss
Measles Case Fatality Ratio

![Graph showing Measles Case Fatality Ratio over different age categories for different countries: Guinea-Bissau (1980-4), Senegal (1983-6), India (1986), Kenya (1988), and Chad (1994). The y-axis represents the percentage case fatality ratio (% CFR), and the x-axis represents age categories (<1, 1-4, 5-9, >10 years). The graph illustrates a descending trend in fatality rates with increasing age for each country.]
Immune Responses

- Life-long immunologic protection
- Antibody responses
  - IgM
  - IgG
- Cellular immune responses
- Immune suppression
Antibody Response to Acute Measles Infection

![Graph showing antibody response to acute measles infection.](image-url)
Clinical, Virologic, and Immunologic Characteristics

- **Virus replication**
  - Skin
  - Liver
  - Thymus
  - Lung
  - Lymphatic tissue
  - Spleen
  - Blood
  - Local lymph nodes
  - Respiratory epithelium

- **Clinical symptoms**
  - Conjunctivitis
  - Cough
  - Fever
  - Rash
  - Koplik's spots

- **Immune responses**
  - CD8 T cells
  - CD4 T cells
  - IgG
  - IgM
  - Immune suppression

Days after infection
Immune Suppression

T Cell

Monoocyte

Lymphocyte Apoptosis

Impaired Lymphoproliferation

Upregulation of IL-10

Upregulation of IL-4

Impaired Immuno-modulatory Cytokines

Downregulation of IL-12

Impaired Antigen Presentation


Source: WHO Global Burden of Diseases 2000
Measles Cases Have Declined

Source: WHO vaccine-preventable disease monitoring system, 2005 global summary
Estimated Worldwide Measles-Related Deaths

*In 2002 the World Health Assembly urged member countries to halve measles death by 2005, compared with 1999 estimates.

Counting Cases of Disease

Estimated Number of Deaths

<table>
<thead>
<tr>
<th>Year</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>873,000</td>
</tr>
<tr>
<td>2000</td>
<td>740,000</td>
</tr>
<tr>
<td>2001</td>
<td>676,000</td>
</tr>
<tr>
<td>2002</td>
<td>594,000</td>
</tr>
<tr>
<td>2003</td>
<td>530,000</td>
</tr>
</tbody>
</table>

Target* for 2005

Number

<table>
<thead>
<tr>
<th>Year</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>820,000</td>
</tr>
<tr>
<td>2000</td>
<td>780,000</td>
</tr>
<tr>
<td>2001</td>
<td>680,000</td>
</tr>
<tr>
<td>2002</td>
<td>590,000</td>
</tr>
<tr>
<td>2003</td>
<td>520,000</td>
</tr>
</tbody>
</table>

2005 target
What Is the Message?


Source: CDC
What Is the Message?

The chart shows the death rate per million children over time, with a sharp decline starting around 1900. The notation 'Immunization begun' indicates the start of vaccination programs, which could be responsible for the decline in deaths.
Measles: Leading Vaccine-Preventable Cause of Death

- Measles: 46%
- Hib: 23%
- Pertussis: 17%
- Polio: 0.1%
- Diphtheria: 0%
- Neonatal tetanus: 12%
- Yellow fever: 2%

Most Measles Deaths Occur in Sub-Saharan Africa

Estimated measles deaths by WHO region, 2000

Section B

Epidemiology
Measles Epidemiology

- Transmission characteristics
- Communicability
- Disease distribution
  - Person
  - Place
  - Time
Transmission Characteristics

- Routes of transmission
  - Respiratory droplet, airborne and direct contact
- Humans only reservoir
  - Monkeys infected, do not sustain transmission
- Incubation period
  - Ten days to fever, 14 days to rash
- Infectious period
  - From five days before rash until four days after rash
Communicability

- Highly contagious
  - 80% of susceptible household contacts
- Outbreaks with only 3–7% susceptibles
- Chains of transmission
  - School children, household contacts, health care workers (HCW)
  - ? transmission from subclinical measles
Disease Distribution

- Person
  - Age distribution
- Place
  - Population density to maintain transmission
  - Urban vs. rural
- Time
  - Seasonality
  - Epidemic cycles
Age Distribution

- Depends on . . .
  - Rate of loss of maternal antibody
  - Rate of contact with infected persons
  - Age at immunization
- In developing countries with high population density and low vaccination coverage, younger children are infected
Age Distribution of Measles Cases

Rural, high coverage
Age Distribution of Measles,
Lesotho, 1988

Developed country, high coverage
Age Distribution of Measles,
United States, 1989

Source: adapted by CTLT from Taylor et al. (1988); Koster et al. (1981).
Epidemic Cycles

- Cyclic pattern of measles incidence
  - Low vaccination coverage: 1–3 years
  - High vaccination coverage: 5–7 years
- Pattern largely due to accumulation and decline in the number of susceptibles
  - Population density and birth rate
  - Migration patterns
  - Vaccination coverage
Measles Outbreak Patterns

Measles notifications in England and Wales, 1950-79

Years

Number of Measles Cases Notified (in Thousands)

Beginning of national measles vaccination program
Section C

Measles Control and Elimination
Control Strategies

- Case management
- Measles vaccination
  - Routine
  - Enhanced
- Surveillance
- Outbreak response
Case Management

- **Vitamin A**
  - Reduced morbidity and mortality
  - As therapy and preventive supplementation
  - Recommended for all children with measles
  - Two doses on two consecutive days

- **Antibiotics**
  - Treat if clinical signs of bacterial infection
  - Little evidence to support prophylactic use
Note: 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. Adapted by CTLT from Al Sommer.
Measles Vaccines

- Types of measles vaccines
  - Inactivated
  - Attenuated
  - High-titer
Measles Vaccines

- Types of measles vaccines
  - Inactivated
  - Attenuated
  - High-titer

- Immunization schedules
  - 9 vs. 12 months
  - Second dose

- Stability and administration
  - Relatively heat-stable in lyophilized form
  - Loss of potency if stored above 8°C (cold chain)
  - Parenteral administration
Immune Protection

- Correlates of immune protection
  - Anti-measles antibody titers
- Determinants of response
  - Age at vaccination
  - Passively acquired maternal antibodies
  - Immunologic immaturity
  - Immune status
- Duration of protection
  - At least 20 years
  - Less in immunocompromised children
Age of Vaccination

- Decline in passive maternal antibody vs. rise in measles incidence
  - “Window of opportunity”
- Proportion responding at different ages
  - 85% at 9 months of age
  - 90–95% at 12 months of age
  - 95% who fail to respond to 1st dose will respond to 2nd dose
Optimal Age of Vaccination

- **Europe**
- **W. Africa**

Appropriate ages for vaccination

Percent of Population

Age in Months

- Maternal antibodies
- Measles - W. Africa
- Measles - Europe

6 12 18 24 48 54

100 50
“The build-up of susceptible children over time in a population is the most serious obstacle to measles eradication.”

— PAHO* Measles Eradication Field Guide

*Pan American Health Organization
## WHO Immunization Schedule

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>BCG, OPV 0, HB 1</td>
</tr>
<tr>
<td>6 weeks</td>
<td>DTP 1, OPV 1, HB 2</td>
</tr>
<tr>
<td>10 weeks</td>
<td>DTP 2, OPV 2</td>
</tr>
<tr>
<td>14 weeks</td>
<td>DTP 3, OPV 3, HB 3</td>
</tr>
<tr>
<td>9 months</td>
<td><strong>Measles</strong>, yellow fever</td>
</tr>
</tbody>
</table>
## Population Immunity—One Dose

<table>
<thead>
<tr>
<th>Percent Coverage</th>
<th>Percent Vaccine Efficacy</th>
<th>Percent Immune</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>95</td>
<td>76</td>
</tr>
<tr>
<td>90</td>
<td>95</td>
<td>86</td>
</tr>
<tr>
<td>95</td>
<td>95</td>
<td>90</td>
</tr>
<tr>
<td>95</td>
<td>90</td>
<td>86</td>
</tr>
<tr>
<td>95</td>
<td>80</td>
<td>81</td>
</tr>
</tbody>
</table>
Late Two-Dose Elimination Strategy

- 2nd dose: decrease susceptibles
  - 1° vaccine failure
  - Missed immunization
- Routine immunization services
  - Finland: two-dose schedule in 1982
  - United States: 12–15 months and 4–6 years
- Supplemental campaigns
  - Rapidly reduce number of susceptibles below the epidemic threshold
  - Successful in polio eradication programs
Countries with Measles Mortality Reduction Strategies

Achieving 90% measles coverage, 2001

Source: WHO/UNICEF
* 2nd Opportunity = country has implemented a two dose routine measles schedule and/or within the last 4 years has conducted a national immunization campaign achieving ≥ 90% coverage of children < 5 years
## Population Immunity—Two Doses

<table>
<thead>
<tr>
<th>Coverage</th>
<th>85% 1st dose</th>
<th>95% 2nd dose</th>
<th>95% 2nd dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>85%</td>
<td>72%</td>
<td>83%</td>
<td>95%</td>
</tr>
<tr>
<td>90%</td>
<td>77%</td>
<td>88%</td>
<td>97%</td>
</tr>
<tr>
<td>95%</td>
<td>81%</td>
<td>93%</td>
<td>98%</td>
</tr>
<tr>
<td>100%</td>
<td>85%</td>
<td>98%</td>
<td>99%</td>
</tr>
</tbody>
</table>
Measles Elimination Strategies: PAHO

- Catch up
- Keep up
- Follow up
- Mop up
Catch Up

- Goal: rapidly interrupt transmission
- One-time-only vaccination campaign
- Conducted during low transmission
- Conducted over short time period
  - One week to one month
- Target wide age cohort of children
  - PAHO: all children 9 months to 14 years of age
- Community mobilization
Keep Up

- Goal: > 90% coverage of birth cohort
- Strategies to improve routine coverage
  - Improve access to vaccination services
  - Integrate with routine health services
  - Tracking systems
  - Outreach activities
  - School-based programs
  - Reduce missed opportunities
Follow Up

- Prevent accumulation of susceptibles
  - Measles vaccine not 100% effective
  - Coverage not 100%
- Conducted when the estimated number of susceptible children = birth cohort
  - Usually about every 3–5 years
- Target children 1–4 years of age
**Mop Up**

- Goal: intensive vaccination efforts to reach unvaccinated children
- Target wide age range
- Target high-risk areas
  - Low coverage
  - Recent measles cases
  - Poor surveillance
  - Crowding, poverty, and migration

Source: adapted by CTLT from the Cuban Ministry of Health.

Source: Cuba, Ministry of Health.

Reported measles cases and deaths by year, in seven southern African countries, 1983-2000

Is - 21

WARD (MEASLES)

Photo source: William Moss.
# Measles Surveillance in Southern Africa, 2000

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of reported cases</th>
<th>Investigated</th>
<th>Cases w/ specimens taken</th>
<th>Specimens taken, results available</th>
<th>Measles IgM pos.*</th>
<th>Measles IgM neg.</th>
<th>Measles IgM indeter.</th>
<th>Rubella IgM pos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botswana</td>
<td>1666</td>
<td>678 (41%)</td>
<td>856 (126%)</td>
<td>210 (25%)</td>
<td>0</td>
<td>210</td>
<td>0</td>
<td>170</td>
</tr>
<tr>
<td>Lesotho</td>
<td>660</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Malawi</td>
<td>303</td>
<td>303 (100%)</td>
<td>303 (100%)</td>
<td>287 (95%)</td>
<td>0</td>
<td>287</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Namibia</td>
<td>261</td>
<td>261 (100%)</td>
<td>237 (91%)</td>
<td>173 (73%)</td>
<td>13 (8%)</td>
<td>158</td>
<td>2</td>
<td>43</td>
</tr>
<tr>
<td>South Africa</td>
<td>1449</td>
<td>1449 (100%)</td>
<td>1303 (90%)</td>
<td>1303 (100%)</td>
<td>77 (6%)</td>
<td>1166</td>
<td>9</td>
<td>471</td>
</tr>
<tr>
<td>Swaziland</td>
<td>230</td>
<td>230 (100%)</td>
<td>230 (100%)</td>
<td>229 (100%)</td>
<td>10 (4%)</td>
<td>219</td>
<td>0</td>
<td>115</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>1090</td>
<td>1090 (100%)</td>
<td>971 (89%)</td>
<td>275 (28%)</td>
<td>17 (6%)</td>
<td>247</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>5659</strong></td>
<td><strong>4011 (71%)</strong></td>
<td><strong>3900 (97%)</strong></td>
<td><strong>2477 (64%)</strong></td>
<td><strong>117 (5%)</strong></td>
<td><strong>2287</strong></td>
<td><strong>22</strong></td>
<td><strong>811</strong></td>
</tr>
</tbody>
</table>

Notes Available

*Zero deaths
Section D

Molecular Epidemiology and Obstacles to Measles Control
Molecular Epidemiology

- Based on most variable region of genome
  - 450 nucleotides coding for COOH region of N
- Virus isolation or RT-PCR
- Taxonomy
  - 8 clades (A–H)
  - 21 genotypes (e.g., D1, D2, D3)
- Identify source and transmission pathways
- Document interruption of transmission and importation
Distribution of measles genotypes associated with endemic transmission in various areas of the world based on information available in 2002. Genotype designations are shown for each measles-endemic area where virologic surveillance has been conducted.
Measles Virus Genotypes in U.S.

1989-92: >55,000 cases

1994: 958 cases

1995: 301 cases

1996: 488 cases

1997: 136 cases

1998: 100 cases

Key to genotypes:
- A
- C2
- D4
- D5
- D3
- D6
- B1
- H
. . . is maintaining the number of susceptible persons below the epidemic threshold.
Herd Immunity Threshold

- Elimination programs aim to increase the number of immunes above herd immunity threshold
- Herd immunity threshold
  - $H = 1 - 1/R_0$ ($R_0$ = basic reproductive number)
  - measles: $R_0 = 12–18$ $H = 93–95\%$
  - polio: $R_0 = 5–7$ $H = 80–85\%$
  - small pox: $R_0 = 5–7$ $H = 80-85\%$
- . . . and vaccine not 100% effective
Obstacles to Achieving High Levels of Immunity

- Established obstacles
  - Failure to vaccinate
  - Vaccine failure
- Unproven obstacles
  - Early loss of maternal antibody
  - HIV epidemic
Failure to Vaccinate

- Lack of political will
- Insufficient resources
- Missed opportunities
- Difficult to reach populations
- Religious and “medical” objections
Difficult to Reach Populations

- Densely populated urban areas
- Remote rural areas
- Nomadic peoples
- Refugees
- Regions of conflict
- Ethnic or racial minorities
Addis Ababa, Ethiopia

Photo Source: Mio Schroeder. Some Rights Reserved.
Northern Ethiopia

Photo Source: Mio Schroeder. Some Rights Reserved.
Religious or “Medical” Objections

- Netherlands 1999
  - 2-dose coverage of 95%
    - Five cases in an elementary school
      - Community with religious objections to vaccination
    - Sustained transmission
      - 2,961 cases
      - Five deaths
- Erroneous association with autism
  - Reduced MMR coverage in U.K.
Experts raise alarm over measles in Europe

Experts from WHO and its partner agencies met to find ways to improve immunization coverage in the European Region, following a recent spate of measles outbreaks that prompted concern over whether enough is being done to get children vaccinated.

Five major measles outbreaks in the last three years and recent scares over the safety of the combined measles, mumps and rubella vaccine in the United Kingdom and Ireland have raised questions about whether coverage is adequate in some countries and whether more needs to be done in other countries to educate the public.
Vaccine Failure

- Technical problems with vaccine
  - Failure to maintain cold chain
  - Improper reconstitution or administration
- Primary vaccine failure
  - Young infants (maternal Abs, immaturity)
  - Genetic differences in host immune response
- Secondary vaccine failure
  - Waning immunity
  - Subclinical measles
Transmission among Adults

- Susceptibility of adults to measles
  - Never vaccinated or infected
  - Primary vaccine failure
  - Secondary vaccine failure

- Outbreaks among adults
  - Sao Paulo, Brazil, 1997: 42,055 cases
  - Majority of cases > 20 years; most not vaccinated

- PAHO: Target young adults at risk
  - HCWs, university students, military recruits
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
  - Primary measles vaccine failure
  - Secondary measles vaccine failure
  - Higher rates of severe adverse events
Vaccine Safety

- Potential transmission of pathogens
  - Hepatitis B, HIV
  - Especially during mass campaigns
- Proper disposal of needles and syringes
  - Autodestruct syringes
  - Non-parenteral vaccines (aerosol, powder)
- Aerosol measles vaccine
## Costs of Global Measles Control

Estimated total financial resources (U.S. dollars, in millions) needed to meet measles control goals, 2001–2005

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Costs of vaccine and injection safety equipment</th>
<th>Operational costs, supplemental immunization</th>
<th>Operational costs, surveillance and laboratory</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countries in the mortality reduction stage</td>
<td>210</td>
<td>441</td>
<td>37</td>
<td>688</td>
</tr>
<tr>
<td>Selected countries in the elimination stage</td>
<td>91</td>
<td>189</td>
<td>16</td>
<td>296</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>301</strong></td>
<td><strong>630</strong></td>
<td><strong>53</strong></td>
<td><strong>984</strong></td>
</tr>
</tbody>
</table>
Can measles be eradicated?
<table>
<thead>
<tr>
<th>Criteria for Eradication</th>
<th>Measles</th>
</tr>
</thead>
<tbody>
<tr>
<td>No nonhuman host or reservoir</td>
<td>No primate reservoir</td>
</tr>
<tr>
<td>Accurate diagnosis</td>
<td>Clinical picture IgM antibodies</td>
</tr>
<tr>
<td>Effective intervention</td>
<td>Long-term immunity after vaccination</td>
</tr>
<tr>
<td>Low infectivity</td>
<td>Highly contagious</td>
</tr>
</tbody>
</table>
## Measles and Smallpox

<table>
<thead>
<tr>
<th>Factor</th>
<th>Smallpox</th>
<th>Measles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonhuman host</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Obvious illness</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Vaccine effectiveness</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>$R_0$</td>
<td>5–7</td>
<td>12–18</td>
</tr>
<tr>
<td>Herd immunity threshold</td>
<td>80–85%</td>
<td>93–95%</td>
</tr>
</tbody>
</table>
Should measles eradication be attempted?