JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

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

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

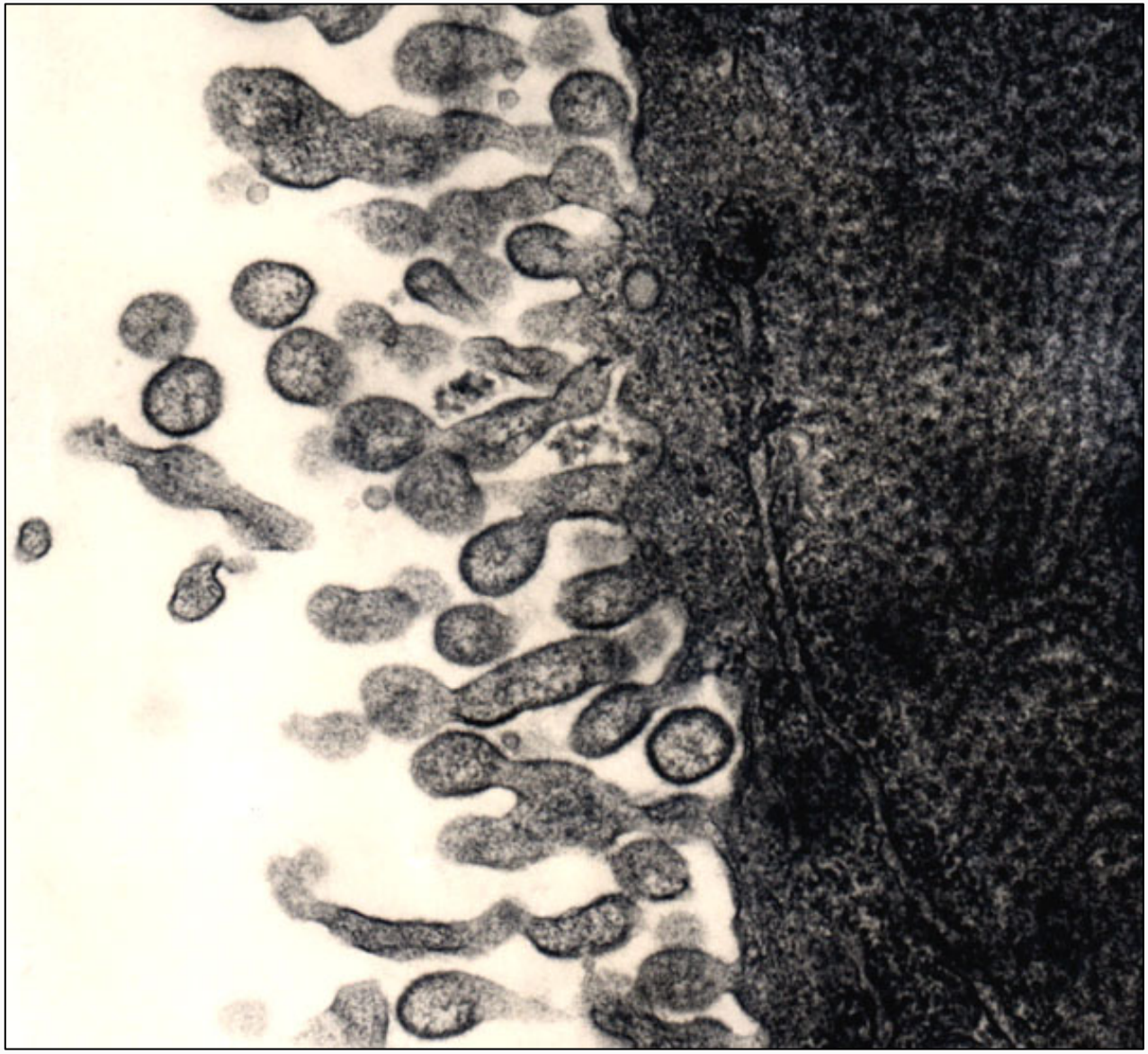
Section A

Background

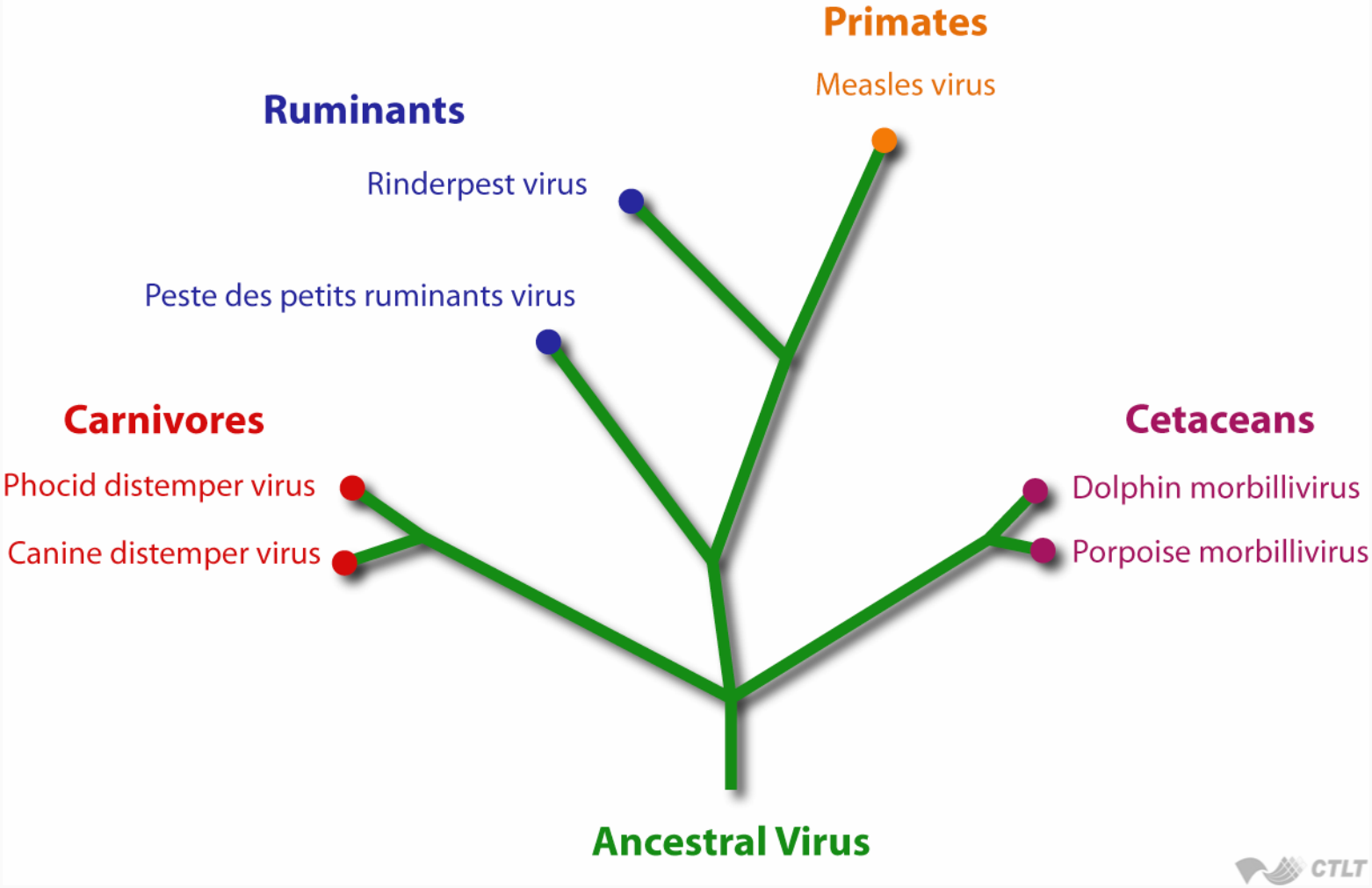
Measles Virus

- 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

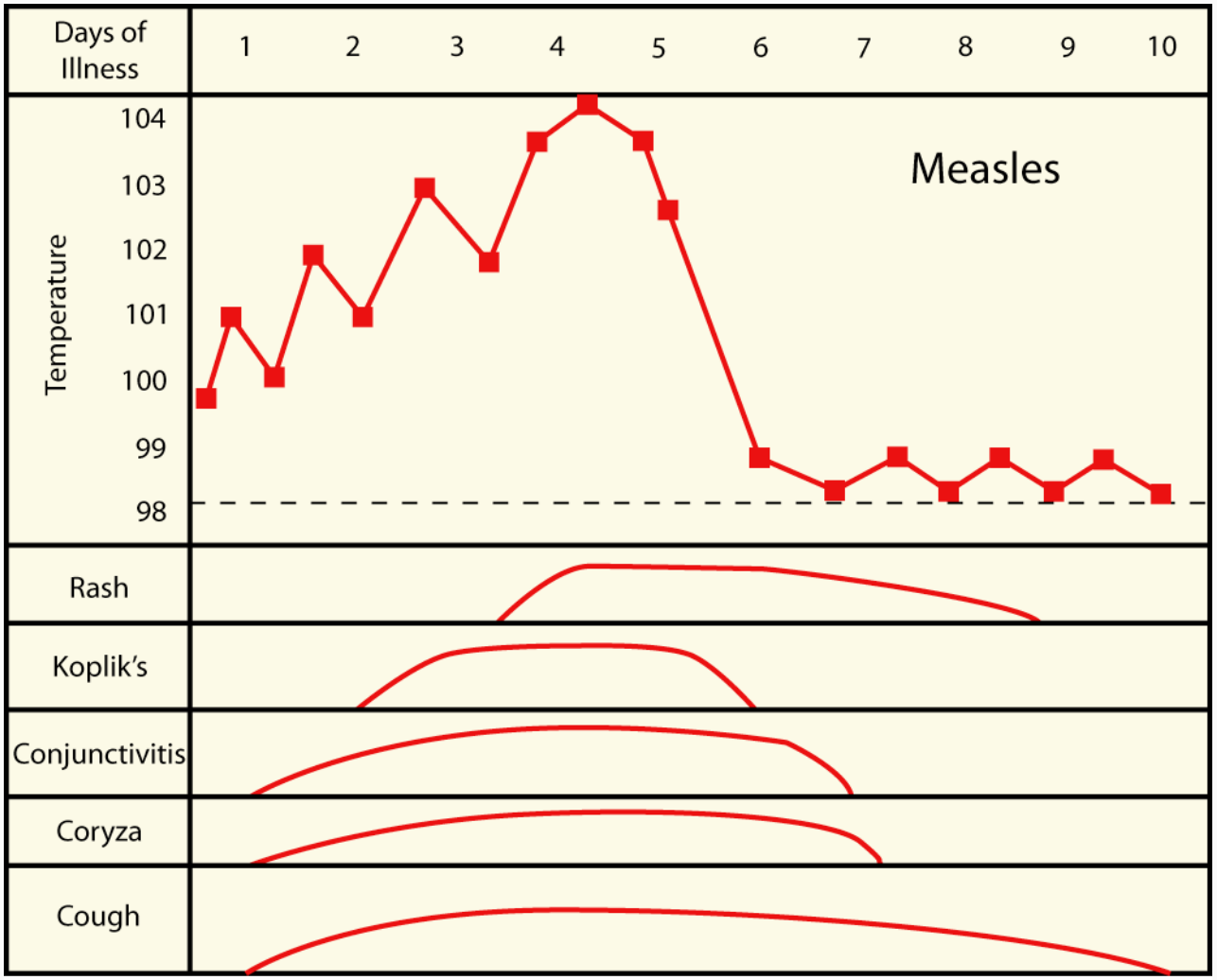
Measles Virus Budding from Cell



Phylogenetic Tree



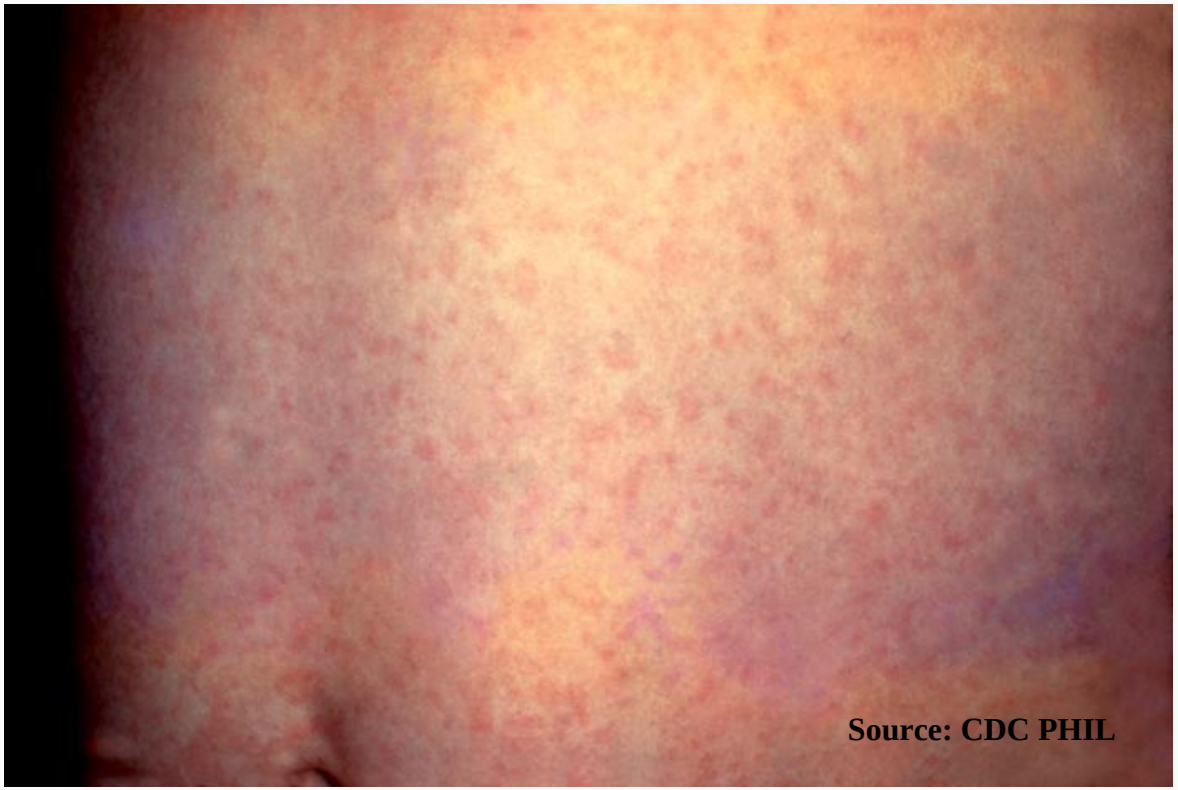
Clinical Features of Measles



Source: *Infectious Diseases of Children*, 9th Edition, Figure 13-1, page 224.
Krugman S, Katz SL, Gershon AA, Wilfert CM, eds. St. Louis: Mosby, 1992.

Source: adapted by CTLT from Krugman, S., Katz, S. L., Gershon, A. A., and Wilfert, C. M. (Eds.). (1992). *Infectious diseases of children* (9th ed.) St. Louis: Mosby.

Measles Rash



Measles Conjunctivitis and Coryza

Complications of Measles Virus

Equivalent of the rash on other epithelial surfaces produced:

- Conjuctivitis
- Sore mouth
- Laryngitis
- Bronchopneumonia
- Enteritis, diarrhea

The possible association between the severity of measles rash and the manifestation of the disease in epithelial surfaces

External rash:

Normal rash develops

▼

Rash darkens to a deep red and violet color

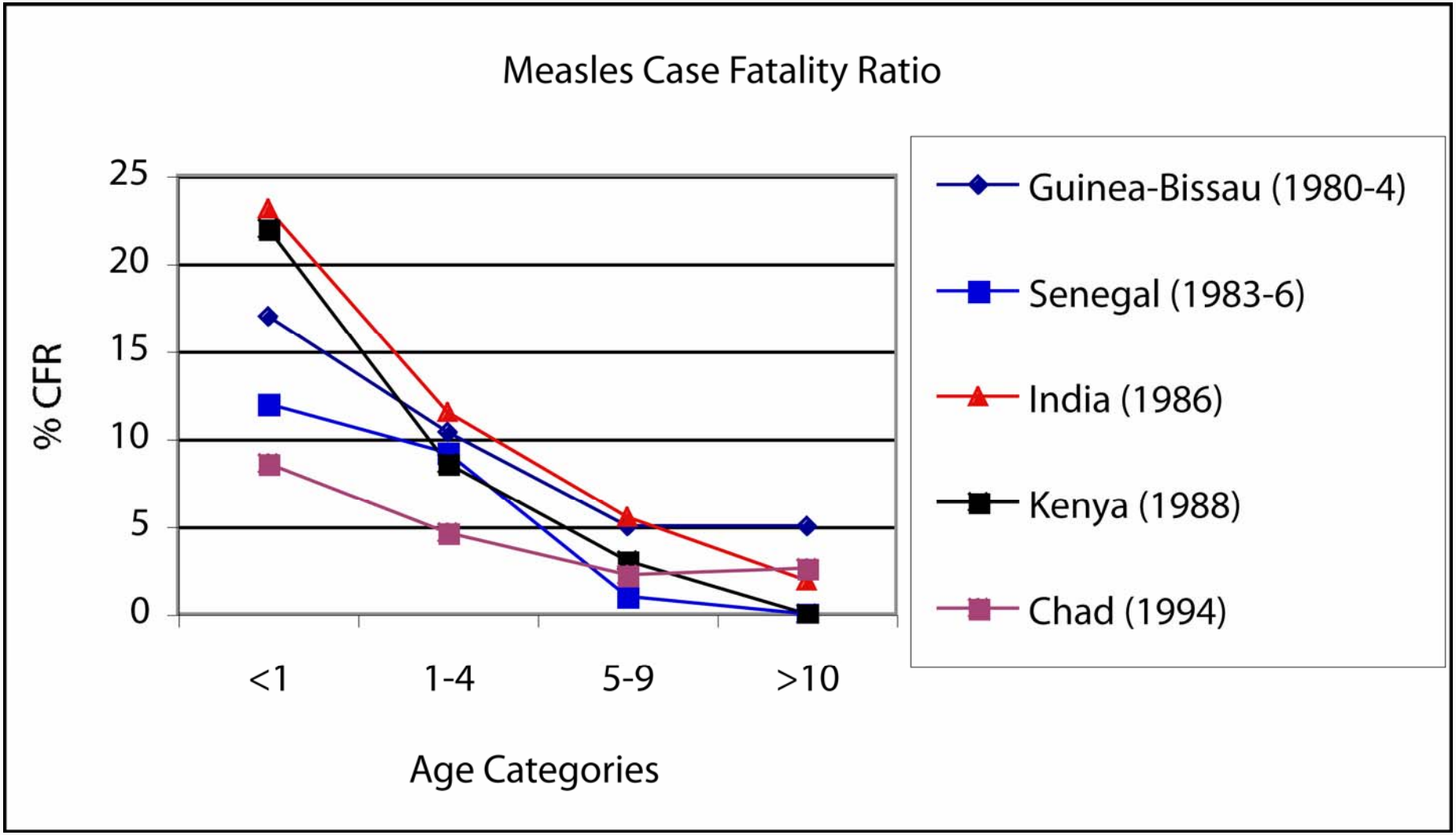
▼

Desquamation (amount depends on the extent of the rash's darkening)

Example of Desquamating Rash

Photo Source: William Moss

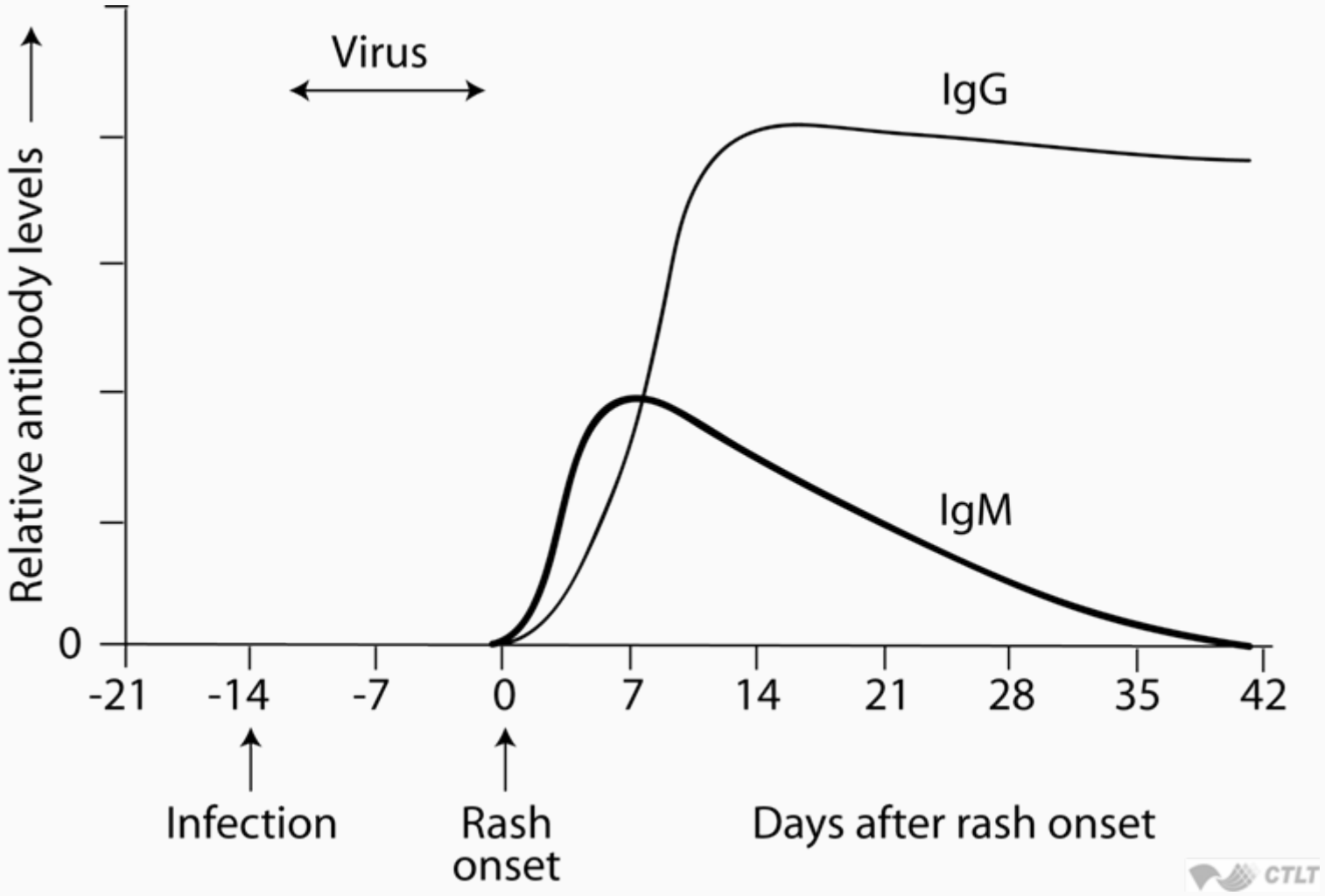
Measles Case Fatality Ratio



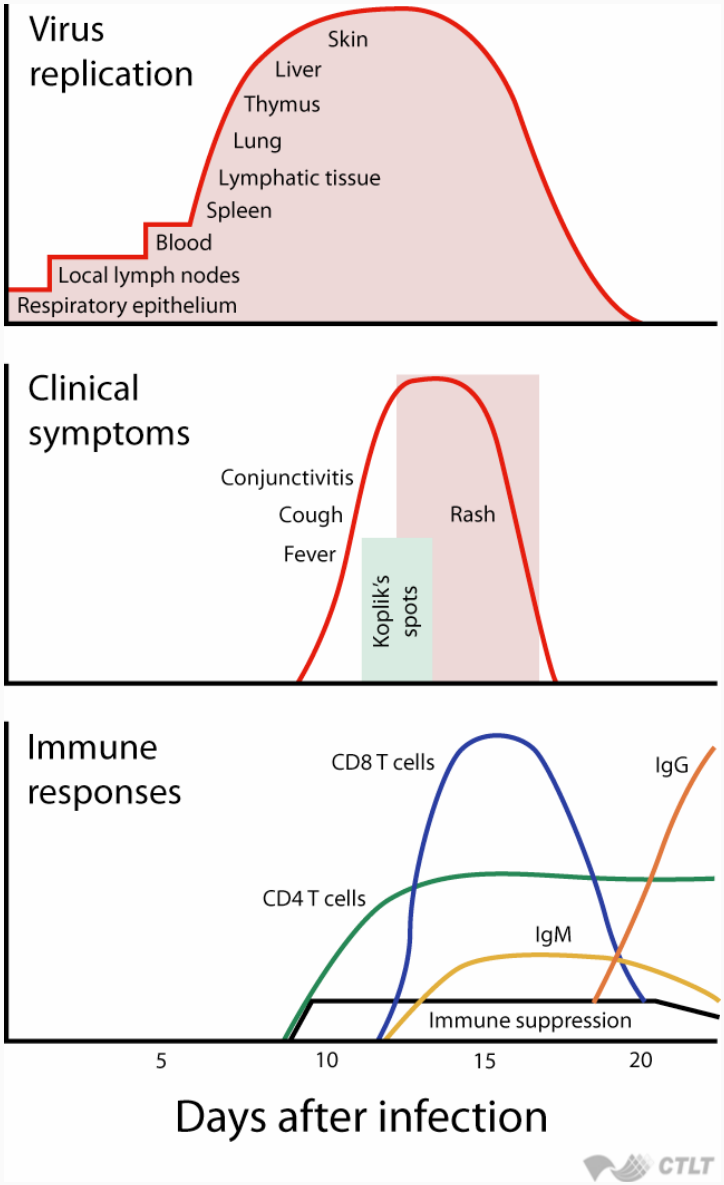
Immune Responses

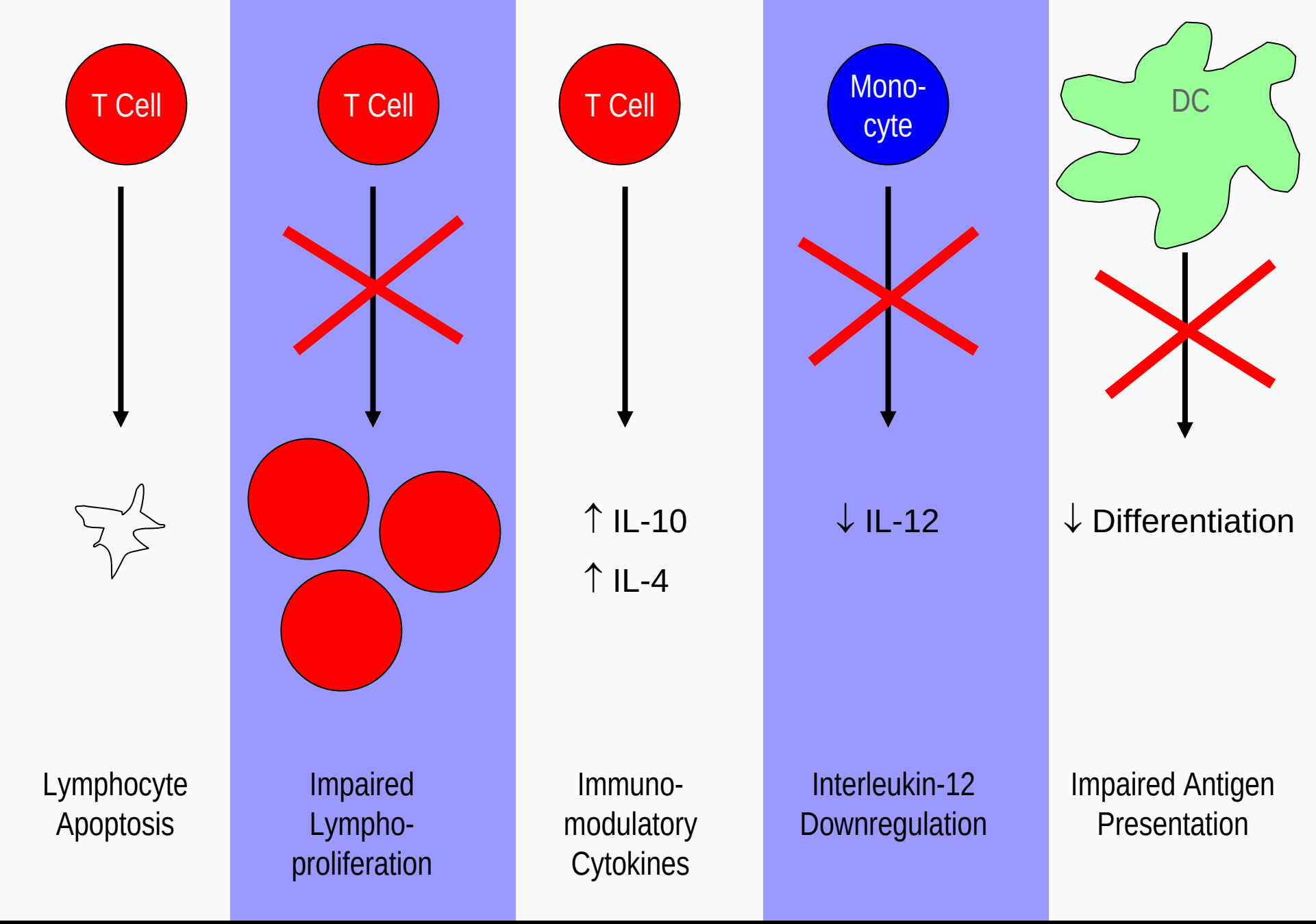
- Life-long immunologic protection
- Antibody responses
  - IgM
  - IgG
- Cellular immune responses
- Immune suppression

Antibody Response to Acute Measles Infection



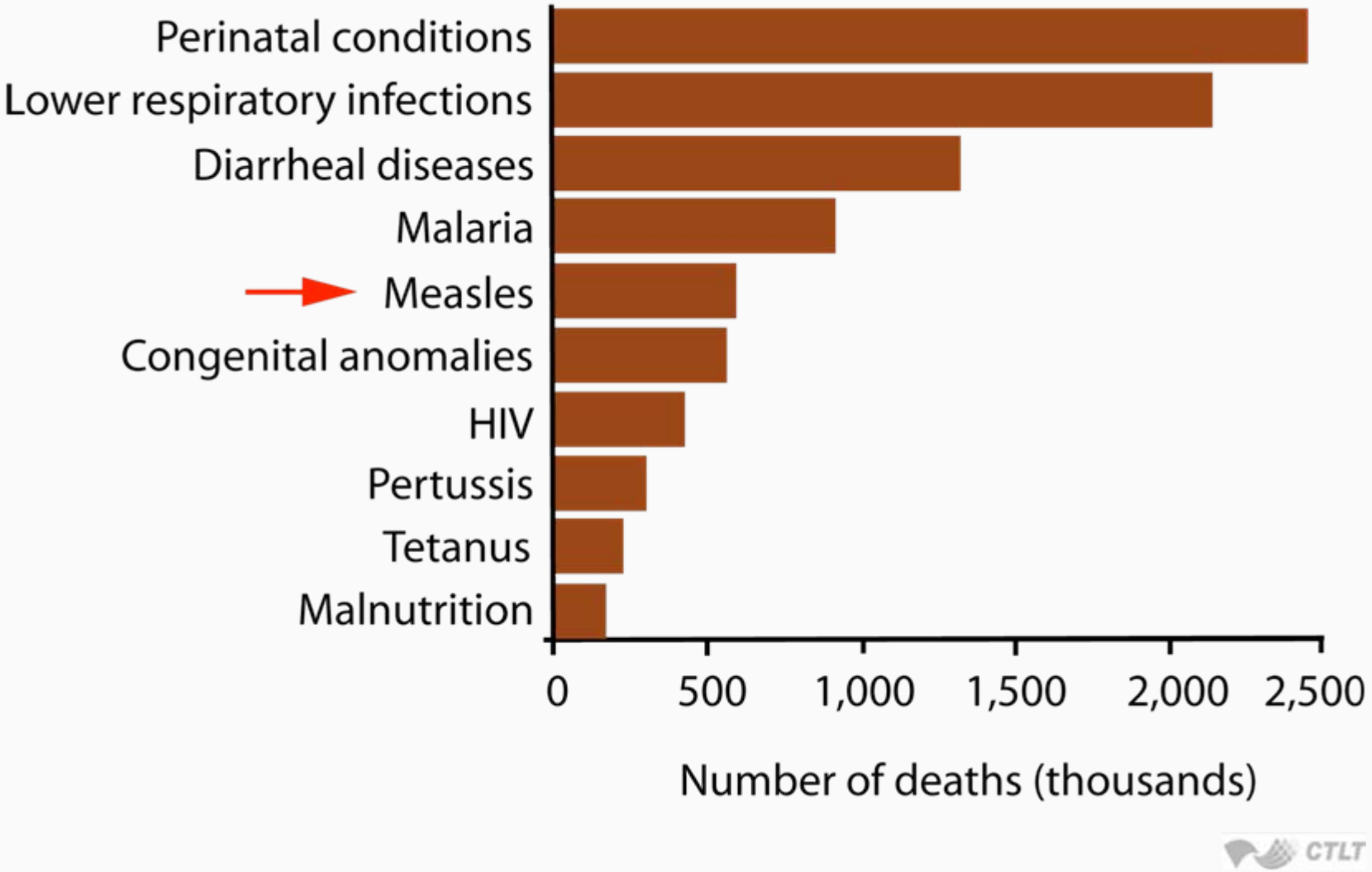
Clinical, Virologic, and Immunologic Characteristics





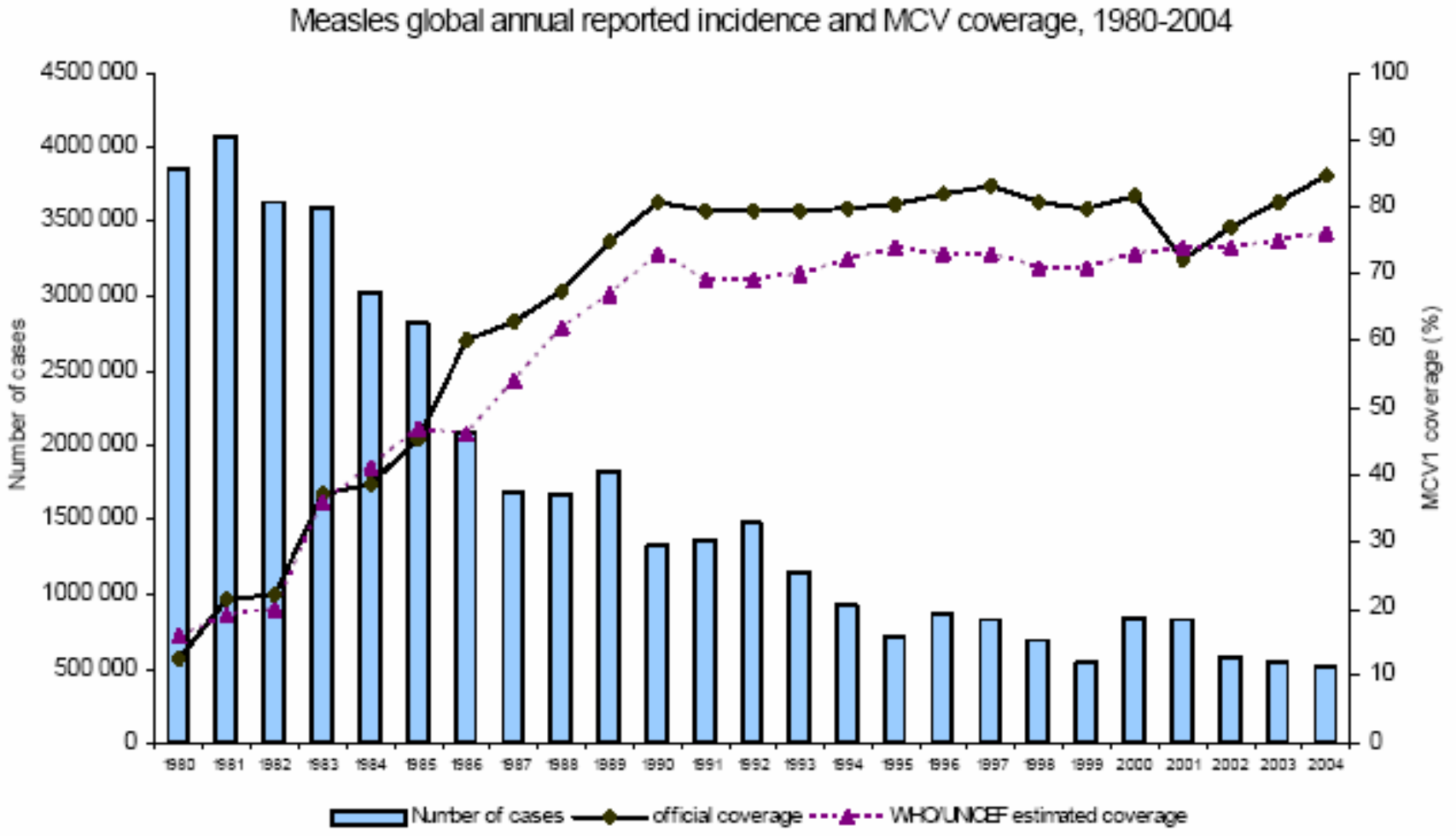
Source: Moss, W. J., Ota, M. O., and Griffin, D. E. (August 2004). Measles: Immune suppression and immune response. *Int J Biochem Biol,* 36, 8, 1380–1385.

Top 10 Causes of Death in Under Fives Worldwide, 2000



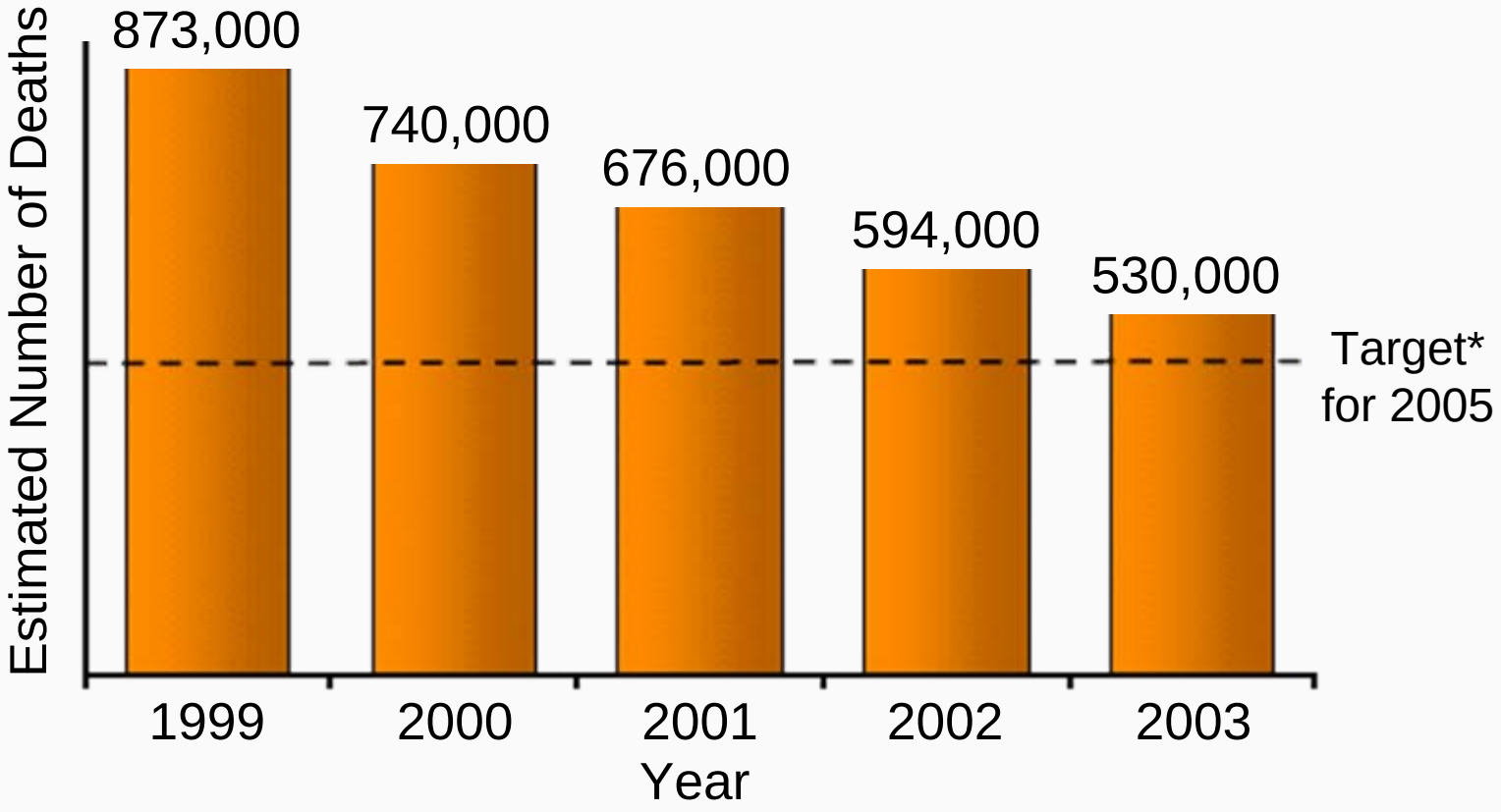
Source: WHO Global Burden of Diseases 2000

Measles Cases Have Declined



Source: WHO vaccine-preventable disease monitoring system, 2005 global summary

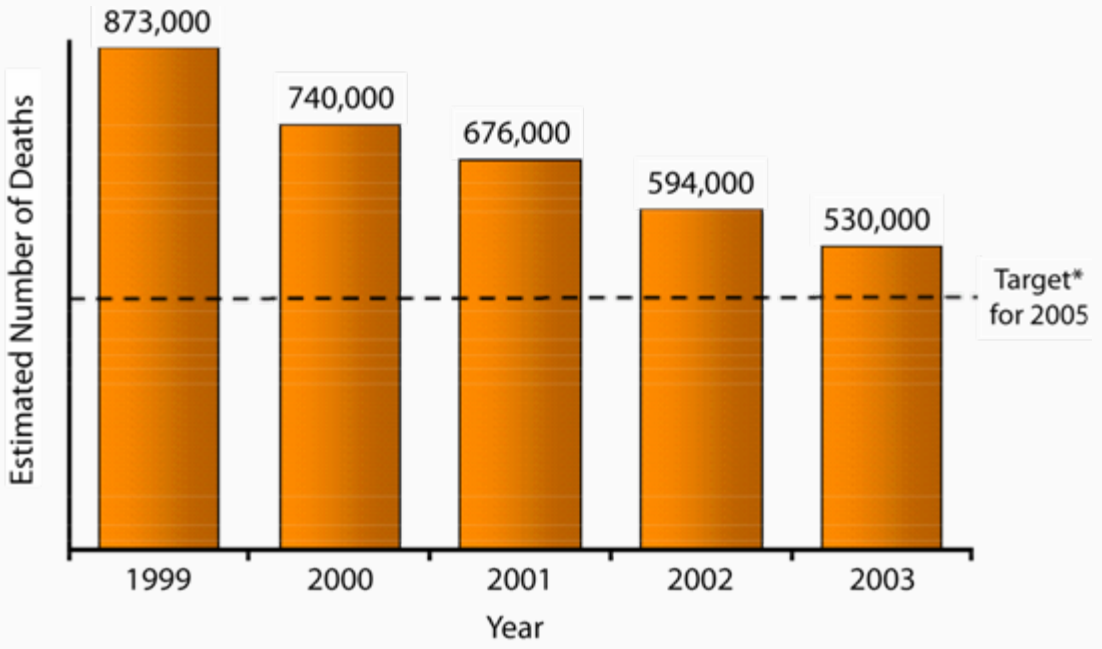
Estimated Worldwide Measles-Related Deaths

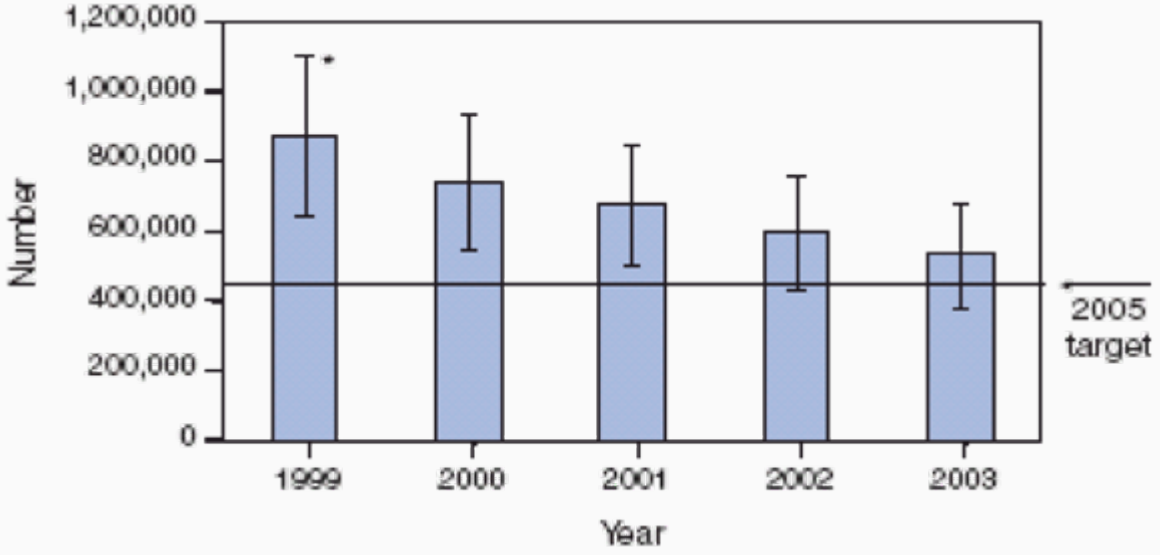


*In 2002 the World Health Assembly urged member countries to halve measles death by 2005, compared with 1999 estimates.

Adapted by CTLT from: (2005). *Weekly Epidemiological Record,* 80, 80.

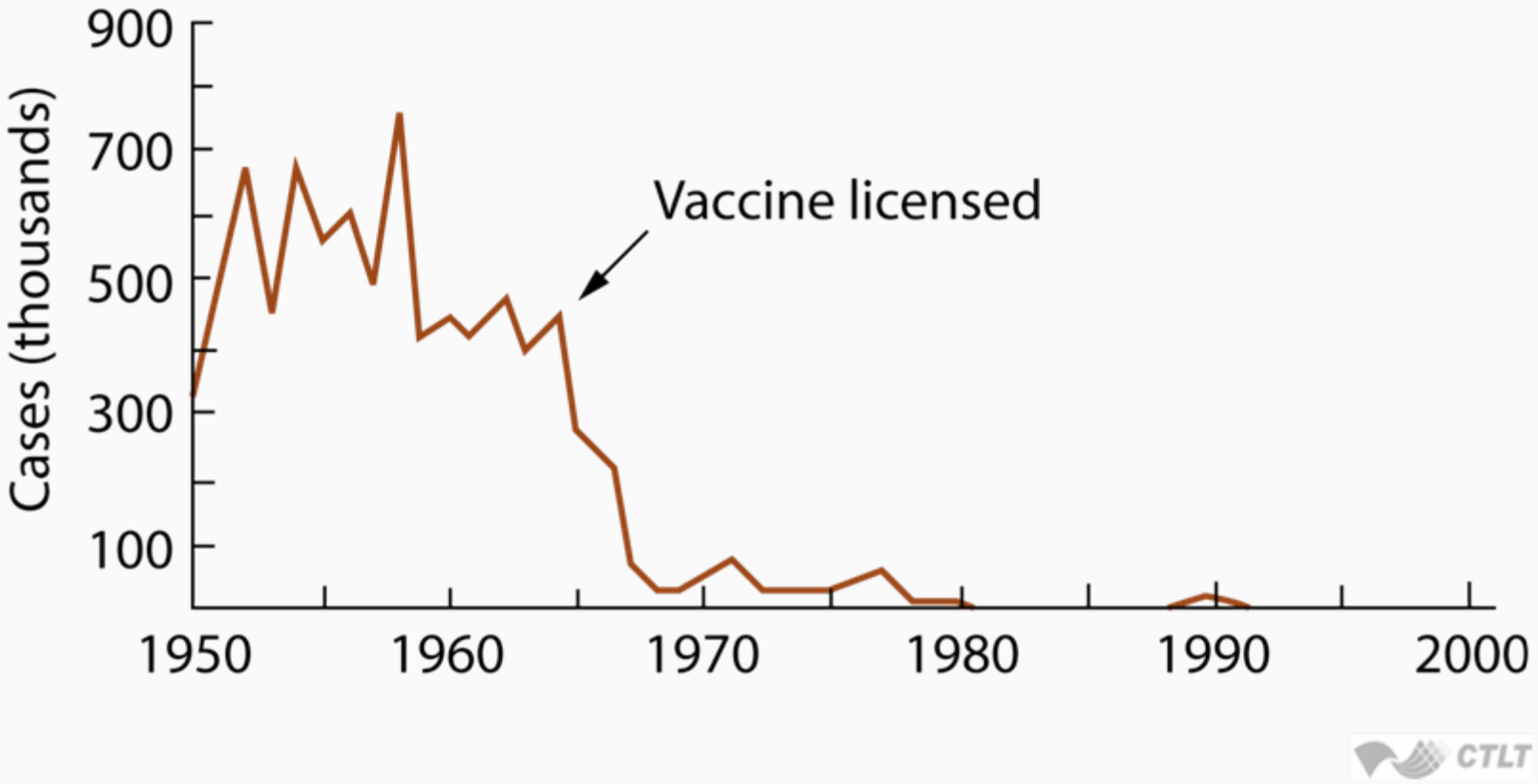
Counting Cases of Disease





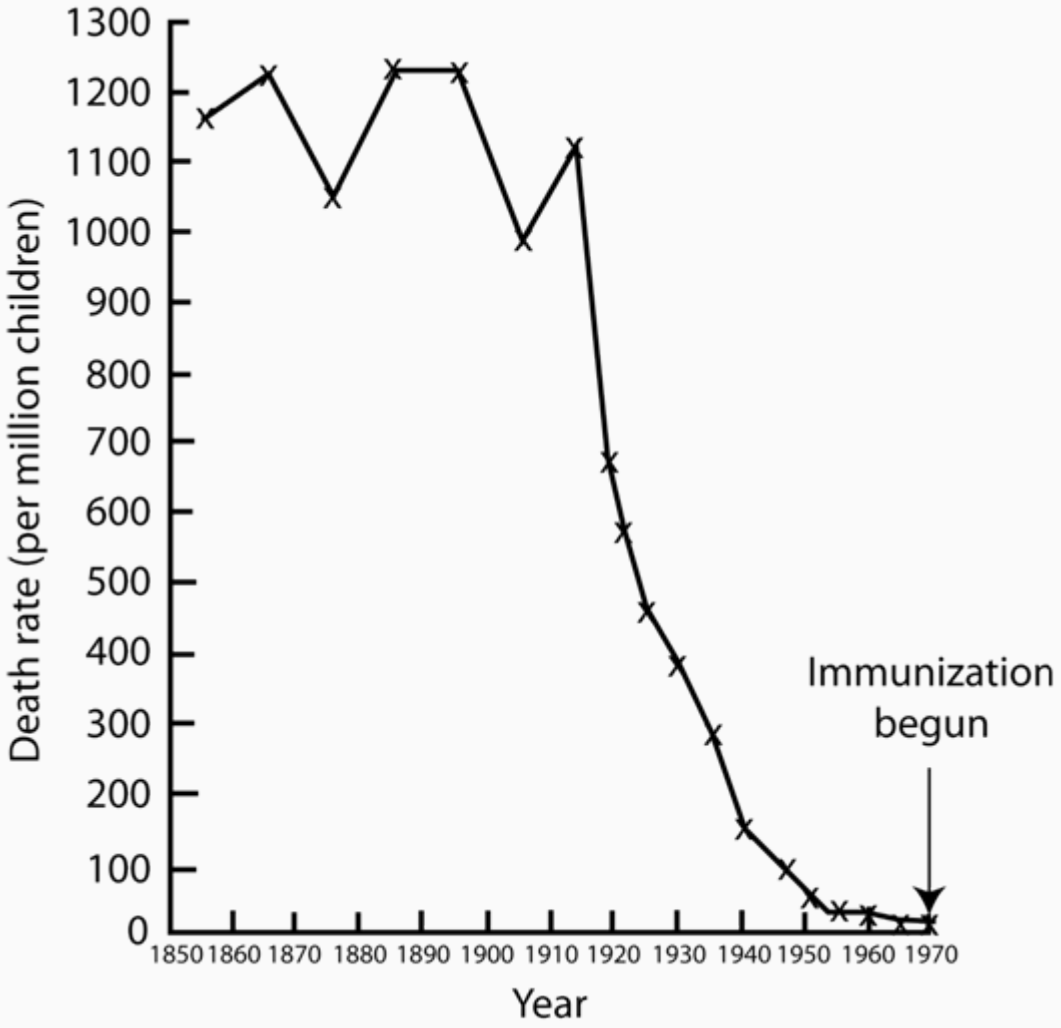
What Is the Message?

- Measles in the United States, 1950–2001

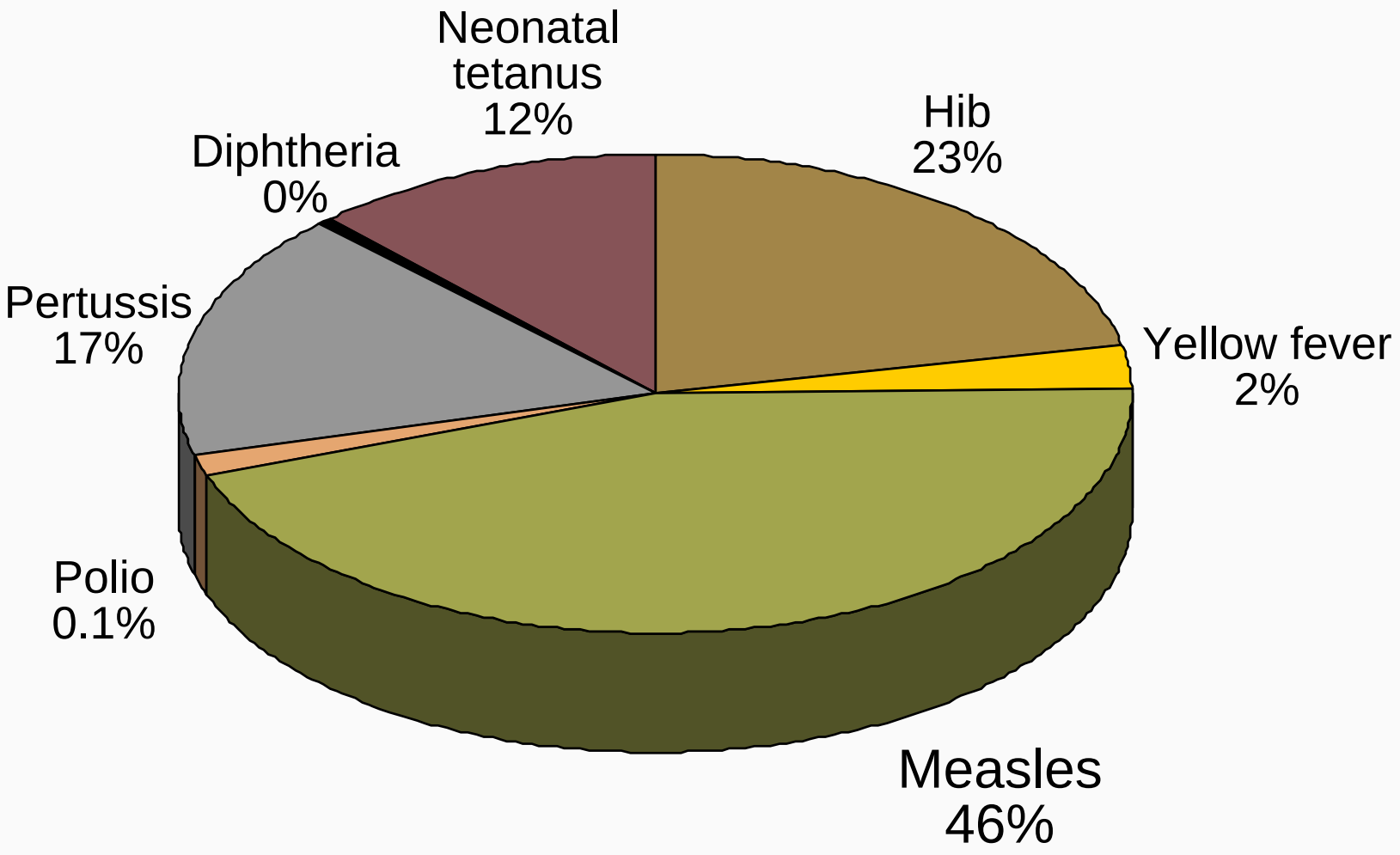


Source: CDC

What Is the Message?



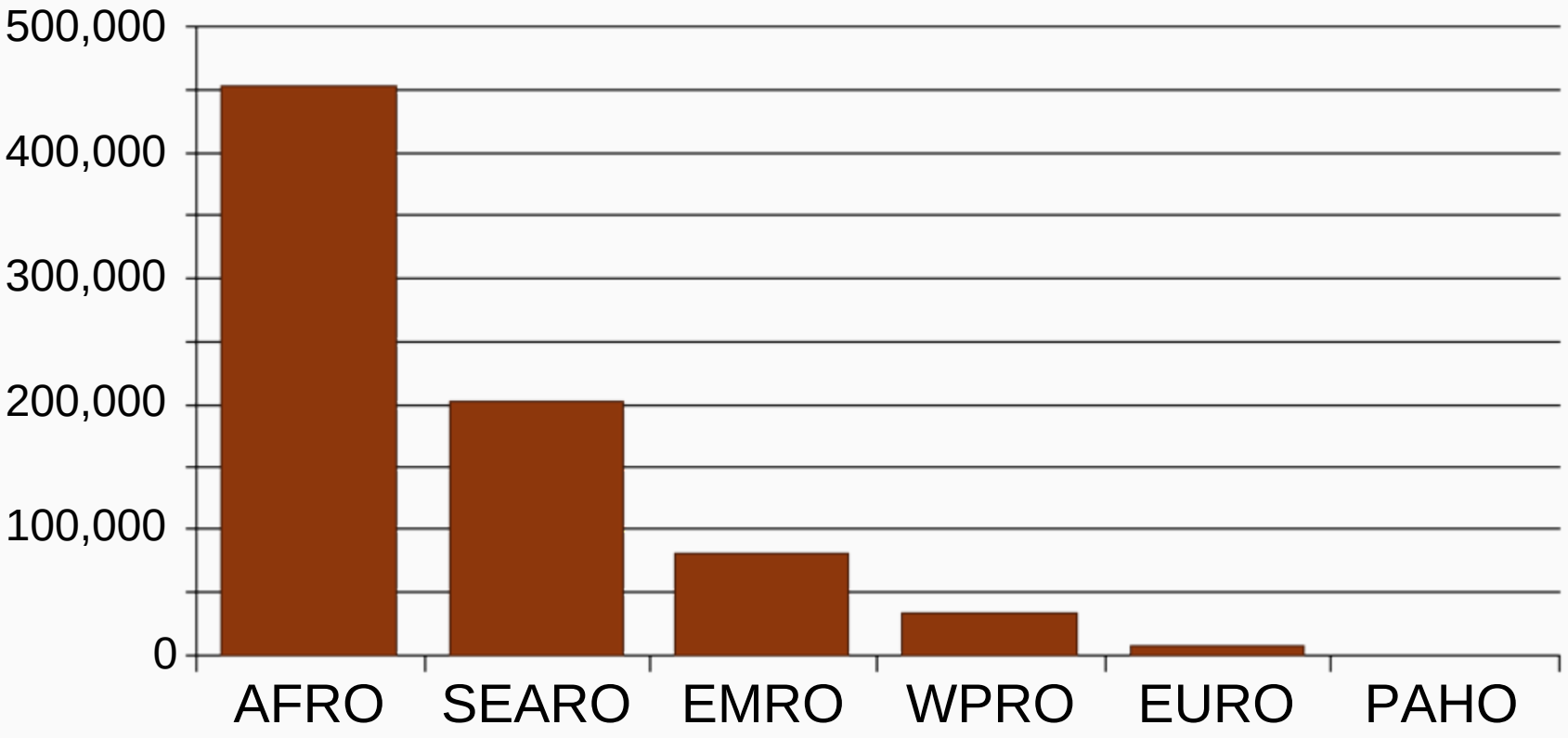
Measles: Leading Vaccine-Preventable Cause of Death



Data Source: (2003). *Journal of Infectious Diseases, 187*(Suppl. 1), S15–S21.

Most Measles Deaths Occur in Sub-Saharan Africa

- Estimated measles deaths by WHO region, 2000



Source: (2003). *The Weekly Epidemiological Record,* 21, 184–187.

JOHNS HOPKINS
BLOOMBERG
SCHOOL of PUBLIC HEALTH

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

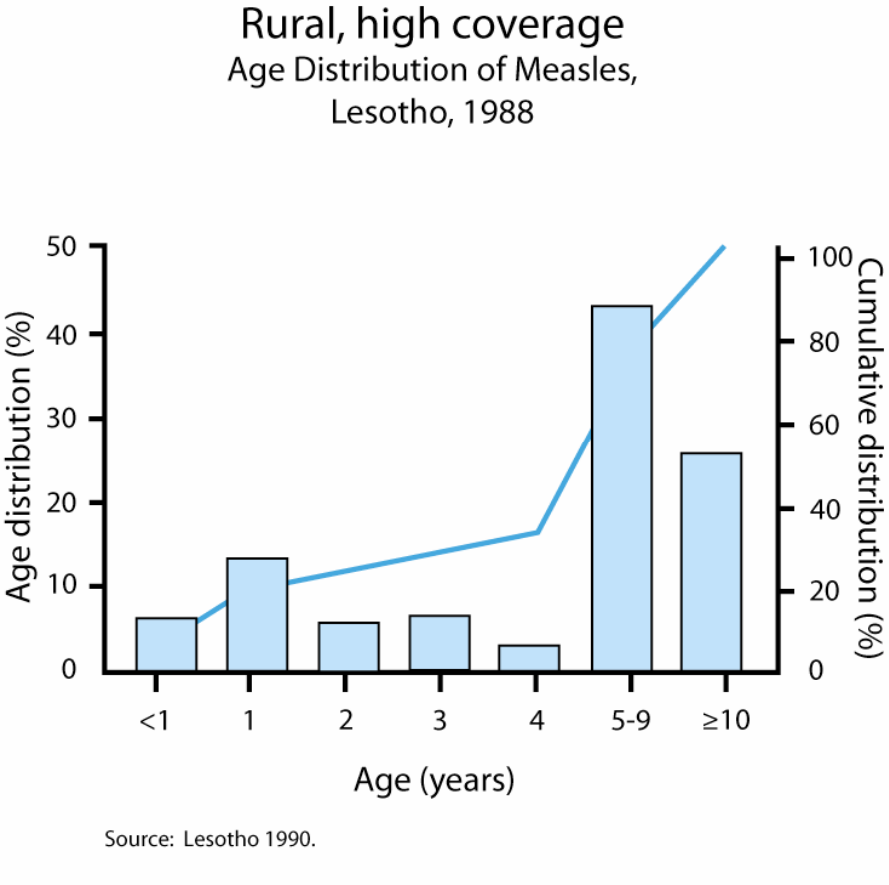
Disease Distribution

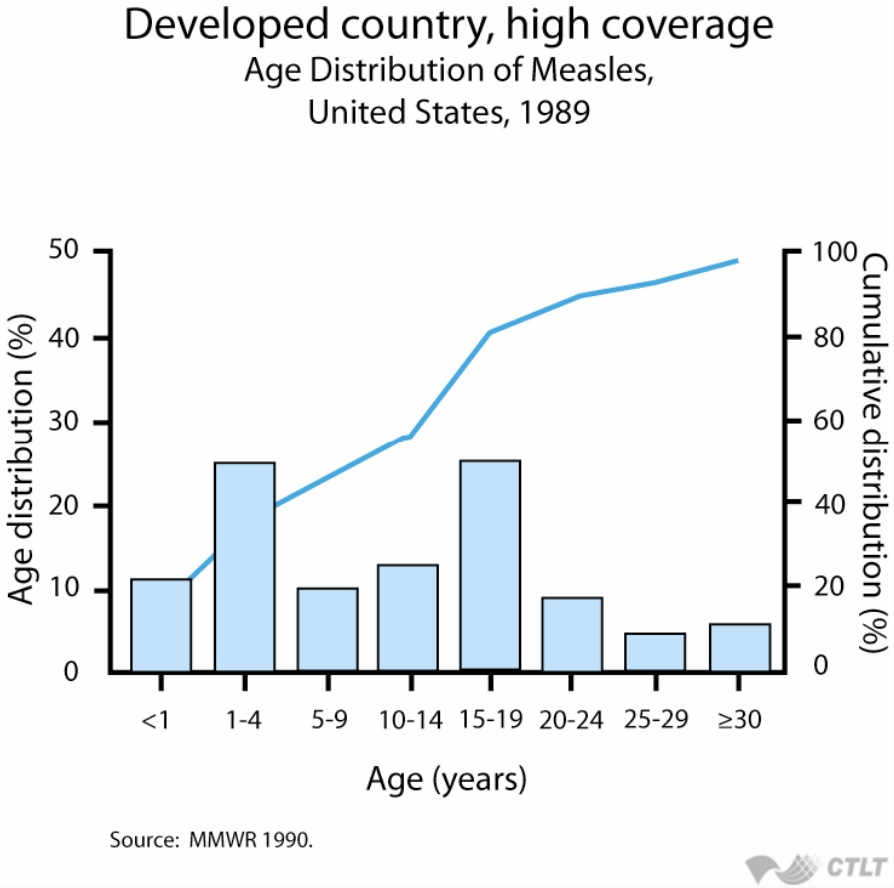
- Person
  - Age distribution
- Place
  - Population density to maintain transmission
  - Urban vs. rural
- Time
  - Seasonality
  - Epidemic cycles

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



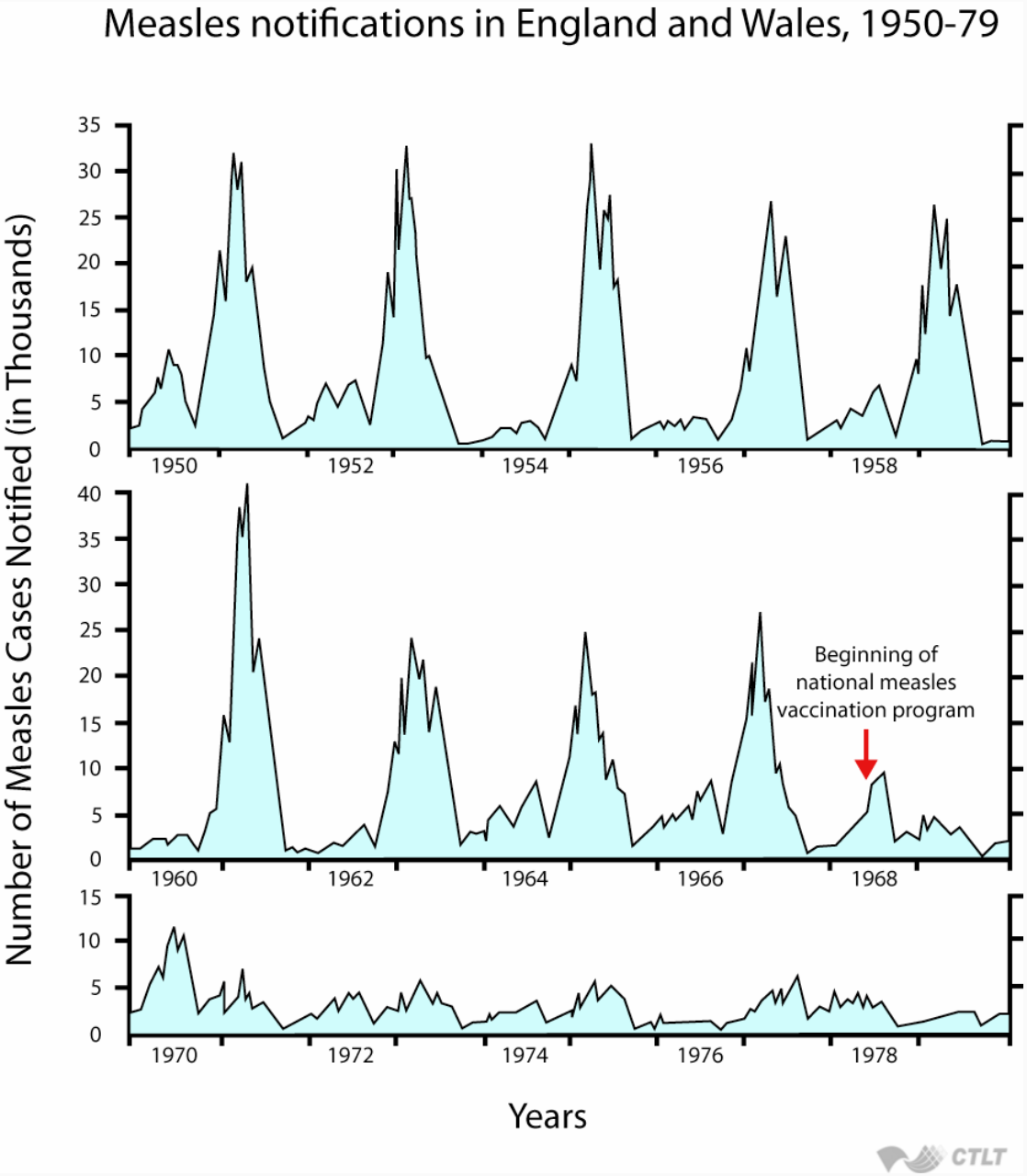


Source: adapted by CTLT from Taylor et al. (1988); Koster et al. (1981).

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



JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

Section C

Measles Control and Elimination

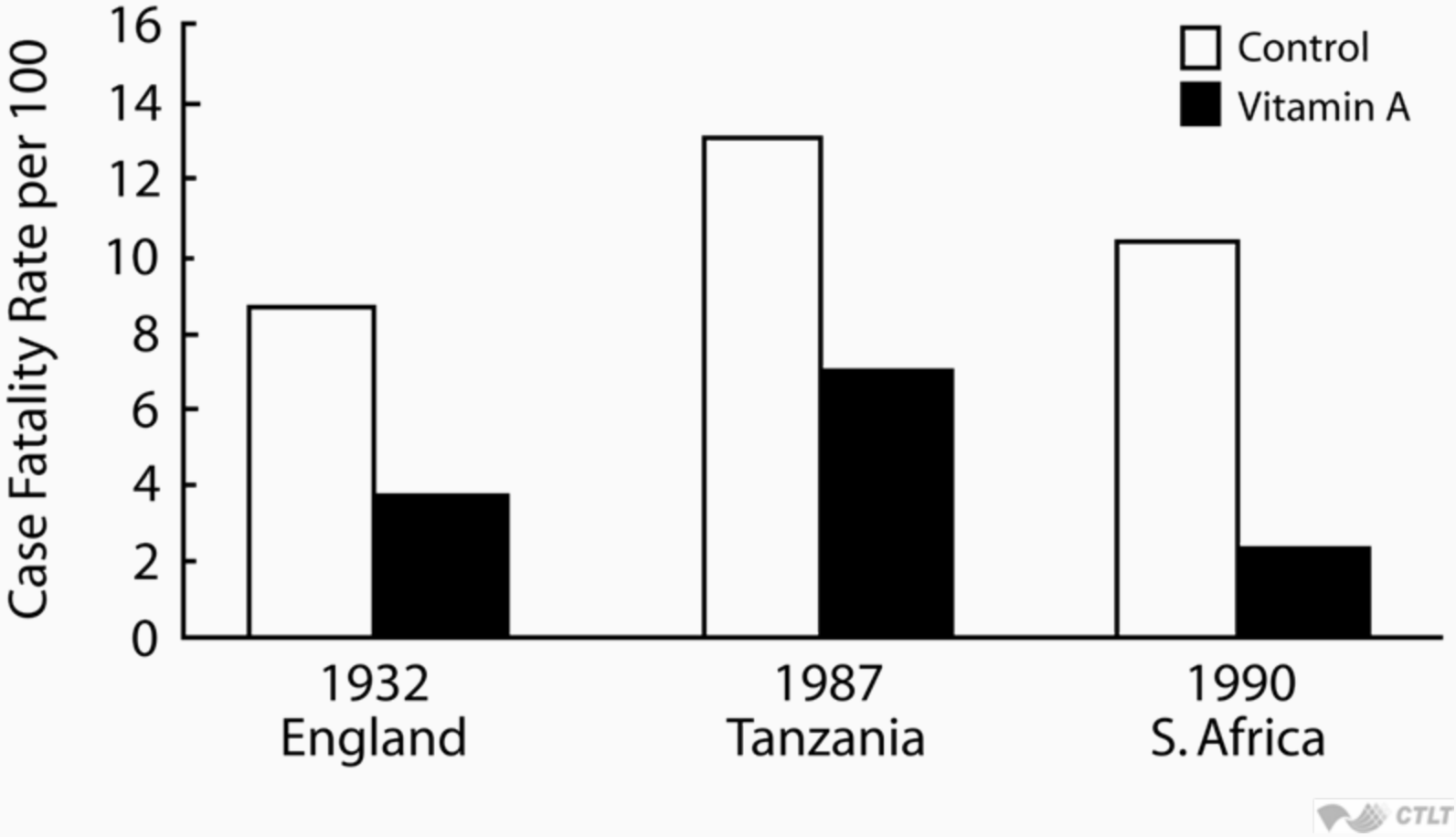
Control Strategies

- 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

Vitamin A and Measles Mortality



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

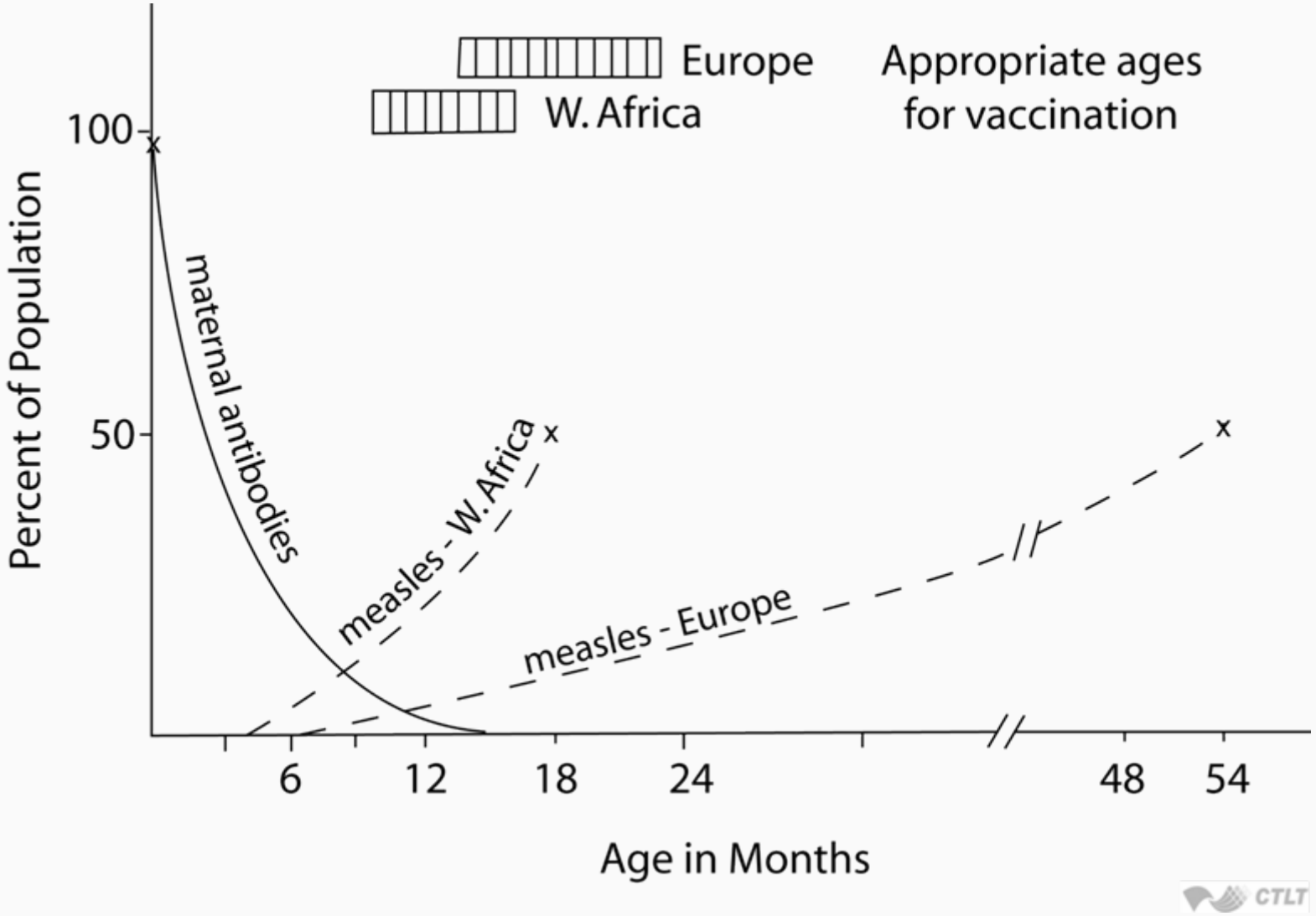
Immune Protection

- 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



Vaccination Strategies

"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

Age	Vaccines
Birth	BCG, OPV 0, HB 1
6 weeks	DTP 1, OPV 1, HB 2
10 weeks	DTP 2, OPV 2
14 weeks	DTP 3, OPV 3, HB 3
9 months	**Measles,** yellow fever

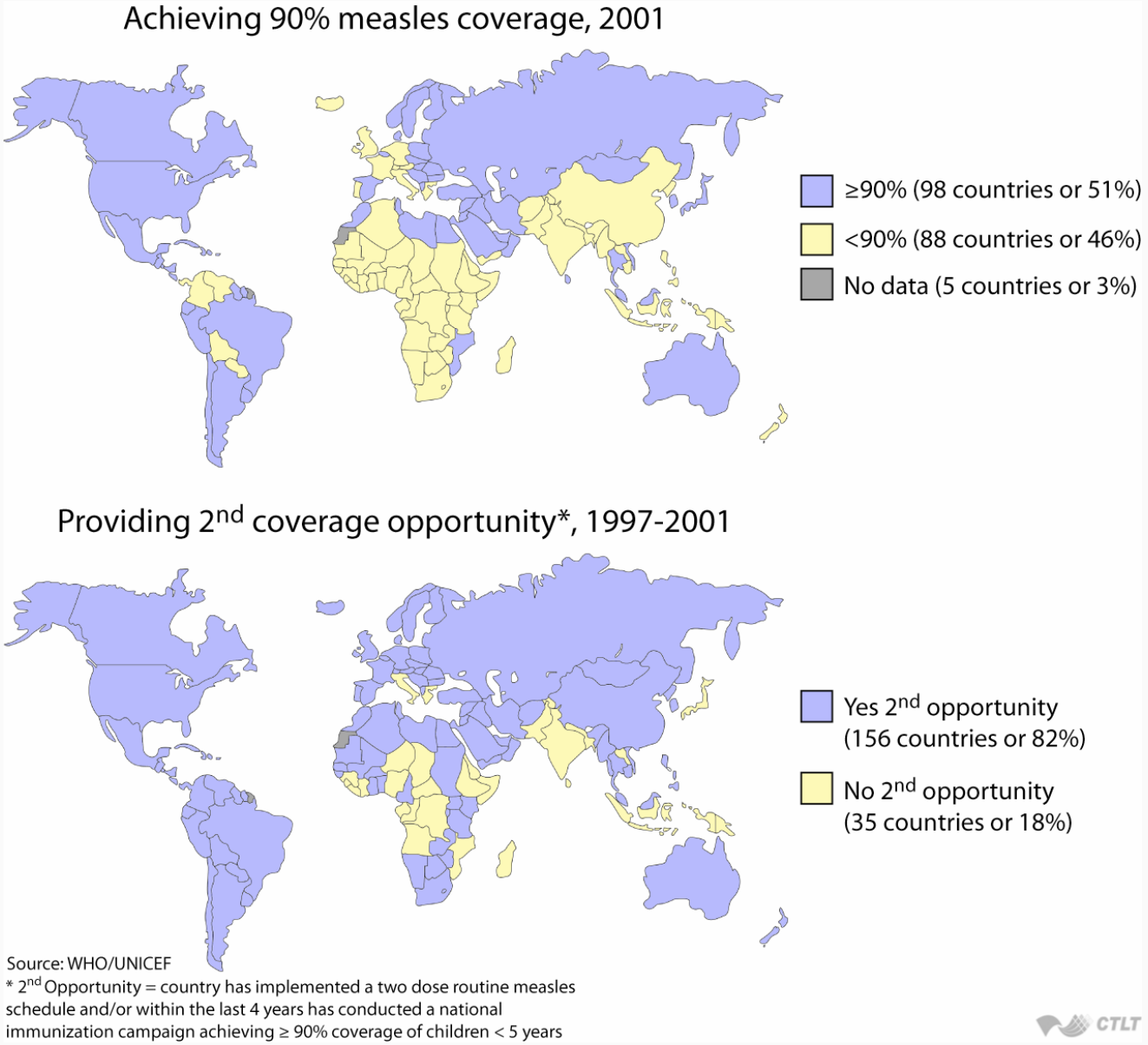
Population Immunity—One Dose

Percent Coverage	Percent Vaccine Efficacy	Percent Immune
80	95	76
90	95	86
95	95	90
95	90	86
95	80	81

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



Population Immunity—Two Doses

Coverage	85% 1st dose	95% 2nd dose	95% 2nd dose
85%	72%	83%	95%
90%	77%	88%	97%
95%	81%	93%	98%
100%	85%	98%	99%

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

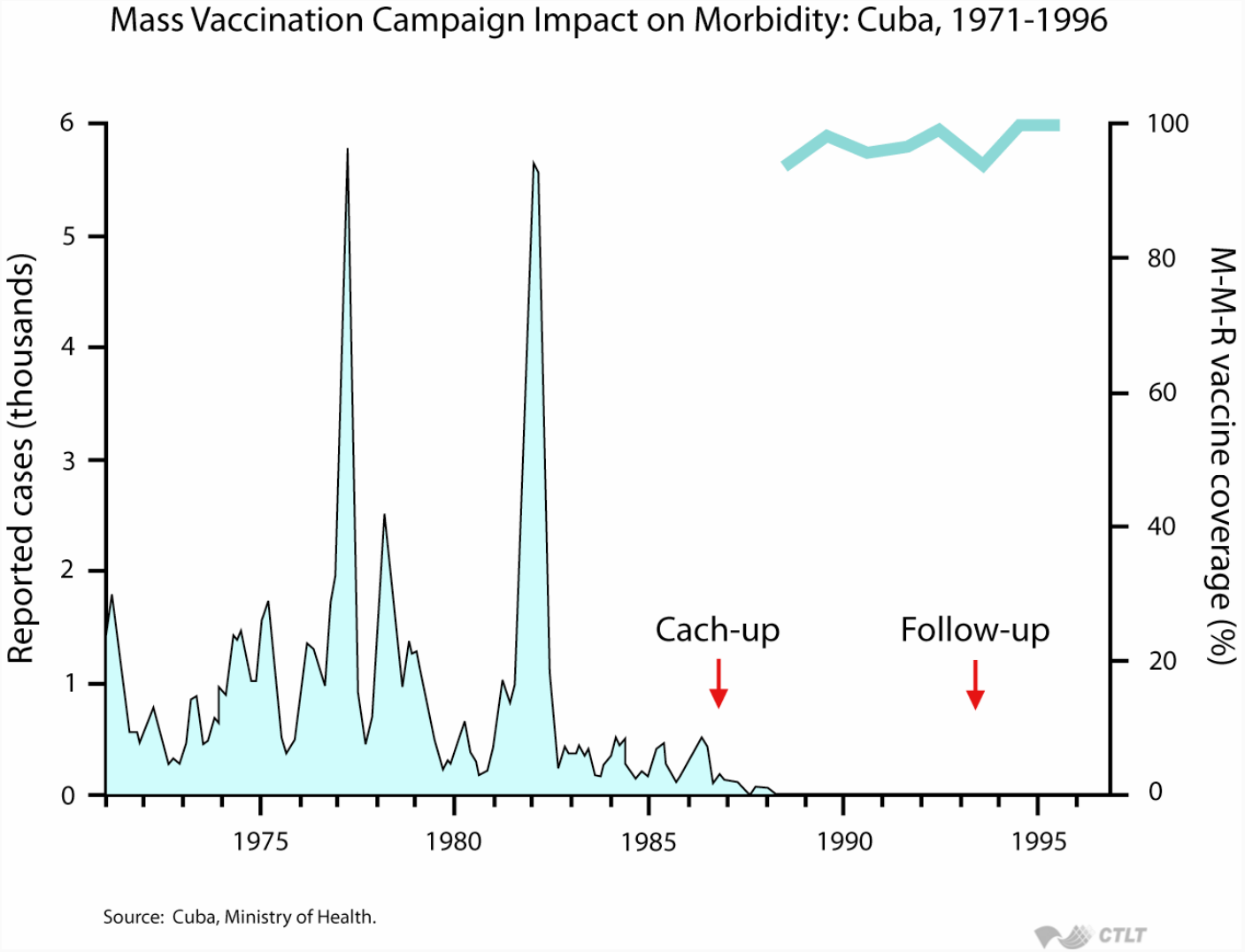
Follow Up

- 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

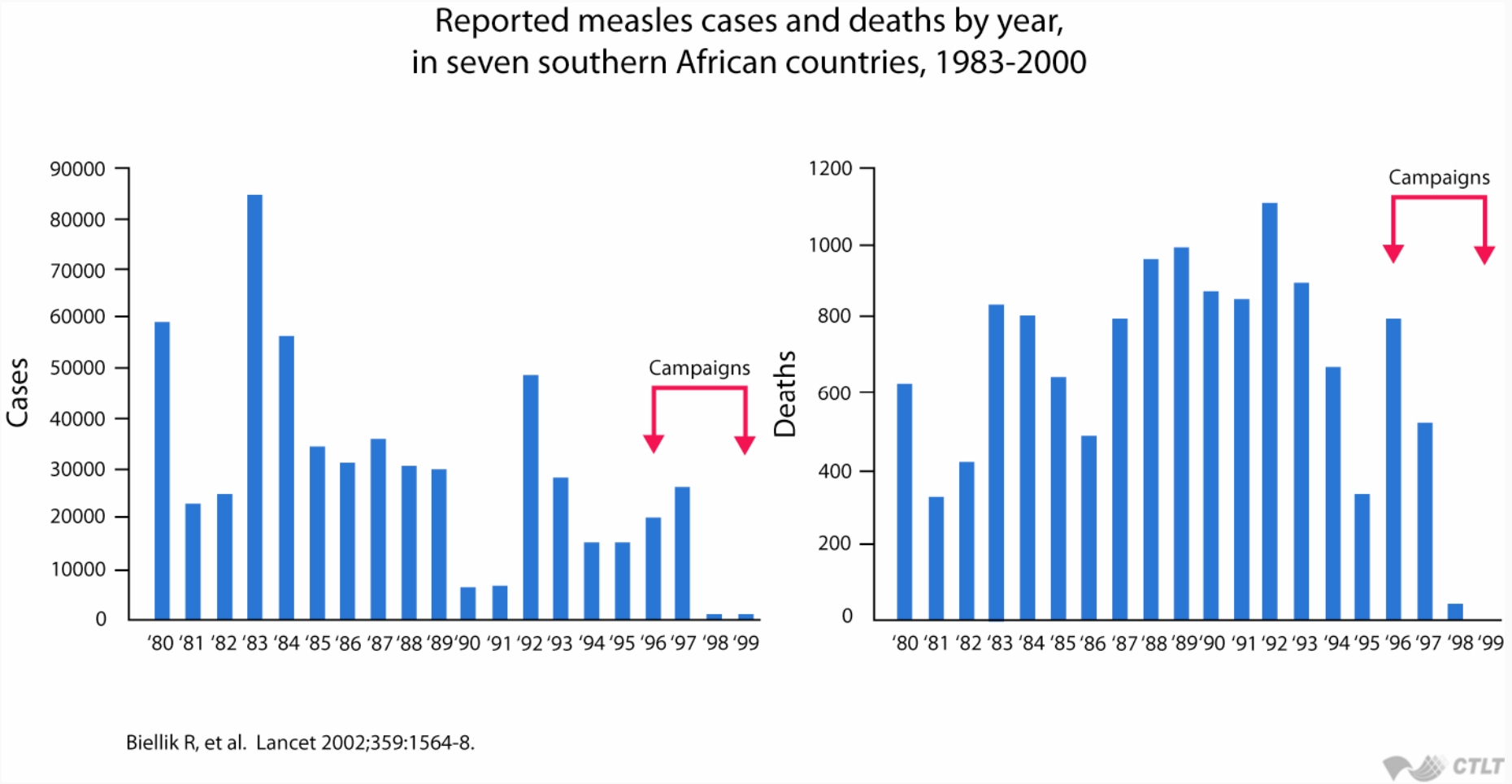
- Goal: intensive vaccination efforts to reach unvaccinated children
- Target wide age range
- Target high-risk areas
  - Low coverage
  - Recent measles cases
  - Poor surveillance
  - Crowding, poverty, and migration

Mass Vaccination and Morbidity in Cuba, 1971–1996



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

Measles in Southern Africa, 1996–2000



Source: Biellik, R. (2002). *Lancet, 359,* 1564–1568.

Photo source: William Moss.

Measles Surveillance in Southern Africa, 2000

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

*Zero deaths

Notes Available

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

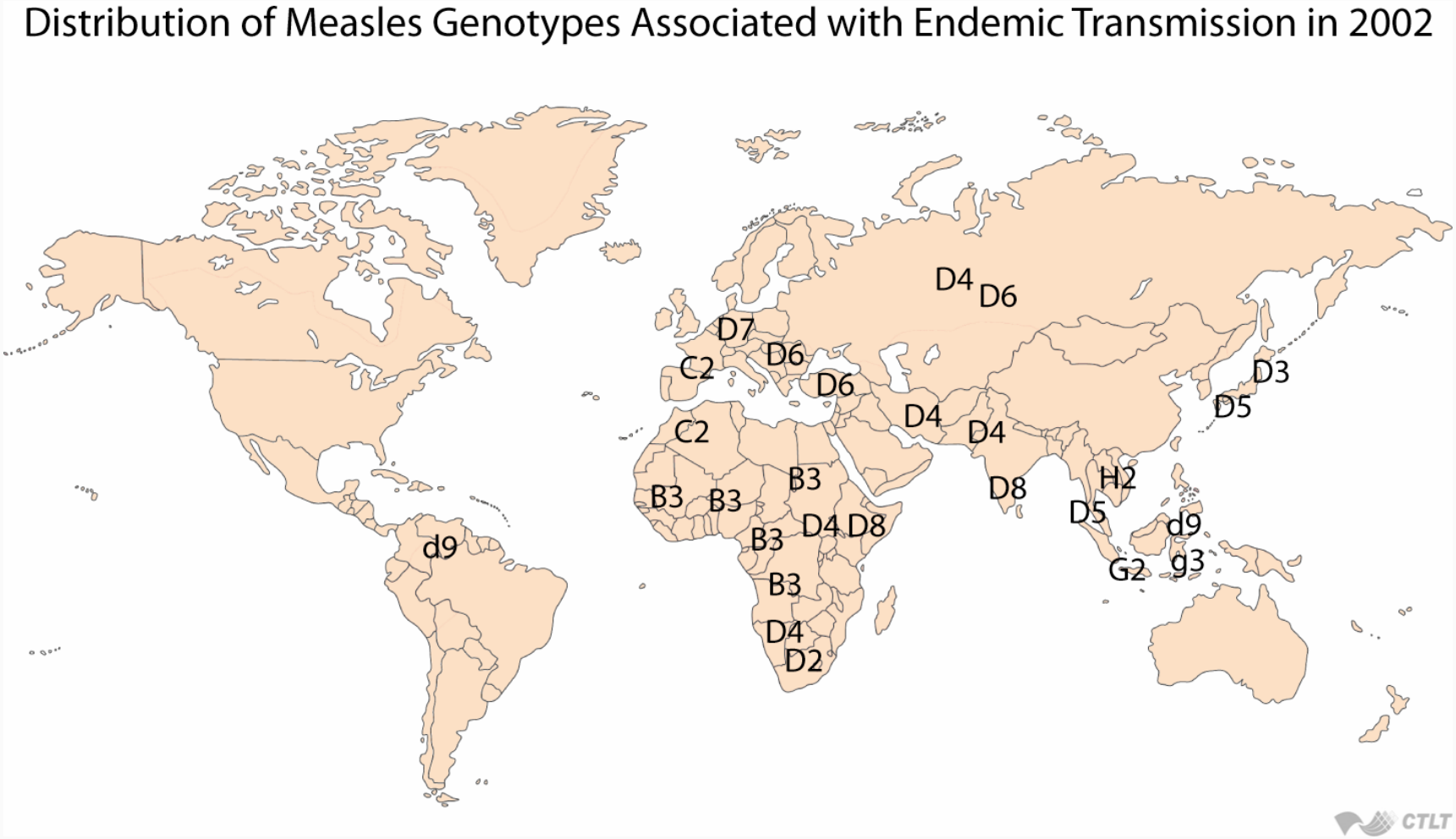
Section D

Molecular Epidemiology and Obstacles to Measles Control

Molecular Epidemiology

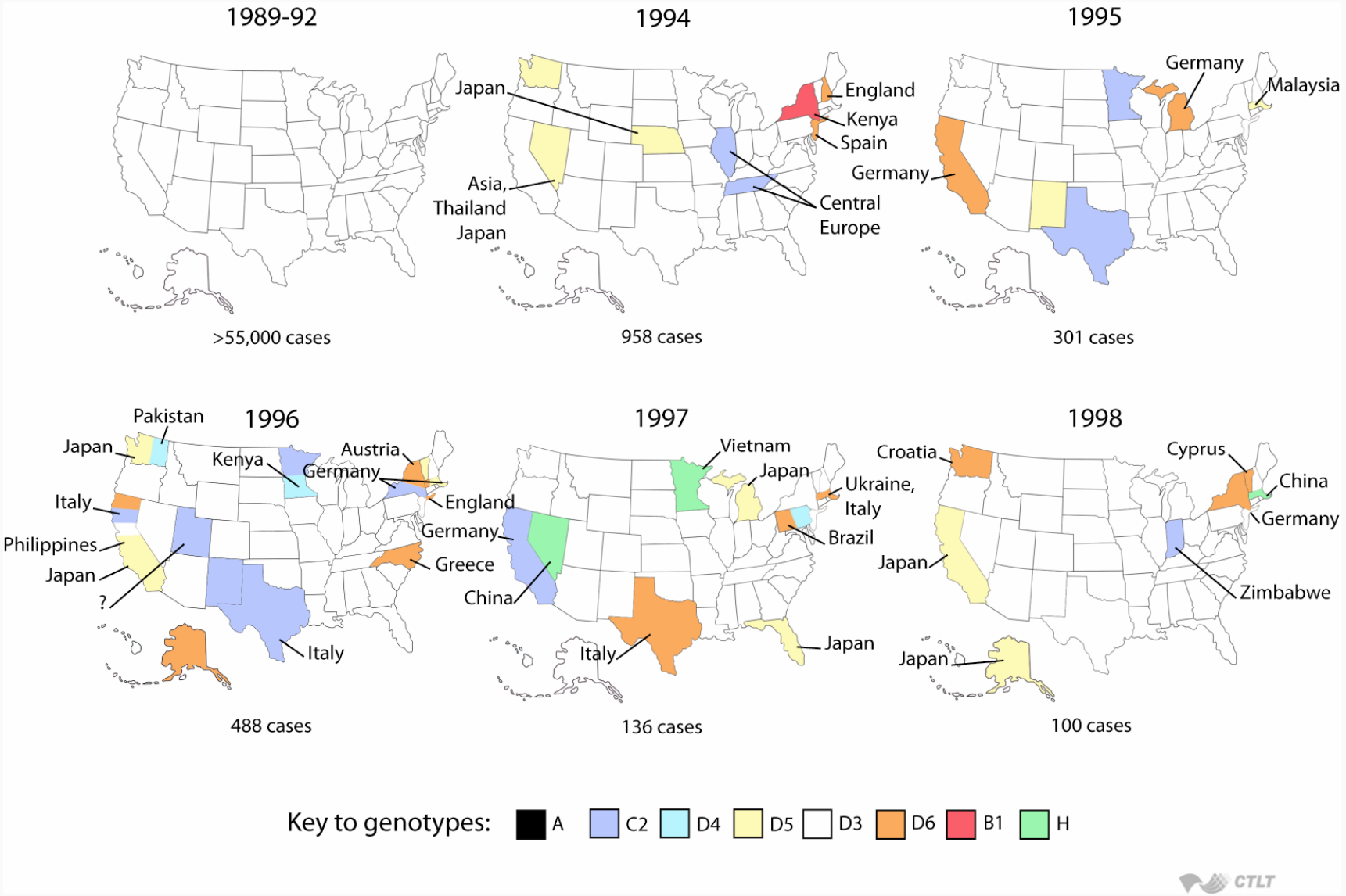
- Based on most variable region of genome
  - 450 nucleotides coding for COOH region of N
- Virus isolation or RT-PCR
- Taxonomy
  - 8 clades (A–H)
  - 21 genotypes (e.g., D1, D2, D3)
- Identify source and transmission pathways
- Document interruption of transmission and importation

Measles Virus Genotypes



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.



The Obstacle to Measles Control and Elimination . . .

. . . 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: $R_0 = 5–7$ $H = 80\text{-}85\%$
- . . . 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

Stratum	Costs of vaccine and injection safety equipment	Operational costs, supplemental immunization	Operational costs, surveillance and laboratory	Total
Countries in the mortality reduction stage	210	441	37	688
Selected countries in the elimination stage	91	189	16	296
Total	301	630	53	984

Can measles be eradicated?

Measles Eradication?

Criteria for Eradication	Measles
No nonhuman host or reservoir	No primate reservoir
Accurate diagnosis	Clinical picture IgM antibodies
Effective intervention	Long-term immunity after vaccination
Low infectivity	Highly contagious

Measles and Smallpox

Factor	Smallpox	Measles
Nonhuman host	No	No
Obvious illness	Yes	Yes
Vaccine effectiveness	High	High
R_0	5–7	12–18
Herd immunity threshold	80–85%	93–95%

Should measles eradication be attempted?