Prospects for measles eradication

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Disclosures

- nil

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- Severity of measles – Sudan, Fiji
- Complications of measles – eyes, post-measles syndrome
- Burden
- Control – Americas, WPRO, AFRO, Europe
- What have we learned about measles?
- Current control strategy – 2 doses of MCVs plus SIAs
- 2015 situation
- The polio legacy
- Prospects for eradication

Lessons from History

- Measles in Africa –
  - Prior to the 1980s child mortality in sub-Saharan Africa close to 50%
- Measles in Fiji –
  - 1875 infected ship docks in Suva
  - Grand Council of Chiefs meeting underway
  - Massive mortality – one third of 150,000 population
- Measles most severe with –
  - Unexposed communities
  - Crowding
  - Malnutrition
  - Poor management

Measles and magic – stories from Ethiopia

- Measles seen as a form of possession

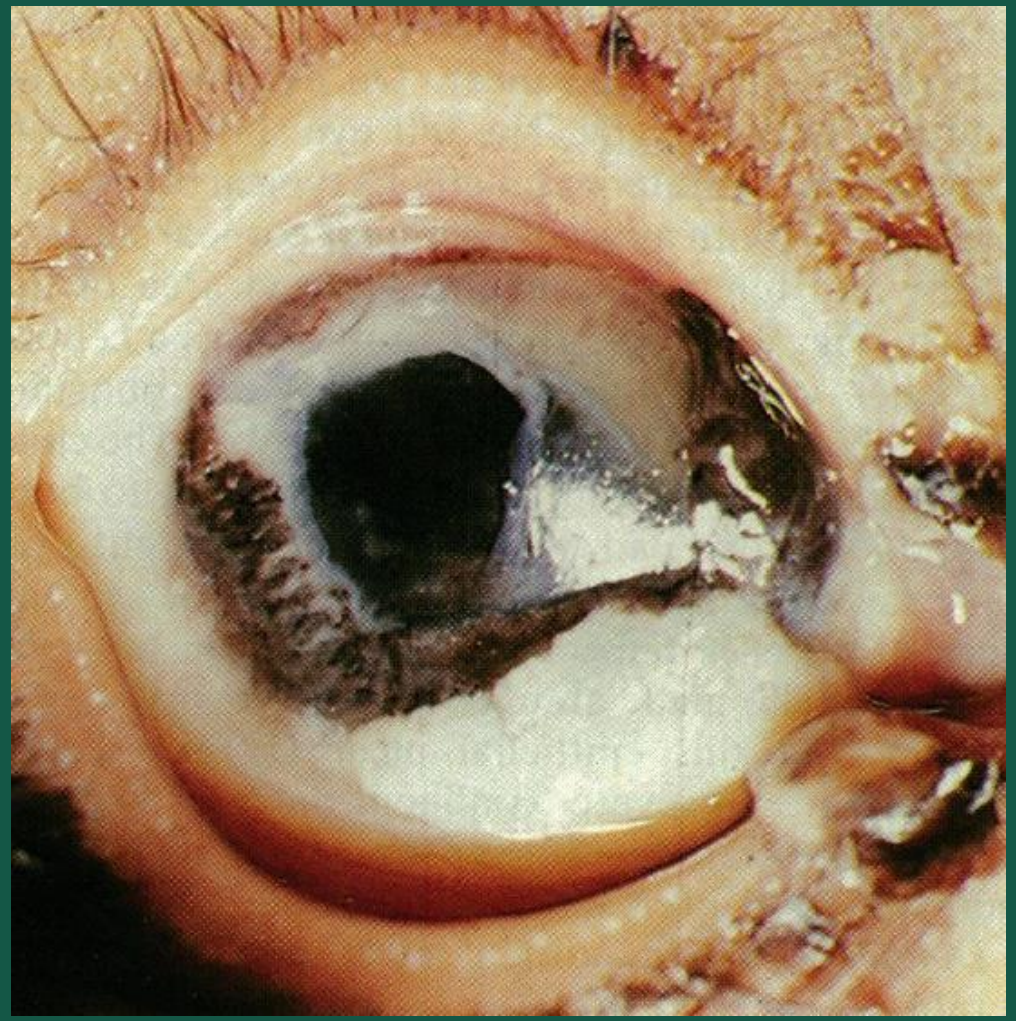
- “Possessed” children:
  - Do not like the shadows of grown-ups to cross them
  - Do not like injections
  - Do not like to be spoken to as if a child
  - Like pop-corn and candy

Severe measles

- 10th century Iranian physician – Zakariya al-Razi (865-925)
  - Distinguished between measles and small pox
  - Described the rash of fatal measles

Measles.....

- As a cause of death
  - Immediate
  - Delayed
- As a cause of blindness (with Vitamin A deficiency)
- As a cause of malnutrition
- As a cause of immune suppression



After 5 days Vitamin A

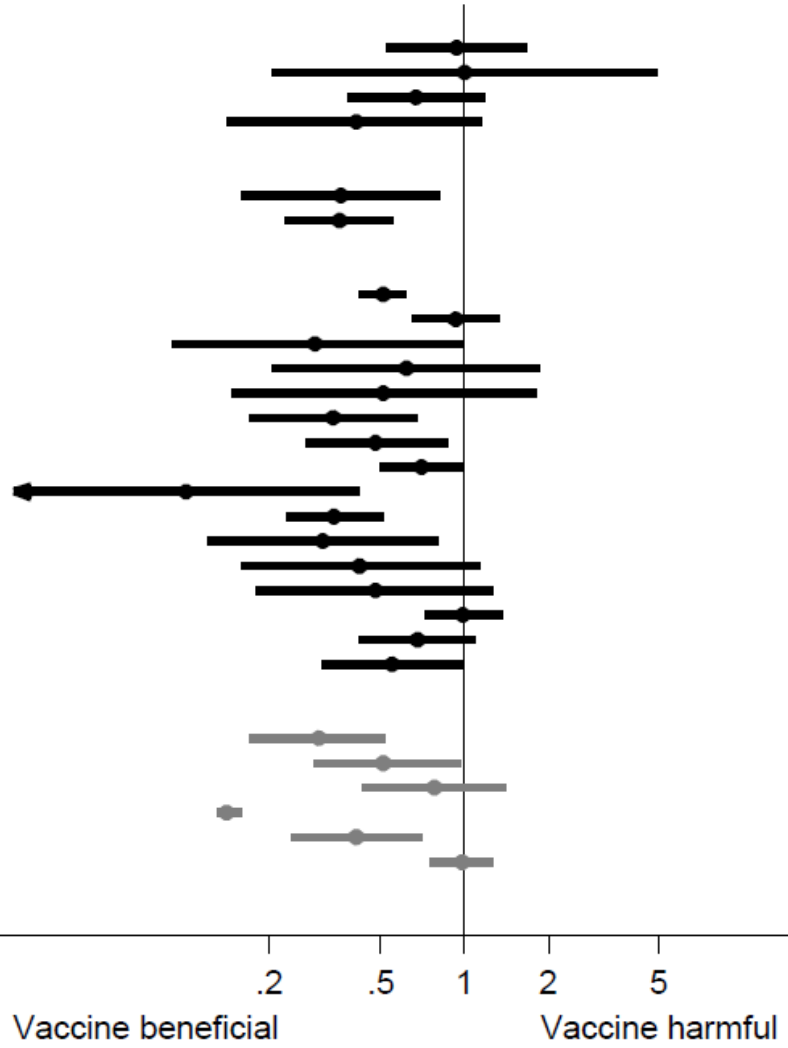
Foster A, Sommer A. Brit J Ophthalmol 1987;71:331-43

The true mortality burden of measles

- Early studies showed greater mortality benefit than could be explained on the basis of measles prevention alone
- Two explanations:
  - Long term effects of measles increase mortality
    - Post measles syndrome – malnutrition, depression, persistent diarrhoea, pneumonia
  - Non-specific mortality benefit attributable to the vaccine
    - Many observational studies by P Aaby and colleagues in Guinea Bissau showed beneficial effect of measles vaccine on mortality
    - Definitive trial underway in Guinea Bissau and Burkina Faso

Measles vaccine and all-cause mortality

	Age at first dose	*Observation period*
1. Randomized trials		
Guinea-Bissau 1989-1999	6 months	age 6-9 months
Guinea-Bissau 1989-1999	6 months	age 6-9 months
Guinea-Bissau 2002-2008	4.5 months	age 4.5-9 months
Nigeria c.1961	6-24 months	6-20 months follow-up
2. Case-control studies		
Benin 1983-1987	NR	age 4-36 months
India 1991-1998	NR (before 12 months)	age 12-60 months
3. Cohort studies		
Bangladesh 1977-1985	NR (from 9 months)	age 9-60 months
Bangladesh 1986-2001	NR (from 9 months)	age 9-60 months
DR Congo 1973-1975	Mean 8.8 months	age 7-21 months
Guinea-Bissau 1978-1983	NR (6-35 months)	13 months follow-up
Guinea-Bissau 1978-1983	NR (6-35 months)	12 months follow-up
Guinea-Bissau 1984-1985	Median 11.1; 15 months	age 17.5 months or more
Guinea-Bissau 1990-1996	Median 10.6 months	age 7-19 months
Guinea-Bissau 1999-2002	NR (by 12 mo in 55%)	age 9-24 months
Haiti 1981-1982	Median 9 months	age 9-39 months
India 1986-1991	NR (at 6-8 [8-11] mo in 85% [15%])	age 12-60 months
India 1987-1989	Median 9.4 months	age 12-60 months
Malawi 1995-1997	Median 10.8 months	age 9-18 months
Papua New Guinea 1989-1994	NR (by 12 months in 74%)	age 6-11 months
Senegal 1985-1987	Mean 15.8 months	age 9-24 months
Senegal 1987-1989	Mean 11.6 months	age 9-24 months
Senegal 1996-1999	NR (by 12 [24] mo in 9% [20%])	age 24 months
Excluded (Very high risk of bias)		
Burundi 1984-1988	NR (at 9-11 months in 59%)	6 months follow-up
Ghana 1984-1991	NR (6-35 months)	4 months follow-up
Ghana 1994-1999	Median 9.1 months	age 9-11 months
Ghana 1998-2004	NR (by 12 [24] mo in 5% [64%])	age 60 months
India 2006-2011	Mean 9.4 months	age 9-15 months
Senegal 1989-1996	Median 9.7 months	age up to 24 months



Source: WHO review, T Nolan

Clin. exp. Immunol. (1978) **32**, 540–544.

Immunological recovery after measles

ANNE WESLEY, H. M. COOVADIA & LINDA HENDERSON *Department of Paediatrics and Child Health*
University of Natal

(*Received 4 January* 1978)

SUMMARY

Twenty-two children with measles were studied at the stage of the rash and 6 weeks later, and results compared with matched controls.

TABLE 1. Lymphocyte counts and transformation in twenty-two children with measles and 6 weeks later and in twenty-two healthy controls: means and standard errors

Group	Absolute lymphocyte counts (per cm^3)	T cells (per cm^3)	B cells (per cm^3)	Null cells (per cm^3)	FT cells (per cm^3)	Lymphocyte transformation (d/min)
Acute	4209±654	2989±455	987±116	234±63	81±22	9100±1784
6 weeks	6918±430	4364±302	1270±151	284±47	162±31	7970±1751
Controls	7603±742	4746±453	2051±247	805±128	140±40	31745±5249

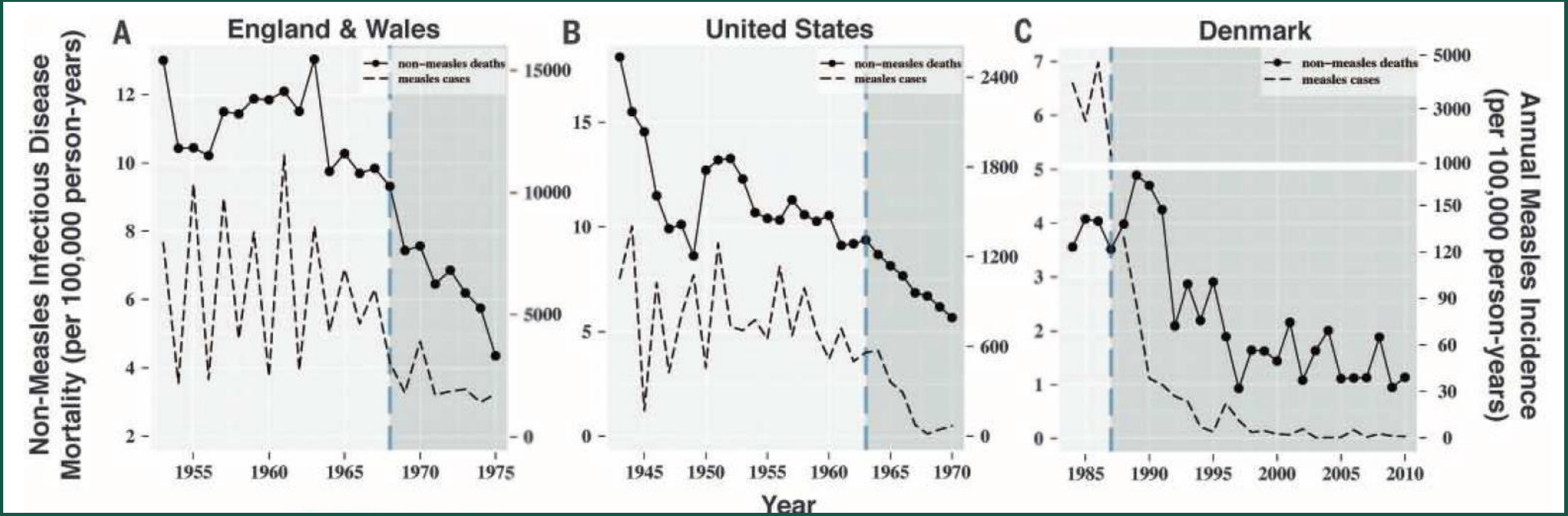
Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality

Michael J. Mina,[1,2*] C. Jessica E. Metcalf,[1,3] Rik L. de Swart,[4]
A. D. M. E. Osterhaus,[4] Bryan T. Grenfell[1,3]

Immunosuppression after measles is known to predispose people to opportunistic infections for a period of several weeks to months. Using population-level data, we show that measles has a more prolonged effect on host resistance, extending over 2 to 3 years. We find that nonmeasles infectious disease mortality in high-income countries is tightly coupled to measles incidence at this lag, in both the pre- and post-vaccine eras. We conclude that long-term immunologic sequelae of measles drive interannual fluctuations in nonmeasles deaths. This is consistent with recent experimental work that attributes the immunosuppressive effects of measles to depletion of B and T lymphocytes. Our data provide an explanation for the long-term benefits of measles vaccination in preventing all-cause infectious disease. By preventing measles-associated immune memory loss, vaccination protects polymicrobial herd immunity.

Science 2015;348:694-9.

Decline in non-measles infectious diseases deaths following measles vaccine introduction



Strategies for measles control

- Isolation of cases – useless
- Effective treatment
  - Vitamin A and antibiotics can reduce morbidity and mortality, but not transmission
- Vaccination and immunity
  - Maternally derived immunity 6-9 months, declining
  - Shwartz live-attenuated vaccine
- During 90s plans developed for eradication of measles based on polio strategy
  - Routine immunization + regular campaigns

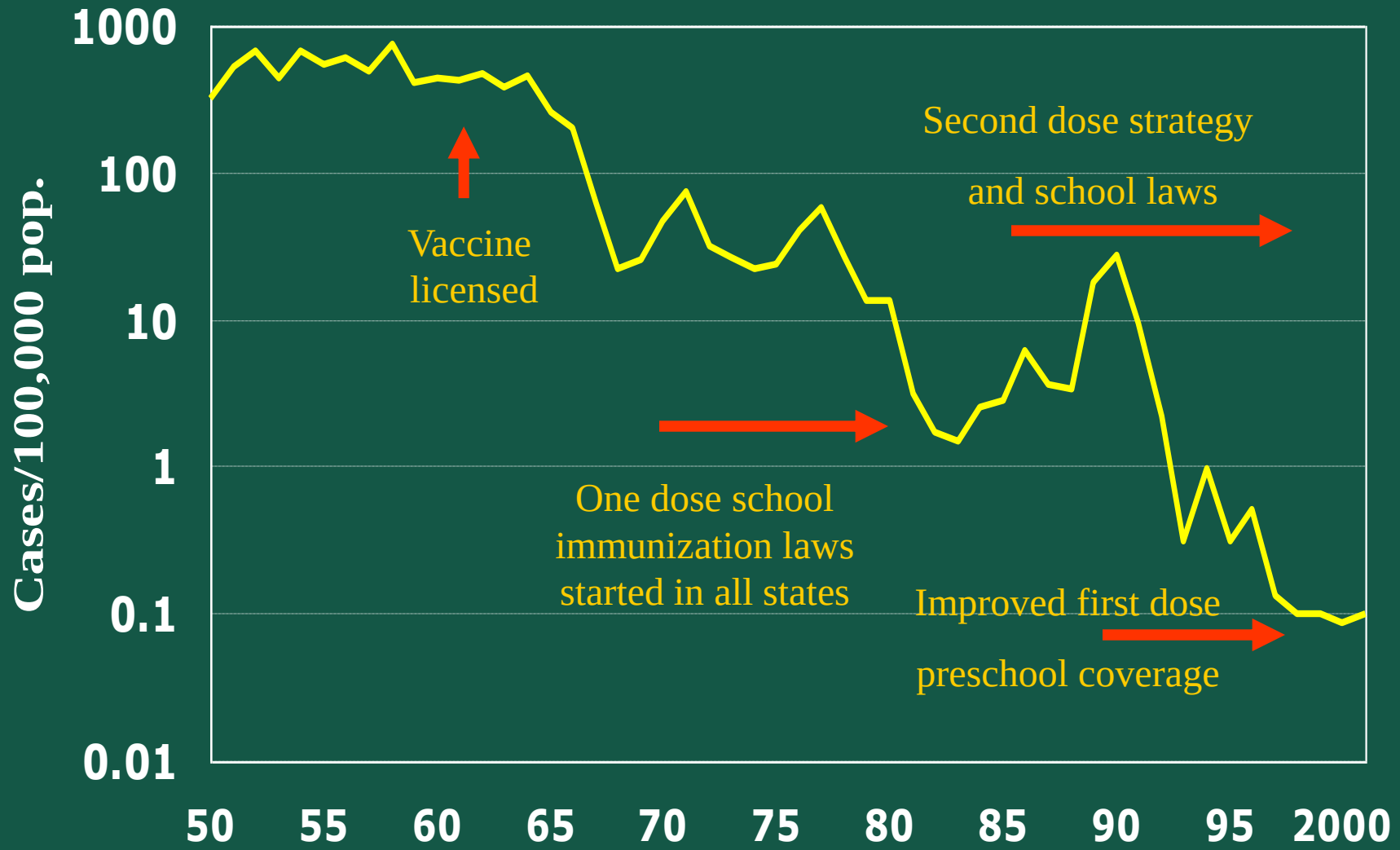

Wahuju

Epidemiologic Basis for Eradication of Measles (1967)

- Virtually universal infection
- Reservoir is humans, no non-human reservoirs
- Chronic carriers do not exist
- Transmission dependent on balance between immunes and susceptibles
- Transmission dies off before all susceptibles exhausted

† Sencer DJ, Dull HB, Langmuir AD. Epidemiologic Basis for the Eradication of Measles in 1967. Public Health Reports 1967; 82:253-256

Reported Measles Incidence, United States, 1950-2001

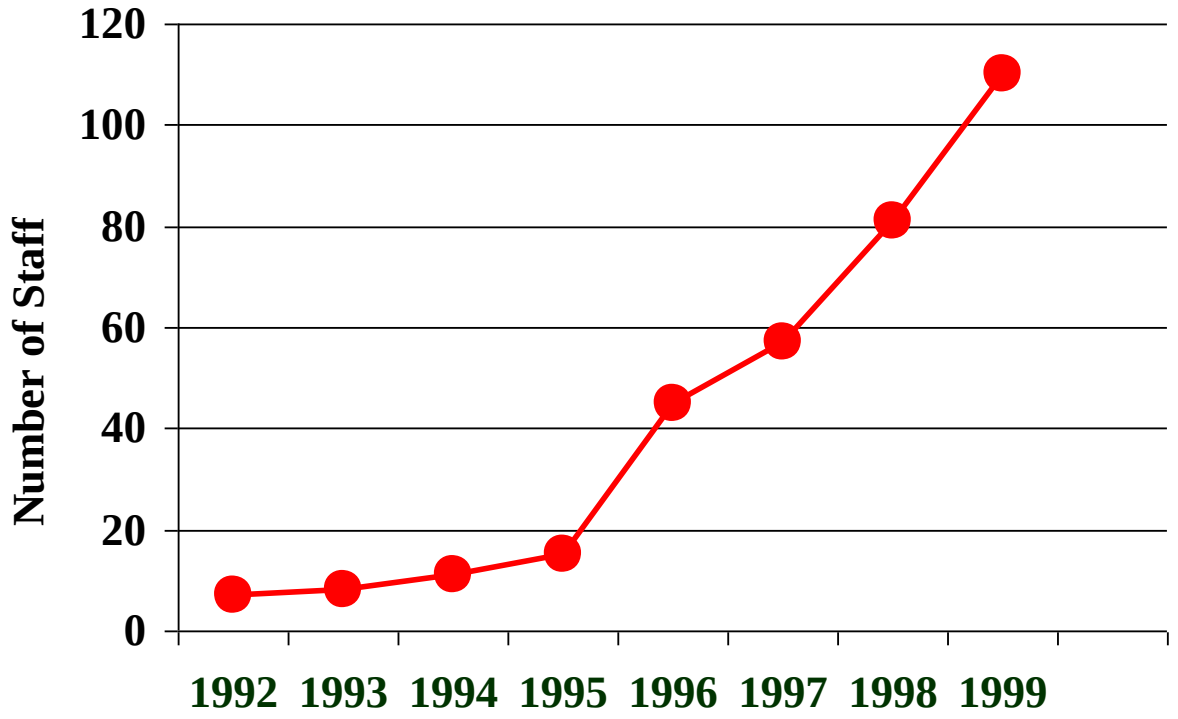


From: Hinman AR et al. JID 2004; 189 (Suppl 1): S17-S22

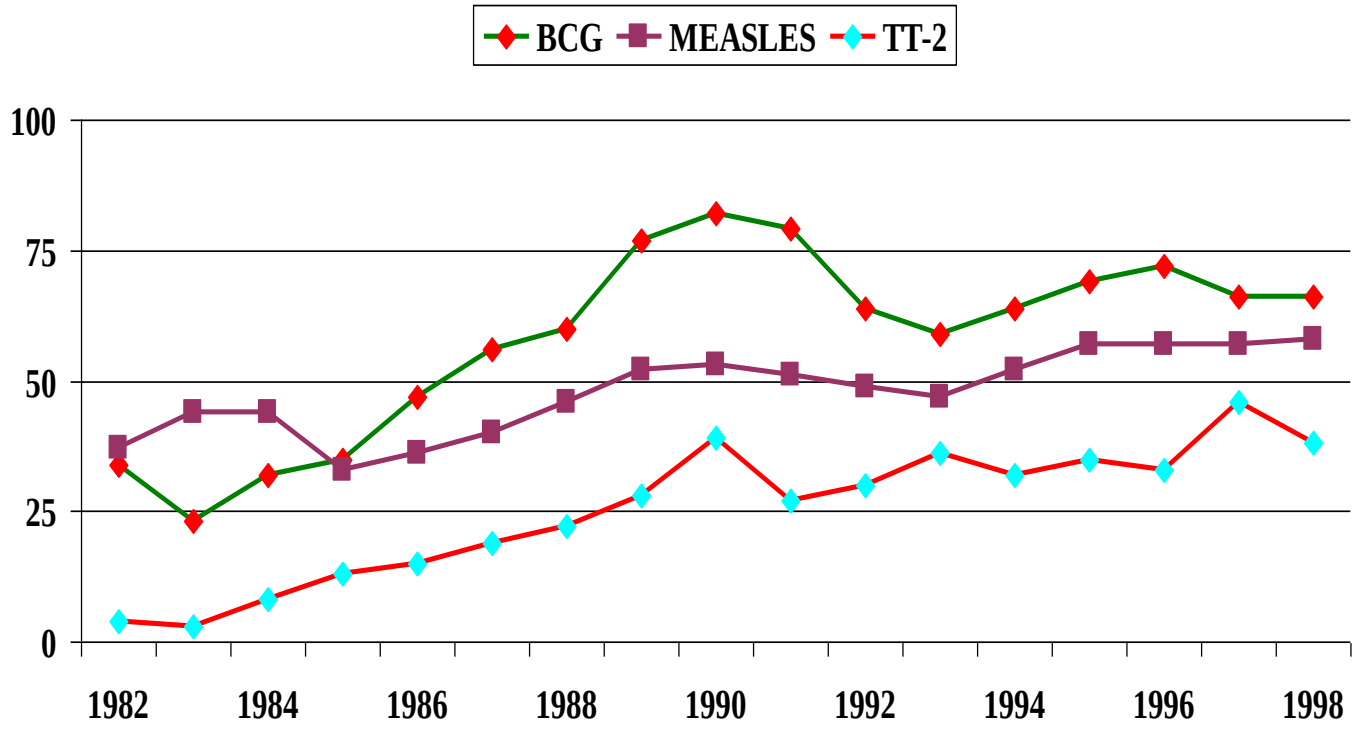
Polio – the model for disease eradication

- By the late 1980s,
  - True burden of polio established
  - Experience in Latin America shows polio can be eliminated
    - NIDs, SNIDs, mopping up, etc.
  - Strong drive from civil society (Rotary International)
- From 1990 WHO adopts polio eradication as a global goal

WHO-EPI Staff Strength
African Region, 1992-1999



Africa
immunization coverage 1980-98



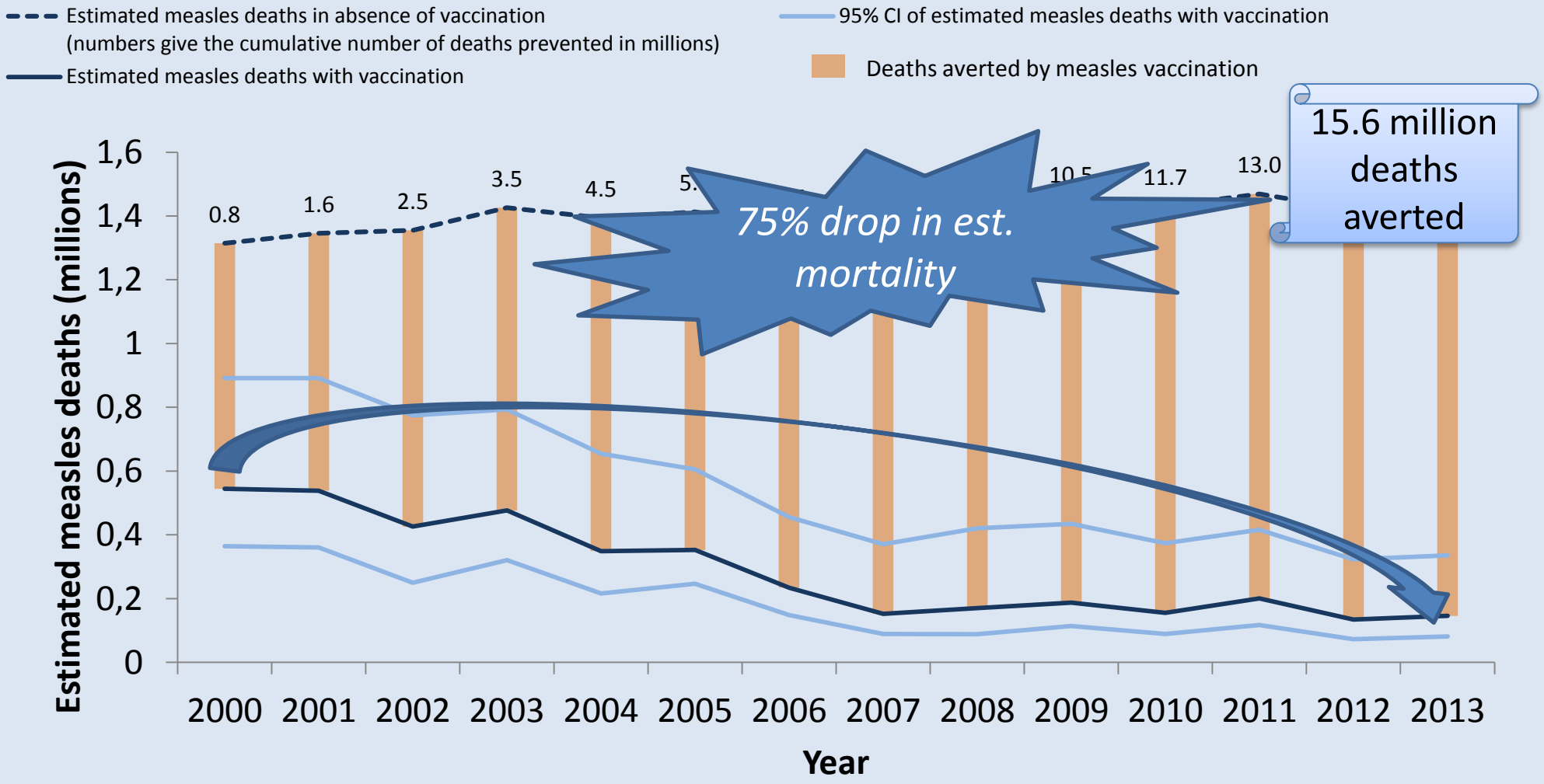
2000 – the polio awakening

- Around March 2000 WHO Director General Bruntland informed that polio would *not* be eradicated in 2000
  - Explosive response with diversion of funds to polio
- “Eradicationists” badly burned
- New strategy –
  - Don’t mention measles until polio is finished

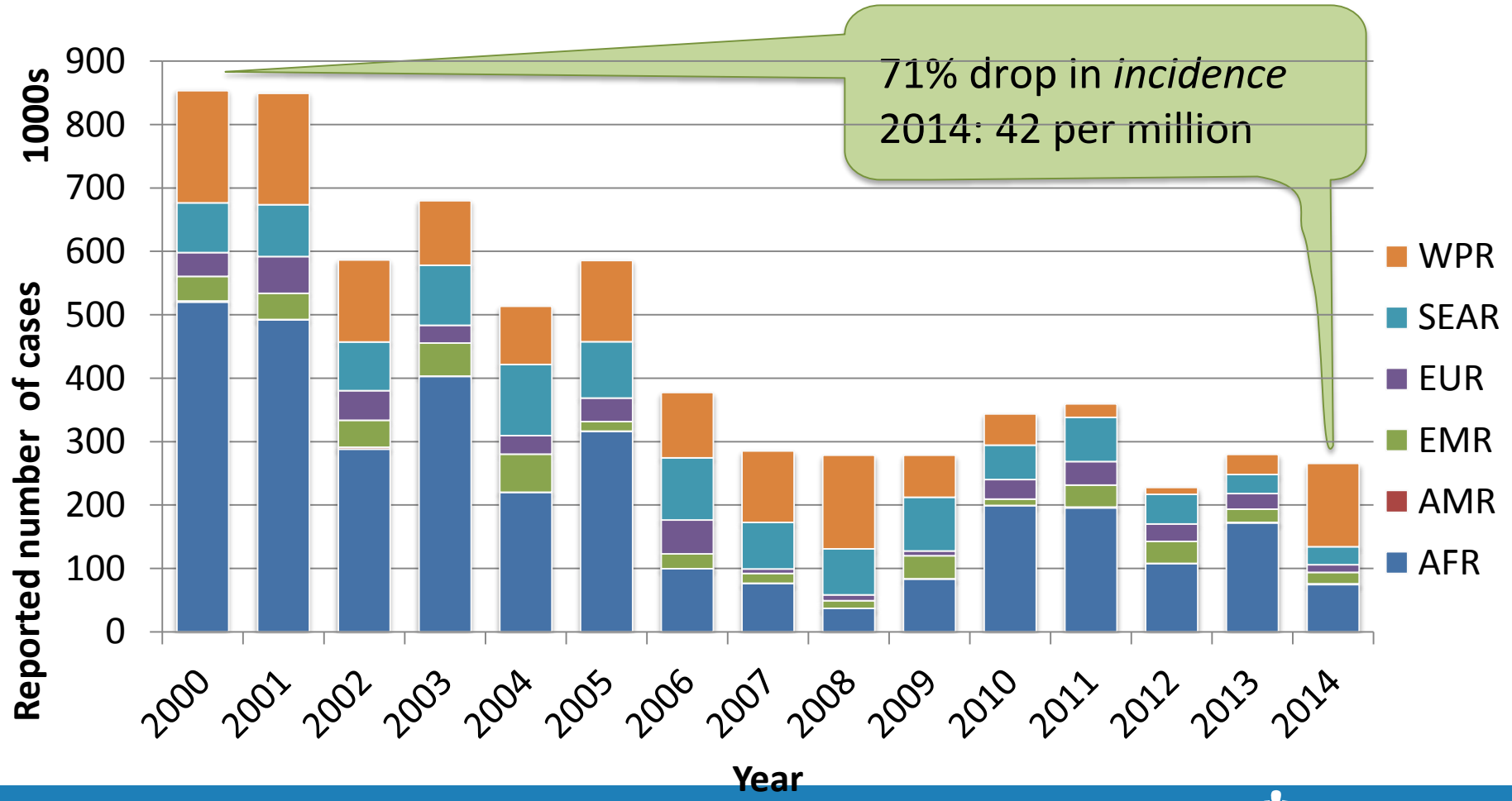
2000 – The measles burden dilemma

- Measles mortality estimates ranged from 770,000 deaths (WHO) to 55,000 (M Garenne)
- All estimates based on models
  - Assume 10% primary vaccine failure
  - Assume all non-immunes will get measles
  - Derive case fatality rate from reports (mainly outbreaks)
- WHO locked into high estimates
  - Deaths $\propto$ money for measles control
- High throughput hospitals in Africa not reporting many cases

Global estimated measles mortality and measles deaths averted, 2000 - 2013



Reported measles cases by WHO Region, 2000-2014



Data as of 27 May 2015. 148 / 194 Member States reporting data for 2014

World Health Organization

Progress in measles reduction since 2008

- In Africa, 172,000 reported cases in 2010 (from 37,000 in 2008)
  - Declining funding
  - Problems with some religious groups
- Many cases in Europe (esp. France)
- Major outbreak in UK in 2013
  - Areas with poor coverage
  - Related to spurious, but ongoing argument about autism
- Outbreaks in countries certified measles free
  - Brazil
  - Mongolia
- Many groups in UK and US choosing not to be vaccinated

WHO Measles Targets

Global milestones by 2015:

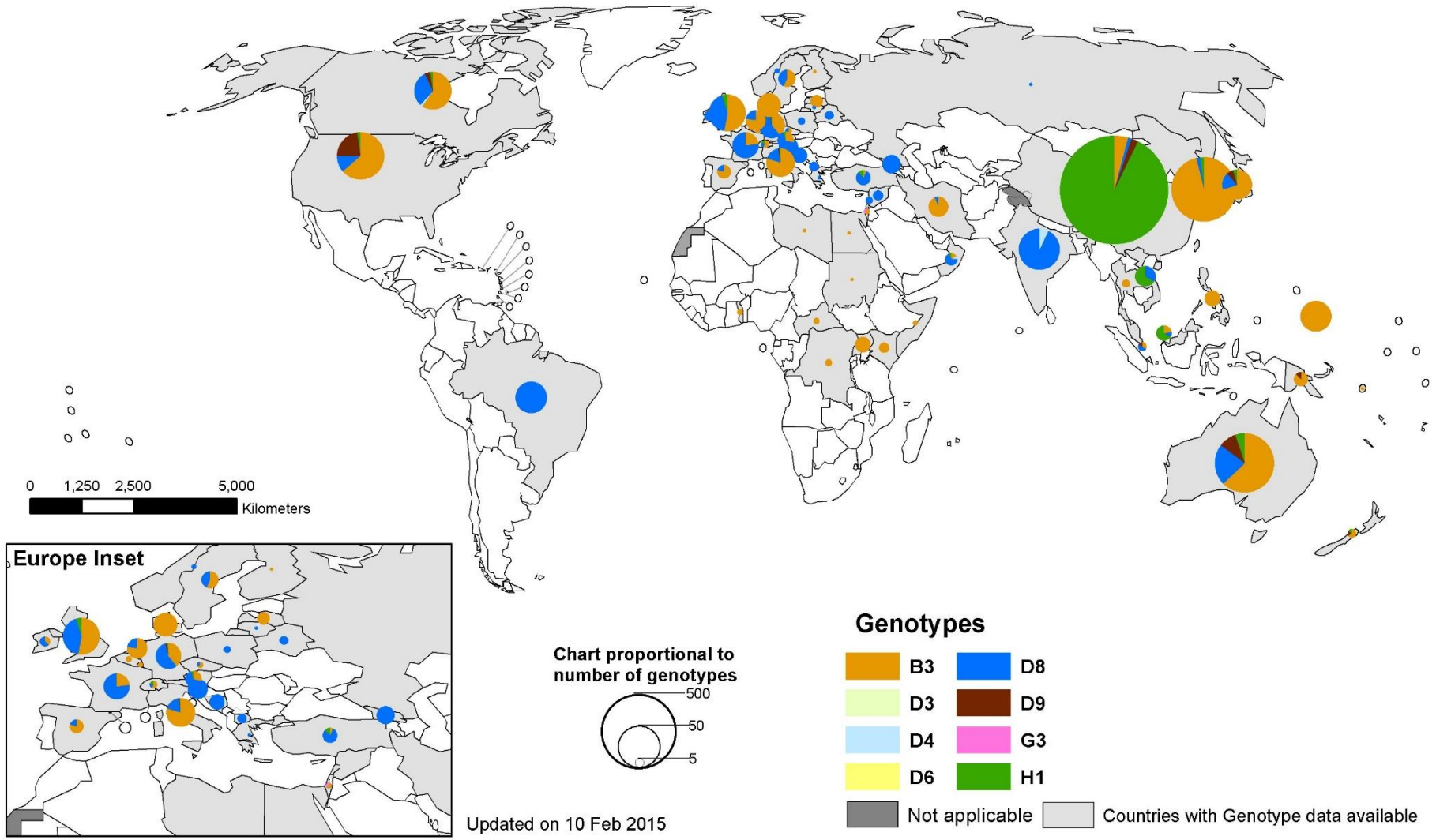
1. Measles dose 1 coverage ≥ 90% national and ≥ 80% in every district
2. Measles reported incidence <5 cases per million
3. Measles mortality reduction of 95% vs. 2000

Regional targets:

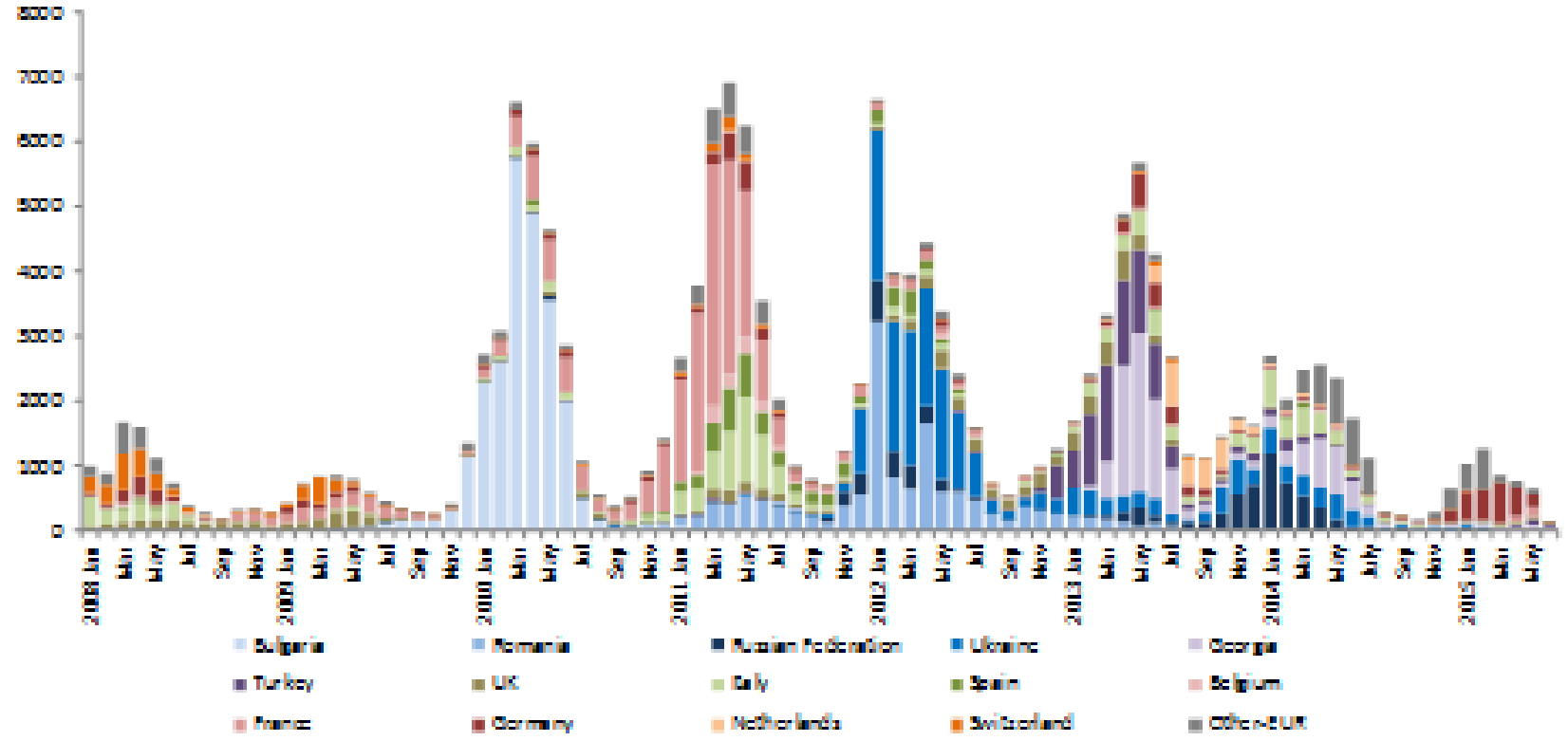
Measles Elimination goals:

2000 PAHO
2012 WPRO
2015 EURO, EMRO
2020 AFRO, SEARO

Distribution of measles genotypes, 2014



Measles Cases Distribution by Month
EUR Region, 2008-2015 (Jun)

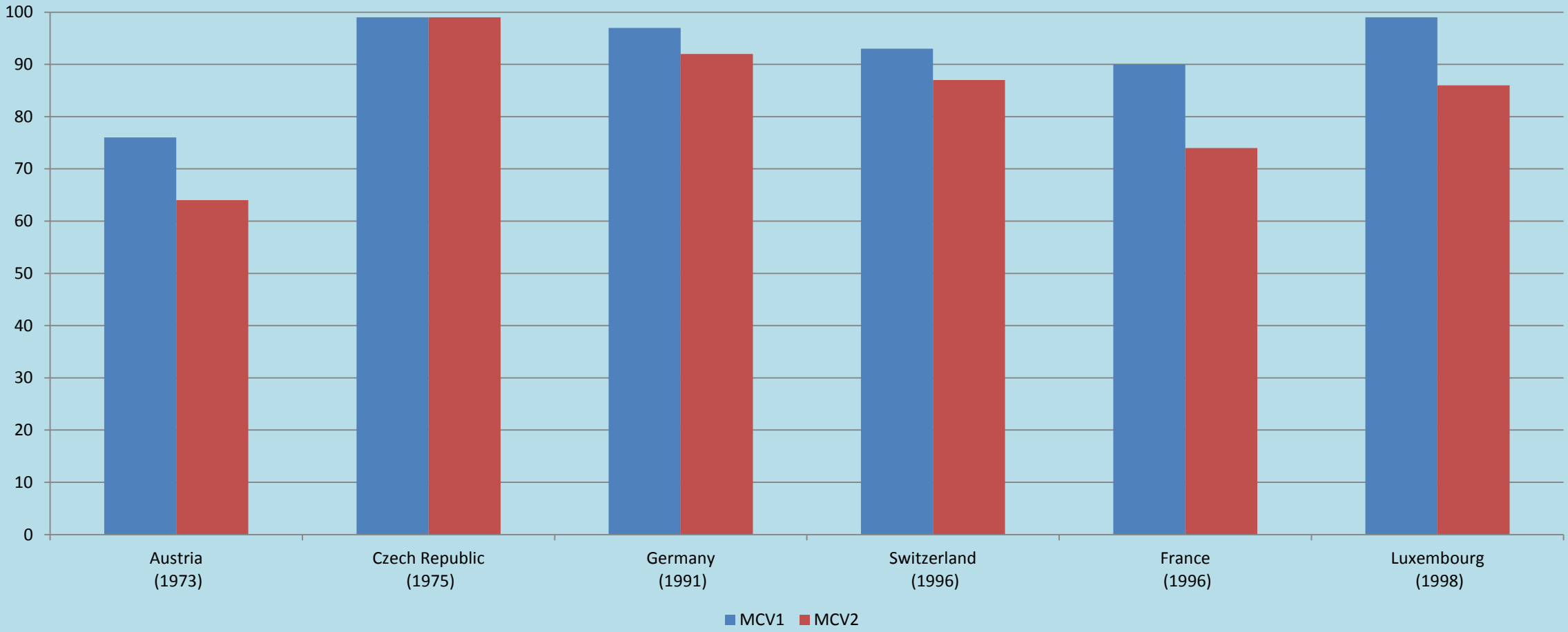


Color scheme by sub-region
Eastern Europe – Light to Darker BLUE
MEDCARA+ – Light to Darker PURPLE
Northern Europe – TAN (UK only)
Southern Europe – Light to Darker GREEN
Western Europe – Light to Darker RED/ORANGE

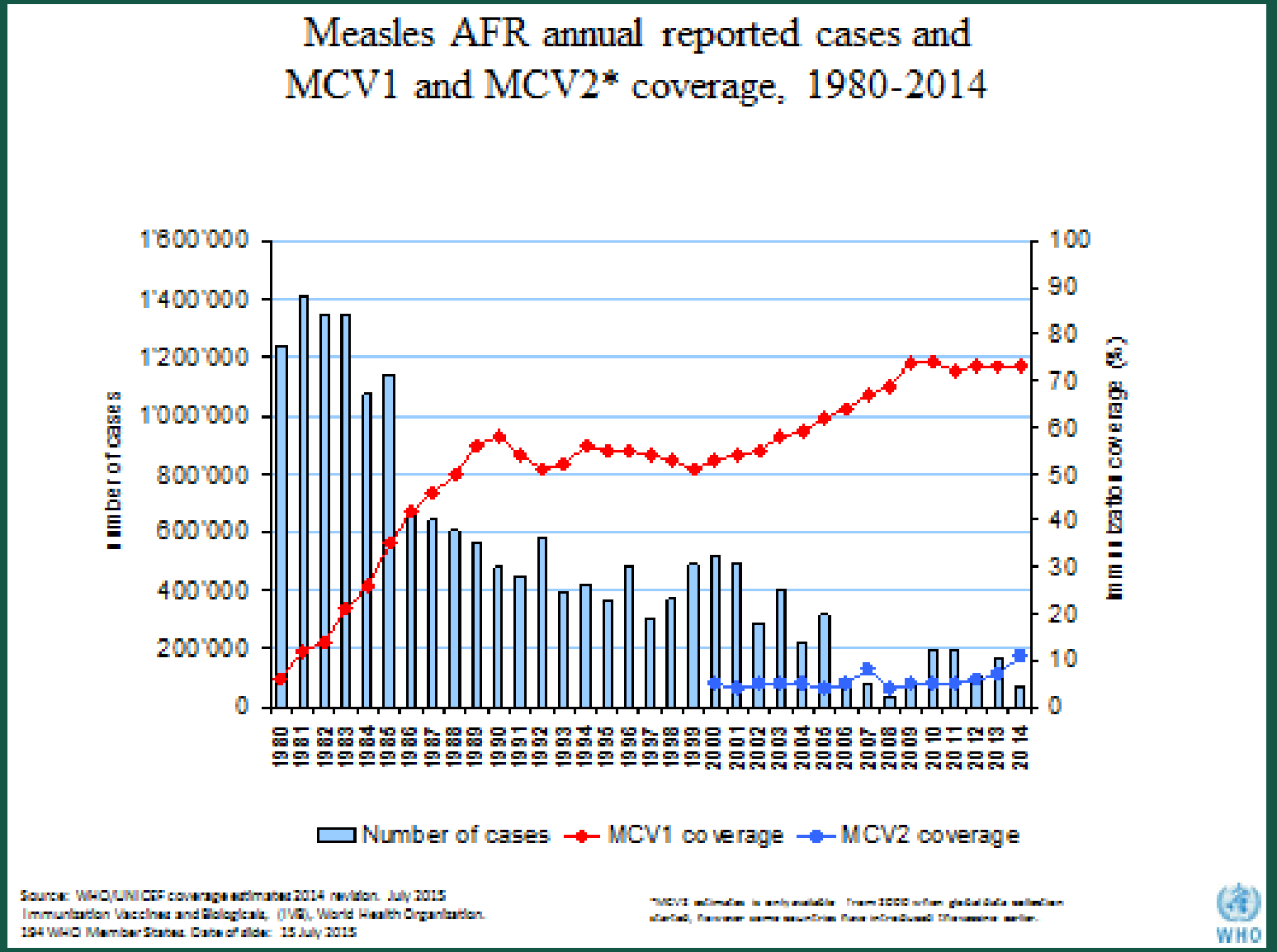
Data source: surveillance OSF file
Data in HQ as of 10 Aug 2015

WHO

Measles vaccine coverage in Europe, 2014



Measles in Africa

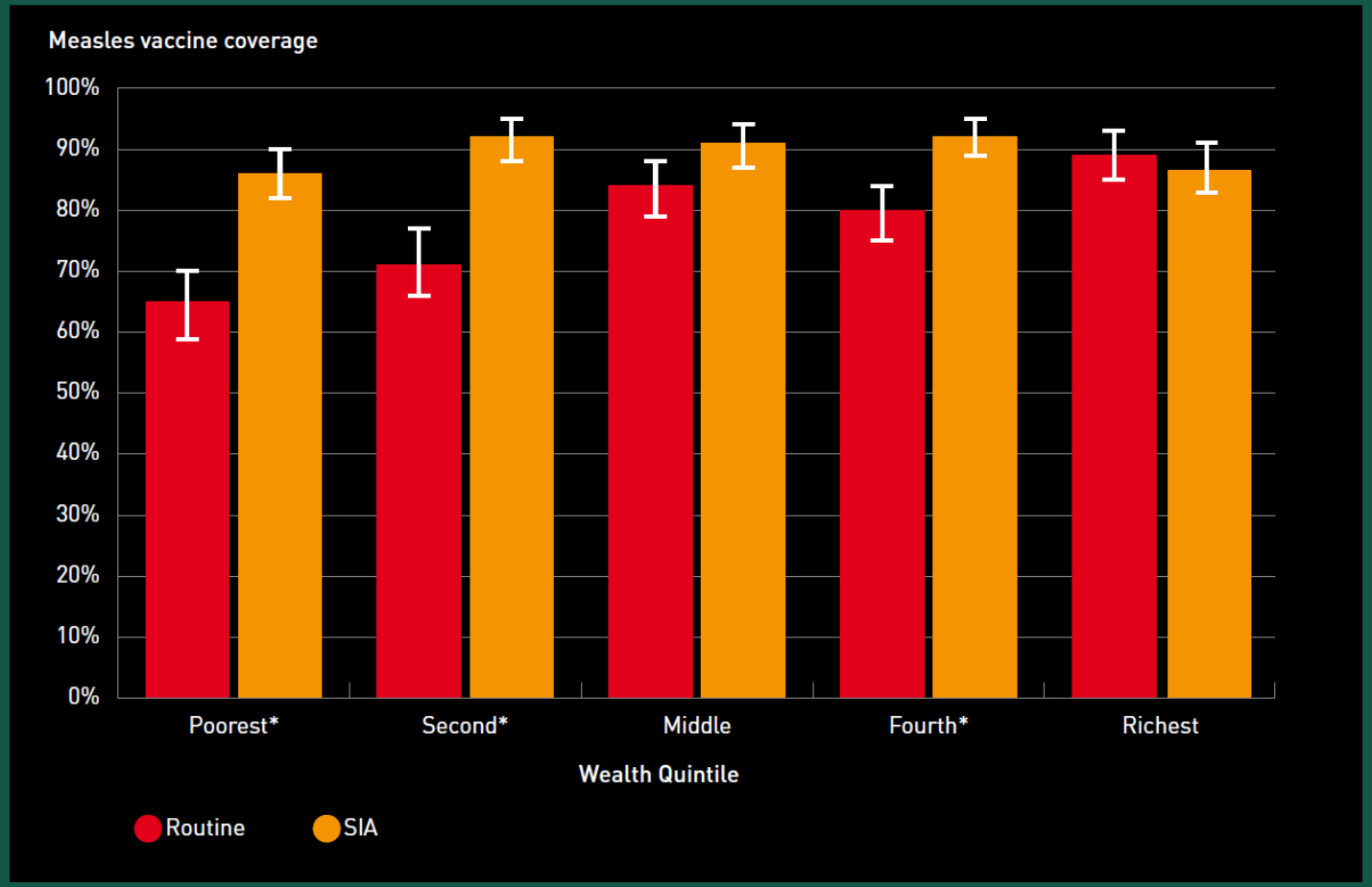


Source: WHO/UNICEF coverage estimates 2014 revision, July 2015
Immunization Vaccines and Biologicals, (IVB), World Health Organization.
194 WHO Member States. Date of slide: 15 July 2015

*MCV2 estimates is only available from 2000 when global data collection started, however some countries have introduced the measles earlier.

WHO

Measles vaccine coverage, Kenya 2002



Does modelling help?

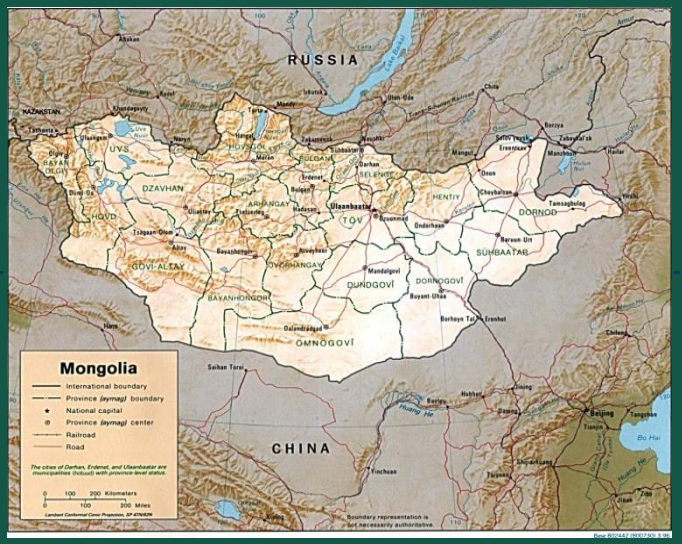
- If >X% of individuals are non-immune then there is a risk of an epidemic
- But:
  - Non-immunes are rarely evenly distributed in any society
    - Marginalized groups not connected with health services
    - Religious groups opposed to immunization
    - Anti-vaccine communities
  - Even apparently highly vaccinated communities can support outbreaks
- Vaccination schedules
  - Timing of 1st dose

Waning maternal immunity and timing of doses

- Vaccine derived and no natural boosting
- In theory children should be vaccinated early
- Does it work? Guinea Bissau study
  - RCT: 892 infants MV at 9 mths vs 441 infants MV at 4&9 months
  - Measles cases 77 cases 8 cases
  - Deaths 12 1
  - Vaccine effectiveness 94%
- So countries with mature vaccination programs with measles well controlled should be vaccinated earlier, *right?*

Mongolia

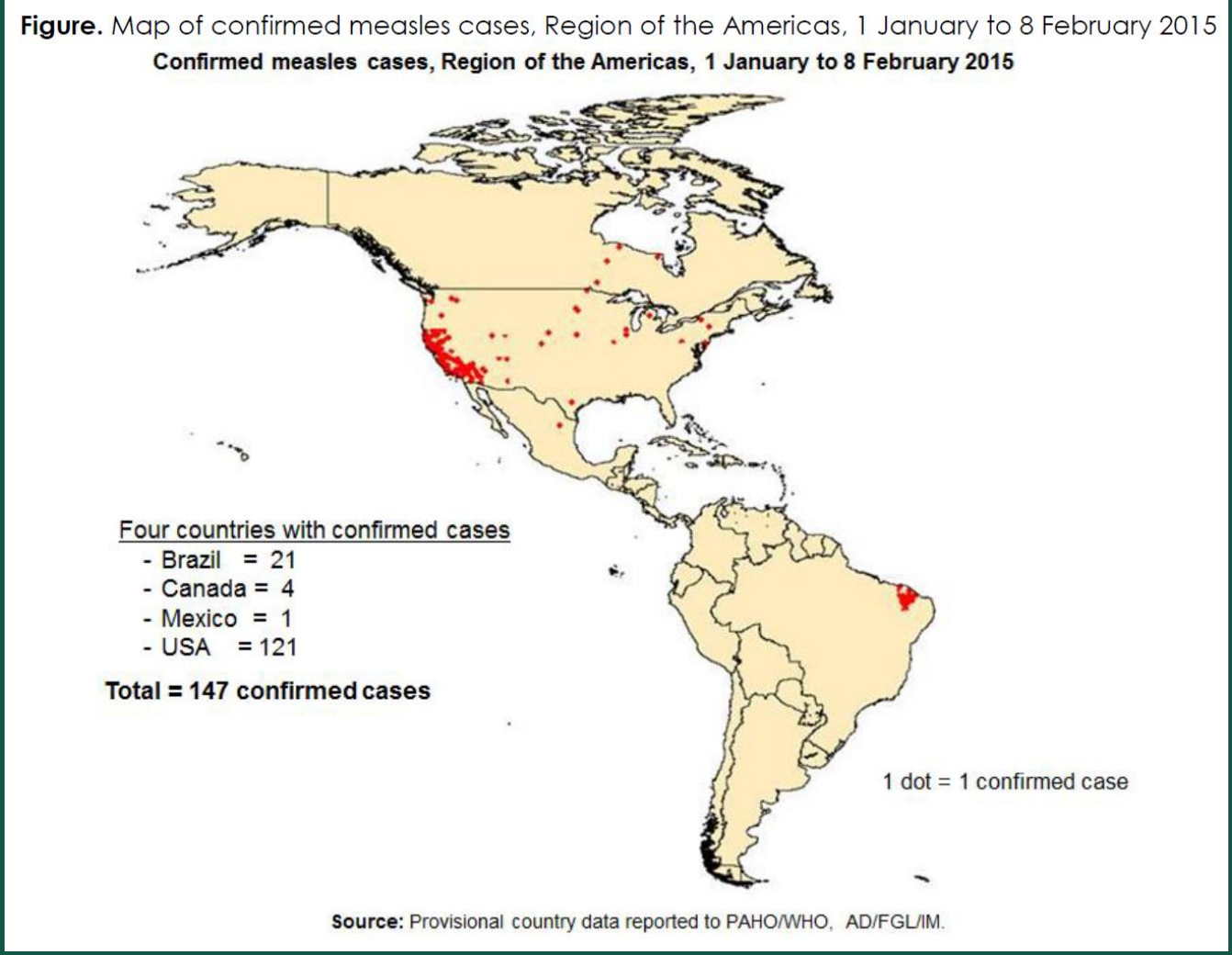
- Territory – 1.6 million square kilometers
- Population – 3.1 million
- Population living in poverty 32%
- Extremely isolated
- Extreme climate
- Very significant indoor and outdoor air pollution, especially in winter



Measles in Mongolia

- Political upheaval 1991 – breakdown of public health
- High vaccine coverage since early 90s
- Declared measles free by WHO 2014
- March – October 2015
  - Over 20,000 suspected measles cases, many 15-24 years
  - 1,434 lab confirmed
  - 50% under 5 years old, half under 9 months
- 2 main groups
  - Young adults
  - Young infants

Measles in the Americas 2015

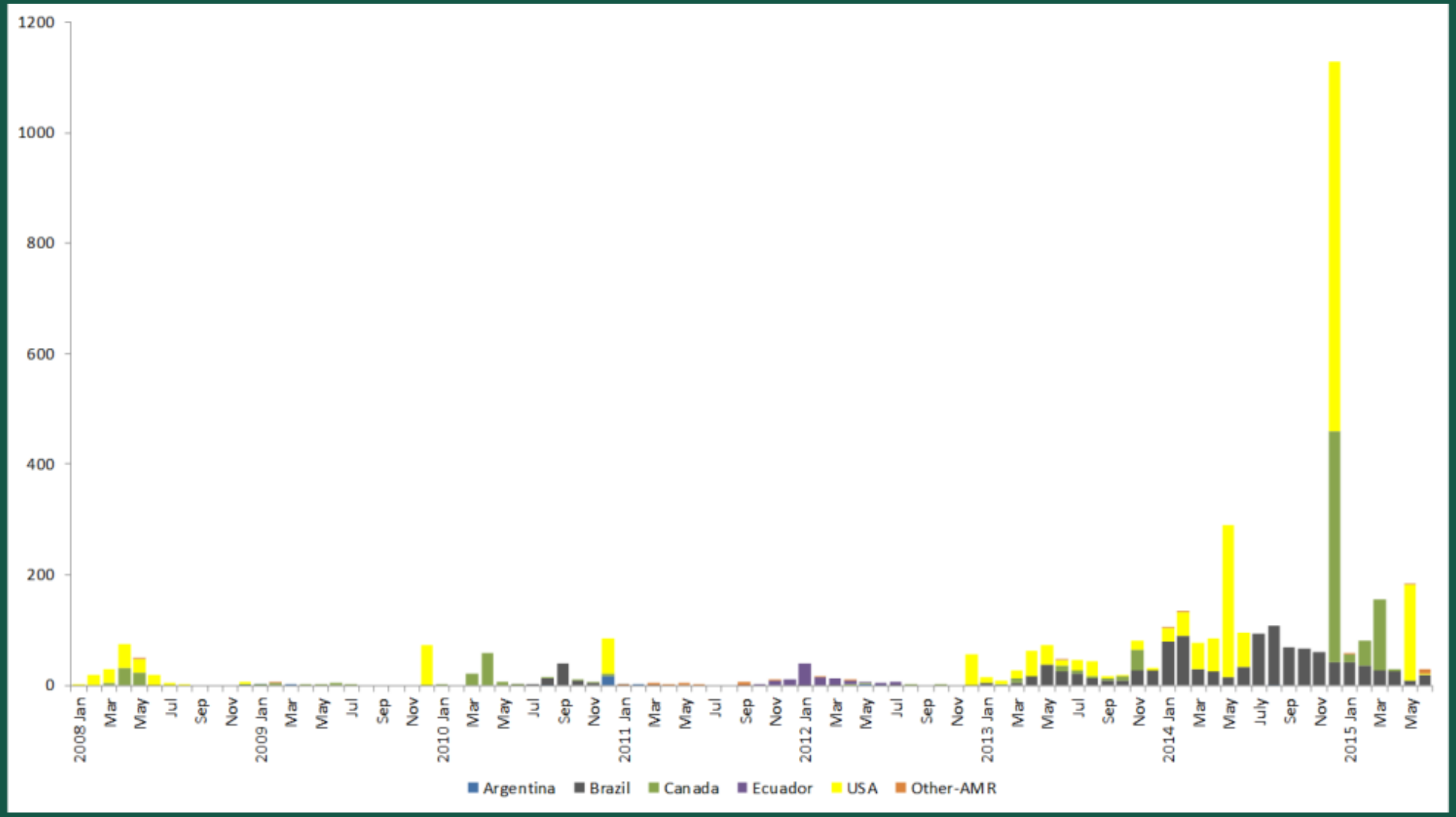


Outbreaks

Brazil (Pernambuco and Ceará, 19 March 2013 – 15 January 2015)

USA - 648 confirmed cases in 2014, 169 cases in 2015

Measles in the Americas 2015



Barriers to measles eradication

- The global political situation is worse than 20 years ago
  - Large areas of the middle-east now no-go areas
  - Polio workers targeted thanks to US military activities
- Global travel much more accessible
- Stepwise country by country; region by region will not work
- Global control in all areas with high coverage of MCV2 needed, followed by co-ordinated “final push”
  - Perhaps this will be achieved by 2020, what then?
  - Proportion of non-immunes will steadily increase…

Verification of Elimination

2014 GVAP Report:

"After consulting with their respective Regional Technical Advisory Group, every region establish a regional verification commission, and after consulting with their respective National Immunization Technical Advisory Group, every country explore options for establishing a national verification commission, to scrutinize and monitor progress towards the measles and rubella elimination targets."

Progress:

- Global Verification Framework published in 2013
  - Definitions
  - Criteria for elimination
  - 5 lines of evidence
- 4 Regions have developed their verification guidelines
- AMR, EUR, WPR have fully functional Regional Commissions
- Differences in definitions and surveillance indicators

Issues - regional

- Africa –
  - More input into SIAs and routine activities
  - Marginalized communities
- Europe –
  - Countries like Austria and UK need to step up
  - Anti-vaccination lobby groups
- Americas and Asia
  - Need to re-establish control

Issues - global

- Do complex regional and national targets really help?
- Are new vaccines needed?
- Dogmatic approach to schedules seems outdated
- Models help, but most conclusions are self evident
- New research, fresh thinking needed

Conclusions

- Regional experiences have shown that measles can be eliminated
- Global political will and cooperation is needed
- The slow progress of polio stands as a barrier
- Eradication push should not start until all countries have adequate control and a final push is adequately resourced