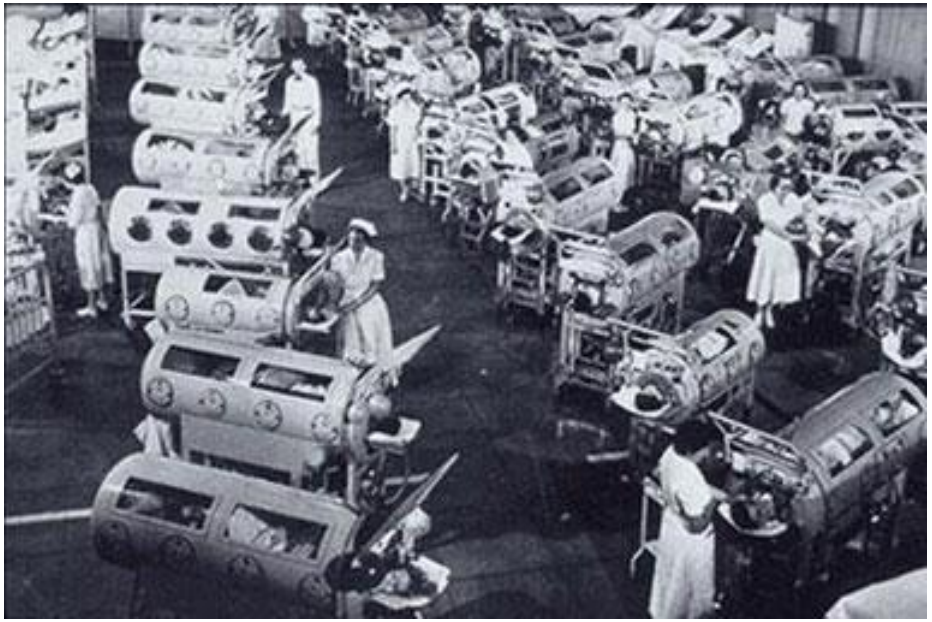
What are the obstacles to elimination of polio?

Dr Kath O'Reilly

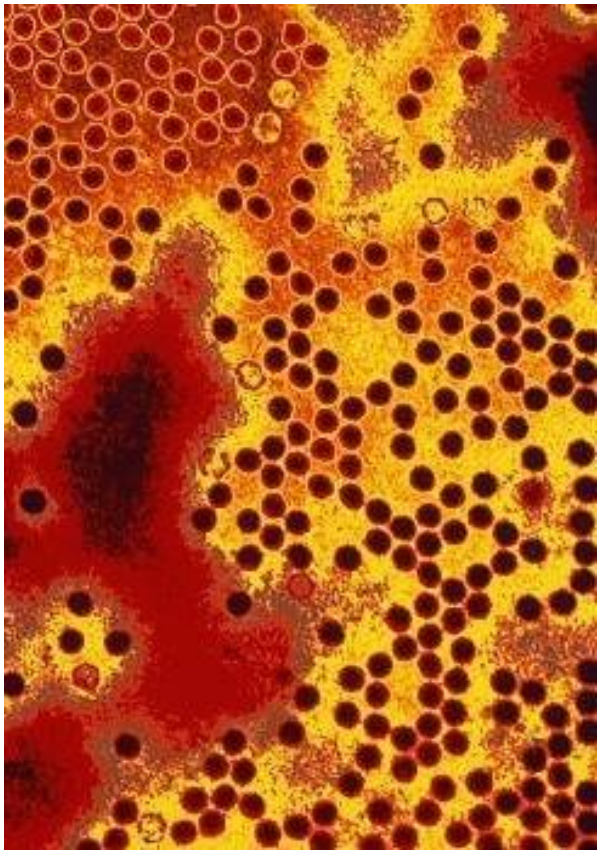


Outline of lecture

- Natural history of polio
- Campaign to eradicate
- Case studies
  - Improving the vaccines
  - Controlling endemic infection
  - Preventing and controlling ‘vaccine-derived’ poliomyelitis
  - Predicting and preventing outbreaks of poliomyelitis

Poliomyelitis: the virus

- ssRNA enterovirus
- Three distinct genetic types with no (very limited) cross immunity (1,2,3)
- Humans are only known natural host

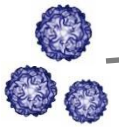


Poliomyelitis: an ancient disease

Egypt ~1500 BC

- Prodromal non-paralytic phase leads to acute flaccid paralysis (AFP) in about 1 in 200 cases
- In approximately 1 in 10 AFP cases the brain stem is affected, leading to paralysis of breathing muscles and death
- Post-polio syndrome (PPS) – polio patients who recovered well due to reinnervation may experience muscular problems in later life

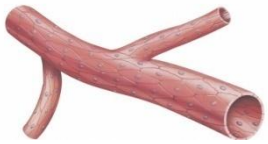
Pathogenesis



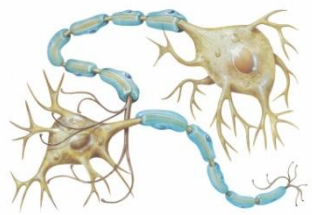
ingested poliovirus

mucosal surfaces in gut and pharynx
(Peyer's patches/tonsils)

lymph nodes
(cervical and mesenteric)

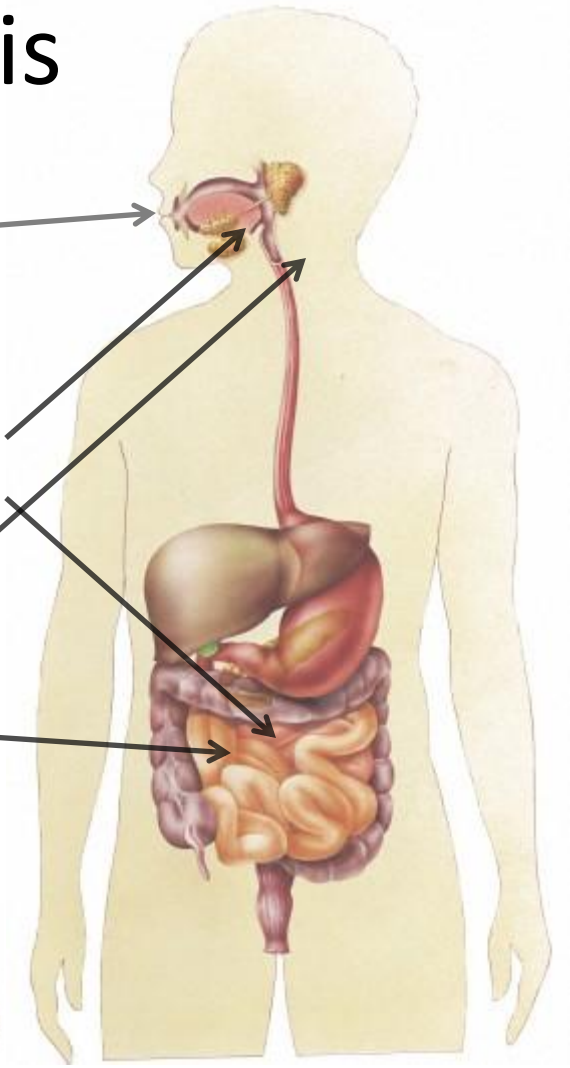


blood

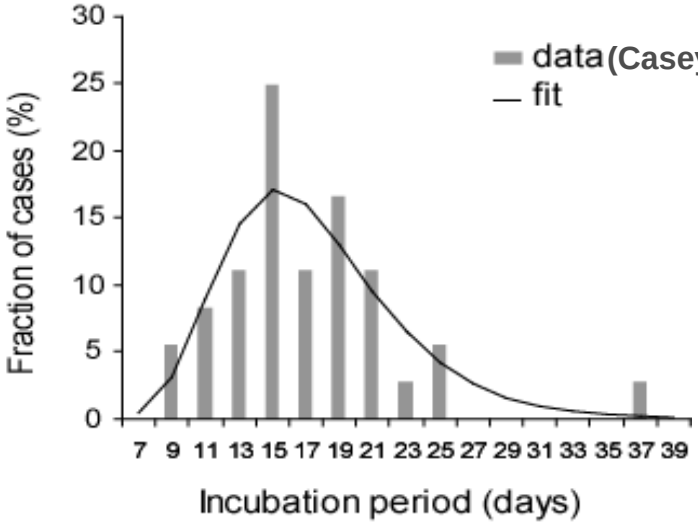


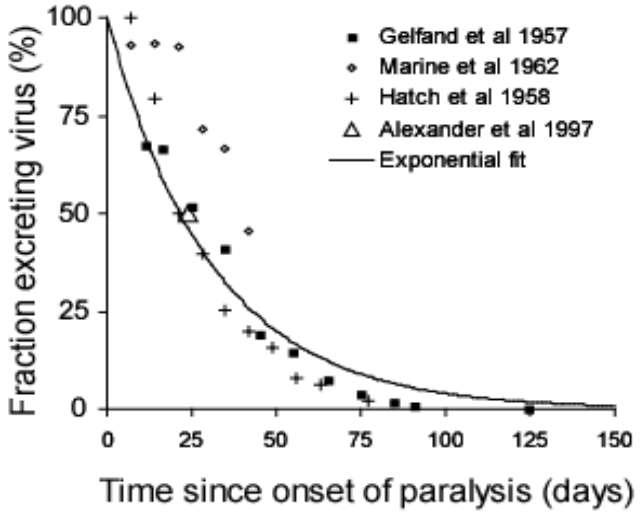
central nervous system

extraneural tissue



Natural history of infection (1)



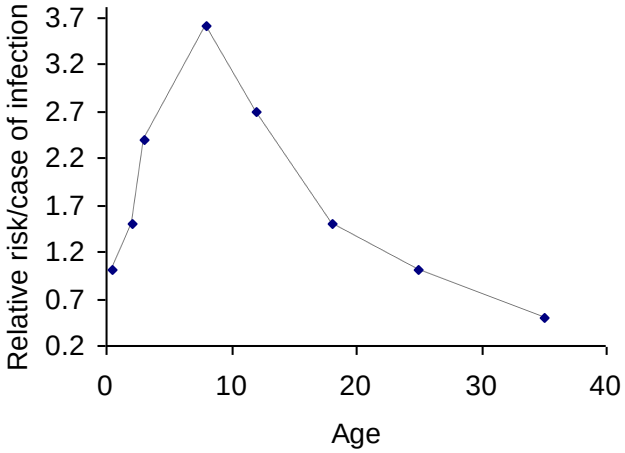


- Incubation period average 16.5 days
- Around 3-5 days after exposure virus can be detected in faeces, blood and throat
- Virus is detected in the faeces for on average 4-5 weeks *after onset of symptoms*, but for only c. 2 weeks in the throat

Natural history of infection (2)

Risk of AFP increased for:

- Age c. 5-15 yrs
- Women at older ages,
- Men at younger ages
- Bigger viral dose
- Subtype (1>3>2)



Following infection long-lasting homologous humoral immunity occurs

Mucosal immunity may wane, facilitating transmission without disease

Limited evidence for short-lived heterotypic immunity

Modes of transmission

1. Droplet
2. Fomite and direct contact
3. Faecal oral

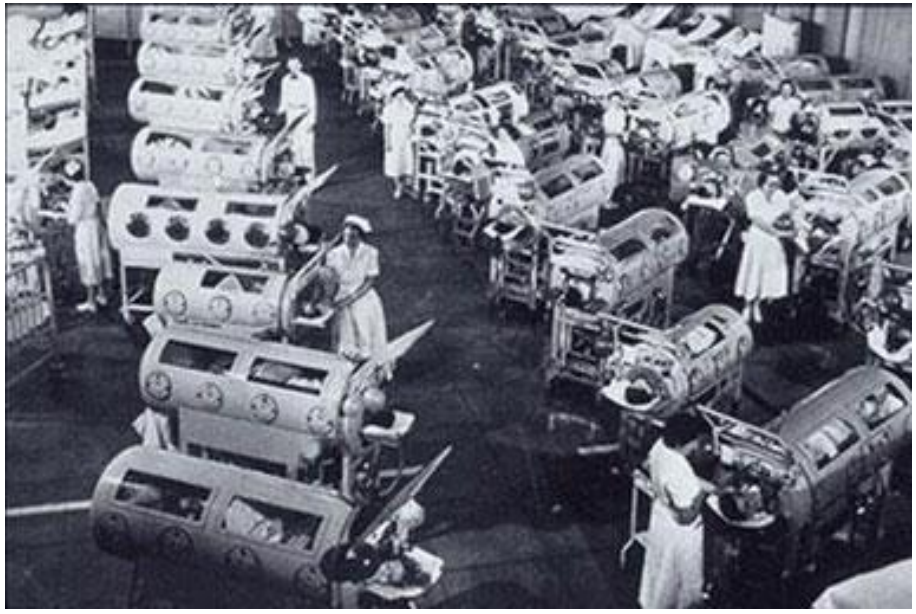
Relative importance of transmission route depends on context and may have implications for dynamics e.g. faecal-oral probably less important in developed world

Descriptive epidemiology

- Pre-vaccination
  - Developing countries
    - Endemic disease
    - Most (>90%) children infected by 4 years of age
  - Industrialized countries
    - Epidemic polio with increasingly severe epidemics perhaps partly due to older average age at infection (e.g. early 1950s average age at infection in US 5-9 years, cf. <5 years in the 1916 epidemic) but also increased diagnosis and care (Anderson and May 1991)
- Post-vaccination
  - Developing countries
    - Ongoing polio eradication efforts in Africa and South East Asia
  - Industrialized countries
    - Disease eradicated

Increasing number of epidemics identified

- Increasingly frequent outbreaks in early 20th century
- Franklin D Roosevelt infected in 1921
- Founded the March of Dimes in 1938 (originally called National Foundation for Infantile Paralysis)
- “Great Race” for a vaccine began

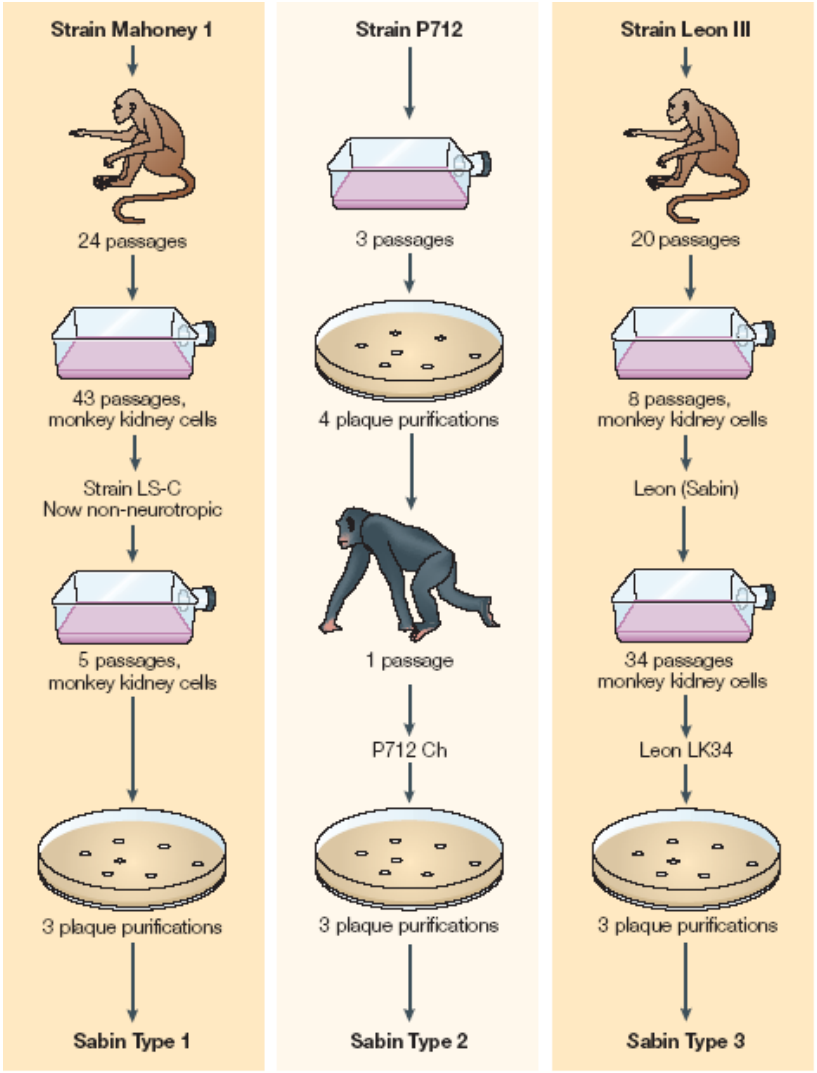


Inactivated Polio Vaccine (IPV)

- First developed by Salk in 1952 by prolonged treatment of virus with formalin
- Injected
- Current preparation is through purification and concentration of inactivated wild poliovirus
- Induces good ‘humoral’ immunity against paralysis
- Much more limited impact on mucosal immunity against infection

Oral Polio Vaccine (OPV) (1)

- Developed by Sabin in 1962
- Attenuated by passage through different host cells
- Stability of attenuated form assessed empirically by inoculating monkeys
- However, only a few mutations separate OPV strains from wildtype (particularly types 2 and 3)
- Vaccine Associated Paralytic Poliomyelitis (VAPP) occurs
  - 1 in 750,000 receiving 1st dose
  - 1 in 12 million receiving 2nd dose



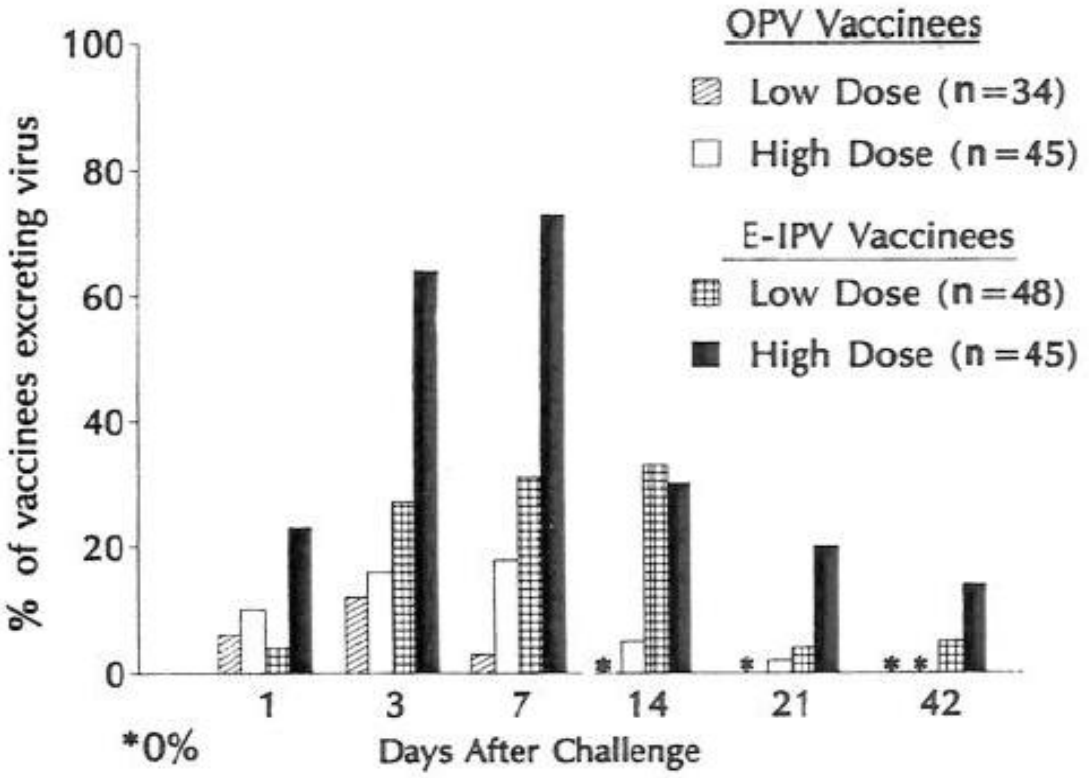
Reproduced from Minor 2004

Oral Polio Vaccine (OPV) (2)

- Trivalent, bivalent and monovalent live virus vaccines have been licensed
- **Vaccine is infectious and may secondarily immunise household contacts of vaccinee (e.g. un-immunized gypsy populations in Europe have high levels of serum neutralising antibodies to polio types 1,2 and 3 probably due to infection with OPV)**
- With trivalent vaccine >95% seroconvert to each poliovirus type after 3 doses in developed countries
- Typically only ~70-80% (or less) seroconvert to type 1 & 3 after 3 or 4 doses in developing countries due to interference by other infections and diarrhoeal disease
- Seroconversion is also associated with induction of good mucosal immunity against infection

Which vaccine to use?

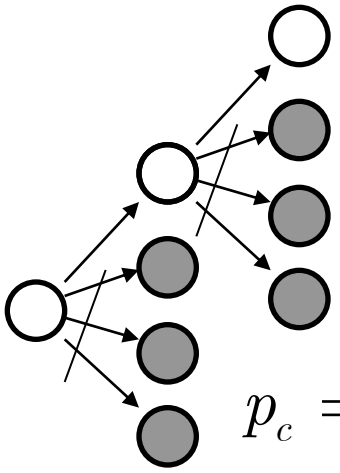
- OPV cheaper, easier to administer, secondarily immunises contacts of vaccinees, protects against infection (mucosal immunity)
- Majority of countries switched to OPV from IPV during the 1960s
- Wealthy countries now switching back to IPV
  - IPV in the UK



From Onorato et al. 1991

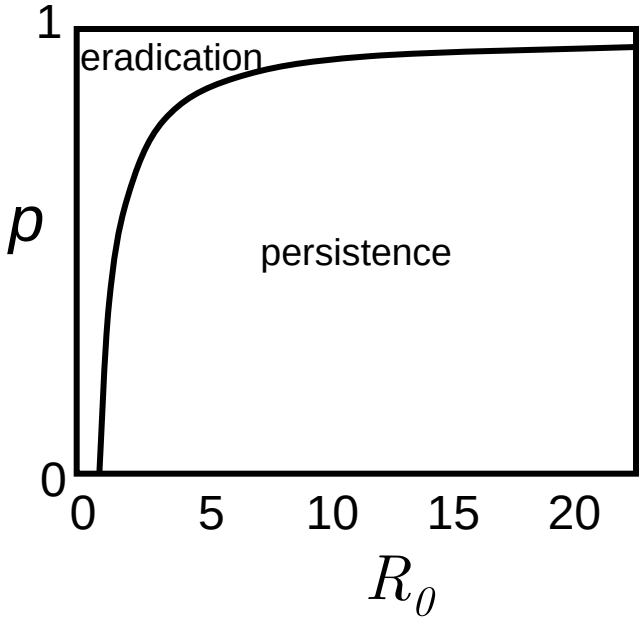
Vaccination and herd immunity

- Direct (individual) effect
  - –vaccinee protected against infection
- Indirect (population) effect
  - –reduced force of infection leading to 'herd immunity'
- Effective reproductive number R



$$p_c = \frac{R_0 - 1}{R_0} = 1 - \frac{1}{R_0}$$

Critical vaccination threshold



$$p_c = 1 - \frac{1}{R_0}$$

Eradication - Justification

- No natural non-human reservoir
- Effective vaccine – lifelong serum immunity
- Although vertical programme, can have positive impact on health services
  - e.g. eradication of smallpox (1958-1980) was basis of EPI
  - (failed) eradication initiative for yellow fever (1915-1977) led to first national administrative health systems in many countries
- Governments of the world committed in 1988 with initial aim to eradicate disease by 2000, revised to 2005, and now 2012...
- Would be second infectious disease to be eradicated after smallpox
  - Guinea worm eradication may occur before polio

Eradication is difficult...

- More difficult than Smallpox eradication since
  - Need more than 1 dose of vaccine
    - (3 in developed countries with good sanitary conditions, 8 or more in countries with poor sanitation)
  - AFP may be caused by other enteroviruses or infections; therefore symptoms less specific
  - Asymptomatic transmission means that infection occurs without knowing about it
  - Larger R0 ? (variable estimates e.g. see Anderson and May 1991)
  - Bigger more mobile population (7 vs 4 billion, international travel)

- Also
  - Expensive (US$6 billion external expenditure to date)
  - Diversion of resources?
  - Achievable?

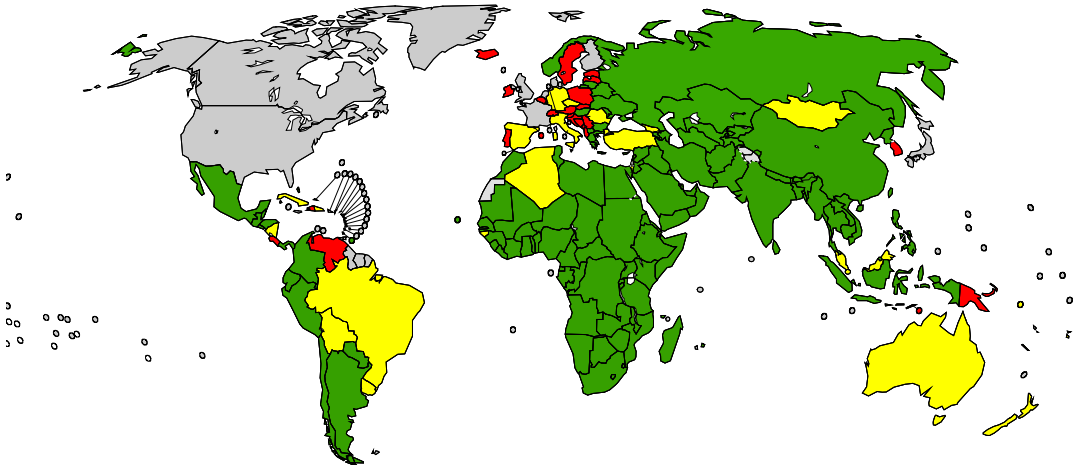
Global polio surveillance

- Monitoring of AFP cases
- Need to distinguish polio derived AFP from other causes (Guillain-Barré syndrome, trauma, transverse myelitis and other enterovirus infections)
- >30,000 AFP cases now undergo clinical, epidemiologic and virologic investigation every year by a network of laboratories co-ordinated by CDC and WHO
- Any wildtype polio viruses are sequenced to allow identification of origin of outbreak
- But ‘silent spread’ can occur, since only 1 in 200 infected develop AFP

Surveillance quality

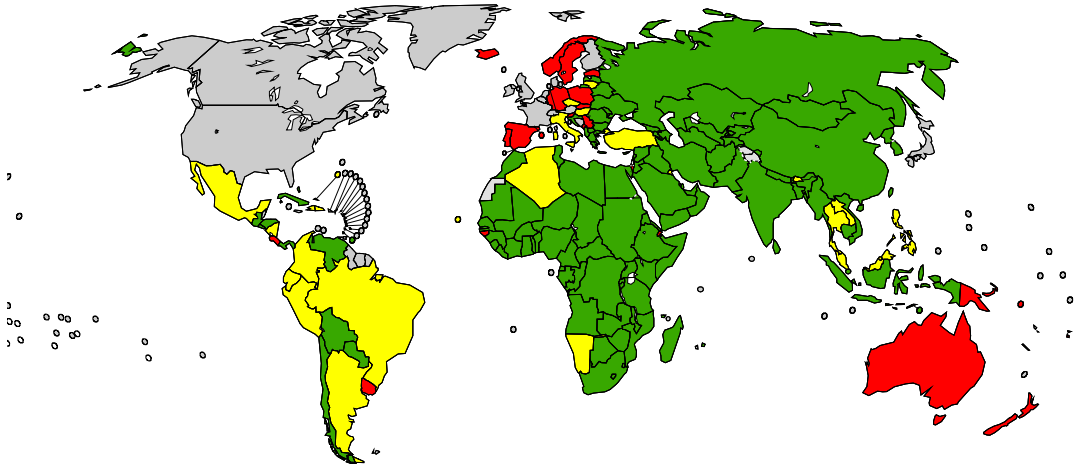
non-polio AFP cases per 100,000

< 0.5	0.5 -1
≥ 1	No AFP



Sample Collection

< 60%	60-80%
≥ 80%	No AFP



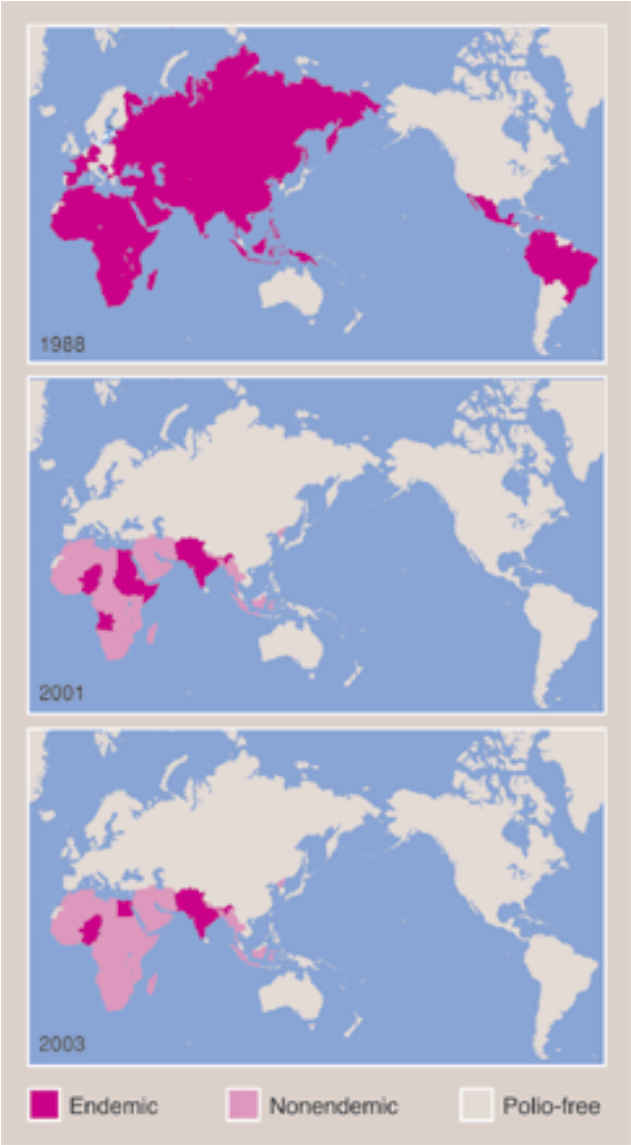
January – December 2008

Mass vaccination campaigns

NIDs Launch Nigeria

- Cuba first country to have a NID in 1963
- e.g. in October 2004 during four day synchronised NIDs 100 million OPV doses given across half of Africa
- Type 2 has been eradicated globally (last detected in Aligarh, India 1999)

Global polio eradication: end stages



Reduction in incident cases of paralytic polio from 350,000 in 1988 to ~2000 from 2001

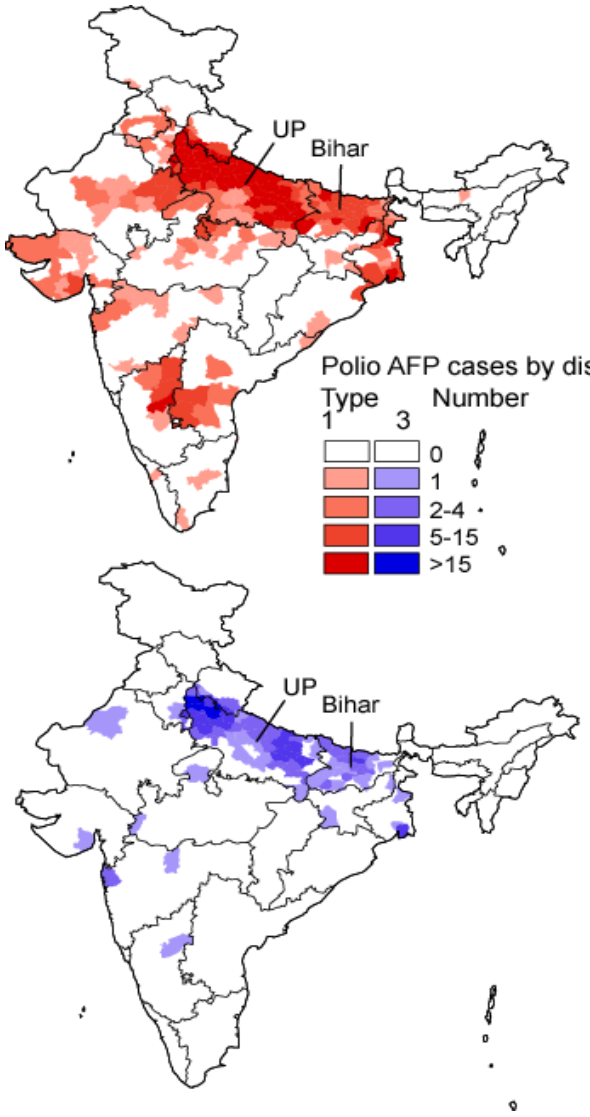
“99% of the job is done”

Stopped poliovirus transmission in the Americas, Western Pacific and Europe

Challenges and cases studies

- Vaccine failure
  - Improving the vaccines
- Failure to vaccinate
  - Controlling endemic infection
- Outbreaks in polio-free countries
  - Predicting and preventing outbreaks of poliomyelitis
- OPV as a source of disease
  - Preventing and controlling ‘vaccine-derived’ poliomyelitis

Vaccine failure - Polio persistence in India



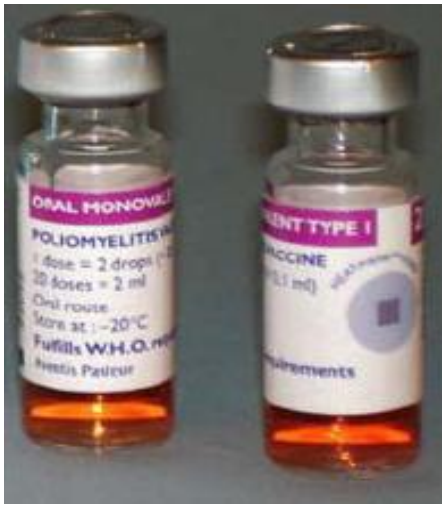
Poliovirus	Location	Cases	Matches	Vaccine efficacy (95% CI)
Type 1	rest of India	1512	361	21 (15 - 27)
	Bihar	387	158	18 (9 - 26)
	Uttar Pradesh	2522	1108	9 (6 - 13) **
Type 3	rest of India	221	79	21 (8 - 33)
	Bihar	136	53	22 (4 - 36)
	Uttar Pradesh	847	342	9 (3 - 15)

** significantly different from rest of India, $p < 0.01$

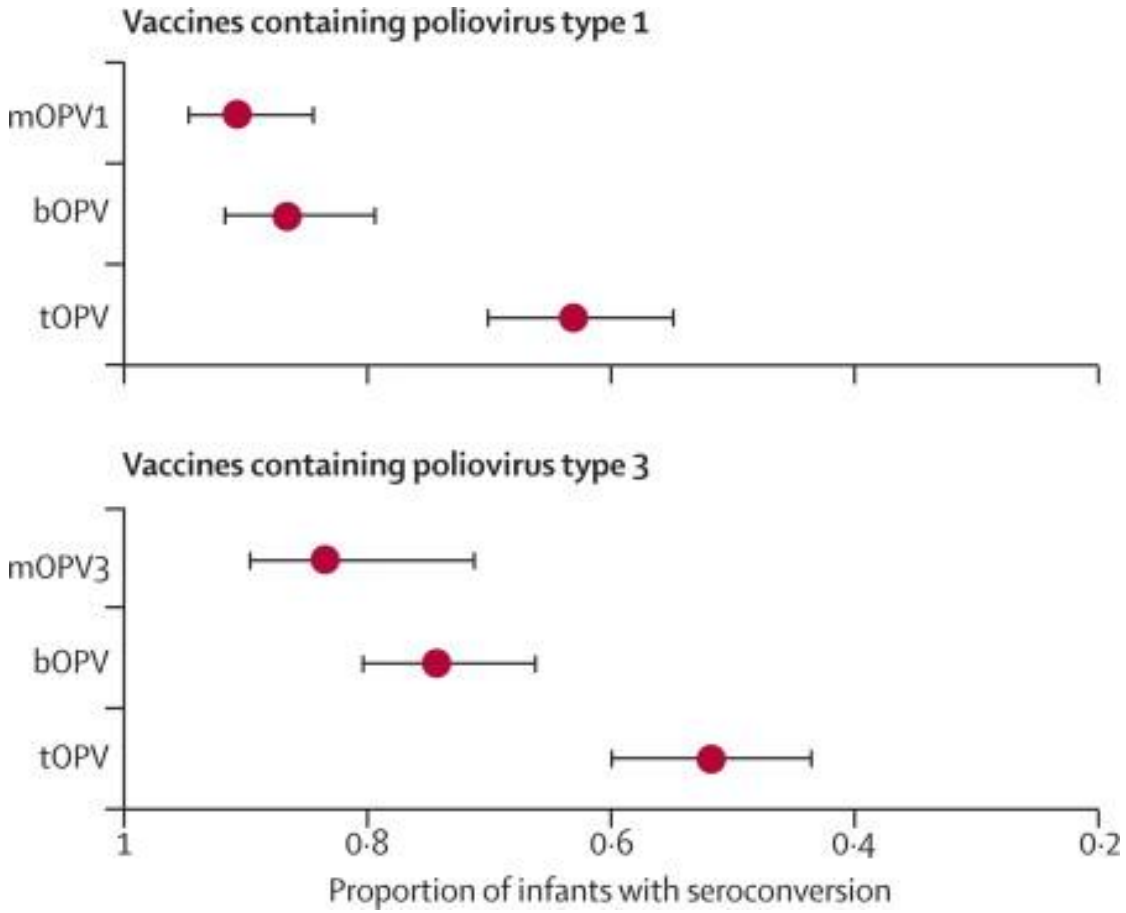
Grassly et al. Science 2006

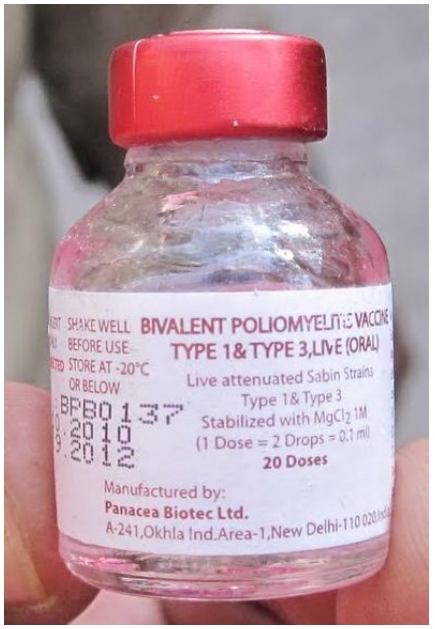
New strategies

- Type 2 wild poliovirus eradicated in 1999 and type 3 transmission geographically limited
- New high potency (10^6 $CCID_{50}$/dose) monovalent type 1 vaccine developed and licensed through extraordinary public-private partnership in less than a year 2004-5
- Potentially more efficacious since no interference between vaccine strains
- First used in India and Egypt in 2005
- Estimated field efficacy in India and Nigeria 3-4 times that of the trivalent vaccine against paralytic type 1 poliovirus



Bivalent OPV – protecting against both wild-type viruses





Non-inferiority and superiority assessments after a cumulative two-dose schedule of vaccines (Sutter et al. *Lancet* 2010)

Failure to vaccinate - Vaccine boycott in Nigeria

Special Report

March 10 - 16, 2007

Weekly Trust

Page 7

OPV can wipe out a whole generation - *Prof Kaita*

Isa Sa'idu

Professor Haruna Kaita is a staff in the faculty of Pharmaceutical Sciences, Ahmadu Bello University (ABU) Zaria. He has carried independent research on the polio vaccine and concluded that the ... tested scientifi... ...ption.

WT: It is quite sometime since you raised the doubts that led to the controversy surrounding polio immunisation; have your doubts been cleared?

Professor Kaita: I am even surprised that you are here; I thought that this controversy has died down naturally because a lot has been said about it. I thought my contribution and other commentators were quite ...

Professor Haruna Kaita

...e found these ...ere you also able ...ally surface since ...ildren.

...That you should ... somebody no ...o ask when the

...dity in a seven

... angle. What ... is a risk to ...rmaceutical ... matter how

... se as it is ... from 0-59 ...ns if it is ... an entire ... that no

... ed and ...mple, it

there is a problem of generational development in the whole world especially in developing countries that are the victims.

In a nutshell, what we are saying is that these OPV are poisonous, those concerned should rectify them before anarchy surfaces especially in our country. We can't see danger and keep on going with it up till everything is destroyed.

WT: Do you sense any conspiracy with the way the polio vaccination is being handled?

Kaita: I do not want to comment over this conspiracy theory because it is political while I am a scientist. I don't want to speculate. I want to pin these issues to hard facts and evidences as we did with the OPV. I have solid evidences with me that the OPV batch we analysed were contaminated.

NAFDAC has also tested these OPVs and

Special Report

March 10 - 16, 2007

Weekly Trust

Page 8

Why we oppose polio vaccines - *Nafi'u Baba-Ahmed*

Nafi'u Baba Ahmed is the secretary general of the Supreme Council for Shari'a in Nigeria. In this interview with Weekly Trust, he gave reasons why his organisation oppose the oral polio immunization exercise as being carried out.

Nasiru L. Abubakar

WT: What is your organisation's position on the ongoing polio immunisation?

Nafi'u Baba Ahmed: Our position has never changed. Our position remains that we are against the polio vaccine programme as it is today and as they are continuing tomorrow, because our basic fears have not been addressed.

As an organisation, the Supreme Council for Shariah in Nigeria, as a policy, has finished what it has to do on the issue of polio. We have undertaken the responsibility of drawing the attention of appropriate authorities- federal, state and local governments, and even individuals. We have sensitised people to be aware of the debilitating effect of the oral polio vaccines (OPV) as is being done in Nigeria. We have finished.

All over the world today, the Supreme

is not so much an issue of concern. Our major concern has to do with the fact that, scientifically it has been tested and proven that there are some agents that are capable of preventing pregnancy. There are also some unknown contaminants. The federal government of Nigeria denied it that there were no contaminations. Then they accepted it that there are contaminants and there is also some level of these agents but that they are not in sufficient quantities to cause concern.

Still on the safety side, the World Health Organisation (WHO) that is at the fore-front, with UNICEF, World Bank and what have you, they have been saying that they have determined that a child has to be vaccinated, given OPV a number of times.

But in Nigeria some children are given 20 times more than that. Nobody has bothered to enquire as to the possible debilitating consequences in future. All they are concerned with is 'make sure everybody is given willingly

these diseases or in even helping parents to alleviate the cost of medical treatments, not even a kobo but they are expending billions upon billions on polio.

Look at, for instance (pointing to a newspaper report) EU spent $12billions-12billion is about is more than one third of the total debt Nigeria was owing, for over 20 years we were worried about that debt. But EU alone is spending over $12billion on polio in Nigeria. But nobody will spend even $1million on measles or malaria. There is more to it than meets the eye.

Why polio? They have forced us to change the order of our priorities in terms of healthcare delivery. And why are they choosing polio vaccination because that can be applied to targeted countries. This is why in Nigeria, they are saying it is only in the north. Even in the north it is in the northwest. For example, they said there is one case in Kaduna, just one. But this is a matter that will be on CNN, BBC and so on when in the vein a thousand people may be killed by cerebrospinal meningitis and no body will show concern. These are food for thought for people to ponder.

Then there is this issue which is at the very root of our concern. In 1971, Henry Kessinger,

Nafi'u Baba Ahmed

available everywhere.

Population control in whatever form is unislamic. But it's not only Islam that is kicking against it. The Catholic Church the world over.

Nigeria – strategies for improving vaccine uptake

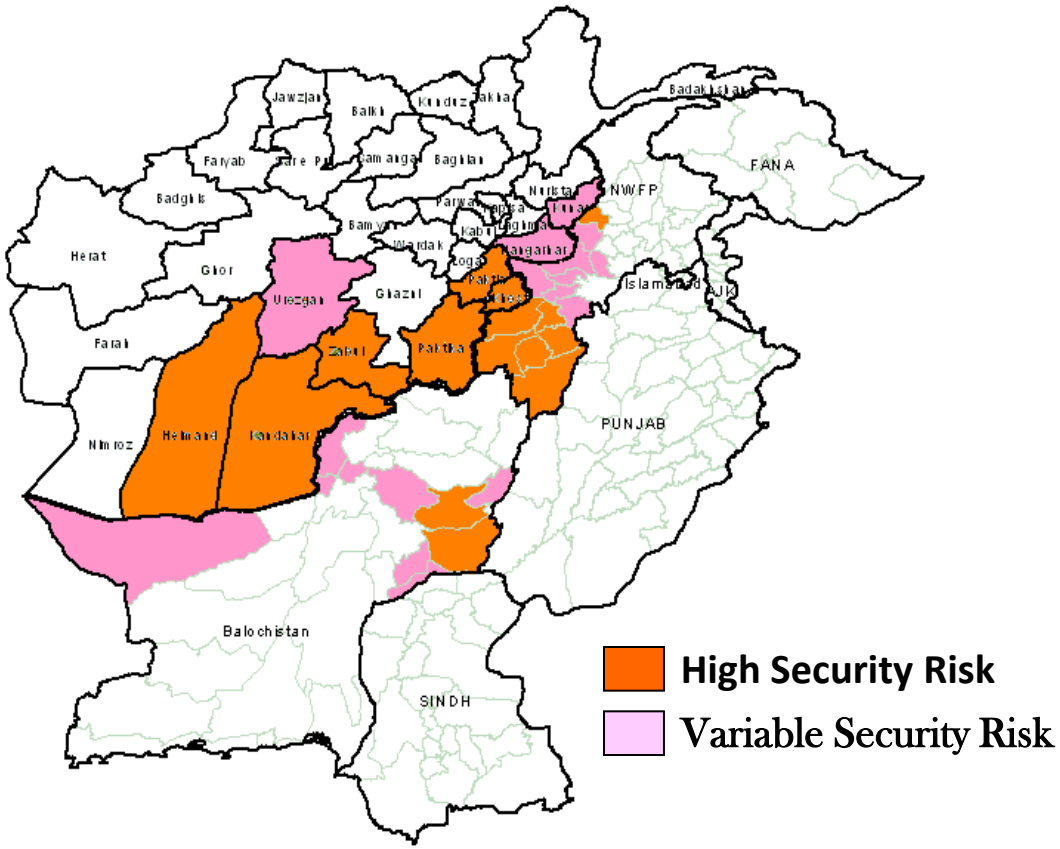
Immunisation Plus Days (IPDs)

- Community dialogue
- Improvements in coverage
- Investment in other healthcare programs

Reduction in transmission in 2009

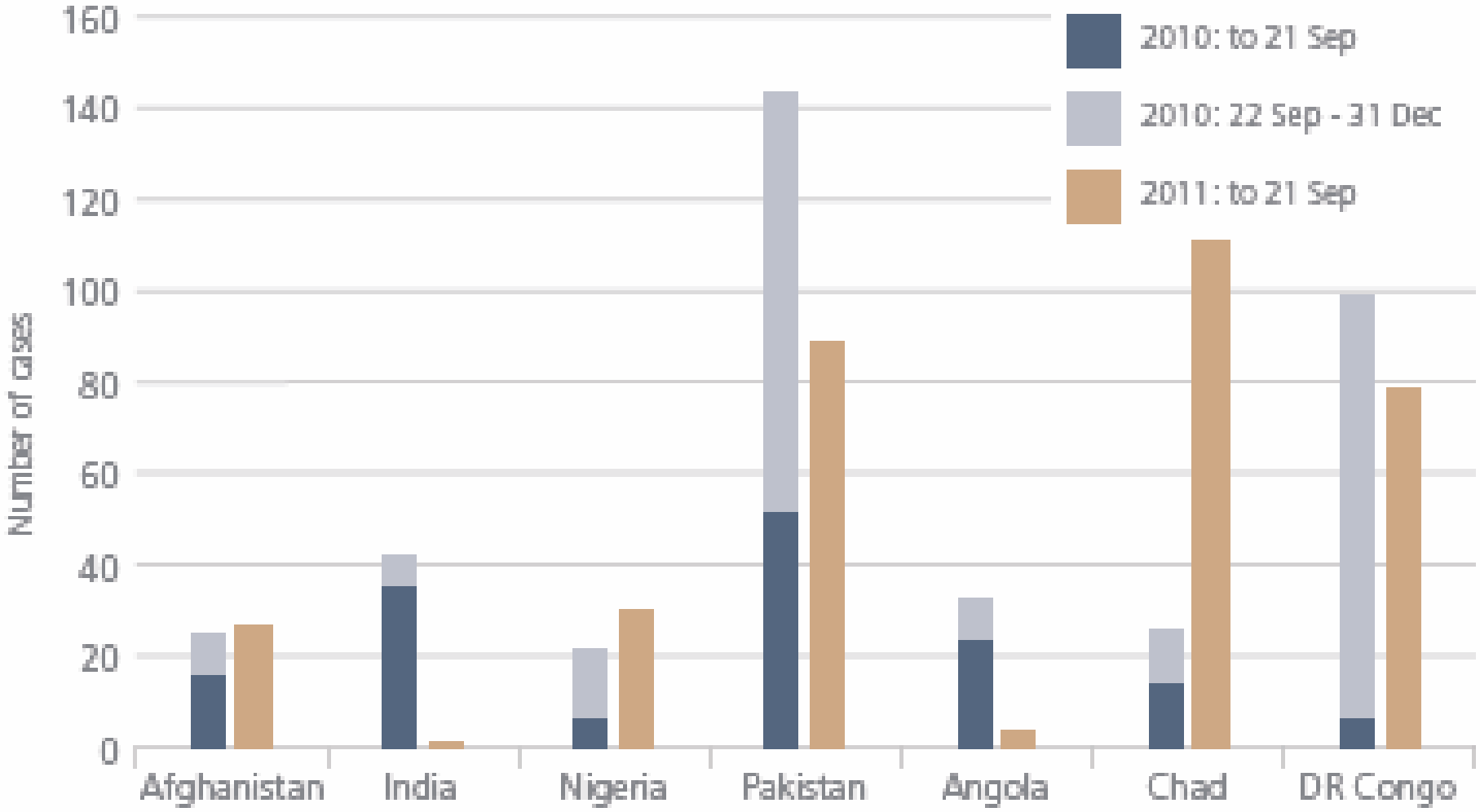
Failure to vaccinate - Pakistan & Afghanistan

- Shared borders areas and populations
- Security risks
- Days of tranquillity



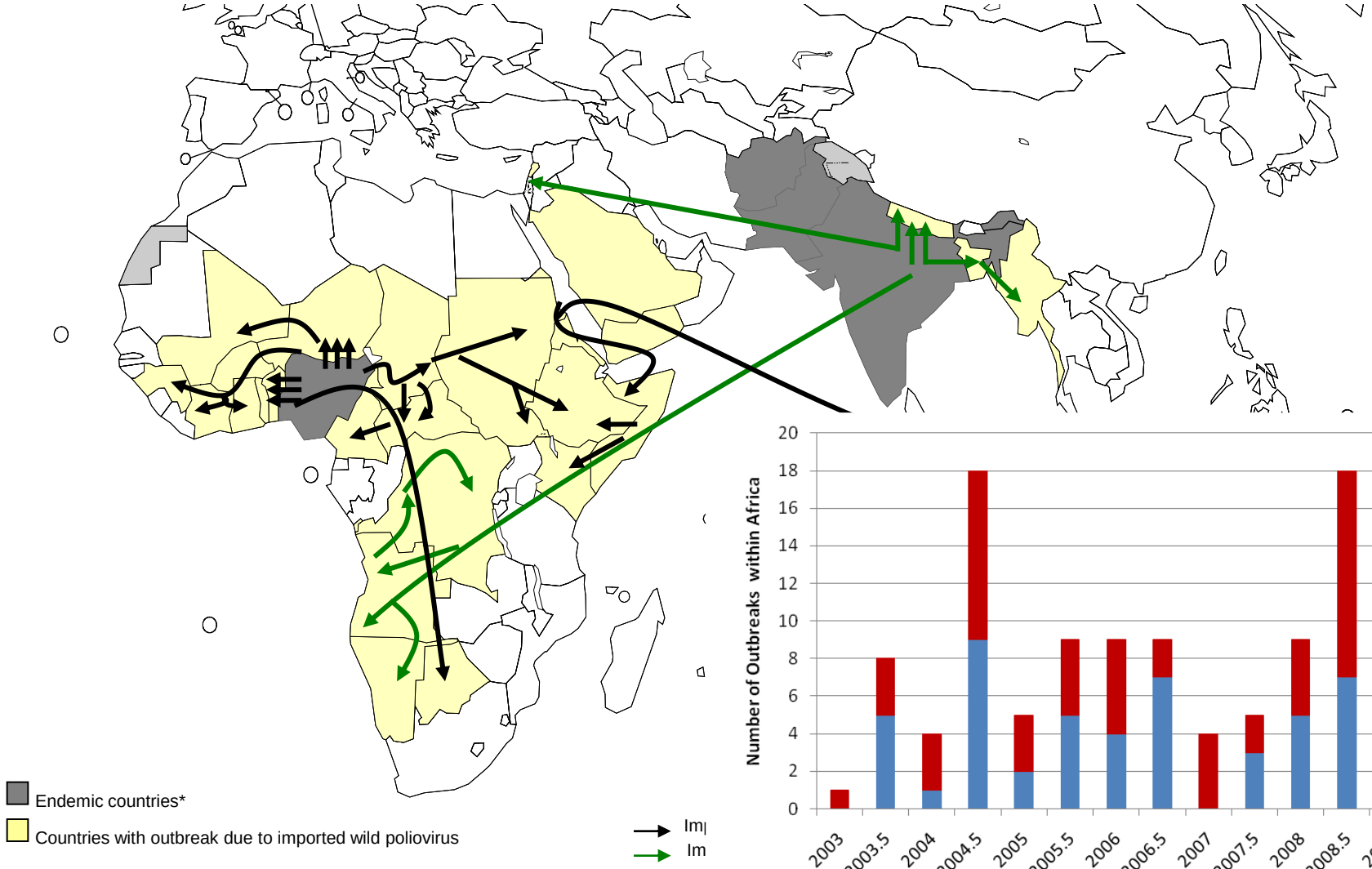
President Karzai Announces Polio Action Group to Coordinate all Ministries

Comparison of 2010 and 2011



Pattern of outbreaks in polio-free countries

Wild poliovirus spread, 2003-2007



*Data in HQ as of 04 June 2009

Objective of study

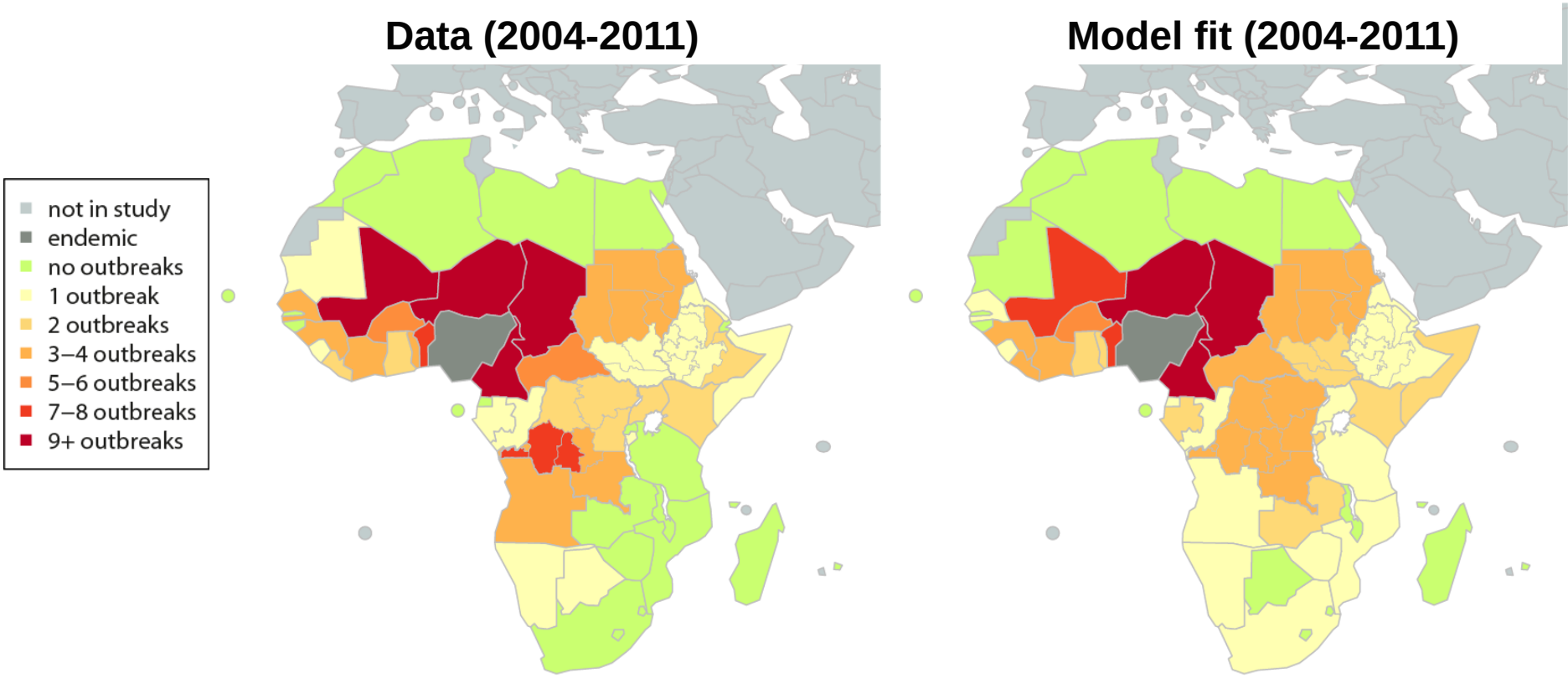
- What factors affect whether an outbreak occurs?
  - Hypothesis is that the following influence where outbreaks occur
    - Population immunity
    - Exposure to poliovirus from affected countries
    - Other variables?
- How can outbreaks be best controlled?
  - Impact of vaccination

Results: Variables associated with outbreaks[a]

- Poor population immunity
  - Low proportion of children aged 0-4 years reporting 3+ doses of OPV[b]
    - Routine coverage and SIAs not as significant
- High force of infection from infected countries
  - Bordering Nigeria
  - Movement of people from infected countries to each country x incidence in each country six months previously[c]
  - Exposure six months ago higher than exposure 18 months ago
- High rate of infant mortality
  - More than 150 deaths per 1,000 population at-risk

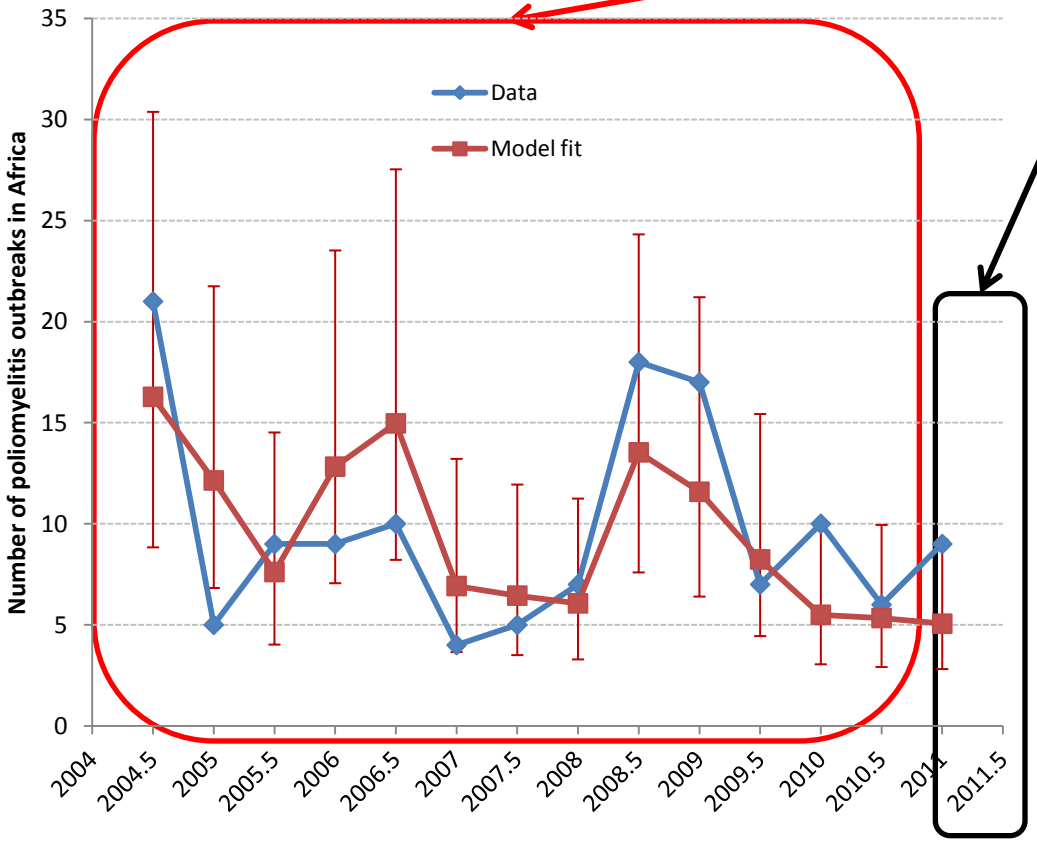
[a]based on mixed effects Poisson regression model fit to data in WHO-HQ as of Sept 2011; [b]based on reports of 'non-polio' AFP cases; [c]based origin of permanent migrants in each country given by census (Parsons et al. 2007)

Results: Spatial trend including partitioned countries



- Model fit captures much of the spatial variation, especially in 'importation belt'
- Overestimation of outbreaks in countries south of DRC

Predicting risk from model variables



1. Estimate parameters for each model variable using data from 2004.5 to 2011

2. Use parameter values from model in 1. with values for each country from 2011 to estimate the outbreaks in 2011.5

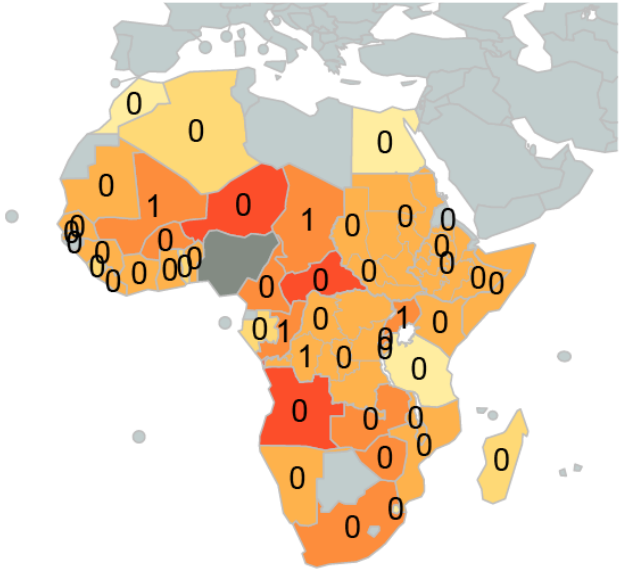
Approach was validated using Receiver-operator characteristic (ROC) analysis.

Analysis suggested a predictive ability of 82%, regarded as a ‘good predictive ability’

The regression model out-performed the approach of using historical propensity

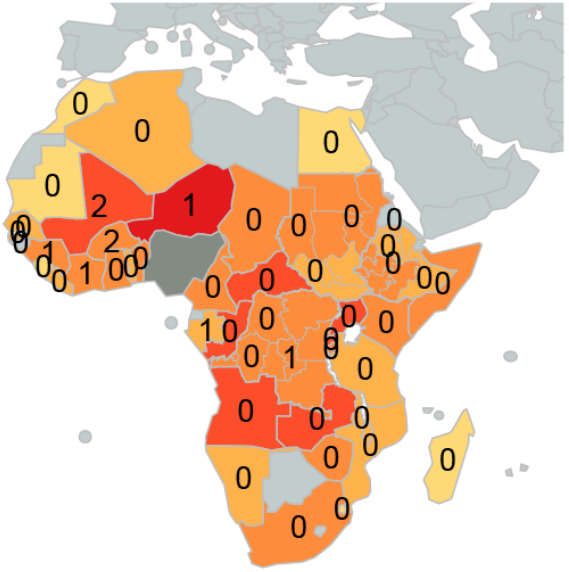
Results: Model predictions for 2010.5 to 2011.5

- Observed and predicted numbers are similar
- Highest risk countries (NIG, CAE, ANG) did not correlate with reported outbreaks
- Some medium risk countries (MAI, CHA, UGA, CNG) reported outbreaks



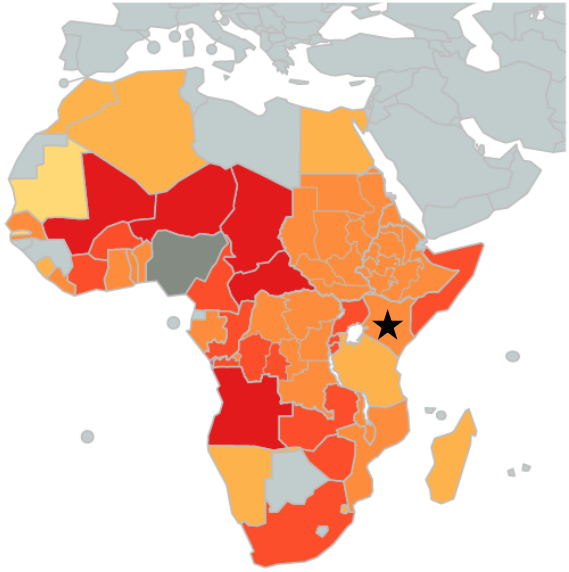
time = 2010.5 Predicted = 4.85 Observed = 5

- Observed and predicted numbers are similar
- Highest risk countries (NIG, MAI, CAE, ANG, ZAM) had some correlation with reported outbreaks
- Some medium risk countries (BFA, CIV, GAB) reported outbreaks



time = 2011 Predicted = 9.1 Observed = 9

- Predicted risk has increased when compared to previous time-periods
- Highest risk countries (NIG, MAI, CAE, ANG, ZAM) are consistent with previous years



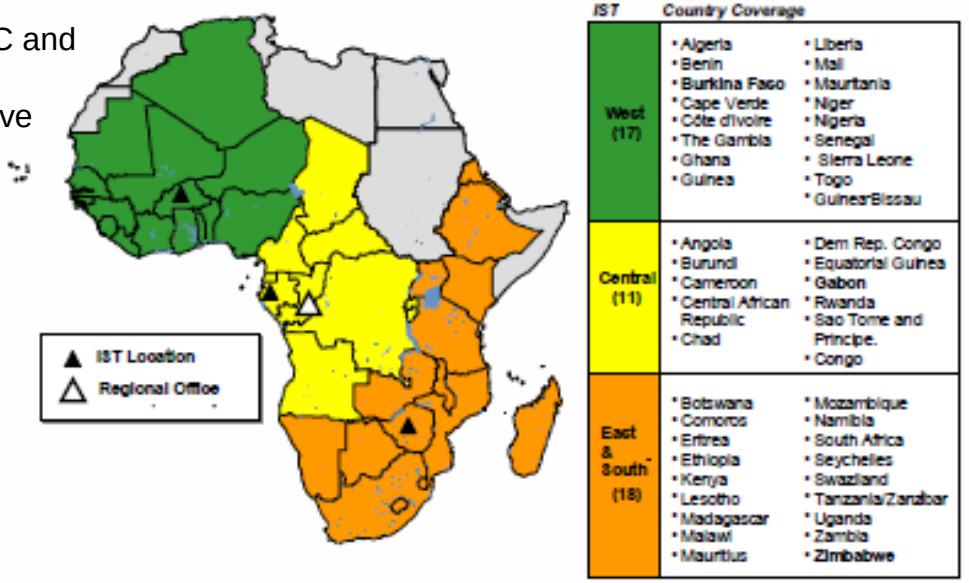
time = 2011.5 Predicted = 15.31

What's driving the predicted increase in risk?

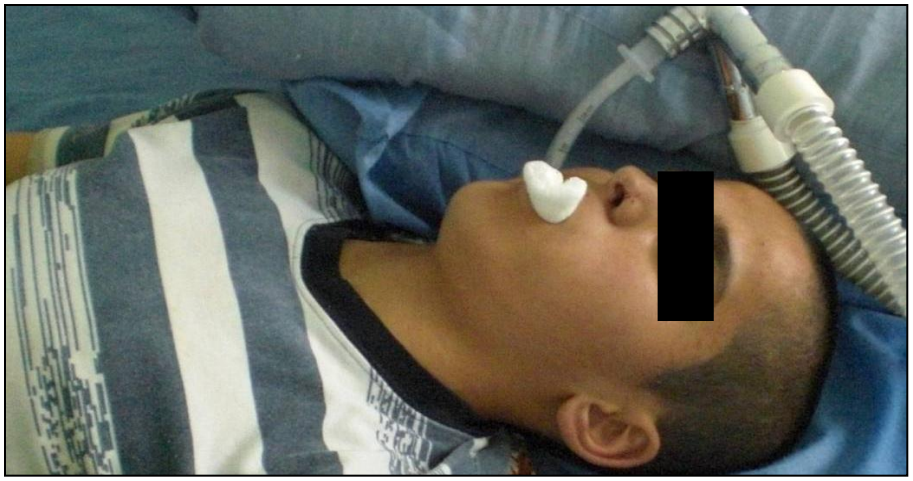
Comparison of data between Jan-Jun 2010 and Jan-Jun 2011

IST region	Number countries included in analysis*	Countries with reduction in AFP**	%	Countries with decrease in 3+ OPV	%	Countries with increase in exposure	%
Central	11	2	92%	7	36%	0	100%
East & south	14	6	57%	8	43%	0	100%
West	14	5	64%	8	43%	2	86%
Emro region	6	1	83%	3	50%	0	100%

*includes partitioning of Sudan, DRC and Ethiopia
** non-polio AFP in children under five years



Explosive new outbreaks due to int'l spread



Tajikistan (Feb-Jul 2010)

458 cases

30% > 5 years of age

Congo (Oct 2010-Jan 2011)

476 cases

80% > 15 years of age

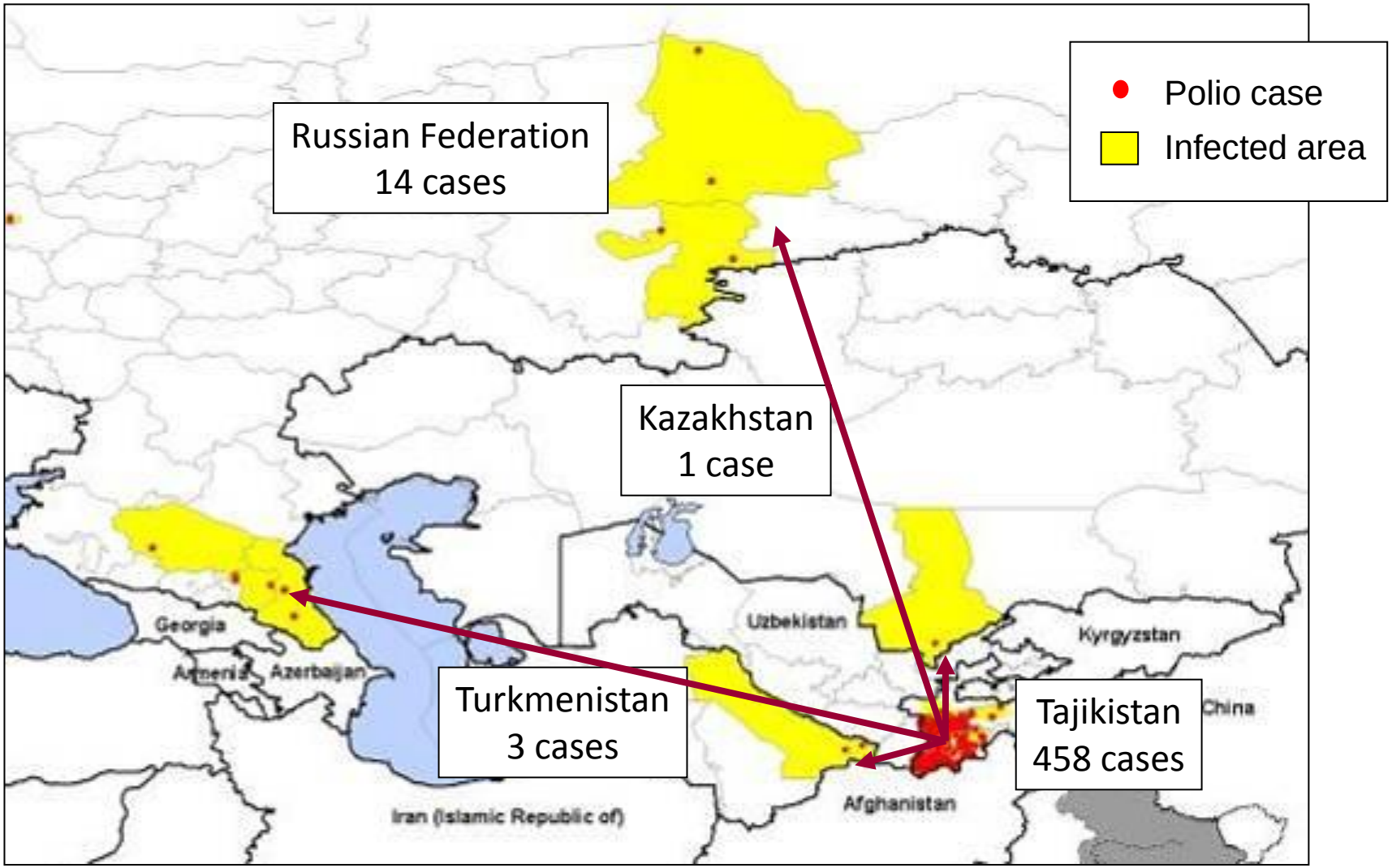
50% mortality

China (Jun 2011 - onwards)

Currently ~10 cases

Older age groups included

2º spread - Central Asia & Caucasus 2010

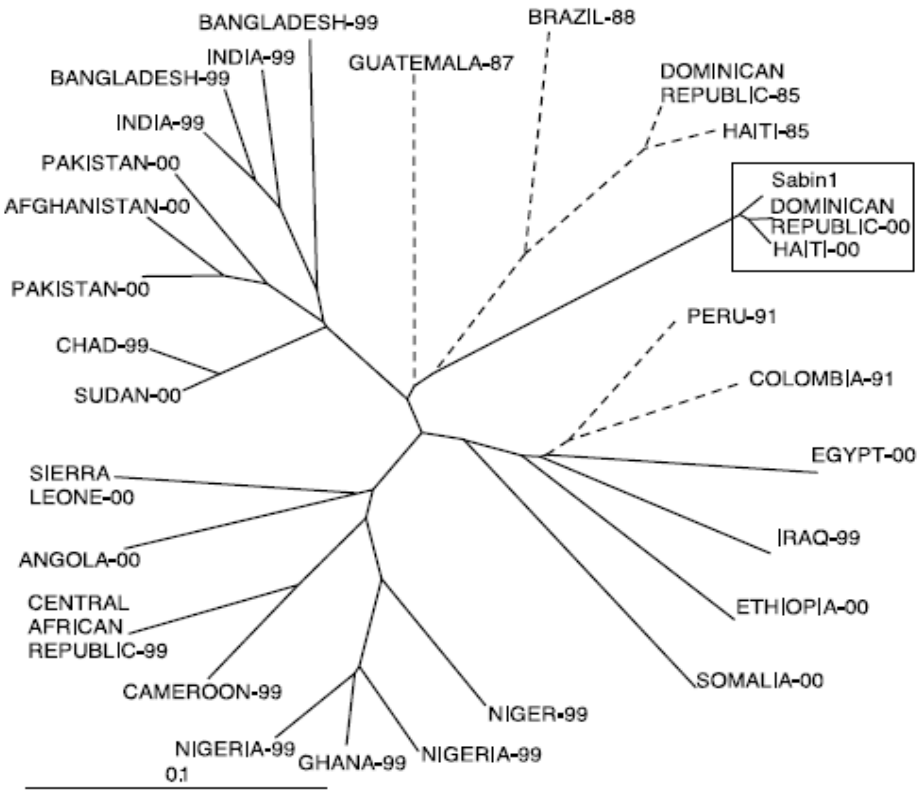


Data in WHO HQ as of
15 Dec 2010

Eradication challenges – cVDPV (1)

- About 30% of immunized subjects excrete partially revertant strains of OPV called vaccine derived polio virus (VDPV)
- If immunization coverage is high, no problem
- However, at low levels of immunity VDPV can spread (i.e. R0 > 1) and fully revert to wild type virulence (cVDPV)
- Leads to outbreaks of paralytic polio

Hispaniola 2000-1



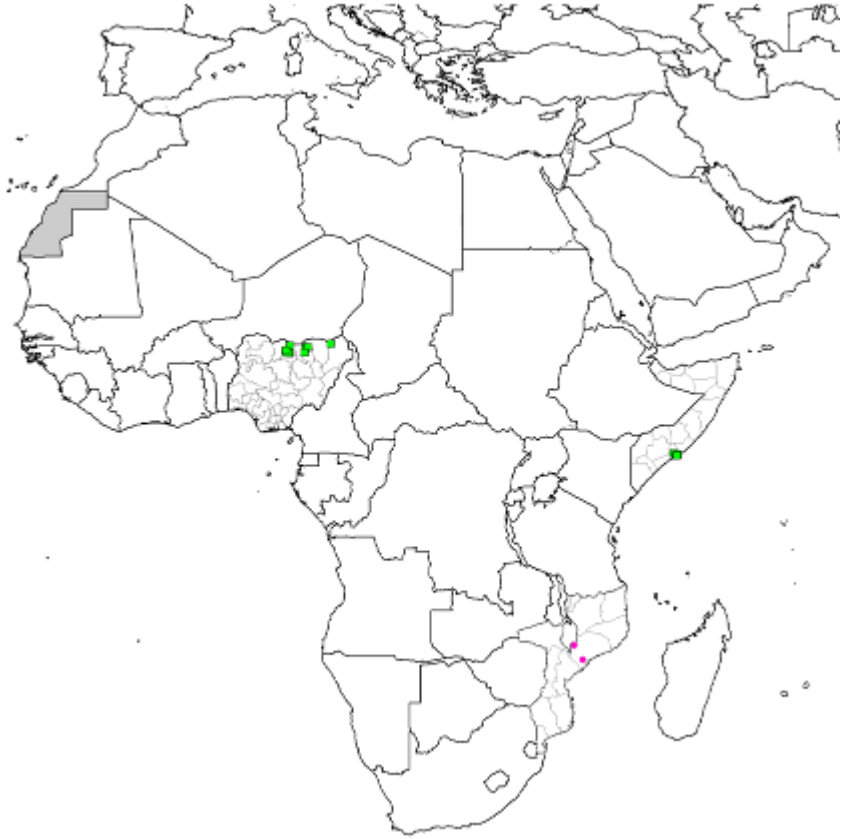
From Kew et al. 2002

Madura Island, Indonesia - cVDPV (2005)

Eradication challenges – cVDPV (2)

- cVDPV outbreaks have now occurred in Hispaniola (2000-1), Philippines (2001), Madagascar (2001-2), China (2004), Indonesia (2005), Nigeria (2004-)…
- Retrospective studies have also identified cVDPV in Egypt (1988-93)
- Many cVDPV have been recombinants with wild enteroviruses
- Will be an important problem as countries scale-down immunization after polio considered to have been eliminated

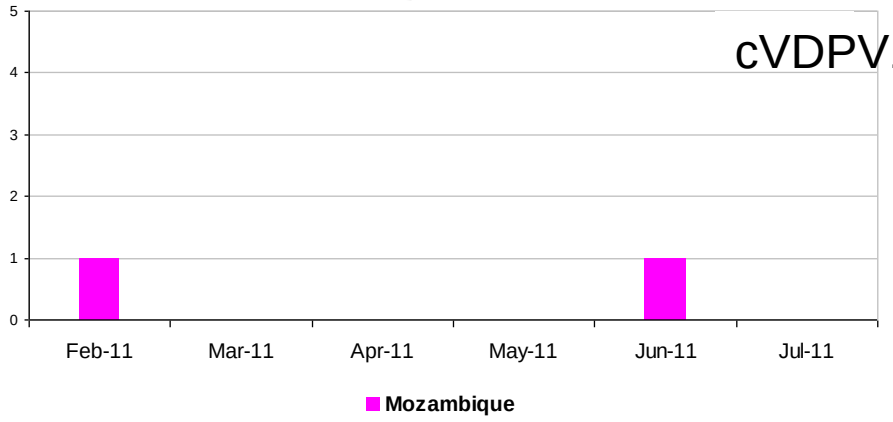
Circulating Vaccine-derived Poliovirus*, previous 6 months

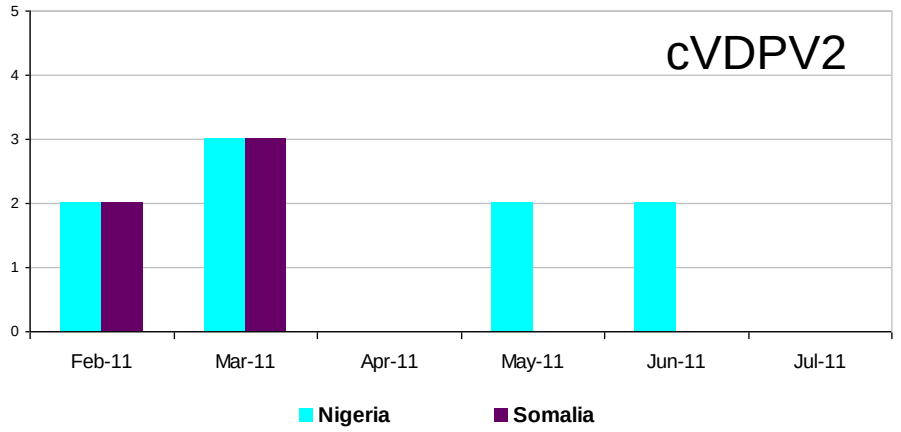


Rolling 6 months
10 Feb – 09 Aug 2011
16 cVDPV cases

- cVDPV1 (2 cases)
- cVDPV2 (14 cases)
- cVDPV3 (0 case)

cVDPV monthly distribution of cases by country (rolling six months)





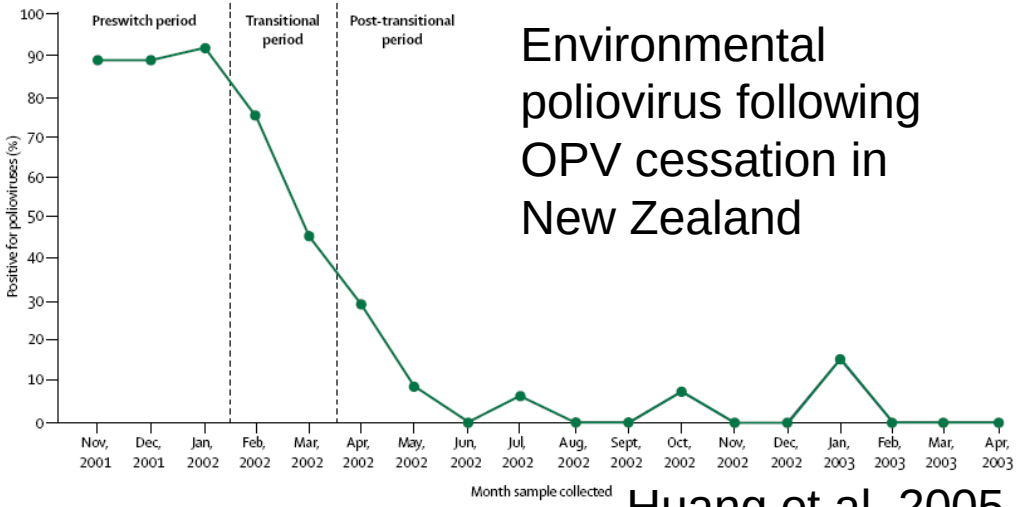
Data in WHO/HQ as of 09 Aug 2011

Additional eradication challenges

- Laboratory escape (esp. as present in stool sample etc. not collected for polio work)
- Factory escape (during manufacture of IPV)
- iVDPV - continued excretion of virus by vaccinated individuals immuno-compromised individuals

Strategies for the cessation of OPV use (1)

- Abrupt (global OPV cessation day)
  - Excretion ceases after <6 months – environmental VDPV should disappear before enough new susceptibles
  - But, many possible sources for wildtype or VDPV introduction
  - Stockpile 850 million doses of monovalent OPV owned by WHO to control outbreaks by localised high coverage repeat immunisation
  - mOPV may itself reintroduce cVDPV depending on population movement



Environmental poliovirus following OPV cessation in New Zealand

Huang et al. 2005

Strategies for the cessation of OPV use (2)

- Potential role for IPV
  - becoming vaccine of choice in wealthier nations (e.g. since 2004 used in UK), since risk of VAPP now outweighs that of wild poliovirus
  - Manufacture from Sabin poliovirus now being developed
- Problems
  - Must be injected
  - Low mucosal immunity (not yet demonstrated effective at preventing transmission in countries with poor sanitation)
  - Waning rather than life-long immunity in absence of circulating OPV?
  - Early vaccination schedule may have low seroconversion rates
  - Currently expensive, but enough to vaccinate all the world's children could be produced within 5-7 years

Further reading

- **Grassly NC et al. New strategies for the elimination of polio from India. *Science* (2006) 314:1150-1153**
- **O'Reilly et al. A Statistical Model of the International Spread of Wild Poliovirus in Africa Used to Predict and Prevent Outbreaks. PLoS Medicine (2011) e1001109**
- **www.polioeradication.org ; up-to-date reports of eradication progress. Look at reports from the Independent Monitoring Board too**
- **TED lecture given by Bruce Aylward (Assistant Director General of WHO; polio and emergencies) in 2010 (definitely worth watching – 20mins)**
- The Bulletin of the World Health Organization Special theme issue (2004) - Polio Eradication End-Stage Challenges Volume 82:1-81
- Minor PD Polio eradication, cessation of vaccination and re-emergence of disease Nature Rev Microbiol (2004) 2:473-482
- Aylward et al. in *The eradication of infectious diseases* (eds. Dowdle, W. R. & Hopkins, D. R.) p. 61-74 (John Wiley and Sons, Chichester, 1998).
- Kew O et al. Outbreak of poliomyelitis in Hispaniola associated with circulating type 1 vaccine-derived poliovirus. *Science* (2002) 296**:**356-359