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Correlates of protection against enteric infections: what can be learned from poliovirus vaccines?

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@VaccineEpi

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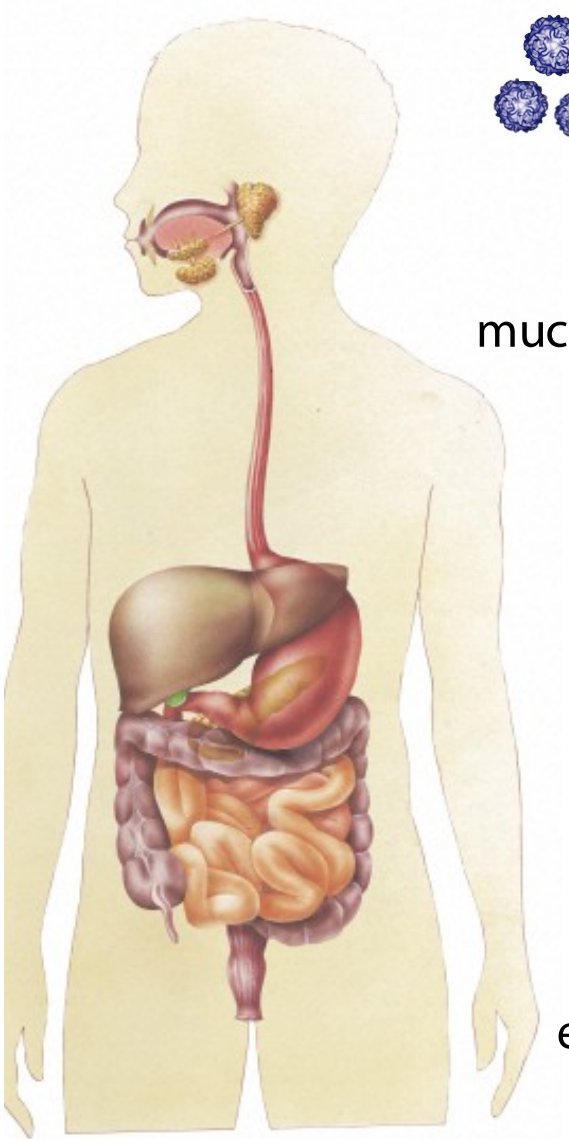
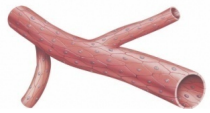
Poliovirus pathogenesis



ingested poliovirus

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

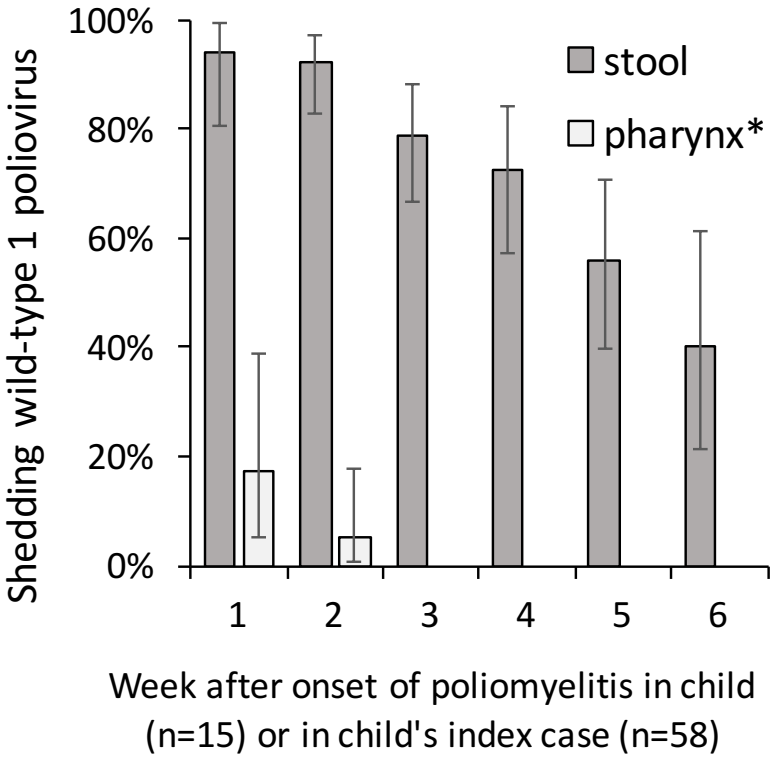
lymph nodes
(cervical and mesenteric)



blood

extraneural tissue

central nervous system

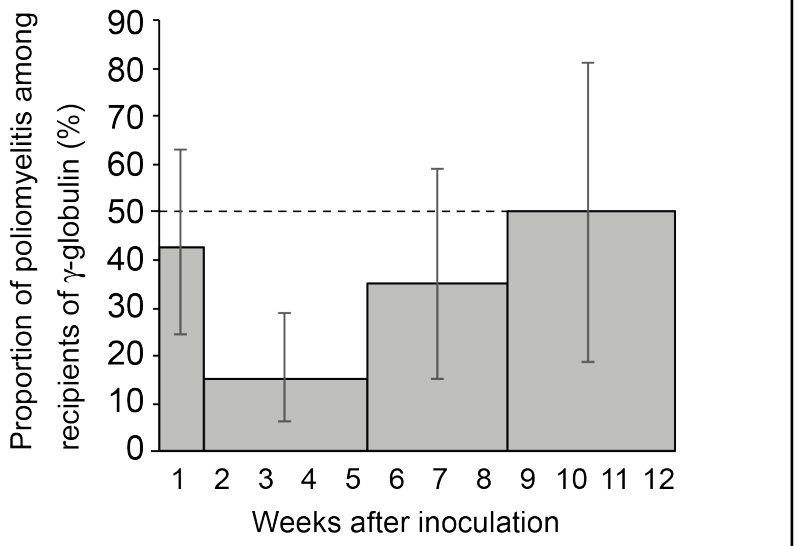


*pharynx sampled weeks 1-2 only; Marine et al. *Am J Hyg* 1962

Serum neutralising antibodies (NAb) are a mechanistic CoP against poliomyelitis

Passive transfer of neutralising antibody is protective against poliomyelitis

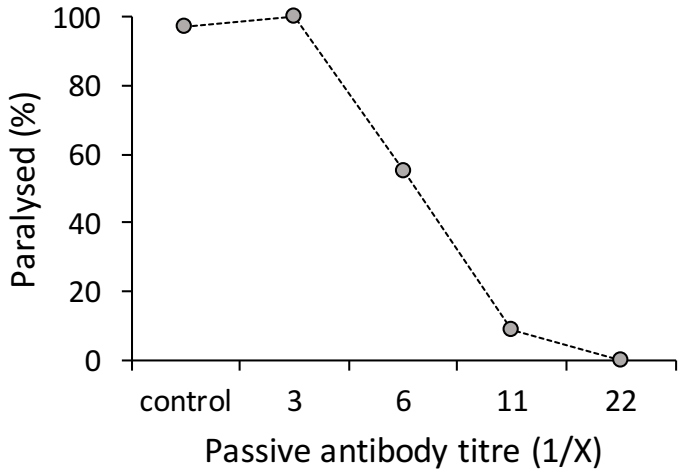
Randomised placebo-controlled trial of gamma-globulin in ~50,000 children in the USA, 1952



Hammon et al. *JAMA* 1953

Protection is dependent on titre of passive antibody in monkey model

IM challenge of monkeys with wild-type 1 PV



Nathanson & Bodian *Bull Johns Hopkins Hosp* 1962

Detection of serum NAb at >=1/8 dilution after active immunisation considered protective

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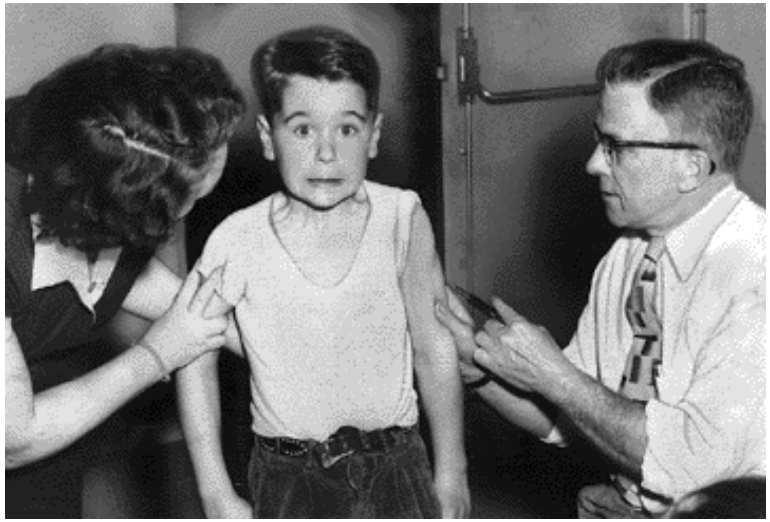

Inactivated Poliovirus Vaccine (IPV)

Oral Poliovirus Vaccine (OPV)

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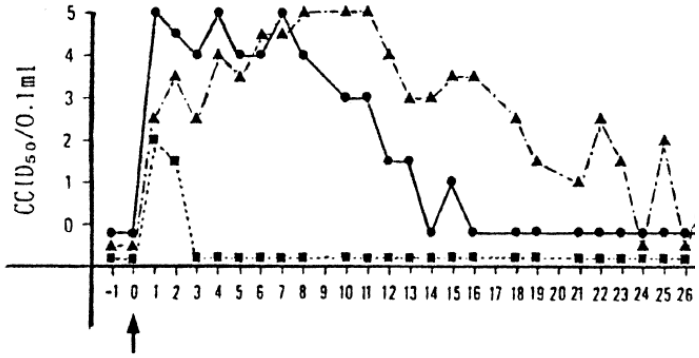
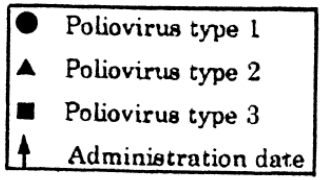
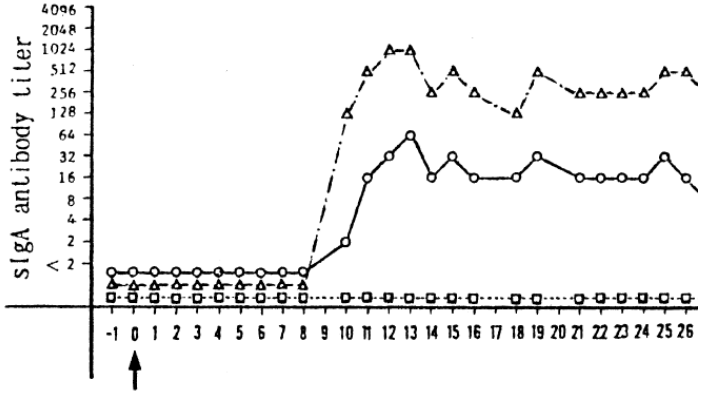
Immunogenicity of OPV

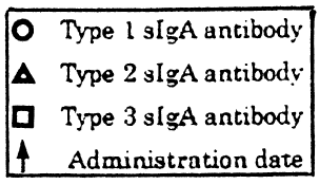
Virus shedding in stool





sIgA in stool (titre)





	Seroconversion (NAb)	
Shed poliovirus (P3) (day 7)	**No**	**Yes**
No	121 (89.6%)	14 (10.4%)
Yes	24 (15.3%)	133 (84.7%)

Morimoto *Kansenshogaku Zasshi* 2001

unpublished data

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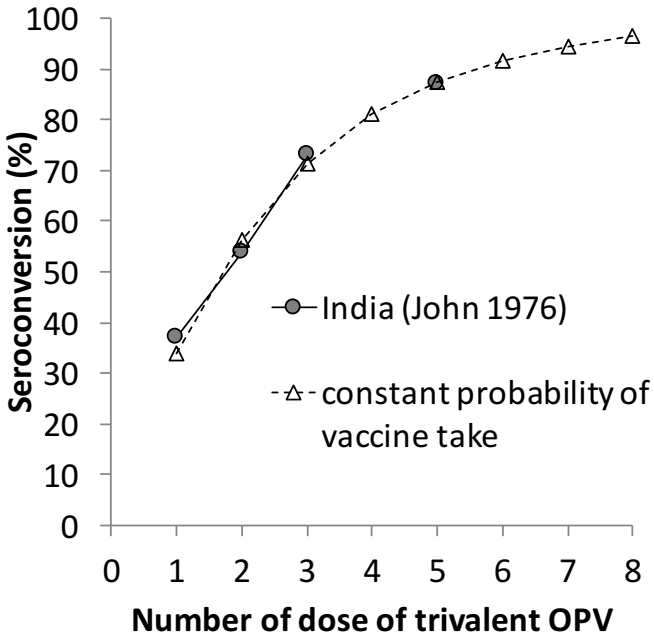
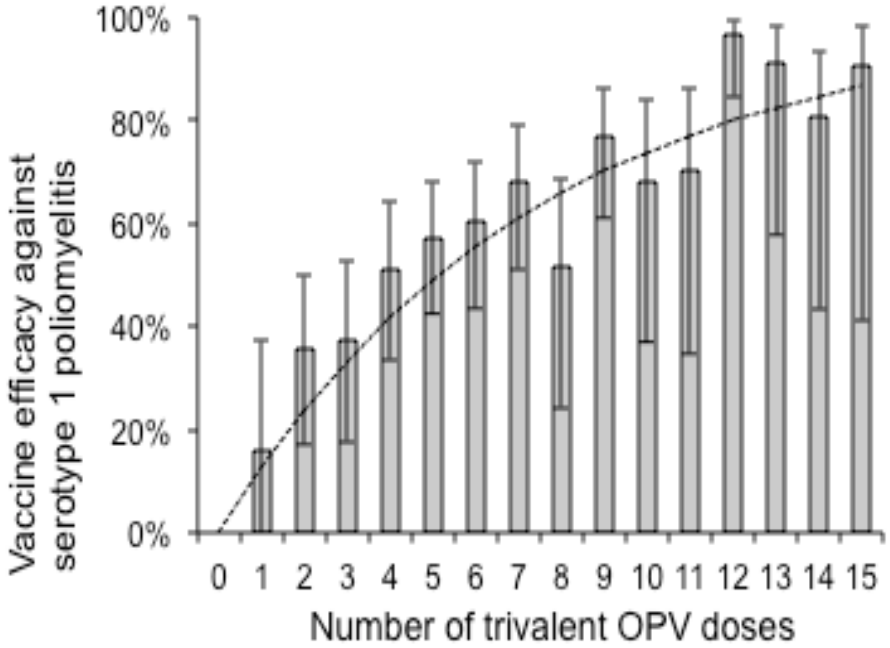
Immunogenicity vs efficacy of OPV

Immunogenicity



John et al. *Br Med J* 1976

Efficacy



Grassly et al. *Science* 2006

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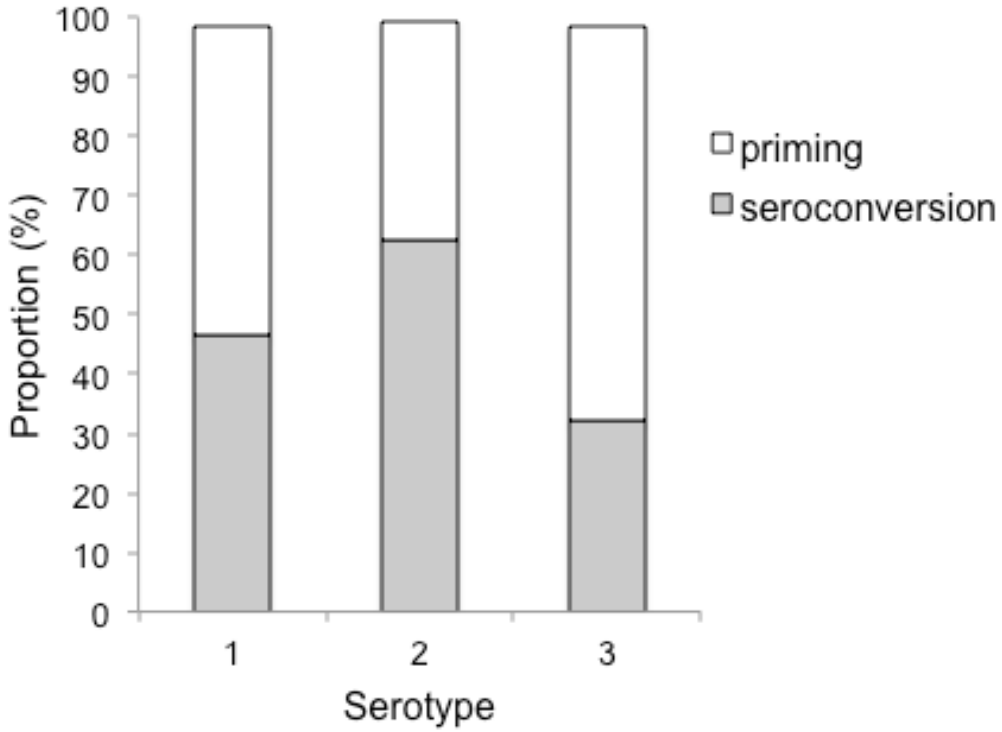
Immunogenicity of 1 dose of IPV given at 4 months of age, Cuba



*'priming' based on detection of serum NAb 7 days after 2nd IPV dose at 8 months; Resik et al. *N Engl J Med* 2013

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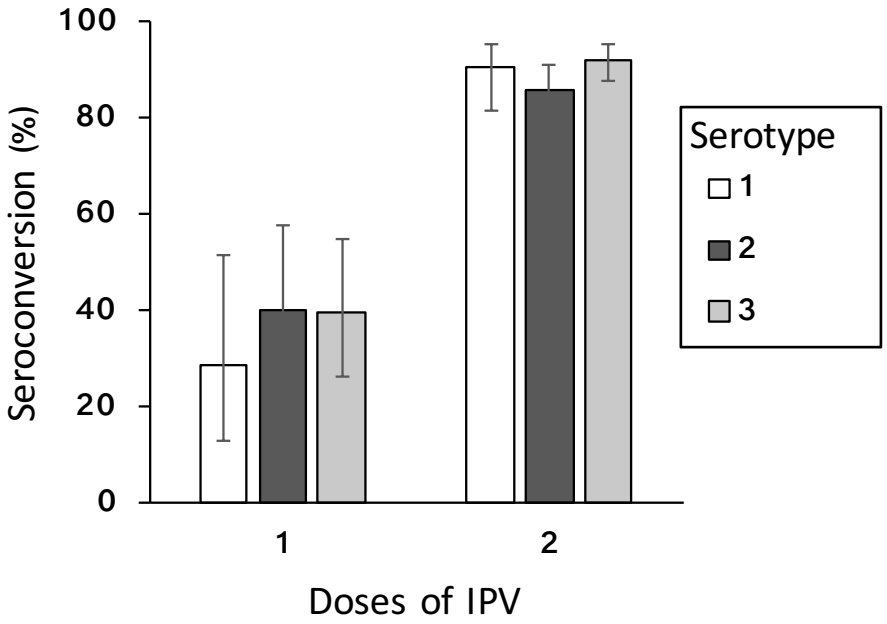
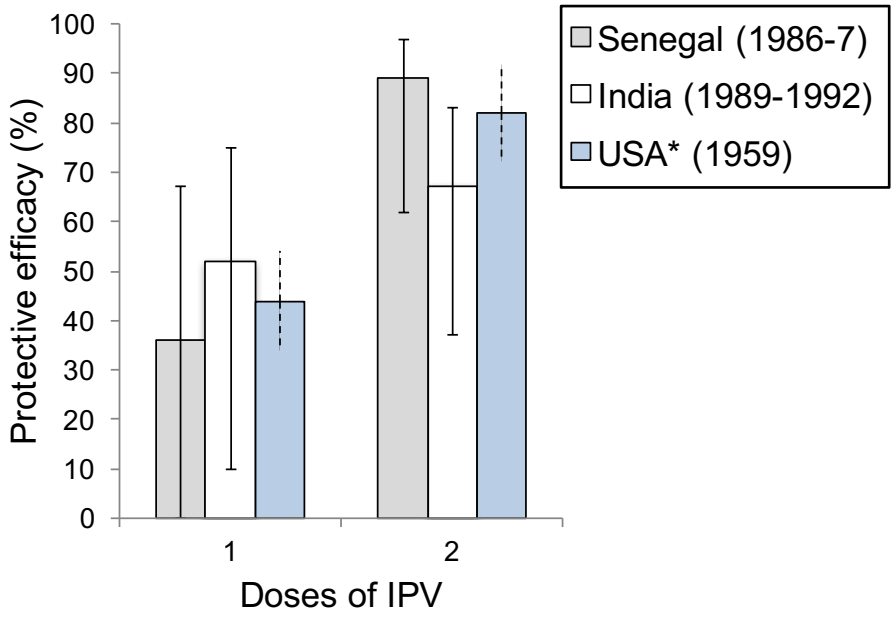
Immunogenicity vs efficacy of 1 or 2 doses of inactivated poliovirus vaccine (IPV)

Immunogenicity



Efficacy



*earlier generation IPV
- - - - 95% CI not available

data from 22 studies reviewed in Grassly *J Infect Dis* 2014

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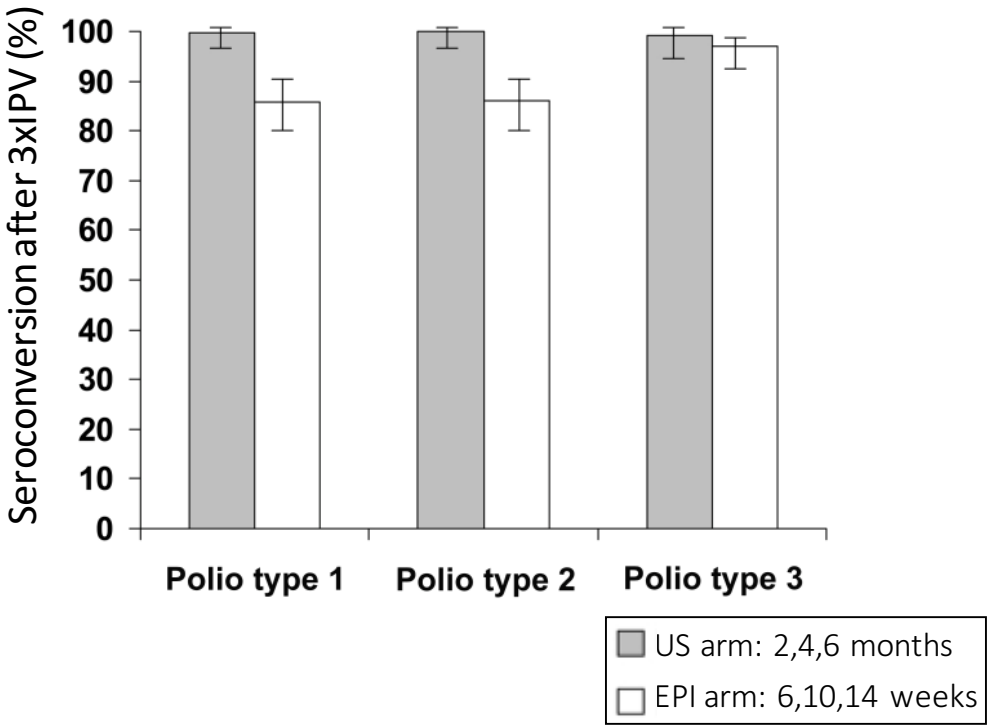
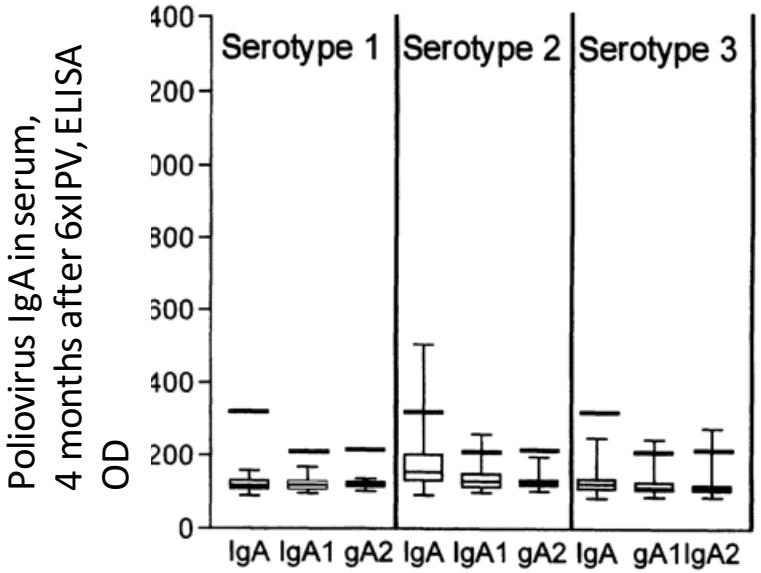
Immunogenicity of full course of IPV





horizontal lines, cutoff levels of the ELISA; boxes show IQR, whiskers show ranges

Dayan et al 2007 *J Infect Dis*; Herremans et al 2002 *Clin Infect Dis*

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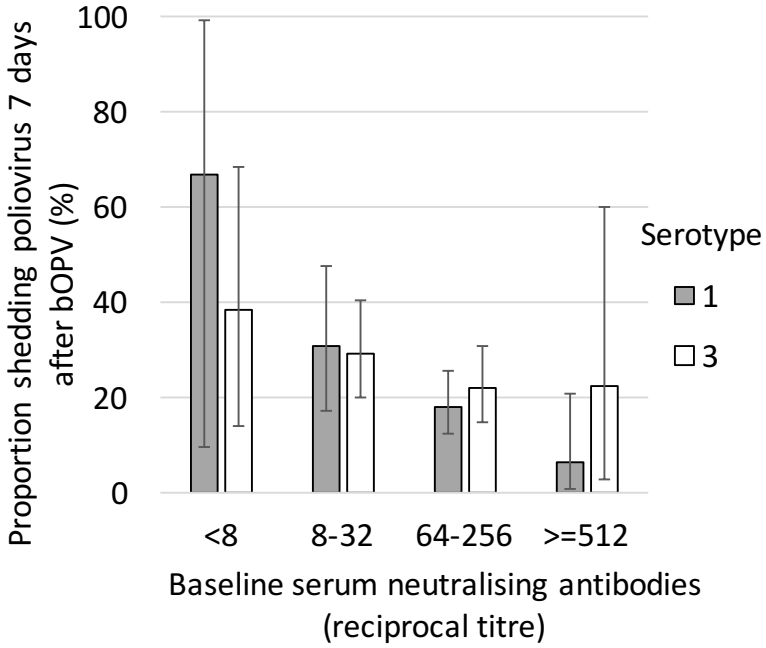
Utility of mechanistic CoP against poliomyelitis

- Permitted licensure of new vaccines (e.g. Sabin IPV in Japan 2012, China 2015)
- Seroprevalence studies used as supplement to poliomyelitis surveillance by Global Polio Eradication Intitiative
- Studies to understand poor oral vaccine effectiveness in low-income countries can use seroconversion as outcome ('correlates of immunogenicity')

Poliovirus infection, OPV challenge model: serum NAb are non-mechanistic CoP after OPV, not IPV

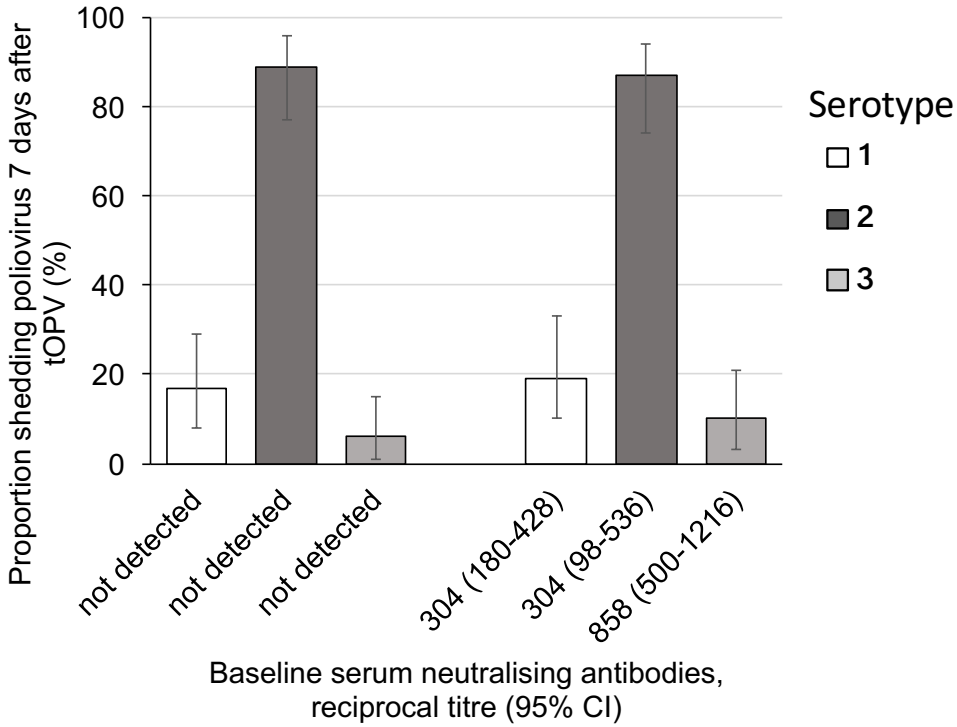
OPV

Children 1-4 years old who had received multiple doses of tOPV



IPV

Infants <1 yr old routinely immunised with IPV or control



unpubl. data

Cuba IPV study collaborative group *N Engl J Med* 2007

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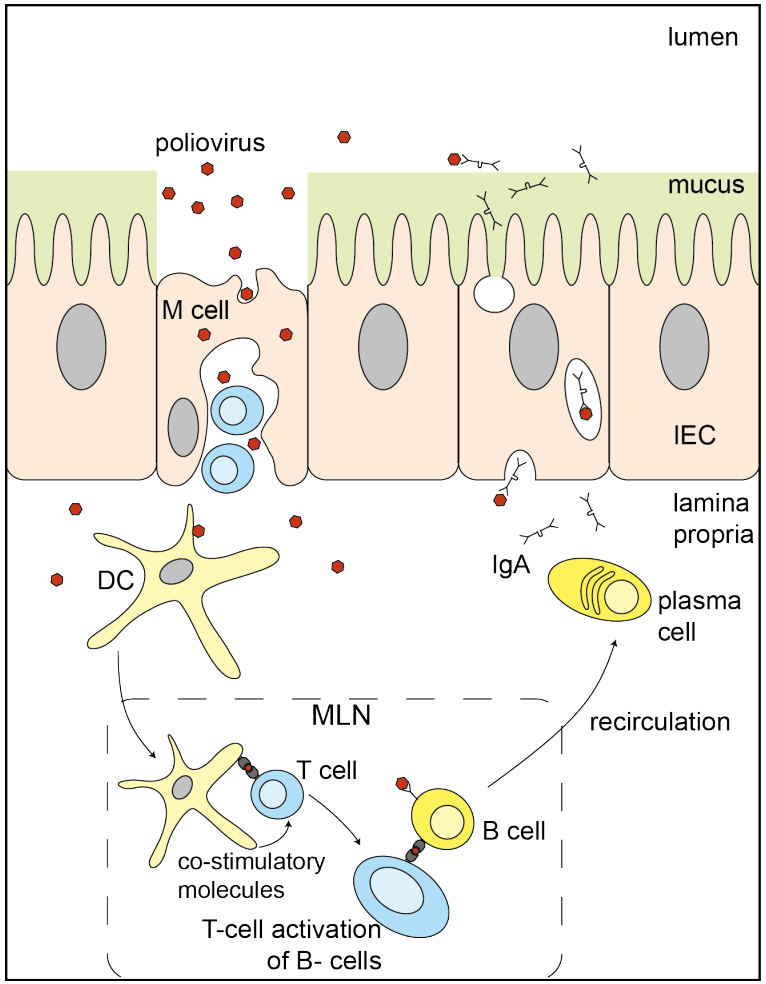
Poliovirus infection: mucosal antibodies are presumed mechanistic CoP

- Neutralising antibodies at mucosal sites: secretory IgA, transudated IgG
- Faecal IgA correlates poorly with shedding after OPV1 challenge (Onorato et al. *J Infect Dis* 1991)
- Few studies of NAb or salivary Ig, esp. in relation to poliovirus infection
- Challenges:
  - Technically difficult
  - ELISA methods non-specific
  - rapid IgA dynamics after vaccination (mucosal immune memory?)



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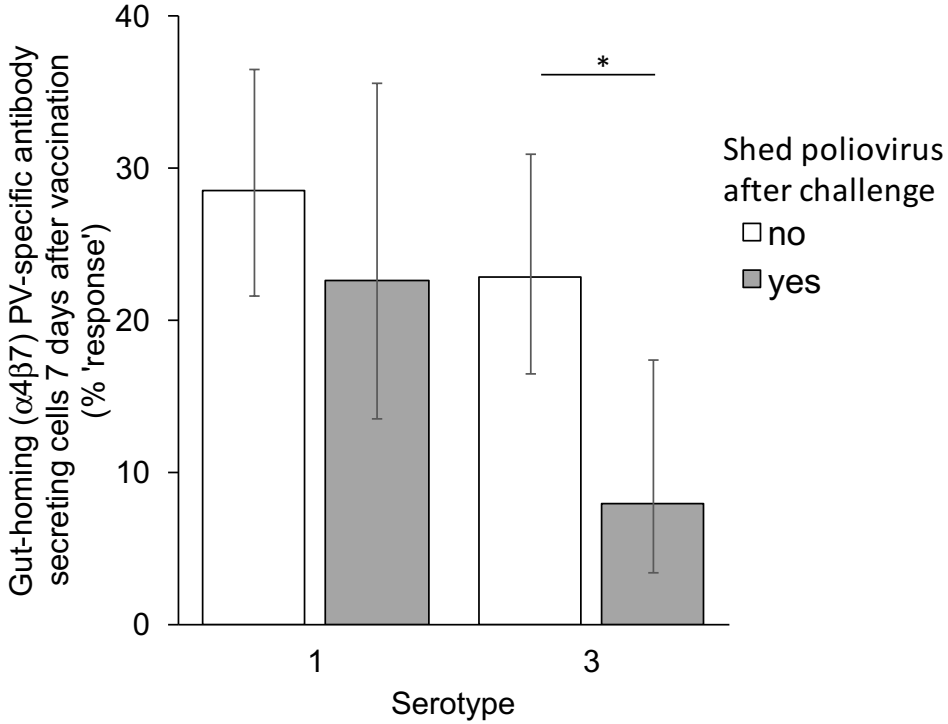
Poliovirus infection: non-mechanistic CoPs in blood after OPV and IPV

Antibody Secreting Cells (ELISPOT)

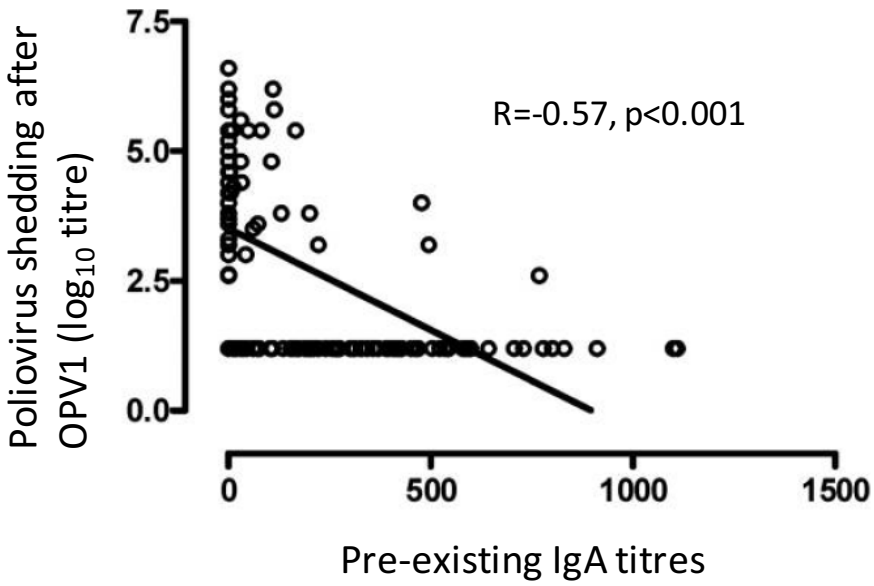
OPV & IPV immunised children



Dey et al. *PLoS ONE* 2016

Serum IgA (ELISA)

Adults, naturally immune & IPV immunised



Buisman et al. *J Infect Dis* 2008

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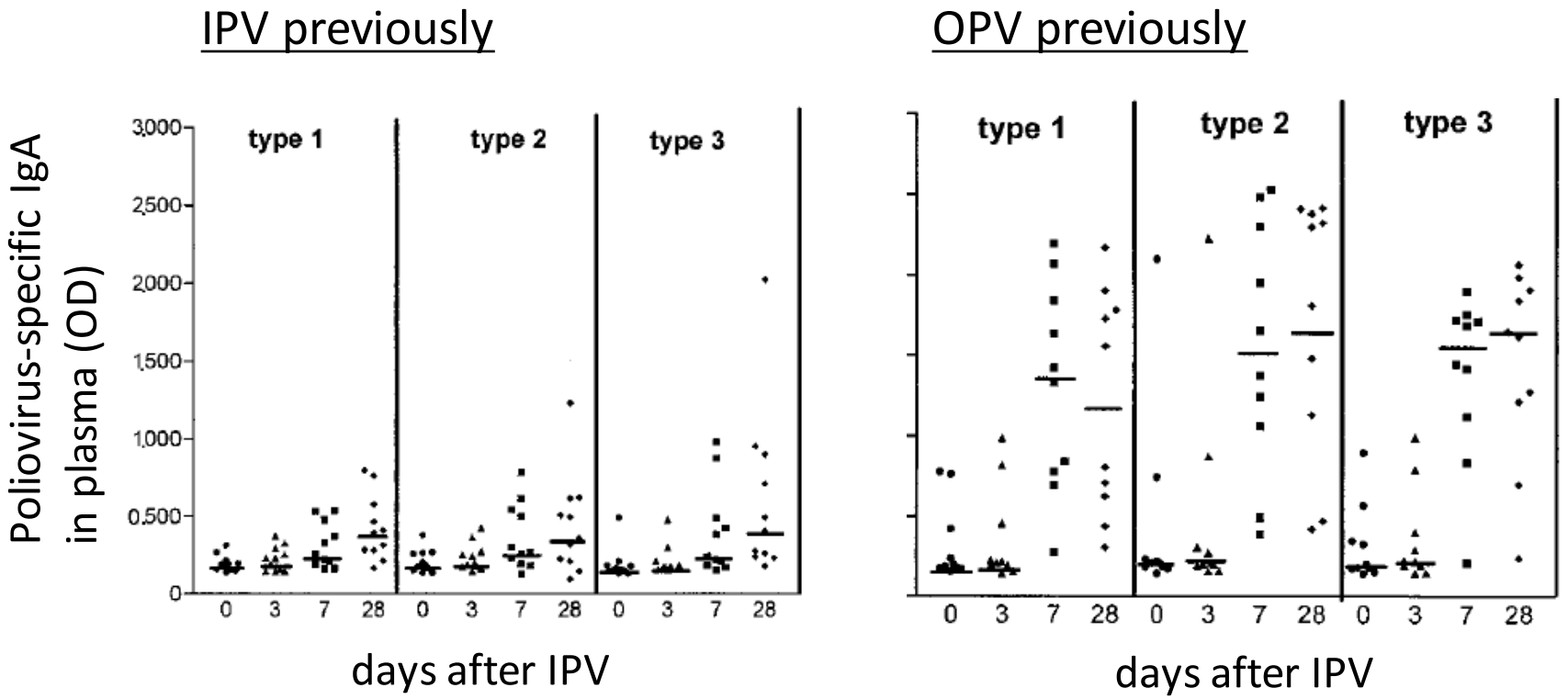
IPV boosts serum and plasma IgA in individuals previously vaccinated with OPV



Herremans et al *J Immunol* 1999

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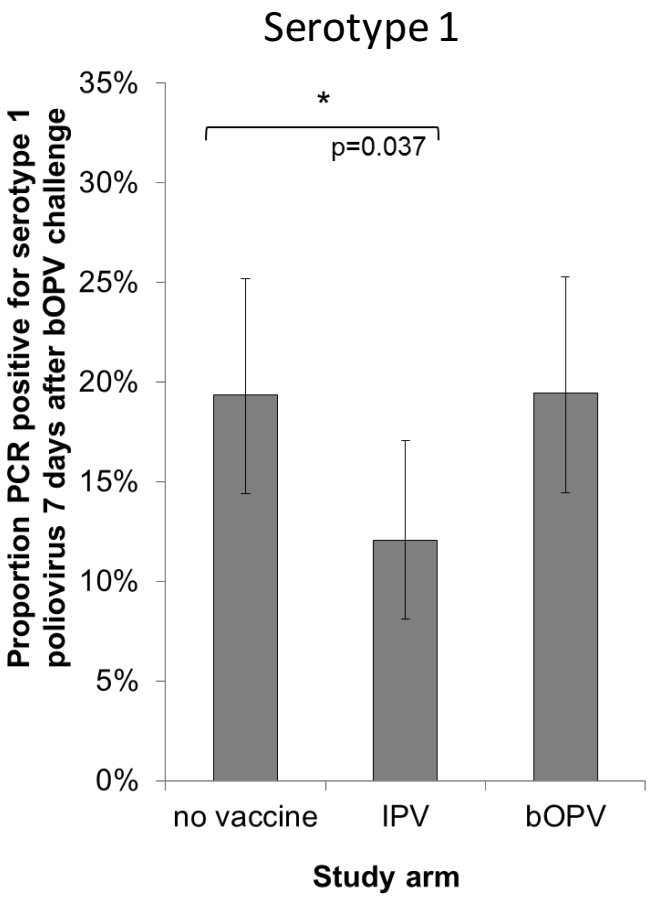
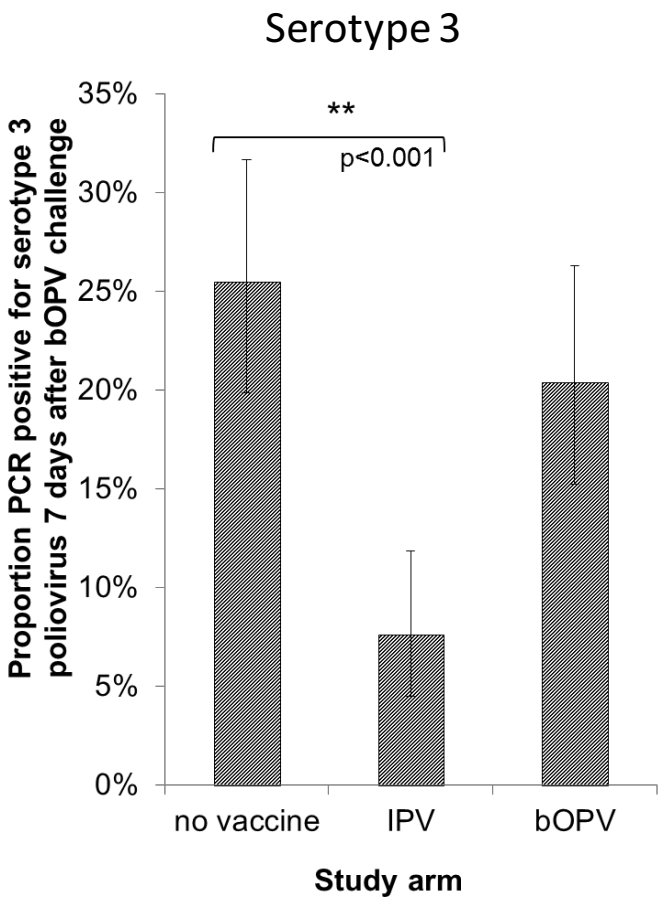
IPV boost protects against bOPV challenge





John et al. *Lancet* 2014

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Summary

- Detection of serum NAb is mechanistic CoP against poliomyelitis

- CoP for mucosal protection against poliovirus infection harder to define and measure – human challenge model has been critical

- Outstanding questions:
  - Role of cellular & innate immunity in mucosal protection
  - Significance & duration of priming for protection against disease
  - Mucosal immune memory

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