



A brief introduction to the non-specific effects of vaccines

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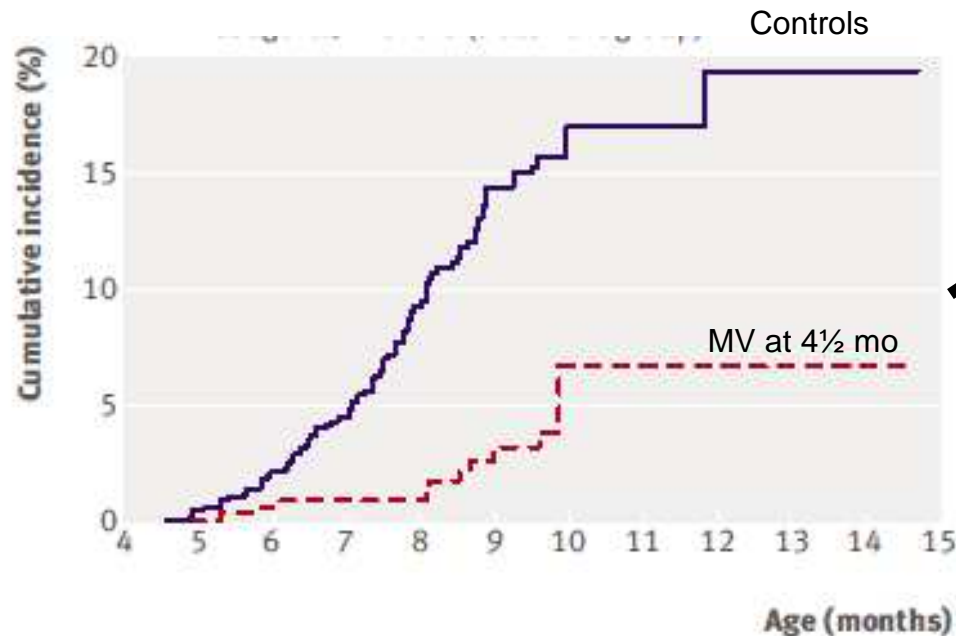
Disclaimer

- I am not an anti-vaccine person
- I am a great fan of many vaccines
- I believe that these vaccines have been instrumental for the incredible reduction in all-cause mortality in low-income countries during the last 3-4 decades
- But not all vaccines work equally well

OPTIMUNISE is built on a conflict of ideas

Public health interventions focus exclusively on prevention or treatment of specific diseases

OPTIMUNISE argues that vaccines often train the immune system: enhancing or misdirecting it!



In this study: measles vaccine also reduced mortality by 30%

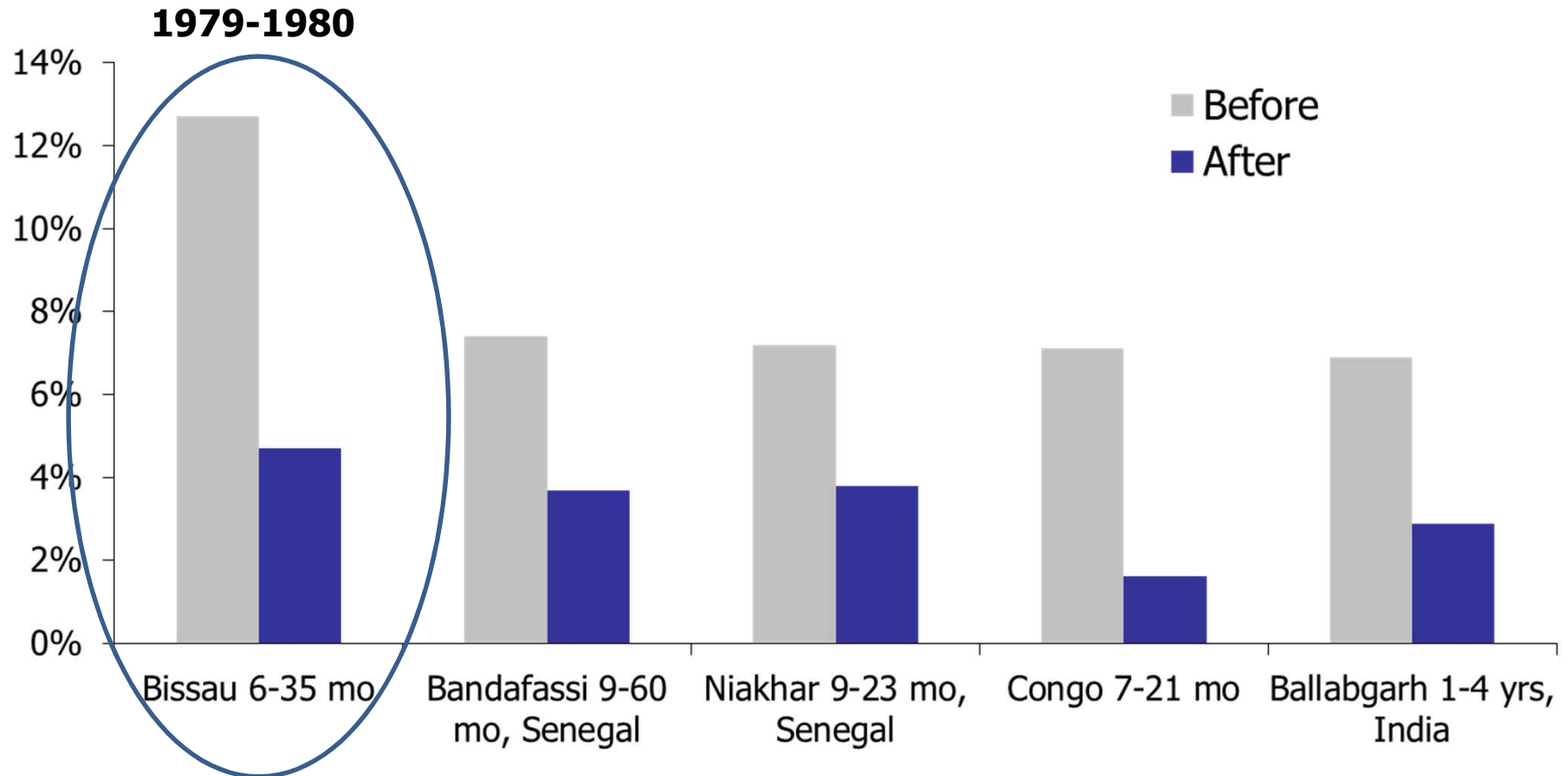
Early measles vaccination reduced measles infection with 94%

The decline in mortality in LMIC cannot be understood without these beneficial effects. If these effects were taken into consideration in planning of vaccination programmes, child mortality could be further reduced

Martins et al BMJ 2008

Good news: Before-after measles vaccine

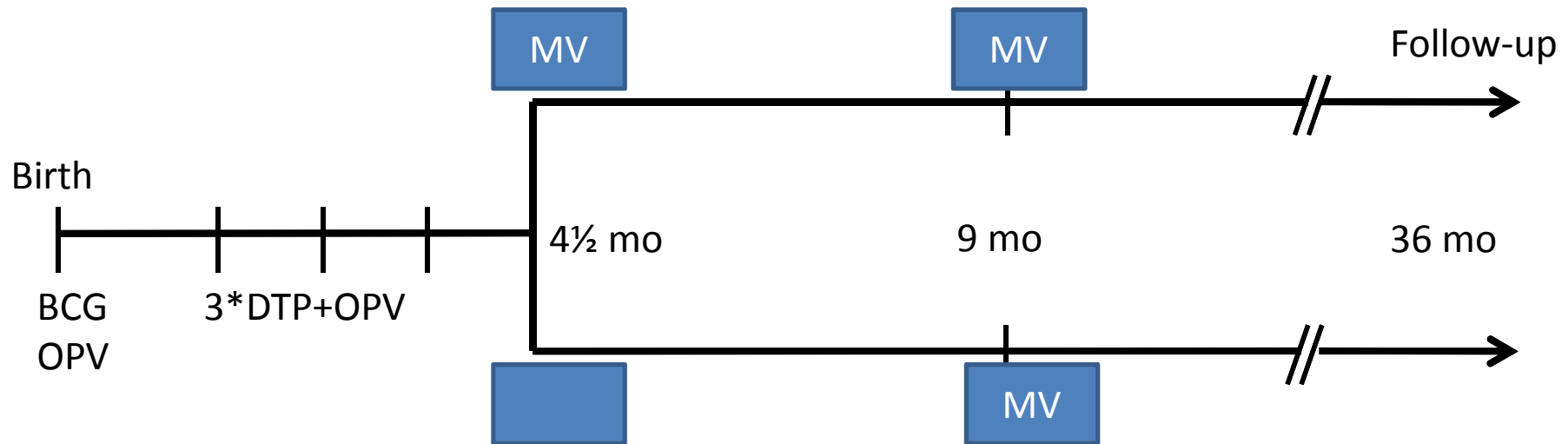
Annual mortality rate in community studies



**>50% reduction - Measles was 10-15% of deaths (WHO)
How is that possible?**

**=> The idea: The vaccine teaches the immune system to fight other infections
=> It has NON-SPECIFIC EFFECTS**

The vaccines were tested for their specific preventive effects but not for overall effects on child survival



How to test whether a vaccine has non-specific effects?



Live vaccines have beneficial non-specific effects in randomised trials

Vaccines may train the immune system beneficially

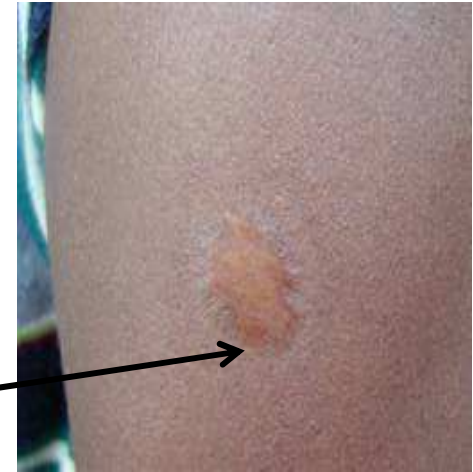
Randomised Trials	Outcome	Overall reduction in mortality	Nonspecific reduction	Specific disease reduction
3 Trials of BCG at birth	Neonatal mortality	38% (17-54%)	38% (17-54%)	0%
Oral polio vaccine at birth	Infant mortality	32% (0-57%)	32% (0-57%)	0%
MV at 4+9 vs 9 mo	Mortality 4-36 mo	30% (10-50%)	26%(0-45%)	4%

Ultimate victory in public health is Eradication=> removing a vaccine with beneficial effects? Smallpox vaccine removed in the 1970s

I. Urban Guinea-Bissau: smallpox vaccination scar associated with 40% (13-59%) lower mortality (Vaccine 2006)

II. Rural Guinea-Bissau: Smallpox vaccination scar associated with 78% (39-92%) lower mortality (PLoS One 2006)

III. Copenhagen 1971-2010: Smallpox vaccination + BCG associated with 46% (19-64%) lower mortality for natural causes of death; no effect for accidents and suicides (Int J Epidemiol 2016)



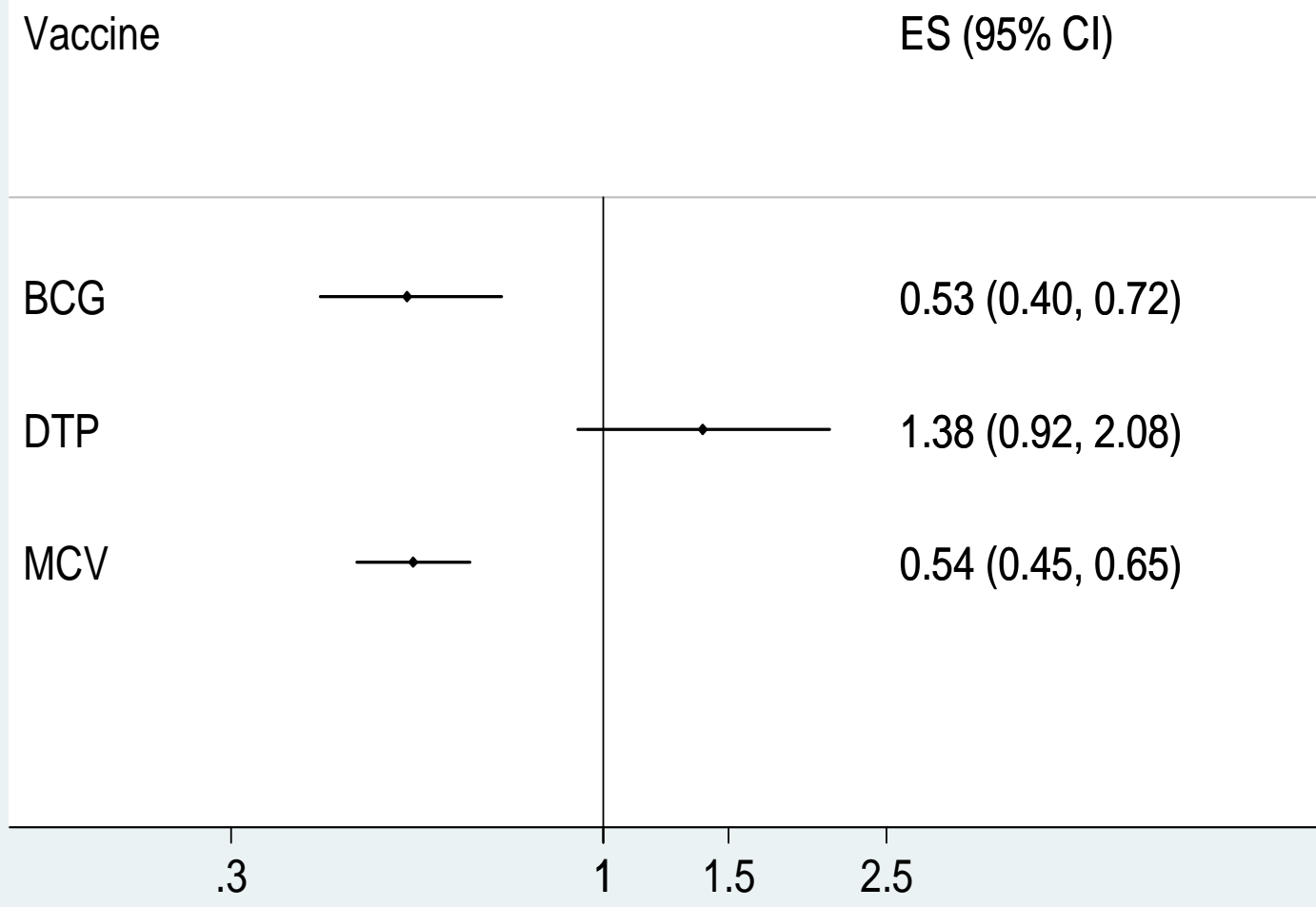
The Good news on non-specific effects of vaccines



The vaccines with beneficial effects are live vaccines which replicate in the vaccinated individual



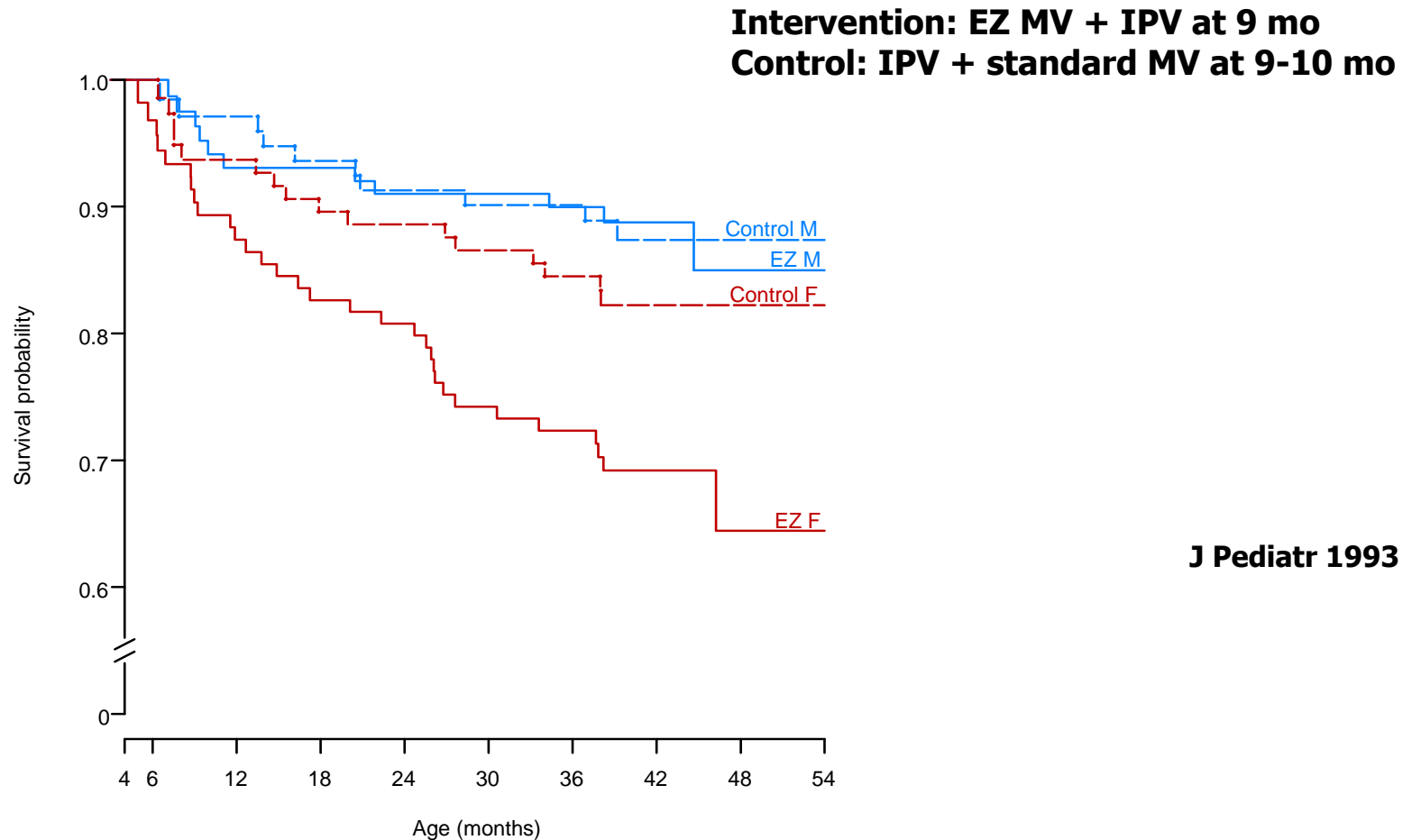
Not all vaccines have beneficial effects: WHO review of non-specific effects of BCG, DTP and Measles Vaccine Effect on child survival of different vaccines



**WHO recommended
Further studies of NSEs**

Bad news: High titre measles vaccine WHO-recommended in 1989 associated with 2-fold higher female mortality

Bissau



5 African studies: 33% excess mortality from 4 mo to 5 years
But the vaccine was protective against measles infection!
And the vaccine made no difference for boys!



**DTP has negative effects for
all-cause mortality for girls**

**Vaccines may misdirect the
immune system**

Vaccine	Studies	Higher mortality for females vs males among vaccinated children
DTP	16 studies	50% (21-85%)

**The effect of DTP for girls explained the higher mortality after high-titre measles vaccine
This vaccine was give so early that nearly all got DTP after measles vaccine and that
had a negative effect for girls.**



Non-live vaccines may have negative effects for all-cause mortality for girls

Vaccine	Studies	Relative mortality for female vs male among vaccinated children
DTP	16 studies	50% (21-85%)
IPV	3 trials	52% (2-128%)
HBV	1 natural exp.	120% (7-354%)
Malaria vaccine	2 trials	33% (2-74%)
Pentavalent vaccine	Health Centre Study	73%(11-74%)

The Good and Bad News on non-specific effects (NSEs) of immune training



Four themes

- Live vaccines have beneficial NSEs
- Non-live vaccines may have negative effects for girls
- Effects often differ for girls and boys
- Sequence of vaccinations may be very important

OPTIMUNISE is use the beneficial effects better and minimise the negative effects