How to optimise immunisation: a live vaccine last policy

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We can no longer assume that a vaccine:

1. Acts independently of other vaccines
2. Influences only infections caused by its target disease.

We must consider the effects of vaccines on all-cause mortality (or morbidity) as well as the effects on the target disease.

Low-income countries

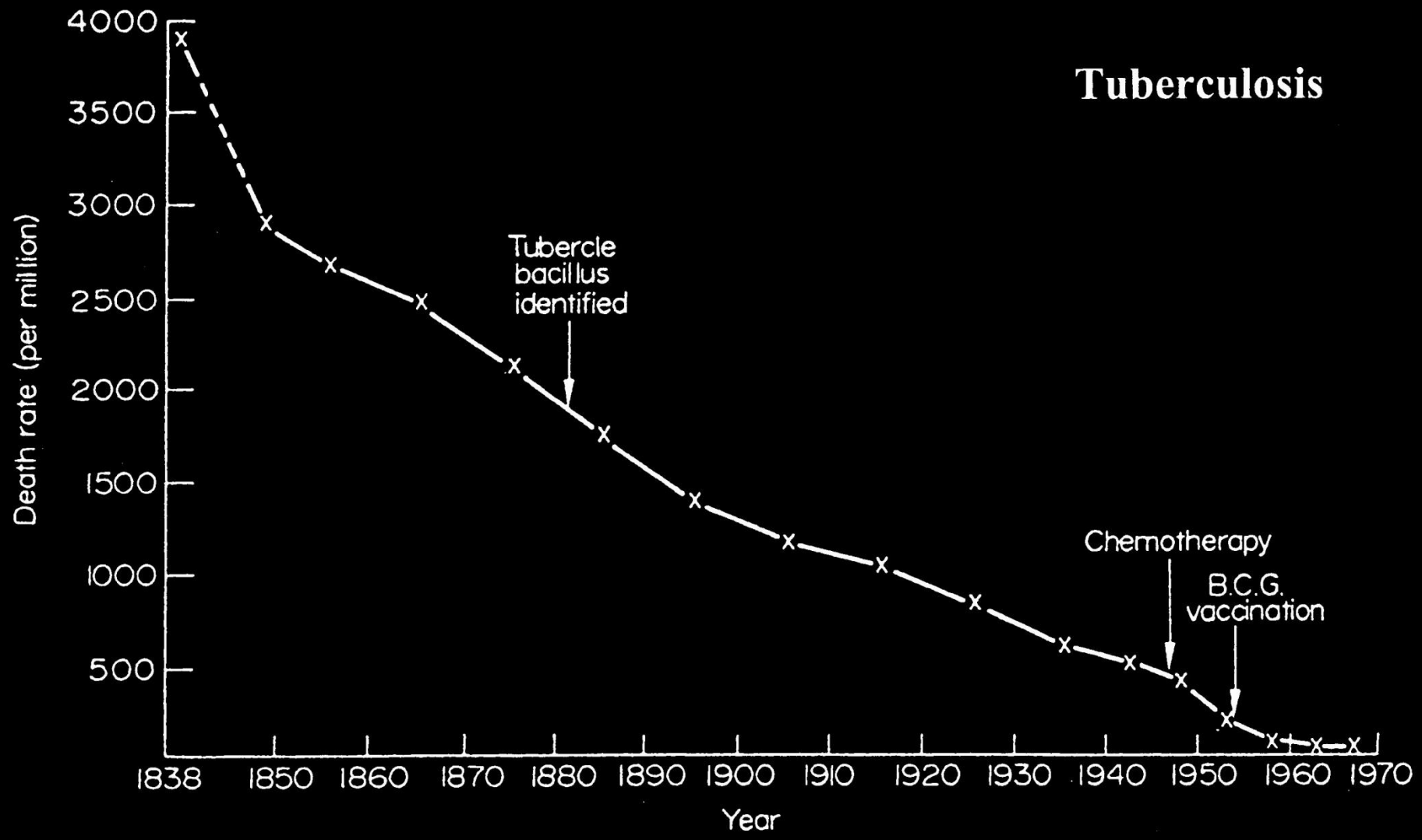
Current Expanded Programme on Immunisation (EPI) schedule

Birth 6,10,14w 9m (18m)

BCG----Penta------MV----------(Penta)

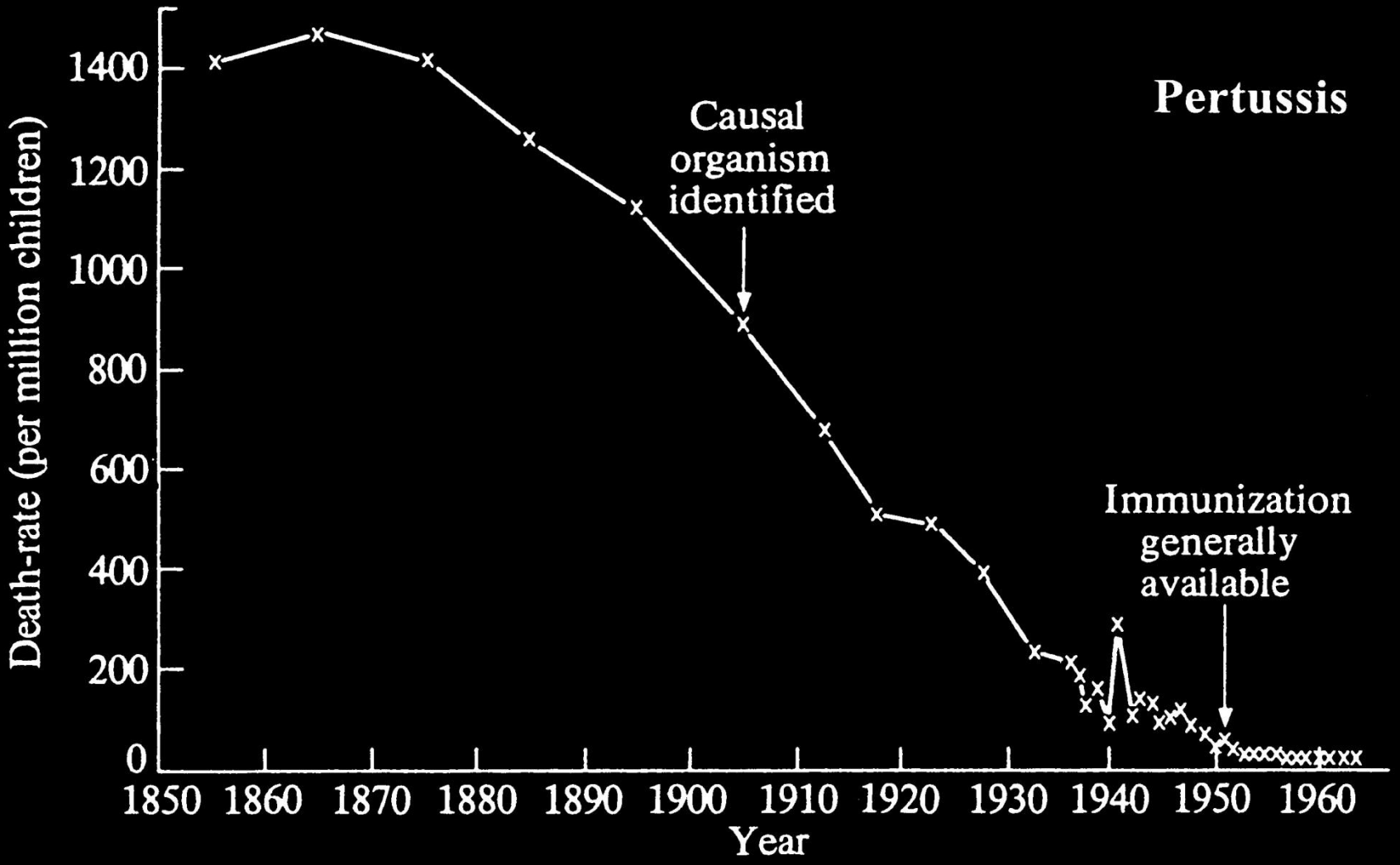
OPV OPV

Live Not-live Live Not-live



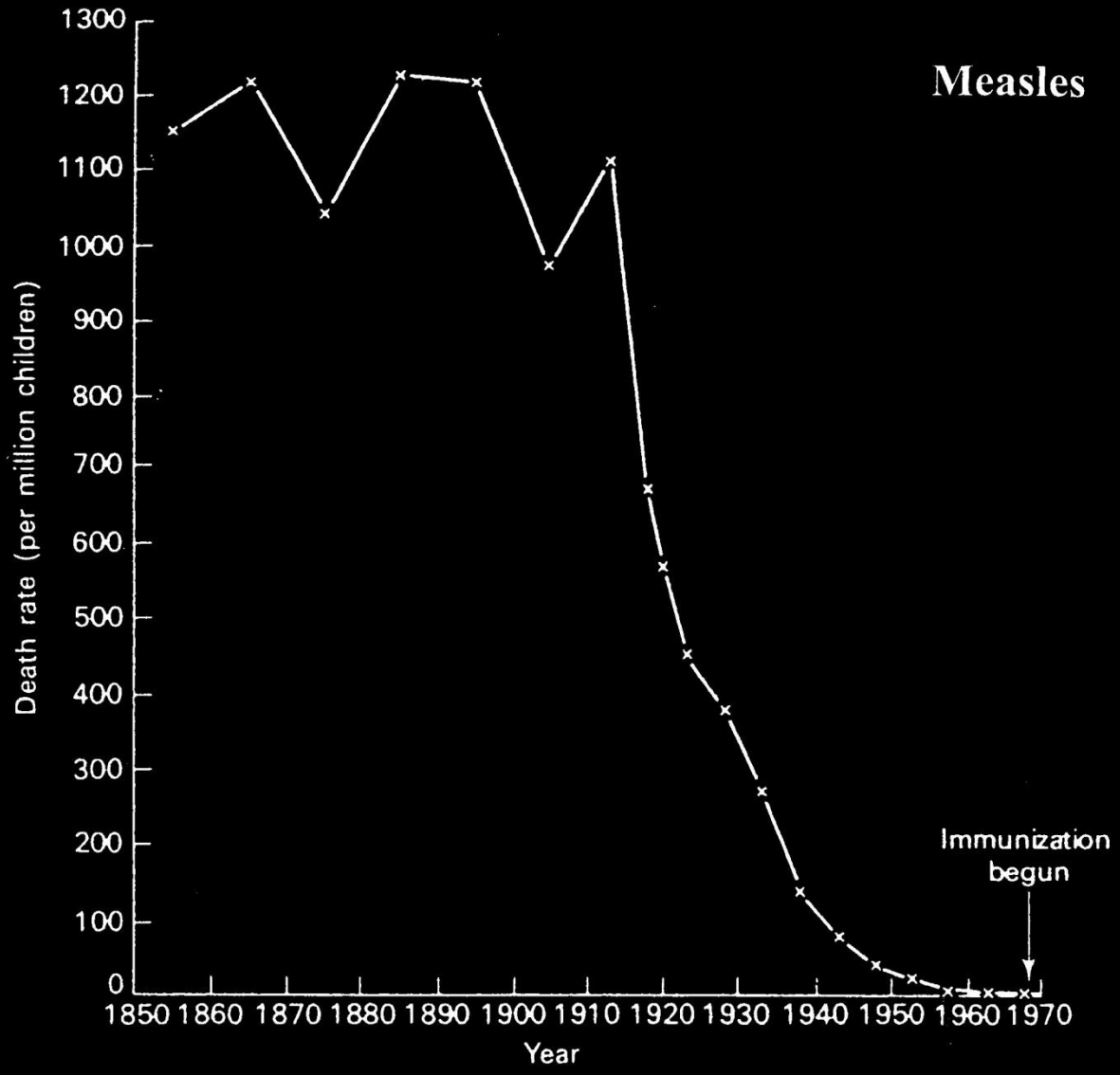
Respiratory tuberculosis -- mean annual death rate: england and Wales

McKeown T. Introduction to Social Medicine. Blackwell, 1974



Whooping cough: death rates of children under 15: England and Wales

McKeown T. An Introduction to Social Medicine. 2nd ed. Blackwell, 1974:97.



Measles: death rates of children under 15, England and Wales.

McKeown T The Modern Rise of Population, Blackwell, 1976:96

The SAGE-Bristol epidemiologic review

Peer review essential: funded by WHO, interpreted by WHO, and supports current WHO policy.

To their credit, WHO have made the data public.

Google “Epidemiologic review for SAGE”

www.who.int/immunization/sage/meetings/2014/april/3_NSE_Epidemiology_review_Report_to_SAGE_14_Mar_FINAL.pdf?ua=1

SAGE-Bristol review of non-specific effects of vaccines

BCG: “The results indicated a beneficial effect of BCG on overall mortality in the first 6-12 months of life.”

Measles vaccine: “Estimated effects are in the region of a halving of mortality risk.” High risk of bias.

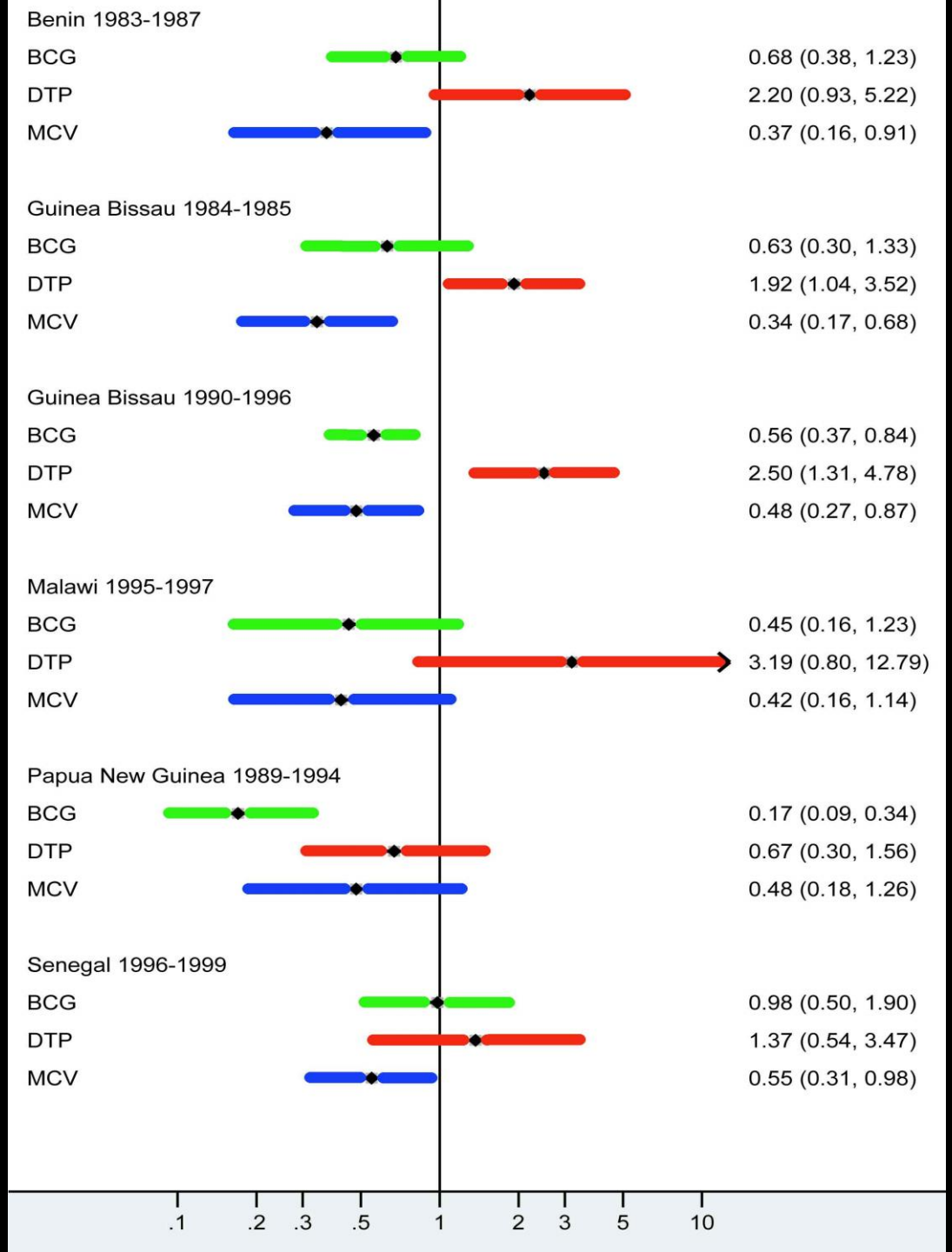
DTP: “The majority of studies indicated a deleterious effect of DTP on mortality.” High risk of bias.

SAGE “considered that the non-specific effects (of vaccines) on all cause mortality warrant further research.” *Wkly Epi Rec 2014;89:234*

Bias alone is unlikely to explain why mortality was reduced after BCG, but then increased after DTP, and reduced again after MV.

“Baseline confounding may have exaggerated the benefits of BCG and measles vaccination” (vaccinated child lower risk than unvaccinated)

… and underestimated the harm from DTP.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BCG
DTP
MCV
0.68 (0.38, 1.23)
2.20 (0.93, 5.22)
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Guinea Bissau 1984-1985
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0.63 (0.30, 1.33)
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0.67 (0.30, 1.56)
0.48 (0.18, 1.26)
Senegal 1996-1999
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0.98 (0.50, 1.90)
1.37 (0.54, 3.47)
0.55 (0.31, 0.98)
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BCG

Two randomised trials of BCG in Guinea Bissau

Low risk of bias in SAGE-Bristol review

	N	Mortality / 100 py from 0-4 wk
BCG at birth	1168	37.0
BCG after 4wk	1152	69.9

Mortality ratio 0.52 (95% CI 0.33-0.82)

48% reduction in neonatal mortality

Aaby. J Infect Dis 2011;204:245-52
Biering-Sorensen, Ped Infect Dis J, 2012;31:306-8

Policy implications

Many babies do not get BCG at birth.

20 dose vials, clinics wait for 8-12 babies.

Median age 7 weeks.

New policy: give BCG even if only 1 baby.

Guinea-Bissau trials used BCG-Danish.

Cannot assume BCG strains are interchangeable.

RCT Hong Kong 303,092 neonates risk of TB:

Pasteur 45% (22-61%) lower than with Glaxo

Comstock, Clin Inf Dis 2000;30(Sup 3):S250-3.

Cohort Kazakhstan 467,693 neonates TB reduced:

Tokyo 69% (61-75%), Russia 22% (7-35%)

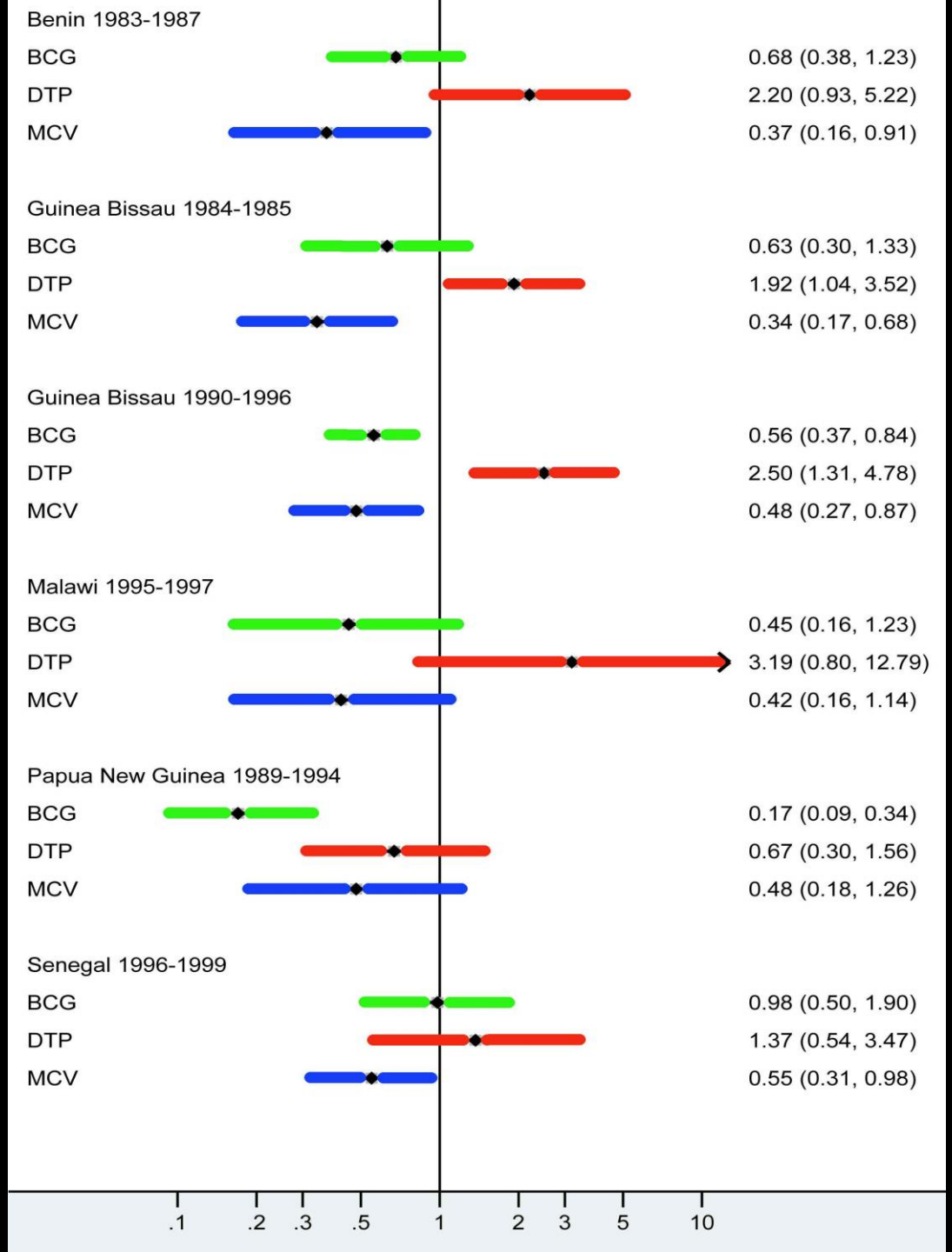
Favorov, PLoS ONE 2012;7:e32567.

UNICEF 2014: Russia 86m, Tokyo 16m, Danish 10m.

Need RCTs to compare NSE; ABAB for TB effects.

DTP

(or Penta or…)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IN 2013, 1.9 million children died aged 1-11 mo.
1.9 / 1.27 = 1.5, and 1.9 - 1.5 = 400,000 excess deaths.

SAGE: “The available data neither exclude nor confirm the possibility of beneficial or deleterious non-specific effects of DTP vaccines on all-cause mortality.”

That is, “The data do not exclude the possibility of deleterious effects of DTP on all-cause mortality.”

RotaShield vaccine was suspended in the USA after 15 cases of intussusception.

Onus of proof is demonstration of safety (not harm).
<u>Urgent</u> need for evidence that DTP is safe for girls.

DTP booster in second year of life (DTP4) given in some countries but not in others.

Ethical to do RCTs of giving or not giving DTP booster after MCV.

Determine the effect on all-cause mortality in girls and boys.

This should be seen as urgent.

DTP often delayed, or given in campaigns.

So some children get DTP after MV.

Increased deaths from pneumonia and sepsis.

New policy: do not give DTP (or other non-live vaccines) with or after MV.

Administration of first dose of DTP with BCG may reduce harmful effects on all-cause mortality.

RCTs of giving an extra (second) dose of BCG at 6 wk with DTP1

(or RCTs of giving DTP1 with BCG at birth).

As with BCG, wP vaccines are not interchangeable

Edwards, Ch 23 in Plotkin "Vaccines" 2013:464.

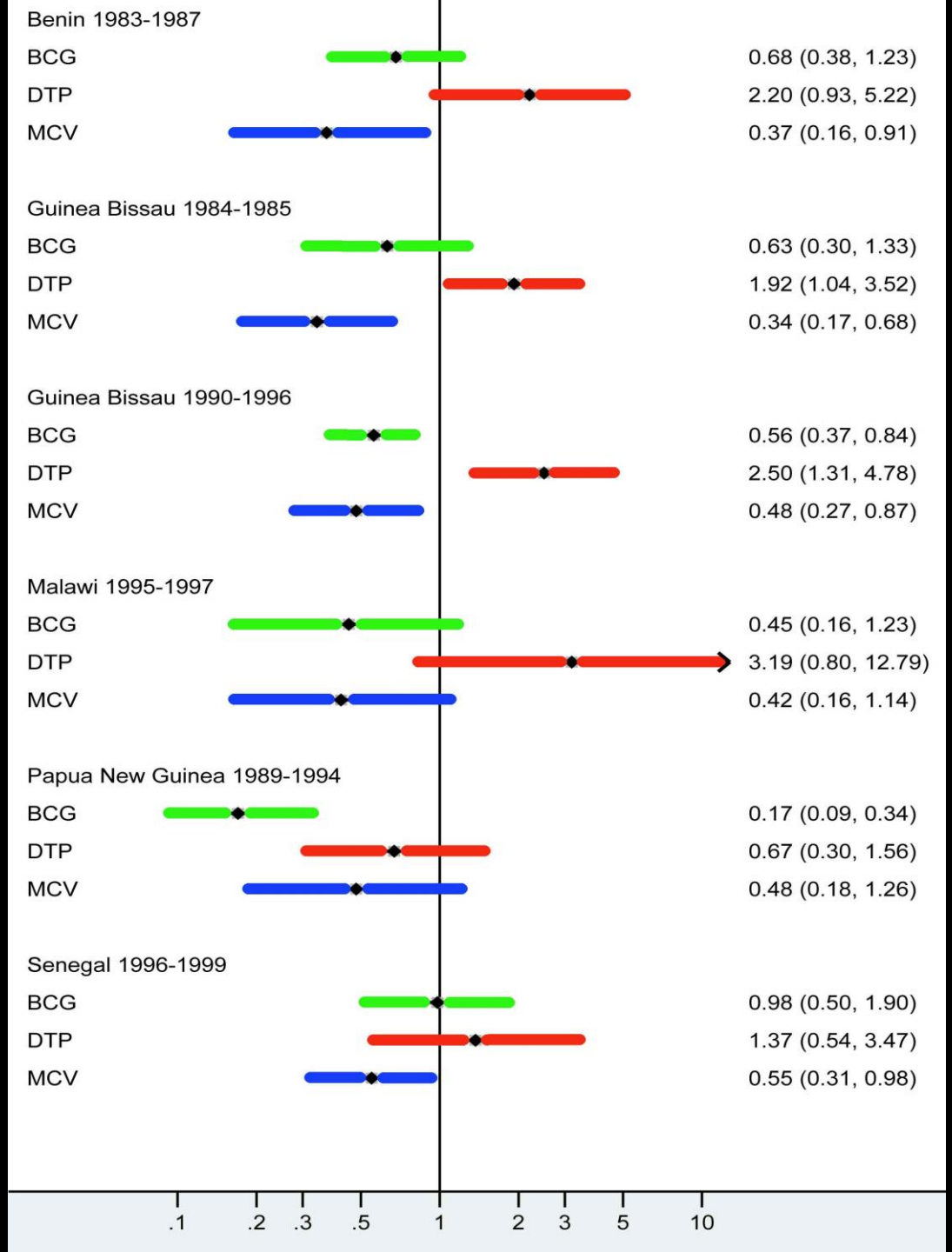
RCTs to compare effects of different wP vaccines.

We do not know how wP protects against pertussis.

Antibody response is not a good surrogate.

Cellular and innate immunity may also be important.

MCV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MV reverses the adverse effects of DTP.

As measles less common, MV delayed or not given at all. Ignores the beneficial NSE, and increases deaths from pneumonia and sepsis.

New policy: do not delay or omit MV (RCTs of extra dose 4-6 wk after DTP3).

Main indicator for EPI is % given DTP by 12 mo.

But DTP is harmful to girls.

MV benefits both boys and girls.

New policy: use % given MV after DTP by 12 mo as main indicator of EPI performance.

Conclusion

We should see NSE as an opportunity, not a threat.

Live vaccine last policy.

Consider all-cause mortality in all EPI policy

Change from OPV to IPV – next talk.

If measles eradicated, may need to continue MV.

If new TB vaccine, may need to continue BCG.

New vaccines: test effects on all-cause mortality…

…for example, RTS,S/AS01 malaria vaccine:
27% (18-36%) efficacy against clinical malaria
24%(-3% to 58%) increase in all-cause mortality.

Change policy now

Give BCG at birth even if only one baby needs it.

Do not delay or omit MCV at 9 mo.

Do not give DTP with or after MCV.

Main indicators: % BCG by 28d, % MCV after DTP by 12mo.

Monitor effects of any change to EPI (especially introduction of a non-live vaccine, or withdrawal of a live vaccine).

Research

RCTs of an extra dose of BCG with DTP1 - **urgent.**

RCTs of booster DTP4 at 18 mo in girls - **urgent.**

RCTs of an extra dose of MCV 4-6 wk after DTP3.

Compare different strains of BCG and wP.

BCG in Spain

Basque Country (BCG) vs rest of Spain (no BCG)

1992 to 2011: 464,611 hospital admissions

Respiratory inftn <15yr : RR 0.59 (0.58-0.60)

Sepsis <1yr: RR 0.47 (0.39-0.56)

De Castro, Clin Inf Dis 2015:10.1.1093

RCTs of BCG in Denmark and Melbourne.

Penta vaccine in Denmark

506,461 children in Denmark 1997-2006:

- 485,876 got DTaP-IPV-Hib3 (Penta3), then MMR
- 20,585 got Penta2, then MMR, then Penta3

Admission to hospital for infection:

3,5,12m *15m* *2y*

-Penta--1.0--MMR--0.86----------

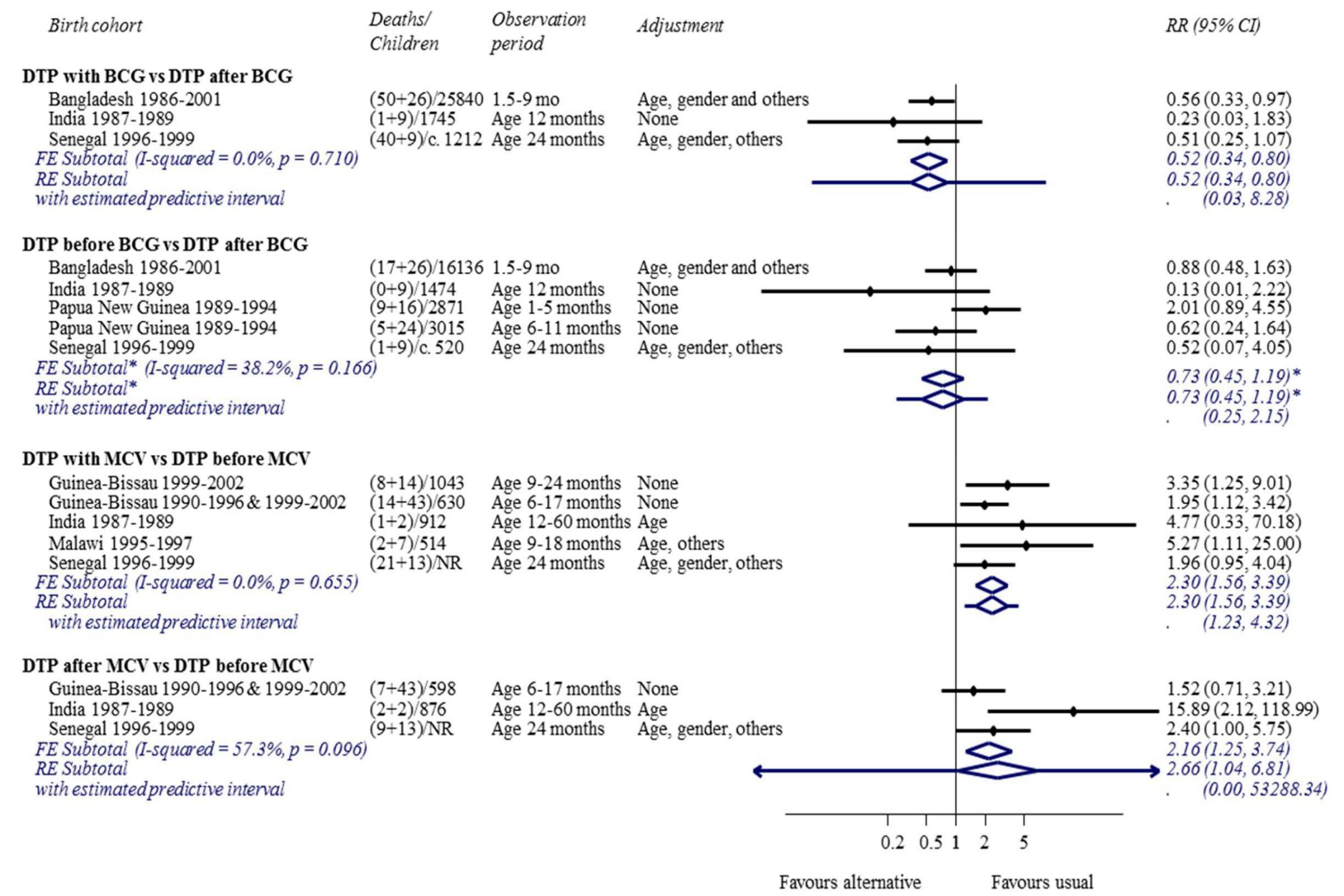
-Penta--1.0--MMR--0.87--Penta--1.62--

Sørup. JAMA 2014;311:826-835

High income countries

Perhaps cluster non-live vaccines between (say) 2-6 mo, then give extra dose of MV 4-6 wk later (for the non-targeted effects)?

In first 2 yr of life, follow booster doses of non-live vaccines with live 4-6 wk later?


Birth cohort
Deaths/ Children
Observation period
Adjustment
RR (95% CI)
DTP with BCG vs DTP after BCG
Bangladesh 1986-2001 (50+26)/25840 1.5-9 mo Age, gender and others 0.56 (0.33, 0.97)
India 1987-1989 (1+9)/1745 Age 12 months None 0.23 (0.03, 1.83)
Senegal 1996-1999 (40+9)/c. 1212 Age 24 months Age, gender, others 0.51 (0.25, 1.07)
FE Subtotal (I-squared = 0.0%, p = 0.710) 0.52 (0.34, 0.80)
RE Subtotal 0.52 (0.34, 0.80)
with estimated predictive interval . (0.03, 8.28)
DTP before BCG vs DTP after BCG
Bangladesh 1986-2001 (17+26)/16136 1.5-9 mo Age, gender and others 0.88 (0.48, 1.63)
India 1987-1989 (0+9)/1474 Age 12 months None 0.13 (0.01, 2.22)
Papua New Guinea 1989-1994 (9+16)/2871 Age 1-5 months None 2.01 (0.89, 4.55)
Papua New Guinea 1989-1994 (5+24)/3015 Age 6-11 months None 0.62 (0.24, 1.64)
Senegal 1996-1999 (1+9)/c. 520 Age 24 months Age, gender, others 0.52 (0.07, 4.05)
FE Subtotal* (I-squared = 38.2%, p = 0.166) 0.73 (0.45, 1.19)*
RE Subtotal* 0.73 (0.45, 1.19)*
with estimated predictive interval . (0.25, 2.15)
DTP with MCV vs DTP before MCV
Guinea-Bissau 1999-2002 (8+14)/1043 Age 9-24 months None 3.35 (1.25, 9.01)
Guinea-Bissau 1990-1996 & 1999-2002 (14+43)/630 Age 6-17 months None 1.95 (1.12, 3.42)
India 1987-1989 (1+2)/912 Age 12-60 months Age 4.77 (0.33, 70.18)
Malawi 1995-1997 (2+7)/514 Age 9-18 months Age, others 5.27 (1.11, 25.00)
Senegal 1996-1999 (21+13)/NR Age 24 months Age, gender, others 1.96 (0.95, 4.04)
FE Subtotal (I-squared = 0.0%, p = 0.655) 2.30 (1.56, 3.39)
RE Subtotal 2.30 (1.56, 3.39)
with estimated predictive interval . (1.23, 4.32)
DTP after MCV vs DTP before MCV
Guinea-Bissau 1990-1996 & 1999-2002 (7+43)/598 Age 6-17 months None 1.52 (0.71, 3.21)
India 1987-1989 (2+2)/876 Age 12-60 months Age 15.89 (2.12, 118.99)
Senegal 1996-1999 (9+13)/NR Age 24 months Age, gender, others 2.40 (1.00, 5.75)
FE Subtotal (I-squared = 57.3%, p = 0.096) 2.16 (1.25, 3.74)
RE Subtotal 2.66 (1.04, 6.81)
with estimated predictive interval . (0.00, 53288.34)
0.2 0.5 1 2 5
Favours alternative
Favours usual