

Estimating the potential impact of alternative Hib conjugate vaccination schedules *at country level*

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SAGE April 2013, Geneva.

Aim

- to provide a tool to help country-level decision makers access/document/evaluate the evidence used to *inform* the choice of Hib schedule e.g. p3+0, p2+1

Inputs

- age distribution of Hib disease, vaccination coverage and timeliness
- estimates from the literature on vaccine efficacy and duration of protection

Outputs

- estimated impact of eg. p3+0 and p2+1, on Hib deaths

Key parameters used to estimate impact

Hib Schedules Model_cs3.xls [Compatibility Mode] - Microsoft Excel

Hib Schedules model

Kenya

Data, assumptions, scenarios

Schedule

2p+1

Primary =

2

Booster = yes

Age at Hib disease

Timeliness

Efficacy & waning

Herd effect <5

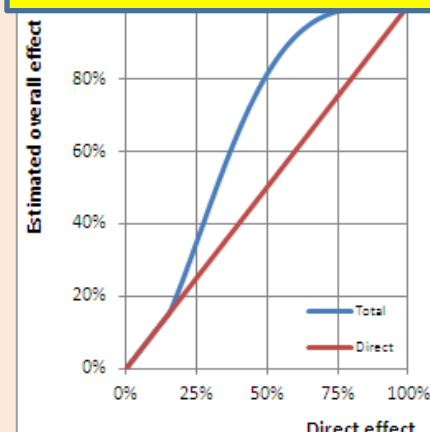
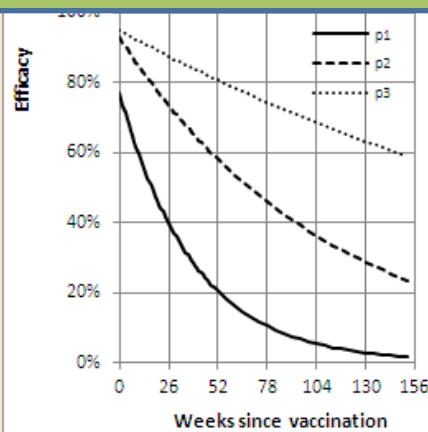
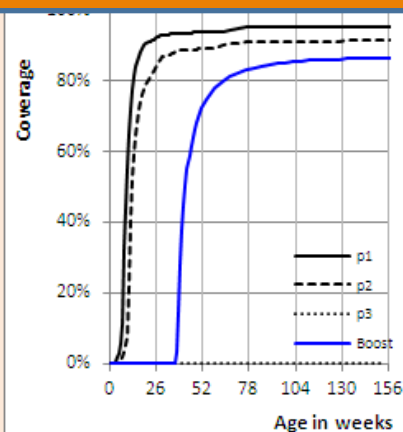
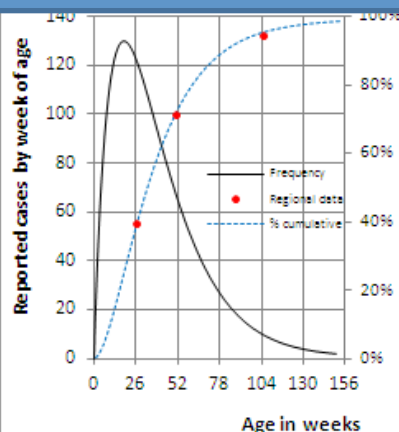
yes

14 countries
Hib meningitis /
invasive disease
(Briere and Hajjeh)

67 countries
DTP1/2/3 and
Measles 1
(DHS/MICS, Sanderson)

Global review
Efficacy & duration
of protection
(Scott et al, Jackson et al)

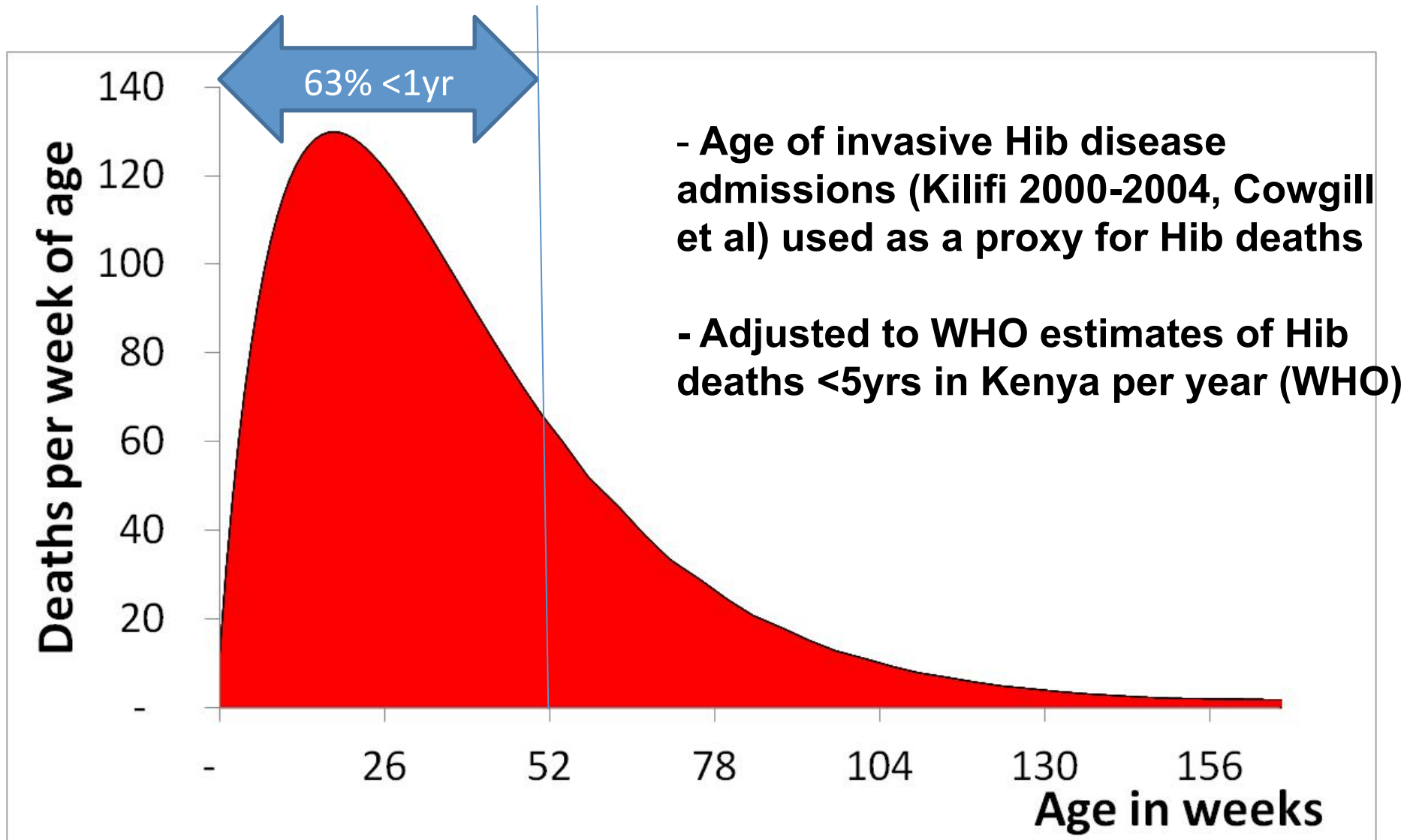
Global review
Comparing direct &
total impact
(Walker et al)



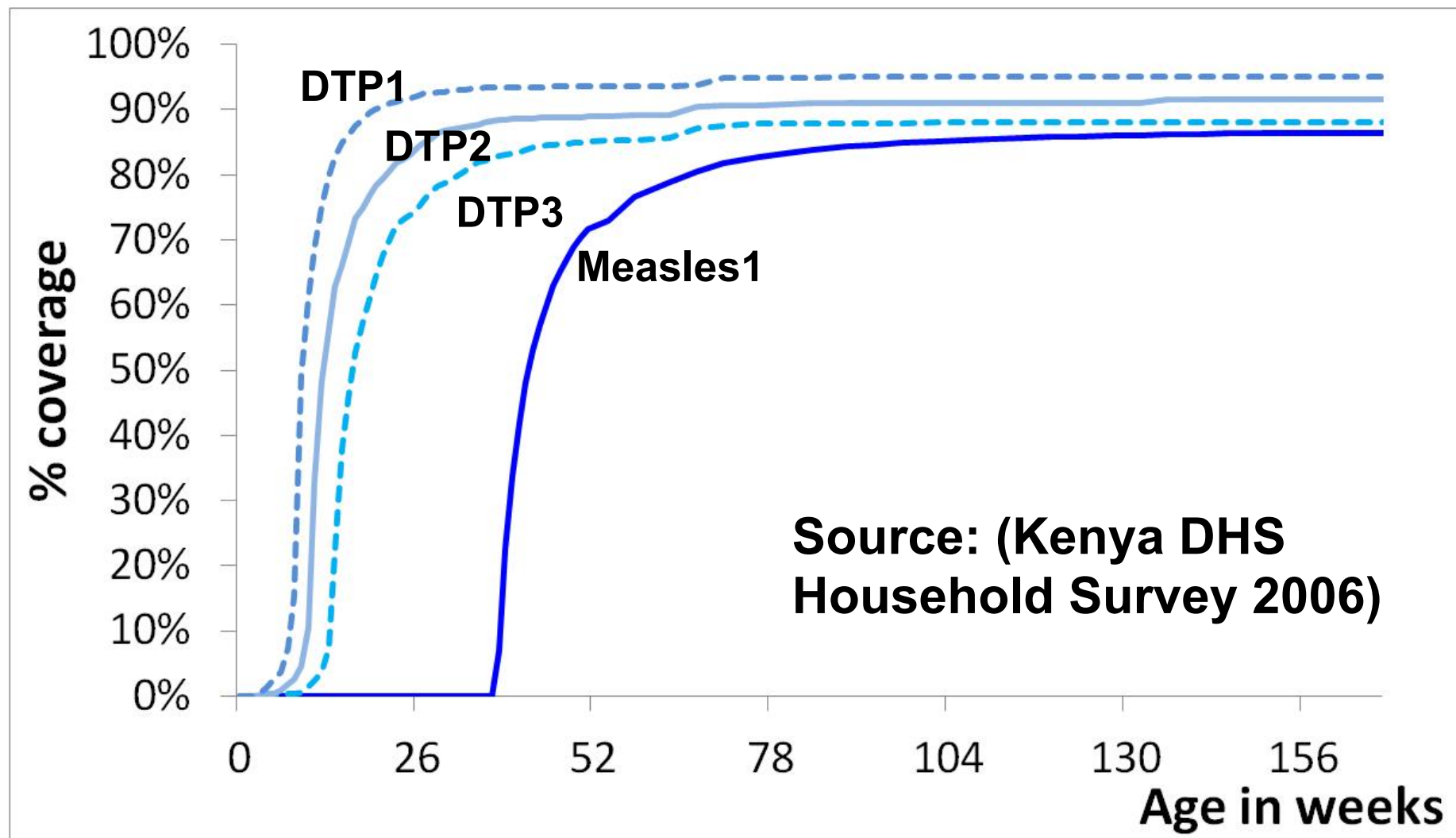
Example - Kenya

How it works in practice...

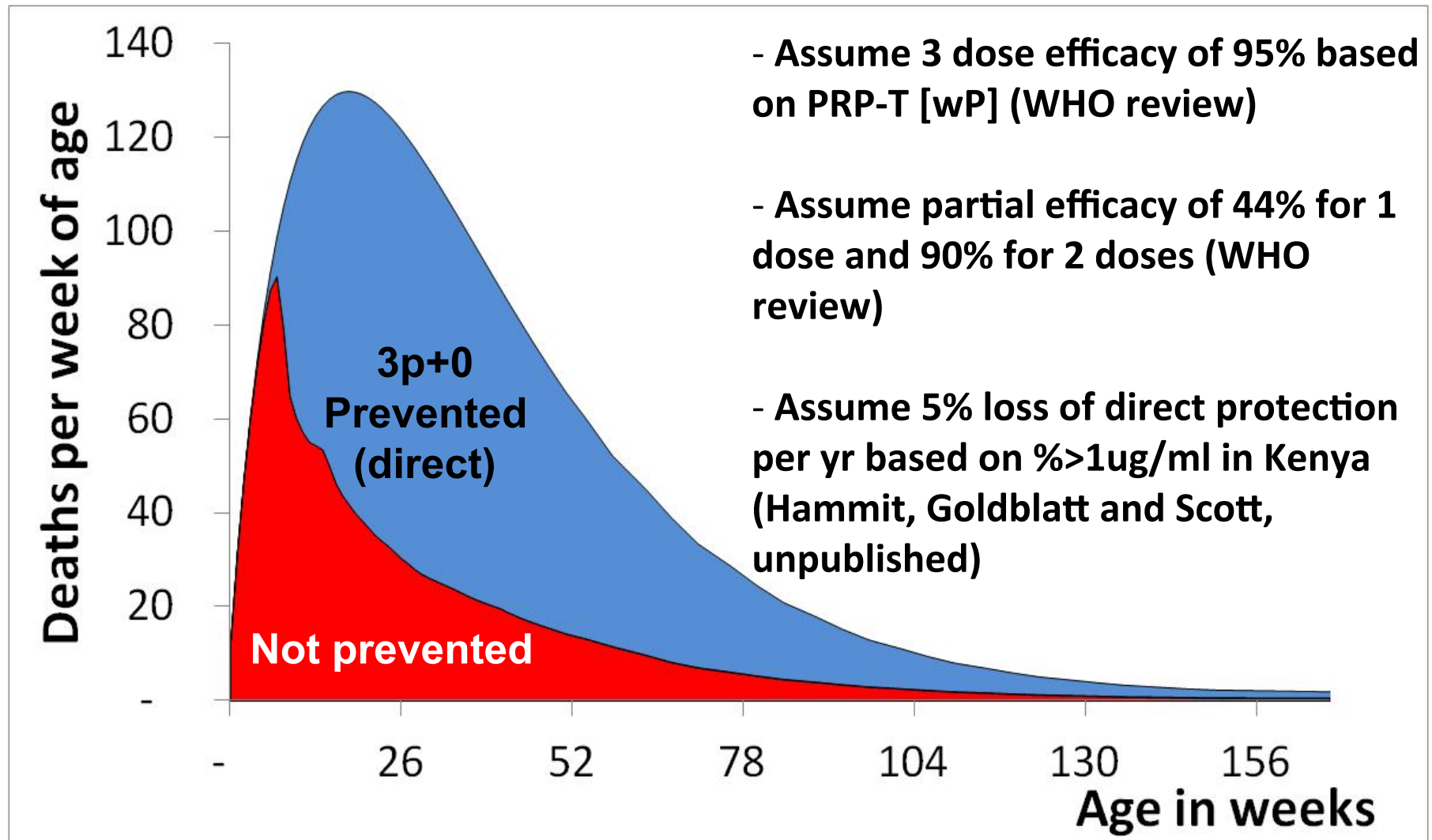
Kenya: age distribution of Hib deaths <5yrs



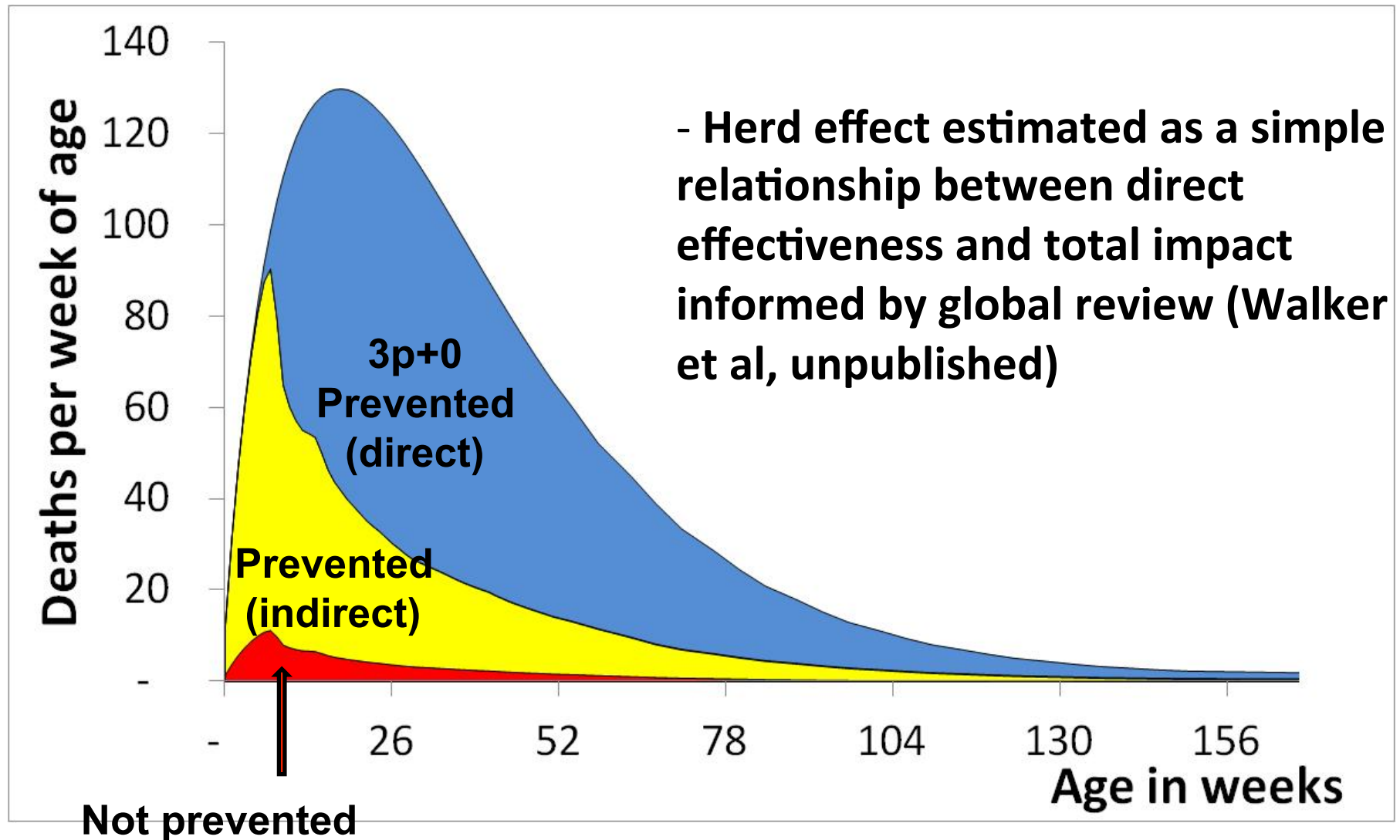
Kenya: coverage and timeliness of doses



Kenya: combine coverage with efficacy and duration of protection to estimate direct impact

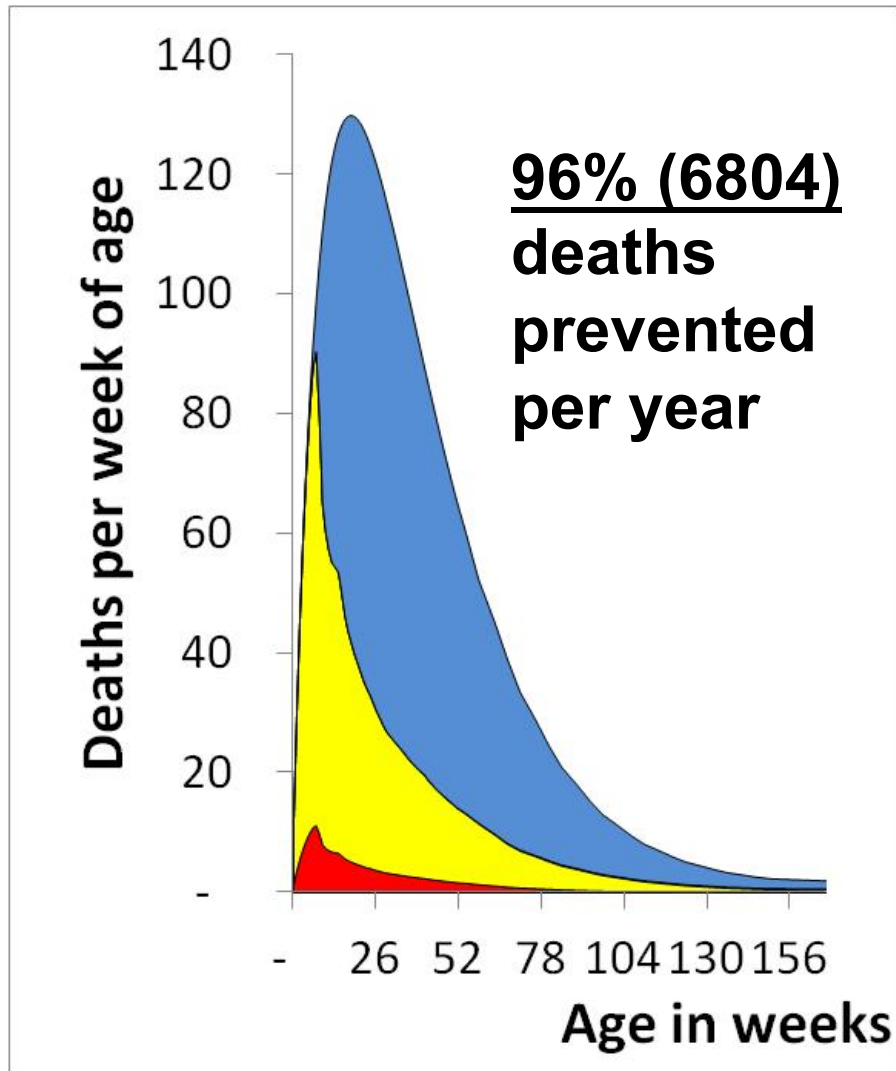


Kenya: adjust direct protection to account for simple estimates of potential herd effect

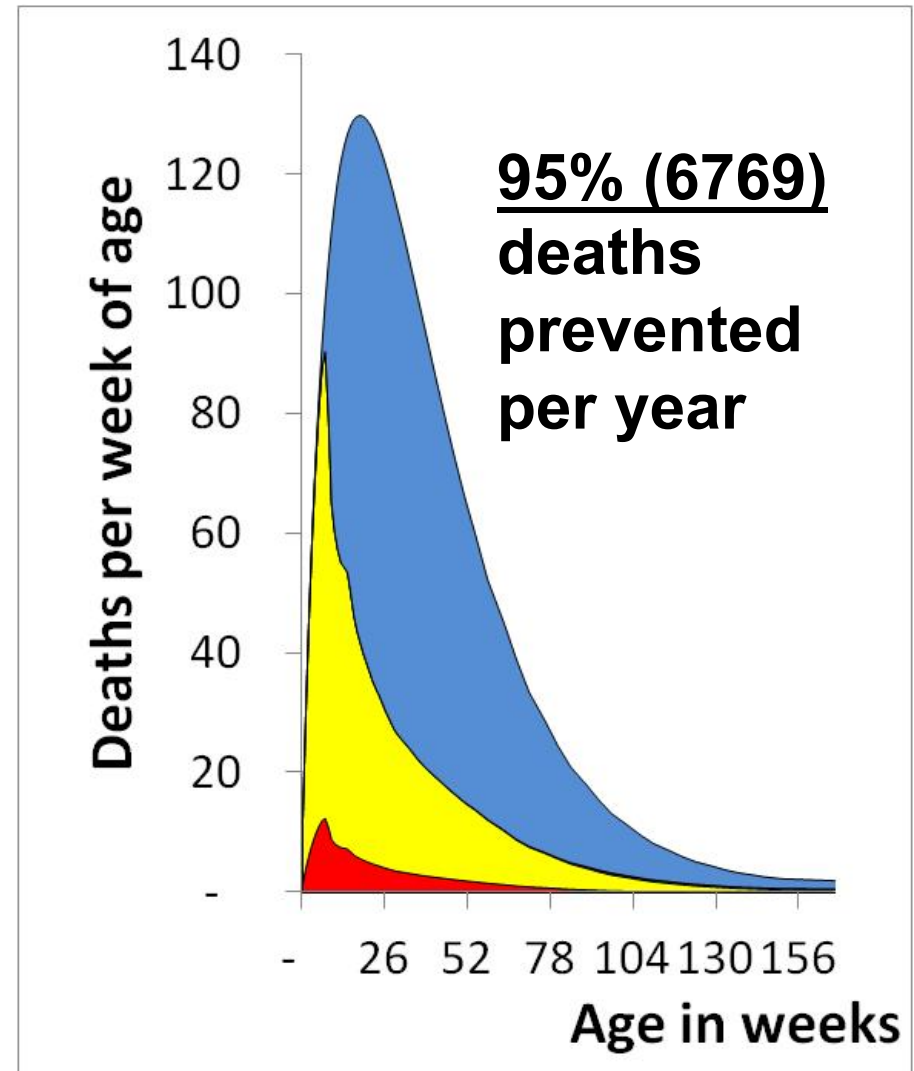


Kenya: estimated impact of p3+0 and p2+1

p3+0



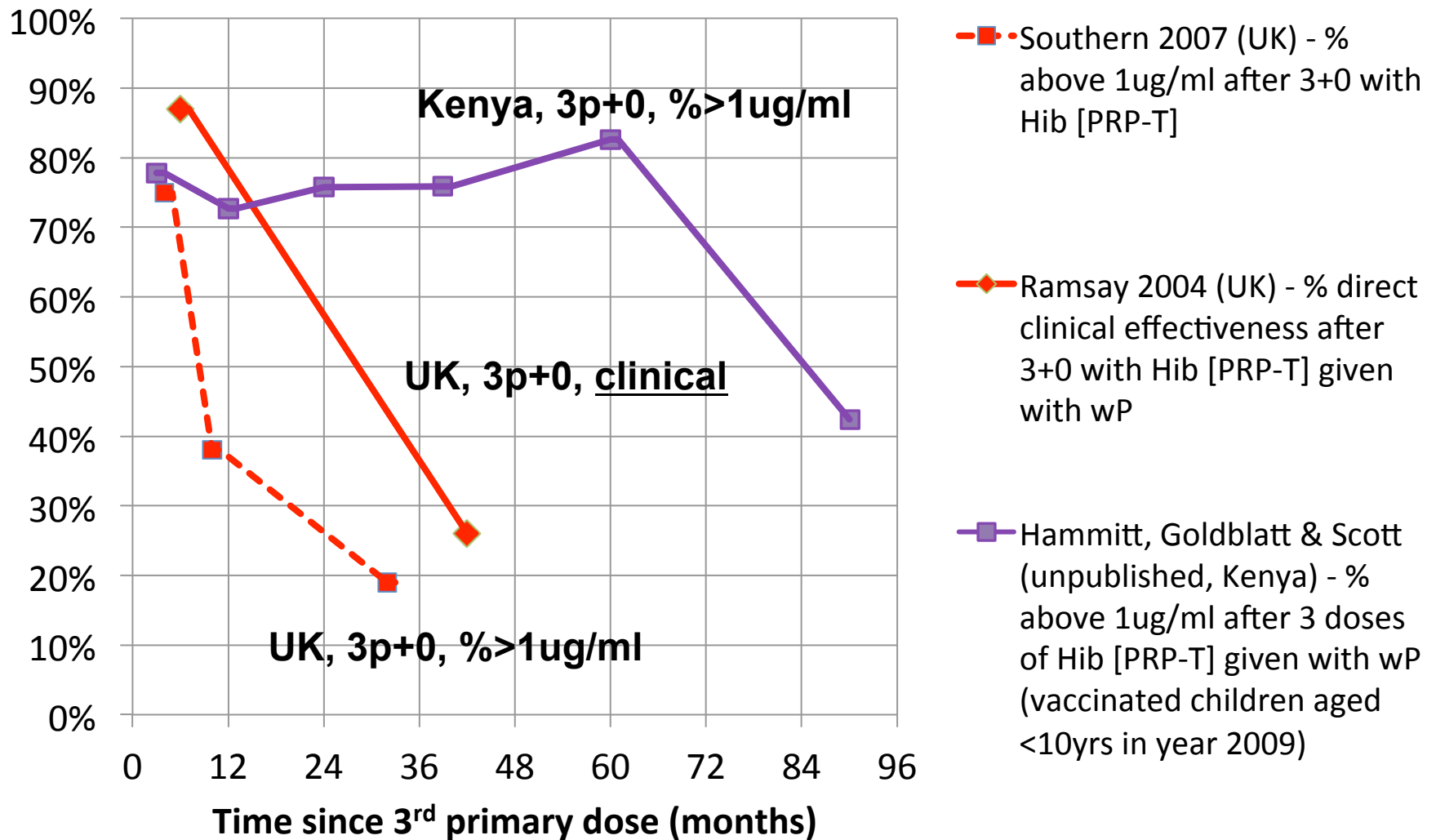
p2+1



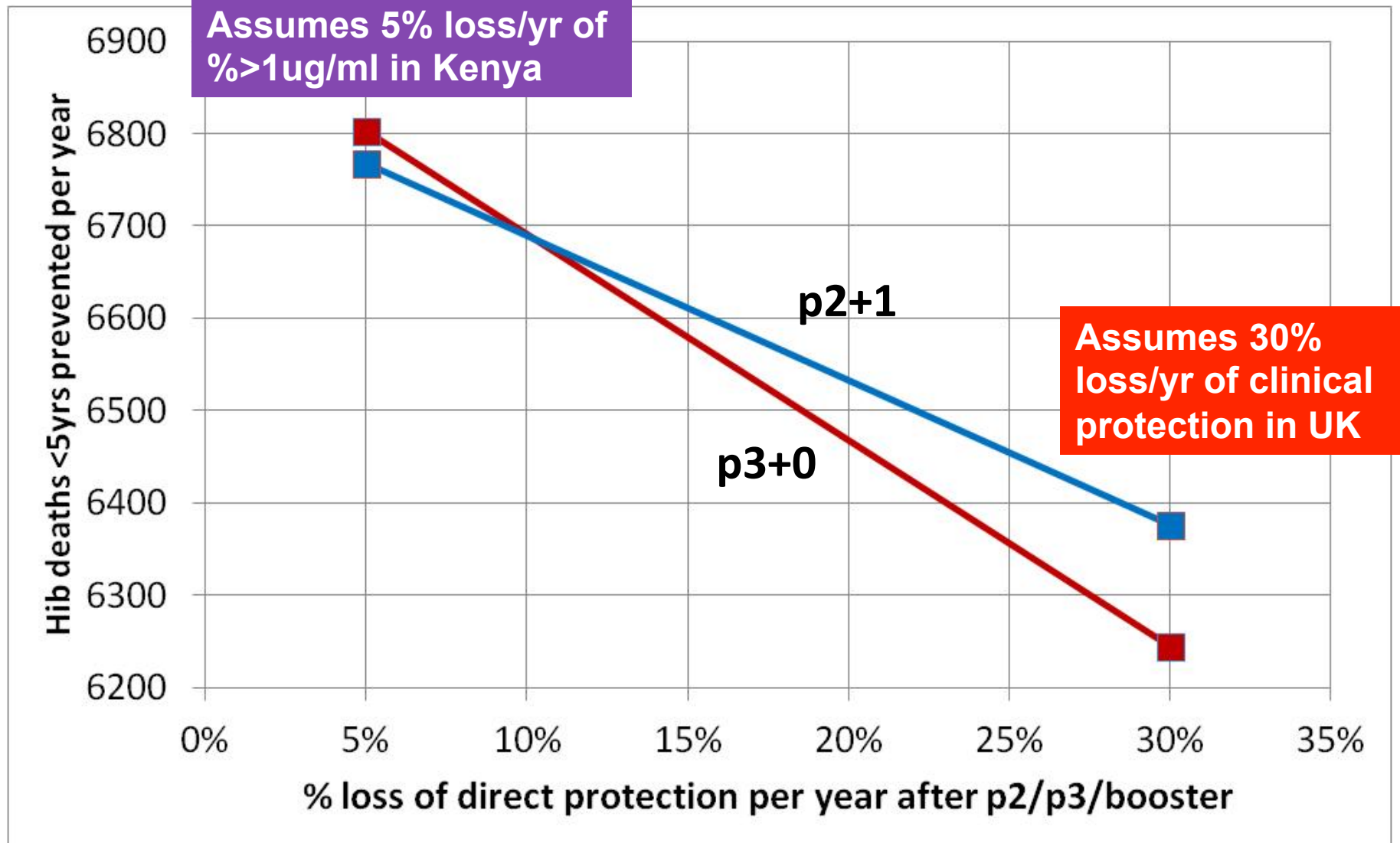
Very small estimated difference in impact of 3p+0 and 2p+1 in Kenya

- A key uncertain parameter driving that choice is the *duration of direct clinical protection*
- Two examples (indication of a range of plausible values):
 - eg. Kenya (5% loss per yr, %>1ug/ml) - BASE
 - eg. UK (30% loss per yr, vs clinical disease)

Duration of protection in Kenya & the UK



Kenya: deaths prevented for different assumptions of duration of protection



Conclusions

- Estimates of impact can help countries access/evaluate/document the evidence used to inform the choice of Hib schedule
- Analysis should be repeated as new data emerges

Backup slides

Estimated herd effect <5yrs by comparing observed total impact with expected direct impact

24 data points

Australia = 2

Brazil = 12

Cuba = 1

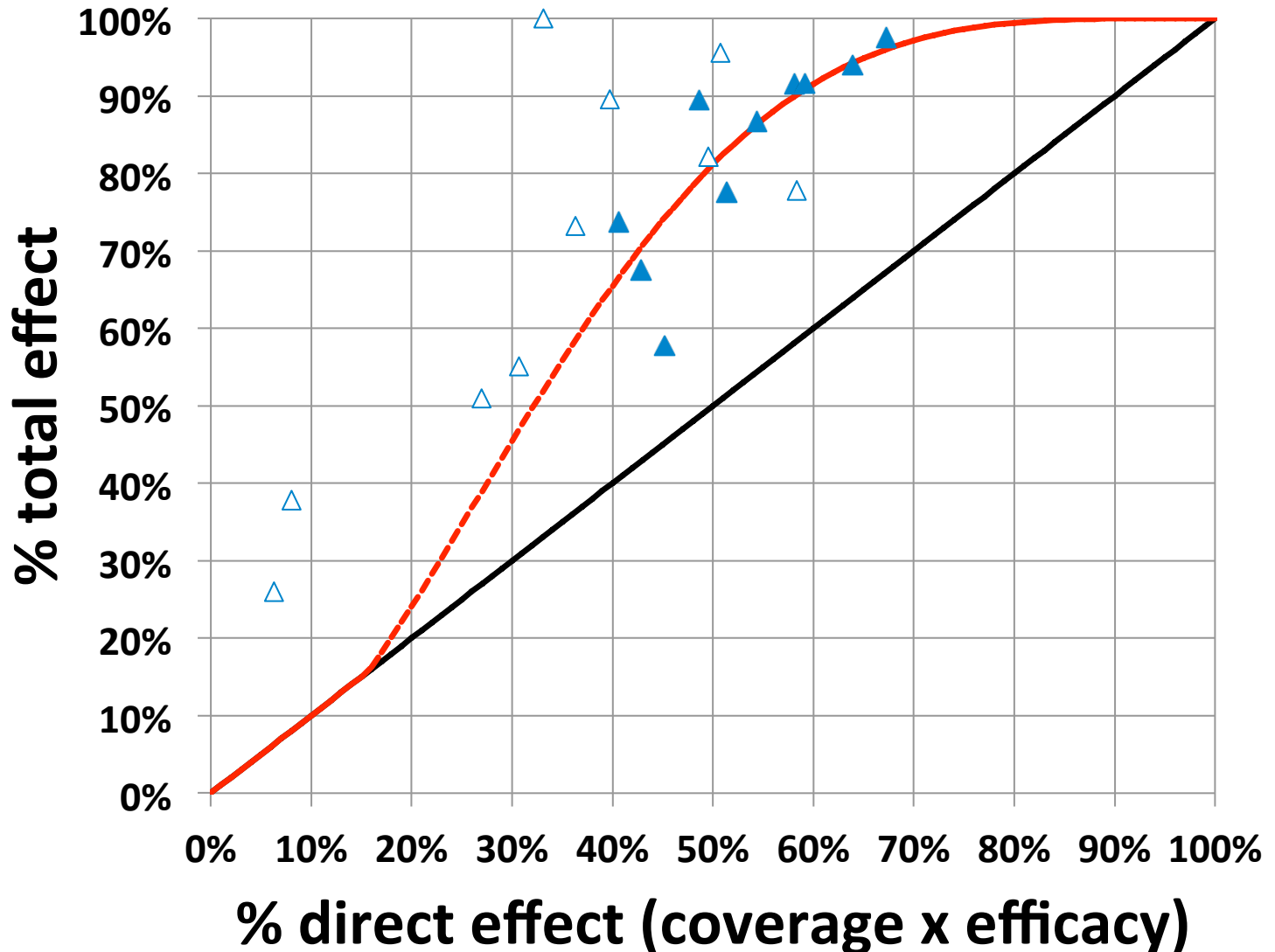
France = 1

Kenya = 2

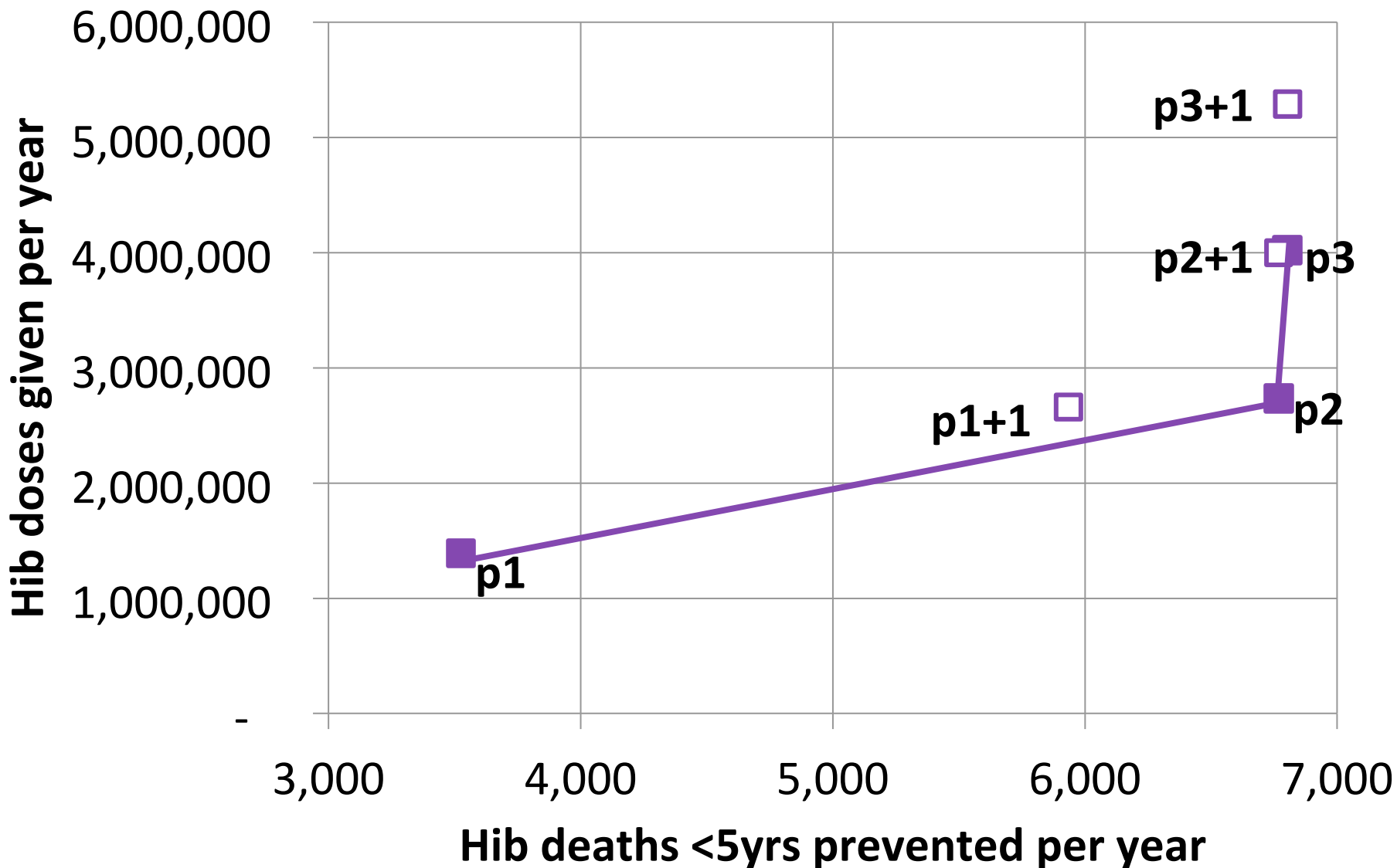
Senegal = 1

Spain = 3

Tonga = 2

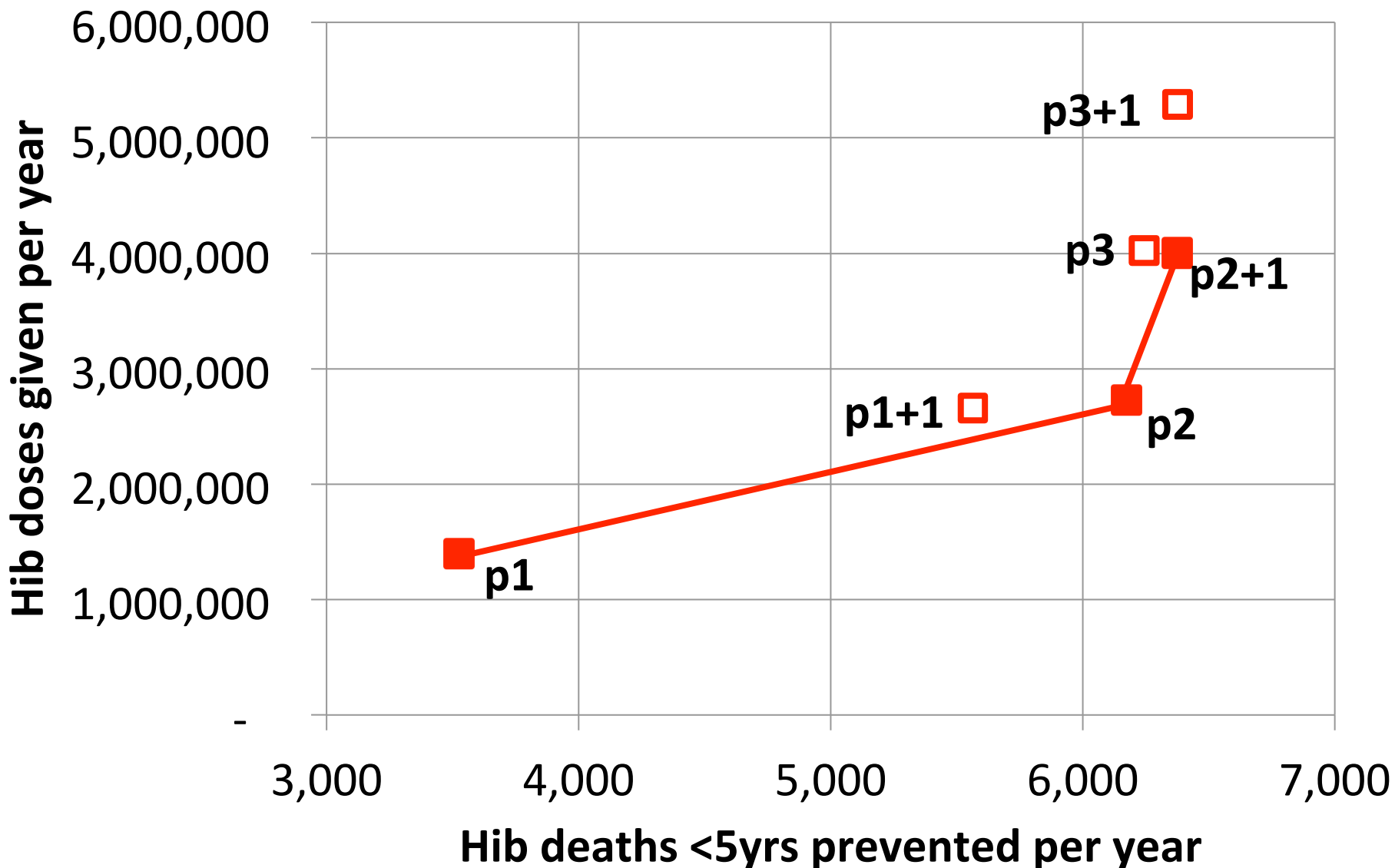


Kenya: doses given vs deaths prevented



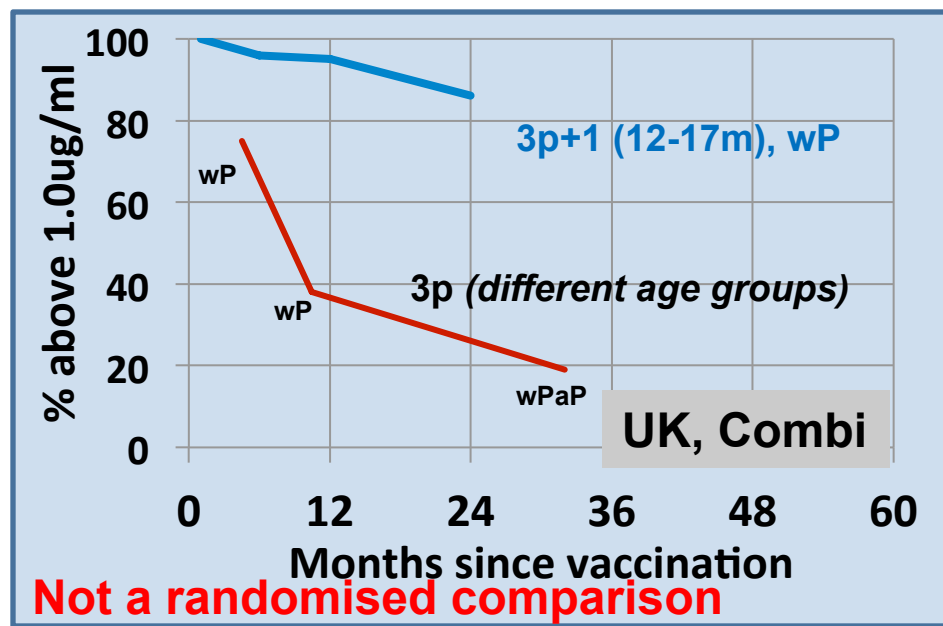
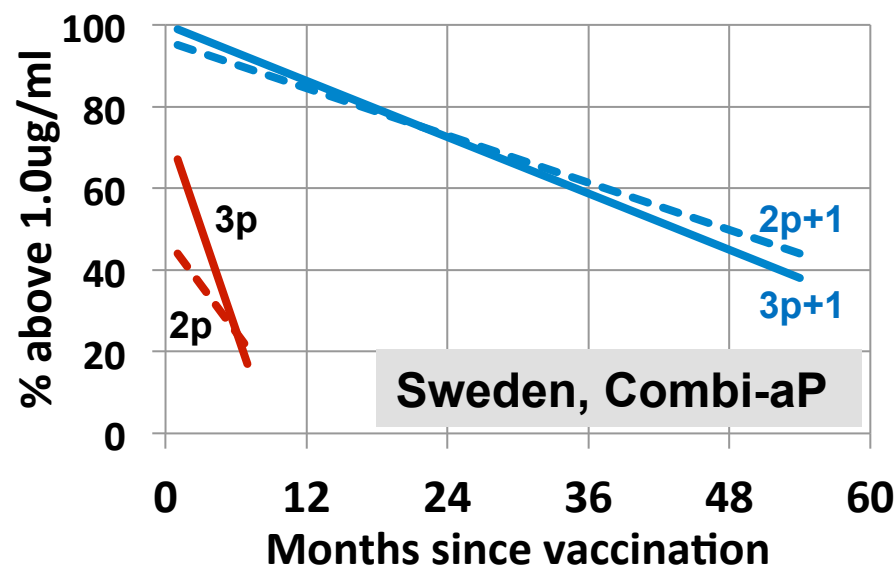
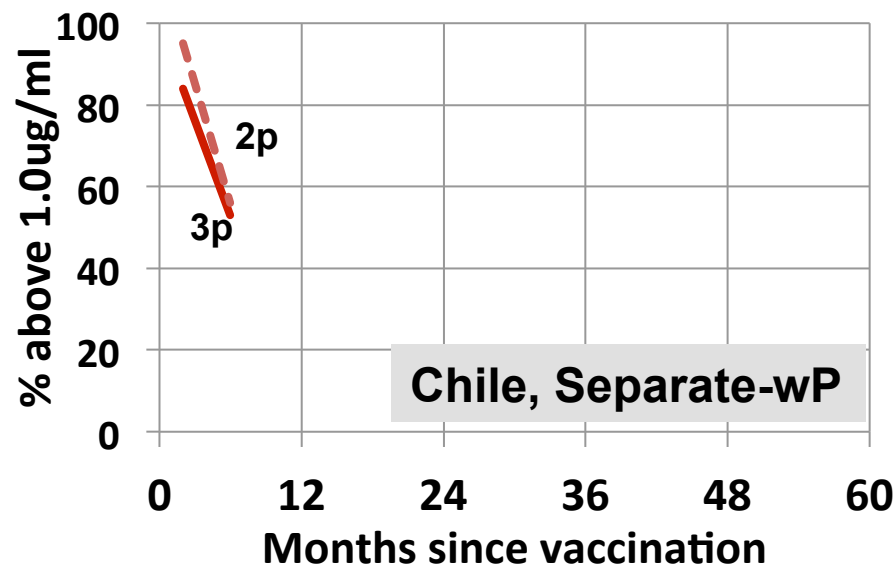
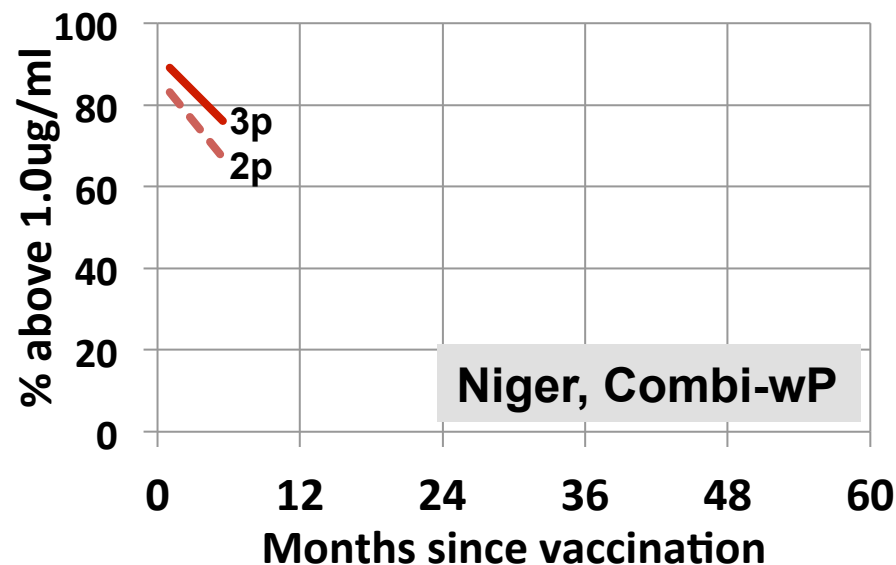
Kenya: doses given vs deaths prevented

Alternative scenario with UK duration of direct clinical protection



Reviewed duration of seropositivity (%>1ug/ml)

PRP-T studies comparing schedules head to head over at least 2 time points



Limitations

1. Simple model unable to capture complex uncertainties

- but a way forward based on best available evidence

2. Too much flexibility to change inputs at country level

- important to represent local situation
 - age distribution of disease, coverage and timeliness
- but other uncertain inputs should be restricted to plausible ranges in LMICs
 - Efficacy by vaccine type and dose (WHO reviews)
 - 30% maximum loss of protection per year (e.g. UK)
 - Herd effect multiplier between 100-160% of direct effect (Walker review)

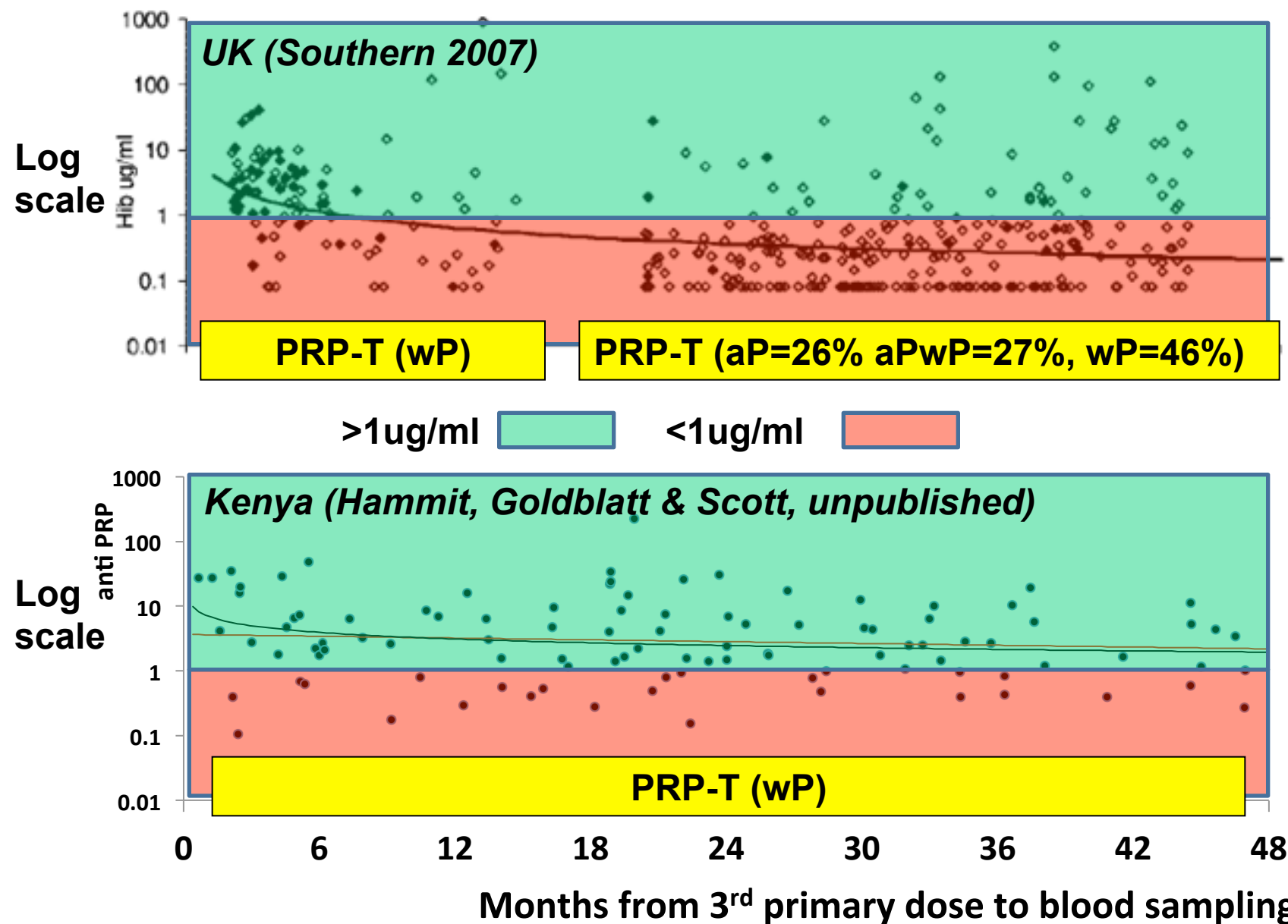
SAGE recommendations (WER 4th Jan 2013)

1. A revised summary of the evidence, including a critical appraisal of the evidence with GRADE tables and justification for proposed recommendations:
 - the number of primary doses
 - the need for booster doses
 - the interval between doses
 - additional immunological studies
 - duration of protection after each dose
 - the effect of Hib combination vaccines including those that include aP
2. The outcomes of the above reviews should also be used to refine the model assumptions and parameters.
 - A refined version should be submitted once more for appraisal by Hib experts to ensure that the revised assumptions and parameters have made it more realistic.

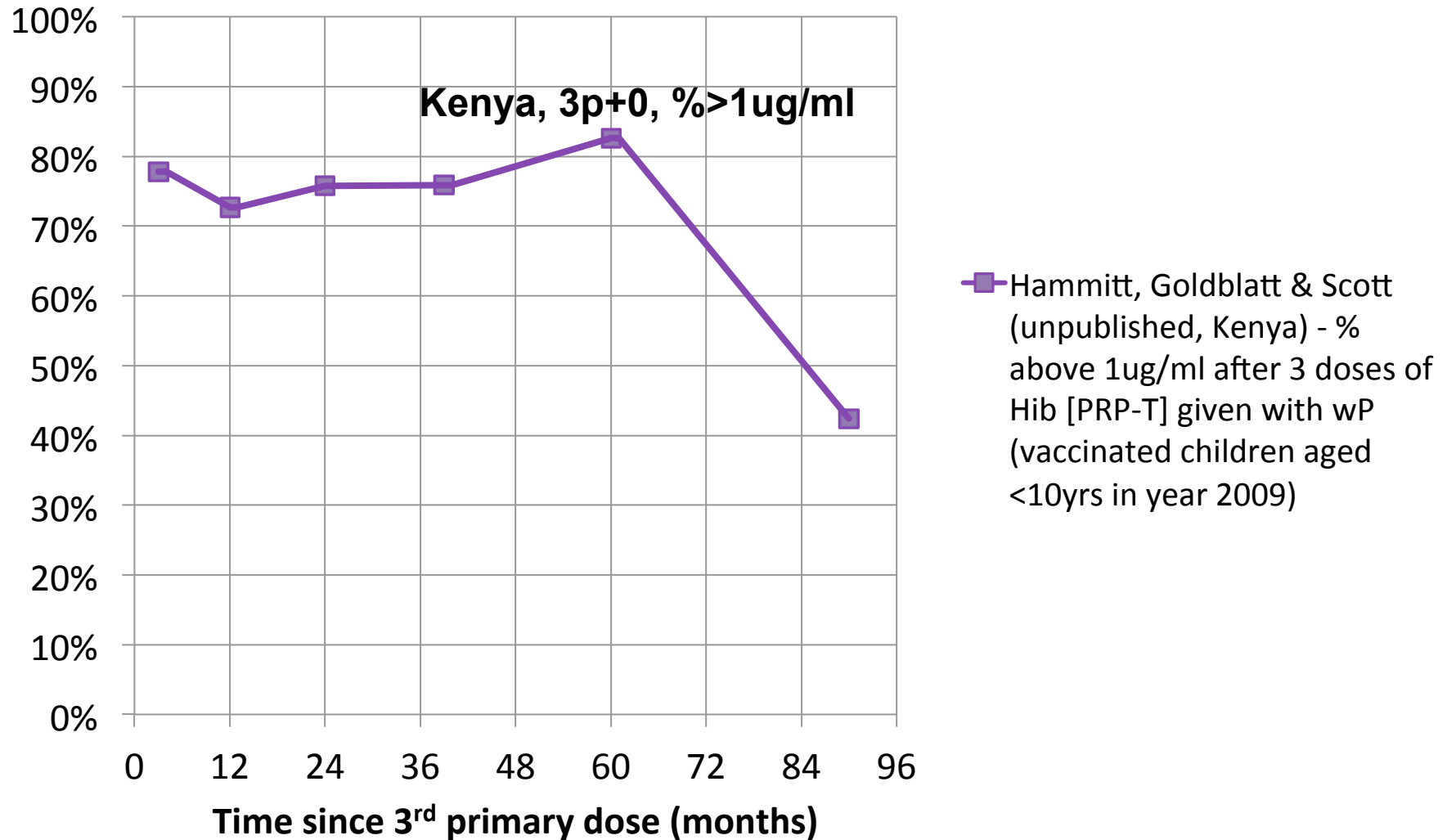
Example: two countries with good data on duration of seropositivity and clinical protection

- Industrialised country (UK)
- Developing country (Kenya)

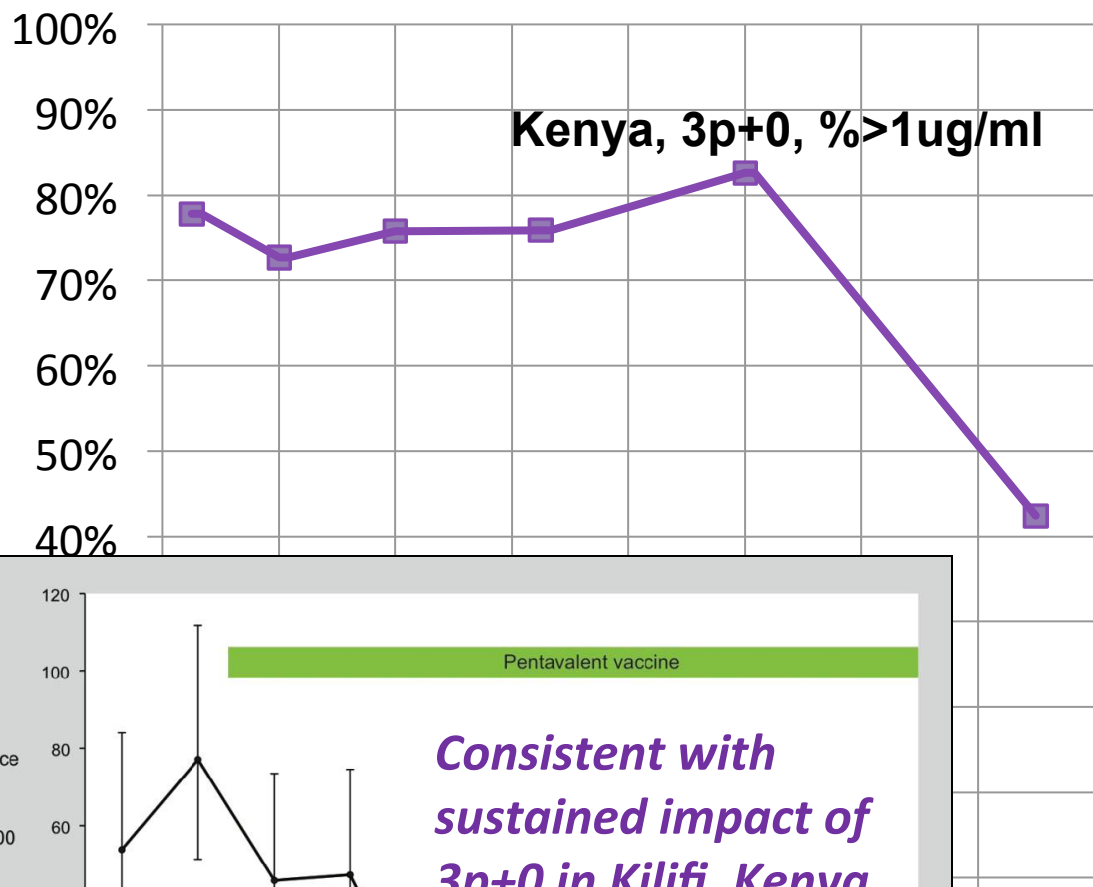
Duration of seropositivity (%>1ug/ml) after p3+0



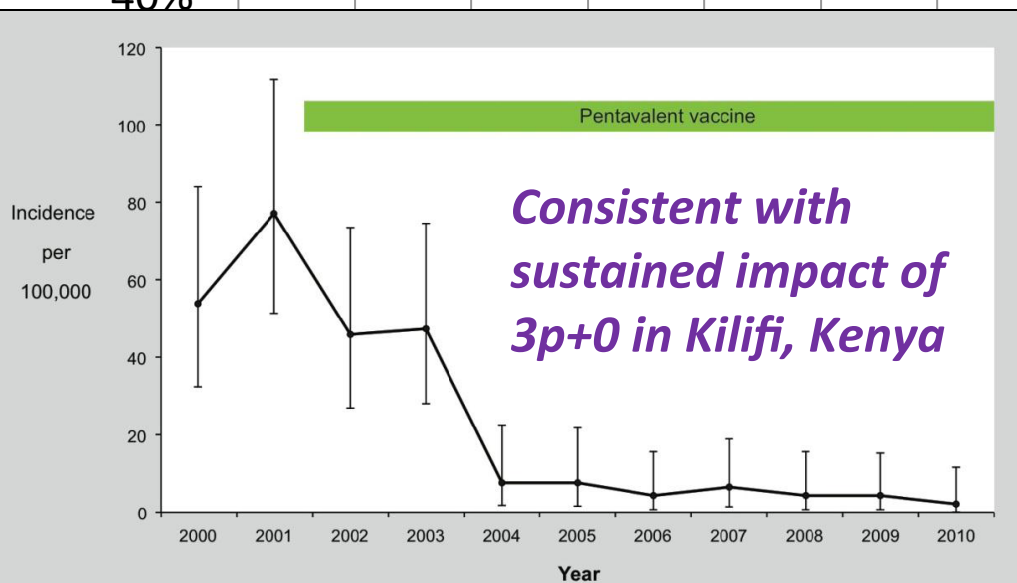
Duration of seropositivity after 3p+0, Hib [PRP-T]: *% above 1ug/ml in Kenya*



Duration of seropositivity after 3p+0, Hib [PRP-T]: % above 1ug/ml in Kenya



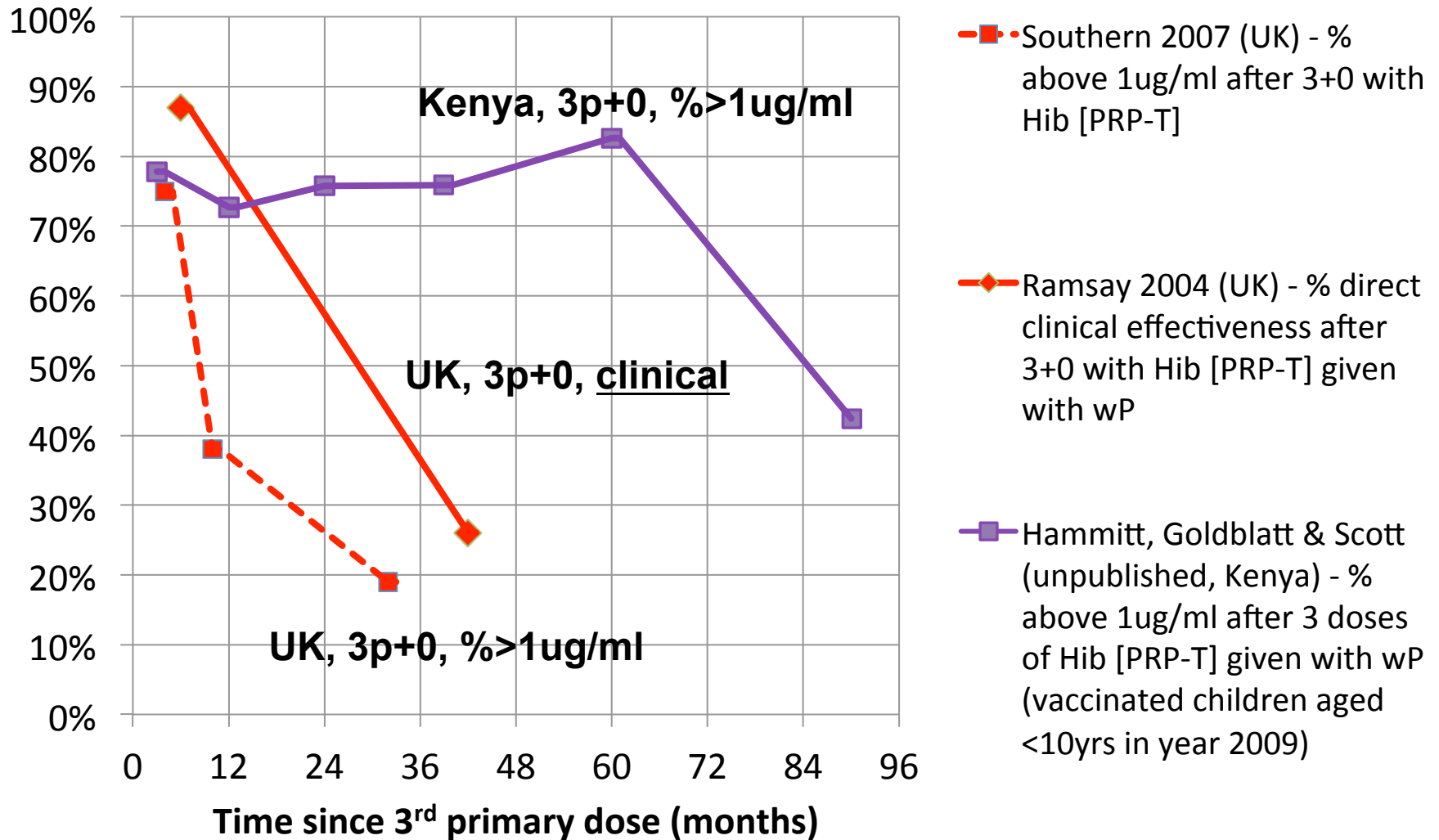
■ Hammitt, Goldblatt & Scott (unpublished, Kenya) - % above 1ug/ml after 3 doses of Hib [PRP-T] given with wP (vaccinated children aged <10yrs in year 2009)



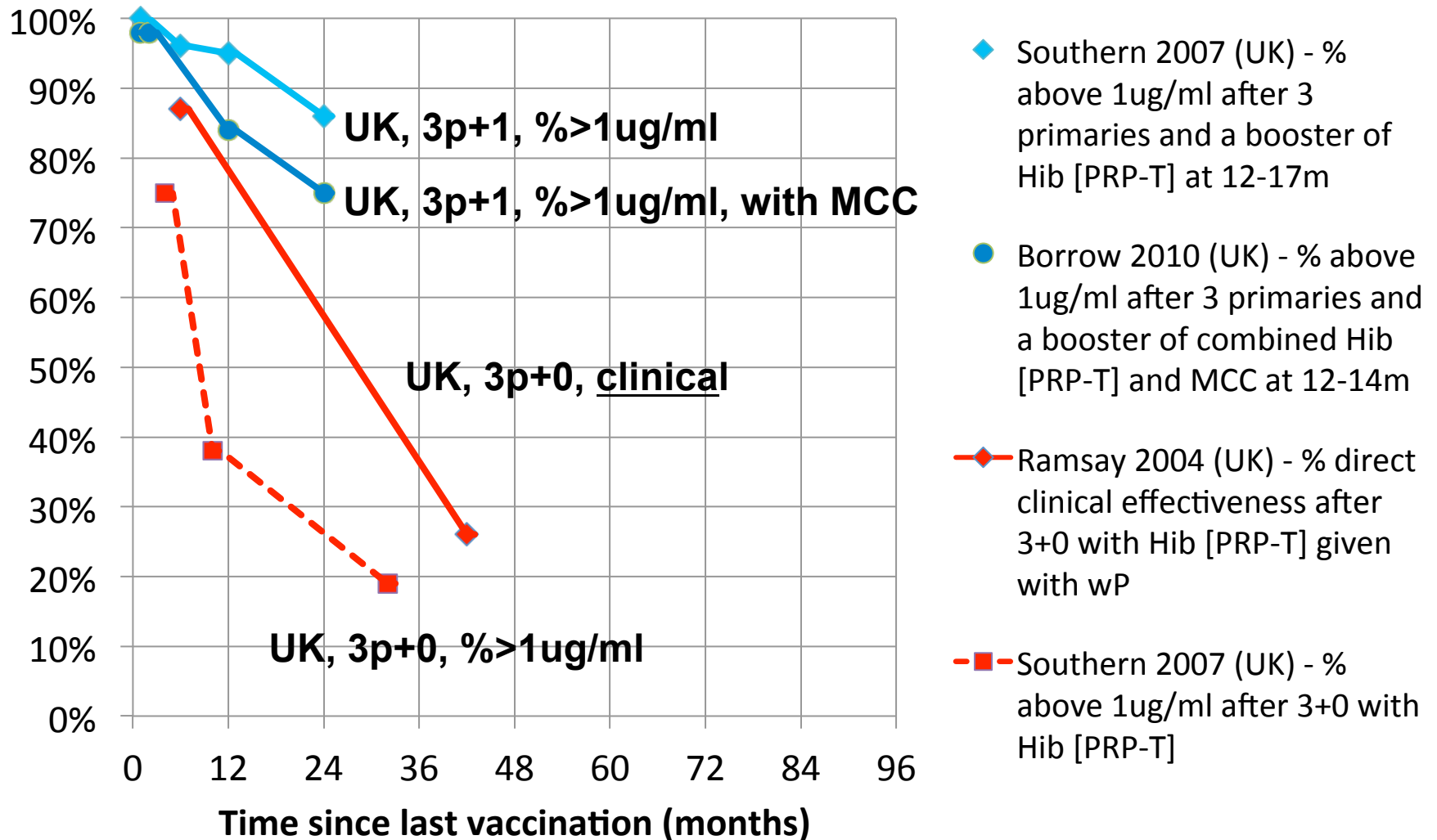
84 96
(ns)

Duration of seropositivity/protection after 3p+0:

% above 1ug/ml in the UK and Kenya, % direct protection vs clinical disease in UK



Duration of seropositivity and protection after 3p+0 and 3p+1 with Hib [PRP-T] in the UK



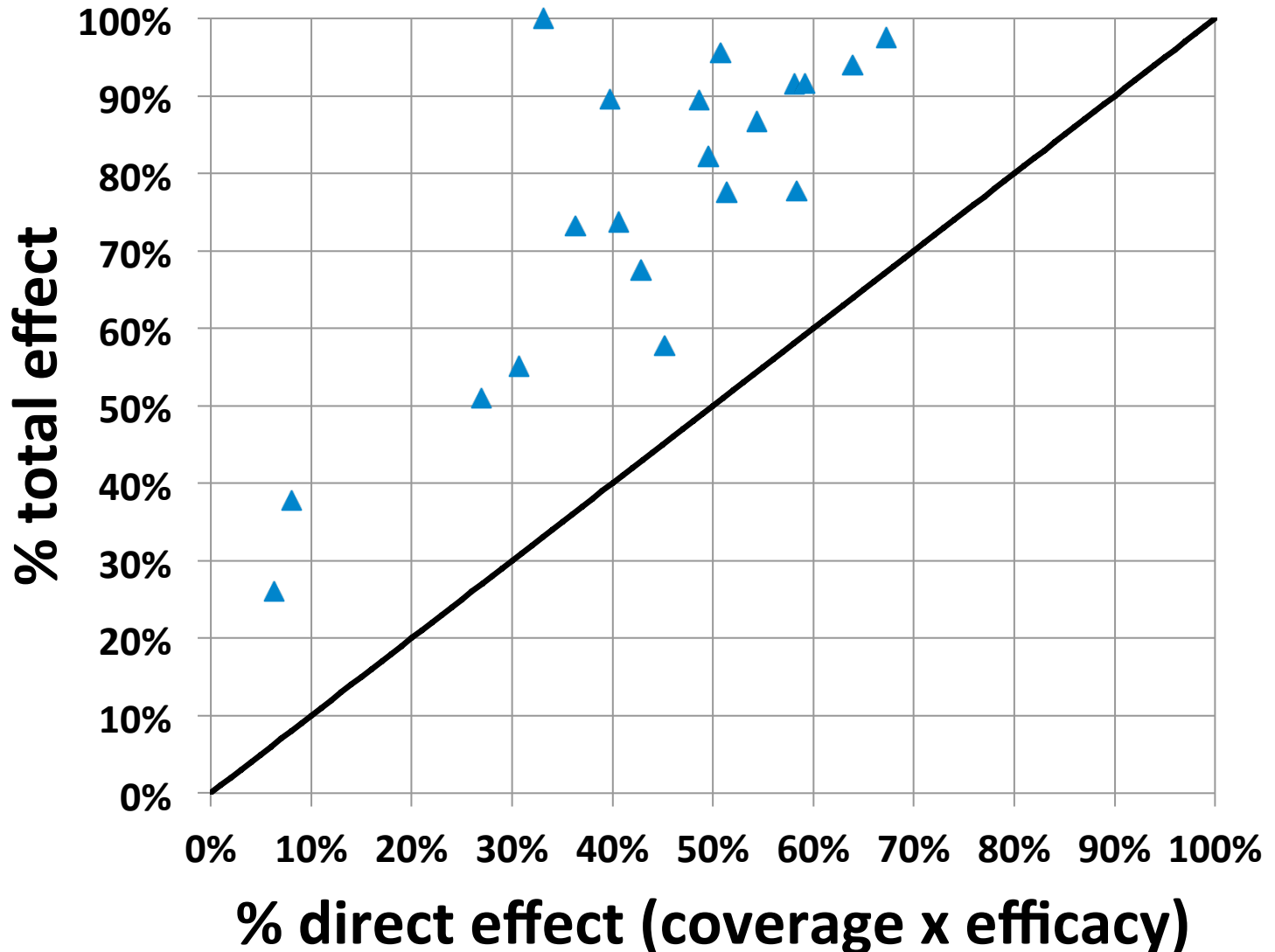
Systematic review of Hib vaccine herd effect <5yrs: total impact vs expected direct impact

- Observed total impact
 - % reduction in Hib meningitis/invasive disease <5yrs
- Expected direct impact
 - Hib dose 3 coverage x 93% efficacy (Griffiths et al, meta-analysis)
- Restricted to studies with weighted average of dose 3 coverage in under five population
 - 24 studies from 8 countries

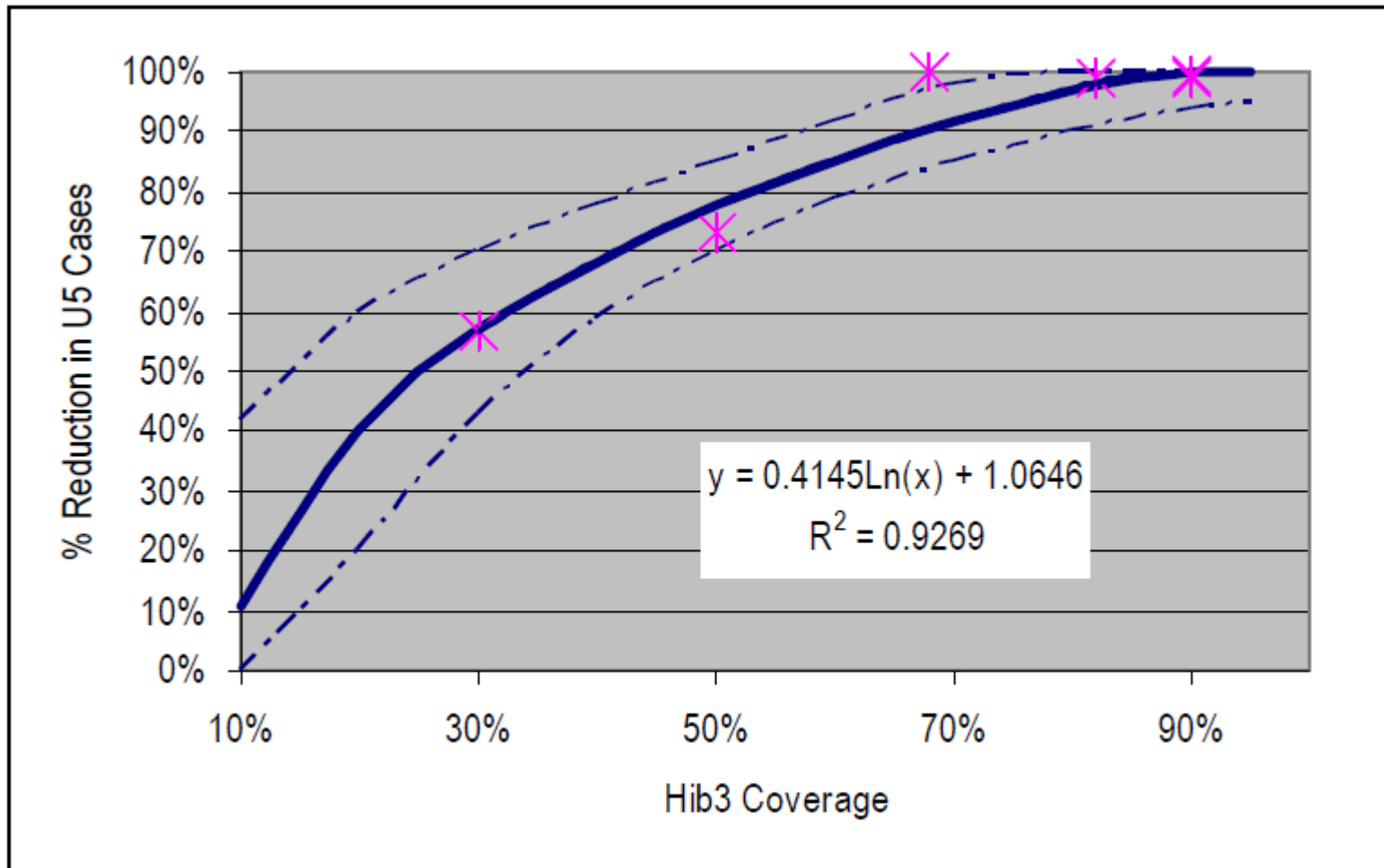
Estimated herd effect <5yrs by comparing observed total impact with expected direct impact

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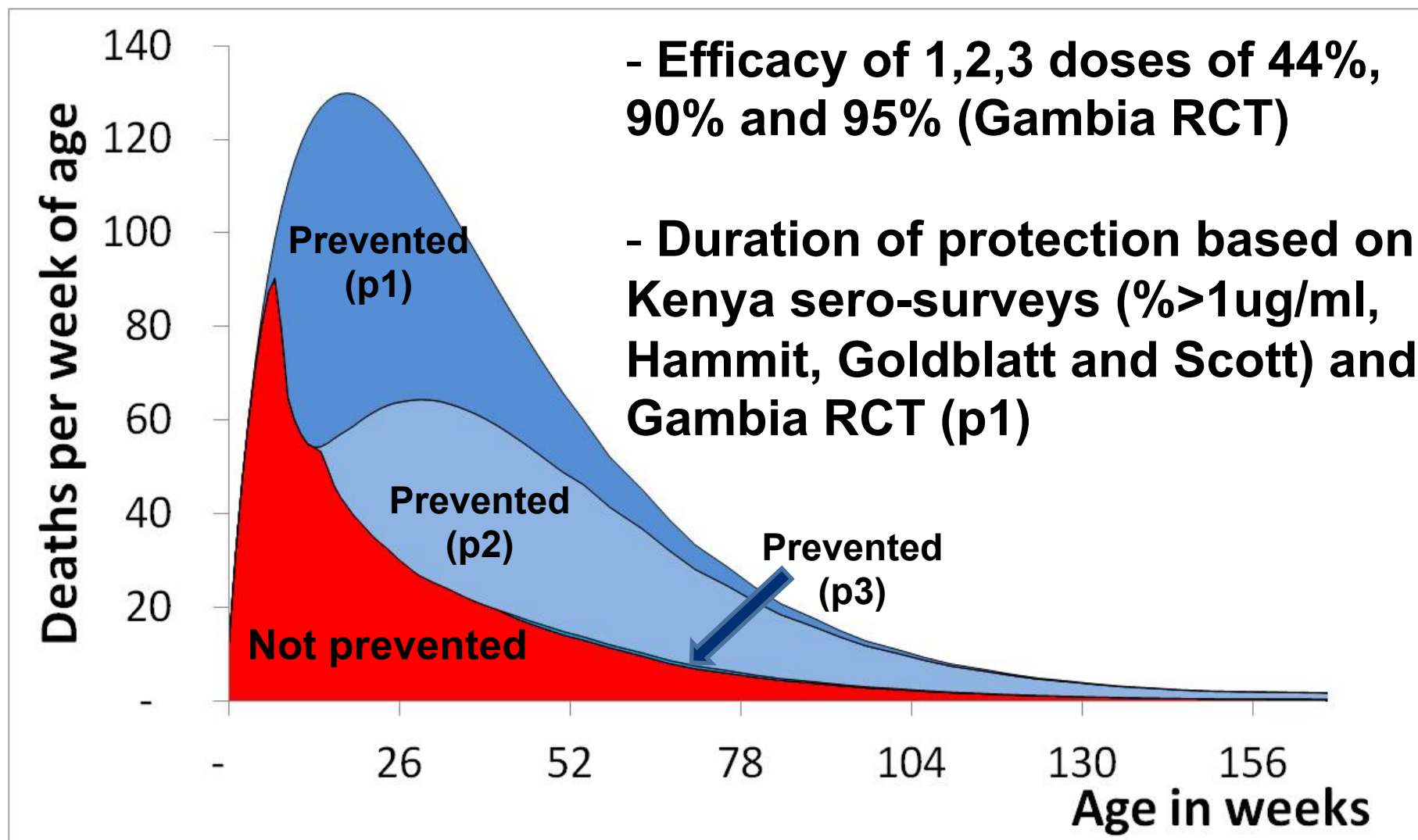
GBD 2000, Wolfson



6 data points from United States, Denmark, Israel, and the Gambia,

Kenya: efficacy and duration of protection

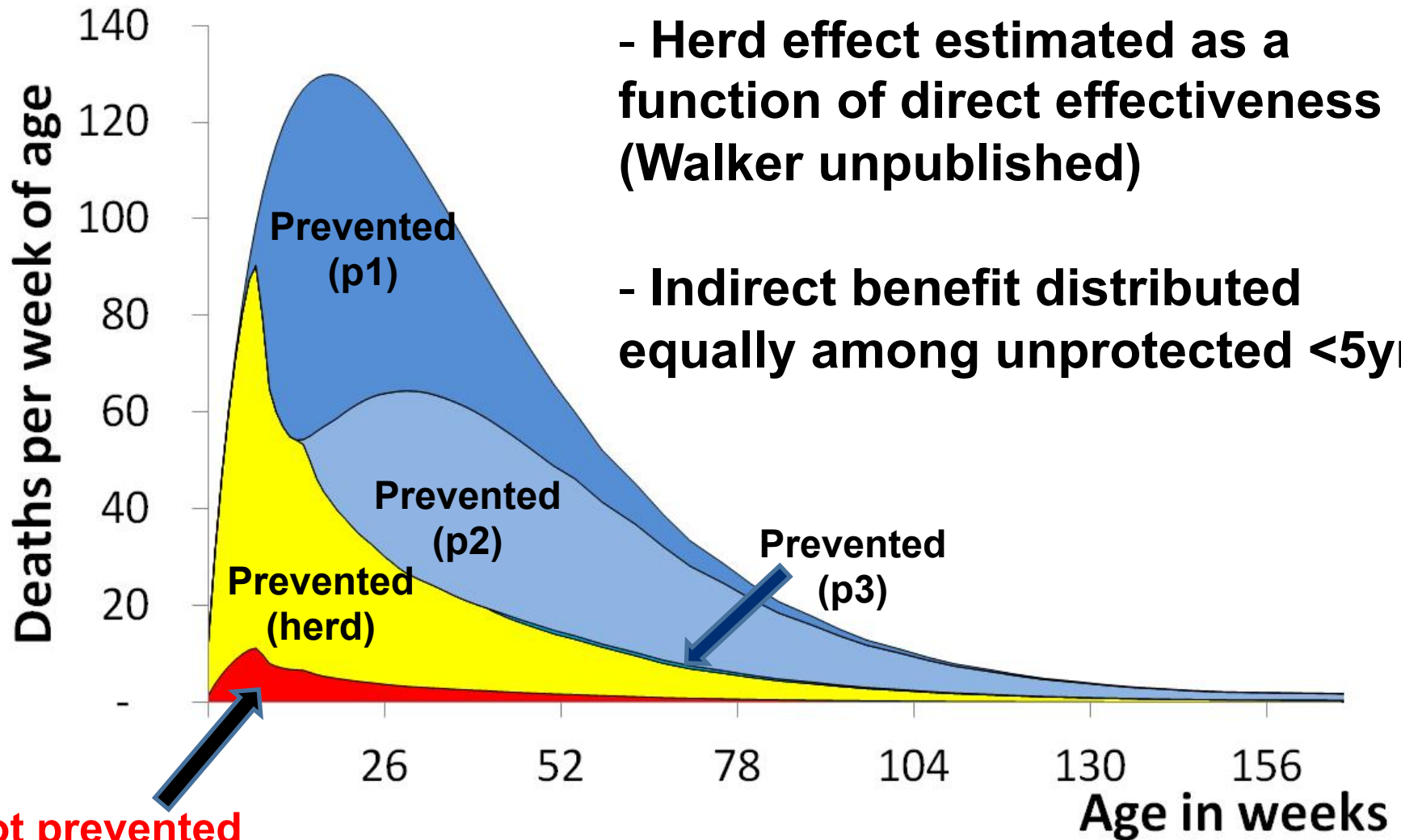
Informed by WHO review of RCTs in Africa with PRP-T (wP)



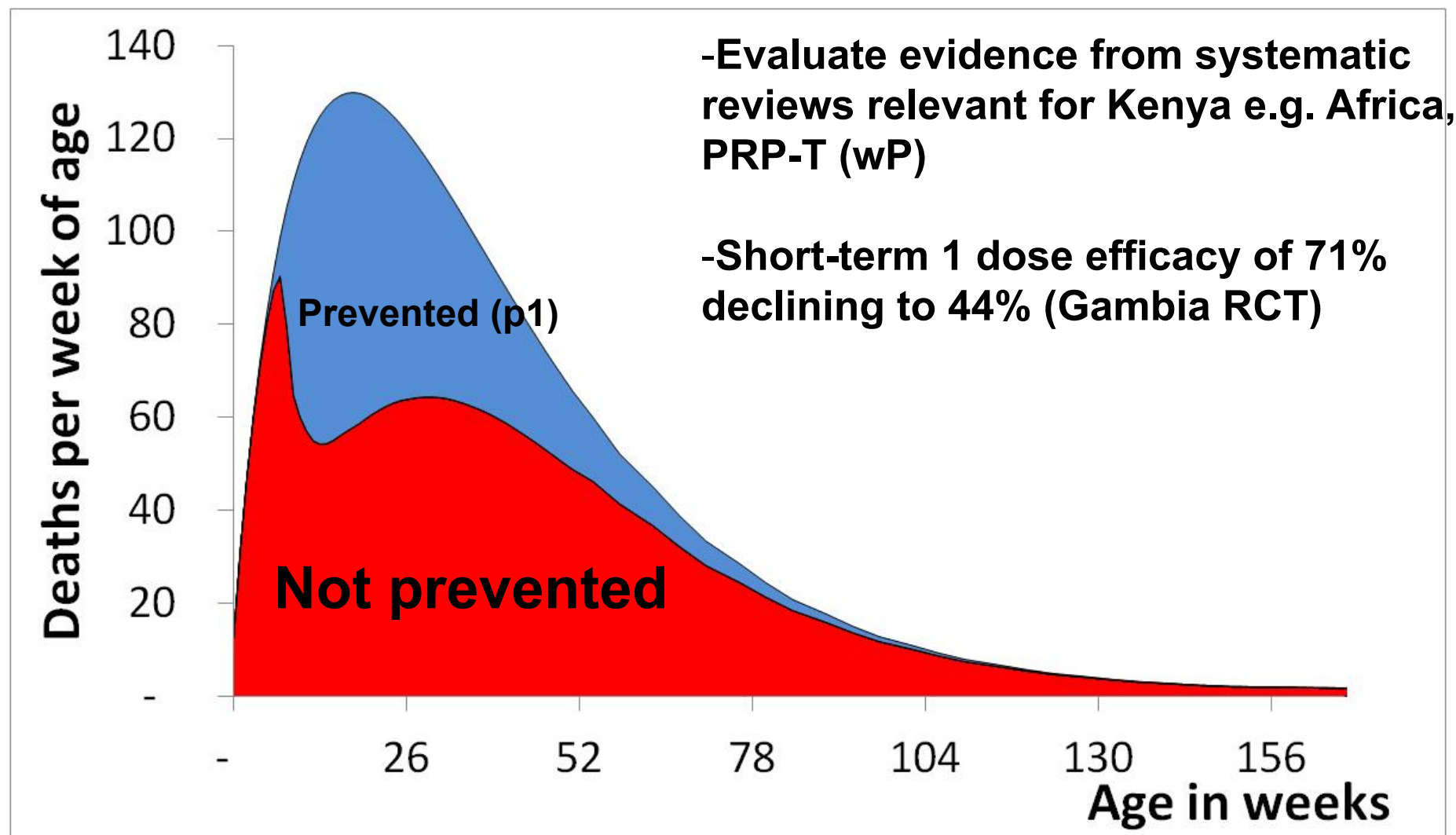
Kenya: herd effect <5yrs

- Herd effect estimated as a function of direct effectiveness (Walker unpublished)

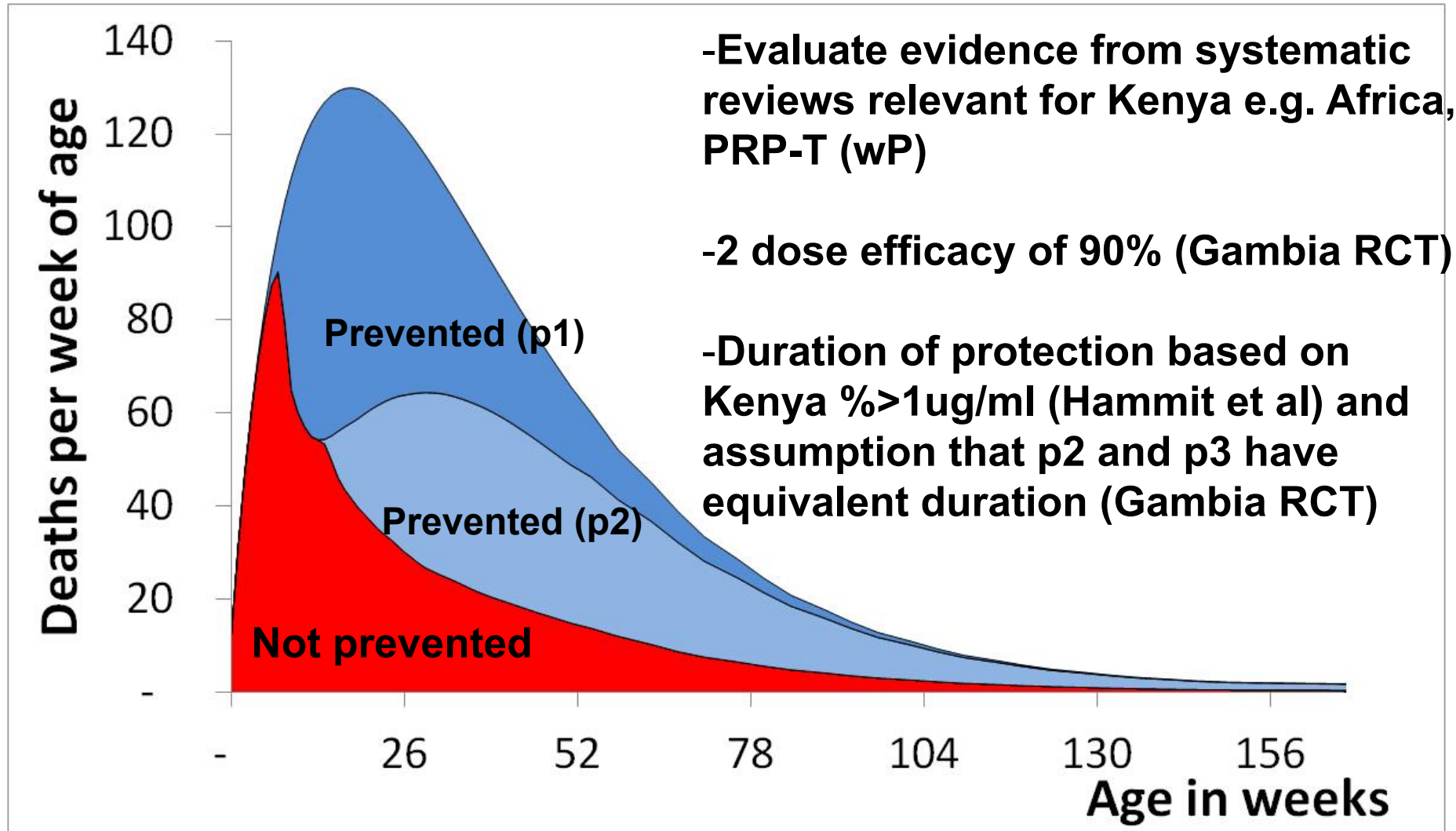
- Indirect benefit distributed equally among unprotected <5yrs



Kenya: direct protection after 1 primary dose

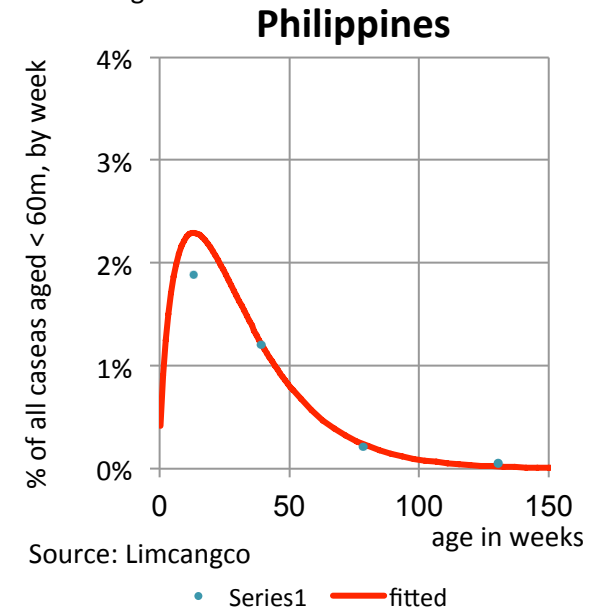
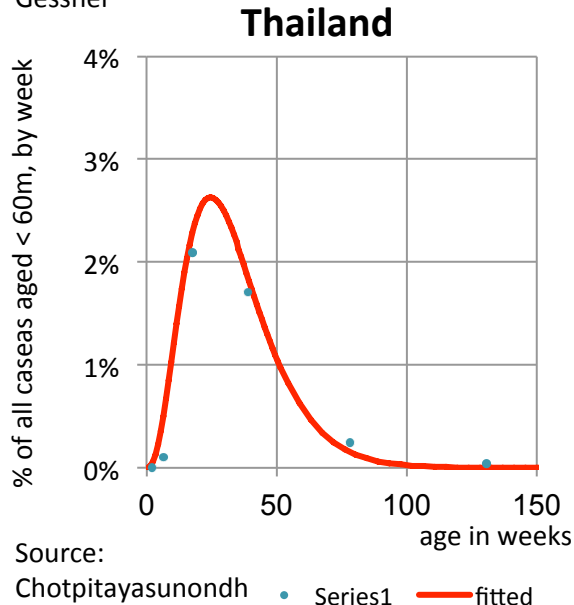
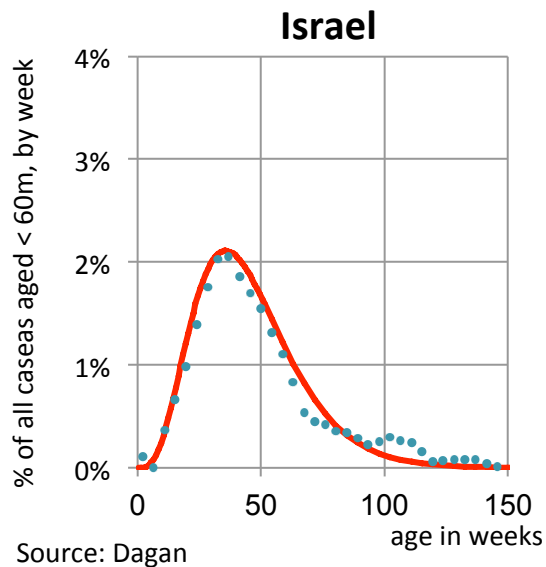
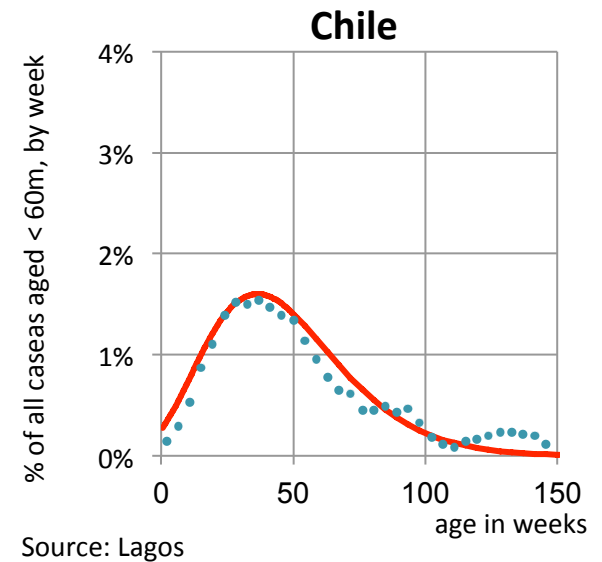
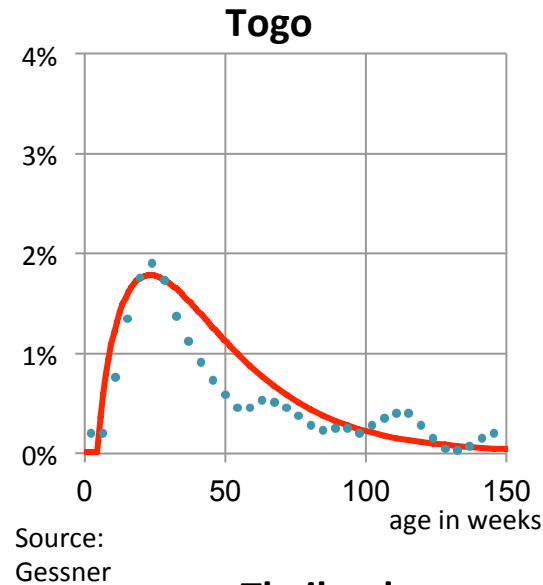
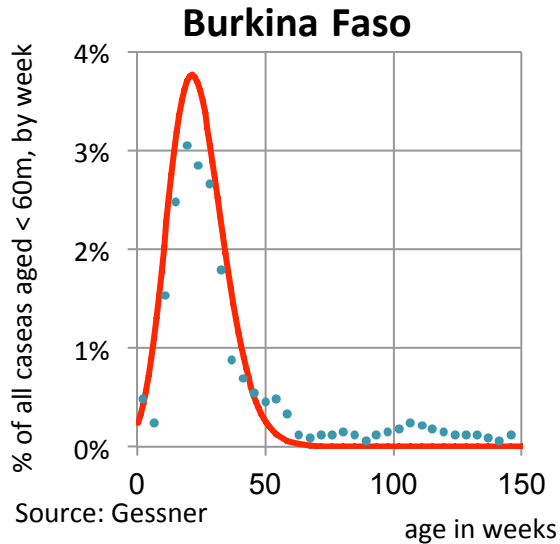


Kenya: direct protection after 2 primary doses



Reviewed age at Hib meningitis/invasive disease

14 country datasets identified (6 examples shown below)



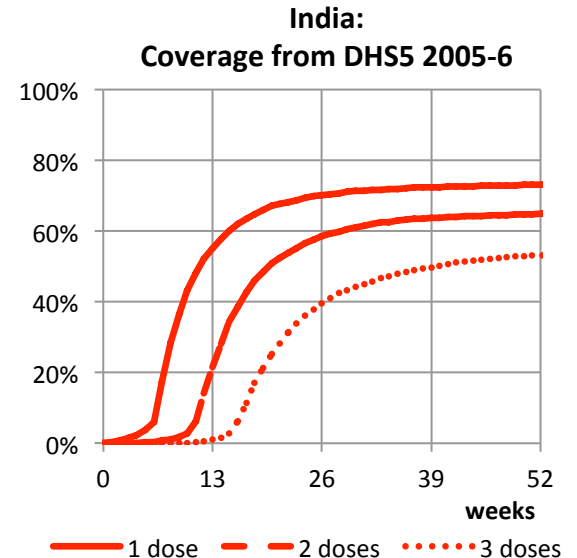
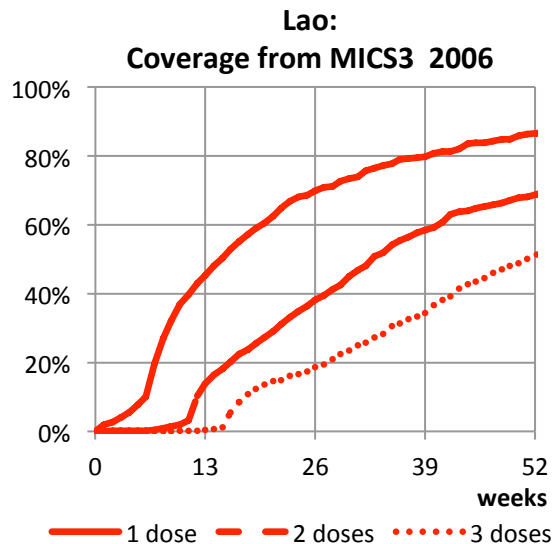
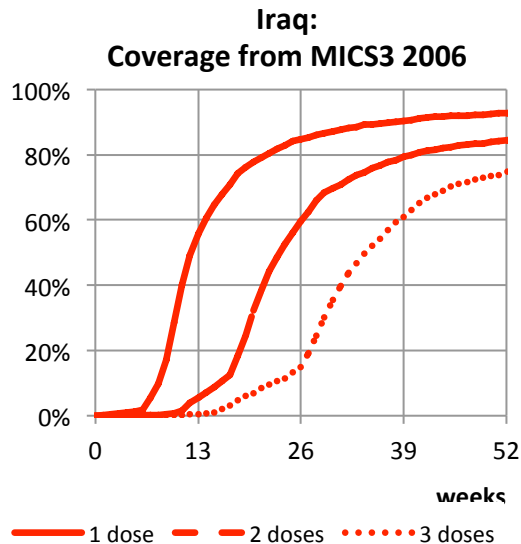
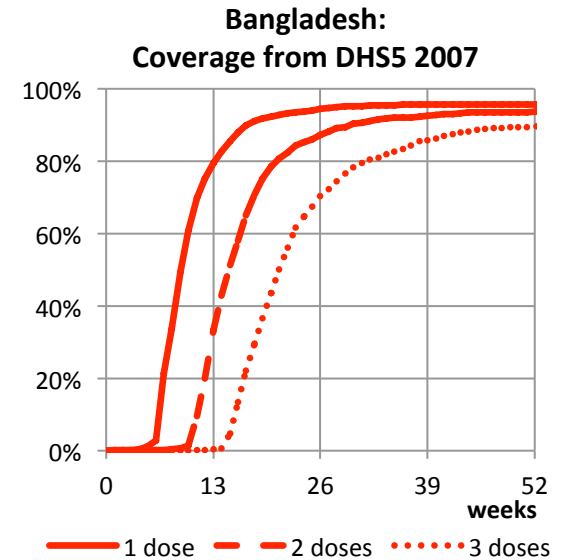
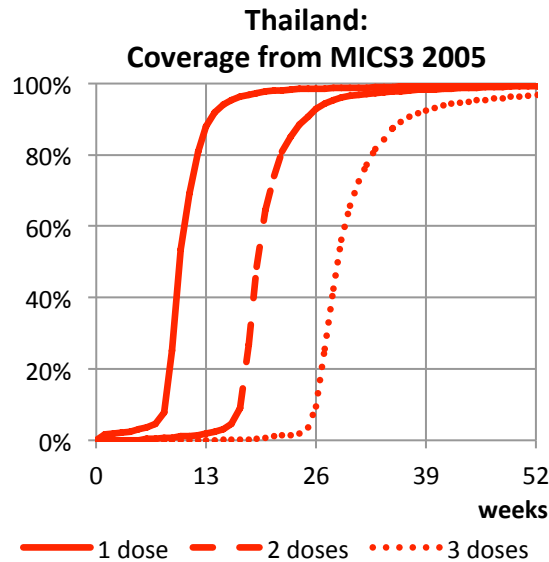
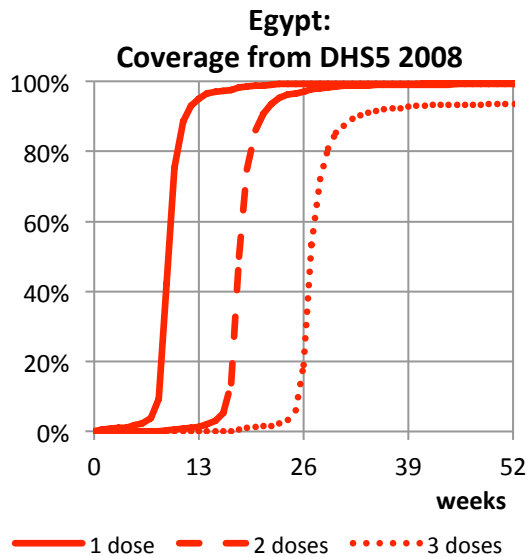
• Series1 — fitted

• Series1 — fitted

• Series1 — fitted

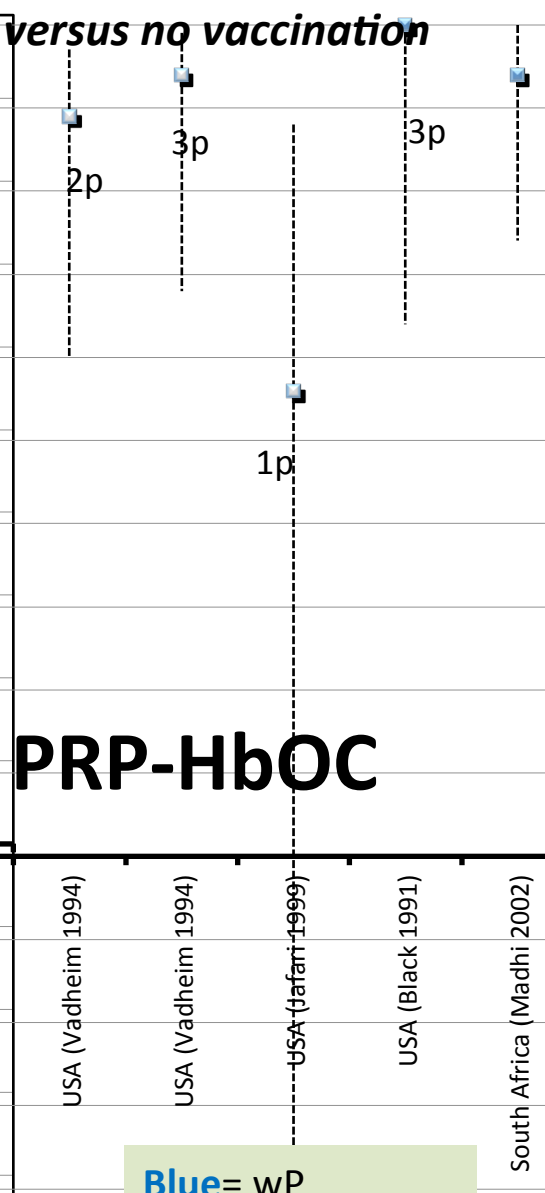
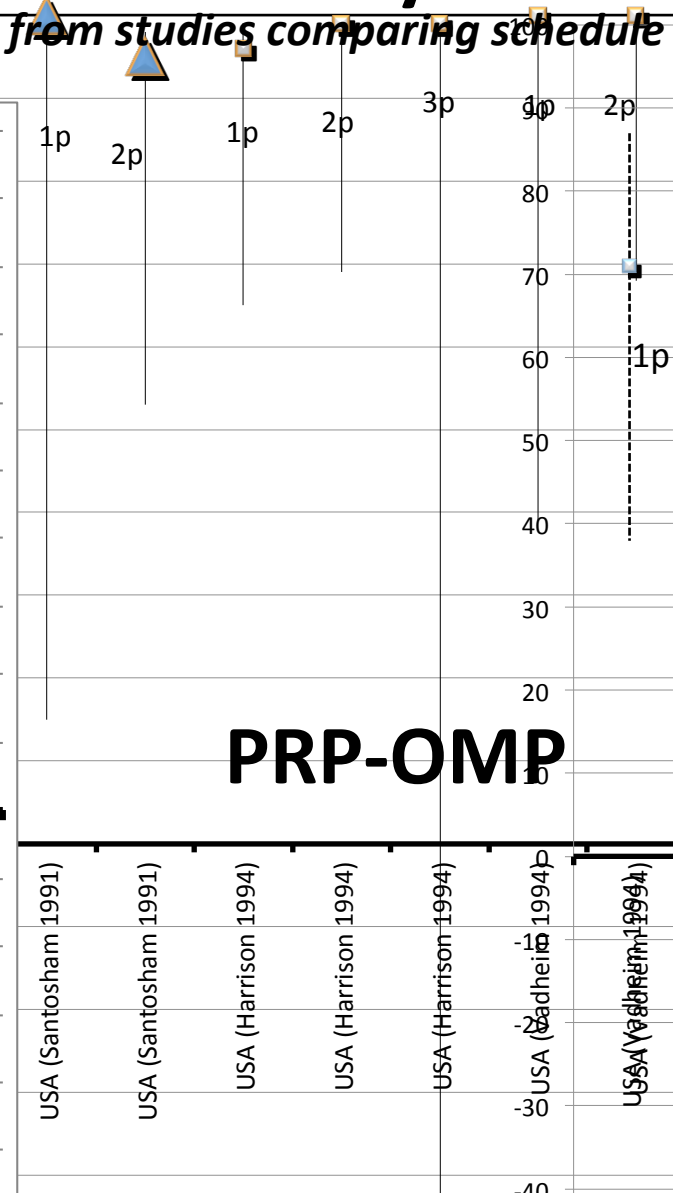
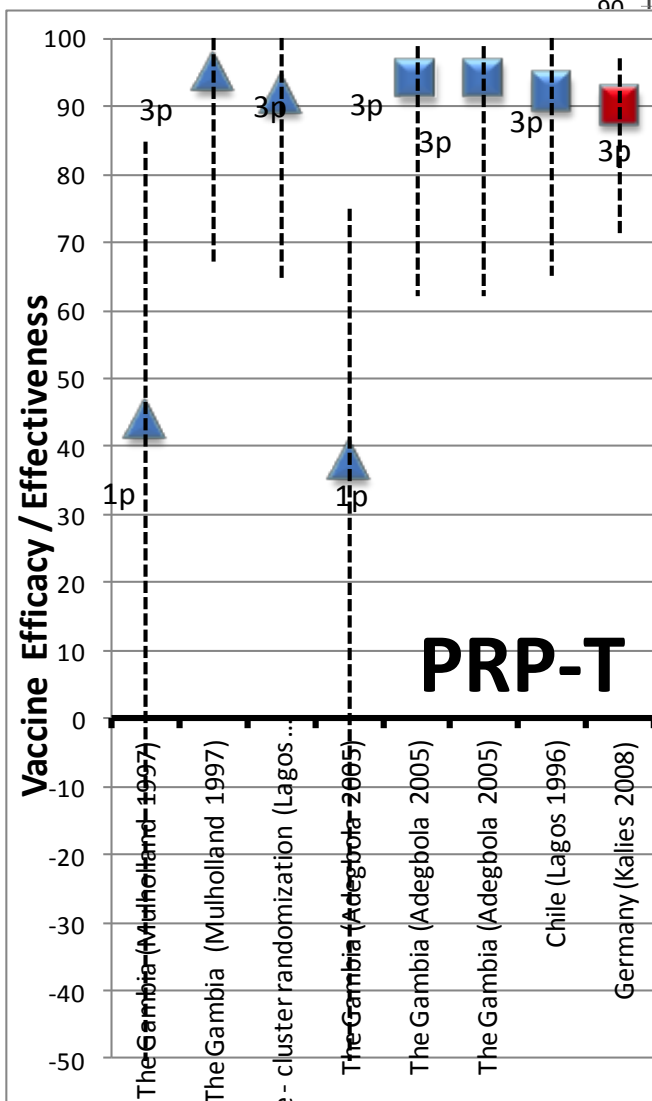
Evaluated timeliness of DTP1,2,3 and measles1

67 countries analysed (6 examples shown below)



Reviewed Hib vaccine efficacy and effectiveness

VE against invasive Hib disease from studies comparing schedule versus no vaccination



RCT



Observational

Blue= wP

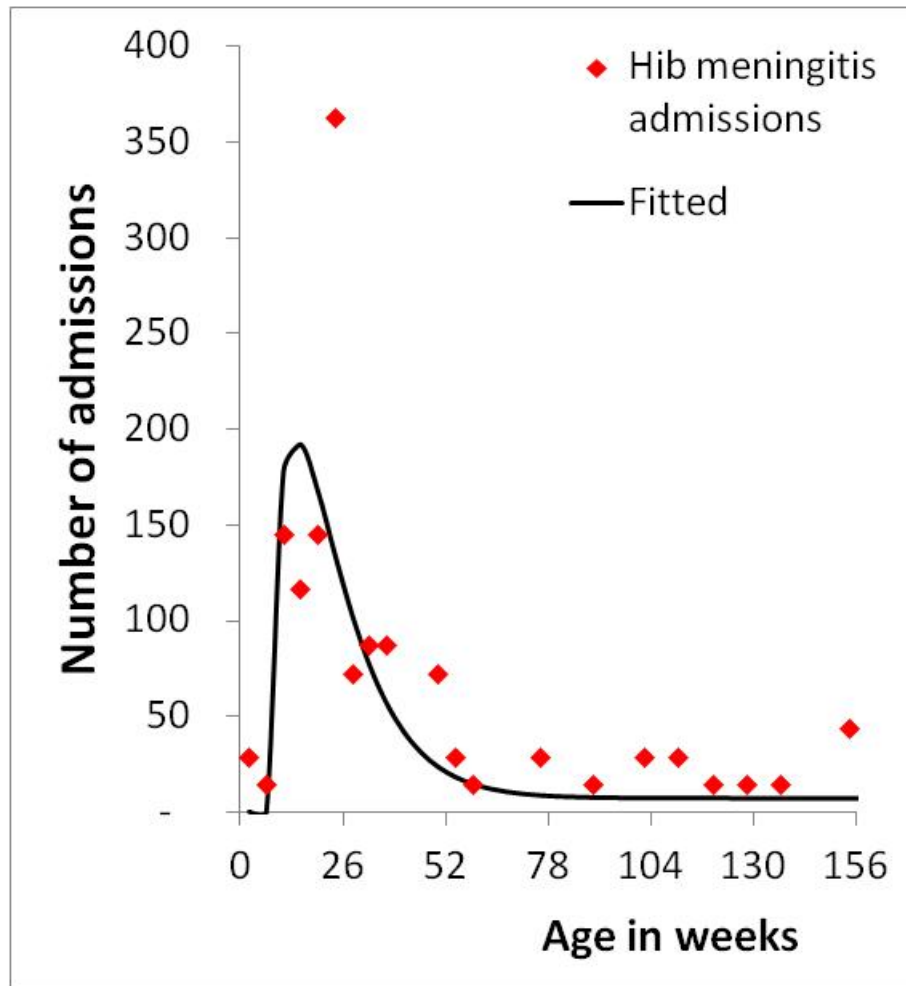
Red= aP

Grey= not stated

Review of RCTs by ISPM, and observational data by LSHTM

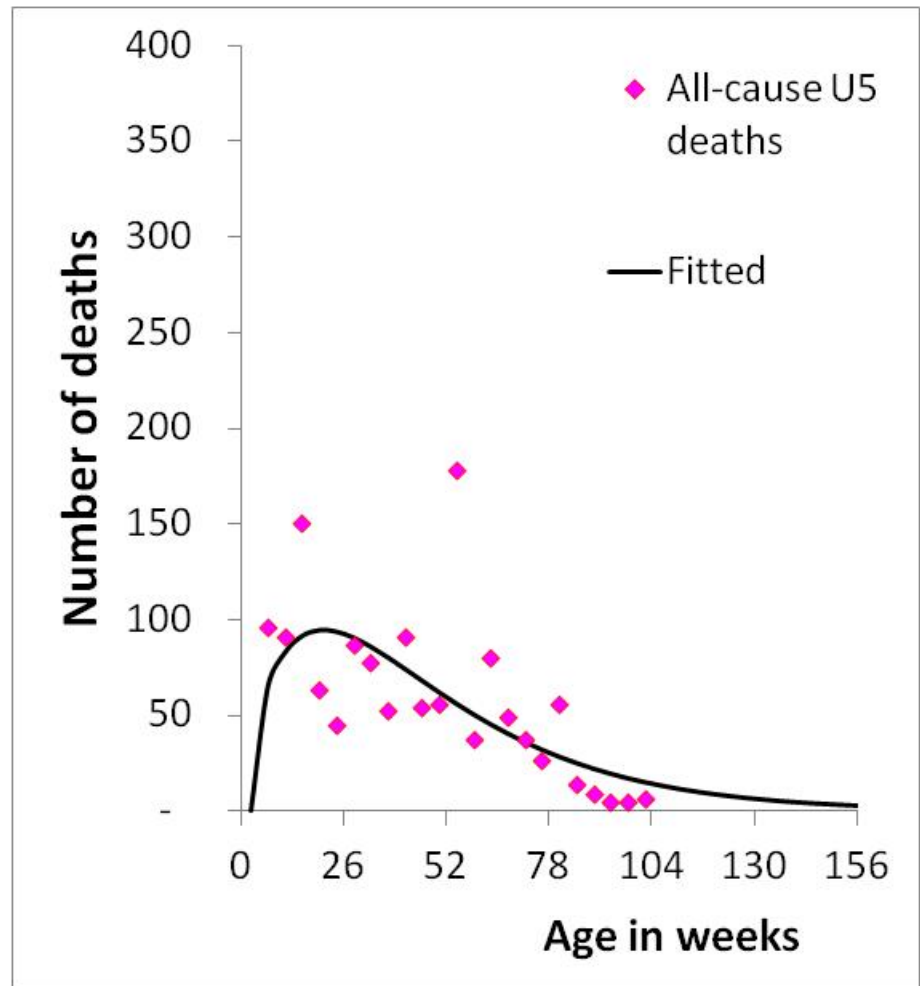
~6000 annual Hib deaths <5yrs in Burkina Faso (2011):
which proxy should be used to estimate age distribution?

Hib meningitis admissions



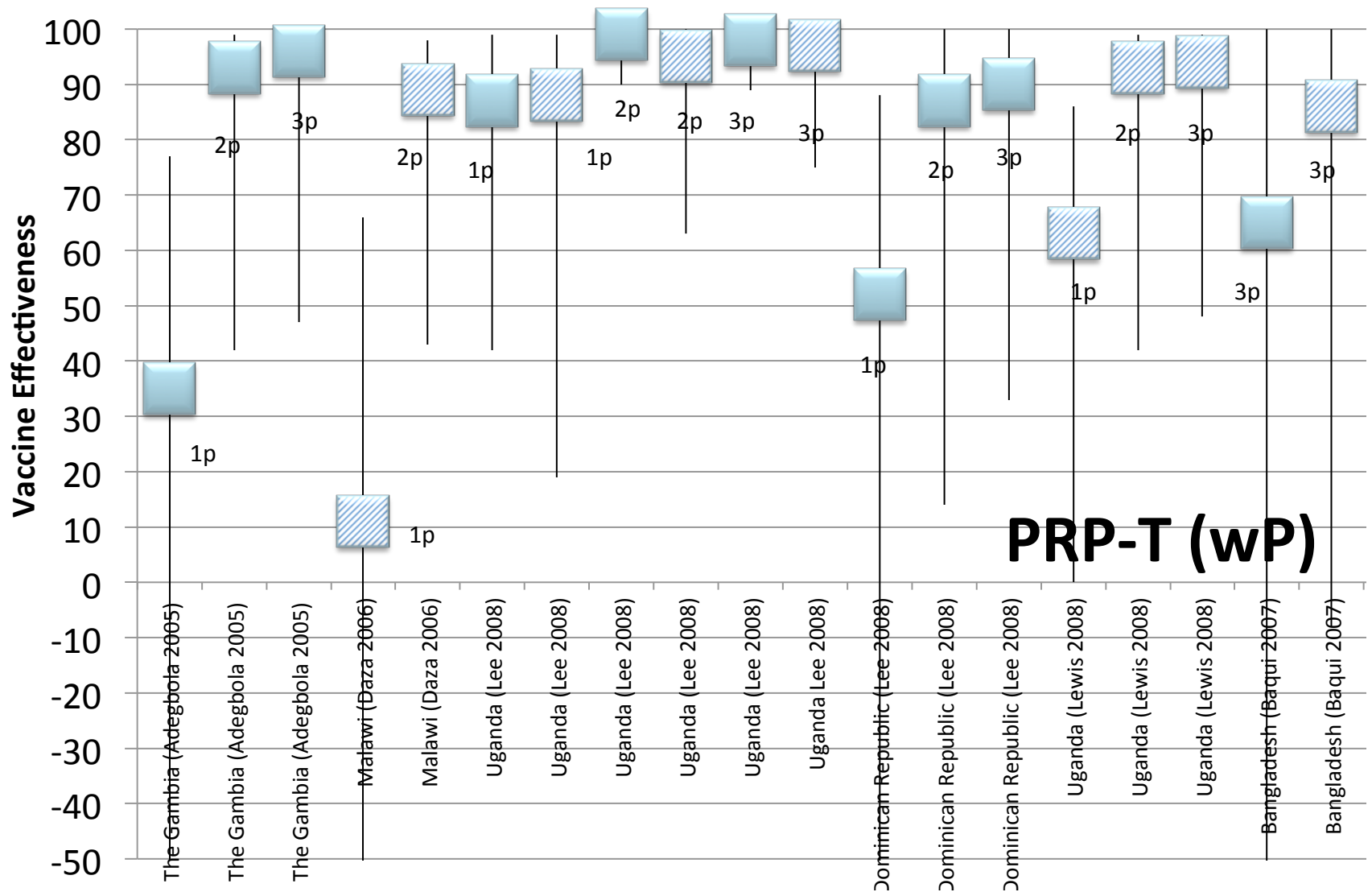
Souro Sanou Hosp. Burkina Faso 1986

<5 deaths due to any cause



DHS, Burkina Faso 2003

Hib vaccine effectiveness on Hib meningitis by vaccination schedule from studies comparing schedule versus no vaccination



All studies used PRP-T conjugate combined with WP except the USA-Santosham 1991, that used monovalent Hib with PRP-OMP conjugate

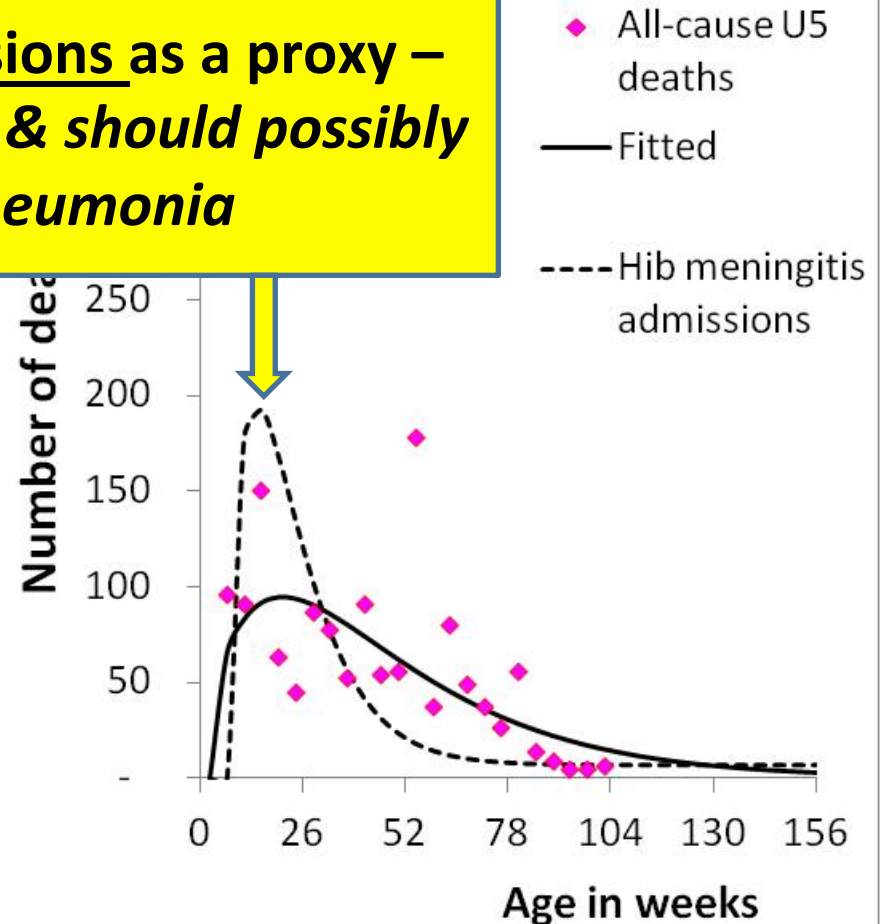
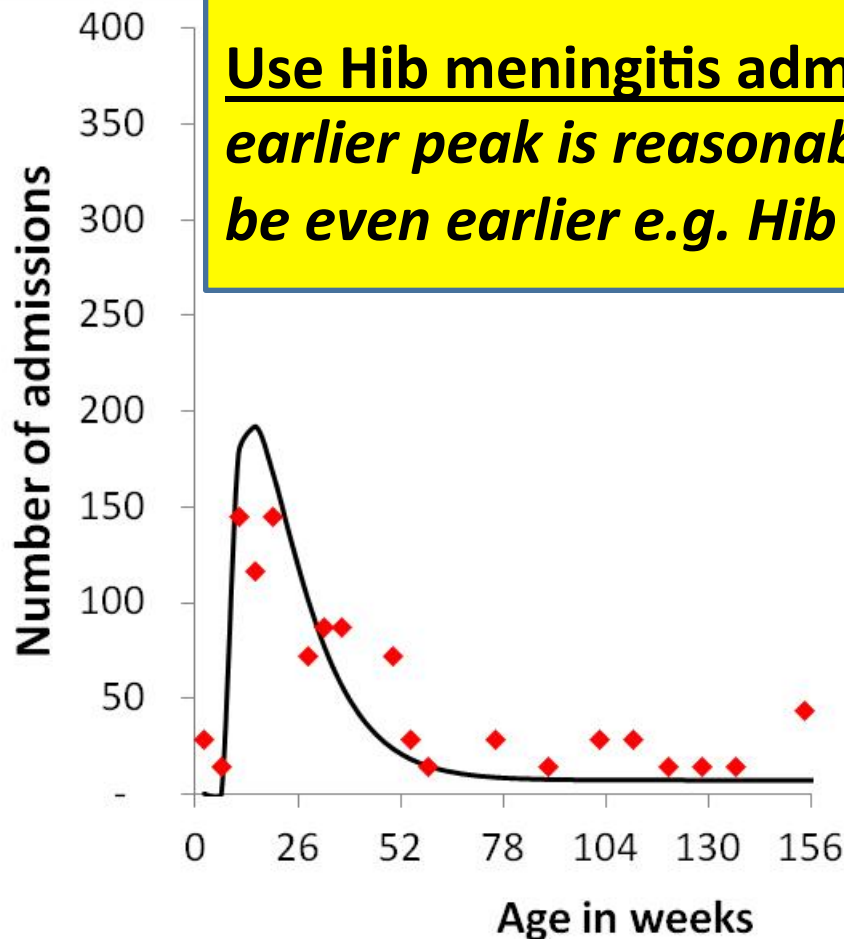
Solid marker = Community controls
Striped marker = Hospital controls

~6000 annual Hib deaths <5yrs in Burkina Faso (2011):
which proxy should be used to estimate age distribution?

Hib meningitis admissions

<5 deaths due to any cause

**Use Hib meningitis admissions as a proxy –
*earlier peak is reasonable & should possibly
be even earlier e.g. Hib pneumonia***



Duration of vaccine protection by dose

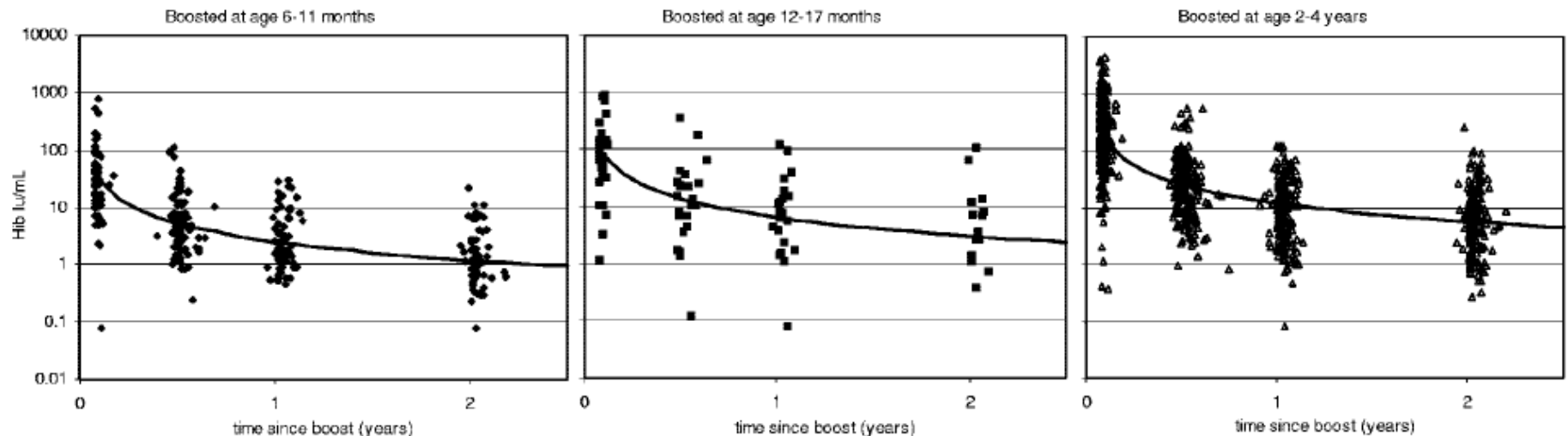


FIG. 4. Decline in Hib IgG antibody concentration by age at boosting and by the time since boosting with fitted trend lines.

Kinetics of Antibody Persistence following Administration of a Combination Meningococcal Serogroup C and *Haemophilus influenzae* Type b Conjugate Vaccine in Healthy Infants in the United Kingdom Primed with a Monovalent Meningococcal Serogroup C Vaccine[▽]

Ray Borrow,^{1*} Nick Andrews,² Helen Findlow,¹ Pauline Waight,³ Joanna Southern,³ Annette Crowley-Luke,⁴ Lorraine Stapley,⁴ Anna England,⁴ Jamie Findlow,¹ and Elizabeth Miller³

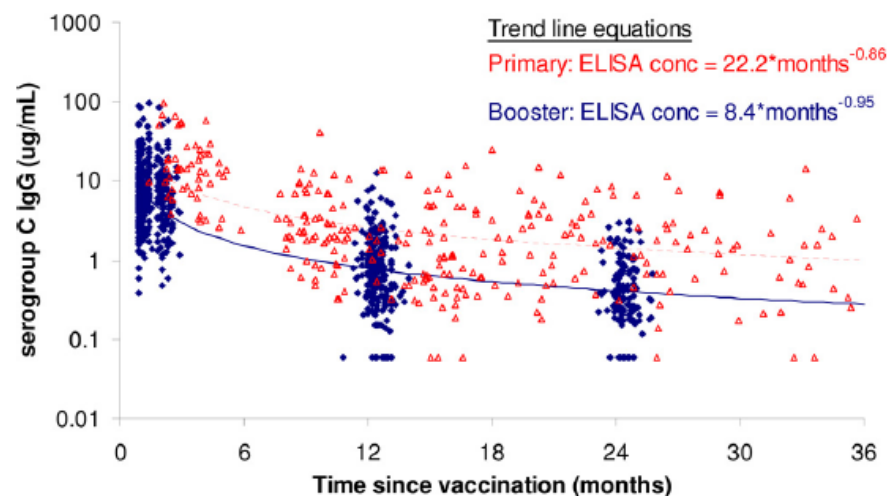


FIG. 2. Meningococcal serogroup C-specific IgG antibody concentrations and trend lines by time since primary vaccination (red triangles and dotted trend line) and time since booster vaccination (blue diamonds and solid trend line).

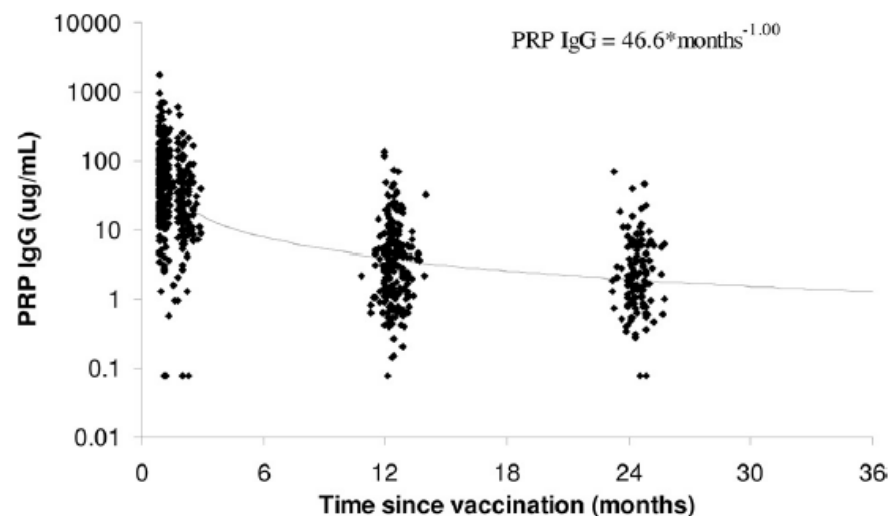


FIG. 3. Hib-PRP IgG antibody concentrations and trend line by time since booster vaccination.