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

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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**

Kenya

**Data, assumptions, scenarios**

Schedule: 2pt+ Primary = 2 Booster = yes

**Age at Hib disease**

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

**Timeliness**

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

**Efficacy & waning**

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

**Herd effect <5**

yes

**Global review**
Comparing direct & total impact (Walker et al)
Example - Kenya

How it works in practice...
Kenya: age distribution of Hib deaths <5yrs

- Age of invasive Hib disease admissions (Kilifi 2000-2004, Cowgill et al) used as a proxy for Hib deaths
- Adjusted to WHO estimates of Hib deaths <5yrs in Kenya per year (WHO)
Kenya: coverage and timeliness of doses

Source: (Kenya DHS Household Survey 2006)
Kenya: combine coverage with **efficacy and duration of protection** to estimate direct impact

- Assume 3 dose efficacy of 95% based on PRP-T [wP] (WHO review)

- Assume partial efficacy of 44% for 1 dose and 90% for 2 doses (WHO review)

- Assume 5% loss of direct protection per yr based on %>1ug/ml in Kenya (Hammit, Goldblattt and Scott, unpublished)
Kenya: adjust direct protection to account for simple estimates of potential herd effect

- Herd effect estimated as a simple relationship between direct effectiveness and total impact informed by global review (Walker et al, unpublished)

![Graph showing deaths per week of age and age in weeks with categories of prevented (direct) and prevented (indirect).]
Kenya: estimated impact of p3+0 and p2+1

**p3+0**

- 96% (6804) deaths prevented per year

**p2+1**

- 95% (6769) deaths prevented per year
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, 3p+0, %>1ug/ml

UK, 3p+0, clinical

UK, 3p+0, %>1ug/ml

Ramsay 2004 (UK) - % direct clinical effectiveness after 3+0 with Hib [PRP-T] given with wP

Southern 2007 (UK) - % above 1ug/ml after 3+0 with Hib [PRP-T]

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)
Kenya: deaths prevented for different assumptions of duration of protection

- Assumes 5% loss/yr of % > 1ug/ml in Kenya
- Assumes 30% loss/yr of clinical protection in UK

Graph showing the number of Hib deaths prevented per year against the percentage loss of direct protection per year after p2/p3/booster.
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

Walker N et al, unpublished
Kenya: doses given vs deaths prevented

Alternative scenario with UK duration of direct clinical protection
Reviewed duration of seropositivity (%>1µg/ml)

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

Niger, Combi-wP

Chile, Separate-wP

Sweden, Combi-aP

UK, Combi

Not a randomised comparison
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 4\textsuperscript{th} 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

UK (Southern 2007)

Log scale

Hib μg/ml

>1ug/ml

<1ug/ml

PRP-T (wP)

PRP-T (aP=26% aPwP=27%, wP=46%)

Kenya (Hammit, Goldblatt & Scott, unpublished)

Log scale

anti PRP

>1ug/ml

<1ug/ml

PRP-T (wP)

Months from 3rd primary dose to blood sampling
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)
Duration of seropositivity after 3p+0, Hib [PRP-T]: % above 1ug/ml in Kenya

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

Consistent with sustained impact of 3p+0 in Kilifi, Kenya
Duration of seropositivity/protection after 3p+0:
% above 1ug/ml in the UK and Kenya, % direct protection vs clinical disease in UK

- Southern 2007 (UK) - % above 1ug/ml after 3+0 with Hib [PRP-T]
- Ramsay 2004 (UK) - % direct clinical effectiveness after 3+0 with Hib [PRP-T] given with wP
- 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)
Duration of seropositivity and protection after 3p+0 and 3p+1 with Hib [PRP-T] in the UK

- Southern 2007 (UK) - % above 1ug/ml after 3 primaries and a booster of Hib [PRP-T] at 12-17m
- Borrow 2010 (UK) - % above 1ug/ml after 3 primaries and a booster of combined Hib [PRP-T] and MCC at 12-14m
- Ramsay 2004 (UK) - % direct clinical effectiveness after 3+0 with Hib [PRP-T] given with wP

UK, 3p+0, %>1ug/ml

UK, 3p+1, %>1ug/ml

UK, 3p+1, %>1ug/ml, with MCC

UK, 3p+0, clinical

UK, 3p+0, %>1ug/ml
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

24 data points

Australia = 2
Brazil = 12
Cuba = 1
France = 1
Kenya = 2
Senegal = 1
Spain = 3
Tonga = 2
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)

- Efficacy of 1, 2, 3 doses of 44%, 90% and 95% (Gambia RCT)

- Duration of protection based on Kenya sero-surveys (%>1ug/ml, Hammit, Goldblatt and Scott) and Gambia RCT (p1)
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

-Evaluate evidence from systematic reviews relevant for Kenya e.g. Africa, PRP-T (wP)

-Short-term 1 dose efficacy of 71% declining to 44% (Gambia RCT)
Kenya: direct protection after 2 primary doses

- Evaluate evidence from systematic reviews relevant for Kenya e.g. Africa, PRP-T (wP)

- 2 dose efficacy of 90% (Gambia RCT)

- Duration of protection based on Kenya %>1μg/ml (Hammit et al) and assumption that p2 and p3 have equivalent duration (Gambia RCT)
Reviewed age at Hib meningitis/invasive disease

14 country datasets identified (6 examples shown below)
Evaluated timeliness of DTP1,2,3 and measles 1
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

Review of RCTs by ISPM, and observational data by LSHTM

**Graph:**
- **PRP-T**
- **PRP-OMP**
- **PRP-HbOC**

**Countries:**
- USA (Santosham 1991)
- USA (Harrison 1994)
- USA (Harrison 1994)
- USA (Vadheim 1994)
- USA (Vadheim 1994)
- USA (Vadheim 1994)
- South Africa (Madhi 2002)

**Legend:**
- Blue = wP
- Red = aP
- Grey = not stated

**Countries:**
- The Gambia (Mulholland 1997)
- The Gambia (Mulholland 1997)
- The Gambia (Research 2005)
- The Gambia (Adegboya 2005)
- The Gambia (Adegboya 2005)
- The Gambia (Adegboya 2005)
- The Gambia (Adegboya 2005)
- The Gambia (Adegboya 2005)
- Germany (Kalies 2008)
- South Africa (Madhi 2002)

**Graph Elements:**
- RCT
- Observational

**Data Sources:**
- 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

<5 deaths due to any cause

Souro Sanou Hosp. Burkina Faso 1986

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

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Souro Sanou Hosp. Burkina Faso 1986

DHS, Burkina Faso 2003
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.

Southern et al, Clinical and Vaccine Immunology 2007
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

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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.