Age at Hib disease, and the implications for different schedules

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Aim: to address 2 questions

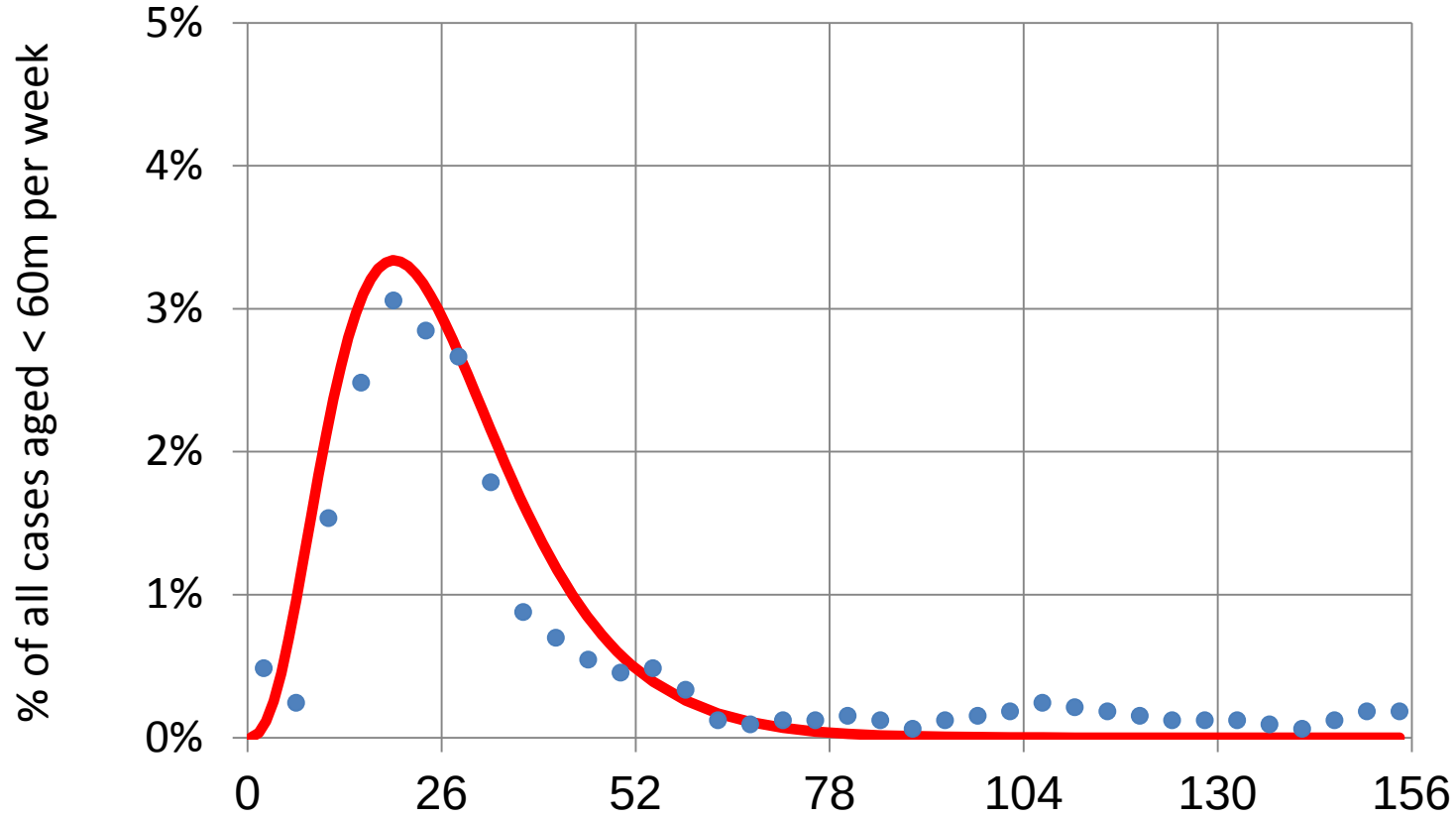
1. What proportion of the children who get Hib disease would have some *direct* protection from a vaccine programme?
   - How old are they when they get disease?
   - How old are they when they are vaccinated?
2. What proportion of cases of Hib disease would be prevented?
   - How does vaccine effectiveness depend on number and timing of doses?

Synopsis

- Data needed to estimate the impact of schedule and timeliness
  - on age at Hib disease
  - on vaccination coverage and timeliness

- Model-based estimates of impact for
  - different vaccination schedules and
  - vaccination delays

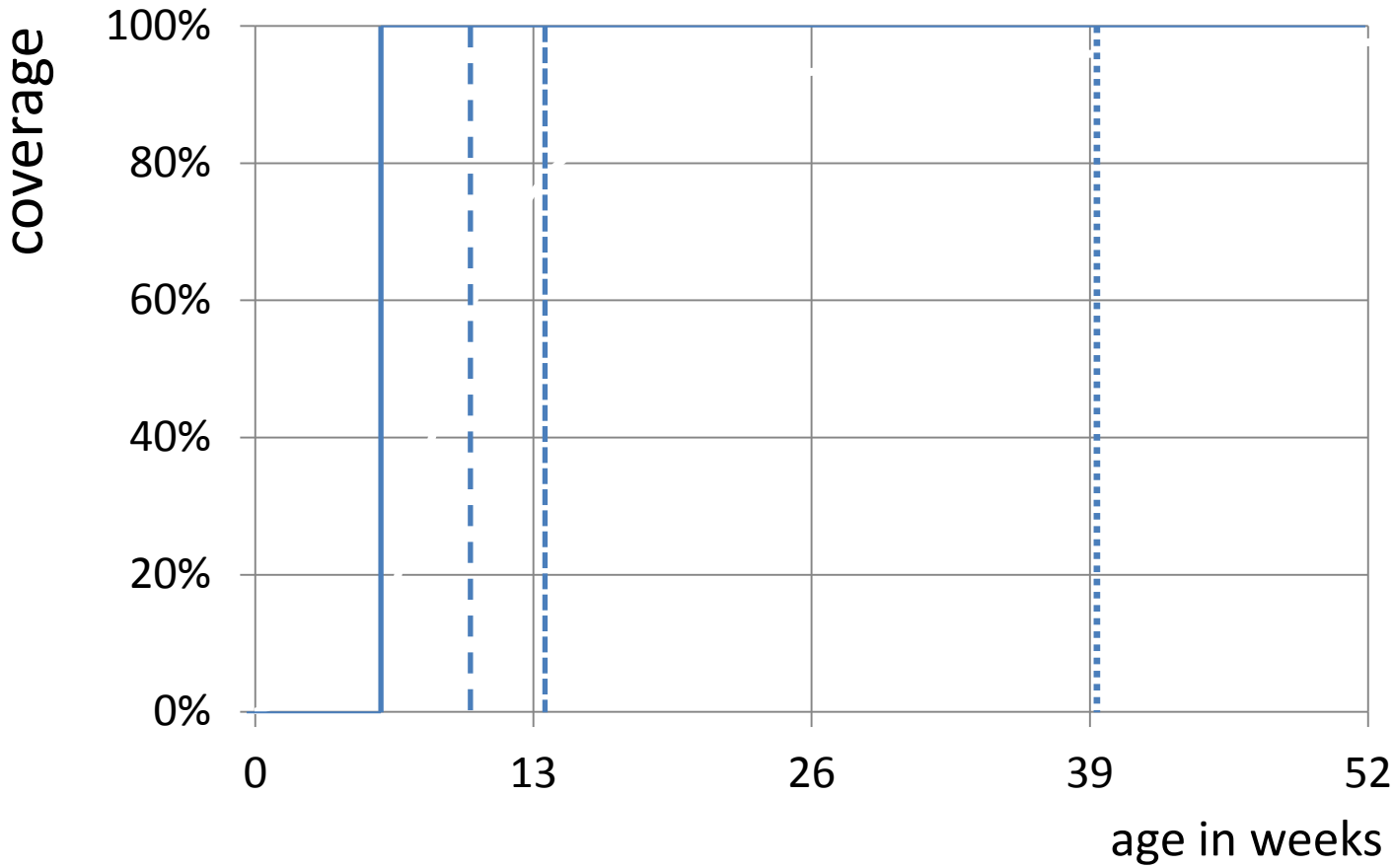
Surveillance for Hib meningitis in Burkina Faso, 2003-5



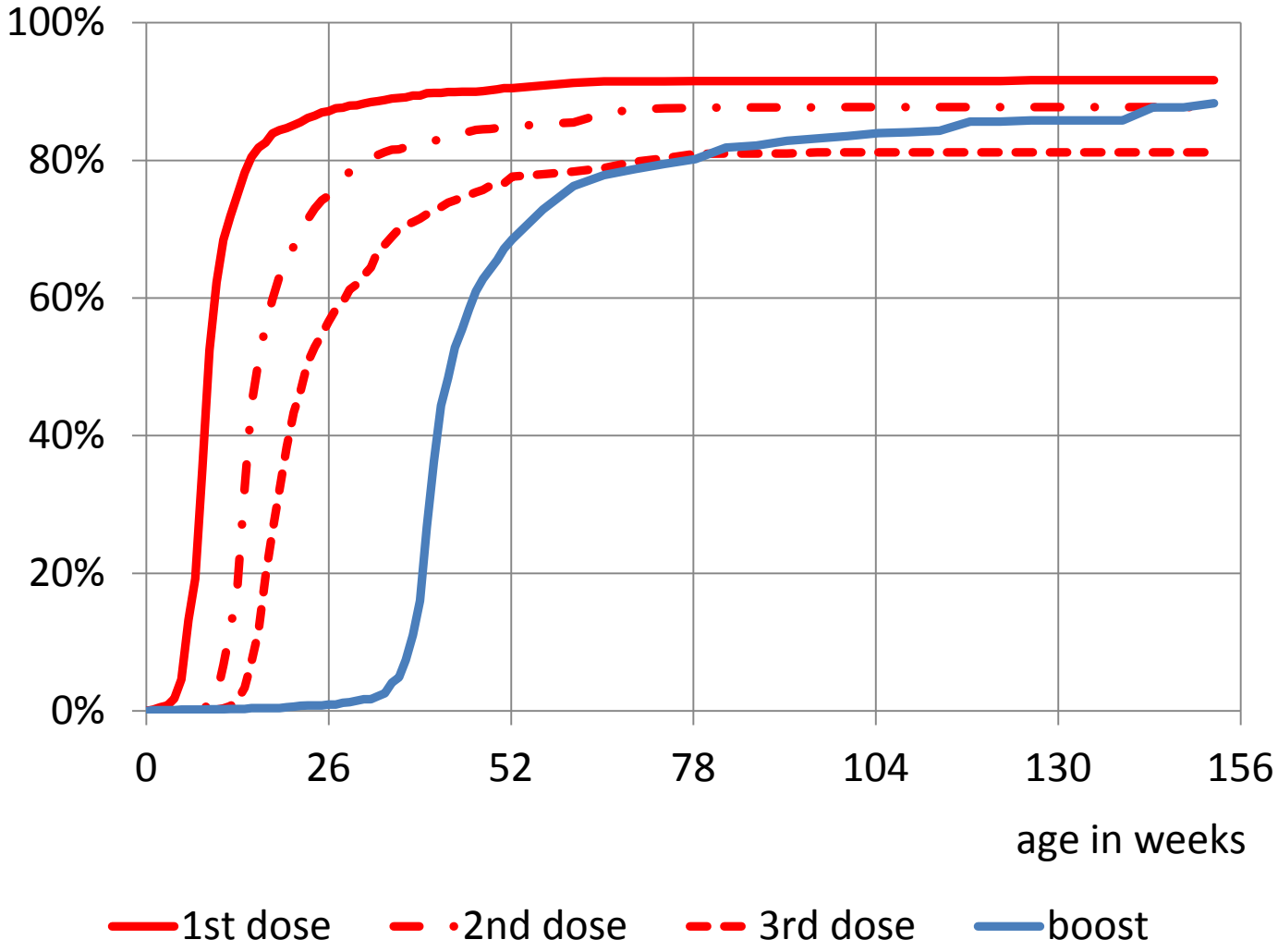
Source: Gessner

Age-specific coverage: an indicator of vaccine delay

ideal ‘survival’ curves with a 6, 10, 14 week schedule



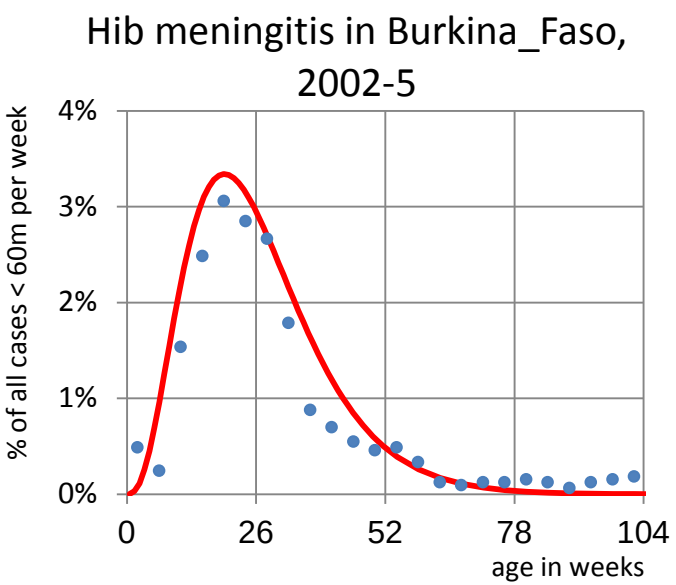
Coverage based on DTP
MICS3 survey data: Burkina Faso 2006

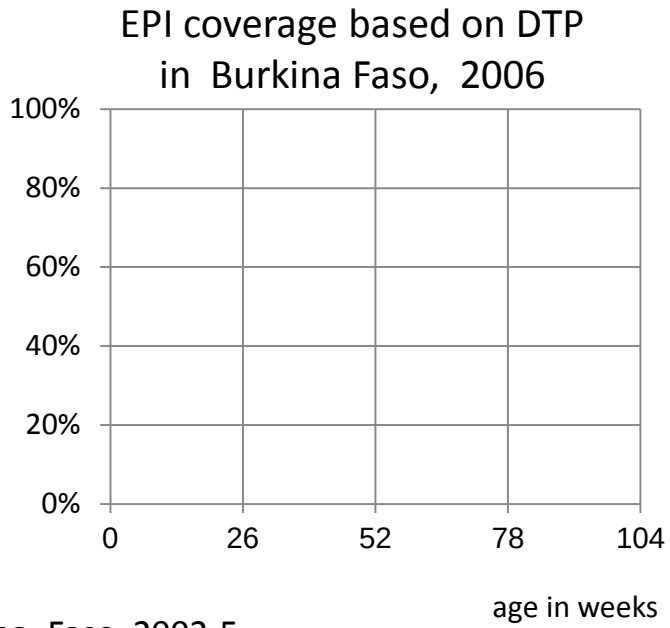


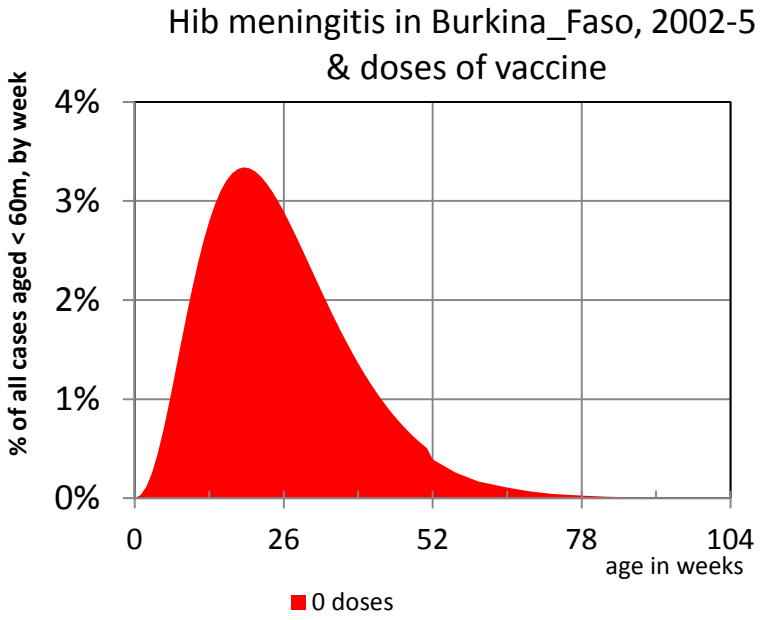
Assumptions

- the age distribution of *exposure* to infection is unchanged by introducing a vaccine
- equal coverage for all risk groups
- vaccine efficacy is unrelated to
  - age at vaccine if > 6 weeks
  - vaccine interval if > 4 weeks
- *variant assumptions for herd and waning effects*

Cases who would have had 1, 2, 3 doses at different ages







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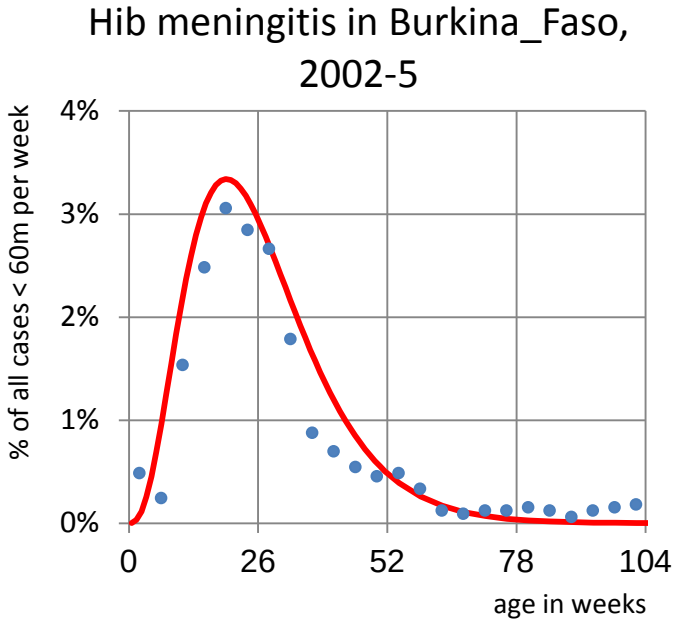
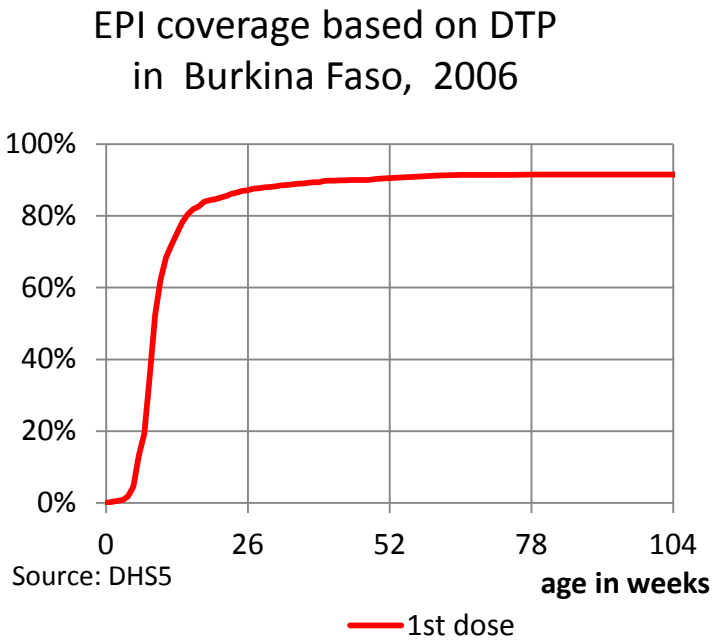
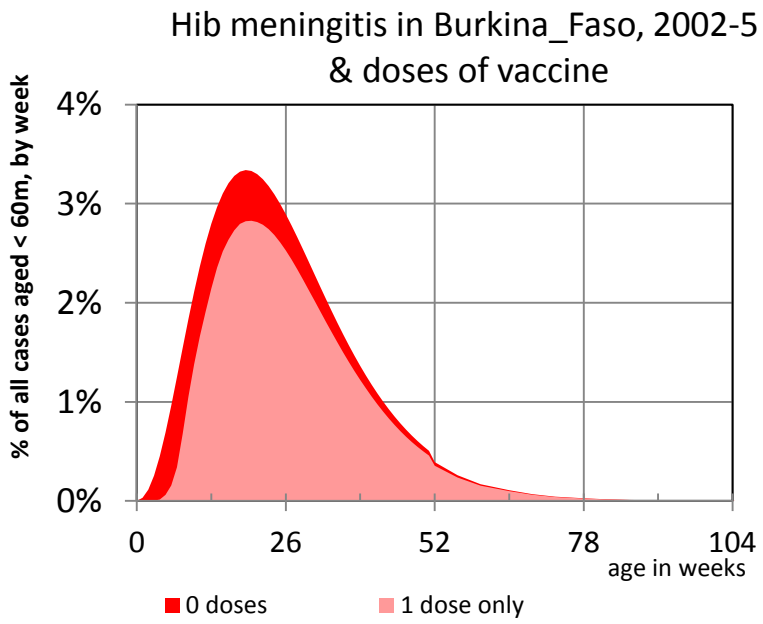
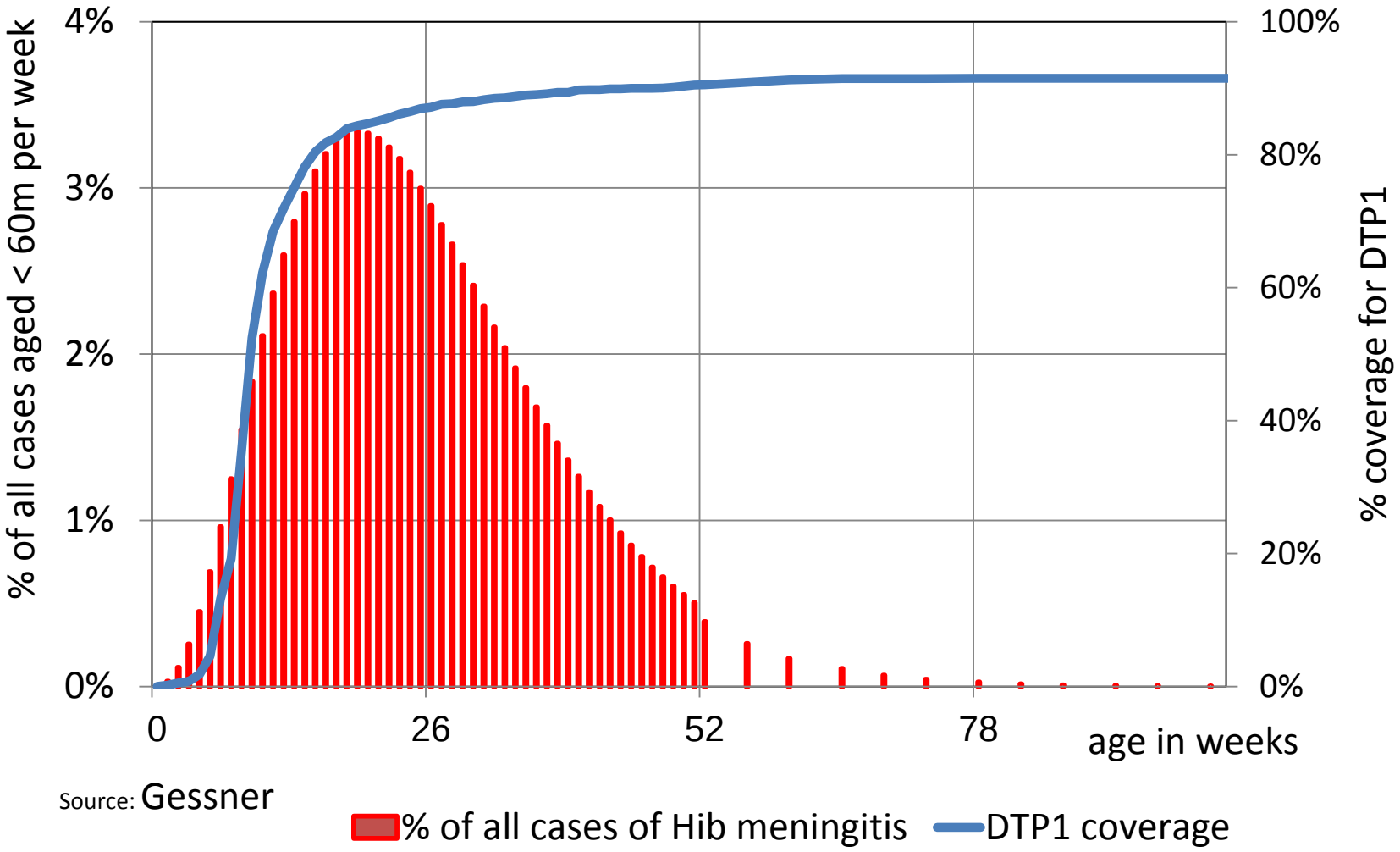




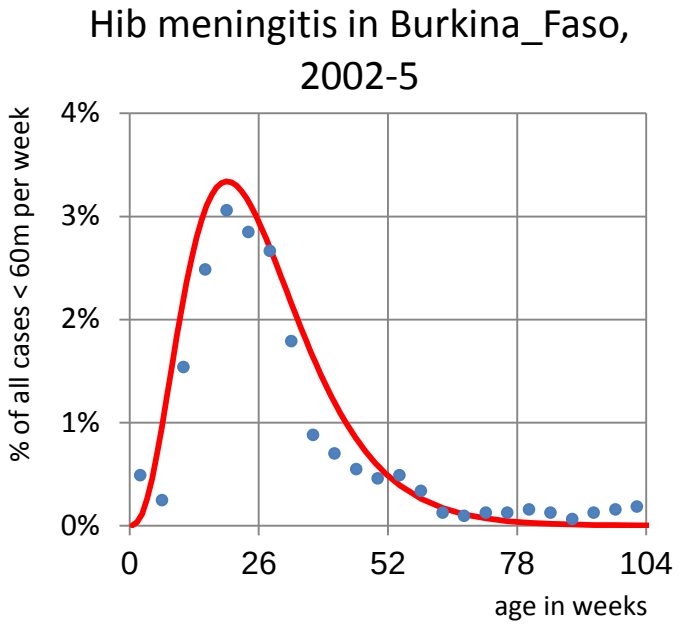


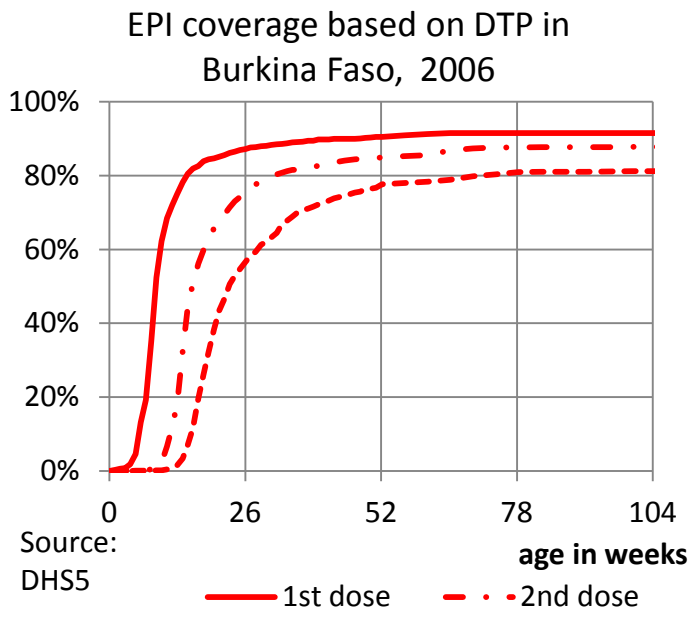
Burkina Faso: age distribution for Hib meningitis (weekly and monthly slices) and coverage for DTP1

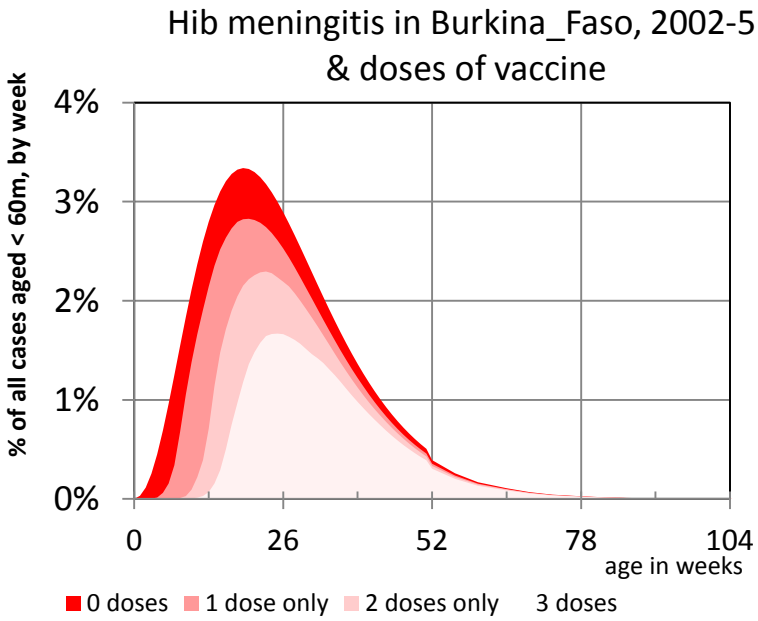


Source: Gessner

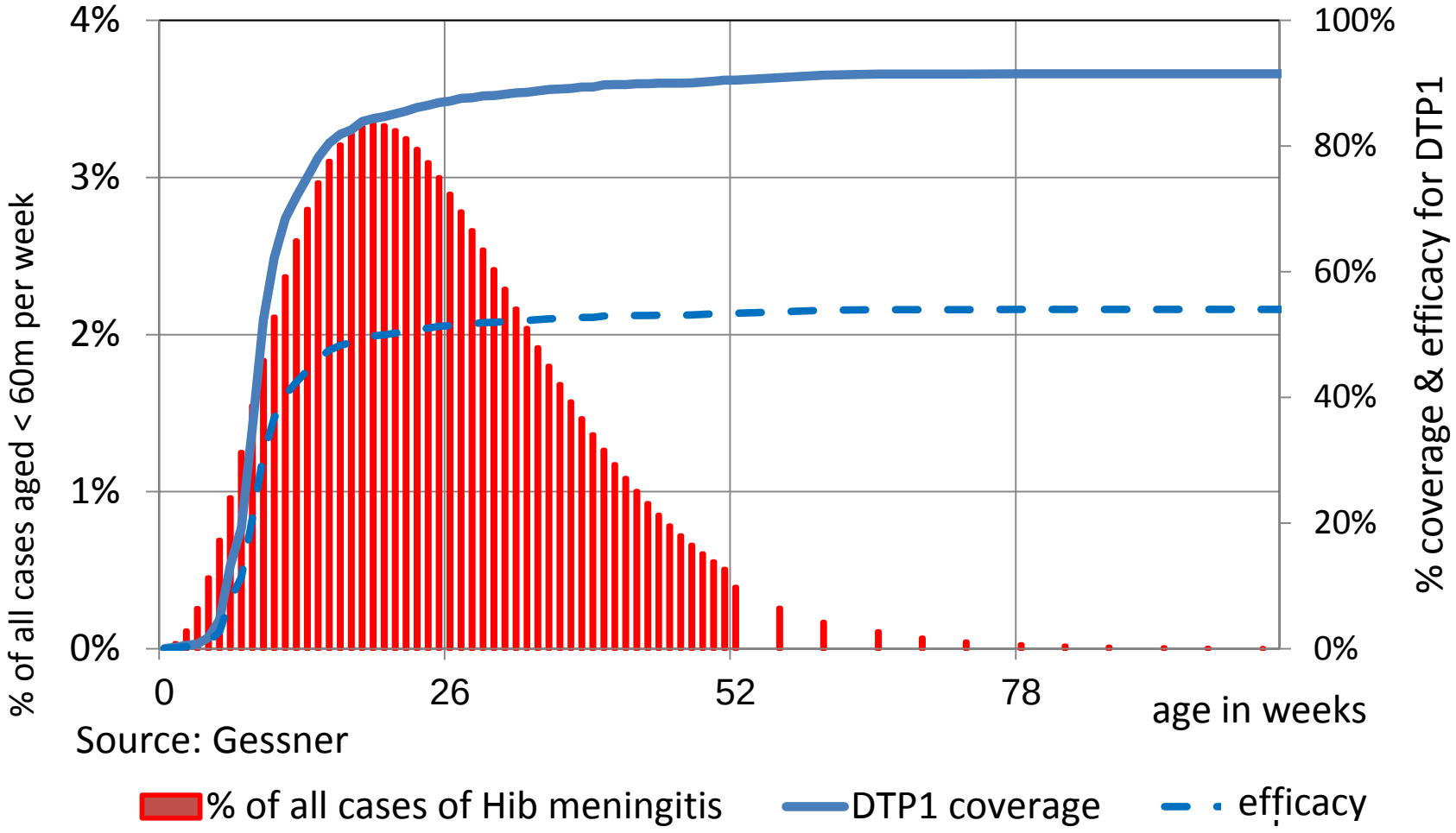
Cases who would have had 1, 2, 3 doses at different ages



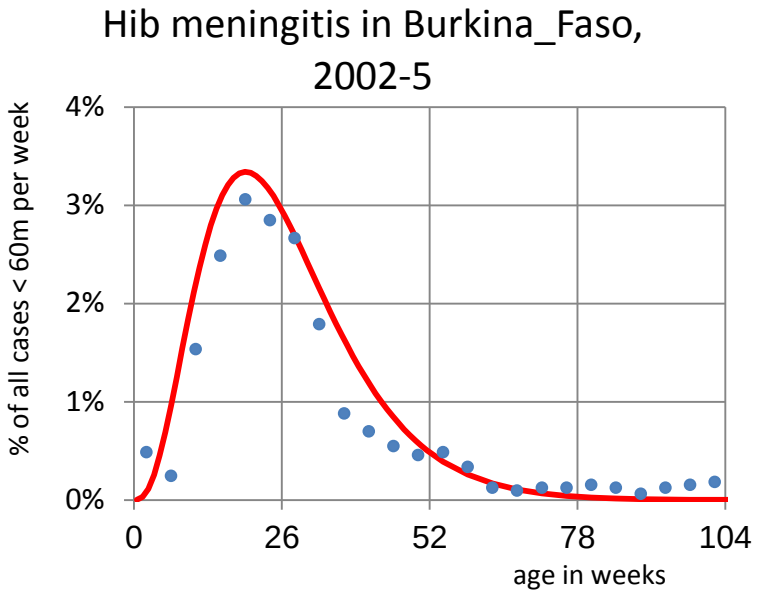


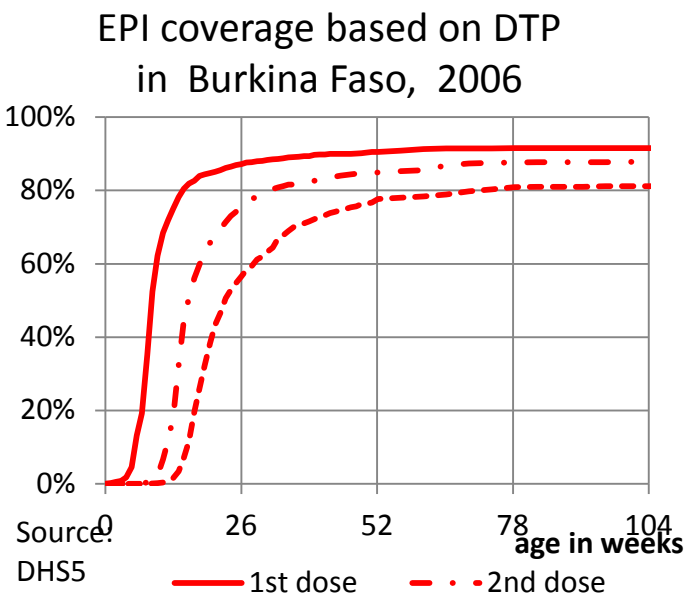


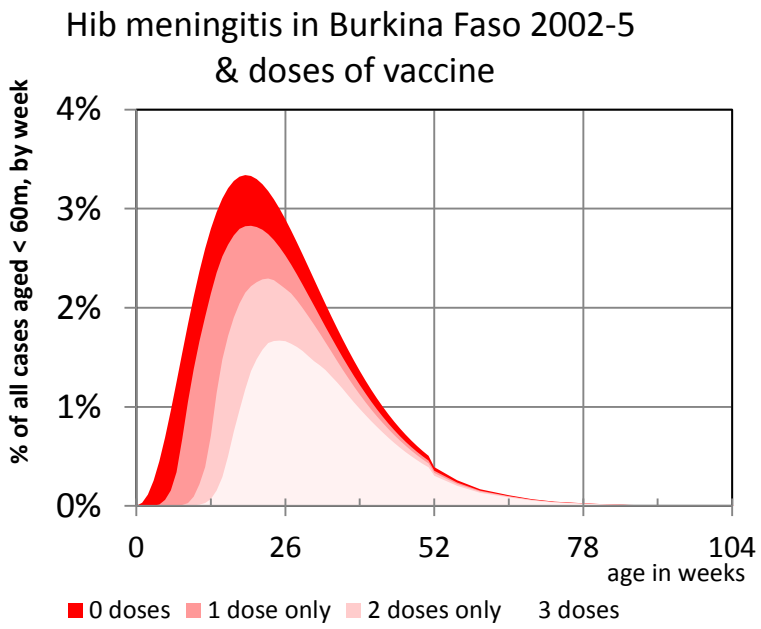
Burkina Faso: age distribution for Hib meningitis, coverage for DTP1 and coverage *x* efficacy for dose 1

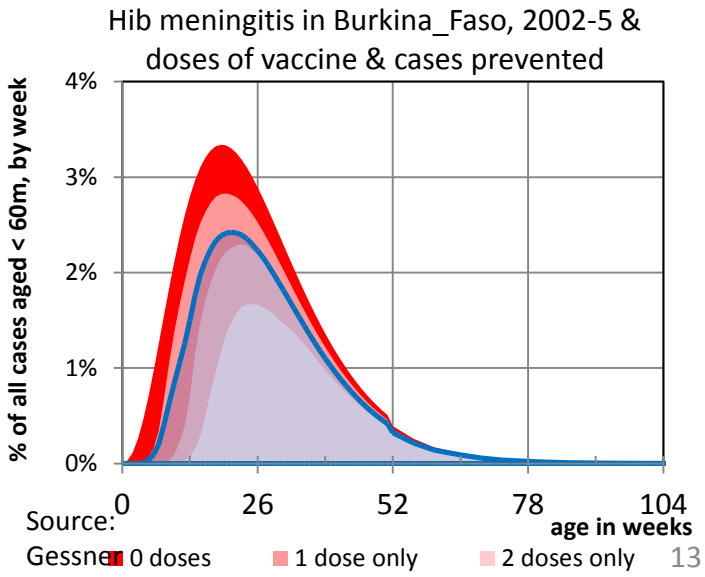


Cases with 1, 2, 3 doses and prevented at different ages









Data collection

Aim: in an as many countries as we can, to:

- compile data on distributions of *age at Hib disease* in children in different populations pre-vaccine, using mainly surveillance data;
- compile data on the distributions of *age at vaccination* in national EPI programmes, using survey data.

Literature review (Briere & Hajjeh)

New review 2005-12 (Earlier review 1980-2005)

- 1492 studies, 28 relevant Hib data, 11 author details.

Chasing data

- 60 investigators: contact attempts ; 7 sent more data .

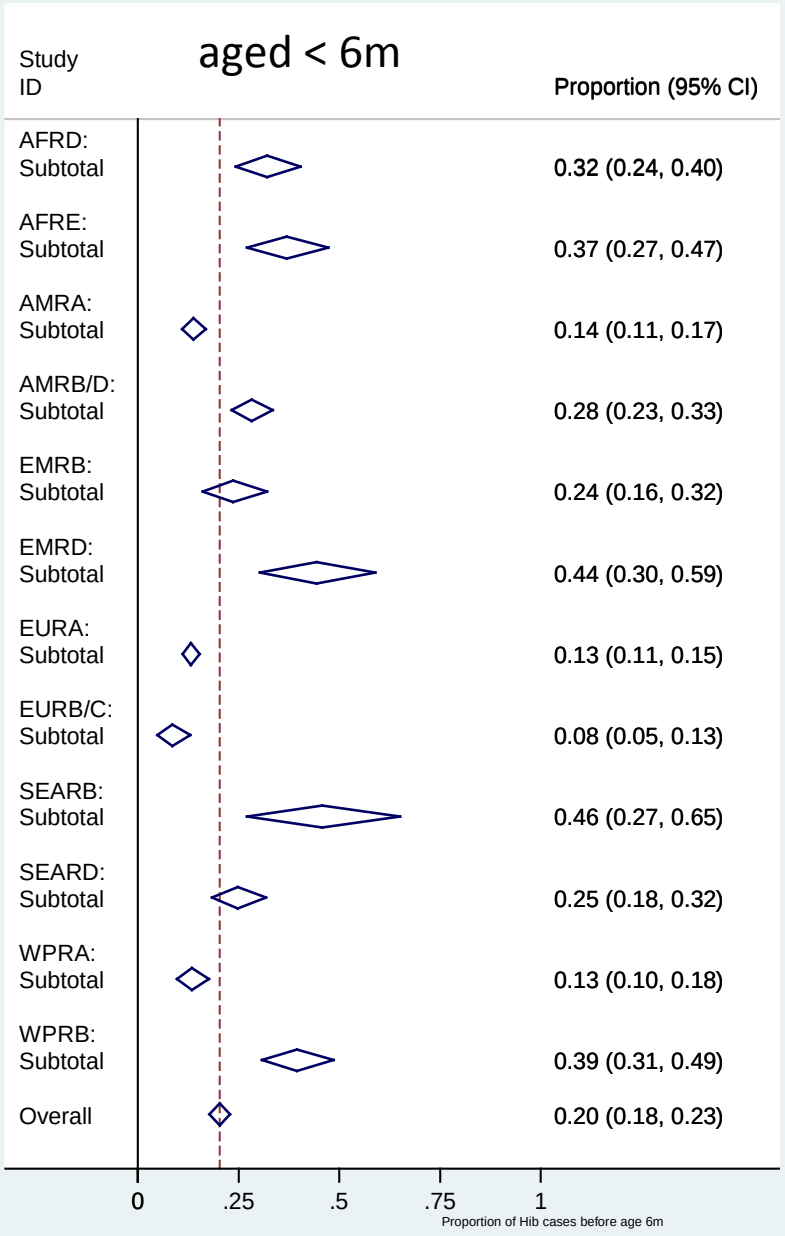
Results

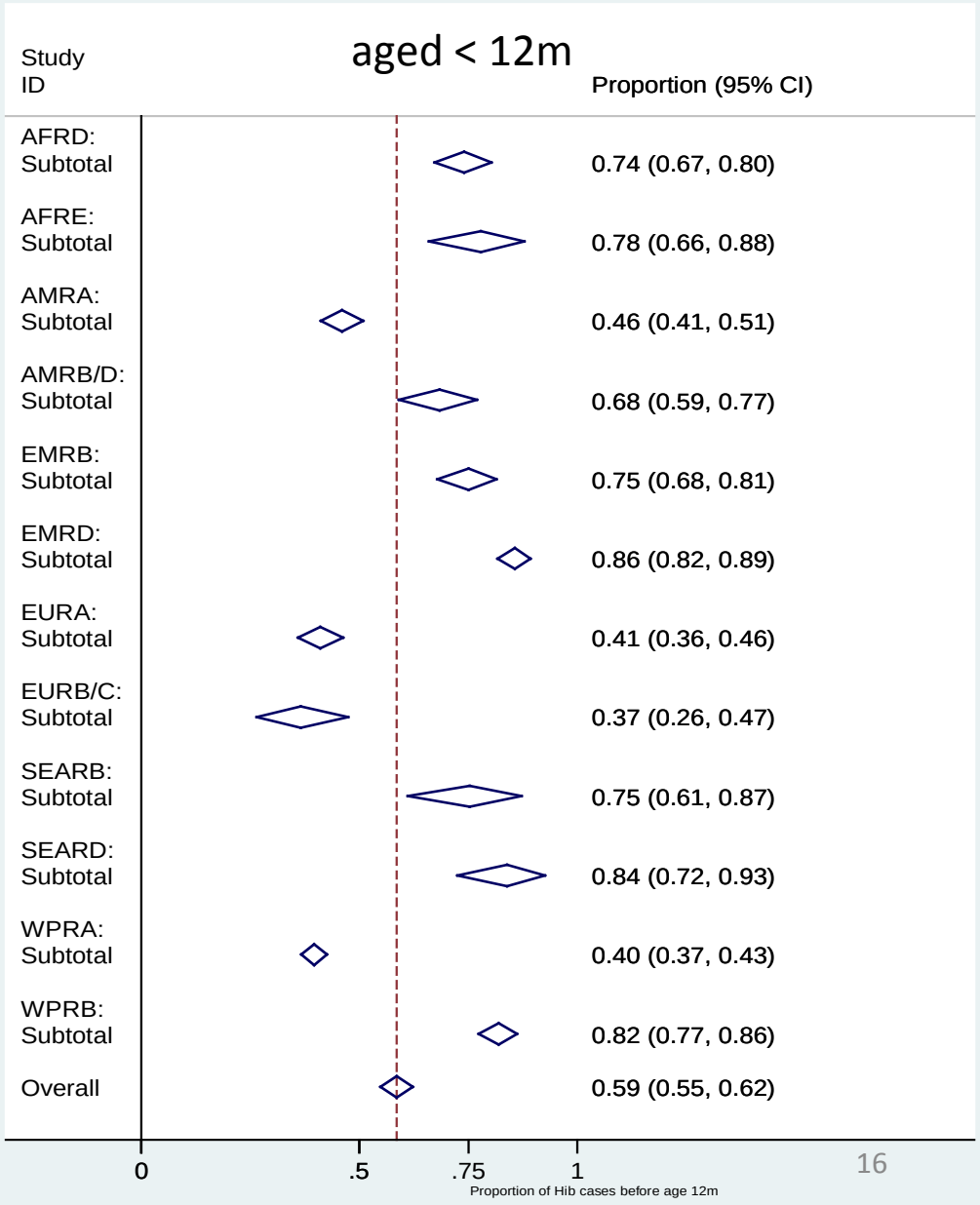
Broad age groups: % < 6m: 65; % < 12m: 104; % < 24m: 65.

Narrow groups (<3m): 16 published + 6 unpublished datasets

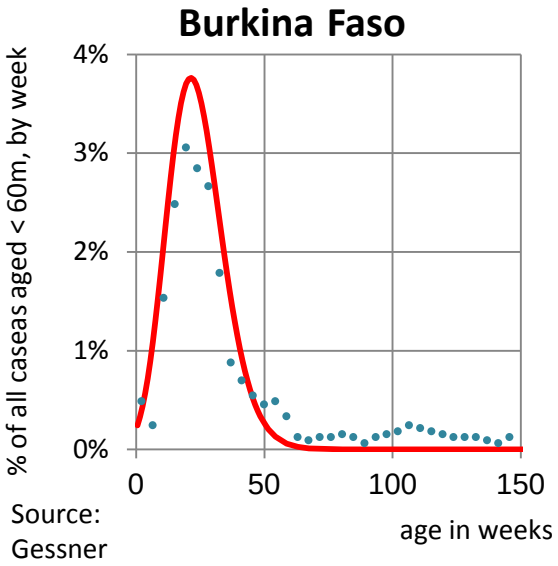
- 17 included more than 100 cases aged < 60m.

Meta-analysis: % of all cases of Hib meningitis aged < 60m who are

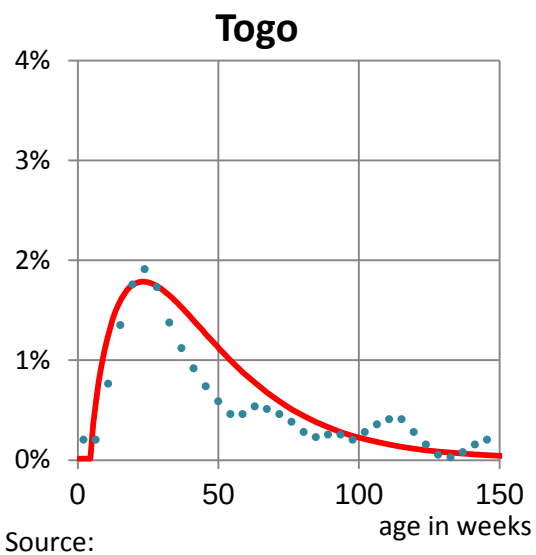




Age at Hib meningitis



Source: Gessner



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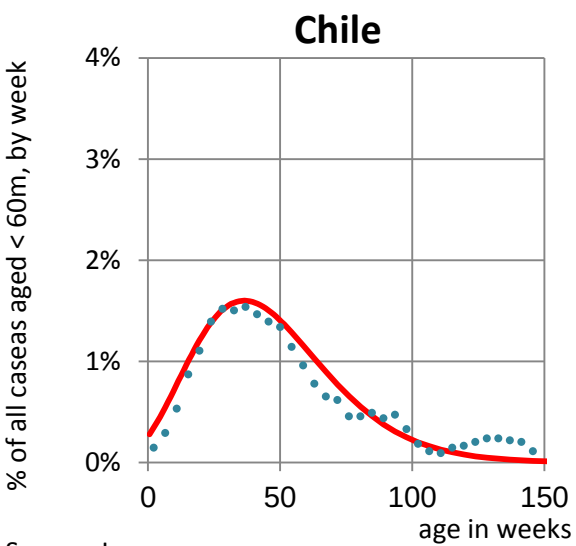
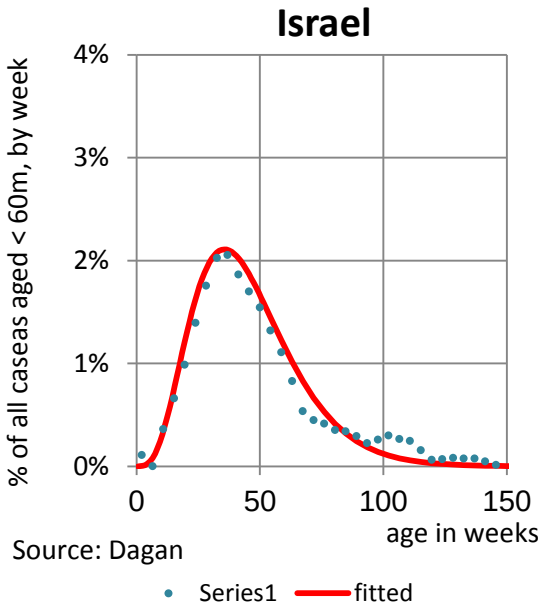
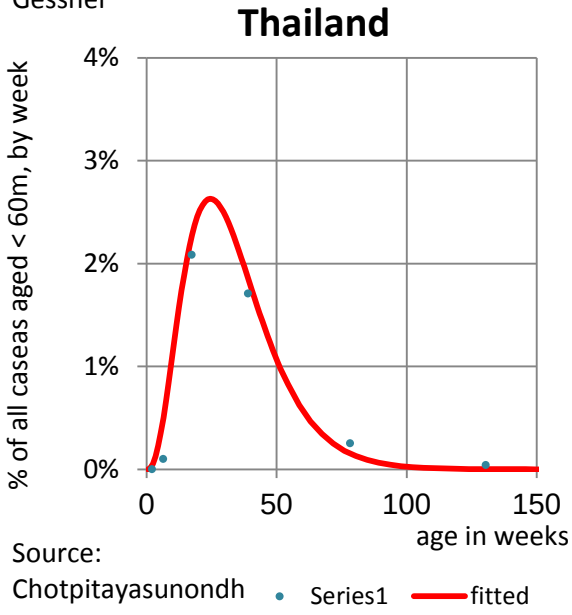


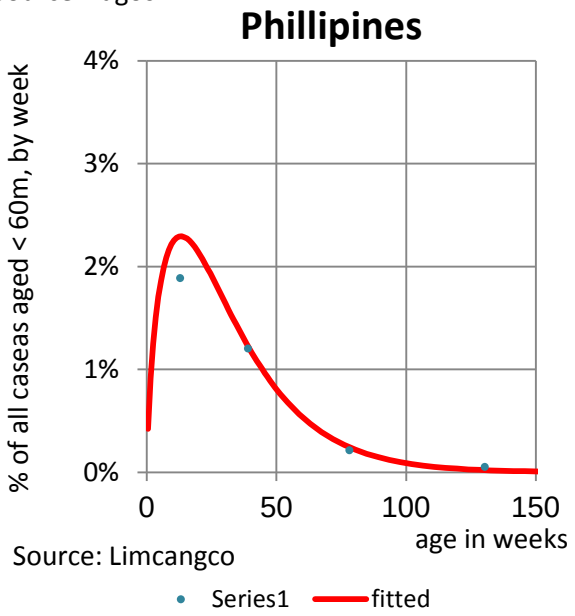
Source: Lagos



Source: Dagan



Source: Chotpitayasunondh



Source: Limcangco

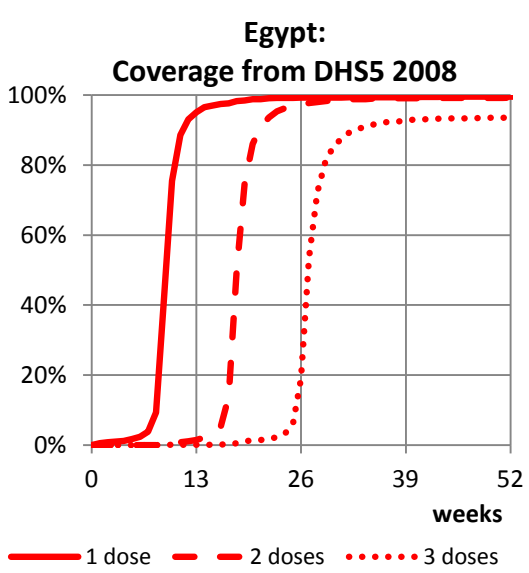
Age at vaccination: data from 69 countries

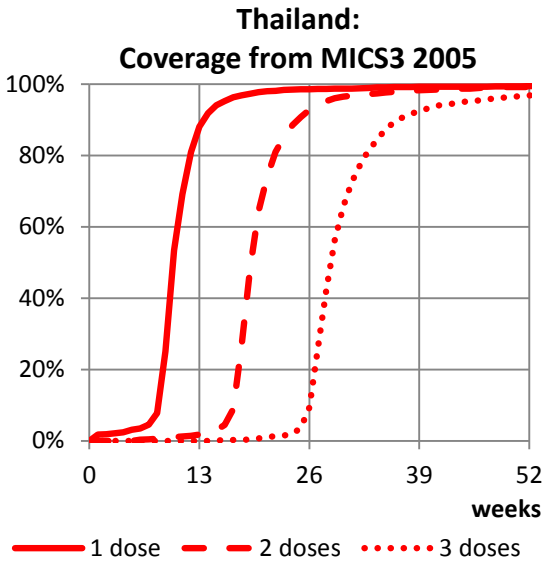
Representative population data from:

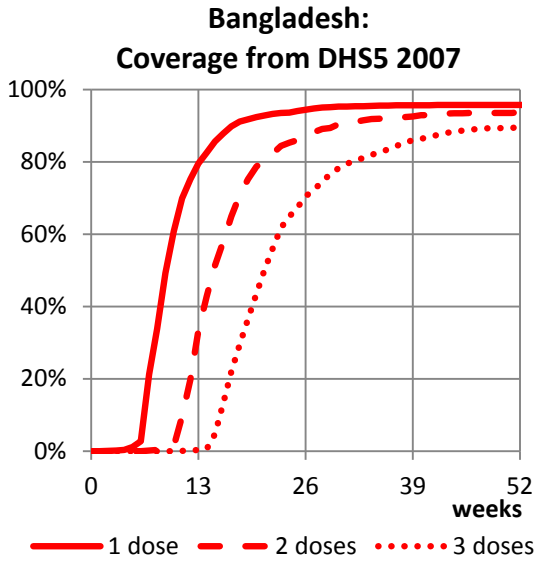
- 42 DHS surveys (rounds 5 & 6)
  - 2004-10 sample median (IQR) = 5,183 (3,491-6,750)
- 27 MICS surveys (round 3)
  - 2005-7 sample median (IQR) = 3,926 (2,355-5,879)

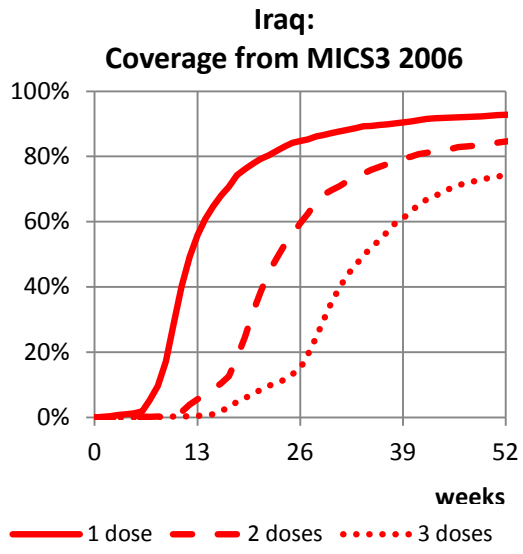
- AFRO 34, AMRO 10, EMRO 6, EURO 8, SEARO 5, WPRO 6

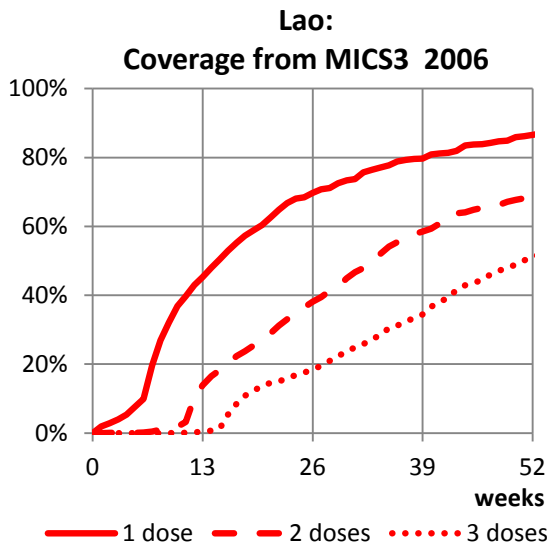
Variation in coverage by age: 6 countries

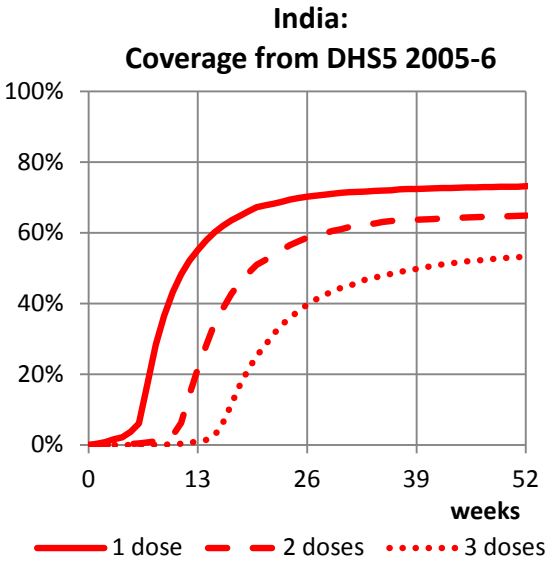










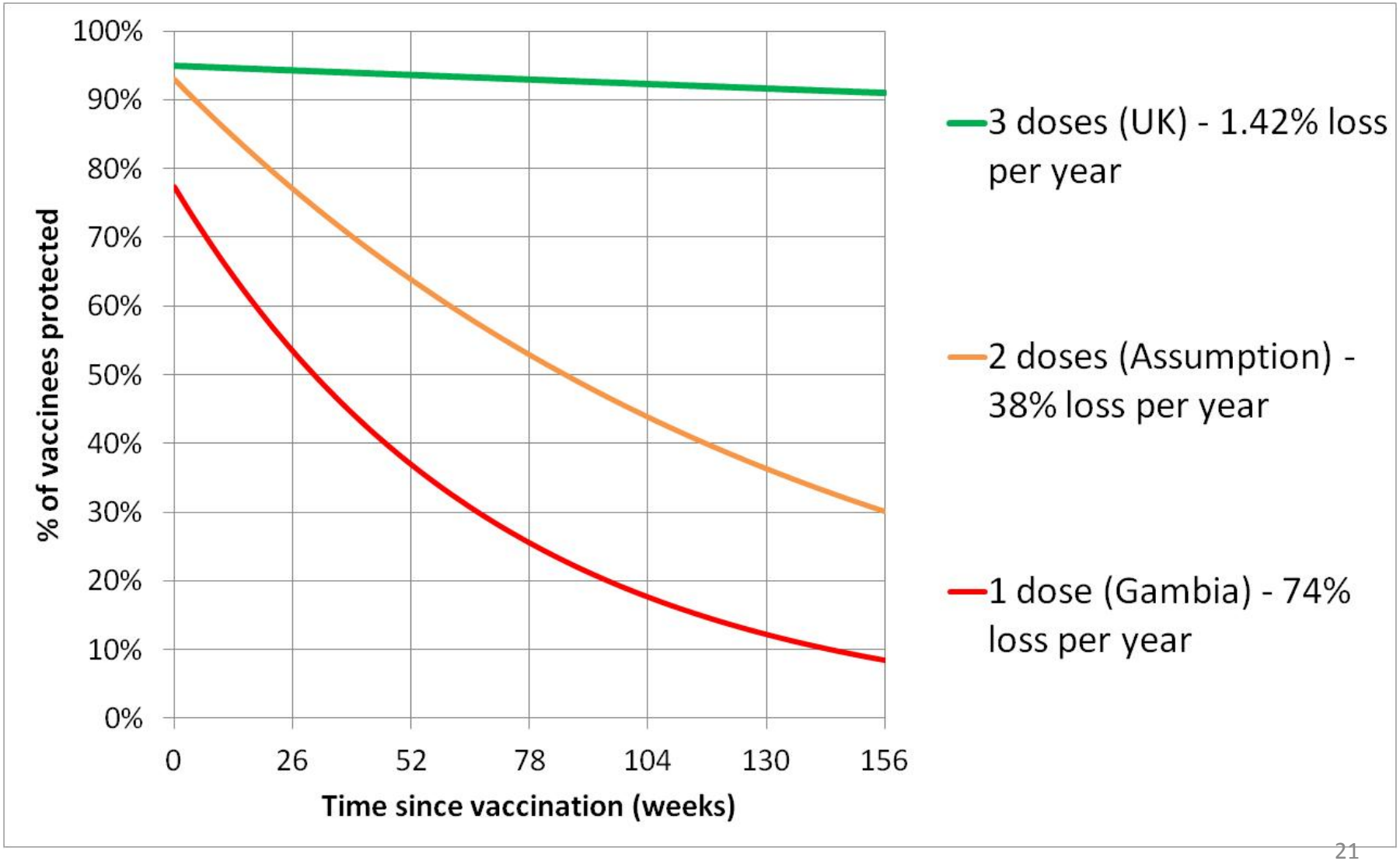


Modelling impact: factors included

% of Hib deaths prevented

=	Hib deaths	*by age*		
x	Coverage	*by age*	*by dose*	*by risk group*
x	Efficacy		*by dose*	
x	Waning	*by time since dose*	*by dose*	
x	Herd effect			*by coverage*

Waning: efficacy & duration of protection, by dose



Herd effect: % direct & total effect on Hib disease <5yrs

24 data points

Australia = 2

Brazil = 12

Cuba = 1

France = 1

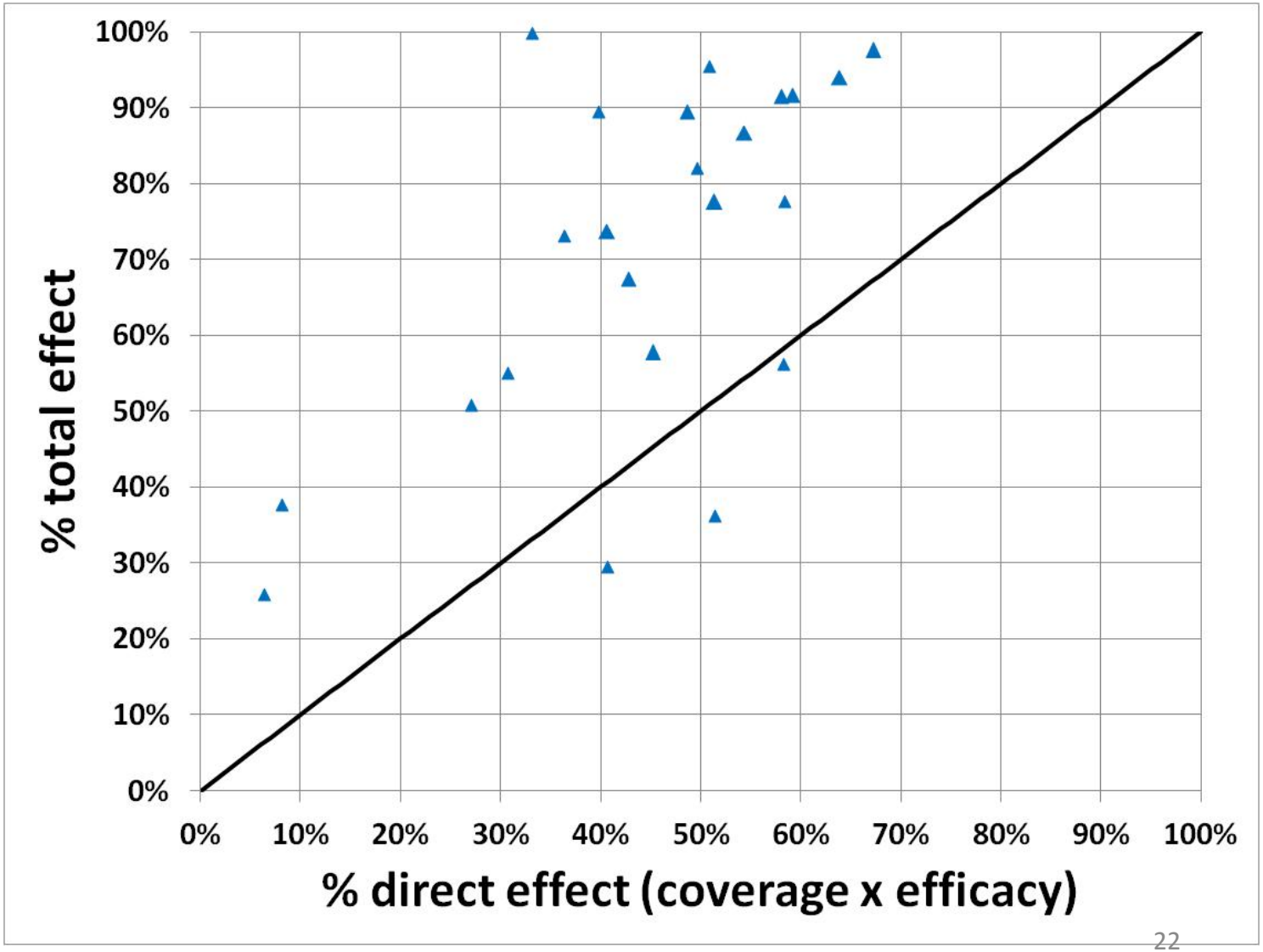
Kenya = 2

Senegal = 1

Spain = 3

Tonga = 2

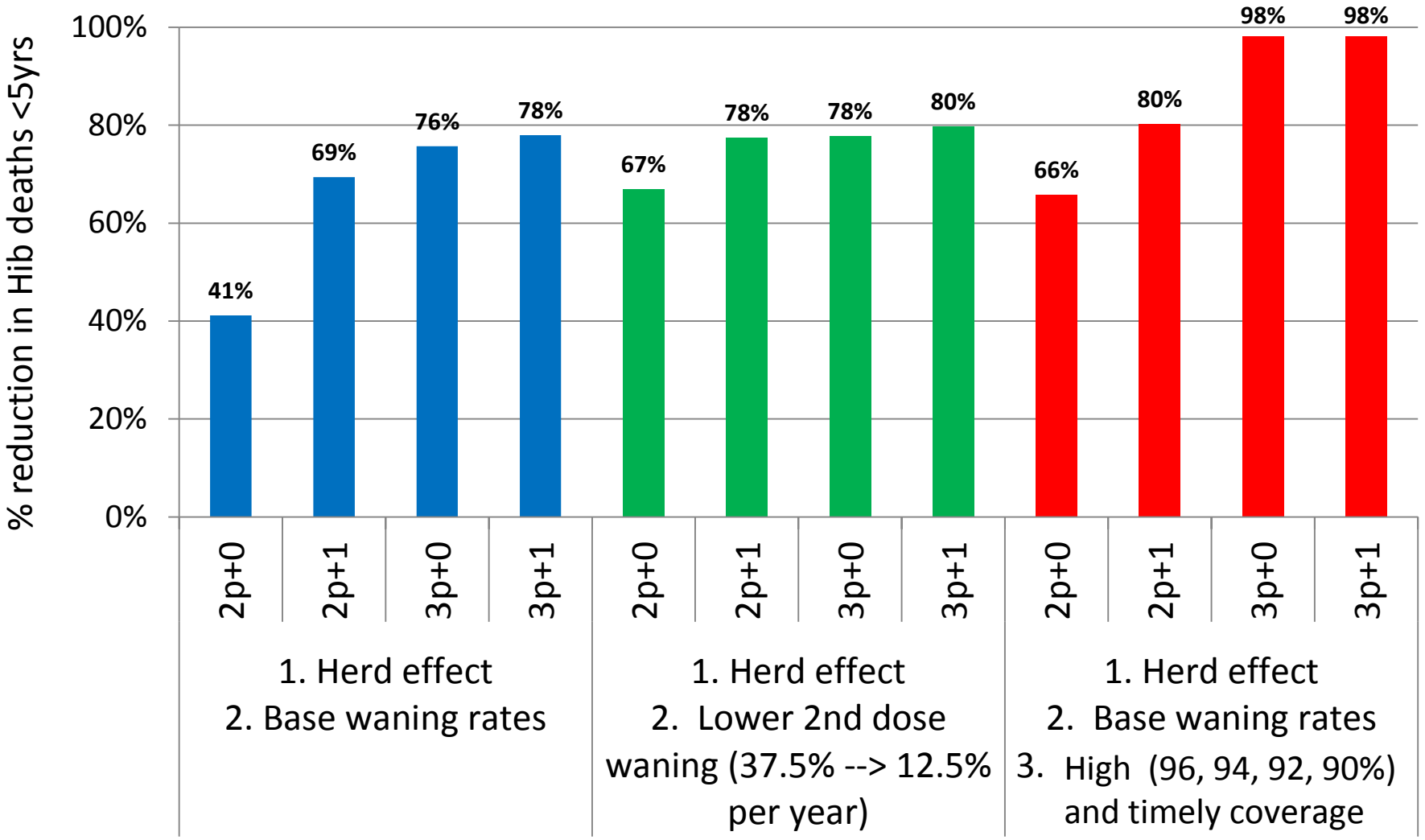
Source:
Neff
Walker



Schedule comparisons are sensitive to waning rate and region

	Global		AFR		AMR	
2nd dose waning rate	*37.5% pa*	*12.5% pa*	*37.5% pa*	*12.5% pa*	*37.5% pa*	*12.5% pa*
2p+1	69%	78%	66%	73%	67%	78%
3p+0	76%	78%	71%	73%	80%	81%

Model estimates of global reduction in Hib deaths aged < 5yrs under varying scenarios

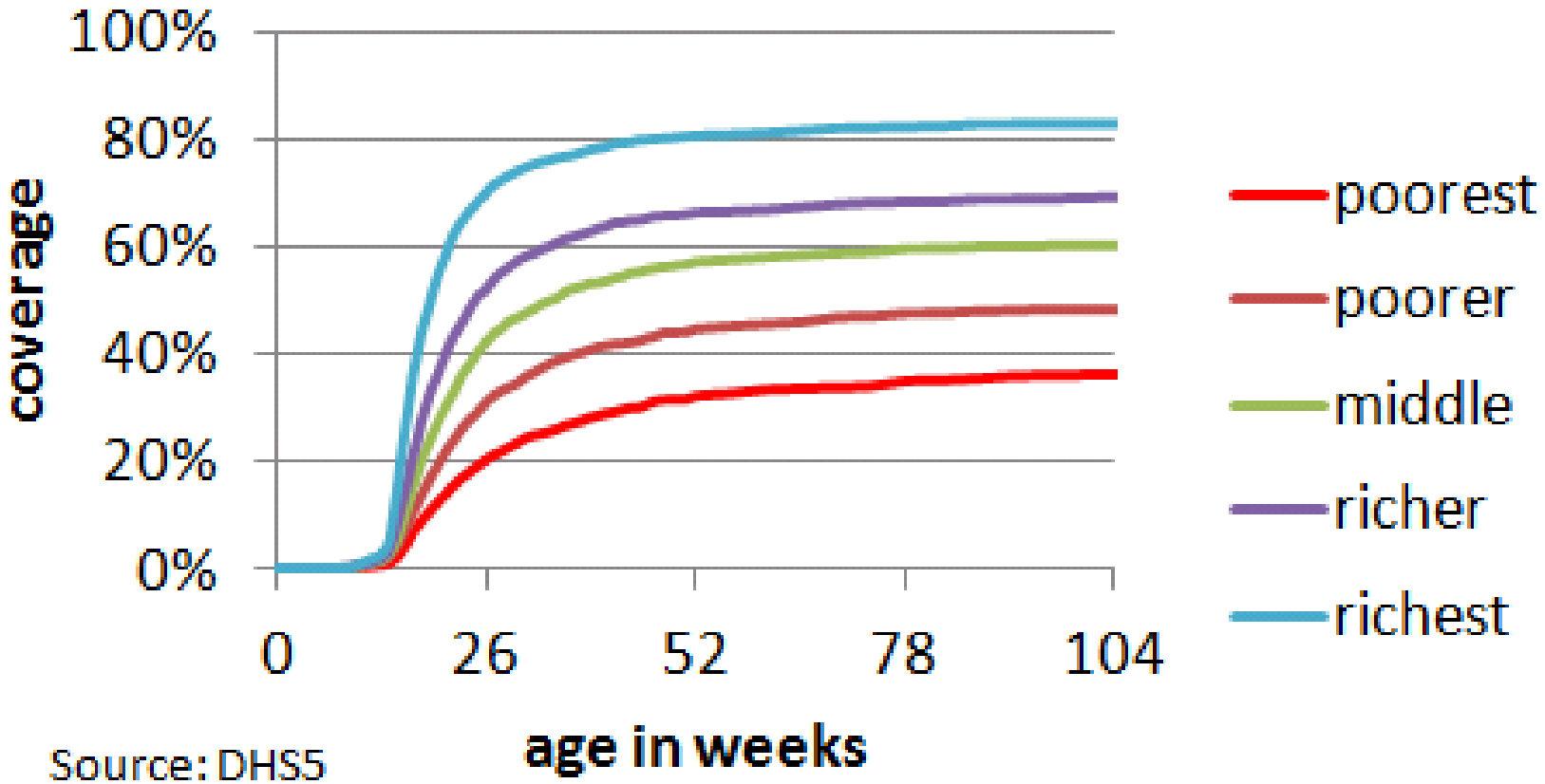


Each 1% represents about 3000 deaths globally per year

Limitations

- Assumes equal coverage for all risk groups
- Crude approach to herd immunity
- Limited data on age distributions for Hib *deaths*
- Limited data on waning rates for different doses
- Estimation methods for countries without data
- Assumes booster given at existing measles visit
  - 9m in ~30% of countries (no visit at 12m+)

Coverage by wealth quintile: DPT3 in India 2003

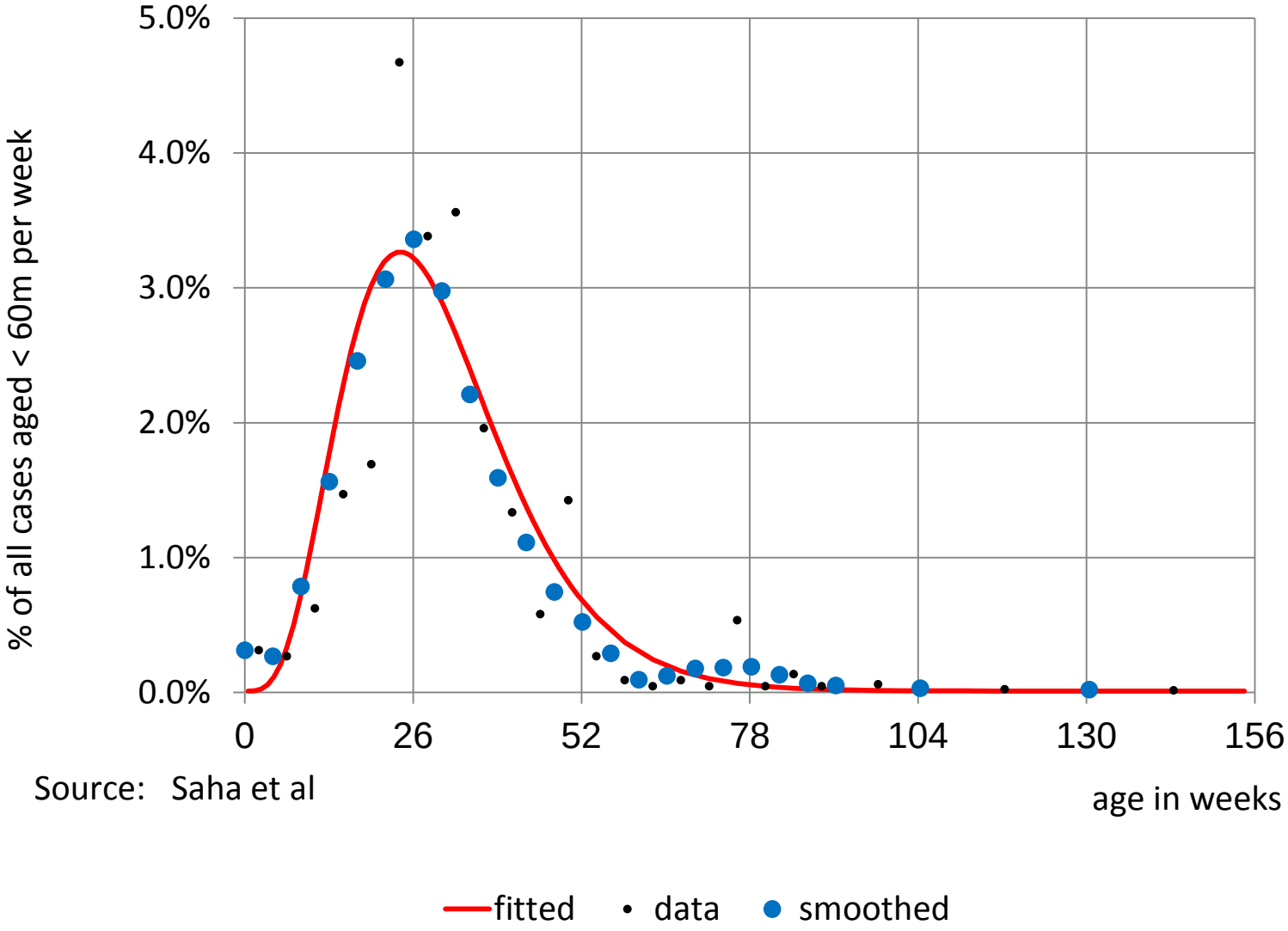


Source: DHS5

Conclusion

- Done at country level

Hospital admission for Invasive Hib in Bangladesh, 1993-2002

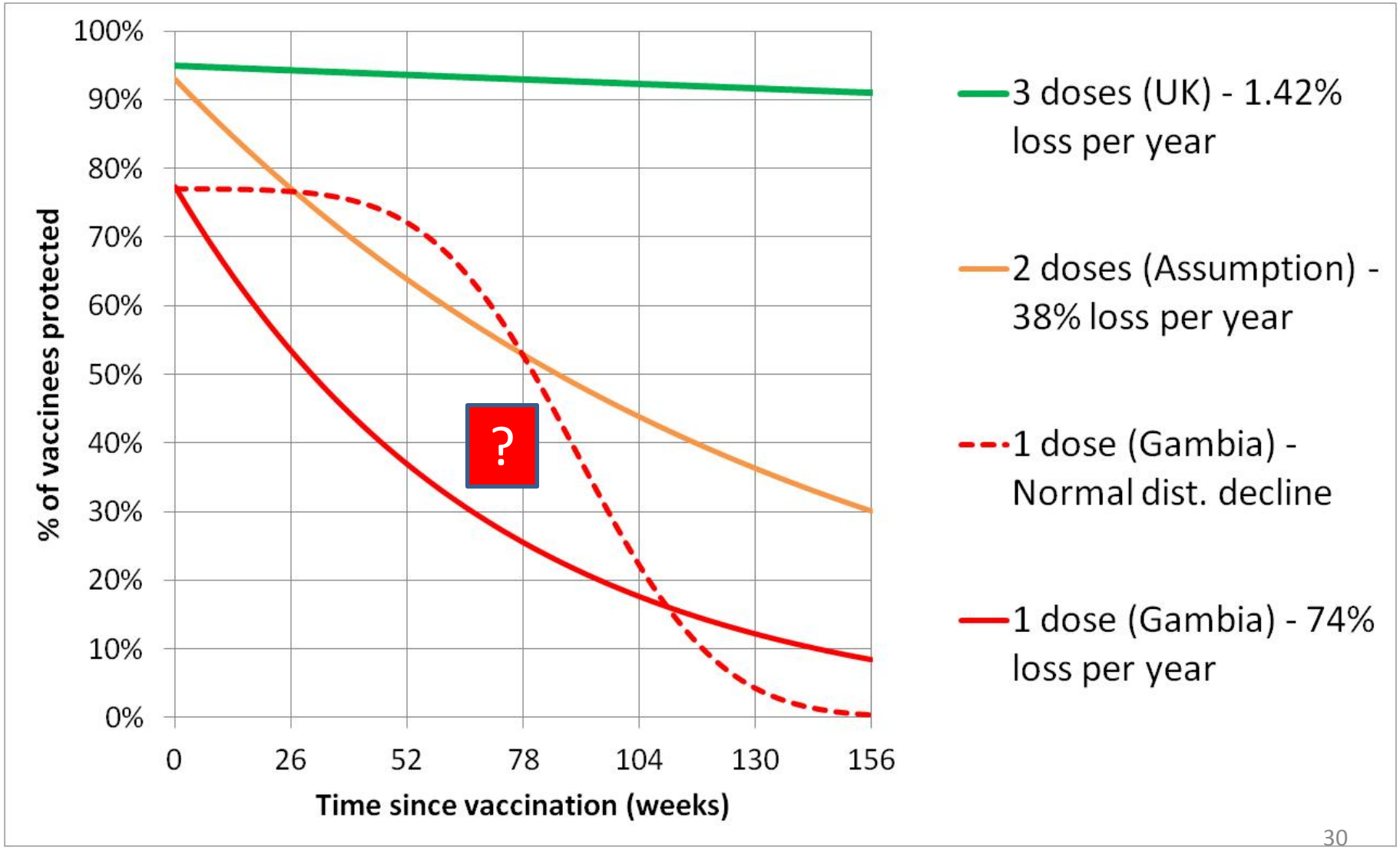


Source: Saha et al

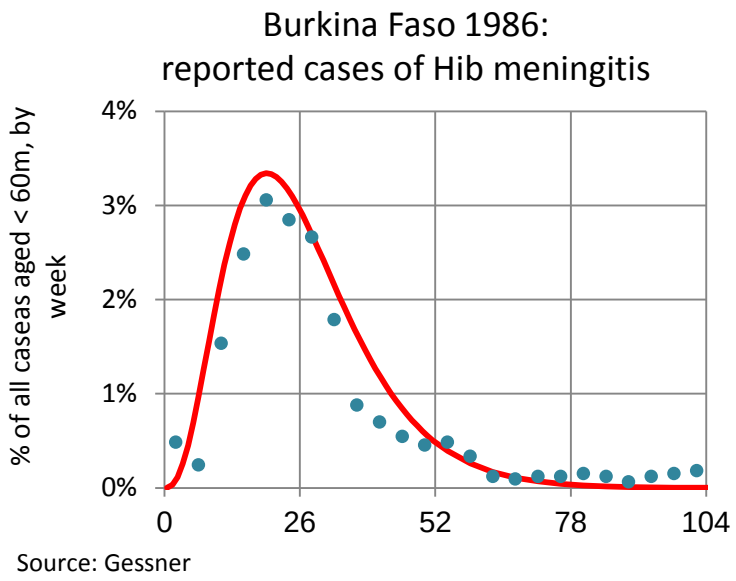
Context: most Hib disease is in childhood

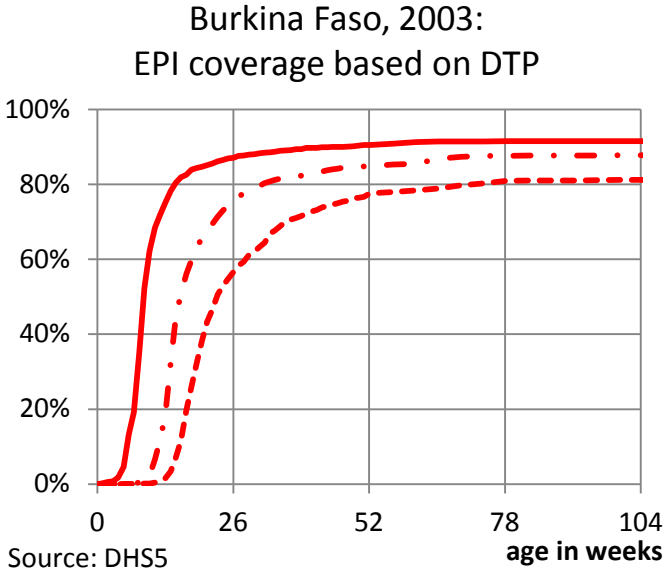
Hib meningitis						% of all cases in study	
Region	*Country*	*Source*	*Study began*	*upper age*	*n of cases with age data*	*age < 5y*	*age < 3y*
AMRO	Brazil	Miranzi	1993	all ages	720	87%	100%
EURO	Sweden	Trollfors	1981	90	266	89%	81%
AFRO	Togo	Gessner		80		81%	69%
AFRO	Burkina Faso	Gessner	1986	26	113	85%	84%
EURO	Denmark	Kristensen	1985	15	156	97%	89%
SEARO	Thailand	Chotpitayasunon	1980	15	229	100%	97%
WPRO	Australia	Gilbert 1990	1985	15	231	97%	86%
EURO	Israel	Dagan 1994	1988	13	280	99%	100%
EURO	Scotland	Coggins	1981	13	151	100%	82%
SEARO	Bangladesh	Saha	1993	12	508	99%	98%
EURO	England	Tudor-Williams	1985	10	142	97%	100%
EURO	England	Booy	1985	10	289	98%	100%
WPRO	Australia	El Saadi	1987	6	150	100%	88%
AFRO	Senegal	Cisse	2003	5	142	100%	95%
AMRO	Cuba	Dickinson	1998	5	127	100%	91%

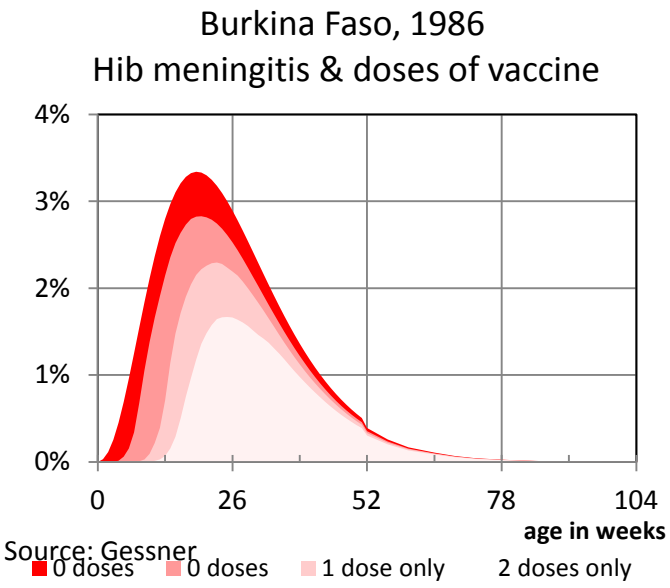
Duration of vaccine protection by dose

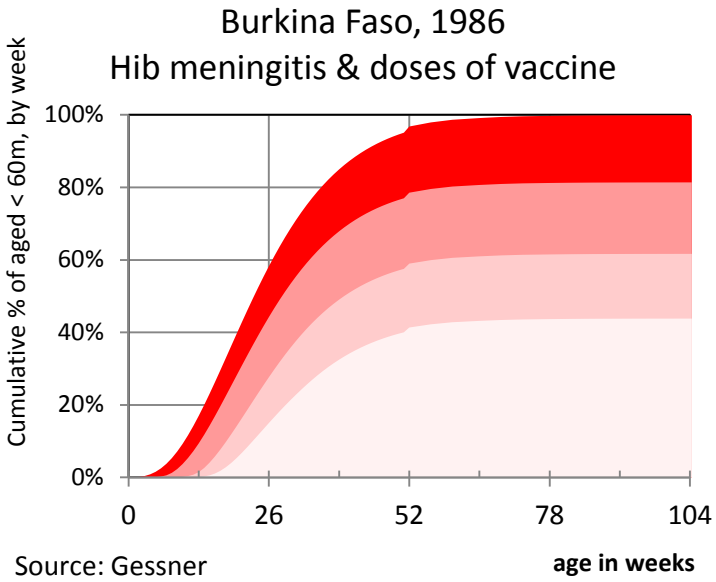


Estimating protection by 1, 2, 3 doses at different ages

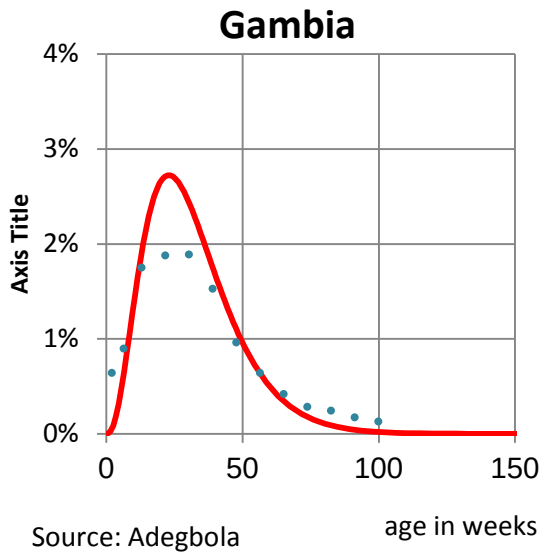




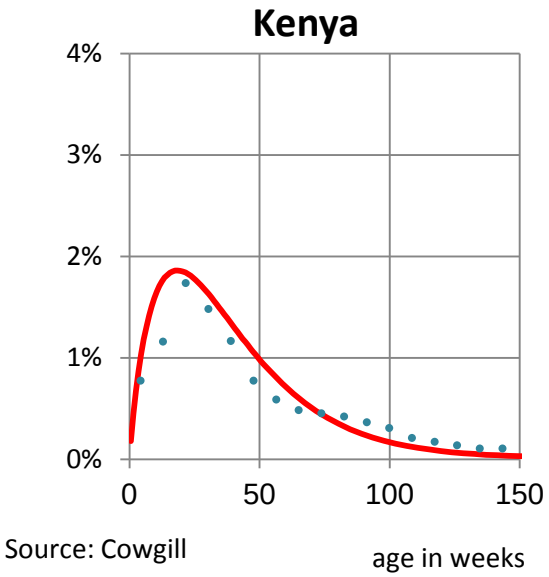




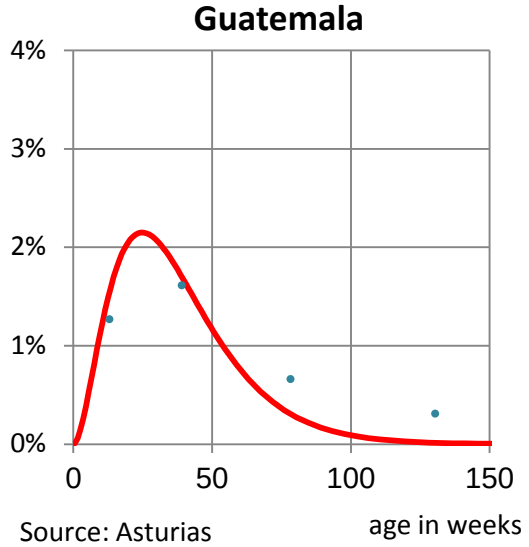
Age at invasive Hib disease



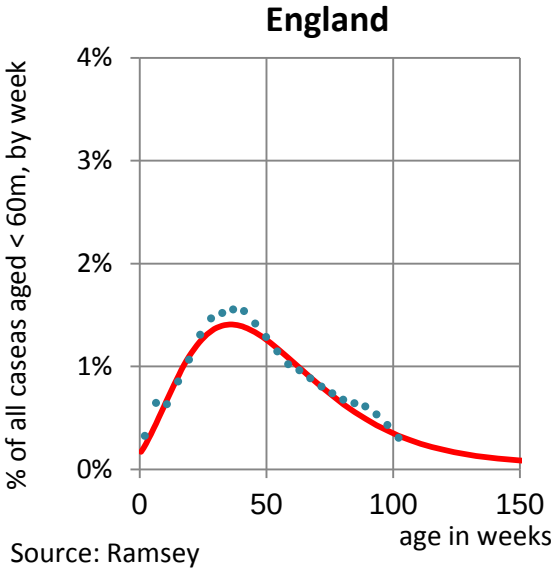
Source: Adegbola



Source: Cowgill



Source: Asturias



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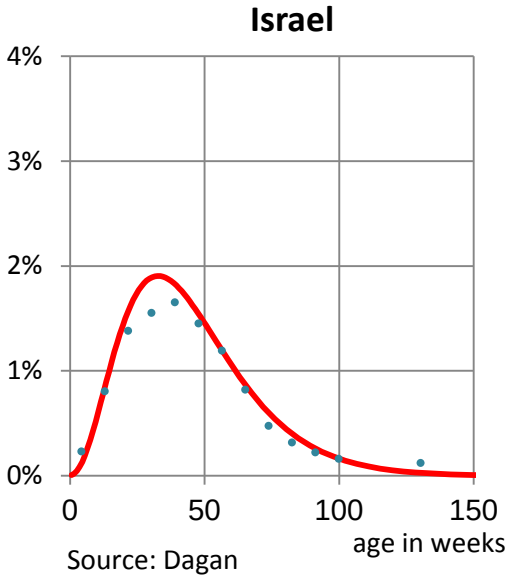
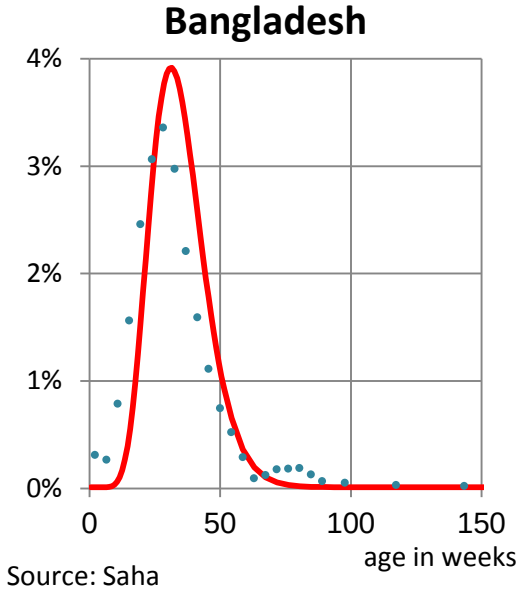
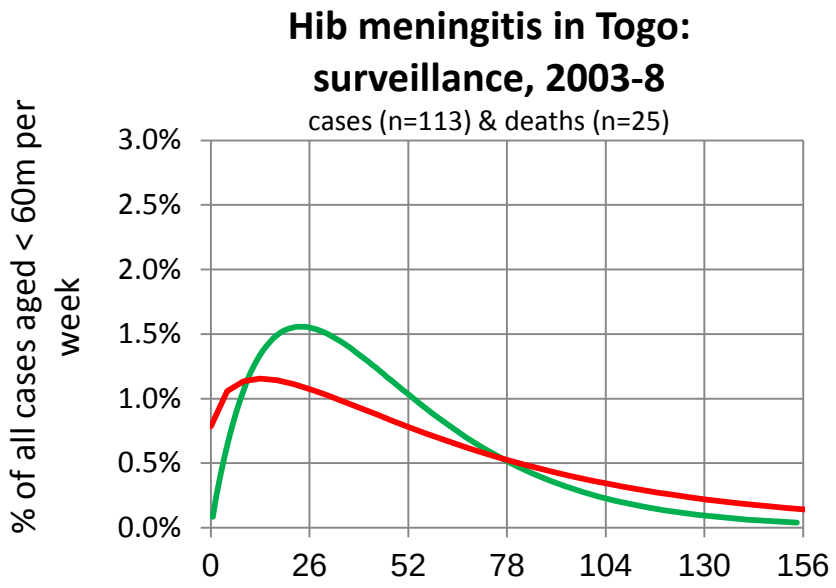


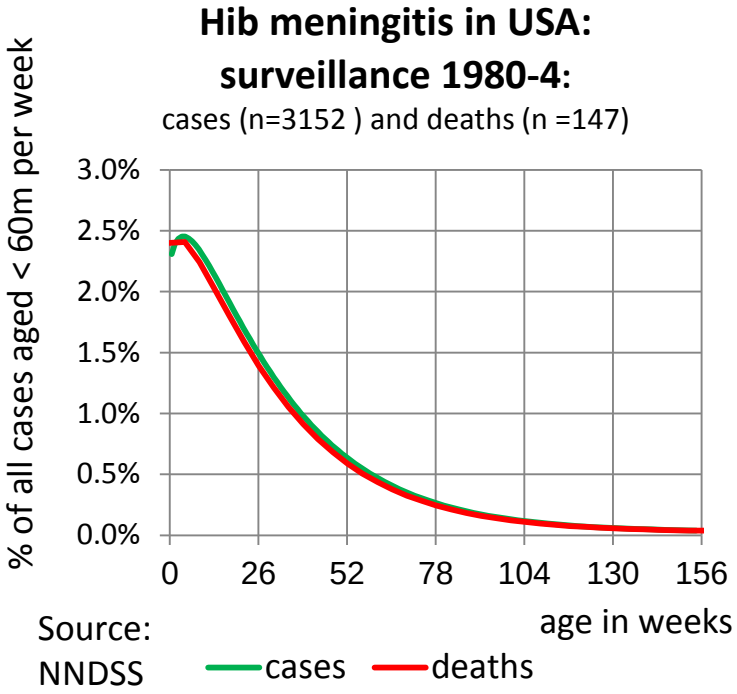
Source: Dagan

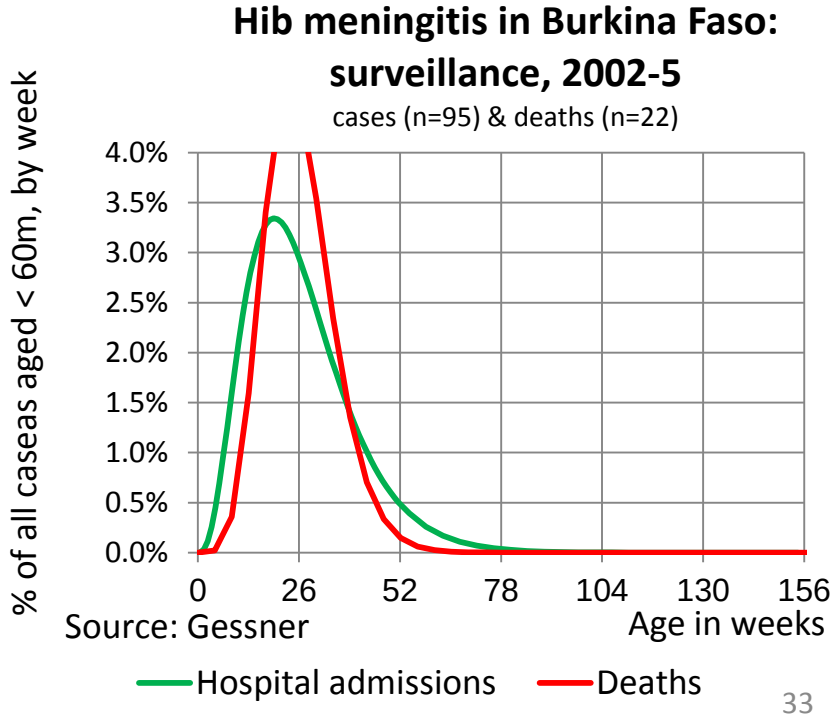


Source: Saha

Some age distributions for cases and deaths

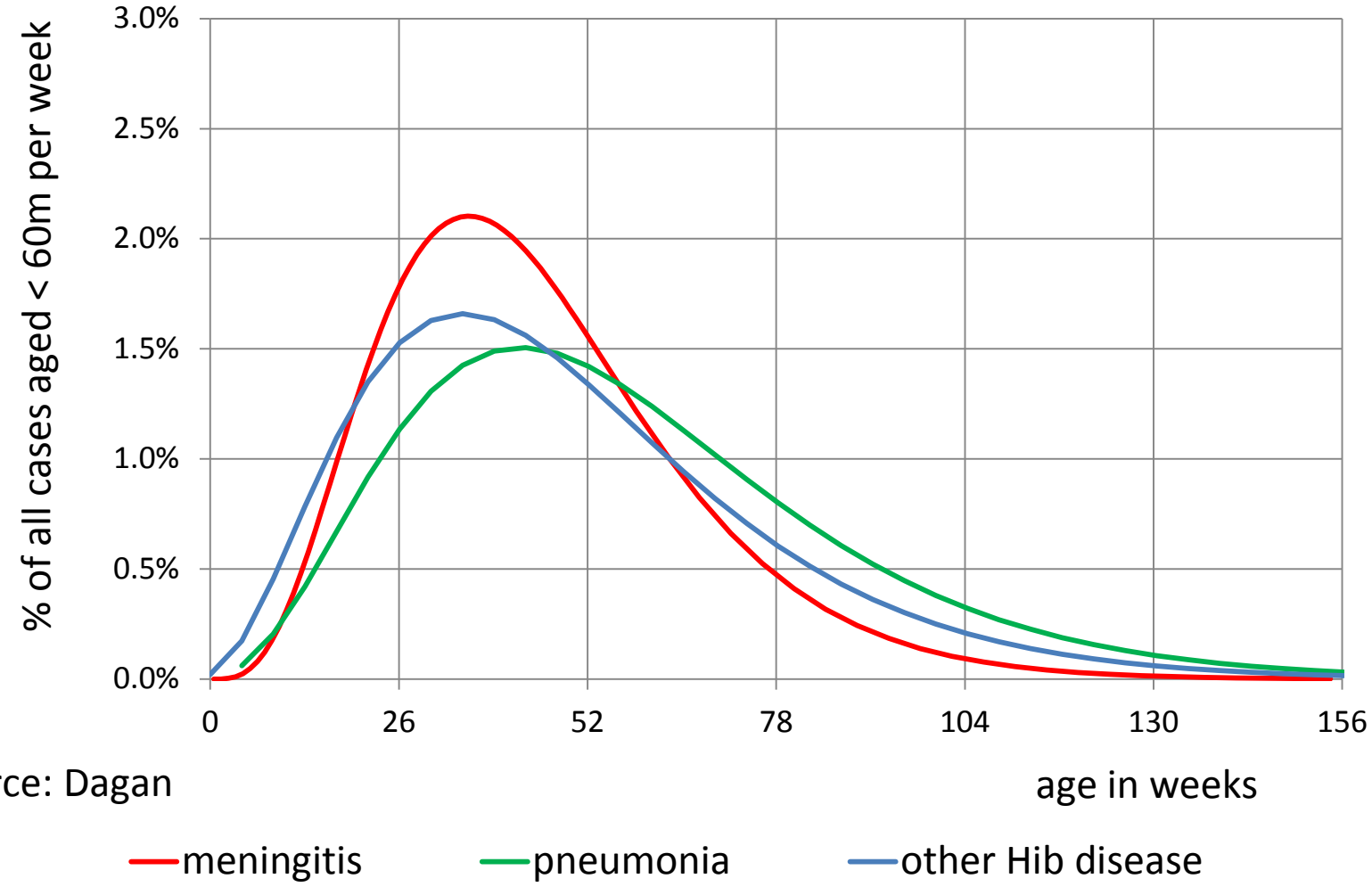






Hib in Israel: surveillance 1988-93:

meningitis (n=423), pneumonia (n=143), other Hib disease (n=222)



Source: Dagan

Estimation for countries without the necessary data

For *Hib age distributions*, estimates based on

- WHO Choice strata

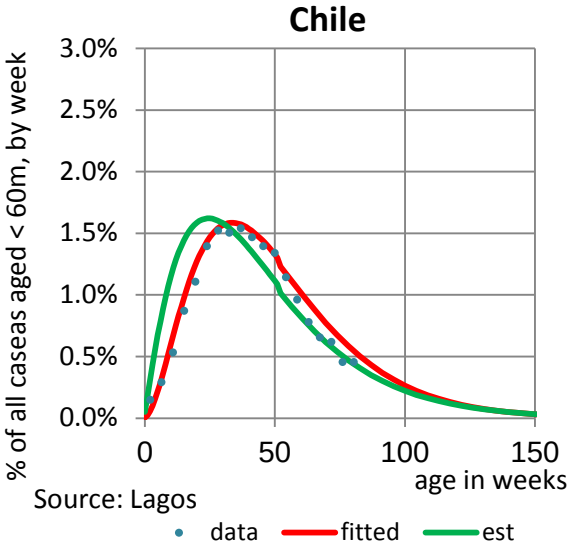
For *timeliness distributions*, estimates based on

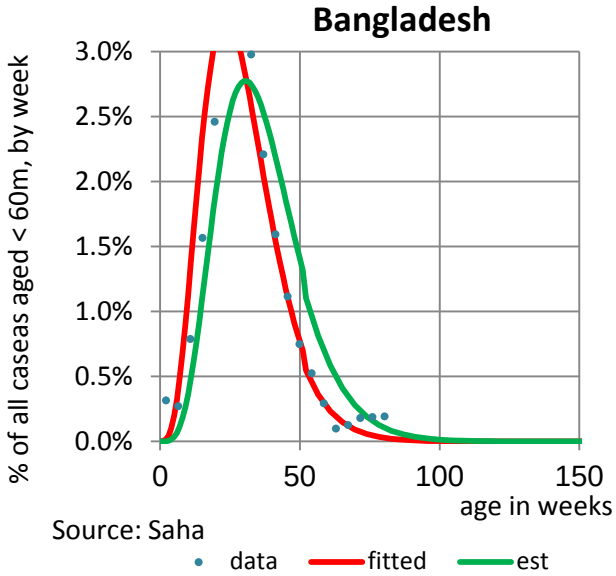
- WHO Choice strata
- WHO reported coverage at 12m for DTP1, DTP3, MCV
- difference in WHO reported covered for DTP1 and DTP3
- GNI per capita (International dollars)
- % with skilled birth attendants

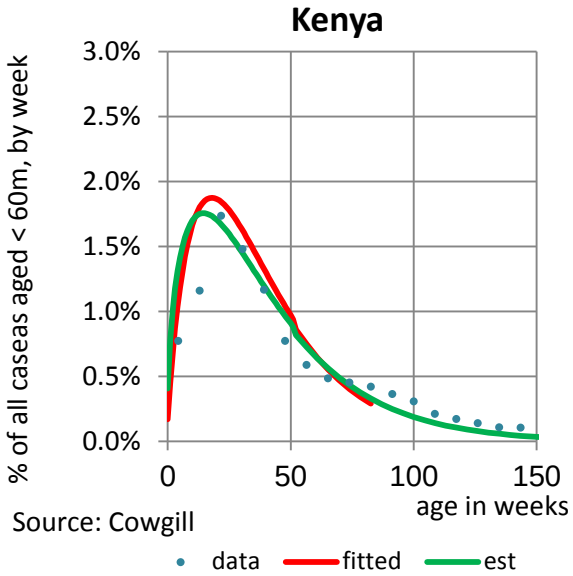
Validation

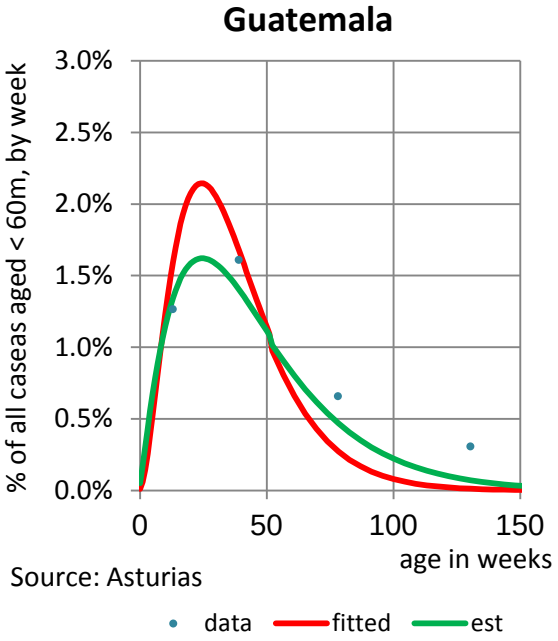
1. Use method to estimate for countries *with* age and/or timeliness data
2. Compare estimate with observed

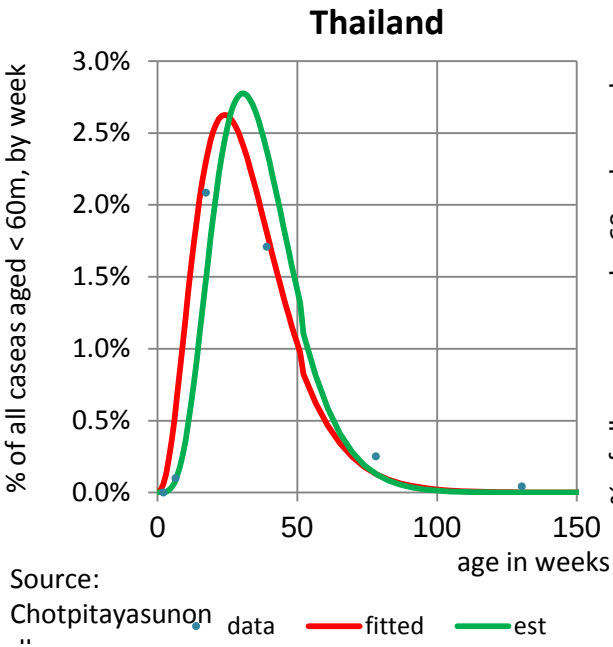
Validity of selected estimated age distributions

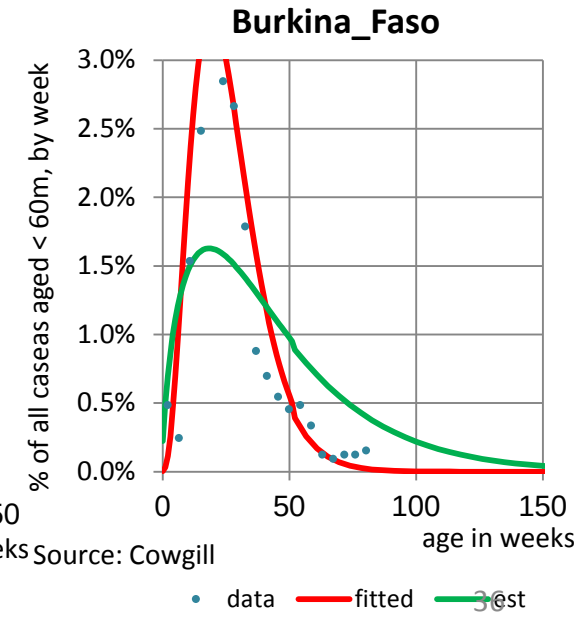




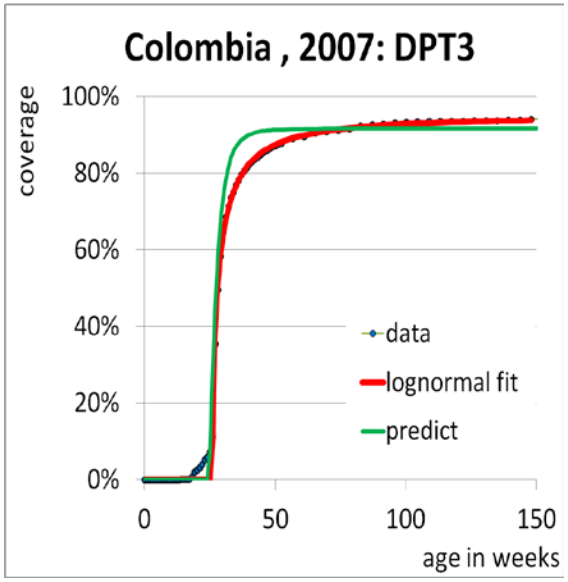


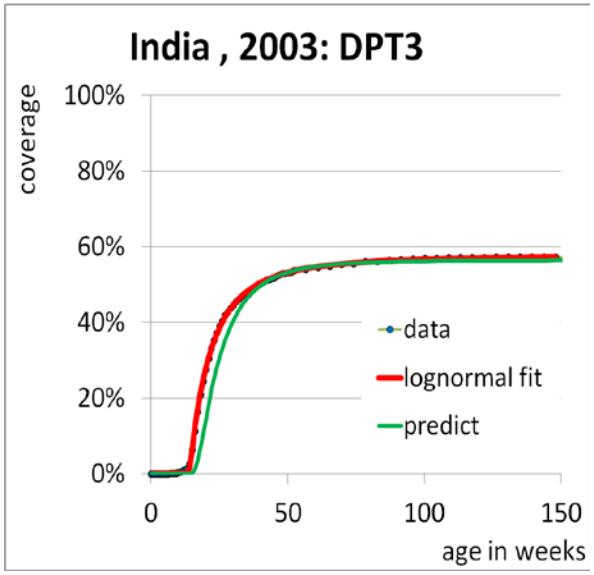


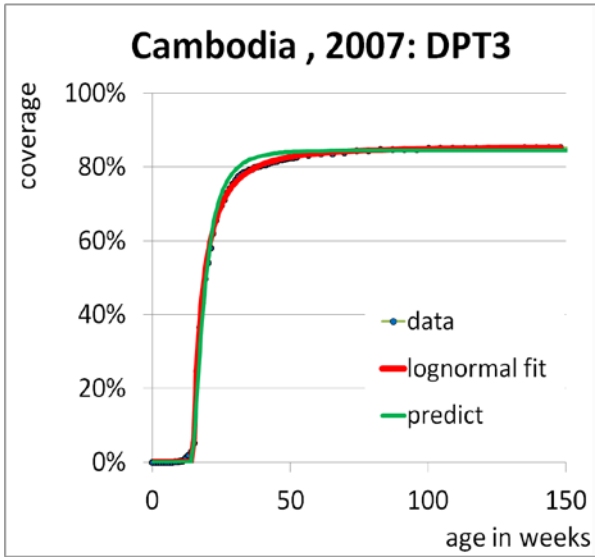


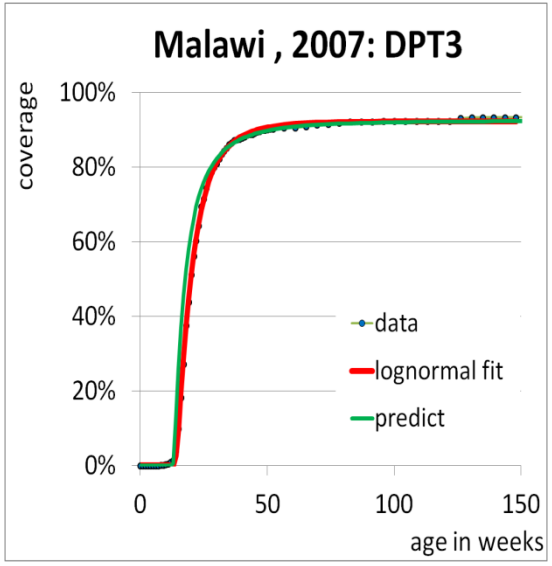


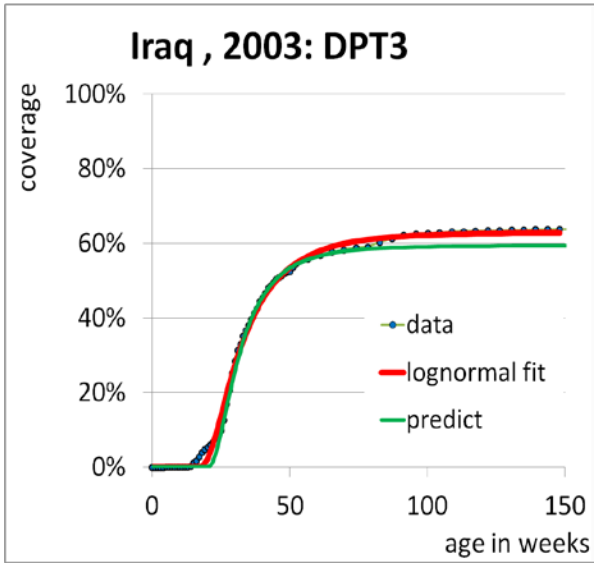
Validity of selected estimated coverage curves

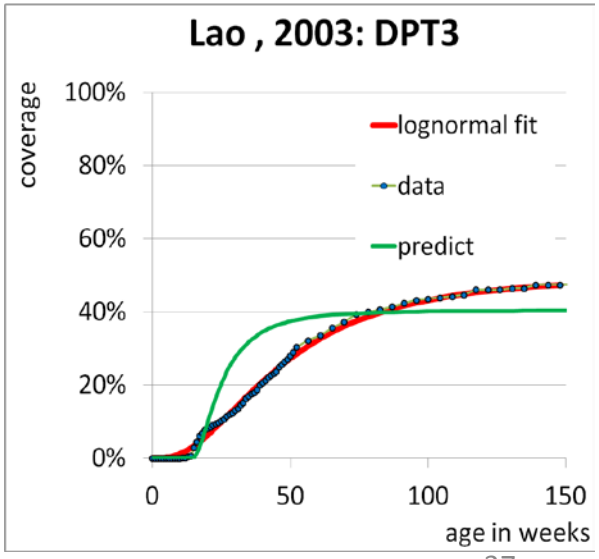






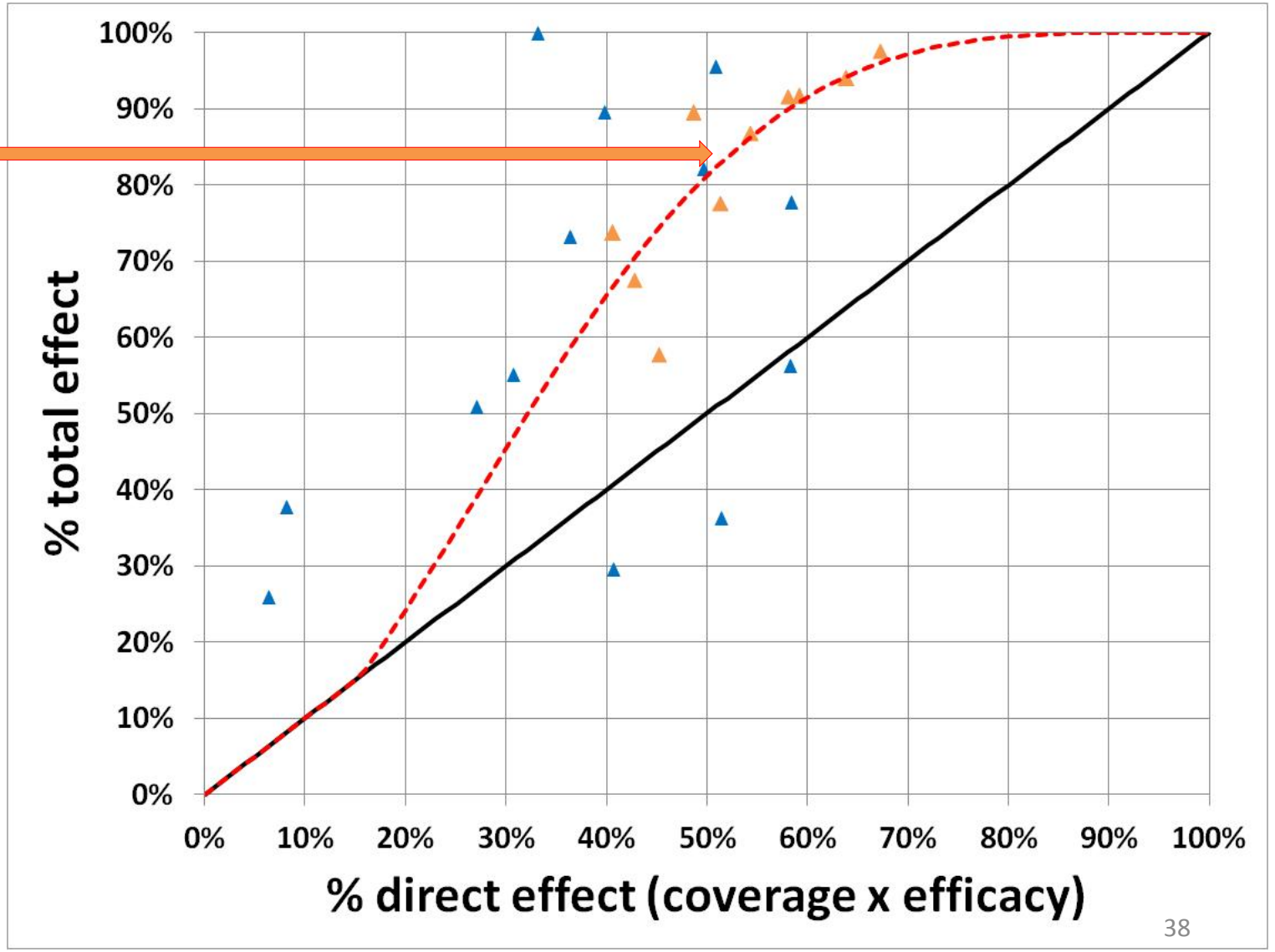




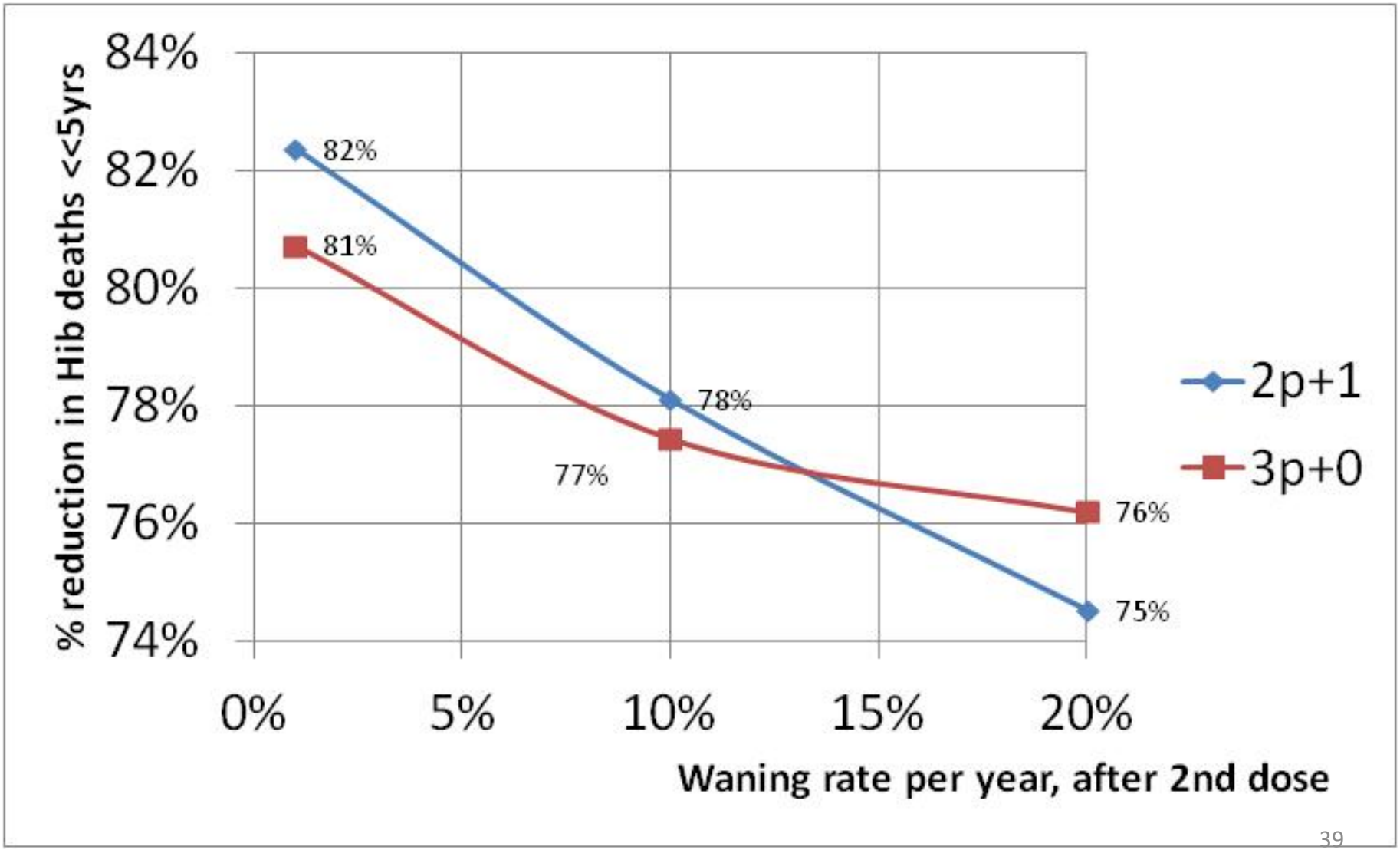


% direct and total effect on Hib disease <5yrs

24 data points
Australia = 2
Brazil = 12
Cuba = 1
France = 1
Kenya = 2
Senegal = 1
Spain = 3
Tonga = 2



3p+0 versus 2p+1:
effect of 2nd dose waning rate on deaths prevented



Country-level assessment/transparency

Country Report Zimbabwe

Scenario:

Schedule	2p+0	mary = 2	Booster = no		Age dist:	WHO region best fit
Herd effect <5yrs	yes	Direct = 31.7%	Total = 47.6%	% herd = 23.2%	Timing:	Zimbabwe

	Current age (wks)	Shift age (wks)	New age (wks)	Efficacy	Waning	# doses thousands
p1	13	0.0	13	77%	73.50%	354
p2	17	0.0	17	93%	37.46%	354
p3	22	0.0	22	95%	1.42%	-
Booster	39	0.0	39	95%	1.42%	-

Baseline deaths	1,304
Deaths prevented	620
% prevented	48%
Doses/death prevented	1,140

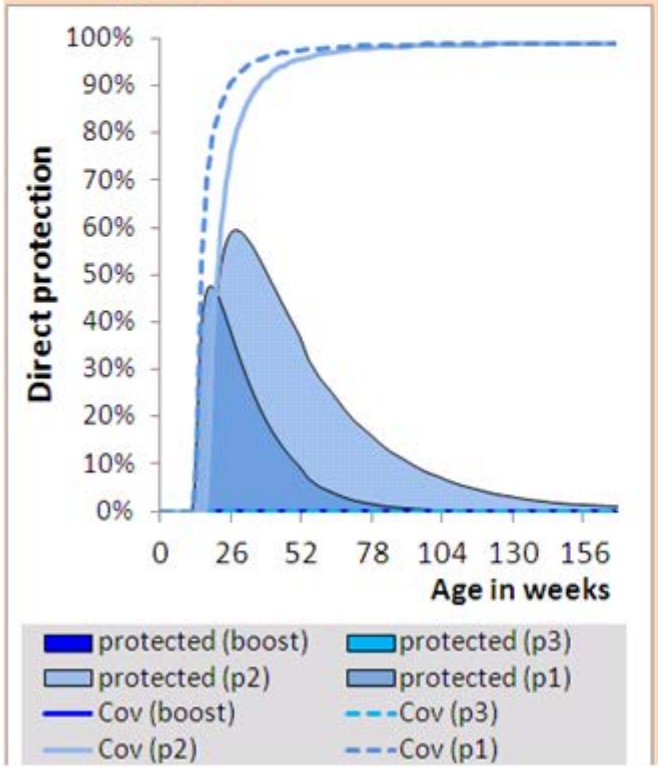
Global Report Calculate global results

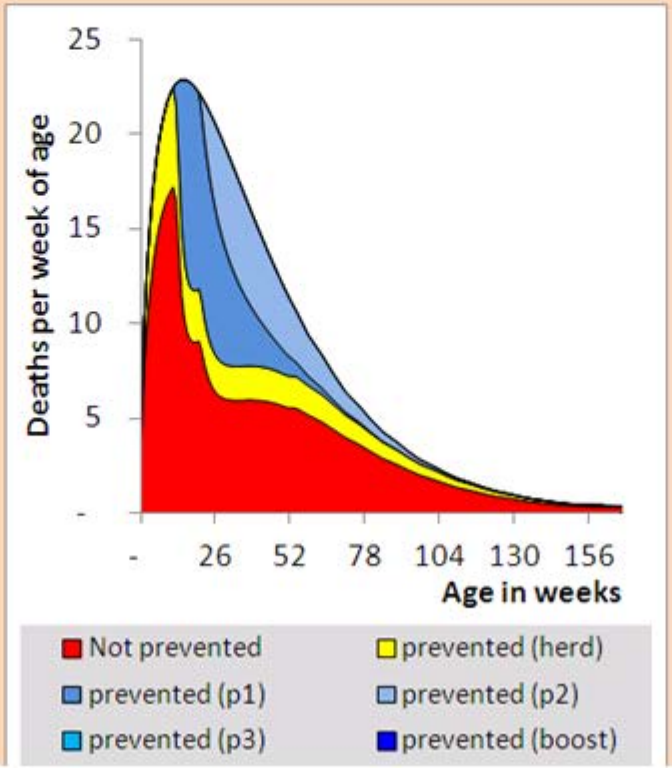
Record of scenario:

Schedule	2p+0
Herd effect <5yrs	yes

	Shift age (wks)	Efficacy	Waning
p1	0.0	77%	73.50%
p2	0.0	93%	37.46%
p3	0.0	95%	1.42%
Booster	0.0	95%	1.42%

Charts showing country results:



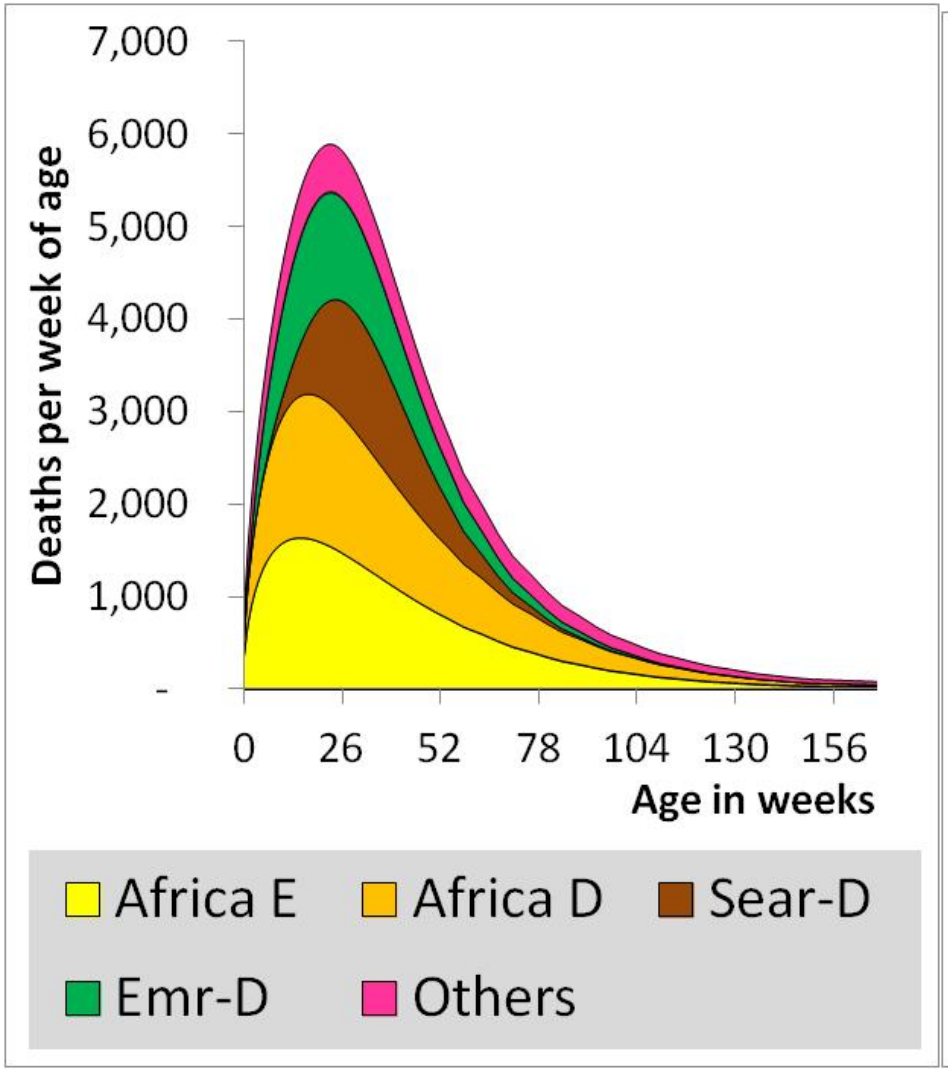


Results: 2011 cohort results

	Deaths	Prevented	% prevented
Afr-D	90,429	28,302	31%
Afr-E	92,812	34,804	37%
Amr-A	372	209	56%
Amr-B	3,810	1,790	47%
Amr-D	3,393	1,120	33%
Emr-B	1,589	1,037	65%
Emr-D	50,336	24,160	48%
Eur-A	168	65	39%
Eur-B	6,873	1,980	29%
Eur-C	769	219	29%
Sear-B	4,596	1,554	34%
Sear-D	46,496	26,248	56%
Wpr-A	57	15	26%
Wpr-B	18,011	8,066	45%
GLOBAL	319,710	129,570	41%
AFR	183,241	63,106	34%
AMR	7,575	3,119	41%
EMR	51,924	25,197	49%
EUR	7,810	2,265	29%
SEAR	51,093	27,802	54%
WPR	18,068	8,080	45%
GLOBAL	319,710	129,570	41%

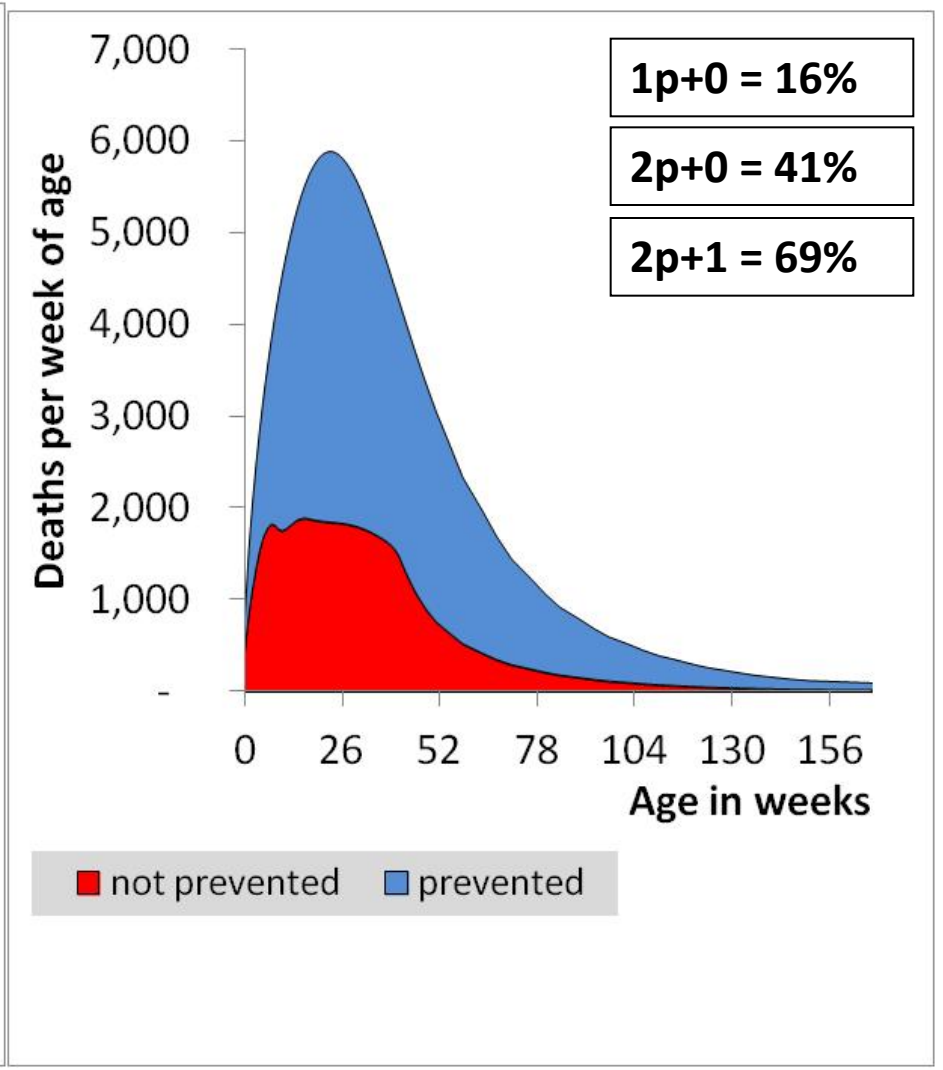
Global, 2p+1

Hib deaths by age and region



Model output

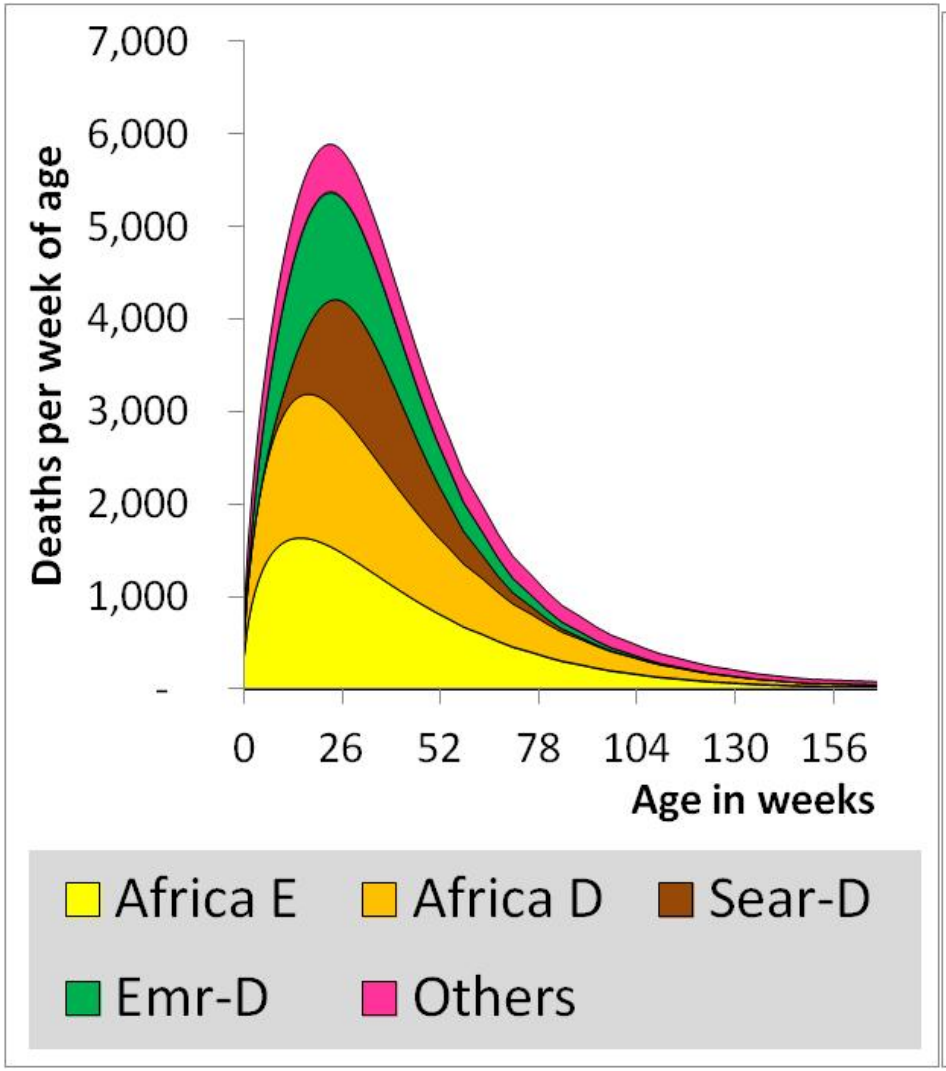
Hib deaths by age (% prevented)



Model output

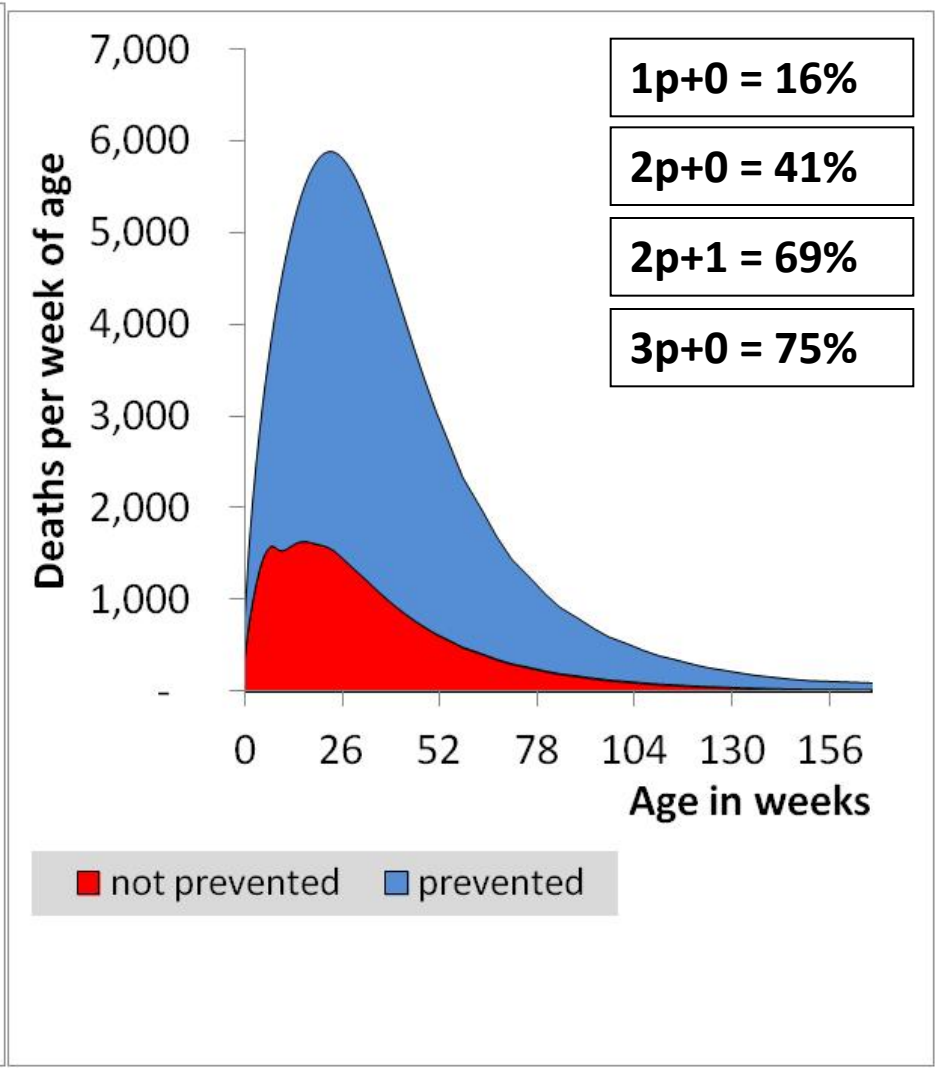
Global, 3p+0

Hib deaths by age and region



Model output

Hib deaths by age (% prevented)



Model output