Global review of rotavirus morbidity and mortality data by age and region

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Abstract

***B**ackground:* In unvaccinated populations in most low and middle income countries the majority of reported cases of rotavirus gastro-enteritis (RVGE) occur in the first year of life. Rotavirus vaccines are typically administered according to the local EPI schedule. In some populations EPI coverage and timeliness may be such that material number of cases of RVGE would have no protection at all, and a substantial number would have only partial protection. It is unclear whether this is a widespread problem, and whether there are implications for rotavirus vaccine scheduling.

Aim: To assemble existing data on age at RVGE and examine it using age groups small enough for assessment of the population impact of rotavirus vaccination according to different schedules.

Methods: Identify researchers in the field through literature review and informal methods. Contact them and seek their cooperation in supplying RVGE age distributions or suitable raw data. Assemble the data. Fit gamma distributions to summarise the data from each study and deal with reporting anomalies. Conduct meta-analyses to summarise the data from all the populations, and meta-regressions to identify factors related to age at RVGE. Compare age distributions for RVGE admissions with those for RVGE deaths, RVGE cases in the community, and 'any diarrhoea'. For countries with survey data on age-specific vaccine coverage, construct age/protection profiles to aid assessment of the timeliness of vaccination in relation to age at RVGE.

Results: Of 191 possible respondents identified in the formal and informal searches, contact was made with 90 (47%). Twenty-nine (15%) supplied data from research or surveillance studies on 38 populations, at least 3 populations from each WHO region. In 33 (85%) of the study populations the qualifying RVGE event was hospital admission. In 32 (83%) the basis for attribution to rotavirus was EIA/ELISA only.

The pooled estimates of the percentages of all RVGE events in children less than 3 years old which had occurred by age 6, 9, 13, 15 and 17, 26 and 32 weeks respectively were 1%, 3%, 6%, 8%, 10%, 22% and 32%. However there was substantial heterogeneity, with 3 studies that could be considered as outliers.

The % of RVGE events before ages 15 and 32 weeks were related to Gross National Income per capita, but there was no evidence for such a link for events before age 6 weeks. Infant mortality was linked only to RVGE events before age 32 weeks. The evidence for relationship between exclusive breast feeding for 6 months and RVGE events before 6 weeks of age was in the expected direction, but very weak indeed.

There were only two distributions of ages at death from RVGE and they were based on very small numbers, but they were not dissimilar to those for age at RV admission in the same populations. Two sources provided distributions for ambulatory and hospitalised cases in the same populations; in one case the distributions were almost identical, and in the other they were reasonably similar. The age distributions for admission with RVGE and any diarrhoea were very similar in the 5 SEARO surveillance studies, but the correspondence was less clear in the two studies from other regions.

Conclusion: In many parts of the world there are relatively few admissions for RVGE before the scheduled first dose of vaccine. However in some populations RVGE in very young children is more common, and EPI coverage is low or delayed. In these circumstances the benefits of a rotavirus vaccine programme will be materially reduced. Also it seems that children in the poorest, typically rural, households with the highest risk of mortality may have the earliest exposure to rotavirus and the lowest level of vaccine protection. Ideally vaccination schedules should be designed to provide benefits to those at highest risk. This implies extending the evidence base to age distributions for different socio-economic groups.

1. Background

The global number of deaths due to rotavirus infection in children aged less than 5 was estimated to have been 527,000 (475,000 – 580,000) in 2004[1], with about 90% percent of them in Africa or Asia.

There are currently two licensed vaccines that protect against rotavirus diarrhoea. Rotarix® should be administered in 2 doses, the first between 6 to 15 weeks of age, and the second after an interval of at least 4 weeks but before age 32 weeks[2]. RotaTeq® should be administered in 3 doses, the first between 6 and 15 weeks of age, with intervals between doses of between 4 and 10 weeks and the series completed by 32 weeks. Administration is usually at the same time as the diphtheria, tetanus and pertussis (DTP) or the oral polio (OPV) vaccines vaccines according to the local standard EPI schedule, the most common of which are at ages 6, 10 and 14 weeks, 2, 3 and 4 months or 2, 4 and 6 months. In practice most vaccines are delivered after the scheduled dates[3].

There may be circumstances in which the protection provided by a vaccination programme is too late. Whether this is a rare or common occurrence will depend on susceptibility and exposure to infection during the first few weeks and months of life, the age at vaccination and the level of protection offered by each dose in the series[4]. This point is illustrated in Figures 1, 2 and 3. Figure 1 shows the shows the percentage of all RV hospital admissions aged less than 36 months that occured in each week of age in a study in Blantyre, Malawi[5], when there was no rotavirus vaccination programme. A distribution (solid line) has been fitted on the assumption that the apparent peaks at 26, 52 and 104 weeks are reporting anomalies.

Figure 1: RVGE in children aged < 36m: Blantyre, Malawi 1997-2007.

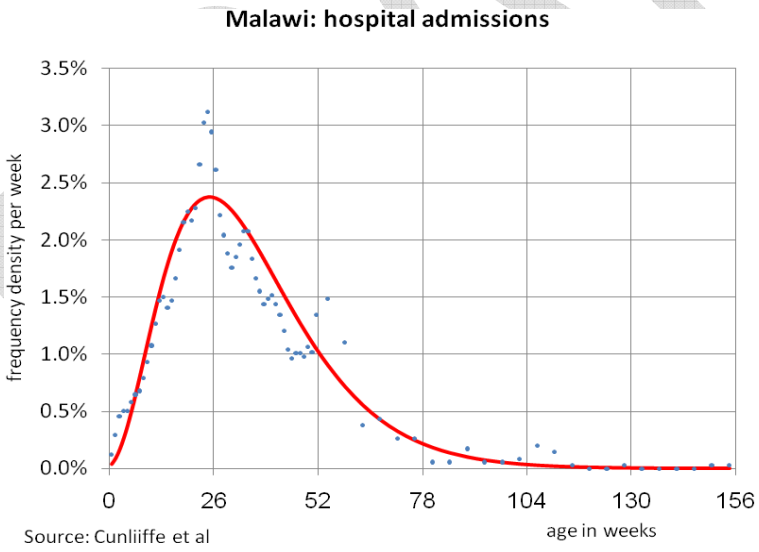


Figure 2 shows the % of children vaccinated by weeks of age up to 1 year given by data from the Multiple Indicator Cluster Survey for Malawi for 2005. (Figures are given for OPV1, 2 and 3 because survey data on DTP coverage were difficult to interpret with both trivalent and pentavalent vaccines involved.) The coloured areas indicate the age 'windows' for rotavirus vaccine, 6 to 15 weeks for the first dose, and up to 32 weeks for the last. It can be seen that with strict adherence to these windows the coverage for a rotavirus vaccine would be somewhat reduced.

Figure 2: % of children vaccinated by age in weeks, for OPV 1, 2 and 3.

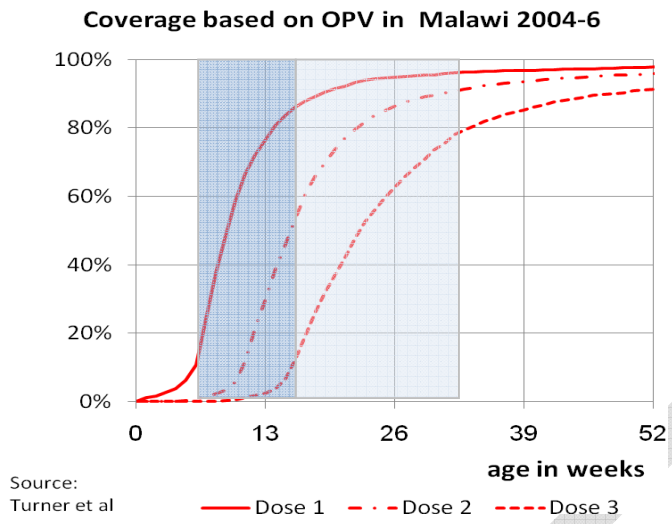
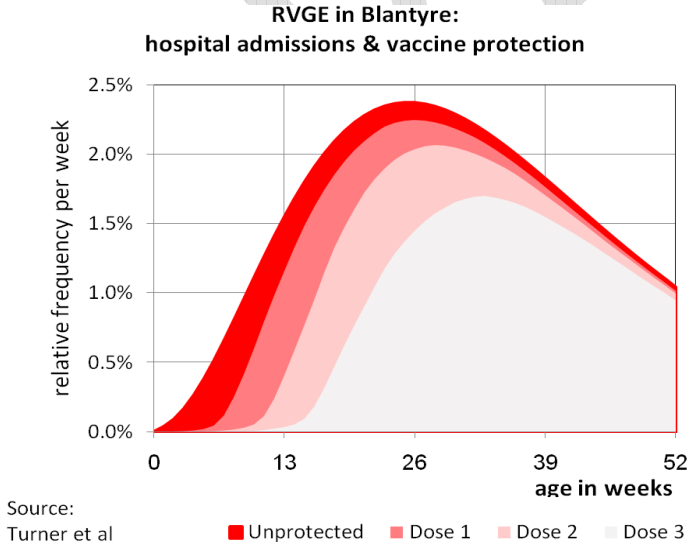


Figure 3 combines data from Figures 1 and 2. The outer envelope of the curve is the same as Figure 1 up to 52 weeks, showing the frequency distribution of RV admissions with no vaccination programme. The dark outer area under the curve labelled 'unprotected' shows the cases that would have had no vaccine protection at the time if the coverage had been the same as for OPV, ie ignoring the 'safe' vaccination window. The areas labelled '1 dose' and '2 doses' indicate the cases which would have had this much protection. For a 3-dose vaccine, only the cases in the palest area would have the level of protection intended by the programme.

Figure 3: estimated % of children with RVGE who would have at least partial vaccine protection



It can be seen that with this combination of age distribution of cases, schedule, adherence to schedule and coverage, a material number of cases would have no protection at all from a rotavirus vaccine programme and a substantial number would have only partial protection, particularly for a 3-dose vaccine.

Is this a widespread problem? There are now reasonable amounts of data on age-specific vaccine coverage, particularly in low income countries, from the Demographic Health Surveys (DHS) and the Multiple Indicator Cluster Surveys (MICS). There are much more limited data on the age distribution of rotavirus disease. The median age at RVGE is widely quoted as being between 6 and 9 months, but this reveals very little about the lower end of the age distribution, which is the important part in this context. The problem is that in most published distributions the age groups are too broad (eg 0-5 months, 6-11 months etc) to throw much light on how many children suffer from RVGE during their first few weeks and months of life.

There are several related questions:

- In low and middle income countries it is the reduction in rotavirus-related mortality which is the main benefit of a vaccination programme. Thus it is particularly important that the programme offers protection before the ages at which significant numbers of children die. However data on age at death from rotavirus disease are very difficult to obtain because data collection usually involves access to health care and thus, in general, rehydration therapy. The question then is whether it is reasonable to assume (on the basis that children who are admitted are at the higher-risk end of the severity spectrum) that the distributions of ages at RVGE death and RVGE admission are similar.
- Most data on age at RVGE are for children admitted to hospital. Although these can be expected to be relatively severe cases and so important from the burden of disease point of view, there will be far more cases in the community. Can data on the age distribution of hospital cases can be used as proxies for data on the age distribution of community cases?
- Many countries do not have data on age at RV events such as hospital admission. Can data on age at admission for diarrhoea of any cause can be used as a proxy for data on age at RVGE admission?
- Are there relationships between age at RVGE and more generally available economic and epidemiological indicators which could be informative in countries with limited data on diarrhoea?

And finally:

- Can data from a particular year be taken as representative of the pattern of rotavirus infection in a population, or is there substantial year-to-year variation?

2. Aim and objectives of the study

2.1. Aim

To examine data on age at RVGE using age groups small enough for assessment of the population impact of rotavirus vaccination according to different schedules.

2.2. Objectives

- To review the global literature on age at rotavirus disease in unvaccinated populations.
- To construct a database of sources, contacts and contextual material.
- To bring together data on age distributions of RVGE in children aged < 5 years. If the categories used in published data are too wide, to contact the researchers concerned and seek data with narrower age groups, or access to raw data.
- To seek, in addition, age distributions for deaths attributable to rotavirus and for diarrhoea of any cause in the same populations.

3. Methods

3.1. Published data:

Relevant studies were identified through a review of the literature using the National Library of Medicine's PubMed and other relevant databases such as EMBASE and the Cochrane Library. The list of relevant studies was cross-checked against articles listed on the following web pages:

1. the Rotavirus vaccine program (http://www.rotavirusvaccine.org/) ;
2. the WHO external review of the burden of disease attributable to Rotavirus[6] rationale/methods: http://www.who.int/immunization_monitoring/burden/Rota_virus_Q5_mortality_estimates_external_review_report_2006_may.pdf; and
3. the WHO country-specific estimates of the fraction of diarrhoea due to rotavirus: http://www.who.int/immunization_monitoring/burden/Global_national_estimates_2004_deaths_under_age_five_attributable_to_rotavirus_infection_2004.pdf

3.2. Unpublished data

For the eligible studies identified, the corresponding author was asked for permission for access either to age distributions of the children with RVGE in narrow age groupings (1 week up to age 52 months, then 1 month up to age 60 months) or to raw ungrouped data.

Surveillance data were sought from the agencies responsible in high income countries (US: CDC, UK: HPA, etc.) and from the Rotavirus Surveillance Network[1].

3.3. Interviews

We sought telephone interviews with at least one author from each study. The purposes of these were:

1. to check that the data extracted during the literature search were correct;
2. to obtain any additional data on the scope and design of the study;
3. to establish what additional unpublished hospitalisation and mortality data the authors held that might be relevant; and
4. to gain permission for access to data.

A computer-based interview schedule was developed to facilitate this.

3.4. Database

A database on global rotavirus data was constructed including information on source, country/region, year, selected details of study design and age-specific rates.

3.5. Analysis

In most studies more than 95% of the children less than 5 years old with RVGE were also less than 3 years old. In this review, studies were included if there were more than 100 subjects aged < 3 years, and data for children

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1 CDC and WHO have developed a generic protocol for standardized surveillance of rotavirus disease, and in collaboration with other RVP partners, CDC supports rotavirus surveillance in five regional networks (over 40 countries) across the globe" **(http://www.cdc.gov/rotavirus/global_surveillance/surveillance.htm).**

less than 1 year old in bands of 1 month or less. Studies specifically of nosocomial infections or with data from periods after the introduction of a rotavirus vaccine programme were excluded.

If we were provided with sufficient data we calculated the age distribution using intervals of one week up to 52 weeks and one month thereafter. In some datasets there were spikes in the age distribution in the months numbered 12, 18, 24 and 30. In these cases wider category intervals were used for the older age groups: 12.0 to 17.9 months, 18.0 to 23.9 months etc. Note that this assumes that partially reported ages are rounded down. If the data were provided in intervals of a week or less, we calculated the percentage that were less than 6, 9, 13, 15, 17, 26 and 32 weeks old at the time of their qualifying rotavirus event. If the data were provided in intervals of a month (or, as in data from the Eastern Mediterranean region, with cut-points at mid-month) the percentages aged less than 9, 13, 15, 17, 26 and 32 weeks were estimated using linear interpolation. The mean and median were calculated for each distribution. Results were presented in tables, and in meta-analysis format using the Stata 'metan' command assuming random effects. For the meta-analyses the percentages in each study were first transformed using the arcsin variance stabilising function.[8]

Metaregression was used to investigate relationships between age at RVGE and gross national income per capita (GNI[7]), infant mortality (InfM[8]) and exclusive breastfeeding for the first 6 months of life[9]. This analysis was repeated excluding 3 possible outlier studies, and also including only the 13 surveillance studies from the East Mediterranean WHO region, which used a standard methodology.

To help summarise and visualise the observed distributions, theoretical distributions were fitted. Before fitting, weekly data were smoothed using a centred 4-point moving average. Monthly data were not smoothed. Statistics calculated for the theoretical distributions included the mean, standard deviation and selected percentiles. Gamma and lognormal distributions were tried. Results reported are for gamma distributions, since these generally provided the better fits[2]. As well as varying the mean and standard deviation of the theoretical distribution, the fitting process allowed for lateral shifting so as to cater for non-zero incidence at age 0 (left/negative shifting) and variations in the durability of protection by maternal antibodies (right/positive shifting). Goodness of fit was measured by weighted root mean square deviation, with increased weight attached to deviations at ages less than 6 months. In each case the parameters giving the minimum weighted root mean square deviation were found numerically from a grid of starting points using Excel Solver.

For some of the countries represented in this survey there were data from the DHS or MICS on the distribution of children's ages at DTP and/or OPV1, 2 and 3. To aid assessment of the timeliness of vaccination in relation to age at RV disease we constructed 'age/protection profiles'. For each week of life, the % of all RV cases at age < 36m in that week *in the fitted distribution* was multiplied by the mean coverage for that week with 1, 2 and 3 doses of OPV. This gives the % of cases at each week of age that would have had 1, 2 or 3 doses of vaccine if RV vaccine had been added to the EPI programme using the standard schedule.

For statistical analyses, Stata 11 was used. Graphs were produced using Excel.

4. Results

4.1. Literature search

The search terms and results of the preliminary literature search are summarised in Table 1.

2 The gamma distribution is the probability distribution of waiting times until the kth arrival in a Poisson process. It is commonly used to model waiting times. Points on a gamma distributions lie between zero and infinity.

4.2. Database of contacts

On the basis of the literature search a database of the contact details of 191 possible informants was constructed. The results of trying to contact the people on this list are summarised in Table 2. At least two attempts were made at contacting an informant for each study.

4.3. Selection of studies

At the last update the dataset included distributions of age at rotavirus event for 50 populations. Seven of these were excluded from the analysis because they had fewer than 100 subjects with RVGE aged less than 36 months. Three were excluded because some of the age groups for children less than 1 year old were longer than 1 month, one because it was concerned with nosocomial infections, and one because there was a vaccine trial in the area within the period of study. This left 38 datasets. Table 3 gives data on the defining RV events for the included studies, Table 4 gives the basis for attribution to rotavirus, and Table 5 gives more detail on each study, including in the right hand column the % of children aged between 3 and 5 years at the time of their qualifying RV event.

4.4. Age at RV infection

Table 6 gives summary statistics on ages at RV event in the included studies. It can be seen from the foot of the table that the median age for all the studies was 43.5 weeks (inter-quartile range 38 to 52 weeks).

Figures 4 to 10 show graphically the percentages of children who have had an RV event by age 6, 9, 13, 15 and 17, 26 and 32 weeks respectively. The pooled estimates are 1%, 3%, 6%, 8%, 10%, 22% and 32%. However there was substantial heterogeneity, with studies that could be considered as outliers from France and USA, and one of the three studies from India.

Table 6 also provides summary data for the fitted gamma distributions. Figure 11 shows the fit of the gamma distribution to the single largest dataset (England and Wales, n = 37,267) and to a dataset from 13 EMRO countries combined (n = 12,484). Figure 12 shows one example of a distribution shifted to the left, and one shifted to the right.

The unsmoothed data are also shown graphically alongside these distributions in a set of diagrams for each WHO region (Figures 13 to 18). Some gamma distributions fit better than others but in general the fit is better when the numbers in the sample are greater. Where the fit was improved by shifting the distribution horizontally, the shifts to the right (consistent with an extended period of near-zero incidence, possibly due to protection by maternal antibodies) were in general small.

4.5. Correlates of age at RVGE

In meta-regression analyses, neither GNI nor infant mortality was associated with the % of RVGE cases before age 6 weeks (Table 7).

Increasing GNI was strongly associated with decreasing % of RVGE cases before age 15 weeks and 32 weeks in the analyses using only the 13 EMRO surveillance studies and excluding the 3 possible outliers (Figures 19 to 21) but this relationship disappeared or weakened if the outliers were included.

Increasing infant mortality was linked with % of cases before age 32 weeks but not 15 weeks. This association was weakened if GNI was also included as an independent variable.

Exclusive breast feeding data were only available from the WHO database for 30 of the 38 countries. The relationship with % of RVGE cases before 6 weeks of age was in the expected direction, but very weak (coefficient in 11 EMRO countries -0.0009, p = 0.38), and unchanged by adding GNI into the analysis.

With regard to variation in age at RVGE admission by year, we were provided with surveillance data from England and Wales that involved large numbers of cases over a 10 year period, and these were examined on a year by year basis. Results are summarised in Table 8, which suggests a stable pattern.

4.6. Age at RVGE admission vs age at RV death.

Only two countries in our database reported enough rotavirus deaths to construct any kind of age distribution: Papua New Guinea (PNG, n = 29) and Sudan (n = 15). In Figure 22 the distributions are compared those for RVGE in the same population. In PNG the median age at RVGE admission was 43 weeks, a little younger than the median age at RV death (50.8). For Sudan the median values were very similar at 40 and 41 weeks respectively, but the distribution of ages at death was less spread out.

4.7. Age at RVGE admission vs age at admission for any diarrhoea

In Table 9 summary statistics on paired distributions (RVGE diarrhoea vs any diarrhoea) are shown for 7 populations. It can be seen that in the data from the SEARO region, the two distributions for each country are very similar. In the data from Kenya and Chile, cases of RVGE are slightly less common in very young children than other forms of diarrhoea. However the median value for Chile is much higher than for Kenya, with more children with RVGE at age 12 to 23 months.

4.8. Age at RVGE admission vs age at RVGE seen in ambulatory care settings

In Figure 23, distributions for two populations in the African region are shown. In the South African study the age distributions for inpatients and ambulatory patients were similar (median values; 32.0 and 34.4 respectively), but in Malawi the inpatients were slightly younger (median values: 31.9 and 35.8). In data from Vellore in India, the community-based cases were materially younger than the hospital inpatients cases. While coming from the same area, these data were from different populations, and were identified by different methods (ELISA vs LA).

4.9. Distributions of age at rotavirus event and age at vaccination: 'age/protection profiles'

In this analysis the focus is on cases of RVGE at age less than 12 months. Figures 24 to 32 show that age/protection profiles vary substantially between countries. In Kenya, for example (Figure 24), the peak of the incidence curve is later than in Malawi (Figure 25) and vaccination is more timely. The result is that the proportions of unprotected and partly protected cases are lower in Kenya, even though the vaccine coverage in Malawi at one year of age is higher (Table 10).

Egypt (Figure 26) and Iraq (Figure 27) also show contrasting patterns, even though in this comparison the peaks of the incidence curves are similar, both quite low at around 26 weeks. In Egypt the vaccination programme is timely and the coverage high. There are some unprotected cases before the first dose of vaccine, but relatively few after that. In Iraq the vaccine programme is less timely and coverage is lower, and the number of cases that would have partial or no protection is much greater (Table 10).

In Bangladesh (Figure 28) the vaccination programme is reasonably timely, although less so than Egypt. However the peak of the incidence curve is later at around 40 weeks. The result would be very few unprotected cases (Table 10). The picture in Thailand (Figure 29) is similar to that in Egypt, with some unprotected cases in the very young in spite of a very timely programme. (In this case the tail of the incidence curve stretches out to the right, with significant numbers of cases aged more than 2 years.)

In the community study in Vellore, India, the incidence or RV disease in very young children appears high, and this, combined with some delays in vaccination, leads to high numbers of unprotected cases aged less than 15 weeks.

5. Discussion

This review suggests that of all the cases of rotavirus diarrhoea in children less than 3 years old that are severe enough for hospital admission, about 3% will occur before the child is 9 weeks old. About 6% will occur before 13 weeks, about 10% before 17 weeks, and 32% before they are 32 weeks old.

Some studies gave much higher figures. The published reports from Gendrel in France and Clark in the US both commented on the relatively high proportions of very young children they had seen. It is possible that differences in breastfeeding rates might have been a factor in this, although the idea that breastfeeding protects against rotavirus remains controversial[10,11]. In France the rates of breast feeding are low and in the US the rates of breast feeding are also low in some populations. However the French study specifically excluded nosocomial infections, which should have biased the age upwards; a review of data from European countries concluded that younger groups were more affected by nosocomial rotavirus (peak incidence in the 0-11 month age group) than community acquired (6-23 months)[12]. The American study was based partly on RT-PCR testing which according to the WHO protocol is not recommended for rotavirus surveillance because of its 'superior sensitivity'[13]. The community study in Vellore also reported a relatively high rate in very young children, but this was based on latex agglutination testing which is described in the WHO surveillance protocol as 'not as sensitive or specific as enzyme immune-assay'.

Comparing data from the different studies suggested a relationship between per capita GNI and age at RVGE at 15 and 32 weeks, consistent with other reports[14]. This effect was not seen in very young children however. This would be consistent with a generalised protective effect of maternal antibodies. Alternatively one might speculate that since exclusive breastfeeding is negatively correlated with GNI, these two effects may be cancelling each other out in this age group. However there was no evidence for this in multiple regression analysis.

Only two sources provided data on more than a handful of deaths from RVGE, and in these the numbers were very small. On this limited basis there was no reason to suppose that for a given population the distributions of ages at RV death and RVGE are very different. However this must be regarded as a provisional conclusion.

Only two studies provided us with separate datasets for ambulatory and hospitalised cases in the same populations. In one case the two age distributions were almost identical, and in the other they were reasonably similar, but again the data are limited.

In five SEARO surveillance studies the distributions for RV diarrhoea and any diarrhoea were very similar. This might have been expected to some extent at least, because in this region the proportion of all diarrhoea cases attributable to RV is reportedly high[15]. The correspondence was less clear in the two studies from other regions.

Figures 24 to 32 provide graphic ways of showing the impact of different combinations of RVGE age distribution and vaccine coverage on the levels of protection that can be expected. Arguably the use of fitted rather than the observed distributions makes these over-tidy, but the gamma family appears to fit the large datasets quite well and deals with artefacts such as digit-preference where they occur. Also the calculations behind these figures assume that a rotavirus vaccine programme has no indirect benefits, ie does not reduce general levels of exposure to infection. Some studies have suggested that there may be indirect benefits, but their nature and extent remain controversial.

Multiplying the ordinates by % vaccine effectiveness would provide an indication of the impact of a vaccine programme in terms of numbers of cases prevented. We did not take this further step because of uncertainty about what figures to use. There is increasing evidence that effectiveness varies not just between populations, but with age at vaccination and with age at exposure.

Overall the picture may seem encouraging, with relatively few admissions for RVGE occurring before the scheduled first dose of vaccine in many parts of the world. However in some areas it is particularly important that a rotavirus vaccine programme should avoid delays if the full benefits are to be realised. And this is not the whole story. Figure 33 is based on the age distribution for RVGE in Trichy and Vellore in India and national vaccination coverage rates in lower, mid and upper wealth quintiles, and shows the levels of protection offered by a vaccination programme assuming that the age distribution of RVGE is the same for each quintile. In spite of an overall DPT1 coverage rate at 12m of 73%, the lower coverage rates and less timely vaccination of children in the lowest wealth quintile mean that about 48% of them would have no protection at all from the programme. This compares with 12% in the upper quintile. If, as seems likely, the incidence of RVGE is higher in poorer children and the median age at RVGE is lower, their disadvantage will be increased; those at the highest risk of mortality would also be exposed to infection earliest and unprotected by vaccination for longest. Ideally vaccination schedules should be designed to provide benefits to those at highest risk. However this would require data on age distributions by socio-economic circumstances.

Table 1: Results of literature search

#	*Searches*	*Results*	*Notes*
1	Rotavirus Infections/ or Rotavirus/	7582	
2	Diarrhoea, Infantile/ or Diarrhoea/	38190	
3	Incidence/	131317	
4	Hospitalization/	56027	
5	3 or 4	184574	Incidence or hospitalization
6	1 and 2 and 5	237	RV and Diarrhoea and (Incidence or hospitalisation)
7	Fetal Mortality/ or Child Mortality/ or Infant Mortality/ or Hospital Mortality/ or Mortality/	63356	All relevant mortality categories
8	1 and 7	5	RV and all mortality categories.
9	6 or 8	242	[RV and D. and (Incid. or Hosp.)] and [RV and All Mort.]
10	limit 4 to (English language and humans and year ="1980 -Current")	200	Limit to Humans, +1980 and English Language.

Table 2: Results of attempts to contact possible informants

Outcome	*n of respondents*	*%*
Contact details incomplete/incorrect	16	8.4%
Contact details correct, no response	85	44.5%
Contact made, unable to help	18	9.4%
Contact made, redirected	16	8.4%
Contact made; data/reanalysis not ruled out but no commitment	18	9.4%
Agreed to prepare suitable data; nothing arrived yet	9	4.7%
Data supplied	29	15.2%
	191	100.0%

Note: some sources provided more than one dataset

Table 3: Breakdown of studies by defining event

Defining event	*n of studies*	*%*
Hospital inpatient with RVGE	33	85%
Mixed: hospital inpatient with RVGE, or hospital rehydration therapy	1	2.5%
Attendance at a hospital casualty/ER or outpatient department with RVGE	2	5%
Positive test for RV in laboratory-based surveillance	2	5%
An episode of RVGE in a prospective outreach study	1	2.5%
Total	38	100%

Table 4: Basis for attribution to rotavirus

Test	*n of studies*	*%*
EIA/ELISA only	32	82.5%
RT-PCR only	2	5%
Latex agglutination (LA) only	1	2.5%
RT-PCR + ELISA	1	2.5%
ELISA (65%) or electron microscopy or LA	1	2.5%
ELISA or LA or PAGE	1	2.5%
	38	100%

Table 5: Information about included studies

Region	Source	Ref	Country	Sub-national region/city	Start	End	Age	RVGE event	test	Number in study	age distribution 0-11m	36-59m
AFRO	Nokes J	1	Kenya	Kilifi	2002	2004	< 5y	hospital admission	EIA	584	63%	1.7%
	Turner AM	1	Malawi	Blantyre	1997	2007	< 5y	hospital admission	ELISA	790	79%	0.1%
	Turner AM	1	Malawi	Blantyre	1997	2007	< 5y	outpatient visit	ELISA	436	77%	0.0%
	Seheri LM	1	South Africa		2003	2004	< 5y	hospital admission	EIA	255	79%	1.6%
AMRO	Racz ML	1	Brazil	Sao Paolo, Salvador, Porto Alegre, Goiania	2005	2006	< 5y	hosp + ORT/IVRT	EIA	221	42%	10.4%
	Diaz Tito J	1	Chile	Santiago	2007	2010	< 5y	laboratory surveillance	ELISA	942	50%	5.7%
	Clark HF		USA	Philadelphia	1994	2006	<5y	hospital visit	ELISA, RT-PCR	1,574	54%	7.9%
EMRO	Ashmony H		Afghanistan		2007	2009	< 5y	sentinel hospital surveillance	ELISA	787	72%	1.5%
	Ashmony H		Egypt		2007	2009	< 5y	sentinel hospital surveillance	ELISA	1,310	65%	3.4%
	Ashmony H		Iran	`	2007	2009	< 5y	sentinel hospital surveillance	ELISA	2,094	49%	8.3%
	Ashmony H		Iraq		2007	2009	< 5y	sentinel hospital surveillance	ELISA	607	73%	4.6%
	Ashmony H		Jordan		2007	2009	< 5y	sentinel hospital surveillance	ELISA	251	69%	1.2%
	Ashmony H		Libya		2007	2009	< 5y	sentinel hospital surveillance	ELISA	936	67%	3.6%
	Ashmony H		Morocco		2007	2009	< 5y	sentinel hospital surveillance	ELISA	671	58%	7.6%
	Ashmony H		Oman		2007	2009	< 5y	sentinel hospital surveillance	ELISA	1,156	43%	6.1%
	Ashmony H		Pakistan		2007	2009	< 5y	sentinel hospital surveillance	ELISA	1,796	57%	5.3%
	Ashmony H		Sudan		2007	2009	< 5y	sentinel hospital surveillance	ELISA	1,271	68%	2.0%
	Ashmony H		Syria		2007	2009	< 5y	sentinel hospital surveillance	ELISA	936	68%	1.7%
	Ashmony H		Tunis		2007	2009	< 5y	sentinel hospital surveillance	ELISA	162	50%	8.0%
	Ashmony H		Yemen		2007	2009	< 5y	sentinel hospital surveillance	ELISA	944	68%	1.8%
EURO	Atchison C	1	England & Wales	national	2003	2005	< 5y	laboratory surveillance	EM, LA, ELISA	39,966	44%	6.8%
	Gendrel D		France	Paris (Saint-Vincent-de-Paul Hospital)	1997	2001	< 3y	hospital admission	ELISA	473	74%	3.4%
	Dagan R		Israel		2006	2010	< 5y	hosp admission	ELISA	383	60%	1.6%
	Medici MC	1	Italy	Parma	2003	2010	< 5y	hosp admission	EM, PAGE, LA	839	27%	15.3%
	Flem ET	1	Kyrgyzstan	Bishkek, Osh	2008	2009	< 5y	hosp admission	ELISA	849	58%	2.9%
	Podkolzin AT	1	Russian Fed	various cities	2005	2007	< 5y	hosp admission	PCR	820	45%	8.4%
	Flem ET	1	Uzbekistan	Tashkent, Bukhara	2005	2009	< 5y	hosp admission	ELISA	2,632	43%	6.8%
SEARO	Zaman	20	Bangladesh	Matlab intervention area	2000	2007	< 5y	hospital admission	ELISA	1,375	57%	0.8%
	Kang G	1	India	Trichy, Vellore	2005	2007	< 5y	hospital admission	ELISA	475	59%	2.5%
	Kang G	1	India	New Delhi	2005	2007	< 5y	hospital admission	ELISA	229	62%	3.5%
	Kang G	1	India	Vellore	2002	2006	< 5y	outreach episode	LA	270	64%	0.0%
	Maneekarn N	1	Thailand	Chaing Mai	2000	2007	< 2y	hospital admission	RT-PCR	497	45%	7.0%
WPRO	Fox K	1	Fiji	Suva and in last few months, Savu Savu also incl	2008	2010	< 5y	hospital admission	ELISA	257	44%	7.0%
	Fox K	1	Lao	Vientiane	2009	2010	< 5y	hospital admission	ELISA	334	43%	2.7%
	Fox K	1	Mongolia	Ulaan Baatar (2 hospitals)	2009	2009	< 5y	hospital admission	ELISA	394	74%	1.0%
	Grimwood K	1	New Zealand	8 centres	1998	2000	< 3y	hospital admission	ELISA	551	44%	1.3%
	Fox K		PNG	Goroka, Eastern Highlands Province	2008	2009		hospital admission	ELISA	152	64%	2.6%
	Fox K		Vietnam	Hanoi, Ho Chi Minh, Khan Hoa	2009	2009		hospital admission	ELISA	1,277	49%	5.0%

Table 6: Age at rotavirus event in weeks: mean, median and cumulative distribution, observed and for fitted gamma distributions

		Observed, children < 36m			Schedule				Window			***Fitted gamma***			
Region	*Country*	*n*	*mean*	*median*	*9w*	*13w*	*17w*	*26w*	*6w*	*15w*	*32w*	*mean*	*std*	*shift*	*WRMSQE**
AFRO	Kenya	574	48.8	44.1	1.0%	2.6%	7.5%	18.5%	0.3%	5.1%	30.5%	47.8	25.3	-0.2	0.18%
	Malawi ip	789	36.3	31.9	4.9%	9.6%	15.2%	38.8%	2.5%	12.9%	50.2%	36.5	19.1	1.7	0.28%
	Malawi op	436	39.9	35.8	2.3%	5.3%	10.1%	28.0%	0.7%	6.7%	42.7%	38.4	21.3	-2.0	0.27%
	S Africa ip	251	39.3	32.0	1.9%	5.5%	14.3%	36.0%	0.6%	9.9%	50.0%	34.8	18.2	0.0	0.16%
AMRO	Brazil	198	62.6	54.9	1.5%	2.5%	4.0%	9.1%	0.5%	3.0%	15.2%	65.8	27.0	6.5	0.24%
	Chile	888	54.7	50.0	4.1%	8.1%	11.6%	23.4%	1.7%	9.3%	31.4%	59.3	42.1	0.5	0.15%
	USA	1449	51.2	44.6	10.6%	15.1%	19.5%	30.2%	6.1%	17.3%	36.9%	57.3	49.7	0.0	0.15%
EMRO	Afghanistan	775	43.0	36.4	1.8%	5.4%	10.7%	27.9%	0.2%	7.6%	40.7%	39.5	20.8	0.0	0.17%
	Egypt	1265	45.6	38.6	2.4%	6.3%	11.9%	26.6%	0.5%	8.7%	38.6%	42.5	24.8	0.0	0.25%
	Iran	1921	56.2	48.3	2.8%	4.6%	7.0%	15.0%	1.6%	5.7%	23.2%	68.8	24.4	17.2	0.14%
	Iraq	579	39.6	31.6	5.0%	10.7%	18.1%	37.4%	1.7%	13.8%	50.8%	35.8	21.3	0.0	0.22%
	Jordan	248	43.1	34.5	3.7%	8.0%	14.4%	32.7%	1.5%	10.6%	45.1%	35.7	24.8	-5.0	0.23%
	Libya	902	46.1	37.3	2.8%	6.1%	10.3%	24.3%	0.8%	7.8%	38.2%	48.3	20.5	10.1	0.29%
	Morocco	620	50.0	39.1	4.2%	9.0%	14.5%	26.6%	1.8%	11.9%	39.7%	46.1	29.2	0.7	0.36%
	Oman	1086	61.4	52.7	0.9%	1.8%	3.5%	10.5%	0.5%	2.3%	18.7%	54.1	29.2	-4.1	0.11%
	Pakistan	1701	49.5	39.5	7.4%	11.8%	16.9%	30.5%	1.9%	14.0%	38.2%	48.6	35.9	0.0	0.21%
	Sudan	1246	44.8	37.9	2.5%	6.5%	12.0%	25.0%	0.7%	9.0%	37.5%	47.9	22.6	6.3	0.20%
	Syria	920	44.1	37.3	1.8%	5.1%	9.8%	25.8%	0.0%	6.9%	39.1%	40.9	21.9	0.0	0.16%
	Tunis	149	53.6	45.2	3.5%	6.7%	11.7%	28.3%	1.9%	8.5%	35.3%	46.9	35.8	-5.0	0.42%
	Yemen	927	45.2	38.0	3.3%	6.3%	9.8%	24.9%	1.4%	7.8%	38.0%	47.8	20.6	7.1	0.24%
EURO	England & Wales	37267	61.5	54.9	3.0%	4.7%	6.7%	13.4%	1.8%	5.6%	20.2%	69.9	33.6	9.0	0.09%
	France	457	33.6	26.3	13.9%	21.8%	30.8%	49.5%	7.9%	26.3%	59.1%	33.0	25.6	0.0	0.14%
	Israel	377	48.5	42.7	2.7%	6.4%	10.6%	23.6%	1.9%	8.8%	30.8%	50.7	29.6	1.7	0.22%
	Italy	711	75.5	69.4	2.0%	2.7%	4.6%	8.7%	1.3%	4.2%	14.1%	85.5	48.8	4.8	0.14%
	Kyrgyzistan	824	51.6	45.2	3.5%	5.7%	8.7%	17.5%	2.2%	6.8%	25.8%	61.6	25.0	11.5	0.22%
	Russian Fed	751	62.5	52.5	2.7%	4.9%	6.5%	14.2%	2.3%	5.5%	20.2%	62.5	31.5	3.9	0.20%
	Uzbekistan	2454	60.6	55.4	1.6%	3.7%	6.2%	13.9%	0.8%	4.6%	21.8%	62.9	36.5	1.4	0.13%
SEARO	Bangladesh	1364	54.9	48.0	0.6%	1.6%	3.0%	10.2%	0.2%	2.3%	18.4%	48.0	23.0	-4.0	0.16%
	India	221	46.8	39.4	8.4%	11.7%	17.1%	29.3%	4.8%	14.4%	40.0%	52.0	32.9	6.4	0.25%
	India 2	463	51.2	44.1	4.8%	7.1%	8.6%	16.6%	3.5%	8.2%	26.6%	59.8	25.6	8.9	0.35%
	India 3	270	50.8	39.0	11.1%	14.8%	22.2%	33.7%	8.1%	17.4%	41.5%	55.8	36.3	13.6	0.25%
	Thailand	462	61.5	54.4	3.0%	5.2%	7.2%	15.3%	1.3%	6.2%	23.7%	67.3	36.7	7.2	0.25%
WPRO	Fiji	239	60.9	53.9	1.3%	3.8%	6.3%	12.6%	0.0%	4.6%	16.7%	70.2	31.1	10.4	0.21%
	Lao	325	59.6	55.6	0.0%	0.3%	2.2%	12.0%	0.0%	1.5%	21.5%	56.9	34.7	-4.0	0.25%
	Mongolia	390	41.0	38.3	3.8%	7.2%	12.1%	25.1%	1.3%	10.8%	34.9%	42.8	23.2	0.1	0.33%
	New Zealand	544	63.1	57.3	3.5%	5.1%	7.7%	15.1%	2.2%	6.8%	21.5%	64.5	38.5	1.5	0.20%
	PNG	148	45.7	43.0	2.0%	3.4%	6.1%	20.9%	2.0%	4.7%	29.7%	43.7	24.6	-4.0	0.38%
	Vietnam	1213	55.7	50.9	3.3%	5.6%	7.9%	15.7%	1.7%	6.4%	22.7%	62.6	31.7	5.9	0.18%
	Median	*665.5*	*50.4*	*43.5*	*2.9%*	*5.7%*	*10.0%*	*24.0%*	*1.5%*	*7.7%*	*33.1%*	*49.6*	*26.3*	*1.1*	*0.21%*
	25th %ile	*380.3*	*44.9*	*37.9*	*1.9%*	*4.6%*	*6.8%*	*15.0%*	*0.6%*	*5.5%*	*22.0%*	*43.0*	*23.1*	*0.0*	*0.16%*
	75th %ile	*1046.3*	*58.8*	*52.1*	*4.0%*	*7.8%*	*13.7%*	*28.2%*	*2.0%*	*10.4%*	*39.6%*	*62.3*	*34.4*	*6.5*	*0.25%*

* WMSQE = weighted mean square error

Table 7: Age at RVGE related to gross national income per capita and infant mortality

% of cases before age	*studies included*	*variables in model*[1]	*GNI per capita $I*		*lnfM*	
			coeff	*p*	*coeff*	*p*
6 weeks	all	one	0.0012	0.10	-0.0004	0.29
		two	0.0011	0.21	-0.0001	0.88
	all but 3 outliers	one	0.0002	0.72	-0.0002	0.47
		two	0.0000	0.97	-0.0002	0.53
	EMRO only	one	-0.0004	0.58	-0.0001	0.76
		two	-0.0006	0.47	-0.0002	0.56
15 weeks	all	alone	0.0001	0.88	0.0002	0.73
		together	0.0005	0.67	0.0003	0.60
	all but 3 outliers	one	-0.0017	*0.05*	0.0006	0.17
	EMRO only	one	-0.0029	*0.00*	0.0005	0.41
32 weeks	all	one	-0.0019	0.19	0.0016	*0.03*
		two	-0.0002	0.89	0.0015	0.10
	all but 3 outliers	one	-0.0039	*0.01*	0.0020	*0.00*
		two	-0.0023	0.17	0.0014	0.07
	EMRO only	one	-0.0042	*0.00*	0.0007	0.38
		two	-0.0043	*0.01*	-0.0001	0.83

1: independent variables: one = either GNI *or* infant mortality; both = GNI *and* infant mortaliity

Table 8: England and Wales: year to year variation in age at infection

Year of infection	*n of subjects*	mean age *(weeks)*	*percentiles and median*		
			p5	*p10*	*median*
1998	13,464	70.7	12.9	21.0	59.4
1999	13,483	72.2	13.7	21.9	60.6
2000	13,708	74.9	16.0	23.9	63.0
2001	14,244	74.0	16.3	23.4	61.4
2002	12,746	75.3	15.0	23.6	62.6
2003	13,605	71.9	14.6	22.7	59.1
2004	13,610	69.5	14.1	22.4	57.0
2005	12,751	70.4	14.4	22.9	58.4
2006	12,627	68.8	13.7	22.4	57.0
2007	11,255	70.5	17.1	25.0	58.6

Table 9: Age distributions for hospital admission with RV diarrhoea vs any diarrhoea

	diarrhoea	*subjects*	*mean*	*median*	*6w*	*9w*	*13w*	*17w*	*26w*	*35w*
Kenya	RV	574	48.8	44.1	0.5%	1.0%	2.6%	7.5%	16.9%	32.2%
	any	2,893	59.0	51.2		5.4%	8.7%	12.7%	22.8%	33.6%
Chile	RV	888	54.7	50.0	1.7%	3.8%	7.0%	10.2%	20.7%	31.4%
	any	3,281	49.7	42.5	4.6%	7.4%	11.5%	16.1%	27.1%	38.3%
Fiji	RV	239	60.9	53.9	0.0%	0.8%	2.1%	5.9%	11.3%	16.7%
	any	800	62.0	53.7	0.9%	2.1%	3.9%	6.4%	11.4%	18.5%
Lao	RV	325	59.6	55.6	0.0%	0.0%	0.0%	1.8%	9.8%	21.5%
	any	500	56.1	53.4	0.4%	0.6%	1.8%	4.0%	12.2%	25.6%
Mongolia	RV	390	41.0	38.3	1.3%	2.6%	6.9%	11.3%	23.6%	34.9%
	any	1,011	42.1	37.6	1.2%	2.1%	7.4%	13.3%	25.3%	38.1%
PNG	RV	148	45.7	43.0	2.0%	2.0%	3.4%	5.4%	17.6%	29.7%
	any	514	46.6	40.8	1.6%	1.9%	3.5%	9.7%	24.5%	35.6%
Vietnam	RV	1,213	55.7	50.9	1.7%	2.6%	5.1%	7.1%	13.5%	22.7%
	any	1,776	55.7	50.6	1.7%	2.8%	5.0%	7.2%	13.7%	23.3%

Table 10: Age at RVGE event, vaccine coverage at 12m, and % of cases unprotected, based on national survey data on vaccine timeliness for OPV

Country	*median age (m) at RVGE**	*% of all RVGE by age < 6w**	*% of all RVGE by age < 12m**	*% of RVGE aged < 12m unprotected by*			*OPV3 coverage at age 12m*
				dose 1	*dose 2*	*dose 3*	
Kenya	44.1	0.3%	64.3%	8.7%	17.0%	36.4%	76.6%
Malawi	31.9	2.5%	78.7%	11.3%	25.0%	43.5%	91.3%
Egypt	38.6	0.5%	68.7%	5.7%	21.7%	47.0%	93.5%
Iraq	31.6	1.7%	78.2%	23.8%	49.3%	69.9%	74.9%
Jordan	34.5	1.5%	71.1%	8.8%	20.1%	35.1%	97.0%
Uzbekistan	55.4	0.8%	46.5%	7.3%	18.2%	23.3%	99.6%
Bangladesh	48.0	0.2%	57.3%	4.4%	11.4%	22.5%	90.1%
India2	44.1	3.5%	60.0%	16.0%	26.6%	43.2%	75.0%
India3	39.0	8.1%	64.1%	29.2%	43.9%	60.2%	75.0%
Lao	55.6	0.0%	44.6%	23.2%	47.9%	68.8%	57.7%
Mongolia	38.3	1.3%	74.9%	6.0%	12.3%	23.7%	94.5%
Thailand	54.4	1.3%	48.3%	8.1%	22.8%	45.3%	96.7%
Vietnam	50.9	1.7%	51.3%	15.1%	20.2%	27.9%	95.4%

* in children aged < 36m

Figure 4: Proportion of children with a rotavirus event by age 6 weeks

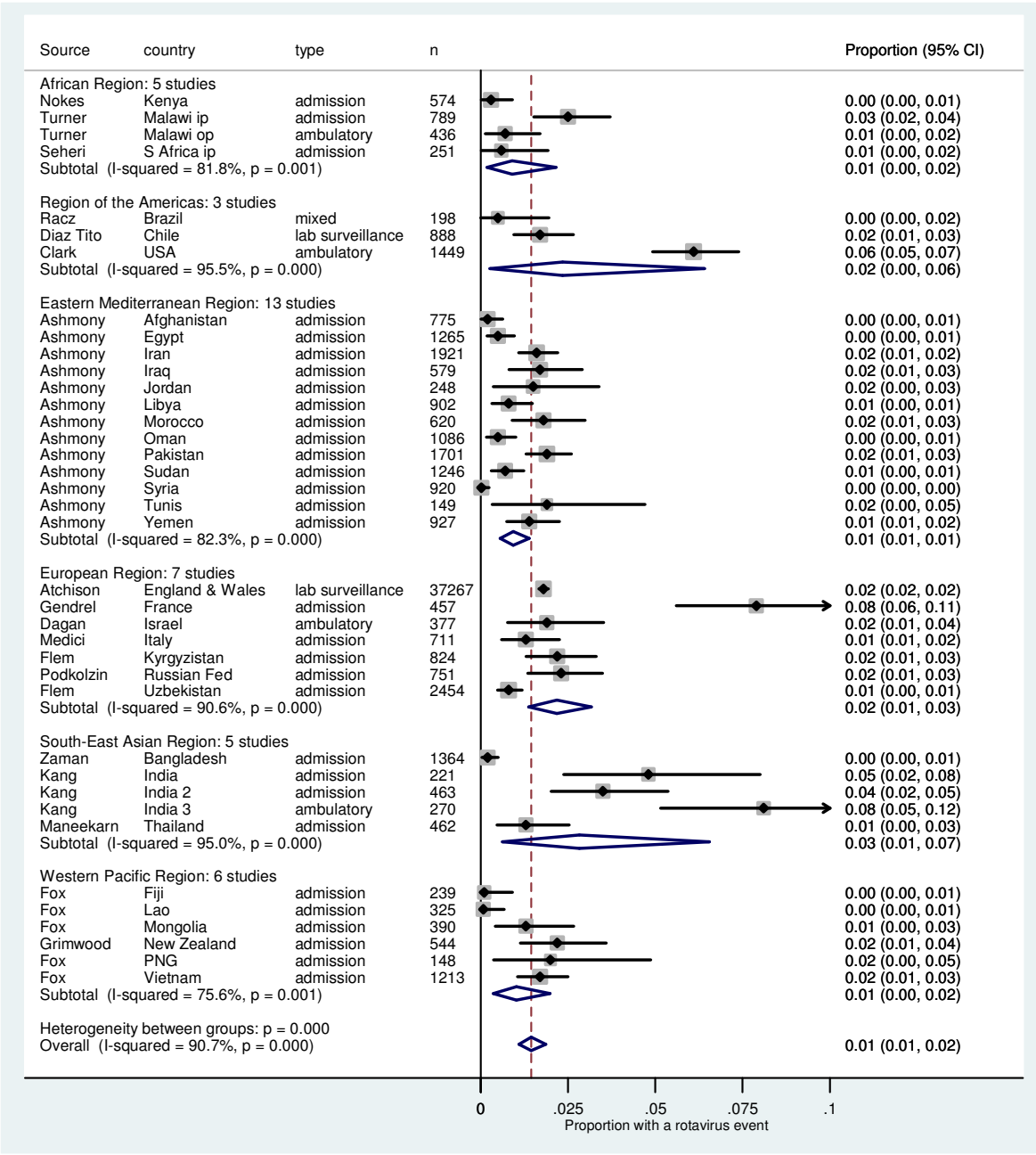


Figure 5: Proportion of children with a rotavirus event by age 9 weeks

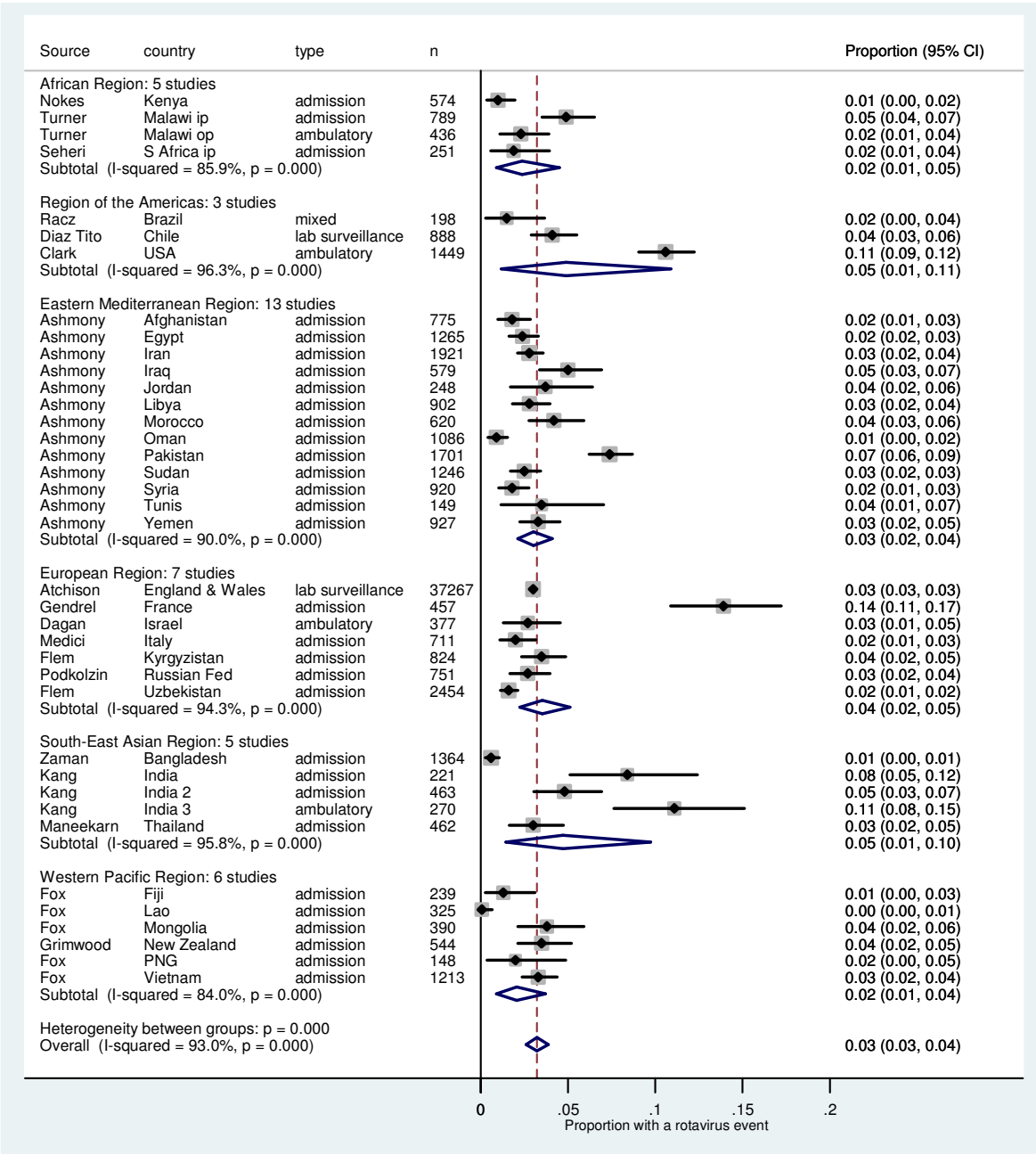


Figure 6: Proportion of children with a rotavirus event by age 13 weeks

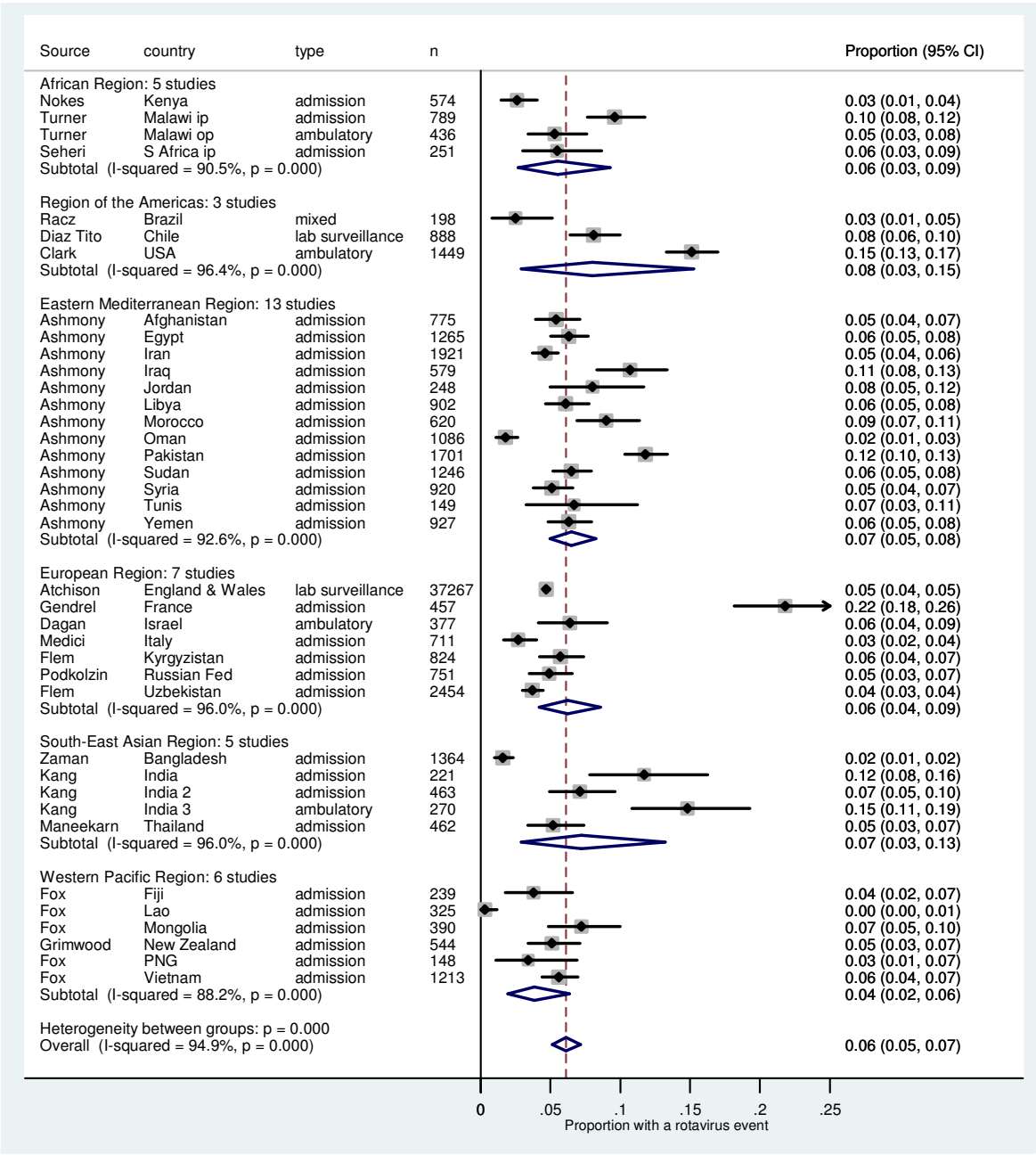


Figure 7: Proportion of children with a rotavirus event by age 15 weeks

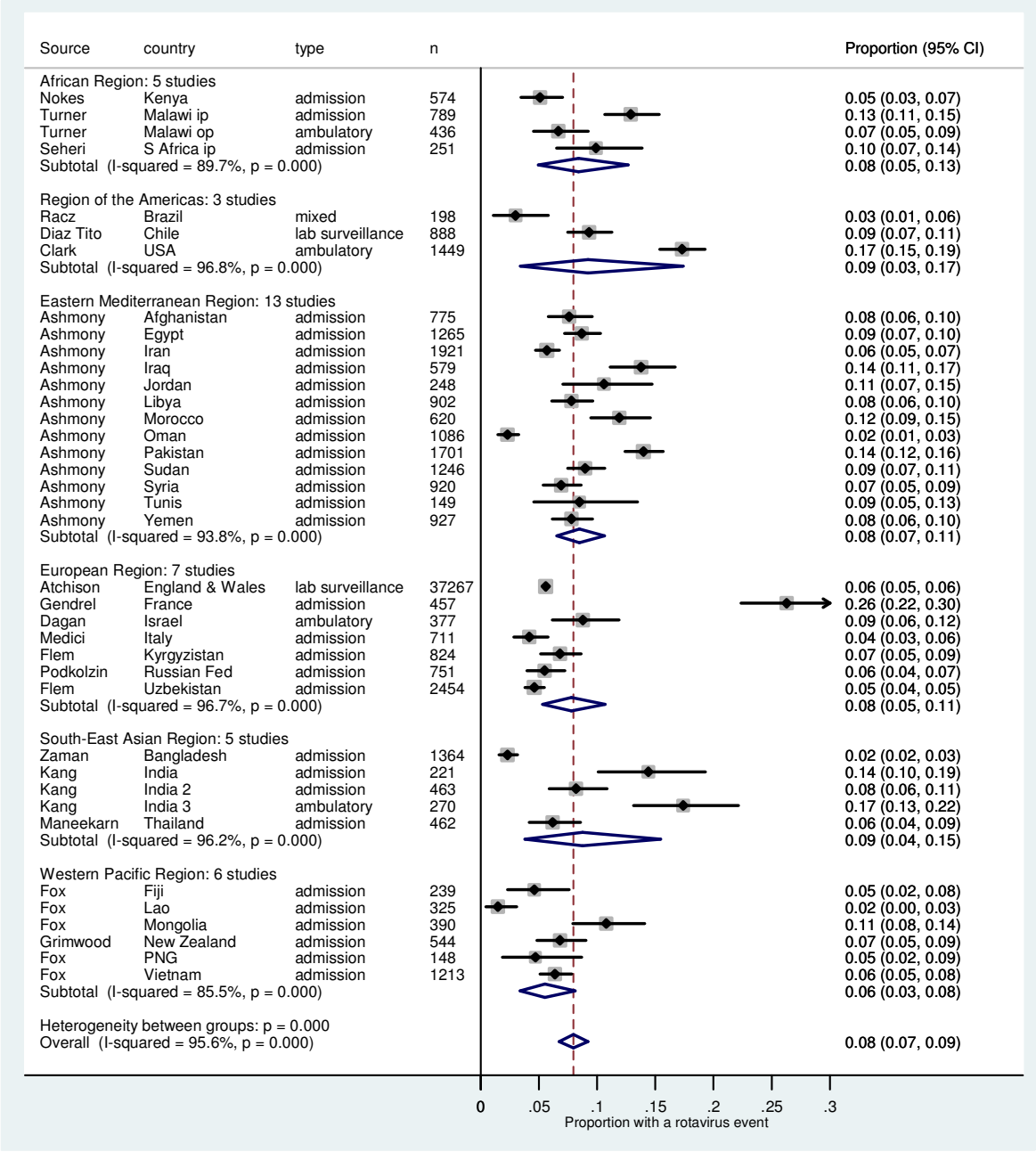


Figure 8: Proportion of subjects with a rotavirus event by age 17 weeks

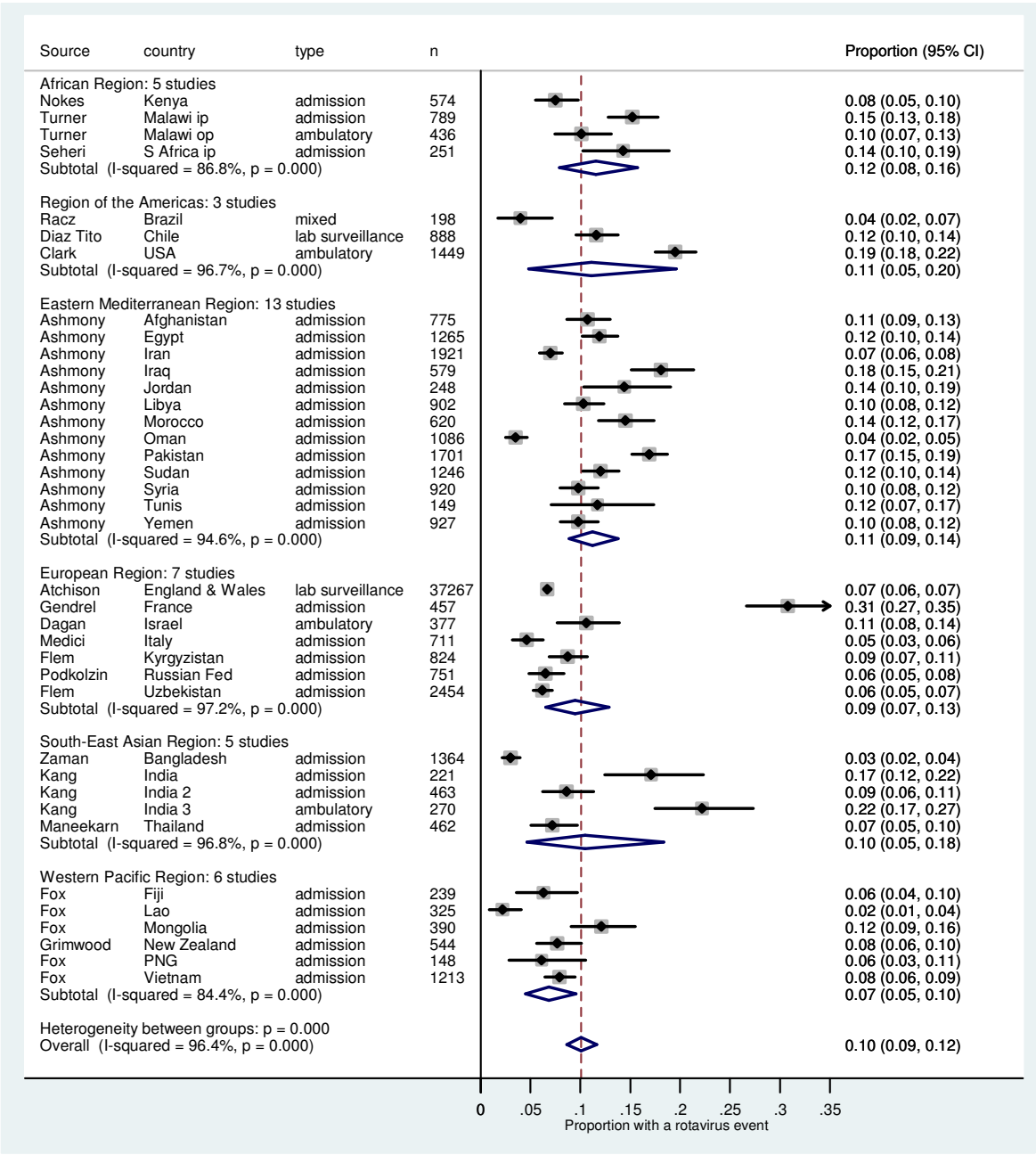


Figure 9: Proportion of subjects with a rotavirus event by age 26 weeks

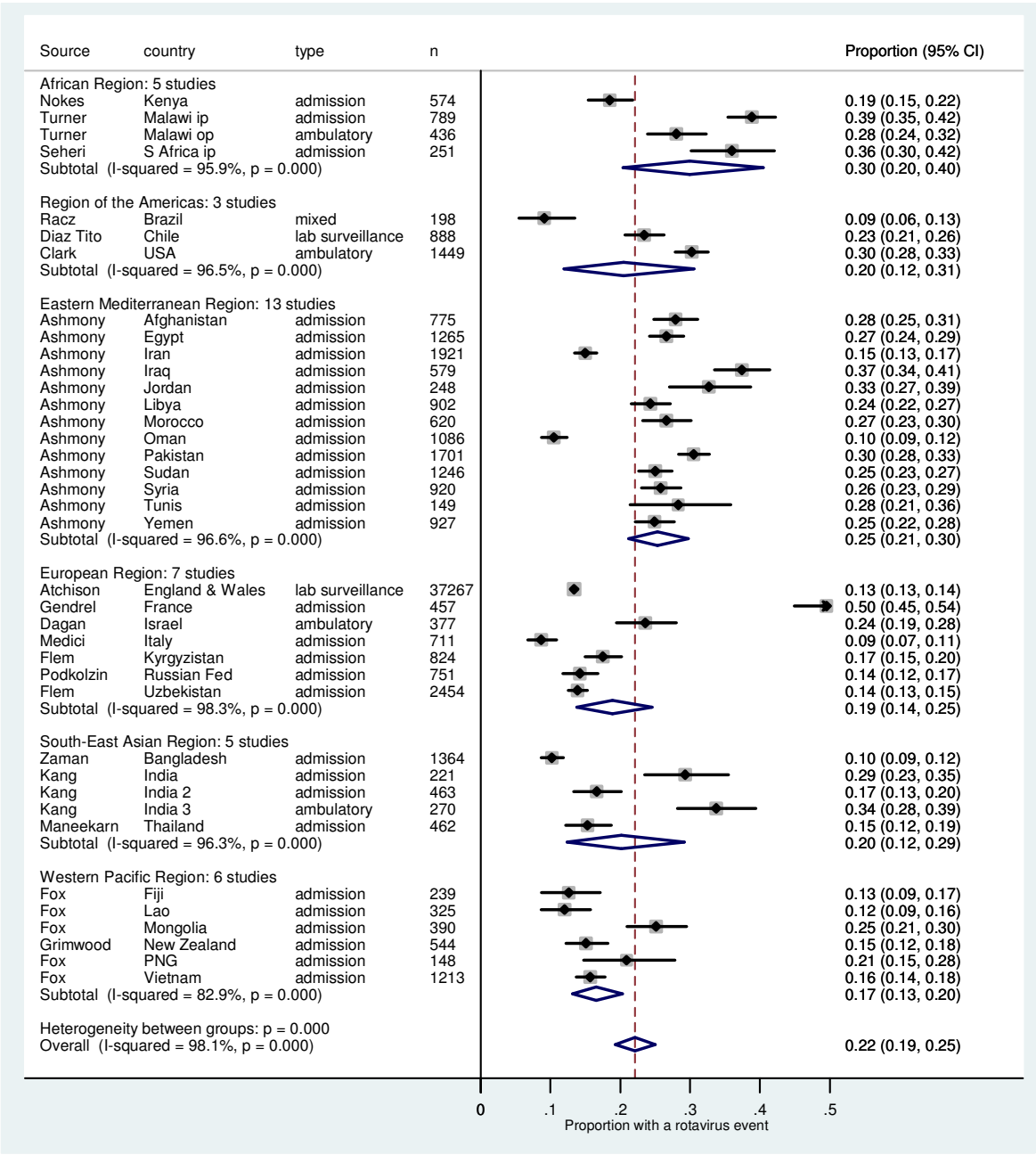


Figure 10: Proportion of subjects with a rotavirus event by age 32 weeks

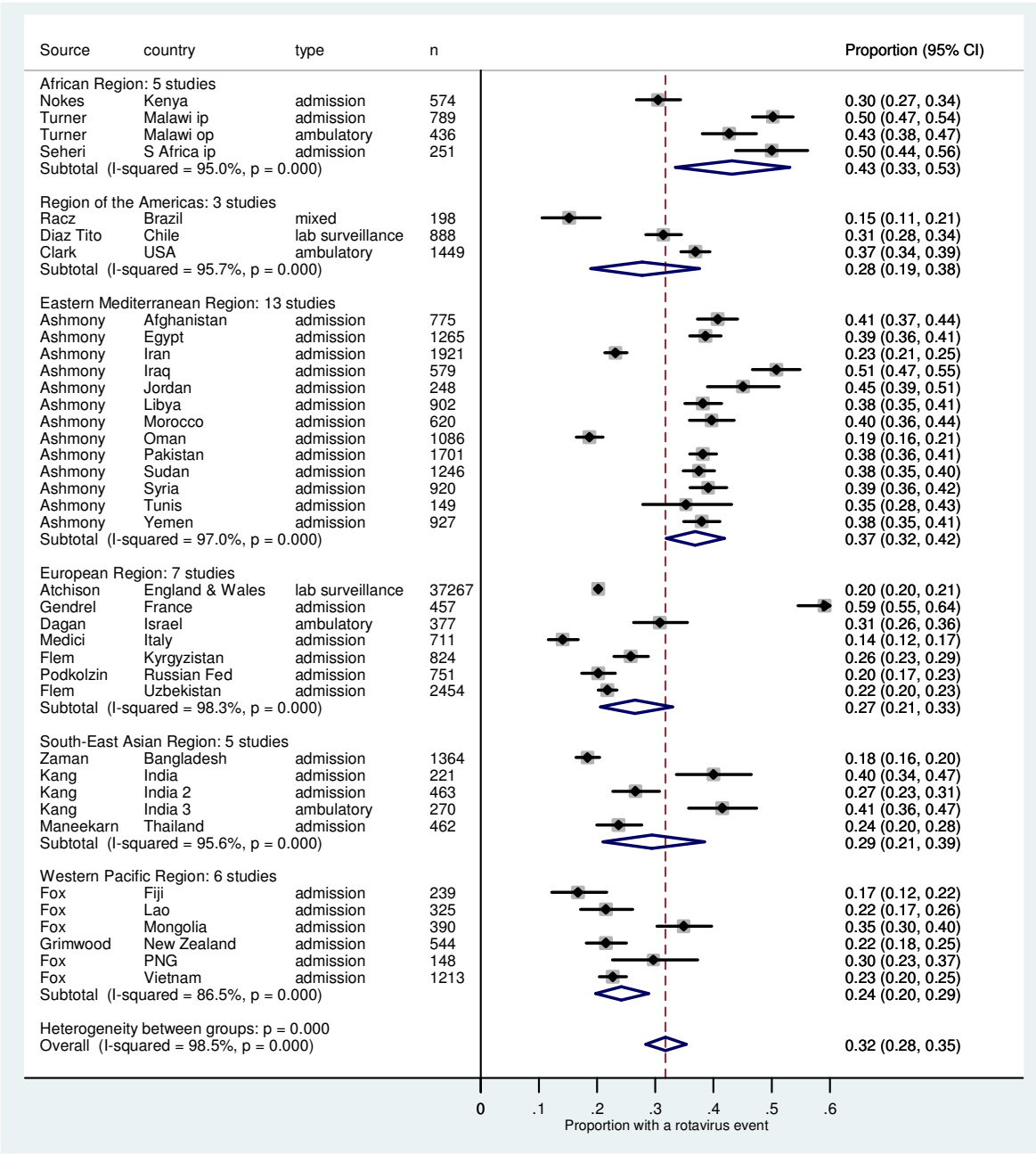


Figure 11: Fitting the gamma distributions: fit to large datasets

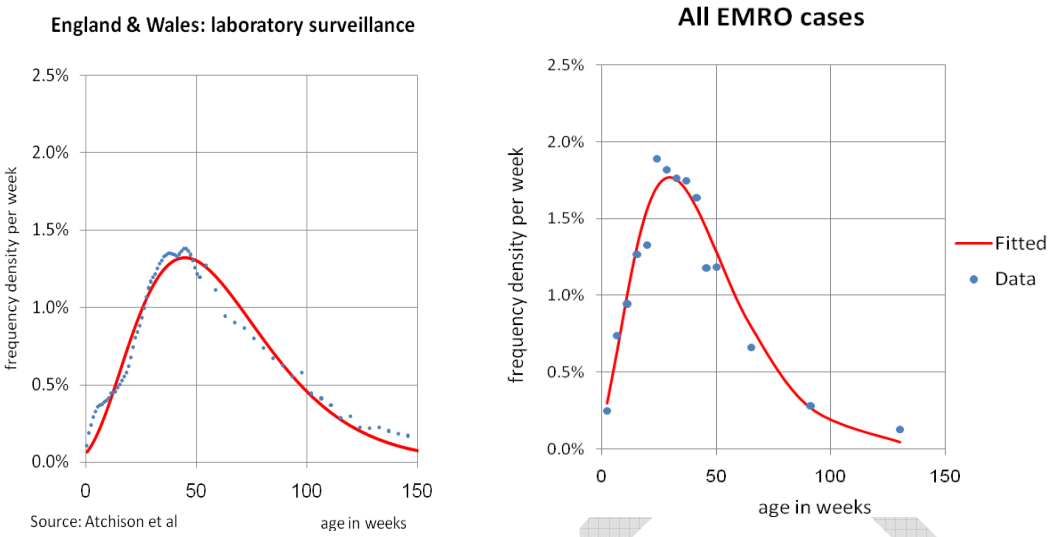


Figure 12: Fitting the gamma distributions allowing for left and right shifts

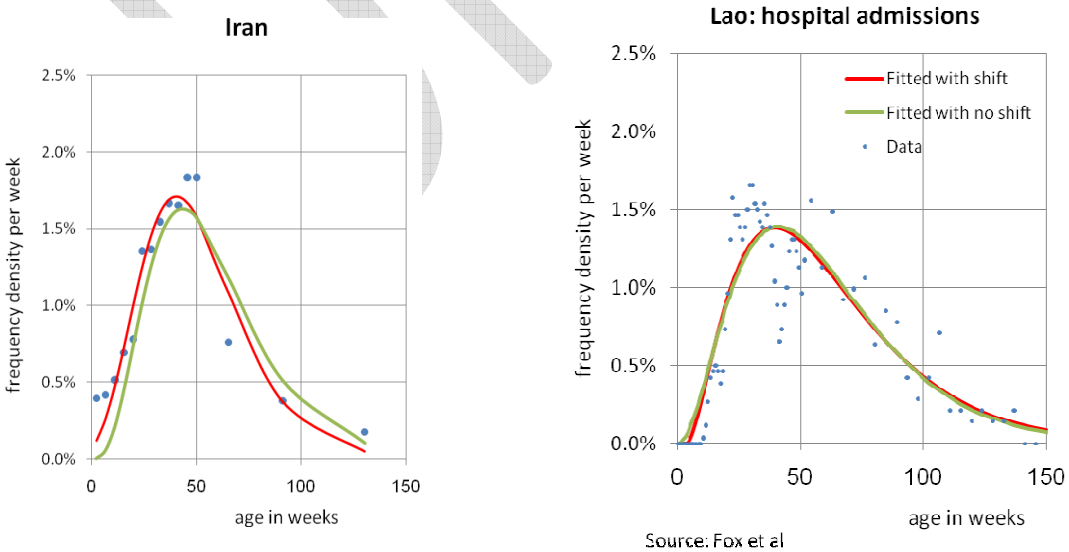


Figure 13: Observed ( ) vs modelled ( ) distributions: African region (AFRO)

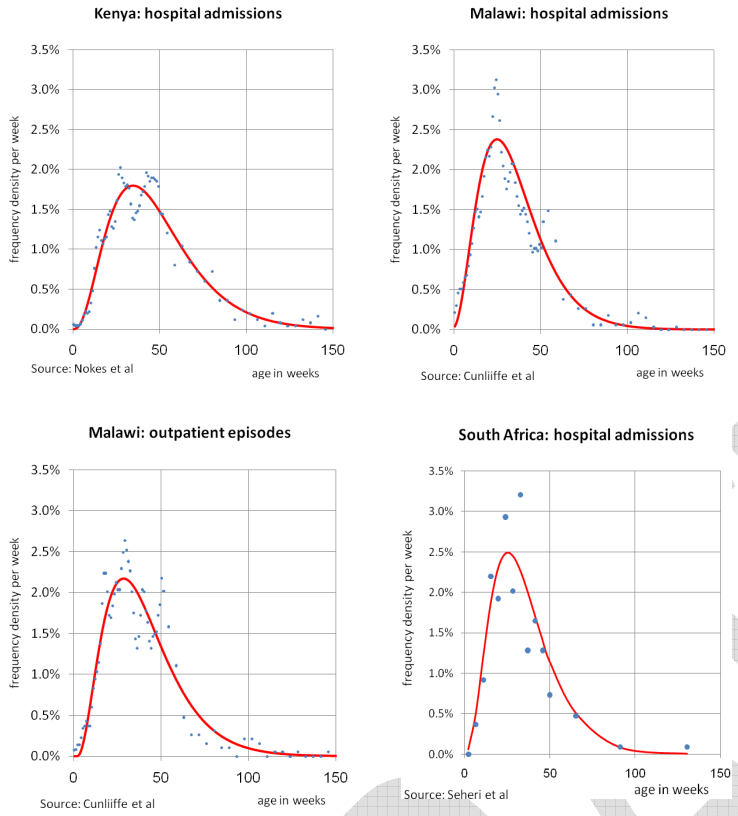


Figure 14: Observed ( ) vs modelled ( ) distributions: Region of the Americas (AMRO)

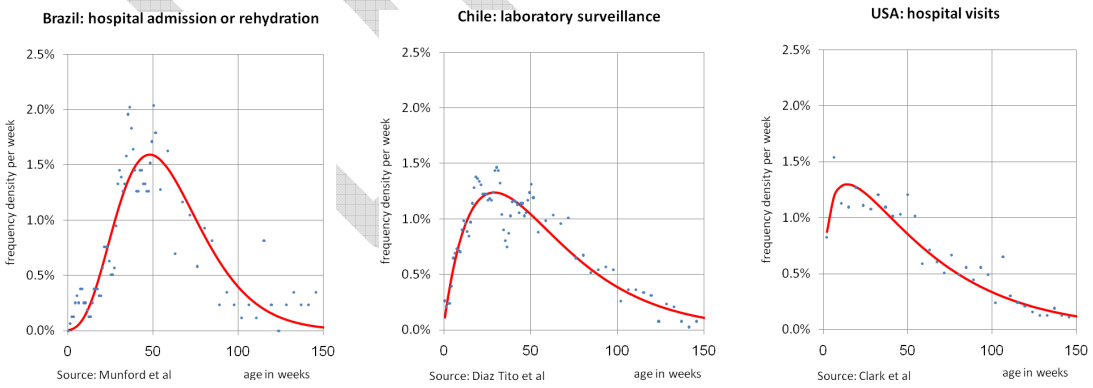


Figure 15: Observed ( ) vs modelled ( ) distributions: Eastern Mediterranean region (EMRO)

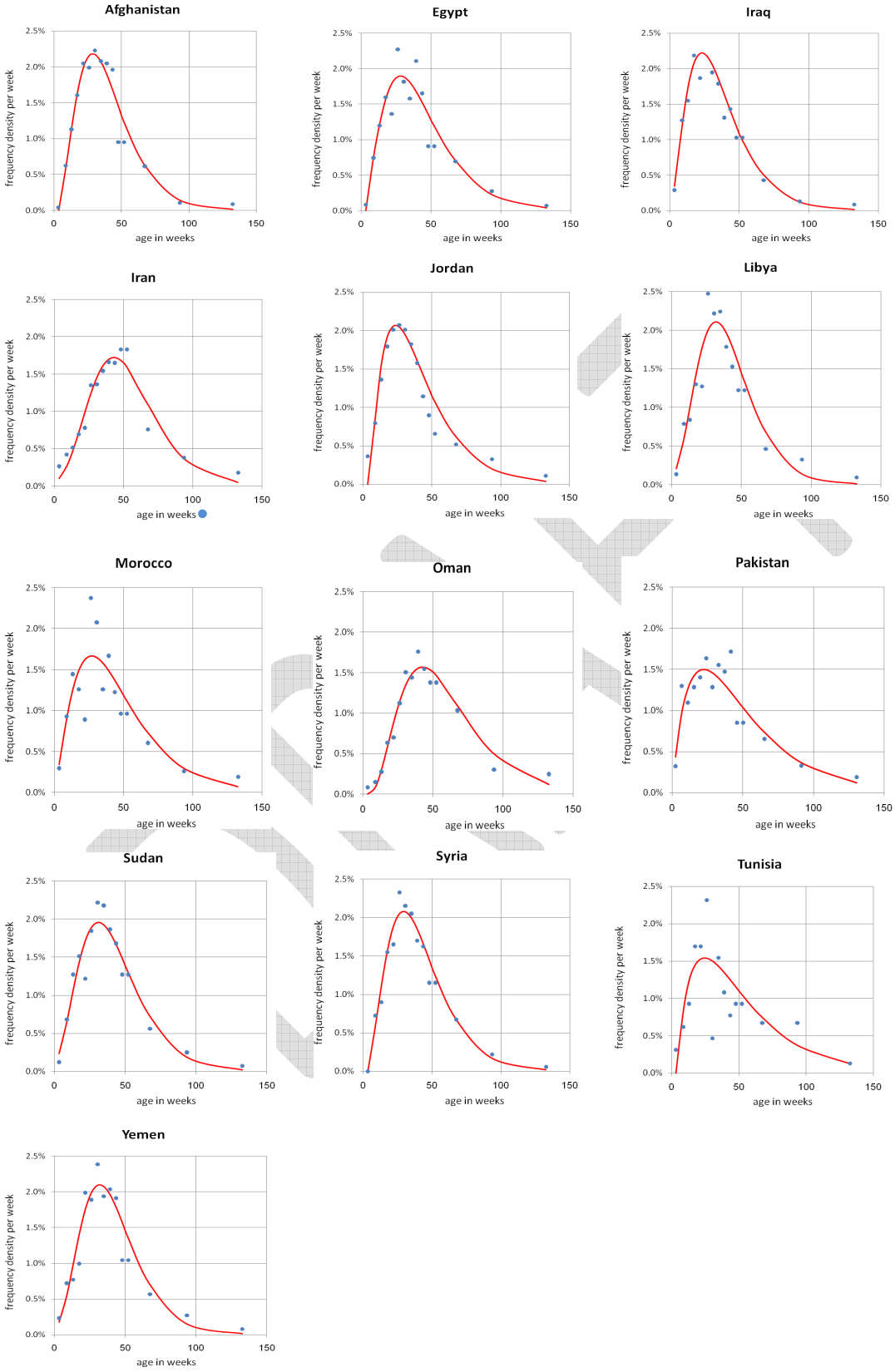


Figure 16: Observed (●) vs modelled (——) distributions: European region (EURO)

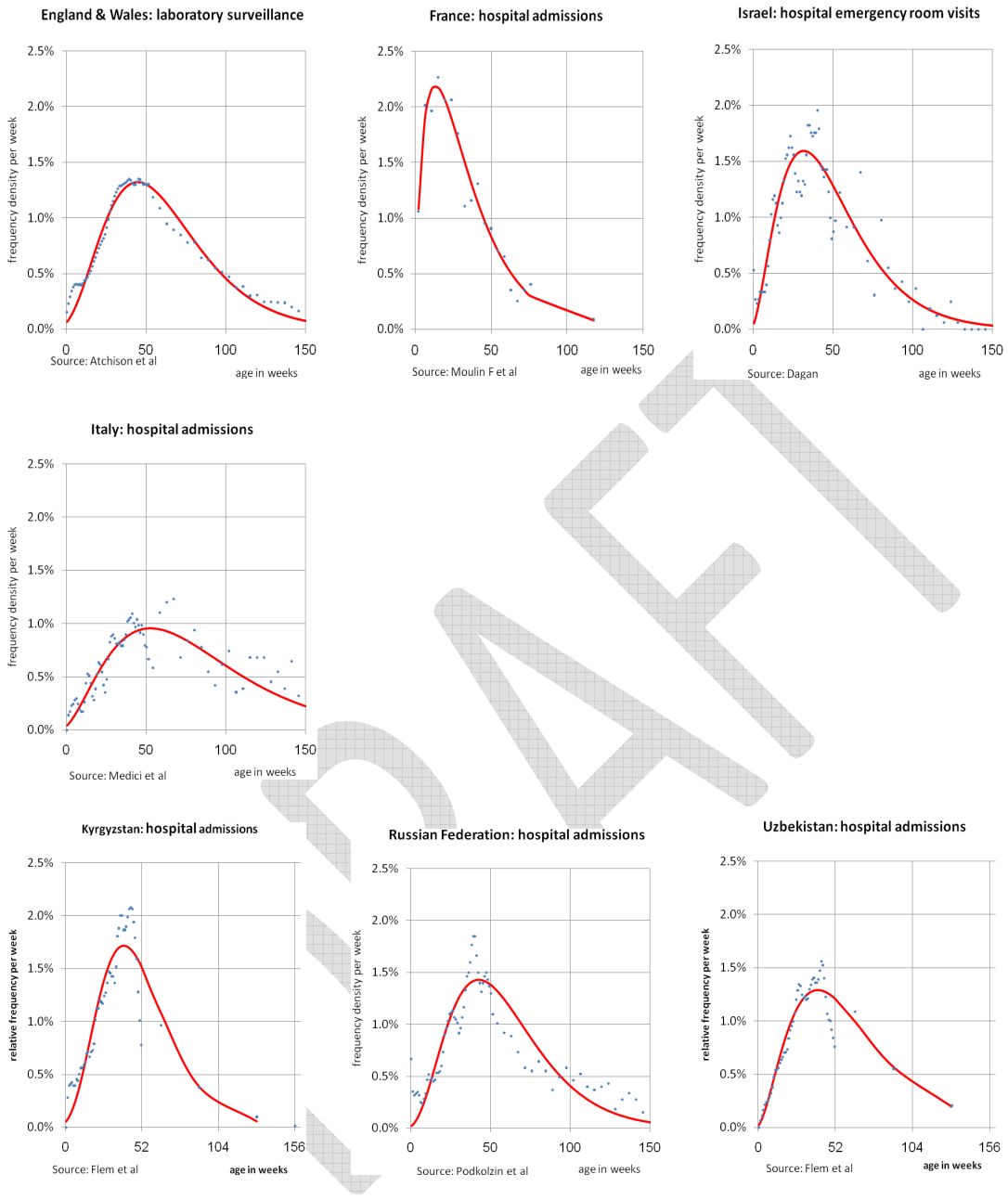


Figure 17: Observed (●) vs modelled (——) distributions: South East Asian Region (SEARO)

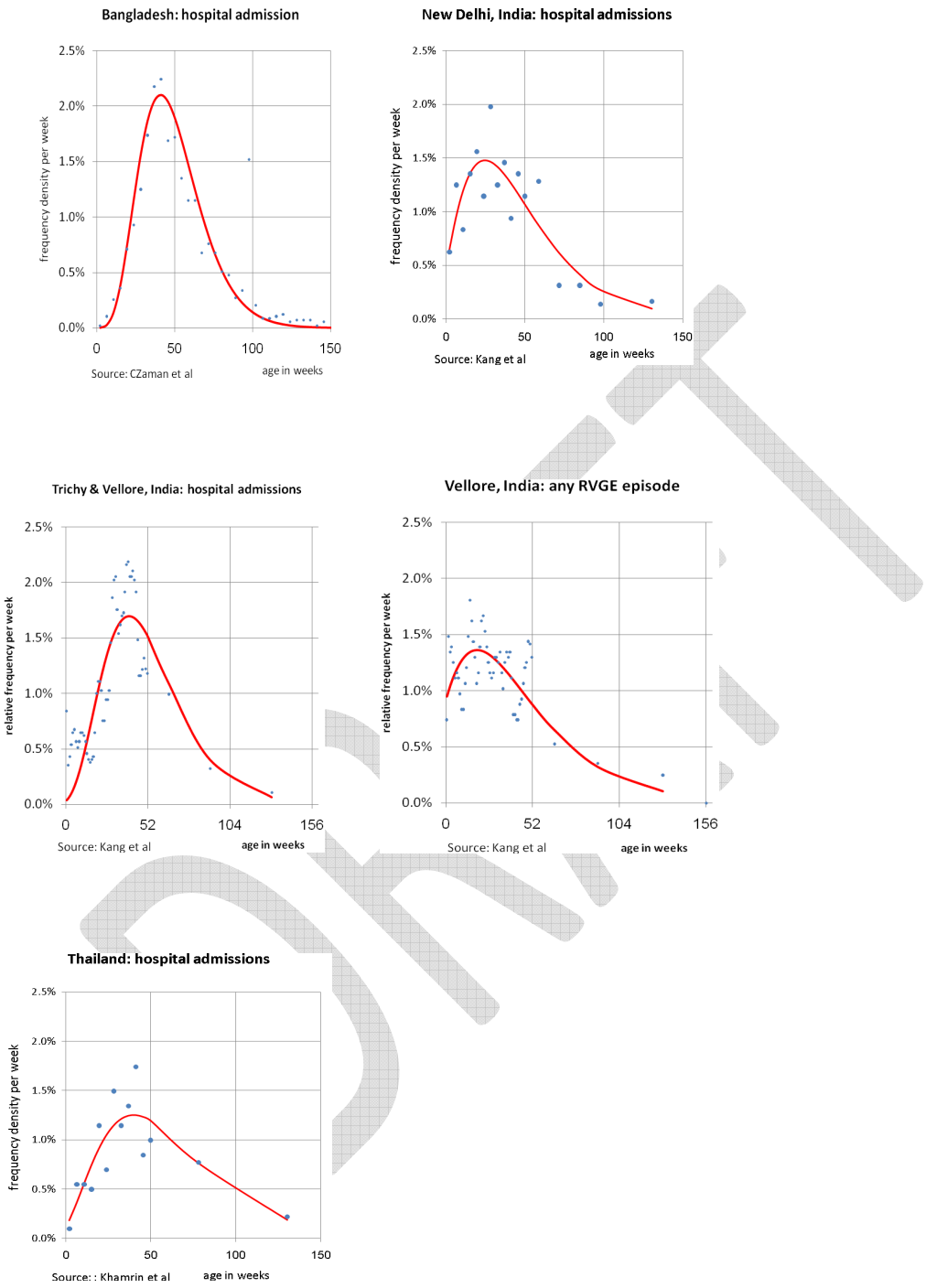


Figure 18: Observed (●) vs modelled (——) distributions: Western Pacific Region (WPRO)

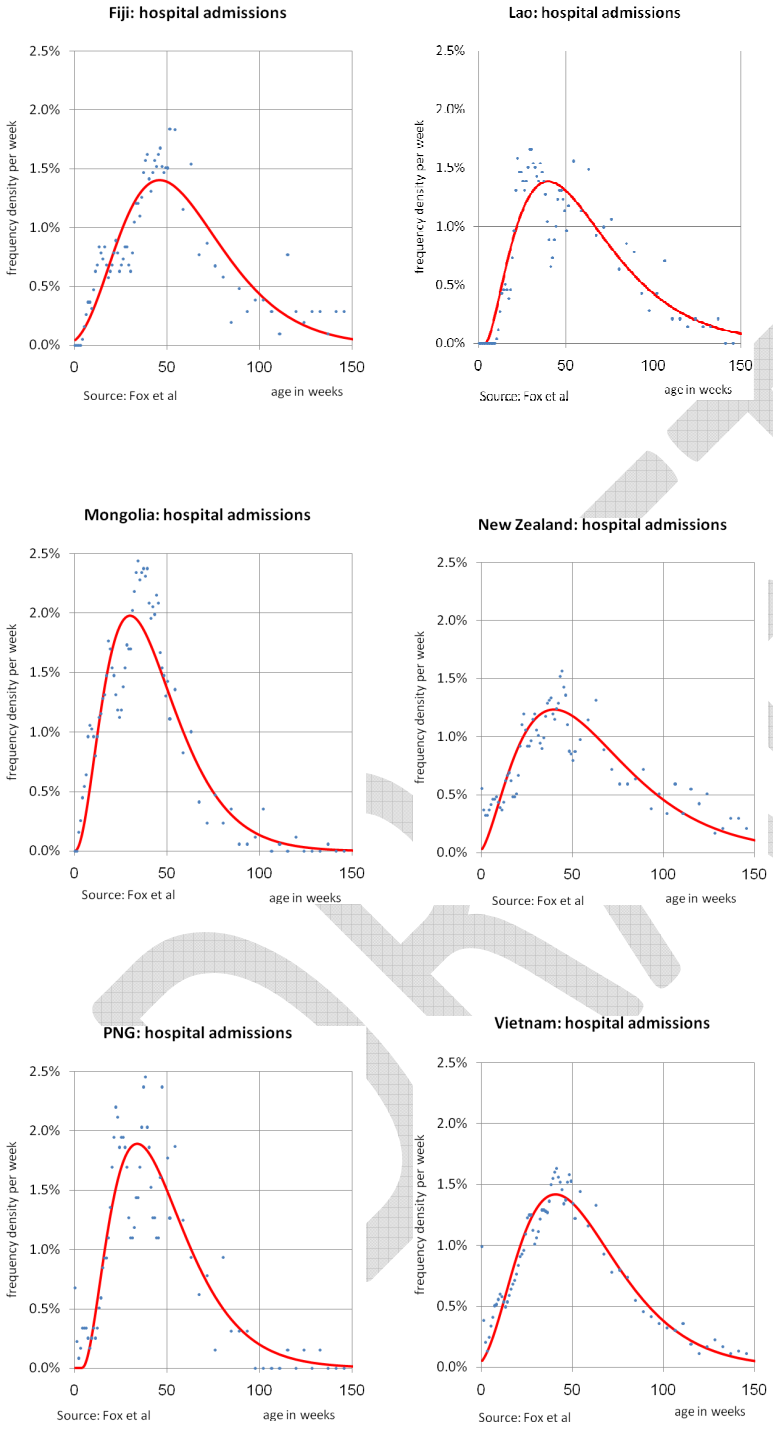


Figure: 19: Proportion of under-age-36m RVGE cases by 6 weeks of age vs GNI per capita

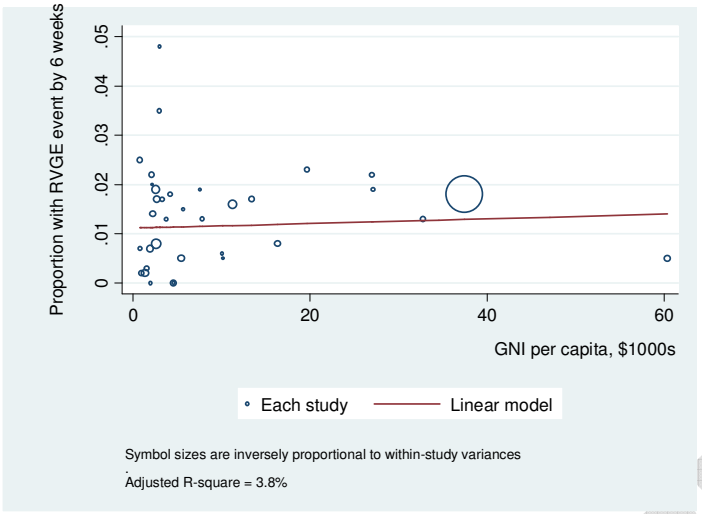


Figure: 20: Proportion of under-age-36m RVGE cases by 15 weeks of age vs GNI per capita

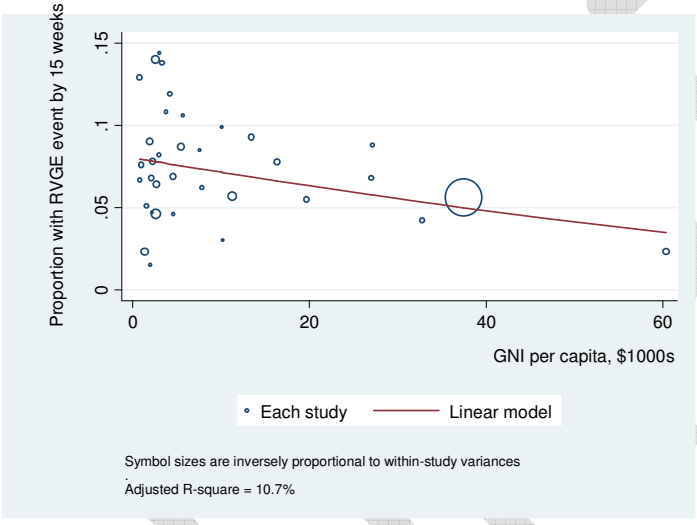


Figure 21: Proportion of under-age-36m RVGE cases by 32 weeks of age vs GNI per capita

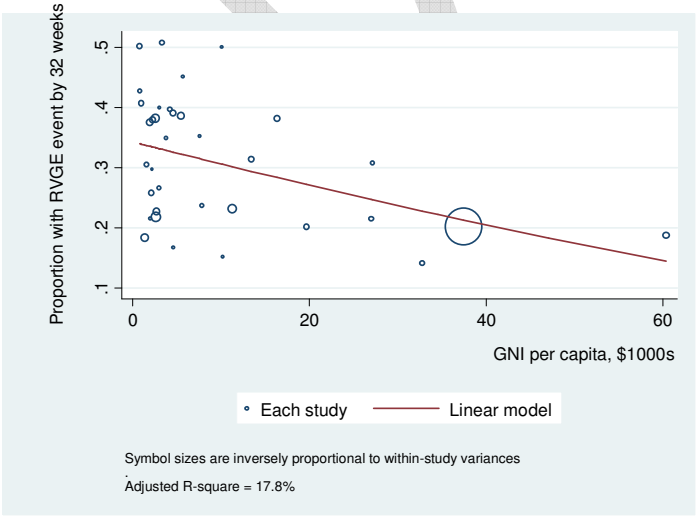


Figure 22: Age distributions of RV deaths vs RV admissions

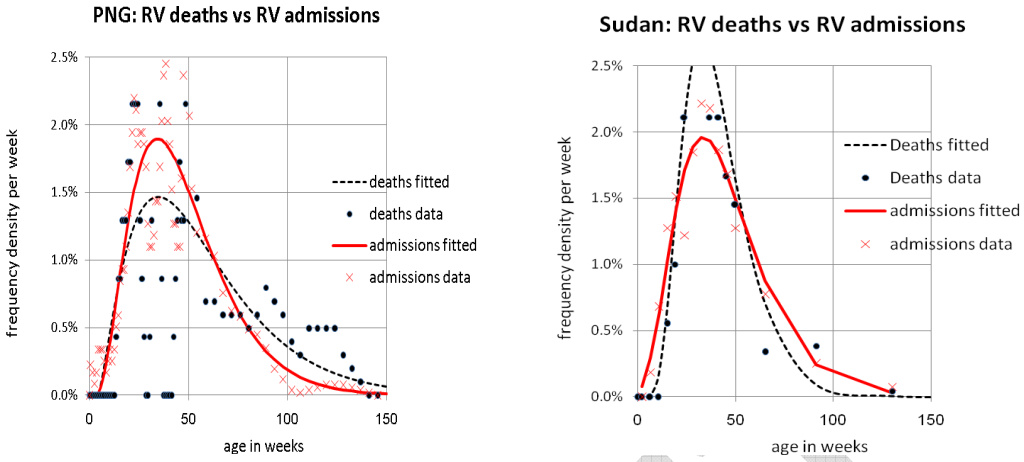


Figure 23: Age distribution of outpatient visits vs hospital admissions

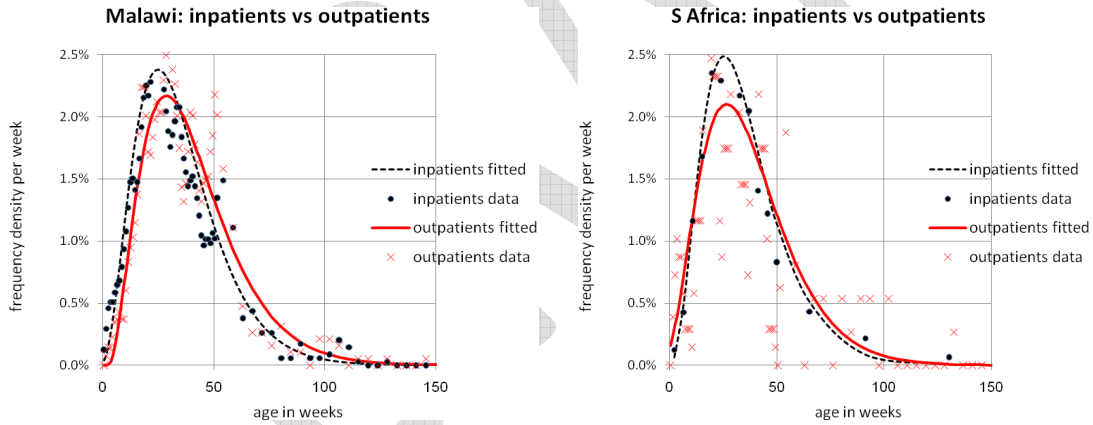
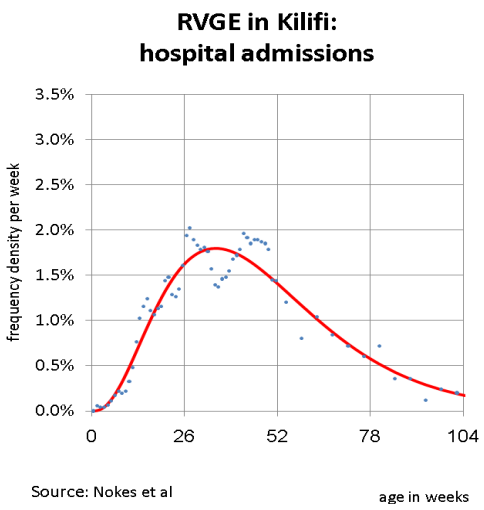
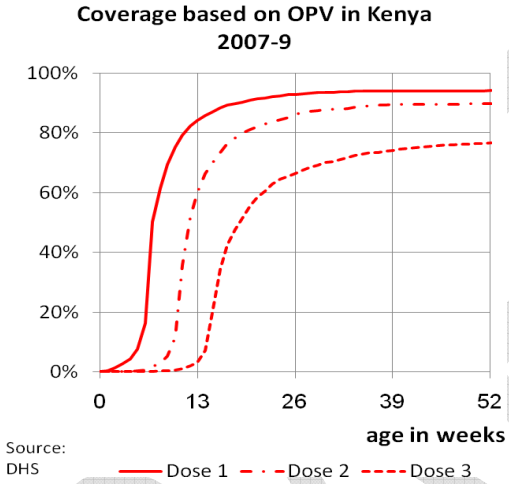


Figure 24: Age/protection profile for Kilifi, Kenya





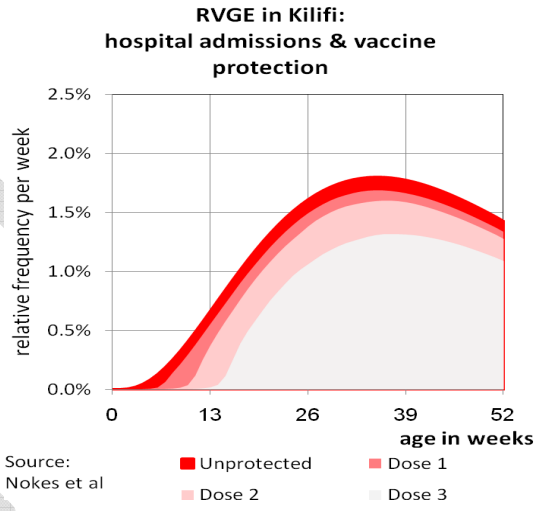
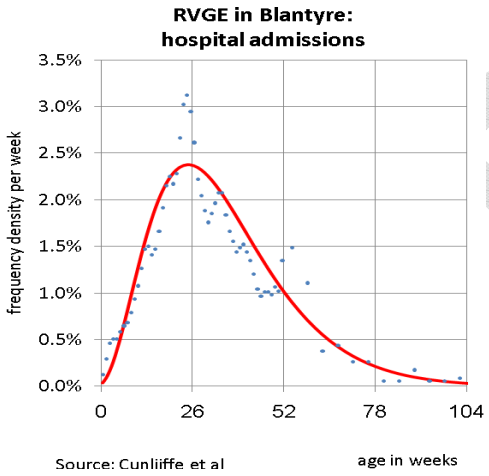
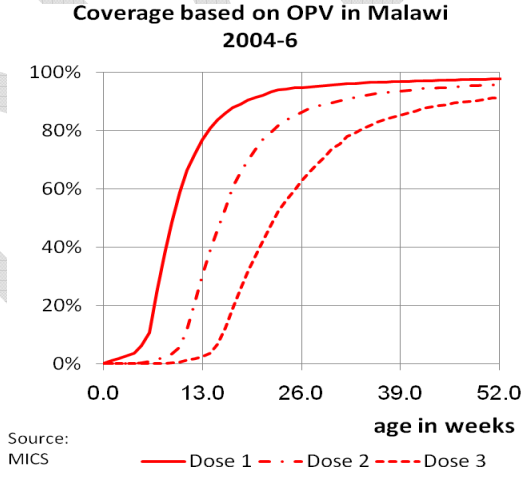


Figure 25: Age protection profile for Blantyre, Malawi





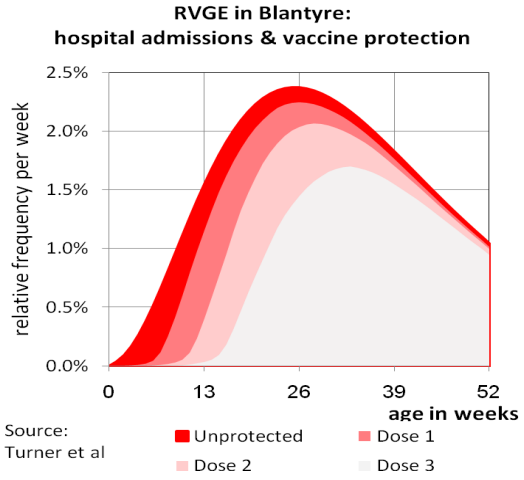
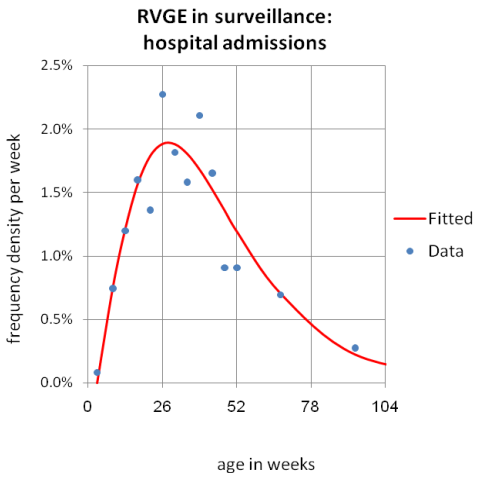
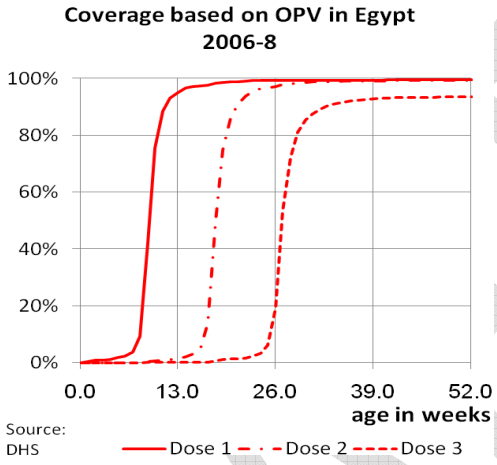


Figure 26: Age protection profile for surveilance, Egypt





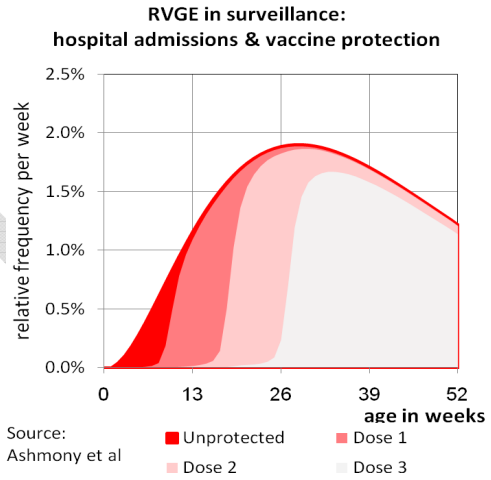
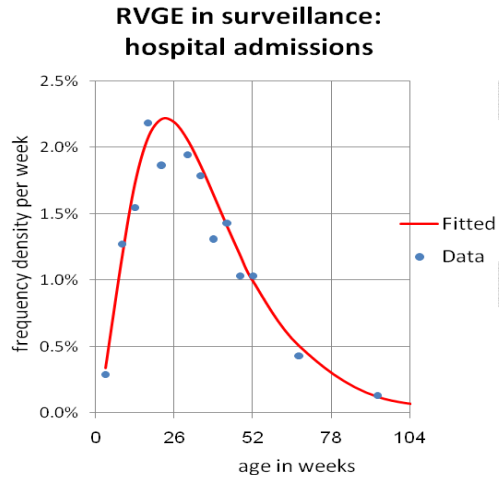
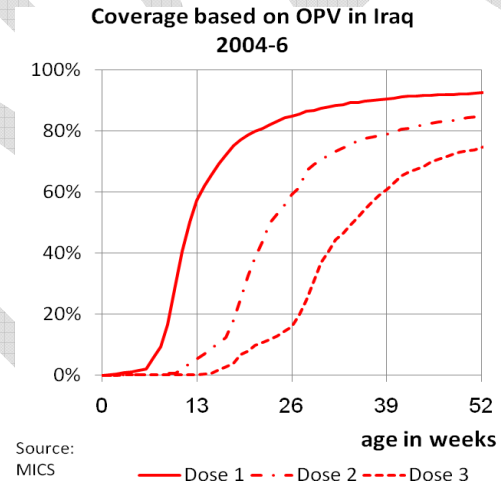


Figure 27: Age protection profile for surveilance, Iraq





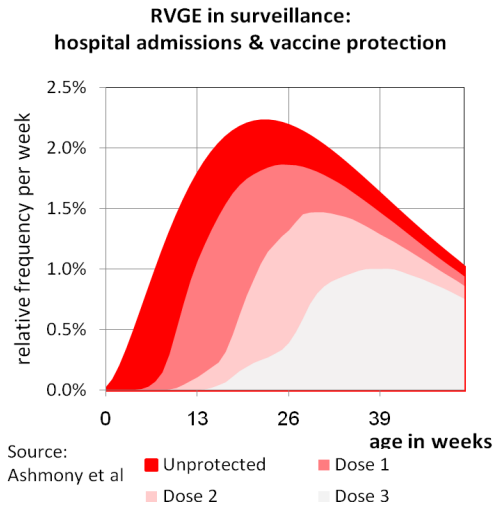
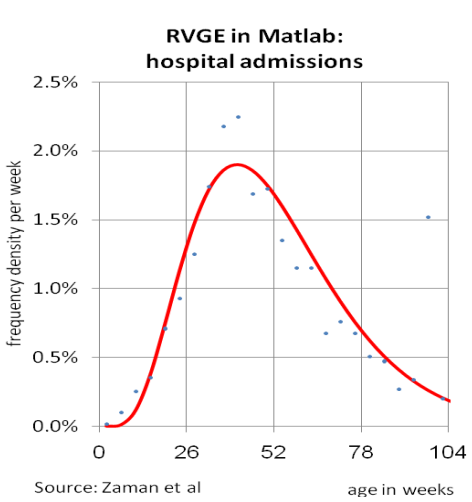
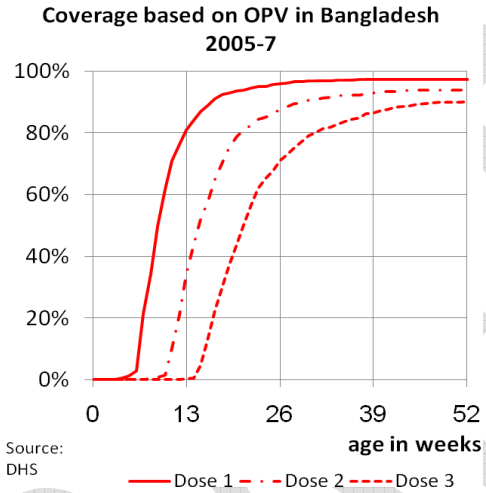


Figure 28: Age protection profile for surveilance, Bangladesh





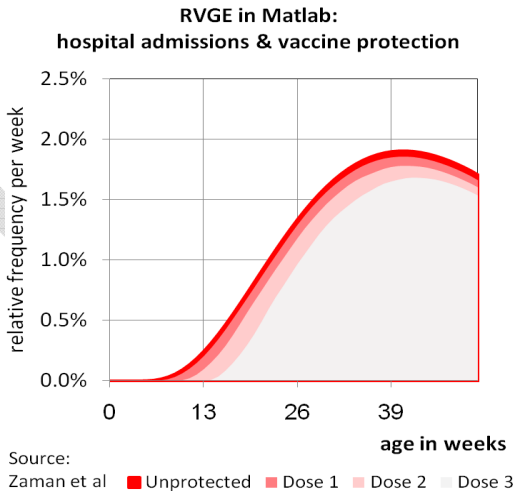
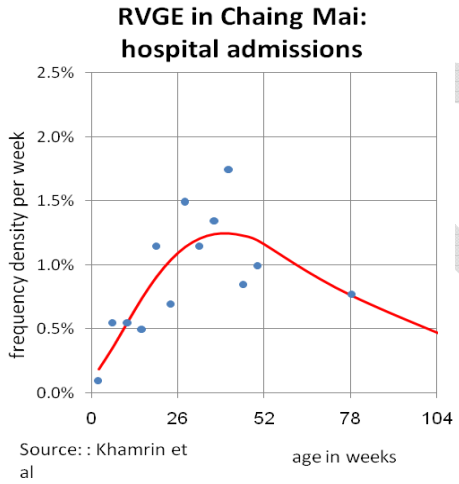
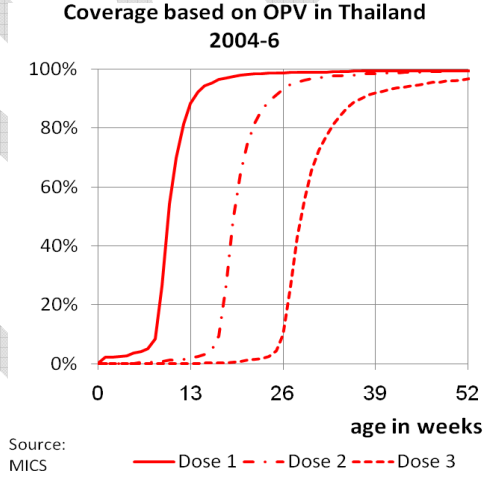


Figure 29: Age protection profile for surveilance, Thailand





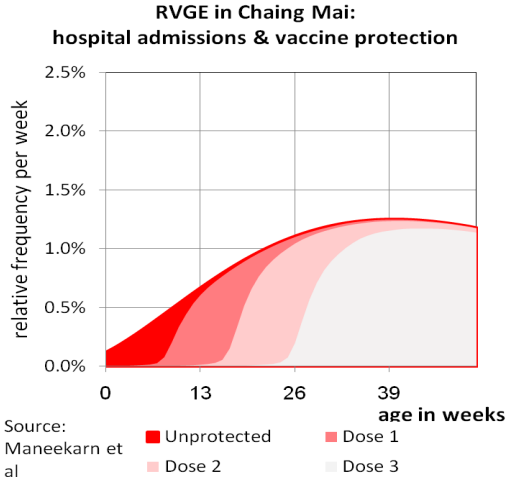
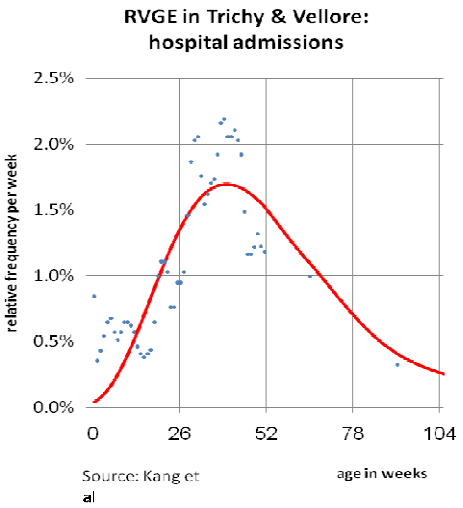
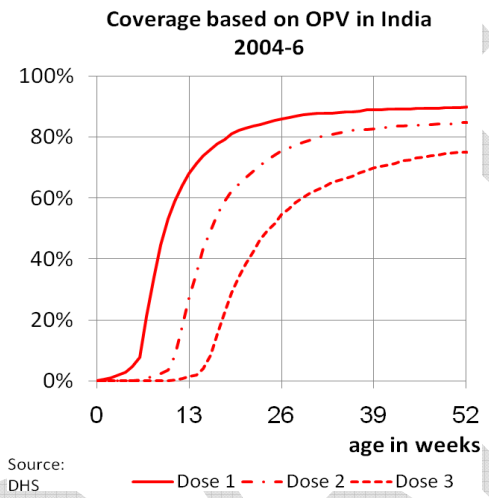
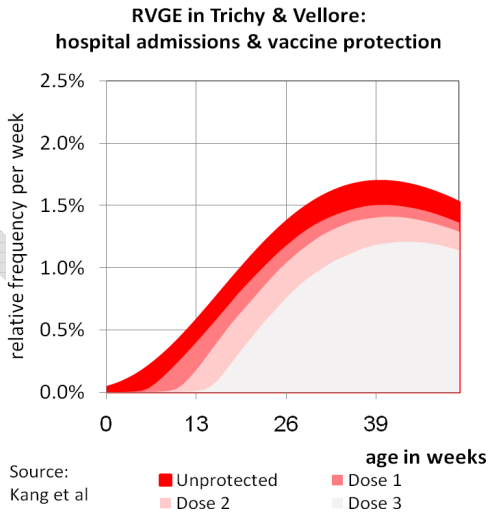
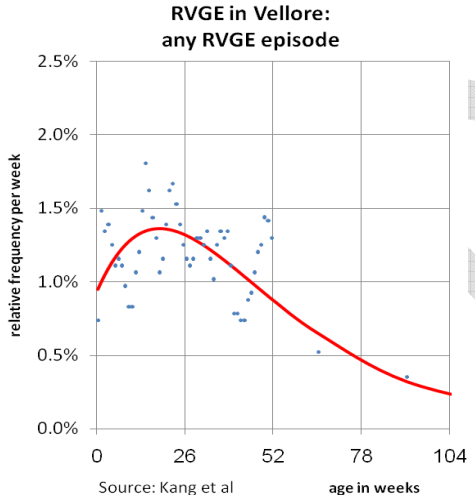


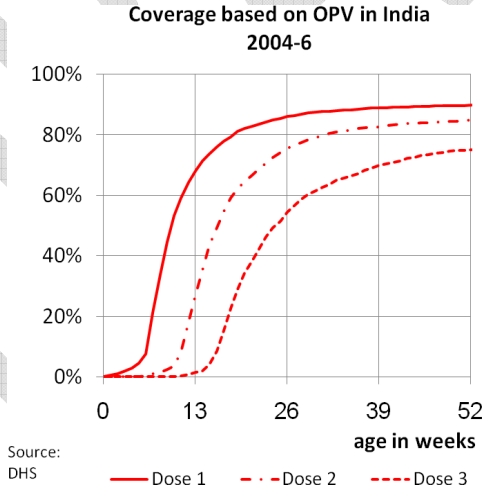
Figure 30: Age protection profile for surveilance, India











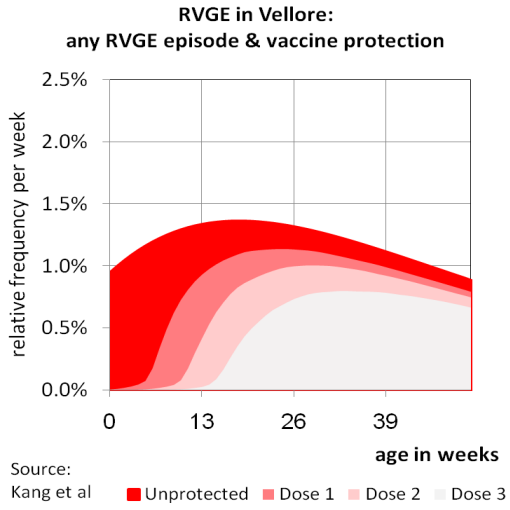
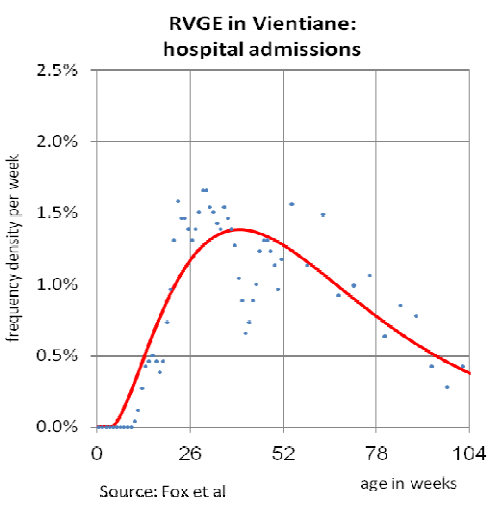
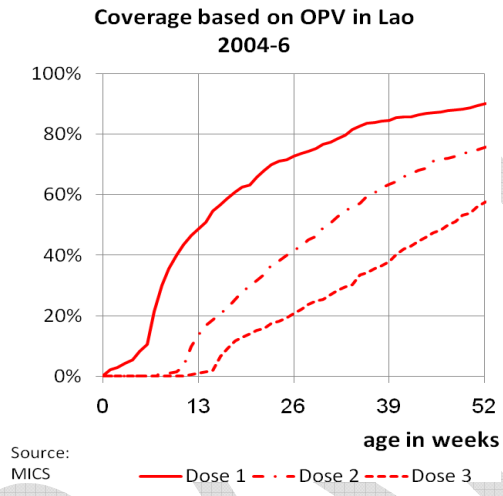


Figure 31: Age protection profile for surveilance, Lao





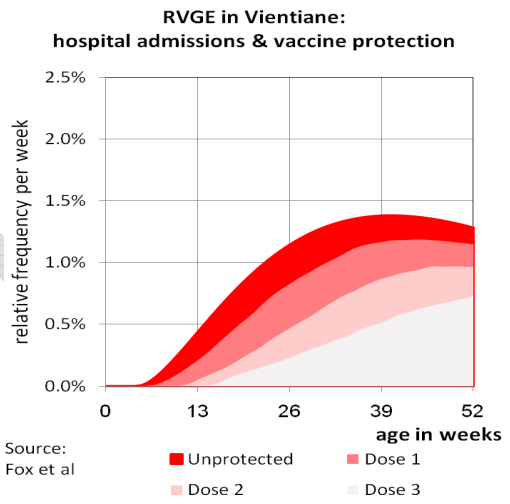
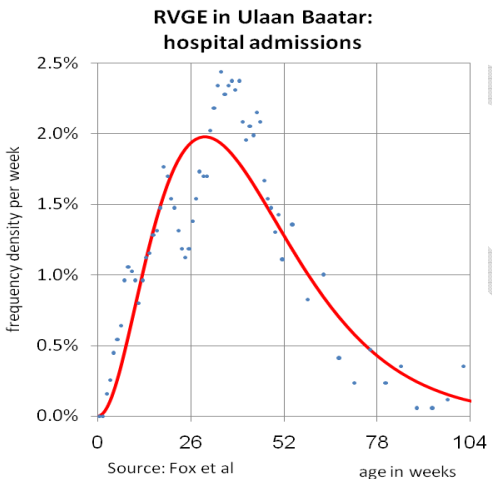
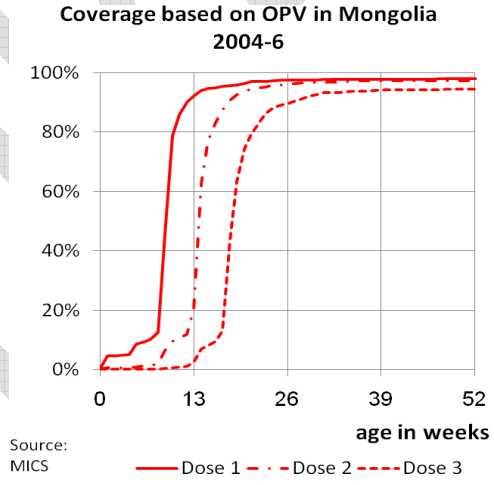


Figure 32: Age protection profile for surveilance, Mongolia





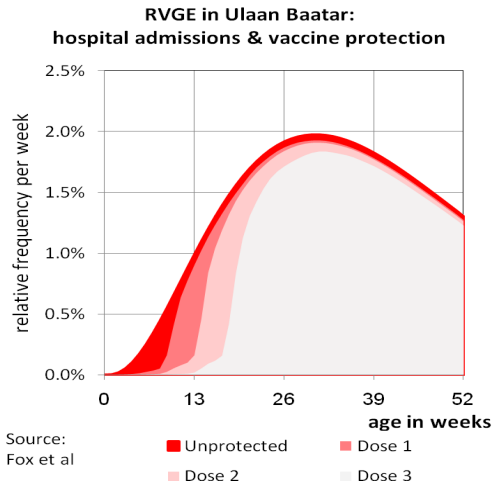
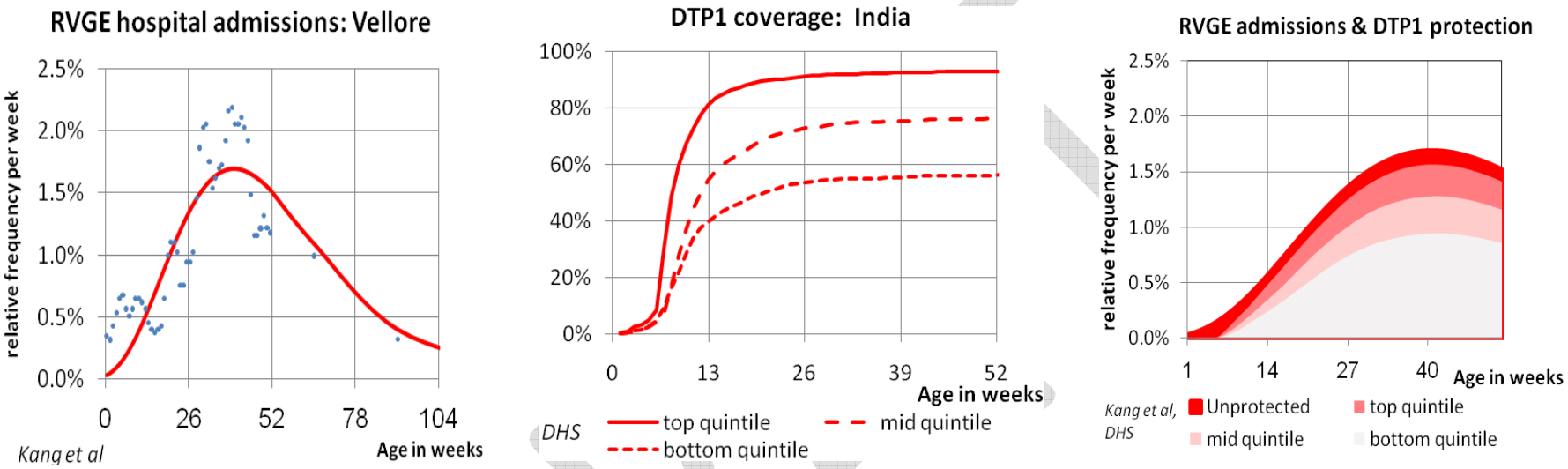


Figure 33: Age at RVGE and vaccine coverage by wealth quintile: Trichy & Vellore, India, 2002-7



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26. Seheri LM, MRC Diarrhoeal Pathogens Research Unit, University of Limpopo (Medunsa Campus), Pretoria, South Africa.
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Appendix 1: References related to included studies if available

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