Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data

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Summary

Background Vaccinations are often delayed until well after the recommended ages, leaving many children exposed for longer than they should be. We estimated vaccination coverage at different ages, and delays in administration, in 45 low-income and middle-income countries.

Methods We used data for 217 706 children from Demographic and Health Surveys between 1996 and 2005 (median 2002), which provided data for vaccination of children on the basis of events recorded on vaccination cards and interviews with mothers, with imputation of missing values and survival analysis. We devised an index combining coverage and delay.

Findings For vaccinated children, the median of the median delays in the 45 countries was 2·3 weeks (IQR 1·4–4·6) for bacille Calmette-Guérin (BCG); 2·4 weeks (1·2–3·3) for diphtheria, tetanus, and pertussis (DTP1); 2·7 weeks (1·7–3·1) for measles-containing vaccine (MCV1); and 6·2 weeks (3·5–8·5) for DTP3. However, in the 12 countries with the longest delays for each vaccination, at least 25% of the children vaccinated were more than 10 weeks late for BCG, 8 weeks for DTP1, 11 weeks for MCV1, and 19 weeks for DTP3. Variation within countries was substantial: the median of the IQRs in the 45 countries for delay in DTP3 was 10·9 weeks, 7·9 weeks for MCV1, 5·4 weeks for BCG, and 5·3 weeks for DTP1. The median of the national coverage rates for DTP1 increased from 57% in children aged 12 weeks to 88% at 12 months, and for DTP3 from 65% at 12 months to 76% at 3 years.

Interpretation The timeliness of children's vaccination varies widely between and particularly within countries, and published yearly estimates of national coverage do not capture these variations. Delayed vaccination could have important implications for the effect of new and established vaccines on the burden of disease.

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Introduction

Late administration of vaccines has implications for the success of child immunisation programmes. Estimates of WHO and UNICEF vaccination coverage[1] are based on the prevalence of vaccinated children in a specific cohort (eg, 12–23 months for diphtheria, tetanus, and pertussis [DTP] vaccines), or numbers of vaccinations in a specific year divided by the number of surviving infants (or, for bacille Calmette-Guérin [BCG], by the number of births).[2] These estimates provide little insight into the extent to which vaccinations are administered on time.[3] In practice, although a few children might be vaccinated early, many will be vaccinated late[4,5] and the effect of some vaccine programmes on the burden of disease might be reduced if there are delays in protecting children in high-risk groups.[6] However, vaccination at older ages, or increased intervals between doses, can provide more durable protection.[7–10] Booster doses can offset the limitations of early doses in some respects, but at extra cost. Thus information about the actual timing of vaccination is needed to help policy makers monitor programmes and respond if need be. Two of the WHO/UNICEF Global Immunisation and Vision Strategies (GIVS) are to strengthen monitoring of coverage and to strengthen the analysis of data,[11] and improved surveillance of deviation from age-appropriate vaccination has been recommended in both low-income and high-income settings.[12–14]

One example of where late administration might cause concern is provided by the new rotavirus programmes. According to a WHO position paper, rotavirus vaccination "should not be initiated for infants aged more than 12 weeks",[15] because of a potentially increased risk of intussusception, a rare bowel disorder. Whether the new vaccines will provide indirect protection to unvaccinated infants is also uncertain, and the implication is that the safety and benefits of the programme might depend on timely administration. We aimed to estimate vaccination coverage at different ages, and delays in administration, in low-income and middle-income countries.

Methods

Study design

The Demographic and Health Surveys (DHS) aim to provide nationally representative data for vaccination of children, on the basis of events recorded on vaccination cards and interviews with mothers. Surveys were administered in 52 countries between 1996 and 2005, and we used the most recent survey for every country. Seven were excluded: four with no data for days of the month of

For more on the **Demographic and Health Surveys** see http://www.measuredhs.com

birth, two with fewer than 250 children with complete and valid data for calculation of exact age at each vaccination, and one with non-standard recording of dates. For the remaining 45 countries (with data for 217706 children), the median survey year was 2002, and the median national sample size of children younger than 3 years at the time of the mother's interview was 3952 (IQR 3012–6043; range 1127–30666). The webappendix (p 1) shows countries and dates covered by the surveys included in the study, together with information about sample sizes and numbers of children for whom the information needed to calculate age at vaccination was complete and valid.

See Online for webappendix

At the time of these surveys, 28 countries used the standard schedule for BCG (birth [lowest–highest target age: birth–8 weeks]), DTP vaccine and oral polio vaccine (6 weeks [4 weeks–2 months], 10 weeks [8 weeks–4 months], 14 weeks [12 weeks–6 months]), and measles-containing vaccine ([MCV1] 9 months [38 weeks–12 months]). Seven countries in South and Central America used birth, and 2, 4, 6, and 12 months as the standard schedule, and the others used local variations.

The survey data for child's month and year of birth were almost complete, but when the day of the month of birth was missing it was imputed. Vaccination cards were the main source for vaccination dates. When the card was not available or a specific vaccination was not recorded, the mother was asked whether the child had been vaccinated. Ages at vaccination were imputed for cases in which the only evidence for vaccination was mother's recall, with separate regression analyses for every country to identify the characteristics associated with variations in age at each vaccination. Then if a vaccination date was missing, an age at vaccination was sampled from a distribution determined by the known values of age at vaccination (ie, values calculated from complete and valid dates of vaccination and dates of birth) for children in that country with similar characteristics.

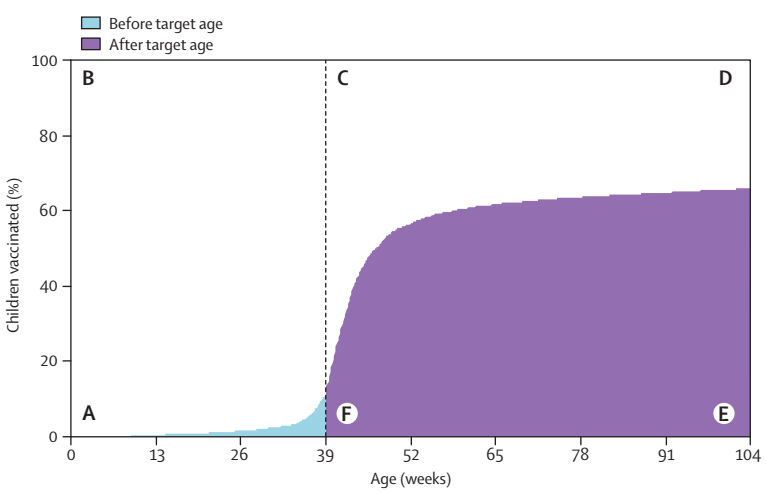

Figure 1: **Plot of cumulative coverage against child's age, and calculation of the coverage index**
The index is calculated from the purple shaded area after the target age as a percentage of the whole area CDEF.

Statistical analysis

We estimated age-specific coverage rates using survival analysis methods,[16,17] and delays after target dates. We used the sampling weights provided in the DHS datasets. Coverage at different ages and delays are closely linked, and we calculated a summary index from the area under the cumulative age-at-vaccination curve (the purple shaded area as a percentage of the rectangle CDEF in figure 1). This curve is analogous to the Kaplan-Meier survival curve and indicates mean coverage between target age and 24 months (104 weeks), or 36 months for MCV1.

One way to improve coverage is to provide opportunities to give children any vaccinations that they have missed when they attend for others later in the schedule. Thus we examined the extent to which opportunities were being taken to give missed doses of DTP vaccines when children attend for MCV1, and vice versa. An opportunity was defined as, for a child at least 9 months old at the time, any dose of DTP if they had not yet had MCV1, or MCV1 if they

	Child's age at interview (years)					Overall
	0	1	2	3	4	
DTP1 not yet given (%)	35·3%	14·2%	14·3%	15·4%	15·8%	19·1%
DTP1 given						
Recorded on card with date (%)	46·8%	54·0%	44·9%	37·4%	33·0%	43·3%
Recorded on card, no date (%)	0·4%	0·8%	0·8%	0·9%	1·0%	0·8%
Mother's recall only (%)	12·3%	23·7%	30·9%	36·3%	39·7%	28·4%
Not known (%)	0·2%	0·5%	0·6%	0·8%	1·0%	0·6%
No data* (%)	5·0%	6·7%	8·5%	9·2%	9·5%	7·8%
Total number surveyed	69859	67858	66713	67903	66734	339067
Children given DTP1 with card record of date† (%)	78·7%	68·7%	58·6%	50·1%	44·8%	59·7%
Coverage in children with data (%)	62·8%	84·7%	84·3%	82·9%	82·4%	79·10%

DTP=diphtheria, tetanus, and pertussis. *91% of children without data were those who had died before their mother's interview. †Calculated as (number with card date)/(number with card date+card[no date]+mother's recall).

Table 1: **Quality of data for DTP1, by child's age at interview, for surveys with data for children aged up to 5 years**

had not yet had all doses of DTP, providing that no dose of DTP had been given in the preceding 4 weeks. The opportunity was regarded as taken if the child was given doses of DTP and MCV1 on the same date. This analysis was based on actual vaccination dates from cards, with no imputation. We used Stata (version 10) for all analyses.

Role of the funding source

The sponsor of the study provided comments on an earlier draft of this report. They also suggested that the work should be presented to the Strategic Advisory Group of Experts (SAGE), whose feedback informed this analysis. The sponsor had no other role in this study. Both AC and CS had full access to the data; CS had final responsibility for the decision to submit.

Results

We examined data quality for all children covered by the surveys. Data for the completeness of the dates needed to calculate age at vaccination are given in the webappendix (p 3). When dates of vaccination were provided, they were almost all complete and valid. However, day of the month of birth was missing in about 20% of cases. The older the child, the less likely they were to have a card record of their vaccination (table 1). Furthermore, reported coverage (card plus mother's recall) dropped slightly as the child's age at interview increased from 2 years to 4 years (table 1), which is consistent with lower levels of reporting for more distant events. We included only data for children younger than 36 months when their mother was interviewed in the main analyses. In children aged 36–59 months, the percentage of all vaccinations with a card date that were given after the age of 36 months was 0·7% for BCG, 1·0% for DTP1, 1·5% for DTP3, and 3·3% for MCV1.

Figure 2 shows the distributions of ages at vaccination for the cohorts of children aged 18–35 months at the time of the mother's interview, using data from vaccination cards only—ie, those with complete follow-up to age 18 months (78 weeks). Each distribution has high peaks near or after target ages, followed by long tails to the right, suggesting delays in vaccination in substantial proportions of children. The different peaks in the distributions for DTP and MCV indicate the two main target ages. The results for oral polio vaccine 1 and 3 were very similar to those for DTP1 and DTP3 (data not shown). These distributions should be interpreted as broad indicators of the nature rather than scale of the problem, since each country's contribution is implicitly weighted by the size of its survey sample, which is only very weakly related to population size. Furthermore, the data are from several survey years.

The predictors of delay that we used in the imputation were rural or urban residence, home or hospital birth, number of years of mother's education and age at birth, child's position in birth order, and child's age at mother's interview. Sex was a significant independent predictor in only two countries and was not used (webappendix p 5).

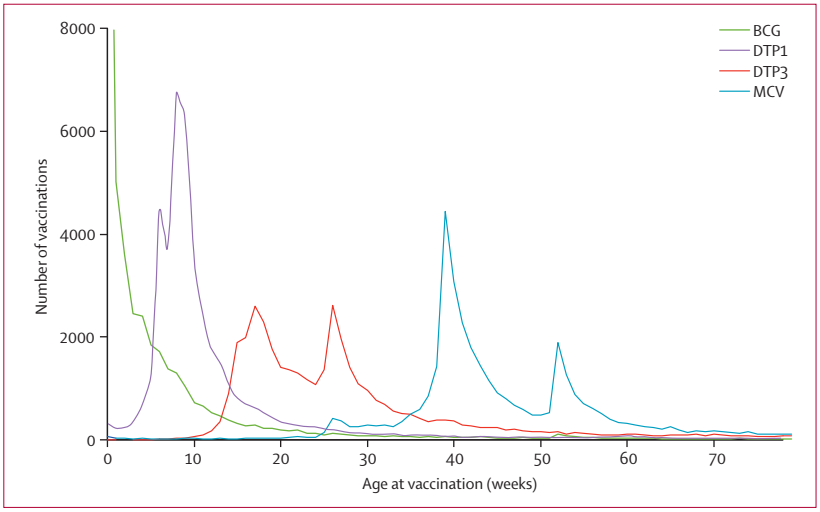

Figure 2: **Age distributions for administration of BCG, DTP1, DTP3, and MCV1 vaccines, based on card dates only in children aged 18–35·9 months**
BCG=bacille Calmette-Guérin. DTP=diphtheria, tetanus, and pertussis. MCV=measles-containing vaccine.

	BCG	DTP1	DTP3	MCV1
Target (weeks)	0 (0–0)	6 (6–9)	14 (14–17)	39 (39–39)
Coverage at				
4 weeks	49% (30–70)			
8 weeks	69% (48–81)	24% (8–36)		
12 weeks	74% (62–86)	57% (46–70)		
4 months	82% (68–90)	73% (60–83)	10% (4–22)	
5 months	84% (70–90)	80% (64–88)	27% (16–42)	
6 months	85% (73–91)	82% (67–89)	36% (23–54)	
9 months	87% (75–92)	87% (75–92)	59% (43–72)	12% (10–14)
12 months	89% (76–93)	88% (73–92)	65% (49–79)	54% (37–69)
18 months	90% (78–94)	90% (75–94)	72% (52–83)	74% (58–82)
24 months	90% (78–94)	90% (76–94)	74% (53–84)	80% (62–88)
36 months	91% (78–95)	91% (76–95)	76% (56–85)	82% (66–91)
Index				
All countries	84% (73–89)	84% (70–89)	63% (45–72)	74% (58–83)
African region*	83% (72–86)	78% (67–85)	58% (40–68)	67% (56–80)
Americas region†	91% (87–93)	91% (88–93)	75% (55–79)	83% (76–87)

BCG=bacille Calmette-Guérin. DTP=diphtheria, tetanus, and pertussis. MCV=measles-containing virus. *27 countries covered by the WHO Regional Office for Africa. †Nine countries covered by the WHO Regional Office for the Americas.

Table 2: **Target ages and median (IQR) for estimated coverage at different ages across 45 countries**

Table 2 shows the median coverage rates across countries at different ages, and summary indices for different regions, using both card and imputed dates. Overall, the median country values for BCG coverage increased from 49% (IQR 30–70) at 4 weeks to 89% (76–93) at 12 months. Median coverage for DTP1 increased from 57% (46–70) at 12 weeks to 82% (67–89) at 6 months and 91% (76–95) at 3 years. Coverage for DTP3 increased from 65% (49–79) at 12 months to 76% (56–86) at 3 years, and MCV1 from 54% (37–69) at 12 months to 82% (66–91) at 3 years; thus for both these vaccines, coverage at 12 months substantially underestimates final coverage. Generally, coverage for the

27 countries in the WHO African region was lower than that in the nine countries in the Americas region, although the highest 25% of African region countries were similar to the lowest 25% of the Americas group, and were much better for DTP1 (table 2). In the other WHO regions, the numbers of countries in the analysis were small.

	BCG					DPT1					DPT3					MCV					OT
	4 w	12 w	6 m	12 m	VCI	8 w	12 w	6 m	12 m	VCI	6 m	9 m	12 m	3 y	VCI	9 m	12 m	18 m	3 y	VCI	
Bangladesh (2004)	8%	72%	90%	93%	85%	33%	71%	89%	92%	88%	57%	75%	80%	82%	72%	10%	69%	78%	80%	75%	31%
Benin (2001)	75%	86%	89%	90%	89%	51%	72%	84%	87%	84%	52%	63%	69%	74%	65%	7%	60%	71%	74%	69%	60%
Bolivia (2003)	59%	79%	87%	92%	88%	8%	54%	84%	92%	88%	12%	52%	65%	79%	65%	5%	15%	64%	90%	74%	18%
Brazil (1996)	36%	80%	88%	91%	87%	3%	70%	89%	94%	91%	5%	68%	76%	89%	75%	9%	75%	89%	94%	87%	55%
Burkina Faso (2003)	42%	66%	72%	77%	73%	10%	43%	67%	73%	70%	30%	44%	50%	62%	48%	12%	47%	58%	67%	58%	32%
Cambodia (2000)	19%	43%	56%	64%	59%	17%	35%	53%	61%	58%	23%	33%	38%	51%	38%	9%	39%	48%	62%	51%	50%
Cameroon (2004)	49%	72%	80%	85%	80%	41%	61%	74%	80%	77%	48%	56%	60%	68%	57%	16%	58%	66%	71%	65%	42%
Chad (2004)	13%	22%	29%	36%	33%	12%	17%	30%	39%	36%	8%	13%	16%	28%	16%	7%	15%	23%	30%	24%	52%
Colombia (2005)	73%	88%	93%	96%	93%	5%	69%	92%	96%	93%	19%	72%	80%	89%	79%	44%	54%	86%	96%	89%	35%
Comoros (1996)	56%	76%	85%	91%	86%	34%	57%	80%	88%	83%	34%	50%	61%	79%	58%	14%	48%	67%	85%	69%	58%
Congo (2005)	65%	86%	89%	89%	87%	14%	61%	82%	84%	82%	55%	63%	66%	70%	63%	12%	59%	66%	73%	67%	17%
Côte d'Ivoire (1998)	55%	71%	76%	80%	77%	30%	52%	71%	76%	73%	36%	46%	53%	66%	50%	14%	50%	67%	74%	66%	57%
Dominican Rep (2002)	71%	90%	93%	93%	91%	6%	63%	85%	91%	88%	26%	49%	54%	62%	55%	54%	74%	82%	95%	87%	23%
Egypt (2005)	70%	96%	98%	98%	95%	11%	90%	98%	99%	97%	25%	93%	94%	95%	93%	25%	95%	96%	98%	96%	16%
Eritrea (2002)	33%	67%	83%	89%	83%	43%	64%	82%	88%	84%	64%	74%	79%	85%	74%	24%	74%	82%	89%	83%	59%
Gabon (2000)	56%	76%	84%	88%	84%	24%	41%	57%	63%	59%	23%	28%	33%	39%	30%	11%	46%	58%	66%	57%	20%
Ghana (2003)	50%	78%	85%	88%	84%	37%	67%	85%	89%	85%	54%	69%	75%	81%	69%	19%	72%	83%	87%	81%	32%
Guatemala (1998)	28%	55%	73%	82%	76%	7%	39%	76%	85%	81%	20%	43%	56%	81%	54%	10%	56%	75%	91%	76%	62%
Guinea (2005)	61%	74%	77%	78%	76%	35%	55%	72%	74%	71%	36%	46%	49%	53%	45%	16%	46%	54%	59%	55%	36%
Haiti (2000)	34%	56%	64%	69%	65%	28%	50%	66%	73%	70%	24%	35%	42%	56%	39%	10%	37%	52%	75%	57%	58%
Honduras (2005)	71%	91%	97%	98%	95%	2%	83%	98%	99%	97%	8%	84%	92%	96%	88%	2%	12%	93%	97%	93%	16%
India (2005)	30%	61%	73%	76%	71%	28%	54%	71%	73%	70%	40%	50%	54%	57%	50%	12%	53%	60%	64%	59%	18%
Kenya (2003)	49%	77%	85%	87%	83%	48%	72%	86%	88%	86%	61%	68%	71%	74%	67%	20%	67%	74%	80%	74%	30%
Kyrgyz (1997)	91%	95%	97%	98%	97%	6%	70%	93%	97%	94%	43%	83%	89%	96%	85%	1%	15%	89%	96%	90%	3%
Lesotho (2004)	66%	88%	91%	92%	90%	58%	81%	89%	91%	89%	66%	76%	79%	85%	75%	7%	74%	84%	91%	84%	17%
Madagascar (2003)	30%	60%	68%	72%	68%	36%	54%	67%	72%	69%	48%	57%	61%	66%	57%	12%	53%	58%	64%	58%	35%
Malawi (2004)	28%	66%	84%	90%	83%	33%	64%	89%	93%	89%	52%	72%	79%	87%	72%	14%	69%	82%	88%	80%	29%
Mali (2001)	33%	46%	56%	63%	60%	25%	36%	49%	57%	55%	22%	29%	34%	48%	33%	14%	37%	48%	61%	50%	51%
Mauritania (2000)	30%	43%	50%	58%	55%	20%	34%	45%	53%	50%	21%	28%	31%	40%	30%	13%	35%	48%	58%	48%	30%
Morocco (2003)	89%	96%	97%	98%	95%	63%	90%	95%	96%	94%	84%	90%	92%	95%	88%	14%	86%	90%	93%	89%	38%
Mozambique (2003)	58%	74%	81%	84%	81%	6%	51%	78%	84%	78%	41%	59%	65%	76%	60%	16%	62%	74%	82%	74%	47%
Namibia (2000)	79%	89%	90%	90%	89%	68%	82%	90%	91%	89%	65%	73%	76%	82%	72%	14%	74%	81%	89%	81%	43%
Nicaragua (2001)	70%	86%	92%	94%	92%	4%	66%	89%	93%	91%	46%	66%	73%	88%	75%	4%	13%	80%	93%	83%	34%
Niger (1998)	21%	36%	44%	46%	43%	14%	27%	39%	45%	42%	15%	22%	24%	28%	22%	12%	29%	37%	42%	37%	58%
Nigeria (2003)	27%	41%	45%	48%	46%	18%	26%	36%	39%	38%	16%	19%	21%	25%	20%	10%	30%	36%	43%	37%	19%
Peru (2004)*	79%	94%	95%	96%	94%	3%	80%	95%	97%	95%	72%	80%	83%	88%	81%	1%	13%	83%	89%	83%	15%
Rwanda (2005)	71%	94%	95%	96%	93%	62%	91%	95%	96%	94%	81%	86%	88%	89%	84%	10%	81%	87%	90%	85%	45%
Senegal (2005)	49%	77%	87%	89%	84%	37%	67%	84%	90%	85%	56%	69%	72%	79%	68%	14%	63%	76%	80%	74%	41%
Tanzania (1999)	59%	85%	91%	93%	89%	53%	75%	89%	92%	88%	60%	73%	80%	85%	72%	16%	74%	82%	84%	79%	54%
Togo (1998)	48%	65%	73%	76%	73%	31%	49%	63%	69%	66%	28%	36%	42%	49%	39%	11%	36%	46%	52%	46%	43%
Turkey (1998)	8%	66%	85%	87%	85%	3%	46%	81%	85%	81%	34%	53%	56%	63%	52%	11%	71%	81%	88%	80%	15%
Uganda (2000)	30%	54%	69%	76%	71%	24%	44%	64%	74%	69%	27%	37%	44%	53%	41%	13%	49%	62%	68%	61%	71%
Uzbekistan (1996)	90%	94%	95%	96%	95%	6%	48%	84%	94%	90%	40%	61%	73%	93%	72%	12%	63%	87%	99%	86%	17%
Yemen (1997)	9%	35%	46%	50%	46%	18%	35%	47%	51%	48%	27%	35%	38%	42%	35%	14%	39%	44%	47%	44%	24%
Zambia (2001)	38%	73%	86%	91%	85%	15%	51%	84%	91%	85%	43%	64%	74%	84%	67%	18%	69%	82%	92%	83%	42%

BCG=bacille Calmette-Guérin. DTP=diphtheria, tetanus, and pertussis. m=months. MCV=measles-containing virus. OT=of children for whom any opportunity arose, the percentage given a missed dose. Rep=Republic. VCI=vaccination coverage index. w=weeks. y=years. 95% CIs are not shown but the SEs of the percentages in the table can be summarised as follows: for BCG, mean 0·7% [SE 0·2%]; for DTP1, mean 0·7% [0·3%]; for DTP3, mean 0·6% [0·4%]; and for MCV1, mean 0·5% [0·5%]. Thus the 95% CIs for the estimates of coverage were typically 1–1·5% above and below the figures given. *Continuous.

Table 3: **Variation between countries in estimated coverage for BCG, DTP1, DTP3 and MCV1, and in opportunities taken**

Table 3 gives coverage rates for each national survey. Countries with generally very high coverage rates included Egypt, Peru, Rwanda, and the Kyrgyz Republic. Countries with generally low rates included Chad, Nigeria, and Yemen. Some countries had a pronounced drop-off in coverage between DTP1 and DTP3, including the Dominican Republic, Gabon, Guinea, Niger, Nigeria, and Togo. In most countries, at least 30% of children vaccinated with DTP1 were older than 12 weeks at the time, and so would have been ineligible for rotavirus vaccine under the existing safety guidelines.[15]

The webappendix (p 6) gives median, quartiles, and IQRs for delays for BCG, DTP1, DTP3, and MCV1 for each country. Table 4 summarises these parameters with median values across the 45 countries. For BCG for example, the median of the 45 country median delays was 2·3 weeks, the 25th percentile of the country medians was 1·4 weeks and the 75th percentile 4·6 weeks (ie, the median delay was more than 4·6 weeks in a quarter of the countries). The distributions of median delays for DTP1 and MCV1 were broadly similar, but delays for DTP3 were more than twice as long (table 4).

In 75% of the countries, a quarter of the children had delays of a week or less for DTP1 and MCV1, and just over a week for BCG (table 4), and so were vaccinated close to the scheduled ages. However, the country-specific distributions of ages at vaccination had long tails. Thus for BCG, the median of the 45 country-specific 75th percentile delays was 6·6 weeks compared with 2·3 weeks for the median of medians and 0·7 weeks for the median 25th percentile. The corresponding figures for DTP1 and MCV1 were broadly similar, and for DTP3 about double (table 4). Furthermore, the 90th percentile delays for each country were typically at least twice as long as the 75th percentile, with medians overall of about 3 months (6 months for DTP3). For 25% of the countries surveyed, 25% of the children had a delay of at least 10 weeks in being given BCG, 8 weeks for DTP1, 11 weeks for MCV1, and 19 weeks for DTP3 (table 4). Data quality tended to be poorer in countries with long delays, and vaccination after the recommended age can be the result of worthwhile, if belated, efforts to increase coverage; however, in our analysis, five countries (Chad, Cambodia, Mali, Mauritania, and Niger) had both consistently long delays and low final coverages.

Table 3 shows, of all the children in each country presenting opportunities for a valid catch-up dose, the percentage in which at least one opportunity was taken. These percentages tended to be higher in countries with lower coverage, suggesting that generally this strategy is making a useful contribution by giving a late boost to coverage rates that would otherwise have been even lower. However, results from some countries did not follow this pattern. For example, DTP3 coverage in Gabon at 12 months was 33% and opportunities taken 20%; in Nigeria these percentages were 21% and 19% respectively (table 3).

Discussion

Variation between countries in vaccination coverage rates is widely reported. In this study we have shown that coverage at 12 months underestimates final coverage, and that adherence to the recommended schedules varies substantially within and between countries.

Our findings are based on survey data. How representative are they? Consistent DHS sampling methods and questionnaires were used in every country, but the survey years varied (1996–2005), so country-specific results are not strictly comparable. We had no vaccination data for children who had died before interviews, which was a limitation in terms of completeness of reporting. The proportions of children affected varied from about 5% of children aged younger than 1 year to about 7% of those aged younger than 3 years, and varied between countries. However, the children who died are unlikely to have had a better vaccination record that those who did not, so we may, if anything, have slightly underestimated the delays and overestimated the coverage.

Incompleteness of data for surviving children is of more concern. When possible, we took the dates of vaccination from record cards. However, the evidence was mothers' recall or a card with no information about the date for 32% of all responses. In some countries, the figure was much higher, and we might have erred on the side of including rather than excluding them from the analysis. We imputed the missing values from the known dates of children from the same country survey who were similar in terms of local predictors of age at vaccination, since we believed that this method would give a more accurate result than would the assumption that the

	BCG across 45 countries			DTP1 across 45 countries			DTP3 across 45 countries			MCV1 across 45 countries		
	Median	25th percentile	75th percentile	Median	25th percentile	75th percentile	Median	25th percentile	75th percentile	Median	25th percentile	75th percentile
Median	2·3	1·4	4·6	2·4	1·2	3·3	6·2	3·5	8·5	2·7	1·7	3·1
25th percentile	0·7	0·3	1·3	0·6	0·3	1·0	2·7	1·4	3·5	0·1	–0·3	0·4
75th percentile	6·6	4·3	10·3	6·3	3·7	8·3	13·5	9·0	19·1	7·6	5·3	11·0
IQR	5·4	3·4	8·6	5·3	3·6	7·1	10·9	8·0	15·6	7·9	5·9	13·9

BCG=bacille Calmette-Guérin. DTP=diphtheria, tetanus, and pertussis. MCV=measles-containing virus. Negative values indicate vaccination before target date.

Table 4: **Delay in vaccination (weeks), showing variation between and within countries, across children in a country sample**

vaccination experience of the children with missing dates was similar to the remainder. This method will not have eliminated information bias altogether, and its extent remains uncertain.

Our index attempts to capture both coverage and timeliness. The implicit weight given to the timeliness element depends on the age range covered; we chose up to 2 years for BCG and DTP, and up to 3 years for MCV1—age ranges that carry heavy burdens of relevant mortality in low-income countries. In this formulation, vaccination of children before target dates does not incur a penalty, but an adjustment could be made by subtracting the shaded percentage of the rectangle ABCF in figure 1.

Countries as diverse as Egypt, Peru, Rwanda, and the Kyrgyz Republic all have fairly high and timely coverage, and in most countries at least a quarter of the children are vaccinated close to the schedule. Prima facie this finding suggests that delays are not inevitable. However, the scale of variation within countries is substantial. This variation could partly be attributable to concerns about safety raised by parents or care-givers or both, particularly if the child is unwell when the vaccination is due;[18,19] however, in a review of nine surveys,[20] "lack of parental acceptance of immunisation" was given in a median of 3% of responses and "was not an important reason for missed opportunities". There will be accessibility, organisational, and cultural factors at work; in almost all the countries in this study, delays were more protracted in rural areas than in urban areas. Reported coverage by 12 months of age has improved since the survey year in some areas, but whether there have been comparable improvements in timeliness is unclear.

Do these delays matter? In principle, if schedules are designed to achieve a balance between effective protection at vulnerable ages, durable protection, and vaccine safety, then adherence to schedules must matter too, but how much it contributes is difficult to know. Other investigators have made the case for more timely vaccination against pertussis,[21] measles,[22] and *Haemophilus influenzae* type b.[23] Delays might be unimportant in children who are protected indirectly by high and timely coverage of their contacts, but many children at high background risk of mortality and of vaccination delay might not benefit from herd effects of this type.

Rotavirus vaccination is a topical case. It is currently scheduled with DTP, but in most of the countries in our study more than 30% of the children were past the WHO-recommended age group for rotavirus vaccination when they were given DTP1. This might be a problem in more developed countries too, at least in some population groups;[24] in a study from Philadelphia, PA, USA, 23% of children were older than the recommended age for vaccination.[25] One possible scenario is strict adherence to the recommendation and no improvement in timeliness, which would compromise the effect of the vaccination programme on the burden of rotavirus disease. However, according to the Global Advisory Committee on vaccine safety, strict adherence would be "extremely difficult to implement in the field" in low-income countries,[26] and a more likely scenario is no improvement in timeliness and widespread violation of the recommended age group. This scenario could compromise safety, although the evidence about level of risk in older children is weak. The WHO recommendation is based on experience of an earlier vaccine, RotaShield (Wyeth-Ayerst, Philadelphia, PA, USA), now withdrawn, which was linked to a rare bowel disorder when the first dose was administered to older infants.[27] Safety trials of the new vaccines did not address the effects of delayed vaccination; and although the investigators of a study of postmarketing safety monitoring data from the USA excluded an overall effect on the scale of RotaShield,[28] the percentage of children covered with materially delayed first doses was small. Even if the new vaccines do carry an as yet undetected excess risk in older children, broadening the age restriction in high-mortality settings could well be advantageous from a utilitarian perspective. The benefits and risks of decisions of this type would have to be considered carefully and in context by policy makers, as will the implications for informing parents.

On the one hand, improvement in timeliness would improve the effectiveness of rotavirus vaccination programmes and reduce any residual risks to safety. Introduction of rotavirus vaccination might stimulate better timeliness, and the rest of the vaccination programme would benefit. The difficulty is that the optimum ages for different vaccines might differ. Delays for pneumococcal conjugate vaccine, for example, might be associated with more durable levels of individual protection.[29] On the other hand, coverage and adherence to schedules could be improved, and family and programme costs reduced, by vaccinating against several pathogens at one visit.[30] In this situation, the design of the schedule should be based on a detailed assessment of several options.

Assessments of vaccination programmes are generally based on evidence from efficacy trials, in which children are vaccinated fairly close to the schedule. Applied to wider populations, these assessments are likely to be optimistic, and there is little evidence about the relative benefits of seeking to improve timeliness rather than expanding final coverage, for example. One approach might be to include different schedules in trials, but the sample sizes needed would have to be increased and it could involve ethics issues. A second approach would be to gather data about the effectiveness of vaccines in countries (or areas within countries) with contrasting levels of delay. The challenge would be to exclude or take account of the other factors involved, such as differences in age-specific patterns of transmission, disease, and antibody protection.[31] A third approach would be to use computer-simulation models. Ideally all three approaches would be used; they would inform

each other and strengthen decision making for vaccine policy.

Monitoring and surveillance should provide a clear basis for remedial action or more focused scrutiny. Accurate information about coverage and timeliness has an important part to play in achieving this aim.

Contributors

AC extracted the datasets, did the first analysis, wrote the first draft and presented the work to WHO's Strategic Advisory Group of Experts (SAGE). CS did the survival analysis and imputation, devised the coverage index, and wrote later drafts.

Conflict of interest statement

We declare that we have no conflict of interest.

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