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Timeliness of vaccination and its effects on fraction of vaccinated population

Manas K. Akmatov, Mirjam Kretzschmar, Alexander Krämer, Rafael T. Mikolajczyk*

Department of Public Health Medicine, School of Public Health, University of Bielefeld, Germany

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ABSTRACT

Delayed vaccination against childhood diseases may lead to increased mortality and morbidity among children and also affect the fraction of vaccinated population necessary for elimination of a disease. The purpose of this study was to assess the extent of the delay in vaccinations in four countries belonging to Commonwealth of Independent States and to assess how the timeliness of vaccination affects the vaccination coverage. The fraction of children vaccinated with delay was substantial in all the studied countries, and the impact of differences between countries was stronger than individual risk factors assessed in this study. In presence of vaccination delay, up-to-date vaccination is a biased estimator of the fraction of vaccinated population. Age-appropriate vaccination should be taken into account when assessing vaccination coverage.

1. Introduction

A frequently used indicator of measuring vaccination coverage is total up-to-date vaccination, defined as the proportion of vaccinated children at a specific age [1–6]. However, up-to-date vaccination coverage does not take into account the possible delay in vaccination [7]. In some countries vaccination coverage rates were reported to be at high levels, but age-appropriate vaccination was much lower [7–9]. In such countries total up-to-date vaccination may be a poor estimate of the vaccinated fraction of the population, and delays in vaccination might explain the persistence of the infections. Also, the age-appropriate vaccination was suggested to be a more precise indicator of health care utilization than total-up-to-date vaccination [10].

Recently the Kaplan–Meier method was proposed to address the issue of delayed vaccination [11,12]. In this study we expand the approach to estimate population coverage with the vaccines, accounting for vaccination delays. We use data from four countries (Armenia, Kazakhstan, Kyrgyzstan and Uzbekistan) belonging to Commonwealth of Independent States (CIS). The health care systems in these countries were developed as a part of the Soviet health care system, which was centrally managed from Moscow. After the dissolution of the Soviet Union some vaccine-preventable diseases, e.g. diphtheria and measles displayed increased incidence and large outbreaks of [13]. Furthermore, mumps and rubella are endemic in these countries. Yet, from 1995 to 2000, the reported vaccination coverage was high: between 81 and 100% for the measles vaccine and between 89 and 99% for the vaccine against diphtheria [14]. A previous analysis of vaccination data in Kazakhstan indicated that a large proportion of children were vaccinated with a substantial delay [15]. Thus, the observed outbreaks might be facilitated by overestimated coverage and delayed vaccination.

Factors responsible for a child not being vaccinated have been extensively studied in both developed and developing countries [1,16–18], but only limited knowledge exists about factors determining delay in vaccination [19–22]. Vaccination delays might be caused by individual risk factors similar to those responsible for not getting vaccinated. However, delays could also be related to structural organization of the health care system. Both aspects would result in different public health recommendations.

The detailed aims of our analysis were: (1) to estimate the age-appropriate vaccination and the extent of delay in vaccinations in the four CIS countries, (2) to estimate the fraction of vaccinated population in these countries, and (3) to examine factors associated with delayed vaccination and factors associated with lacking vaccination in these countries.

2. Materials and methods

Information about vaccination was obtained from Demographic and Health Surveys (DHS), a nationally representative household surveys, conducted in more than 70 developing countries [23]. DHS

* Corresponding author at: Department of Public Health Medicine, School of Public Health, University of Bielefeld, P.O. Box 100131, D-33501 Bielefeld, Germany. Tel.: +49 521 106 6889; fax: +49 521 106 2968.

E-mail addresses: manas.akmatov@uni-bielefeld.de (M.K. Akmatov), mirjam.kretzschmar@uni-bielefeld.de (M. Kretzschmar), alexander.kraemer@uni-bielefeld.de (A. Krämer), rafael.mikolajczyk@uni-bielefeld.de (R.T. Mikolajczyk).

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data existed for four out of eleven CIS countries: Armenia (survey conducted in 2000), Kazakhstan (1999), Kyrgyzstan (1997) and Uzbekistan (1996). These surveys provide the most recent information about vaccination coverage in CIS countries, independent of the official health reports which are known to overestimate vaccination coverage [24]. In all four countries a multi-stage sampling technique was used to obtain representative samples. In the first stage, sampling areas were selected separately in urban and rural areas. In rural areas the sampling unit was a village whereas in urban areas it was a health block (urban areas are subdivided into health blocks – "therapeutical districts" – for which doctors from local clinics are responsible). A list of all households was obtained from the respective authorities. In the second stage, a random selection of households including women of reproductive age (15–49 years) was conducted. Information about the reproductive health of women, infant and child mortality, nutrition of women and children, and vaccination data were collected in the surveys using standard DHS questionnaires [23]. The vaccination data were obtained mostly from child health cards available at medical centers in Armenia (cards were identified for 92.4% of the children) and Kazakhstan (88%). In Kyrgyzstan (with cards available for 75.6% of the children) and Uzbekistan (87.8%) parental recall was also used for collecting data about vaccinations. In this analysis we used only information from child health cards, and excluded children with information about vaccination reported by their parents as this has been shown to be a less reliable source of information [25,26]. Information about vaccination was obtained in the survey for all children under five years of age in Armenia (1726 children) or Kazakhstan (1345) and under three years of age in Kyrgyzstan (1127) and Uzbekistan (1324).

In this analysis we focused on the diphtheria, tetanus and pertussis vaccine (DTP) and the vaccine against measles. Polio vaccine was omitted from the analysis because it has the same timing of administration as DTP-vaccine, and consequently most children either received both or neither. We restricted our analysis to the third dose of DTP-vaccine since problems with vaccination are usually related to the final doses, necessary to complete vaccination [11].

2.1. Statistical analysis

First, we calculated the up-to-date vaccination coverage based on a restricted sample with respect to age, i.e. for DTP from 12 to 59 months in Armenia and Kazakhstan, and from 12 to 35 months in Kyrgyzstan and Uzbekistan. This restriction resulted in a sample size of 1288 children in Armenia, 1106 children in Kazakhstan, 524 children in Kyrgyzstan and 757 children in Uzbekistan. Since the third dose of DTP-vaccine should be administered around the age of 6 months, there were additional 6 months in which the youngest of the children included in the analysis could receive vaccination (and the older children up to their age at the interview). Similarly for measles, which should be administered at the age of 12 months, we included all children older than 18 months; this resulted in a sample of 1111 children in Armenia, 888 children in Kazakhstan, 335 children in Kyrgyzstan and 499 children in Uzbekistan.

Second, we used the Kaplan–Meier method to estimate the vaccination coverage at any given age [12]. Kaplan–Meier is a method to analyze time-to-event data while taking censoring into account [27]. Birthday and date of vaccination were used to calculate the age at vaccination in days. Birthday and date of vaccination were used to calculate the age at vaccination in days. For this analysis we used the total sample without age restrictions including all children for whom information on birthdays and dates of vaccination were available. If vaccination had not been received by the day of interview, the case was classified as censored. The survival function $S(\text{age})$, i.e. the proportion of children not vaccinated at the end of an age interval divided by those not vaccinated at the beginning of the age interval, was estimated for each interval. At any given age, vaccination coverage was calculated as $1-S(\text{age})$, i.e. the cumulative fraction of vaccinated children for the given age. 95% confidence intervals (CI) for proportions were obtained for both methods based on a binomial distribution.

To estimate the fraction of vaccinated population we fitted a three-parameter function to the coverage estimates derived from the Kaplan–Meier method:

$$y(x) = \frac{a_0(x-v)}{1+a_1(x-v)}$$

where $y(x)$ is the cumulative fraction of vaccinated persons up to the age x, v is the minimal vaccination age and a_0, a_1 are the parameters defining the function. We chose to estimate the minimal vaccination age v from the data to allow additional flexibility in the model. The form of the function was selected because it seems to fit the shape displayed in the graphs well. For high age values the function asymptotically a constant a_0/a_1. If $a_0/a_1 < 1$, there is no vaccination for higher age groups; if $a_0/a_1 > 1$, we calculate the fraction of vaccinated population as $\min(y(x), 1)$. For ages just above the minimal vaccination age the function shows a steep monotone increase. Below the minimal vaccination age we set the fraction to 0. So in total the fraction of vaccinated population is computed as $f(x) = \min(\max(y(x), 0), 1)$. Using the parameter values obtained from the best fit, we extrapolated the fraction of the vaccinated population in specific age groups for age groups up to 80 years. Next we computed the contribution of each age group to the fraction of vaccinated population by multiplying the fraction of the population in each age group by the age specific fraction of vaccinated population and computing the overall sum of those fractions (Model 1). The age distributions for each of the four countries was obtained from DHS [28–30]. In a second variant of the analysis we assumed no further vaccination after the age of 5 years and thus all older age groups got the vaccination status of the 5 year old (Model 2).

For the analysis of risk factors for delayed vaccination we defined delayed vaccination as vaccination which was given 1 month, i.e. 30.5 days or more, after the age specified in the national schedules. Since the national immunization schedules differed in the four countries (Table 1), children were classified as vaccinated with delay with the third dose of DTP-vaccine if they received the vaccine by the age of 7 months or more in Armenia, 6 months or more in Kyrgyzstan and 5 months or more in Kazakhstan and Uzbekistan. For instance, the recommended age of 7 months for DPT vaccination equals to 244 days and thus the child was considered being vaccinated with delay if he/she received the vaccination on or after day 245.

Table 1
Recommended age in months for childhood vaccination in the studied countries (according to national vaccination schedules)

Countries	Vaccines			
	DTP1	DTP2	DTP3	Measles
Armenia[a]	3	4.5	6	12
Kazakhstan[b]	2	3	4	12
Kyrgyzstan[c]	2	3.5	5	12
Uzbekistan[d]	2	3	4	12

DTP, Vaccine against diphtheria, tetanus and pertussis.
[a] Vaccination schedule for the year 2000.
[b] Vaccination schedule for the year 1999.
[c] Vaccination schedule for the year 1995.
[d] Vaccination schedule for the year 1993.