



***Bordetella pertussis*: Vaccine Coverage and Immune Status among Children Under Five Years Old in Sana'a City, Yemen**

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Authors' contributions

This work was carried out in collaboration between both authors. Author HAAS designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author HHMAW managed the analyses of the study. Author HAAS managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: This study was made to evaluate the immune response to pertussis among children under five years old by measuring the level of circulating Immunoglobulin G (IgG) antibodies against pertussis toxin (IgG-PT) after immunization with the primary series of DPT (DPT1-3) and then determining the coverage rates of universal childhood vaccines.

Study Design: Cross-sectional laboratory study.

Place and Duration of Study: Department of Medical Microbiology and Clinical Immunology, Faculty of Medicine and Health Sciences, Sana'a University, between June and October 2010.

Methodology: A total of 345 children were randomly selected and investigated for universal childhood vaccination coverage rates; of these, 273 children who had received 3 full doses of DPT were studied for their pertussis immunological status. Blood samples were collected from the latter group and then tested for levels of IgG-PT by ELISA method. For assessment IgG-PT levels more than 24 units/ml were considered protected against pertussis. Data were analyzed according to

gender and age groups.

Results: The coverage rate of pertussis vaccine was 79.1%; only 71.4% of vaccinated children responded to the vaccine with mean level of 33 U/ml. A statistically significant difference was observed with respect to sero-protective IgG-PT between males and females (63.8% and 84.8% respectively, with $\chi^2 = 15$, $p = 0.0001$). Also, a statistically significant difference was observed with respect to sero-protective IgG-PT in different age groups, with older children (>48 months) having a higher rate of antibodies than younger (13-24 months) (90% and 59.1% respectively, with $\chi^2 = 3.87$, $p = 0.04$).

Conclusion: We conclude that a considerable proportion of vaccinated children with a normal immune status were not serologically immune to pertussis. They remain to be reconsidered for either revaccination or booster doses due to lack of or inadequate response. Also, the rates of vaccine coverage for the main universal childhood vaccines are low.

Keywords: Children; coverage rates; DPT vaccine; IgG-PT; pertussis.

1. INTRODUCTION

Pertussis is a very communicable disease caused by *Bordetella pertussis* (*B. pertussis*) and all age groups are susceptible to this respiratory infection, with special problems from vaccine development to vaccine coverage [1,2]. The incidence of adult pertussis has been estimated to be 200 to 500 per 100,000 person-years, even in highly immunized populations. WHO suggests that, in 2008, about 16 million cases of pertussis occurred worldwide, 95% of which were in developing countries and that about 195 000 children died from the disease [3-7], which is thought to reflect waning of the protective immunity from childhood vaccination [4].

Pertussis vaccine use in routine pediatric vaccination programs has dramatically decreased the incidence and complications of whooping cough in children [8,9] but protection is thought to be minimal due to many factors including age, sex, nutrition status etc [10]. In Yemen, the pertussis vaccine is administered in the 2nd and 3rd and 4th months of life, in combination with two booster doses, one administered in month 18 and the other between the years 4 and 6.

In spite of the worldwide decline in the incidence of infection, the circulation of *B. pertussis* has not been eliminated [3,11]. During recent decades, numerous studies have documented that a significant percentage of prolonged cough illnesses among children, adolescents and adults are due to *B. pertussis*, with serological studies indicating a high rate of unrecognized infections [5,12-17]. These groups act as a source of infection for young infants who have not yet completed their primary immunization [14,18,19].

This study was made to evaluate the immune response to pertussis among children of both

sexes and different ages under five years. It was implemented by measuring the level of circulating anti-pertussis antibodies after immunization with the three doses of DPT vaccine, and then determining the coverage rates of universal childhood vaccines in Yemen in order to provide local epidemiological data. This study, together with other national studies, can supply information about the evaluation of vaccination programs and suggest recommendations for the use of booster vaccination.

2. METHODS

This cross-sectional sero-epidemiological study was conducted in healthy children less than 5 years of age in Sana'a city, Yemen. The Yemen is located on the Arabian Peninsula in Southwest Asia. It is bordered by Saudi Arabia to the north, the Red Sea to the west, the Sultanate of Oman to the east and the Arabian Sea to the south. The population in 2008 was estimated at 21,843,554, living in 3,058,299 households. Population structure is typical of a developing country, with the rural population comprising about 71% of the total population. The majority of the population is young, with nearly half (45%) below age 15 years, while the elderly age group (over 64 years) represents only about 3.4%. The literacy rate is about 47% among those 15 years and older (males 63%, females 31%), the total fertility rate 6.2, the average household size 7.1 persons, the poverty rate about 47%, and the annual growth rate of population 2.9%. Life expectancy at birth male/female is about 63/67 years, and the probability of dying under five years in 2012 was 160/1000 live births. These and other factors contribute to Yemen's low ranking in the Development Index cited in the World Human Development Report - 160 among

the 162 countries that were rated in the year 2013 [20].

Previous to this study, Yemen did not have any records of the rate of pertussis vaccine failure. We considered the rate of pertussis vaccine failure, difference and confidence interval as 30%, 0.07 and 95% respectively. According to our calculations, a sample size of 345 subjects was required; this was selected by systematic random method. All health centers in Sana'a were listed (27 centers), then by simple random selection 4 of these centers were selected; finally, every 5th child admitted to these health centers for normal check and vaccination was selected (about 5% of male children and 2% of female children who refused to donate blood were excluded). All individuals were asymptomatic, with normal immune systems, while participating in the study. A total of 273 participants who had received diphtheria, tetanus and whole pertussis vaccine (DTwP) were included in the pertussis immune status (the vaccines are provided by the UNICEF from different reliable sources). The information about vaccines previously administered to the participants was supplied by the official vaccination document.

A full history was taken from each individual studied, and the findings were recorded in the predesigned questionnaire. The collected data included name, age at the time of the study, sex, residence and vaccination date for universal vaccines, namely DPT, measles, BCG, HBV and mumps.

For serological assessment, a venous blood sample of 2-3 ml was drawn after at least one month of administration of DPT vaccine. Immunoglobulin G (IgG) antibodies against pertussis toxin, IgG-PT were measured by Enzyme-Linked Immunosorbant Assay (ELISA) kits and results were interpreted according to the instructions provided by the manufacturer (IBL Immuno-Biological Laboratories, Hamburg, Germany). For qualitative assessment, IgG antibody levels more than 24 units (U)/ml were considered protected against pertussis [21]. Results were also analyzed with regard to quantitative values and were presented as GMT (geometric mean titres).

2.1 Data Analysis

The collected data and the results of this research were analyzed by using EPI-Info version 6, CDC Atlanta, USA. Age and sex

distribution at enrolment, the total prevalence of seropositivity results and mean level of pertussis IgG-PT in the subjects studied were calculated. In addition, the findings were stratified according to the age groups. Difference in sero-positivity percentages was calculated using the chi-square test. The study was approved by the Ethics Committee of our university and informed consent was obtained from all study participants.

3. RESULTS

A total of 345 children were randomly selected and investigated for universal childhood vaccination coverage rates; of these, 273 children who had received 3 full doses of DPT were studied for their pertussis immunological status. The children ages ranged from 4 months old to 48 months old, with a mean of 28.6 months. The majority 34.1% were in age group 13-24 months, followed by 17.6% in age group 25-36 months. Age group 7-12 months constituted 15.4%, age group <6 months 14.3%, age group 37-48 months 7.7% and age group > 48 months 11%. The coverage rate of DPT vaccine was 79.1%, and was slightly higher among male children (81%) than female children (76%) (Table 1). Table 2 shows the immune response to pertussis vaccine by quantifying anti-toxoid IgG antibody level among male and female children. A total of 195 (71.4%) of 273 children responded to the vaccine with antibody level ≥ 24 U/ml. 78 (28.6%) of 273 children had non-protective antibody level (<24 U/ml) and the protective rate among both sexes was 71.4%, being higher among female (84.8%) than males (63.8%). There was no statistically significant variation between the sexes.

When we measured the GMT of serum levels of IgG pertussis toxin among pertussis vaccinated children, the female antibody level ranged from 0.3 to 395 U/ml with mean \pm SD equal to 39 ± 64 U/ml, higher than that of the male children values (1.5 to 184 U/ml with mean \pm SD equal to 33 ± 45 U/ml (Table 2). Table 3 shows the protective rate among different age groups, the rate being higher in older age groups than in younger age groups. Children aged 48 months had the highest protective rate (90%) and the lowest protective rate was in the age group 13-24 months (59.1%) (Table 3).

4. DISCUSSION

Pertussis is a major public health problem affecting thousands of infants and children here

Table 1. Coverage rates of the routine immunization schedule for children attending selected health centers in Sana'a, Yemen, 2010.

Vaccine	Male n=220		Female n=125		Total n=345		X ²	P
	No	%	No	%	No	%		
DPT	178	81	95	76	273	79.1	1.06	0.3
BCG	174	79.1	91	72.8	265	76.8	1.54	0.21
Measles	130	59.1	83	66.4	213	62	1.5	0.22
HBV	159	72.3	83	66.4	242	70.1	1.0	0.3
Polio	155	70.5	91	72.8	246	71.3	0.13	0.72
Mumps	30	13.6	19	15.2	49	14.2	0.1	0.76
Others	26	12	11	9	37	10.7	0.57	0.44

X²=Chi-square > 3.8 (significant)
P =Probability value < 0.05 (significant)

Table 2. Serum levels of IgG pertussis toxin among pertussis vaccinated children

Level U/ml	Male n=174		Female n=99		Total n=273		X ²	P
	No	%	No	%	No	%		
1-10 U/ml	12	6.9	6	6.1	18	6.6	0.07	0.7
11-23 U/ml	51	29.3	9	9.1	60	22	15	0.0001
24-30 U/ml	66	37.9	42	42.4	108	39.6	0.53	0.46
31-40 U/ml	30	17.2	27	27.3	57	21	3.84	0.04
> 40 U/ml	15	8.6	15	15.2	30	11	2.8	0.09
Total protected ≥ 24 U/ml	111	63.8	84	84.8	195	71.4	3.9	0.04
	Male		Female		Total			
Mean	31 U/ml		39 U/ml		33 U/ml			
Variance	94 U/ml		422U/ml		210 U/ml			
SD	31 U/ml		64 U/ml		45 U/ml			
Min	1.5 U/ml		0.3 U/ml		0.9 U/ml			
Max	184 U/ml		395U/ml		395 U/ml			
Median	23 U/ml		27 U/ml		24 U/ml			

Table 3. Positive rate of IgG antibodies of *Bordetella pertussis* among different age groups tested for immunological status against pertussis in Yemen, 2010

Age group in months	Male n=174		Female n=99		Total n=273		X ²	P
	No	%	No	%	No	%		
<6 months	16	59.3	9	75	25	64.1	0.03	0.8
7-12 months	18	60	9	75	27	64.3	0.5	0.47
13-24 months	33	58	22	61.1	55	59.1	0.03	0.85
25-36 months	25	83.3	18	100	43	89.6	1.02	0.3
37-48 months	15	83.3	3	100	18	85.7	0.69	0.4
>48 months	9	75	18	100	27	90	3.87	0.049

P =Probability value < 0.05 (significant)
X²=Chi-square > 3.8 (significant)

in Yemen, as throughout developing countries [22]. Pertussis is a major cause of morbidity and mortality in infants and children world-wide, in spite of the availability of a good protective vaccine [3,23,24]. Yemen introduced universal immunization against pertussis for infants (DPT) in early 70s of the last century, but feedback on the coverage rate of vaccinations and their efficacy in the community have been ignored for

a long period. In addition, information on the prevalence and risk determinants of pertussis and on vaccination coverage rate and immune status against pertussis among children in Yemen has been inadequate or non-existent. Consequently, this study has been carried out to help our understanding of some of these questions.

One of the aims of this study is to determine the coverage rate of DPT vaccine among children. The study findings showed that the vaccination coverage rate was only 79.1%. This result is similar to findings in other developing countries, where DPT vaccine coverage rates among infants and children ranged from 50 - 80% [25,26]. Also, the study findings showed that the vaccination coverage rate of DPT (79.1%) was slightly higher than the coverage rates of other types of bacterial and viral vaccines that are in the universal vaccination program of Yemen, such as BCG (76.8%), measles (62%), and polio (71.3%). This result is different from the findings of Baker and Ketz [27], where DPT vaccine coverage rates among infants and children were similar to the coverage rates of other types of vaccines such as BCG and measles.

When the relative coverage rates of pertussis among male and female children were considered, there was a slight increase of the rate among males (81%) compared with females (75.7%), but this result was not statistically significant (Table 1). It is reminiscent of the findings of Kakar et al. [28] in Afghanistan, where the pertussis vaccine coverage rate among male infants and children (75%) was, however, considerably higher than that for females (50%). These results reflect continuing sex discrimination against females in 3rd world countries, particularly in Islamic countries. In addition the increased morbidity in girls following DTP which makes the mothers keep the girls at home for 2nd and 3rd vaccination might play a role. What's more diphtheria-tetanus-pertussis vaccine administered simultaneously with measles vaccine is associated with increased morbidity and poor growth in girls as described in a randomised trial from Guinea-Bissau by Agergaard and others [29].

Also, the study findings showed that only 71.4% of all vaccinated individuals were regarded as protected (≥ 24 U/ml) [21] and that the protective rate of pertussis IgG antibody was higher in females (84.8%) than in males (63.8%). Different findings were reported in the UK among children, where a higher protective response rate was found among vaccinated children (85%), but both male and female children showed an equal protective rate [30]. This difference in findings could be attributed to that males and females do have differences in their immune systems [10]. In addition, different antibody response in males and females have been reported previously [10] – but not for pertussis, so this is a new finding.

Concerning the rest of the study group, 28.6% developed antibody amounts < 24 U/ml or negative, indicating a poor anti-pertussis response after receiving a full course of vaccine as shown in Table 2. It can be guessed from this finding that these vaccinated individuals were hypo-responsive to the immunization, and that their antibodies may rapidly wane over time, or that the quality of vaccine used was very bad. Even in these instances, losses of antibody dose do not necessarily imply loss of protection [21]. Considering anti-pertussis may disappear in a substantial proportion of vaccinees after an initially successful vaccination, a booster dose of vaccine, following the administration of the primary course is recommended by most national bodies. However, is it necessary to boost after initially successful vaccination? The result of long-term follow-up studies, together with assessment of the role of immunological memory among vaccinees, now question the necessity of providing booster doses following a successful course of primary immunization [31]. Other studies showed that protection is still maintained among vaccinees, even in developing countries, despite waning or undetectable anti-pertussis antibody levels and also that pertussis is not a serious problem after 5 years of age [32]. As a final point we emphasize in the importance of protection of the unvaccinated infants by vaccinated them in which pertussis vaccines are highly effective, strongly recommended and save many infant lives every year [33]. In addition more information, however, needs to be gathered first on the occurrence of clinical/subclinical pertussis cases (morbidity and mortality from pertussis in Yemen) and the overall morbidity and mortality following DPT vaccination to confirm the need for revaccination or booster doses due to lack of or inadequate response as recommended by WHO [3].

Host factors such as age may influence the immune response to the vaccine [34]. Increasing age was shown to be correlated with an increasing level of the antibodies (Table 3). Protective response rate of anti-pertussis IgG increased from 59.1% in age 13-24 months to 90% in age group > 48 months. Different findings were reported from other countries where ages less than 12 months showed a greater protective response to the vaccine than older age groups [35]. In another study conducted in European countries, younger children had a better a response to pertussis vaccine than older children [33,35]. Our different result might be due to the higher level of exposure of older children to

organisms circulating in the community [36] and to DPT booster vaccinations in older children. So booster doses of the pertussis vaccine at the 6th and 12th months of life should probably be recommended in Yemen.

5. CONCLUSION

We conclude that a considerable proportion of vaccinated children with a normal immune status were not serologically immune to pertussis, and remain to be reconsidered for either revaccination or booster doses due to lack of or inadequate response; more information, however, needs to be gathered first on the occurrence of clinical/subclinical pertussis cases (morbidity and mortality from pertussis in Yemen) and the overall morbidity and mortality following DPT vaccination. Also, the rates of vaccine coverage for the routine immunization schedule of childhood vaccines were low.

CONSENT

All authors declare that 'written informed consent was obtained from the parents of the children for publication of this work.

ETHICAL APPROVAL

The study was approved by the Ethics Committee of our university.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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