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Pertussis seronegativity in pregnant women in the city of Al Ain, United Arab Emirates

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ABSTRACT

Objective: As the current recommendation of administering Tdap (tetanus-diphtheria-acellular pertussis) to all pregnant women has not been widely implemented in the United Arab Emirates (UAE), we aimed to ascertain the prevalence of pertussis seronegativity during pregnancy.
Methods: IgG antibodies against *Bordetella pertussis* toxin (PT) were measured in 213 women attending the antenatal clinic at Oasis hospital, Al Ain, UAE. Results were compared by maternal age, nationality and gestational age with the Kruskal–Wallis test for IgG-PT levels and the Chi-squared test for serology status.
Results: The mean age ± SD of the participants was 30.4 ± 5.6 years, mean gestational age ± SD of 25.5 ± 3.3 weeks. Serum concentration of IgG-PT <10 IU/ml were found in 160 out of 213 women (75%; 95% confidence interval 69%, 81%). There was no significant difference in the geometric mean of serum IgG-PT concentration across maternal age ($P = 0.80$) or nationality ($P = 0.90$). There were no differences in the prevalence of seronegativity with maternal age ($P = 0.65$) or nationality ($P = 0.90$).
Conclusion: With a high prevalence of pertussis seronegativity in pregnant women, there is a potential benefit of introducing pertussis vaccination during pregnancy into our national immunization program.

Introduction

Pertussis (whooping cough) is caused by the exclusively human pathogen *Bordetella pertussis* (*B. pertussis*) and other *Bordetella* species such as *B. parapertussis*. This highly infectious disease can cause significant morbidity in infants and the elderly. The whole-cell pertussis vaccines, which were introduced in the late 1940s, have led to a decrease in cases of pertussis. However, the development of minor side effects, such as fever, pain, and swelling at the injection site, and the rare but serious neurological complications, have resulted in a decrease in vaccination uptake (Bouchez and Guiso, 2015). These reasons have led to the development of the less reactogenic acellular pertussis component of the vaccine (Tdap), with protection waning during the five years following the 5th dose of Tdap, with the risk of pertussis increasing by 42% each year after the 5th Tdap dose (Klein et al., 2012).

The waning of post-vaccination antibodies with age suggests that the seronegativity rate increases from infancy and childhood throughout adolescence and adulthood, resulting in an enlarging human reservoir of *B. pertussis*, which would increase the risk of infecting infants and the elderly (Sheridan et al., 2014). The prevalence of pertussis has been recently surging in adolescents and adults in almost all countries that have switched from whole-cell to acellular pertussis vaccine (Marconi et al., 2012). Epidemiological studies have demonstrated that 7% to 17% of cases of prolonged cough are attributable to *B. pertussis* infection in adolescents and adults (Philipson et al., 2013). The reasons for this waning of vaccine-induced immunity are multiple. For example, alterations in *B. pertussis* populations including antigenic divergence with vaccine strains have been noticed following vaccine introduction. These pathogen changes have diminished the period in which pertussis vaccines are effective and thus enhanced the waning of immunity (Esposito et al., 2019).

Pertussis infection remains prominent among young infants, causing severe illnesses especially during the first three months of age, before their primary immunization (Marconi et al., 2012;

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Paddock et al., 2008). Household contacts, especially mothers and siblings, are responsible for up to 75% of *B. pertussis* infections in infants (Hanson et al., 2011).

In the United Arab Emirates (UAE), the current pertussis vaccination program consists of a series of consecutive doses of acellular or whole-cell pertussis (as part of a combination vaccine) at the age of two, four, six and 18 months, then, twice in school, in the first and the eleventh grades. No further doses are routinely given in adulthood. In the year 2018, pertussis containing vaccines coverage estimate for the United Arab Emirates was 99% (WHO Report, 2018). Despite the high coverage, the number of notified cases of pertussis in the Emirate of Abu Dhabi, UAE has increased from 15 cases in 2014 to 51 cases in 2016, with 37 (72%) of the reported cases in 2016 being infants less than one year of age ("Communicable Diseases Bulletin", Department of Health, Abu Dhabi, 2016). These alarming figures highlight the high vulnerability of this age group and indicate the need for different preventive strategies.

One choice of improvement is to intervene by vaccinating the reachable population of pregnant women at antenatal clinics (Centers for Disease Control and Prevention (CDC), 2013). No studies have been performed in the UAE on maternal pertussis sero-status. The only study on pertussis seroprevalence from the UAE was among healthy children and has demonstrated that up to 70% of children between two and six years of age are seronegative after having received their primary pertussis immunizations (Al-Mekaini et al., 2016). Determining the seroprevalence of *B. pertussis* in pregnant women would provide evidence for a maternal pertussis vaccination program in the UAE.

This study aims to ascertain pertussis seronegativity in pregnant women attending the antenatal clinic at Oasis hospital in Al Ain city by measuring maternal immunoglobulin titers against pertussis toxin (IgG-PT). This toxin is the most specific and most virulent antigen of *B. pertussis* (Barkoff et al., 2015; Paddock et al., 2008), with well recognized efficient placental transfer of these immunoglobulins (Villarreal-Pérez et al., 2014).

Materials and methods

Al Ain city has several antenatal clinics. As each one caters toward pregnant women based on their individual health insurance provider, thus on their nationality, the majority either deal with mostly UAE nationals or exclusively expatriates. Medical care at Oasis hospital, a 100-bed private Joint Commission International accredited medical institution, is covered by the majority of health insurance providers, and this is reflected in the wide range of nationalities of the patients they cater to, making it an ideal setting to study a representative segment of the multinational population in the city and also the country. The hospital handles yearly over 150,000 outpatients, admits 7600 patients, and performs 3000 deliveries per year.

Pregnant women attending the antenatal clinic at Oasis hospital in Al Ain are routinely offered a booster Tdap in the third trimester of pregnancy. After written informed consent, we enrolled in the study an unselected cohort of women who attended that clinic at different gestational ages, before Tdap was administered.

Exclusion criteria included a history of vaccination for pertussis in the previous twelve months, or a history suggestive of pertussis or exposure to a contact with proven or suggestive pertussis infection.

With an estimated pertussis seronegativity of 85% in pregnancy (Orenstein, 1999), a sample of 215 pregnant women was calculated to give the study adequate power with a confidence level (ci) of 95% with 5% precision.

Blood samples of 5 ml were collected from each participant. The serum was separated by centrifugation and stored at −80 °C before measurements. Enzyme-linked immunosorbent assay (ELISA) (NovaLisa *Bordetella pertussis* IgG ELISA, NovaTec Immundiagnostica GmbH, Dietzenbach, Germany) was employed for the quantitative determination of IgG antibodies against *B. pertussis* toxin (IgG-PT) in the participants' sera, a toxin contained in all pertussis vaccines. All ELISA procedures were tested following the directions of the manufacturer. All tested sera were initially diluted with the sample diluent (1:100) before adding to the *B. pertussis* toxin pre-coated microtiter strip wells. After incubation, unbound antibodies were washed out, followed by addition of horseradish peroxidase-conjugated anti-human antibodies. After washing substrate was added, absorbance was measured at 450 nm. The titers of test samples were calculated using a standard curve generated using known standards provided in the kit. The lower limit of detection (LOD) was 10 IU/ml (international units per milliliter) and, for the purpose of calculations in this study, concentrations below that LOD were assigned half that value (5 IU/ml). Titers <10 IU/mL defined seronegativity, and titers >10 IU/ml were considered as positive and protective against pertussis. Concentrations >100 IU/ml suggested recent pertussis infection

Table 1
Pertussis serology status in 213 pregnant women. Results expressed as number (percent).

	Seroprotective (IgG 10–100 IU/mL) n = 53	Seronegative (IgG < 10 IU/mL) n = 160	Total	*P*
Nationality				
Europe or North America	0 (0)	2 (100)	2 (0.9)	0.9
Africa	1 (12.5)	7 (87.5)	8 (3.6)	
South East Asia	2 (20)	8 (80)	10 (4.5)	
Other	4 (25)	12 (75)	16 (7.2)	
GCC	10 (29)	24 (71)	34 (15.4)	
Emirati	35 (25.9)	100 (74.1)	141 (63.8)	
Middle East	2(22.2)	7 (77.8)	10 (4.5)	
GA (weeks)				0.05
<24	9 (52.9)	8 (47)	17 (7.9)	
24–28	37 (22.7)	126 (77.3)	163 (76.5)	
28–32	7 (25.0)	21 (75.0)	28 (13.6)	
28–36	0 (0)	5 (100)	5 (2.3)	
Age (yrs)				0.6
<20	1 (50)	1 (50)	2 (0.9)	
20–30	21 (23.1)	70 (76.9)	91 (42.7)	
30–40	27 (25.2)	80 (74.8)	107 (50.2)	
>40	4 (30.8)	9 (69.2)	13 (6.1)	

The percent in the Total column represents the percentage of all the 213 participants.
Chi squared test or Fisher exact test for small numbers. GCC: Gulf cooperation council (Saudi Arabia, Bahrain, Kuwait, Oman).

(Guiso et al., 2011; Riffelmann et al., 2010), and these participants were excluded from the analysis.

Maternal age, gestational age, and IgG-PT titers were described as mean, standard error of the mean, standard deviation and 95% confidence intervals (ci). However, as the titers did not follow a normal distribution (Shapiro Wilk test), they were reported as geometric mean (GMC) with 95% ci. The non-parametric independent sample Kruskal-Wallis test was used to assess differences in IgG-PT levels, and also in their GMC between groups. The proportions and percentages of serology status among the groups were compared with the Chi-squared test or the Fisher exact test for small numbers. The 95% ci for the prevalence of seronegativity were also calculated. The software STATA version 15 (StataCorp, Texas, USA) was used for all analyses and, for all tests, a two-tailed *P*-value <0.05 defined statistical significance.

Results

A total of 221 women were enrolled in the study. Eight were excluded from the analysis as they had serum IgG-PT levels >100 IU/ml. The data from the remaining 213 women were analyzed and their demographics are described (Table 1). Their mean age ± SD was 30.4 ± 5.6 years and the mean gestational age ± SD was 25.5 ± 3.3 weeks, ranging from 8 to 36 weeks. None had pertussis immunization, symptoms suggestive of pertussis or contact with a suspected case within a year of the enrolment date. Seven women had received pertussis immunization three to five years earlier and none of the others remembered having received any vaccination for at least the past 10 years.

A total of 160 pregnant women (75%; 95% ci 69%, 81%) had serum concentration of IgG-PT <10 IU/ml, making them, and their offspring after delivery, susceptible to pertussis (Table 1 and 2). Fifty-three women (25%, 95% ci 19%, 31%) had adequate IgG-PT serum levels (10–100 IU/ml) (Table 1).

IgG-PT concentrations (IU/ml) by gestational age, maternal age, and nationality are reported in Table 3. The mean concentration of serum IgG-PT was not significantly different among maternal ages ($P = 0.8$) (Figure 1a), gestational ages ($P = 0.06$) [Figure 1b], or nationality ($P = 0.9$) (Figure 1c).

However, although there was no significant difference in IgG-PT geometric mean (Table 3) across maternal ages ($P = 0.3$) (Figure 2a) or nationalities ($P = 0.9$) (Figure 2c), the geometric mean concentration of serum IgG-PT was significantly higher in gestational ages below 24 weeks ($P = 0.02$) (Figure 2b).

Although there were no differences in the prevalence of seronegativity with maternal ages ($P = 0.6$) [Table 1 and 2] and [Figure 3a], or nationalities ($P = 0.9$) (Table 2 and Figure 3 c), there were significant differences among the different gestational ages ($P = 0.05$) (Table 1 and Figure 3b). The prevalence of seronegativity by gestational age increased significantly from 47% (95% ci 23%, 72%) in pregnancies under 24 weeks to 100% in pregnancies above 32 weeks of gestation ($P < 0.04$) (Table 2 and Figure 3b), but that trend was not statistically significant ($P = 0.2$).

Discussion

While the recently observed increase in the incidence of reported pertussis cases among infants in the UAE ("Communicable Diseases Bulletin", Department of Health, Abu Dhabi, 2016) may reflect better disease awareness and reporting by pediatricians, it may also reflect the waning of the pertussis vaccine-induced immunity among the general population, including pregnant mothers. Low serum IgG-PT levels correlate with increased susceptibility to pertussis (Taranger et al., 2000). This has prompted us to study the seroprevalence of maternal IgG-PT in order to determine the serological baseline among pregnant women who did not receive a maternal Tdap. We found that 75% of pregnant women had a serum concentration of IgG-PT <10 IU/ml, making them, and their offspring after delivery, susceptible to pertussis, confirming previous reports (Meng et al., 2018; Wanlapakorn et al., 2017). This prevalence is probably an underestimate as it is possible that serum levels above 30 IU/ml might be necessary to seroprotect their newly born infants (Esen et al., 2007).

Although IgG-PT and IgA-PT have been used together in pertussis seroprevalence studies, our data are based entirely on IgG-PT measurements. Recent evidence suggests the combination performed no better than IgG-PT alone. Moreover, there is evidence of an age-related increase in the prevalence of isolated positive IgA-PT results which did not appear to be associated with recent pertussis infection (May et al., 2017).

Several strategies have been considered to increase protection and prevent pertussis in infants including postpartum immunization, cocooning (targeted vaccination of the mother and close contacts of the newborn), neonatal (at birth) immunization and maternal immunization (vaccination with Tdap during pregnancy) (Argondizo-Correia et al., 2019). The first two strategies offer only indirect protection to infants. Cocooning, on the other hand, necessitates the vaccination of large numbers of people which can be costly and difficult to implement. Although at birth immunization can theoretically induce early and direct protection to the infant, it can result in immunological tolerance with reduced levels of antibodies to *B. pertussis* compared to those in children who were vaccinated later (Argondizo-Correia et al., 2019).

Maternal immunization aims at inducing protection in mothers and transmitting specific passive protection to the fetus and newborn, until the infant's first pertussis vaccination. Maternal Tdap is routinely recommended in many countries such as the US,

Table 2
Prevalence of pertussis seronegativity (IgG-PT <10 IU/ml) in 213 pregnant women.

		Number of seronegative women	Mean prevalence (%)	95% ci	*P* value[a]
213 women		160	75	69, 81	
Age (years)					
	< 20	1	50	12, 98	0.65
	20–30	70	77	67, 85	
	30–40	80	75	65, 82	
	>40	9	69	38, 91	
Gestational age (weeks)					0.04
	<24	8	47	23, 72	
	24–28	126	77	70, 83	
	28–32	21	75	55, 89	
	32–36	5	100	48, 100[¶]	

ci: confidence intervals
[a] Chi-squared test or Fisher exact test for small numbers.
[¶] One-sided 97.5% confidence interval.

Table 3
Serum *Pertussis* IgG-PT concentrations (IU/ml) in 213 pregnant women.

	Gestational age (weeks)				Age (years)				Nationality						
	<24	24–28	28–32	32–36	<20	20–30	30–40	>40	Africa	UAE	Europe/North America	GCC	Other	Middle East	South East Asia
Number of participants	17	163	28	5	2	91	107	13	8	135	2	33	16	9	10
Mean	30.8	12.9	13.3	3.7	32.8	13.1	14.4	17.9	6.3	14.0	2.5	18.6	13.4	12.4	13.6
SD	36.2	22.7	20.9	2.8	42.8	23.4	23.7	29.2	9.6	23.3	0	28.9	25.8	22.7	26.0
SEM	8.8	1.8	3.9	1.2	30.3	2.4	2.3	8.1	3.4	2.0	0	5.0	6.4	7.5	8.2
Lower 95% ci	12.1	9.4	5.1	0.2	−352	8.2	9.8	0.3	−1.7	10.1	2.5	8.3	−0.3	−5.0	−5.0
Upper 95% ci	49.4	16.5	21.4	7.2	417.5	17.9	18.9	35.5	14.3	18.0	2.5	28.9	27.2	29.8	32.2
Geometric mean	11.2	4.8	5.0	3.2	12.5	4.8	5.2	5.9	3.7	5.2	2.5	6.1	5.0	4.6	4.6
95% ci geometric mean	4.9, 25.5	4.0, 5.8	3.0, 8.1	1.6, 6.5	NA	3.8, 6.2	4.1, 6.7	2.4, 13.9	1.8, 7.8	4.2, 6.4	2.5, 2.5	3.7, 10.0	2.6, 9.6	1.7, 12.3	1.8, 11.6

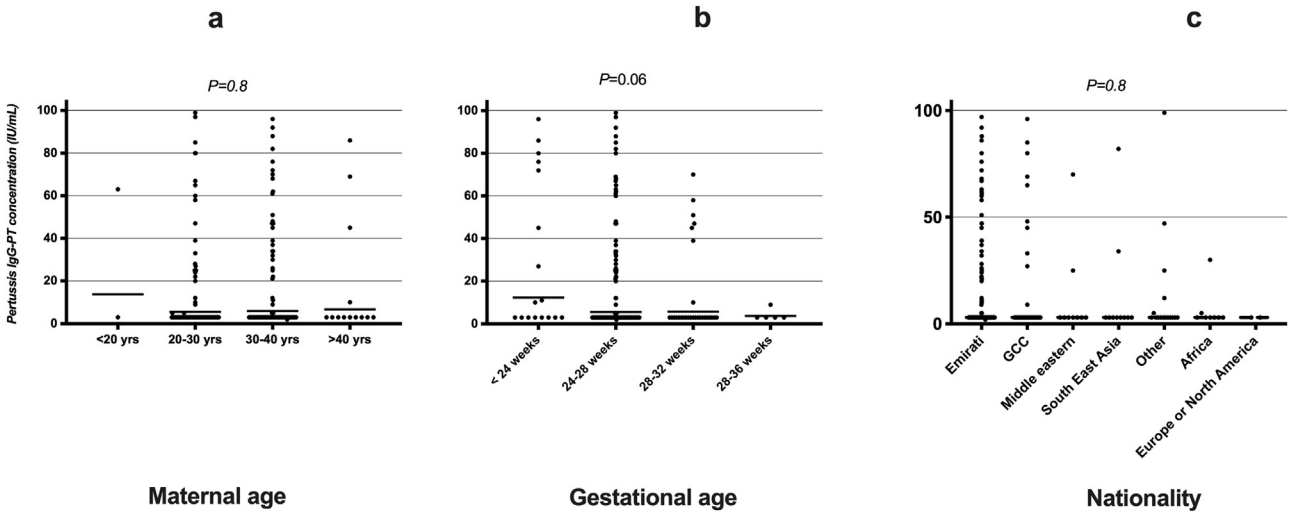

Figure 1. Serum IgG-PT concentrations in 213 pregnant women by (a) maternal age, (b) gestational age, and (c) nationality.

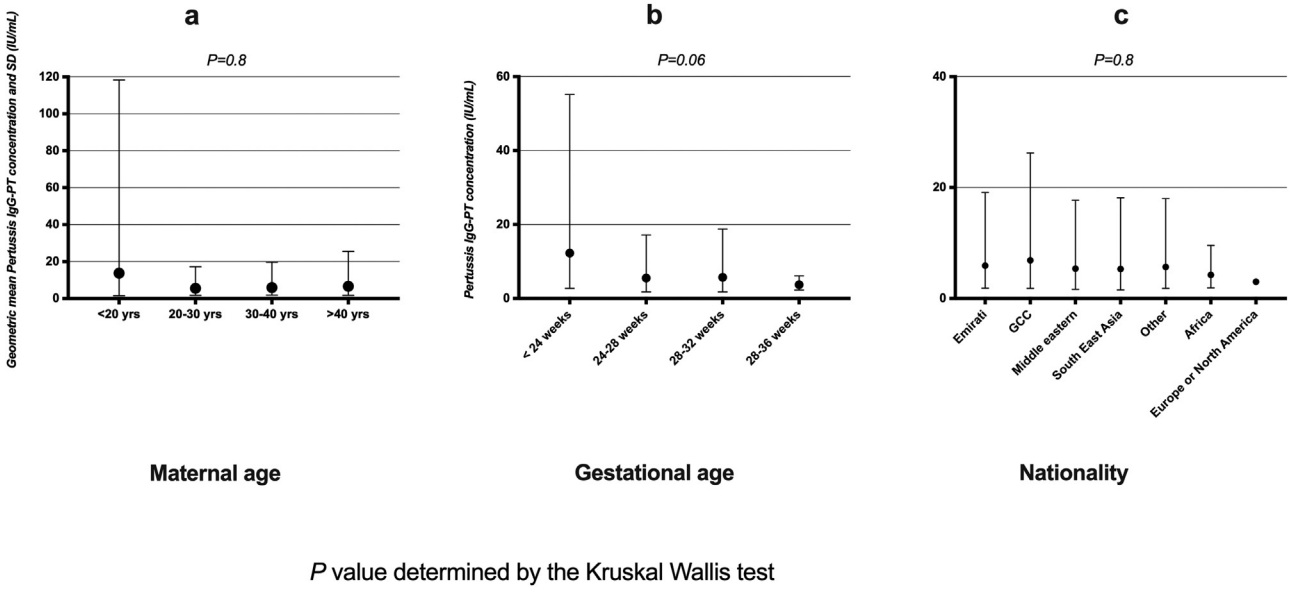

Figure 2. Geometric mean concentrations (and 95% confidence intervals) of serum IgG-PT in 213 pregnant women by (a) maternal age, (b) gestational age, and (c) nationality.

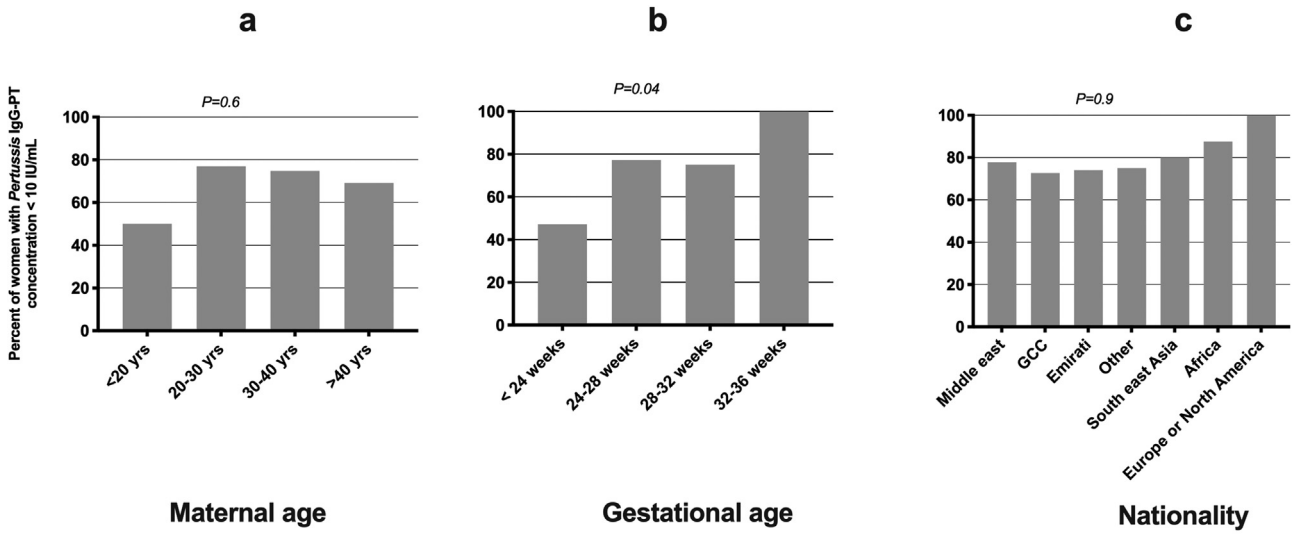

Figure 3. Prevalence of seronegativity for pertussis (IgG-PT <10 IU/ml) in 213 pregnant women by (a) maternal age, (b) gestational age, and (c) nationality.

UK, and New Zealand. Studies from these countries suggest that this intervention is safe and successful in preventing pertussis among infants (Abraham et al., 2018; Amirthalingam et al., 2016; Petousis-Harris et al., 2016). In the UAE, we anticipate this intervention to be easily implemented based on the existing maternal care system. Furthermore, modeling data suggest that this strategy can be cost-effective (Atkins et al., 2016). Nevertheless, local cost-effectiveness studies are warranted.

In our cohort, we also attempted to see if there were differences in IgG-PT levels among subgroups. We found that seronegativity to pertussis increases significantly with increasing gestational age, reaching 100% in pregnancies above 32 weeks of gestation. Although the sample size was small, this finding suggests a potential benefit in providing Tdap to pregnant women in our community earlier than the suggested 27 to 31 weeks of gestation (Abu Raya et al., 2016; Eberhardt et al., 2017). Early second trimester Tdap maximizes antibody transference to the newborn (Eberhardt et al., 2016).

As no women had received recent Tdap booster, the lowest seronegativity rate in pregnant women not of European and North American origin might be explained by a higher prevalence in those communities of previous exposure to, or infection with, pertussis (Katfy et al., 2017; Omer et al., 2016).

This study suffers from limitations. As the history of previous immunizations, prior infection with *B. pertussis* or of contact with a person suspected or proven to have that infection depended uniquely on the participants' recollection, the study might also suffer from recall bias. This is because post-vaccination antibody titers do not persist very long, especially after the acellular pertussis vaccine, and, lacking accurate information of prior illness or exposure to pertussis makes it impossible to evaluate the conceivable effects of natural boosting in our results. In addition, we cannot exclude a possible selection bias as the study was performed in a single hospital and generalization of the results cannot be made. Because of the above mentioned limitations, our results may not be generalizable, as they can either overestimate or underestimate the calculated results for the whole population, depending on differences in the recall bias or in the demographic or pertussis susceptibility of patients attending other antenatal clinics. Furthermore, with umbilical cord pertussis titers reported to be 50% to 100% higher than maternal titers, as a result of the efficiency of transplacental transfer, we cannot rule out that some the offspring of mothers with undetectable titers during pregnancy may in effect be seroprotected at birth (Abraham et al., 2018), causing an overestimation of neonatal susceptibility in our results.

Future studies therefore need to be multi-centered in order that the results could be generalized to our community. Such studies should include accurate pertussis vaccination records and information on the personal history of pertussis disease.

Conclusion

In our study, three quarters of pregnant women have undetectable serum concentration of IgG-PT, making them, and their offspring after delivery, susceptible to pertussis infection. In order to protect infants from serious clinical forms of pertussis in their first 6 months of life, it is important to consider immunizing pregnant women with Tdap with the expectation of maternal immunity. This intervention is easily implemented based on the existing maternal care system and would cover gaps in the current national immunization program.

Conflict of interest

All authors declare that they have no conflicts of interests.

Ethical approval

Ethics approval was granted by the Al Ain Medical District Human Research Ethics Committee (ERH- 2016- 4264) and written informed consent was obtained from all participants and their anonymity maintained.

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