Author's response to reviews

Title: Clinical presentation of pertussis in fully immunized children in Lithuania

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Dear Editorial Team,

Thank you for the comments provided by reviewers regarding our paper. According to the referees suggestions and revisions our manuscript has been revised. We passed the manuscript on to a colleague for language corrections. All authors suppose that our manuscript has improved and hope that it will be considered suitable for publication.

Best regards,

Irena Narkeviciute

Answers to Juhani Eskola (Reviewer 1)

Answers to Major Compulsory Revisions
Collecting detailed clinical information of the current illness from the patient or from the parents of the patient we found out that 11 children had had two episodes of successive coughing, we mean that they had two waves of coughing (the second started when the first one was not ended), in other words cough became more intensified when first one was not ended. These patients cough duration was longer than those with one episode (21 children). In our view and also literature data suggest that duration of cough increased when more than one agent (B.pertussis with atypical pathogens, i.e. M.pneumoniae, C.pneumoniae) is detected.

We state that 35% of all pertussis cases were diagnosed in vaccinated children during the period from 1991 to 1995, 33.4% of the cases from 1996 to 2000 and 43.2% in 2001. These official data we received from Centre of Infectious Disease Control and Prophylaxis in Lithuania. Part of cases of pertussis were diagnosed by clinical data (clinical case), some cases were confirmed using bacteriological or serological method.

We agree with your comment according criteria used in our paper (more than two weeks of cough with certain symptoms and positive IgM/IgA antibodies). This criteria does not follow the generally used criteria in the scientific literature. We refuse from this criteria in our paper. We made the correction in the Methods”.

Answer to Minor Essential Revision
We agree that our conclusion when prolonged cough is present in fully vaccinated children, it is frequently (84.4%) associated with the classical pertussis symptoms needs clarification. Our data suggest that pertussis should be considered in the differential diagnosis of persistent cough in fully vaccinated children. We made the corrections in the "Discussion”.

Answers to Alberto E. Tozzi (Reviewer 2)
Answers to Major Compulsory Revisions
We agree that our study gives information on the clinical presentation and describes some epidemiological aspects of immunized cases: time period between the last (the fourth) vaccination dose and the clinical manifestation of pertussis. We briefly described the epidemiology data of pertussis in Lithuania in the "Background" and in the "Discussion". We changed the title of our paper to Clinical presentation of pertussis in fully immunized children in Lithuania".

We agree that in general the current opinion is that pertussis is relatively mild in vaccinated individuals. We made the corrections in the "Background", we changed our statment according clinical course of pertussis in fully immunized children.

70 cases included in our study were consecutive. The patients were referred to the hospital by general practitioners or pediatricians, because detailed investigation of the children with prolonged cough of unknown etiology was only available in the hospital. We made the corrections in the "Methods".

The data regarding to the patient's age, vaccination history, clinical symptoms and signs of the current illness, previous treatment was collected on to computer database. The clinical information was collected from the patients and their parents. We analyzed medical history, examined patients and viewed medical documentation.

We agree that case definition of pertussis for confirmed case is unusual. We refuse from this case definition. In our study diagnosis of pertussis was confirmed serologically.

We agree with your comment that hospitalization occurred long time after the cough had begun. This may have improved the capacity of serology in detecting cases. We made the corrections in the "Methods" according one-point serology.

We agree that obtaining culture for B.pertussis and B.parapertussis could have corroborated the results of our study and would made the case series more comparable to others, but late stage of illness (mean duration 61.4+-68.3 days) and antimicrobial therapy before hospitalization kept us for not using this diagnostic method.

We agree that more severe cases could be selected in this study. We should take into account other fully vaccinated children who had mild pertussis, but were not referred to the hospital. We made the corrections in the Discussion".

There were no contact of cases with laboratory confirmed pertussis. Contact children with cough from families were reffered at the hospital at the same time.

The statement that protection from acellular pertussis vaccines lasts 4-6 years is supported by the references [13,14].

We agree that antibiotics could be markers of severity. Tozzi et al. [7] has showed that children treated with antibiotics had cough which lasted 6 to 11 days longer and spasmodic cough 4 to 13 days longer than untreated patients. The difference between groups regarding to the duration of cough be explained by the disease severity, but not by antibiotic impact, that's why antibiotic treatment could be a marker of the disease severity. We made the corrections in the Discussion".

We agree that since culture has not been performed, no information is available on B. parapertussis infection. We made the corrections in the "Methods".

Answer to Minor Essential Revision
We agree that in the abstract and in the disscussion classical pertussis symptoms should be listed instead the term "typical pertussis". We made the corrections in the "Abstract" and in the "Discussion".

We made the corrections in the "Abstract" and in the "Methods". The time frame of our study was 8 month.

70 patients were consecutive in our study.

In the "Background" the comments on resurgence of pertussis present the data from the USA, from the Netherlands and from Finland. We agree that it would be appropriate to mention this point one time. We leave it in the "Background" only.
Two pieces of information on vaccination coverage in Lithuania and on pertussis incidence we put together at the end of the introduction.

In the Table 1 we mentioned the number of patients (n=32) included in the analysis.

Answers to Hester E de Melker (Reviewer 3)

Answers to Major Compulsory Revisions

Background

We agree that we need to mention improved diagnosis and awareness as one of the (possible) reasons for increased incidence among adolescents and adults. We made the corrections in the "Background".

Too much detail is given because we wanted to show the increasing percentage of pertussis cases among vaccinated children in Lithuania with pertussis in two periods (1991-1995; 1996-2000) and in 2001 year, when our study was performed.

We present the percentage of vaccinated children against pertussis among the pertussis cases. We made the corrections in the "Background".

We agree that in general the current opinion is that pertussis is relatively mild in vaccinated individuals. We made the corrections in the "Background".

Methods

The definition of prolonged cough - cough lasting two weeks or more.

We made the corrections in the "Methods".

From May to December 2001, 70 children aged 1 month to 15 years with prolonged cough (duration [greater than or equal to] two weeks) and siblings with shorter duration cough (but not less than 7 days) were investigated at Vilnius University Children's Hospital, Centre for Paediatrics. The patients were referred to the hospital by general practitioners or pediatricians, because detailed investigation of the children with prolonged cough of unknown etiology is only available in the hospital.

According manufactures instructions (Labsystems, Finland) B.pertussis antibodies (EIU) results in a single serum sample were interpretated:

IgA:
Negative < 15
Uncertain positive 15-30
Low positive 31-50
Positive >50

IgM:
Negative < 55
Uncertain positive 55-100
Low positive 101-140
Positive >140

We made the corrections in the "Methods" and present medians.

Two-sided t test was used to compare two groups of children with two episodes and with one episode of cough, but it was replaced by Wilcoxon test. We made corrections in the "Methods".

Results

53 from the 70 with prolonged cough showed laboratory evidence of pertussis and 32 of them were fully vaccinated against pertussis. The aim of our study was to describe clinical presentation of fully vaccinated children with pertussis.

We made the corrections in the "Results" and added medians.

Discussion

We agree that sometimes too much detail is given (e.g. on percentages etc.), but we wanted to show full and detailed data presented in scientific literature and epidemiological data of pertussis in Lithuania.

Despite high vaccine coverage there is a significant increase of pertussis cases among vaccinated children, thus Lithuania is not an exception. We think that our paper to the current scientific literature would add
some value information about pertussis classical symptoms frequency, clinical manifestation of pertussis of 
vaccinated older (age median 11 years) children and time period between the last (the fourth) vaccination 
dose and the illness of pertussis. Our study showed that children immunized with four doses of DTP 
vaccine, fall ill with pertussis at the median of 11 years old, following 9 years after vaccination.

Thank you very much for your comments and advices.

Sincerely yours,

Irena Narkeviciute