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Research Article

# Respiratory Pathogens Identified in Patients with a Clinically Suspected *Bordetella pertussis* Infection

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**Abstract**

**Background and objective:** Because of the low sensitivity of the suggested two-weeks cough duration to guide the management of suspected cases of pertussis, using duration of one week have been recently used instead. The aim of this study was to identify *Bordetella pertussis* and other respiratory pathogens in patients coughing for at least one week.

**Methods:** Prospective, observational, cohort study of 39 patients (13 males, 33%), aged between 16.5 and 65 years, presenting to Oasis hospital, Al Ain city, United Arab Emirates, between March and July 2017. Nasopharyngeal samples were analysed by real-time multiplex polymerase chain reaction assay. Quantitative determination of serum IgG and IgA antibodies against *Bordetella pertussis* toxin was performed by enzyme-linked immunosorbent assay.

**Results:** The median duration of cough was 13 days. No *Bordetella pertussis* or *parapertussis* were isolated in any patients. Four patients (10%), had serum pertussis-toxin IgA >12 IU/ml (of whom one also had the serum IgG >10 IU/ml), indicating probable pertussis infection. Only two of them had had a cough for more than two weeks. Twenty-four (61%), patients had no detected pathogens and in 15 (39%), at least one pathogen was detected, mainly *rhinovirus*, *coronavirus C43*, and *Mycoplasma pneumoniae*.

**Conclusion:** Applying the case definition of a two-weeks cough duration would have missed half of the cases of pertussis. Even with the cut-off of one week of coughing, it remains more often associated with viruses or other bacteria.

## ABBREVIATIONS

AdV: adenovirus; B. parapertussis: Bordetella parapertussis; B. pertussis: Bordetella pertussis; C. pneumoniae: Chlamydophila pneumoniae; CDC: Centers for Disease Control and Prevention; covoc: Coronavirus; ELISA: Enzyme-linked immunosorbent assay; C. pneumoniae: Chlamydophila pneumoniae; H. influenzae: Haemophilus influenzae; hBoV: human bocavirus; hEV: human enterovirus; HI: Haemophilus influenzae; hMPV: metapneumovirus; HRV: human rhinovirus; L. pneumophila: Legionella pneumophila; LOC: lower limit of detection; M. pneumoniae: Mycoplasma pneumoniae; NA: not available; PCR: Polymerase Chain Reaction; PIV: parainfluenza virus; PT: pertussis toxin; RSV: respiratory syncytial virus; S. pneumoniae: Streptococcus pneumoniae; S. pyogenes: Streptococcus pyogenes; SP: Streptococcus pneumoniae.

## INTRODUCTION

Persistent cough is a common symptom for which the etiology often remains uncertain [1-3]. Infectious causes may include pertussis and other bacterial or viral pathogens [4,5].

Despite the vaccination programs and their high coverage, the incidence of pertussis has been increasing in many countries [6]. The disease has been diagnosed in all age groups, including adolescents and adults, who, despite having mild symptoms, are an important source of transmission to young infants [7]. It has been demonstrated that 7% to 15% of the cases of prolonged cough in adolescents and adults are caused by *Bordetella pertussis* (*B. pertussis)* [8,9]. However, early diagnosis of pertussis is challenging as other respiratory pathogens can cause pertussis-like illnesses.

The clinical presentation of pertussis varies with age and vaccination status [10,11]. Cough is the only symptom in adults [10,12]. Furthermore, as pertussis is generally thought of as a disease of infants and young children, diagnosing it is often not made in adults, increasing, therefore, the risk of spread [13,14]. Although clinical criteria have been developed to direct clinicians towards appropriate pertussis investigation [14-16], they have limited sensitivity and specificity [10,14,17-22]. It has been shown that decreasing the cough duration to more than one

week, instead of two weeks or more, as recommended by the Centers for Disease Control and Prevention (CDC), would result in 95% of positive PCR results meeting the confirmation criteria for pertussis [17]. Furthermore, other respiratory pathogens may be isolated when *B. pertussis* infection is suspected, some of which are treatable.

We, therefore, designed this prospective observational study of patients fulfilling the clinical case definition of pertussis, using cough duration of more than one week, to identify in their nasopharyngeal aspirates the respiratory pathogens, especially those amenable to therapy, in addition to *B. pertussis*.

## MATERIALS AND METHODS

### Study design

In this prospective descriptive cohort study, patients of all ages presenting to Oasis Hospital, Al Ain city, United Arab Emirates, between 1st March and 31st July 2017 with a cough lasting for more than one week, were enrolled.

### Ethical approval

The project received ethical approval from the Al Ain Medical District Human Research Ethics Committee (ERH_2016_4264). Written informed consent was obtained from all participants to take part in the study.

### Variables

Exposure was defined by the isolated pathogen, outcome was the symptoms used in the case definition for pertussis (paroxysmal cough and its duration, stridor or post-tussive vomiting). Potential confounders were age, gender, and information on any contact with a person with suspected or confirmed pertussis infection.

### Microbiological Methods

**Specimen Collection and Initial Processing:** We collected nasopharyngeal samples using swabs (eNAT®, Copan Italia SpA, 25125 Brescia, Italy), following the manufacturer's instructions. Samples were stored at -80°C until analyzed. The eNAT® sample collection pouch was opened, the tube and swab removed from it, the cap was unscrewed and removed from the tube while making sure not to spill the medium. The participants were asked to clear their nasal passages of mucous prior to the insertion of the swab. Their head was then tilted back 70 degrees, the swab inserted into one nostril at least half the distance from the tip of the ear to the nostril, rotated then kept a few seconds before slowly removing it. After completing the collection, the swab was reinserted and broken into the tube. The broken handle of the swab shaft was then discarded. The excess fluid was extracted by pressing the swab against the inside of the vial then the swab was removed and discarded. The cap was replaced on the tube, secured tightly and the tube was stored at -80°C until analyzed.

**Real-time PCR analysis:** Total nucleic acid was extracted from the nasopharyngeal aspirates using STARMag cartdrige kit(Seegene Biotechnology Inc., Seoul, Korea), employing the Nimbus automated workstation. The multiplex one-step real-time PCR Allplex™ Respiratory Full Panel panels (1, 2, 3 and 4) (Seegene Biotechnology Inc., Seoul, Korea), as per the manufacturer's protocol. These included 16 viruses: influenza (Flu A, B, A-H1, A-H1pdm09, and A-H3), parainfluenza (PIV 1-4), respiratory syncytial virus (RSV A and B), adenovirus (AdV), human enterovirus (hEV), human metapneumovirus (hMPV), human bocavirus (hBoV), human rhinovirus (hRV) and coronaviruses (CoV NL63, CoV 229E, and CoV OC43). They also included seven bacteria: *Streptococcus pneumoniae* (*S. pneumoniae*), *Haemophilus influenzae* (*H. influenzae*), *Mycoplasma pneumoniae* (*M. pneumoniae*), *Chlamydophila pneumoniae* (*C. pneumoniae*), *Legionella pneumophila* (*L. pneumophila*), *Bordetella pertussis* (*B. pertussis*), and *Bordetella parapertussis* (*B. parapertussis*). For the detection of *Streptococcus pyogenes (S. pyogenes)*, we used the previously published TaqMan primer/probe set to detect *S. pyogenes* (based on spe B gene) DNA (Dunne et al., 2013). We extracted total nucleic acid from the nasopharyngeal swabs using the Seegene virus cartridge kit. Each reaction contained 9l of template DNA and was assayed in duplicate in 20 µL reactions containing 1× final concentration TaqMan Universal Master Mix (ABI), 18 µM each primer, and 5 µM probe.

All reactions were also performed on relevant positive and negative controls. We performed amplification and detection of the DNA with the ABI 7500 Fast (Applied Biosystems, Foster City, CA, USA), using the following reaction conditions: 3 min at 95°C, and 40 cycles of 20 sec at 95°C, 1 min at 55°C and 15 sec at 72°C. Cycling conditions for S. pyogenes were 3 min at 95°C, and 40 cycles of 20 sec at 95°C, 1 min at 58°C and 15 sec at 72°C. We calculated cycle threshold (Ct) using the automated settings. A Ct value $\leq$ 40 was considered positive and all negative results were accepted when the internal control had a Ct <40.

**Single-sample pertussis serology:** A blood sample of 5 ml was collected from each patient at presentation. Serum was separated by centrifugation and stored at −80°C before measurements. Enzyme-linked immunosorbent assay (ELISA) (NovaLisa *B. pertussis* IgG/IgA ELISA, NovaTec Immundiagnostica GmbH, Dietzenbach, Germany) was used for the quantitative determination of IgG and IgA antibodies against *B. pertussis* toxin (PT). All ELISA procedures were tested following the directions of the manufacturers. We initially diluted all sera 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 and, for the purpose of calculations, concentrations below that LOD were assigned half that value (5 IU/ml). As per the manufacturer's recommendations, we considered samples with IgG-PT titers >10 IU/ml (international units per milliliter) as positive and protective against pertussis. For patients with IgG-PT concentration >100 IU/ml, simultaneous IgA-PT concentration >12 IU/ml suggested recent infection (Cherry, Gornbein, Heininger, & Stehr, 1998; Guiso et al., 2011; Riffelmann, Thiel, Schmetz, & Wirsing von Koenig, 2010). Although IgG-PT concentrations between 10 and 100 IU/ml associated with IgA-PT concentrations >12 IU/ml do not correspond to active or recent infection, we considered them indicative of *B. pertussis* infection in the previous year and,

therefore, considered them as a recent pertussis contact. (de Melker, Versteegh, Schellekens, Teunis, & Kretzschmar, 2006)

### Clinical variables

Demographic data included age, gender, presence of symptoms used in the case definition for pertussis (paroxysmal cough and its duration, stridor or post-tussive vomiting) and information on any contact with a person with suspected or confirmed pertussis infection.

### Sample size

With an estimated 6% rate of pertussis infection in participants fulfilling the case definition of clinically suspected pertussis, in order to give the study a confidence level of 80% with a 5% precision, we calculated that a minimum sample size of 38 participants was required. (OpenEpi, Version 3, open source calculator).

### Statistical Analysis

Descriptive statistics and the prevalence of each pathogen detected were calculated. We compared proportions with the Chi-square test of the Fisher exact test when appropriate. We used the statistical package Stata version 14 (StataCorp, College Station, Texas) for all statistical analyses and statistical significance was defined by a two-tailed *P*-value < 0.05.

### Data availability

The data sets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

## RESULTS

### Demographics

A total of 39 patients (13 males, 33%), aged between 16.5 and 65 years were enrolled during the study period.

### Clinical data

Their characteristics are shown in Table 1. Mean duration of cough was 27 days, standard deviation 36 days, median 13 days, and ranged from seven days to six months. Cough was the only symptom in 11 (73%), of the 15 patients who had pathogens detected (*P*=0.03). No patient had received immunization against pertussis in the preceding five years. The suspected diagnosis made by the attending physician was isolated nasopharyngitis or rhinitis in six patients, asthma in five (two of whom also had nasopharyngitis), acute bronchitis in two, and pneumonia in two participants.

### Microbiological results

Twenty-four patients (61%), did not have any organisms detected. Pathogens were identified in 15 patients (39%), Table 1. Infection with only one organism occurred in 10 patients (26%): five patients (33%), had only viruses identified and five (33%), had only bacteria. Co-infection occurred in five patients (33.3%): four grew *H. influenzae* and rhinovirus, while one patient had, in addition, *S. pneumoniae*. Three potentially treatable bacteria (*H. influenzae, Mycoplasma pneumoniae,* and *S. pneumoniae),* were isolated in 11 patients (28.1%). The number of symptoms was not significantly associated with the isolated pathogens (*P*>0.05).

Although no *B. pertussis* or *para-pertussis* was isolated in any patient, 4 patients (10%), had a single-sample serum PT-IgA concentration >12 IU/ml (of whom one also had a serum PT-IgG concentration >100 IU/ml), indicating a possible pertussis infection (Table 2). Two of them had a cough for more than two weeks (CDC criteria to suspect pertussis), while all four had been coughing for over seven days.

The distribution of the number of pathogens as per the duration of cough is shown in Table 2, Figure 1 and 2. Coronavirus C43 and *S. pneumoniae* were isolated exclusively when the cough was less than two weeks' duration, and *Mycoplasma pneumoniae* mainly between two and four weeks.

## DISCUSSION

In this study, no *B. pertussis* or *parapertussis* was identified in any of the patients. PCR is the most sensitive diagnostic tool for pertussis when performed during the first two weeks of cough [23]. We are confident that no false negatives for pertussis PCR occurred because we compared all measurements against appropriate controls, and because, in contrast to the reported false positives, these false negatives become more common after the fourth week of the infection [23].

**Table 1**: Demographic, clinical and microbiology data of the 39 studied patients in the United Arab Emirates (March to July 2017).

| | **Number (%)** |
|---|---|
| Demographics | |
| Males | 13 (33) |
| Median age [range] in yr | 34.4 [16.5, 65] |
| Clinical presentation | |
| Cough duration >7 days | 39 (100) |
| Median cough duration [range] in days | 13 [7, 179] |
| Paroxysms of cough | 9 (23) |
| Stridor | 1 (2.5) |
| Post-tussive vomiting | 0 (0) |
| History of contact | 9 (23.0) |
| Patients with isolated pathogens | 15 (38.5) |
| Rhinovirus | 8 (29.5) |
| *Haemophilus influenza* | 7 (17.9) |
| *Mycoplasma pneumoniae* | 3 (7.7) |
| Coronavirus C43 | 2 (5) |
| *Streptococcus pneumoniae* | 1 (2.5) |
| *Bordetella pertussis* | 0 (0) |
| *Bordetella para-pertussis* | 0 (0) |
| Patients and number of pathogens isolated | |
| No pathogens | 24 (61.5) |
| 1 pathogen | 10 (25.6) |
| 2 pathogens | 4 (10.2) |
| 3 pathogens | 1 (2.5) |
| Results are expressed as number (percentage) unless stated otherwise | |

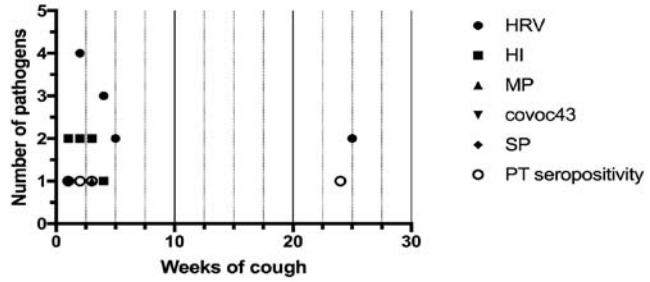


**Figure 1** Duration of coughing and number of isolated pathogens or suggestive pertussis infection by serology (IgG-PT > 10 IU/mL with IgA-PT > 12 IU/mL) in 39 patients presenting with cough for at least one week in the United Arab Emirates (March to July 2017).
HRV: human rhinovirus; HI: *Haemophilus influenzae*, MP: *Mycoplasma pneumoniae*; covoc43: Coronavirus C43; SP: *Streptococcus pneumoniae*, PT: pertussis toxin

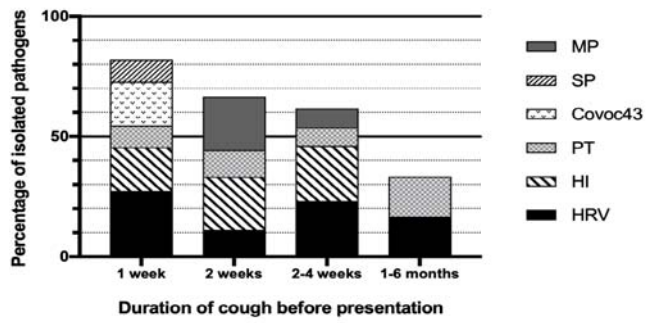


**Figure 1** Duration of cough before presentation in 39 patients in the United Arab Emirates (March to July 2017) and percentage of isolated pathogens, or suggestive pertussis infection by serology (IgG-PT > 10 IU/mL with IgA-PT > 12 IU/mL).
HRV: human rhinovirus; HI: *Haemophilus influenzae*, MP: *Mycoplasma pneumoniae*; covoc43: Coronavirus C43; SP: *Streptococcus pneumoniae*, PT: pertussis toxin

Four patients with negative pertussis PCR results had single-sample serology results suggestive of pertussis infection. Although we acknowledge that commercial pertussis serology assays are not always accurate, PT antibodies are more specific than antibodies to other *B. pertussis* antigens sharing cross-reactivity. The minimal single-sample antibody titers suggesting current/recent pertussis infection are still debated and range from 50 to 200 IU/mL [24-26]. The suggestive serology results in our patients could either indicate a possible old pertussis infection, unrelated to the current presentation, or pertussis vaccination that had occurred in the last three years, which was not the case in our patients. In the one patient who had been coughing for 24 weeks, the suggestive serology in presence of a negative pertussis PCR might be caused by late presentation to the health services well after their PCR became negative. It is noteworthy that only two of these four patients had a cough for more than two weeks fulfilling, therefore, the CDC criteria to suspect pertussis, while all four had been coughing for over seven days. Applying the CDC criteria of cough duration of at least two weeks would, therefore, have missed half of these cases, when cough was present for less than two weeks and when the diagnostic value of PCR is higher [19].

The main pathogens isolated in this study included mainly rhinovirus and coronavirus, with occasionally *H. influenzae, M. pneumoniae* and *S. pneumoniae* also identified. These findings confirm previous studies that showed that bacterial pathogens are relatively common causes of lower respiratory diseases, including cough [4]. The majority of the pathogens, in our study, were isolated in patients with a cough of less than 3-weeks duration. Although, if pathogenic, the identified bacteria could be treated with antibiotics, the design of the study does not permit, however, to distinguish between a pathogenic role for these pathogens during the episode of cough or a mere colonization unrelated to the symptoms. As shown in previous reports, *Mycoplasma pneumoniae* has been identified in the nasopharynx of asymptomatic individuals, with an estimated false positive rate up to 20% [27]. Furthermore, the identified pathogens at presentation may be different from those that might have initially triggered the cough.

Instead of the CDC case definition for pertussis that includes a cough of at least 2 weeks, we selected a cough duration of more than seven days, as used in recent guidelines [28]. That duration has been reported to be better for detecting mild pertussis [8,22], and also results in 95% of positive PCR results meeting the confirmation criteria for pertussis [17]. Another reason is that we were trying to identify, in addition to pertussis, a wide range of other respiratory pathogens some of which may not necessarily lead to a cough lasting more than two weeks [4,5].

Strengths include its prospective nature and the use of PCR instead of culture to identify the respiratory pathogens as it had a better yield. Furthermore, it looked for all the main respiratory pathogens, in addition to pertussis. Limitations include a small sample size, use of a commercial kit for serology assays, single-sample pertussis serology, absence of information on the prescribed therapy and on the follow up of the enrolled patients.

Further larger studies addressing the limitations of the study are needed, including the exploration of the role of seasonality. The clinical case definition of pertussis requires refinements to emphasize overlapping presentations with other clinically relevant organisms.

## CONCLUSION

Applying the CDC clinical case definition of suspected pertussis of a cough duration over two weeks would have missed half of the cases of pertussis. Even when using a cut-off of one week of coughing instead, it still more often describes a cough associated with other respiratory pathogens such as *rhinovirus*, *coronavirus C43*, and *Mycoplasma pneumoniae*.

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**Table 2:** Patients, in the United Arab Emirates (March to July 2017), with pathogens identified by PCR on nasopharyngeal secretions or with suggestive pertussis infection by PT serology (IgG-PT and IgA-PT levels expressed as IU/mL).

| Patient number | Gender | Age (yr) | Cough duration (days) | Pathogens | Diagnosis |
|---|---|---|---|---|---|
| 7 | Male | 32 | 7 | Covoc43 | Asthma |
| 8 | Female | 50 | 7 | HI, SP | NA |
| 10 | Male | 29 | 7 | Covoc43 | Nasopharyngitis |
| 11 | Male | 20 | 7 | HRV | Rhinitis |
| 13 | Female | 34 | 7 | HRV | Nasopharyngitis |
| 39 | Female | 60 | 7 | Suggestive PT serology (IgG 87.8, IgA 16.4) | vNA |
| 6 | Male | 22 | 8 | MP | Acute bronchitis |
| 2 | Female | 19 | 13 | MP | Pneumonia |
| 4 | Female | 54 | 13 | HRV, Hi | Asthma |
| 14 | Female | 39 | 13 | HI | Acute bronchitis |
| 4 | Female | 19 | 13 | Suggestive PT serology (IgG 53.4, IgA 13.2) | Pneumonia |
| 12 | Female | 22 | 15 | HRV, HI | NA |
| 15 | Male | 21 | 15 | HRV, HI | Nasopharyngitis |
| 1 | Male | 27 | 20 | MP | Rhinitis |
| 6 | Female | 16 | 20 | Suggestive PT serology (IgG 86.5, IgA 16.4) | Asthma |
| 5 | Female | 30 | 29 | Hi | Nasopharyngitis |
| 9 | Male | 58 | 29 | HRV | NA |
| 3 | Male | 43 | 179 | HRV | Nasopharyngitis, asthma |
| 7 | Male | 43 | 179 | Suggestive PT serology (IgG 185.3, IgA 40.3) | Nasopharyngitis, asthma |

HRV: human rhinovirus; HI: *Haemophilus influenzae*, MP: *Mycoplasma pneumoniae*; covoc43: Coronavirus C43; SP: *Streptococcus pneumonia*e, PT: pertussis toxin; NA: not available

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