Journal of Infection (2016) xx, 1–8

BIA
British Infection Association

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Differences in *Bordetella pertussis* DNA load according to clinical and epidemiological characteristics of patients with whooping cough

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Accepted 26 January 2016
Available online ■ ■ ■

KEYWORDS
Bordetella pertussis;
Prognostics;
Children;
Bacterial load;
Real-time PCR;
Whooping cough

Summary *Objective:* To identify associations between nasopharyngeal *Bordetella pertussis* DNA load and clinical and epidemiological characteristics and evaluate DNA load prognostic value in pertussis severity.
Methods: Prospective observational multi-centre study including nasopharyngeal samples positive to pertussis DNA by real-time PCR collected from children and adult patients in more than 200 health centres of Catalonia (Spain) during 2012–2013.
Results: B. pertussis load was inversely correlated with age (rho = −0.32, $p < 0.001$), time to diagnosis (rho = −0.33, $p < 0.001$) and number of symptoms (rho = 0.13, $p = 0.002$). Median bacterial load was significantly higher in inpatients *versus* outpatients (4.91 *vs.* 2.55 $\log_{10}$ CFU/

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http://dx.doi.org/10.1016/j.jinf.2016.01.013
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Please cite this article in press as: Brotons P, et al., Differences in *Bordetella pertussis* DNA load according to clinical and epidemiological characteristics of patients with whooping cough, J Infect (2016), http://dx.doi.org/10.1016/j.jinf.2016.01.013

mL, $p < 0.001$), patients with complications *versus* those without (6.05 *vs.* 2.82 $\log_{10}$ CFU/mL, $p < 0.001$), disease incidence in summer and autumn *versus* spring and winter (3.50 *vs.* 2.21 $\log_{10}$ CFU/mL, $p = 0.002$), and unvaccinated-partially vaccinated patients *versus* vaccinated (4.20 *vs.* 2.76 $\log_{10}$ CFU/mL, $p = 0.004$). A logistic regression model including bacterial load and other candidate prognostic factors showed good prediction for hospital care (AUC = 0.94) although only age and unvaccinated status were found to be prognostic factors. *Conclusions:* We observed strong positive associations of nasopharyngeal bacterial load with severity outcomes of hospitalisation and occurrence of complications. Bacterial load and other independent variables contributed to an accurate prognostic model for hospitalisation.
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Introduction

Bordetella pertussis is a Gram negative pathogen causative of pertussis (whooping cough), an acute respiratory infection that results in severe disease in young children and mild but prolonged cough in adults. Pertussis continues to impose an important burden worldwide despite initial declines of incidence following the introduction of whole-cell and acellular vaccines.[1,2] A re-emergence of the disease has been observed over the past two decades, even in developed countries with high vaccination coverage.[3–5] Limited effectiveness of the current acellular vaccine and proved genetic changes in circulating strains have been associated with pertussis resurgence, among other factors.[3,6,7]

It has extensively been documented that clinical characteristics and severity of pertussis infection depend on factors such as age and immunisation status of individuals.[8,9] However, little has been described about the role of *B. pertussis* bacterial load in the disease severity and the extent to which epidemiological and clinical characteristics influence bacterial load. At present, testing for detection and quantification of *B. pertussis* DNA load in direct sample including both viable and non-viable bacteria is typically performed using nucleic acid amplification techniques such as quantitative polymerase-chain reaction (PCR). PCR techniques targeting *B. pertussis* are highly sensitive and specific although positive high cycle threshold (Ct) values obtained may sometimes mislead interpretation of results.

The present study aimed to investigate the associations between *B. pertussis* nasopharyngeal DNA load quantified by real-time PCR and epidemiological and clinical features. A secondary objective was to evaluate the potential prognostic value of nasopharyngeal bacterial load and other variables in the severity of pertussis.

Patient and methods

Study design and patients

This is a prospective observational multi-centre study that included all children and adults with clinical suspicion of pertussis and microbiologically confirmed diagnosis of the disease who were attended in more than 200 health care centres of Catalonia (Spain) during the period 2012–2013. Sites participating in the study included both reference hospitals, secondary-level hospitals and all the primary health care centres integrated into the network of public utility health care facilities of Catalonia, covering a wide diversity of locations across this geographical region.

All participating centres shipped a nasopharyngeal swab for study of *B. pertussis* bacterial load by real-time PCR to the Molecular Microbiology Department of University Hospital Sant Joan de Déu (Barcelona), which is the reference laboratory of the Catalan Public Health Agency for molecular surveillance of pertussis disease. In addition, some laboratories delivered a second nasopharyngeal swab for bacterial culture. Data recovered from medical records included patient's demographic characteristics and immunization status, seasonality, disease symptoms, time elapsed since first symptoms onset until diagnosis, type of health care services provided (outpatient care and hospital care), admission to Intensive Care Unit (ICU), occurrence of complications, length of stay (LOS) in hospital, and length of stay in ICU.

The pertussis acellular vaccine was routinely introduced in Catalonia in 2002 and is administered at 2, 4, 6, 18 months and 4–6 years of age.[10] Patients were classified into 5 age groups to analyse whether they were unvaccinated, partially vaccinated or up to date according to the vaccination schedule. Break points established to differentiate age groups were 2 months (before vaccination), 6 months (3 first vaccine doses completed), 18 months (fourth dose received), 6 years (booster dose received), and 15 years. Incidence of pertussis in Catalonia markedly peaked from 4.4 cases per 100,000 persons in 2010 to 20.9 cases per 100,000 persons in 2011 and then decreased to 15.6 cases per 100,000 persons in 2012.[5] Individual notification of pertussis cases to regional public health authorities for epidemiological surveillance is mandated under Catalan sanitary regulations.[11]

Definitions

Pertussis cases were defined as patients with clinical criteria of pertussis disease (≥2 weeks of cough with an additional symptom such as whoop, paroxysmal cough, post-tussive vomiting, fever, or apnoea) and laboratory-confirmed *B. pertussis* diagnosis. Patients aged <1 year with cough <2 weeks were also considered cases if they presented paroxysm as well as another symptom and had a confirmatory diagnosis by PCR. The criterion for laboratory confirmation was detection of *B. pertussis* DNA by quantitative real-time PCR in nasopharyngeal swab, complemented by isolation of *B. pertussis* by bacterial culture if available. Severity of pertussis was assessed using diverse

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