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Under-recognized pertussis in adults from Asian countries: a cross-sectional seroprevalence study in Malaysia, Taiwan and Thailand

M. T. KOH[1], C.-S. LIU[2], C.-H. CHIU[3], W. BOONSAWAT[4], V. WATANAVEERADEJ[5], N. ABDULLAH[1], XH. ZHANG[6], R. DEVADIGA[7] AND J. CHEN[6]*

[1] *University of Malaya, Kuala Lumpur, Malaysia*
[2] *Family Medicine Department, China Medical University Hospital, Taichung, Taiwan*
[3] *Division of Pediatric Infectious Diseases, Department of Pediatrics, Chang Gung Children's Hospital, Chang Gung University, Taoyuan, Taiwan*
[4] *Khon Kaen University, Thailand*
[5] *Department of Pediatrics, Phramongkutklao Hospital, Bangkok, Thailand*
[6] *GSK Vaccines, Singapore*
[7] *GSK Vaccines, Bangalore, India*

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SUMMARY

Surveillance data on the burden of pertussis in Asian adults are limited. This cross-sectional study evaluated the prevalence of serologically confirmed pertussis in adults with prolonged cough in Malaysia, Taiwan and Thailand. Adults ($\geqslant$19 years) with cough lasting for $\geqslant$14 days without other known underlying cause were enrolled from outpatient clinics of seven public and/or private hospitals. Single blood samples for anti-pertussis toxin antibodies (anti-PT IgG) were analysed and economic impact and health-related quality of life (EQ-5D) questionnaires assessed. Sixteen (5·13%) of the 312 chronically coughing adults had serological evidence of pertussis infection within the previous 12 months (anti-PT IgG titre $\geqslant$62·5 IU/ml). Three of them were teachers. Longer duration of cough, paroxysms (75% seroconfirmed, 48% non-seroconfirmed) and breathlessness/chest pain (63% seroconfirmed, 36% non-seroconfirmed) were associated with pertussis ($P < 0{\cdot}04$). Of the seroconfirmed patients, the median total direct medical cost per pertussis episode in public hospitals (including physician consultations and/or emergency room visits) was US$13 in Malaysia, US$83 in Taiwan ($n = 1$) and US$26 in Thailand. The overall median EQ-5D index score of cases was 0·72 (range 0·42–1·00). Pertussis should be considered in the aetiology of adults with a prolonged or paroxysmal cough, and vaccination programmes considered.

Key words: *Bordetella pertussis*, epidemiology, infectious disease epidemiology, pertussis (whooping cough), public health.

INTRODUCTION

Infant vaccination programmes have been highly successful in reducing severe disease and childhood deaths due to pertussis. Despite these substantial gains, pertussis continues to circulate in all populations and most often affects very young, unimmunized or incompletely immunized infants, with a rising incidence in adolescents and adults [1, 2]. Family members have been implicated as important sources of pertussis for unprotected infants who are at highest risk of complications and death [1–4].

* Author for correspondence: Dr J. Chen, GSK Vaccines, 150 Beach Road 22-00, Gateway West, Singapore 189720.
(Email: jing.j.chen@gsk.com)

High coverage of infant pertussis vaccination has been longstanding in Southeast Asian countries (ranging from 82% to 99% coverage in 2009) [5]. Although few data are available describing the epidemiology of pertussis disease in Asian countries [6], the available evidence suggests that, as in other countries with high pertussis vaccine coverage in infants and young children, pertussis continues to circulate in adolescents and adults [6]. In Taiwan, a seroprevalence study found that adolescents and adults remain at risk of pertussis despite successful immunization programmes, and a surveillance study of patients with cough lasting more than 1 week estimated an incidence of up to 21%, with pertussis disease especially prevalent in adolescents and adults [6, 7]. Another seroprevalence study in Singapore also showed pertussis to be prevalent in adults [8]. Although adults rarely die from pertussis infection, the medical costs and morbidity associated with pertussis in this age group can be considerable [9]. Possible complications of adult pertussis include secondary pneumonia, rib fractures and incontinence [9]. In a hospital-based study of confirmed pertussis cases in Taiwan the complication rate was 30·4%, of which pneumonia was most common (92·3%) [10]. An analysis of the 2011–2012 pertussis outbreak in England estimated an overall loss in quality of life of 0·097 quality-adjusted life years (QALYs) for pertussis patients, and 0·0365 QALYs for coughing household contacts [11].

Findings from such epidemiological studies justify the need for pertussis vaccination in adolescents and young adults. We performed a cross-sectional study to determine the prevalence of serologically confirmed pertussis in adults in Malaysia, Taiwan and Thailand with prolonged cough. Pertussis vaccination schedule for these countries is shown in Table 1 [12–14].

METHODS

This cross-sectional study was conducted between 20 June 2012 and 2 May 2013 according to the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent or assent was obtained from subjects (or parent/legally acceptable representative in Taiwan and Thailand where the age of consent is 20 years) prior to enrolment.

Study design and participants

Adult patients aged at least 19 years with prolonged cough were recruited from two centres in Malaysia (International Medical University and University of Malaya Medical Centre), three centres in Thailand (Phramongkutklao Hospital, Srinagarind Hospital and Songklanagarind Hospital) and two centres in Taiwan (China Medical University Hospital and Chang Gung Memorial Hospital). Centres in each participating country were secondary or tertiary public/private hospitals. These participating hospitals provide ambulatory primary healthcare facilities and treatment for outpatients besides accepting referral cases from other primary healthcare practitioners. Thus, a spectrum of mild to severe pertussis cases was anticipated.

All patients with prolonged cough (present for $\geqslant$14 days) were screened for eligibility. Patients with known pulmonary disease causing chronic cough (including pulmonary tuberculosis, chronic obstructive airways disease, bronchiectasis, asthma) and patients with suspected or known immunodeficiency were excluded. Patients treated with angiotensin-converting enzyme inhibitors within the previous 4 weeks prior to enrolment were also excluded from participation.

Data collection

Demographic information (age at enrolment, gender), medical history including vaccination history for pertussis, pneumococcal disease and influenza, and as well as information on clinical symptoms and treatments received were documented and a physical examination was performed. Results of laboratory or radiological tests performed to investigate the cough episode were recorded. Health-related Quality of Life [EuroQoL-5D (EQ-5D)] and structured health economic questionnaires were administered by study staff to individuals at the time of enrolment.

Patients' medical records were reviewed approximately 30 days after enrolment to re-validate the diagnosis and record the clinical outcome and results of additional medical procedures.

Sample collection and laboratory testing

A blood sample was collected from each patient for anti-pertussis toxin (anti-PT) level of IgG antibodies testing. Anti-PT was measured by ELISA (Euroimmun, Germany) according to the manufacturer's instructions at a laboratory designated by GSK Vaccines with an assay cut-off for sensitivity of 10 IU/ml. Sera were classified into four categories, based on manufacturer's instructions, previous experience in the available literature [15–17] and the absence of

Table 1. *Pertussis vaccination schedule in Malaysia, Taiwan and Thailand*

	Primary doses			Booster doses		
Country	Month 2	Month 4	Month 6	Month 18	4–6 years	11–12 years
Malaysia	DTaP-Hib-IPV	DTaP-Hib-IPV	DTaP-Hib-IPV*	DTaP-Hib-IPV	—	—
Taiwan	DTaP-Hib-IPV	DTaP-Hib-IPV	DTaP-Hib-IPV	DTaP-Hib-IPV	Tdap-IPV†	—
Thailand	DTwP-Hib (or DTaP)	DTwP-Hib (or DTaP)	DTwP-Hib (or DTaP)	DTwP (or DTaP)	DTwP (or DTaP)	Tdap

Dark grey cells (■) indicate optional vaccine. Light grey cells (■) indicate EPI/NIP vaccine.
DTaP, Diphtheria, tetanus, pertussis (acellular) vaccine; Hib, *Haemophilus influenzae* type B vaccine; IPV, inactivated poliomyelitis vaccine; DTwP, diphtheria, tetanus, pertussis (whole cell) vaccine; DTaP/Tdap, diphtheria, tetanus, and pertussis (acellular) vaccine [reduced antigen(s)]. EPI, Expanded Programme on Immunization; NIP, National Immunization Program.
* Month 5.
† After 5 years of age and before entering elementary school.

vaccination against pertussis in the last 12 months: a seronegative patient had an anti-PT IgG level below the sensitivity limit of the assay (<10 IU/ml); a seropositive patient had an anti-PT IgG level $\geqslant$10 IU/ml; an anti-PT IgG $\geqslant$62·5 IU/ml was considered serological evidence of pertussis infection in the last 12 months; and an anti-PT IgG level $\geqslant$100 IU/ml was considered indicative of active or recent infection.

Assessment of quality of life

Health-related quality of life was assessed using the EQ-5D questionnaire [18], which comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), with three levels of severity within each dimension. There are 245 possible health states, for which a mapping of utility scores can be conducted and the range of results is [0; 1] where 0 = death and 1 = perfect health.

Assessment of health economic impact

Health economic impact such as absenteeism from work or school and associated income loss of the subjects or family members, healthcare resource utilization, and direct costs (including medical costs and transportation costs) were recorded using a standardized questionnaire. All costs were adjusted to 2012 US$ using the historical yearly mean exchange rate from www.oanda.com/currency/historical-rates/.

Statistical methods

Statistical analyses were performed using SAS v. 9.2 (SAS Institute Inc., USA). Previous studies have demonstrated a prevalence of pertussis of between 10% and 20% in adults with prolonged cough [19, 20]. Considering a 10% pertussis prevalence, 139 subjects would provide 5% precision on the estimate. Considering a prevalence of pertussis of 18%, 70 subjects would provide a precision of 9%. Assuming a drop-out rate of 10%, we therefore aimed to enrol 154 subjects in Thailand and at least 78 subjects in Malaysia and Taiwan.

The according-to-protocol (ATP) cohort included all subjects with valid laboratory test results and excluded those subjects vaccinated with pertussis vaccines within 1 year before the blood sample. Prevalence of pertussis infection with exact 95% confidence intervals (CIs) was determined by the number of patients with laboratory evidence suggestive of pertussis infection in all subjects presenting with prolonged cough. In addition, clinical characteristics (such as cough paroxysms, whoop, night cough, post-tussive vomiting, cyanosis, fever, etc.), contact with people with coughing disease before onset, comorbidities, antibiotic treatment and laboratory results of subsets of patients with and without serological evidence of pertussis, were assessed. The health economic impact in terms of absenteeism from work, healthcare resource utilization, and direct costs were described only for subjects with serologically confirmed pertussis.

RESULTS

There were 337 patients enrolled in the study, of whom 25 (7·4%) were excluded from the analysis leaving 312 subjects in the ATP cohort (Fig. 1). Of the 312 subjects included in the analysis, 296 (94·9%) had anti-PT IgG levels below the pre-defined cut-off of

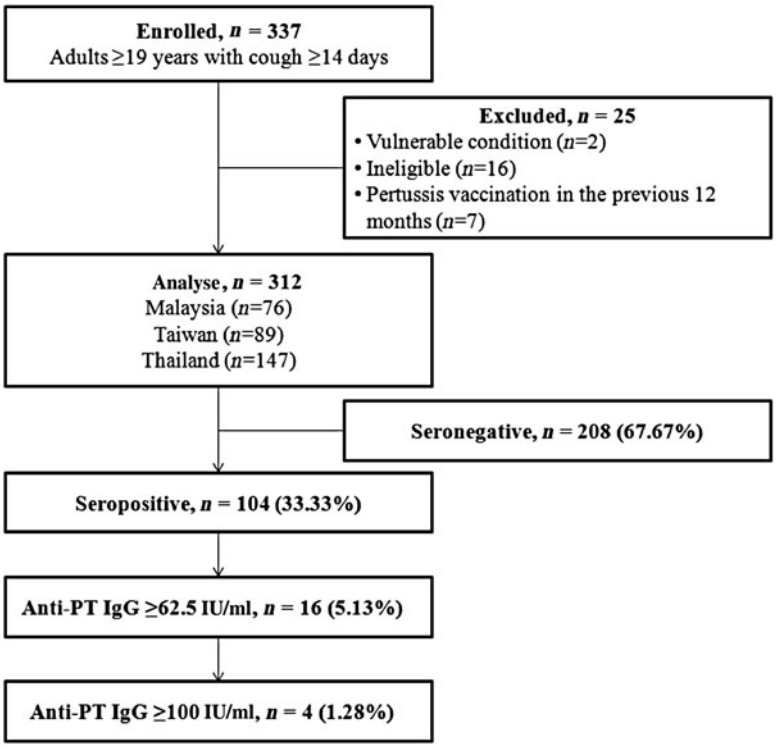

Fig. 1. Flow of study subjects and serological results.

62·5 IU/ml, including 208 (66·67%) seronegative subjects (anti-PT antibodies IgG <10 IU/ml). The other 16 of the 312 subjects (5·13%, 95% CI 2·96–8·19) had serological evidence of pertussis infection in the last 12 months (anti-PT ⩾62·5 IU/ml): 6/76 (7·9%, 95% CI 2·95–16·40) in Malaysia, 1/89 in Taiwan (1·1%, 95% CI 0·03–6·10) and 9/147 (6·1%, 95% CI 2·84–11·30) in Thailand. Four of these 16 subjects (overall 1·3%, 4/312, 95% CI 0·35–3·25) had anti-PT antibodies ⩾100 IU/ml indicative of active or recent infection.

The demographic characteristics of enrolled patients with and without serological evidence of pertussis infection (anti-PT ⩾62·5 IU/ml) are shown in Table 2. Pertussis cases were distributed across all age groups, and were highest in age groups 50–59 years (9·8%, 5/51, 95% CI 3·26–21·41) and 19–29 years (7·6%, 5/66, 95% CI 2·51–16·80) (Figs. 2, 3). Serological evidence of active pertussis (anti-PT IgG ⩾100 IU/ml) was most commonly observed in the 19–29 years age group (3·0%, 2/66, 95% CI 0·37–10·52). The median duration of cough was not significantly different between patients with and without serological evidence of pertussis (anti-PT IgG ⩾62·5 IU/ml): 43 days (range 15–120) *vs.* 31 days (range 14–1682), respectively ($P = 0·1$). Duration of cough was >90 days in 3/16 (18·8%) of patients with serological evidence of pertussis compared to 40/296 (13·5%) patients without (Table 3). The most frequently reported duration of cough was longer in patients with serological evidence of pertussis (31–60 days) compared to those without (14–30 days). A greater proportion of patients with serological evidence of pertussis (75·0%, 12/16) than those without (48·3%, 143/296) reported paroxysms ($P = 0·04$). Breathlessness/chest pain was reported by 62·5% (10/16) of patients with serological evidence of pertussis *vs.* 35·8% (106/296) of patients without ($P = 0·03$). No other significant differences in clinical symptoms presence were observed between the two groups (Table 3). The most commonly recorded comorbid conditions were categorized as 'other non-respiratory tract diseases'; however, there was no difference between those with/without serological evidence of pertussis in terms underlying medical conditions [1/16 (6·3%) *vs.* 36/296 (12·2%), respectively, $P = 0·70$, Fisher's exact test].

Chest X-ray was performed on 212/312 (67·9%) patients (seven with serological evidence of pertussis). The majority of chest X-rays [71·4% (5/7) in serologically confirmed and 86·3% (177/205) in patients with anti-PT IgG <62·5 IU/ml] were negative. Polymerase

Table 2. *Demographic characteristics of enrolled patients with and without evidence of pertussis in the last 12 months (anti-PT IgG ⩾62·5 IU/ml)*

Category	Anti-PT ⩾65·5 IU/ml (*N* = 16)	Anti-PT <65·5 IU/ml (*N* = 296)
Age (years)		
Mean (SD)	40·7 (13·3)	43·1 (15·5)
Range	21–63	19–83
Age group, years, *n* (%)		
19–29	5 (31·3)	61 (20·6)
30–39	3 (18·8)	86 (29·1)
40–49	2 (12·5)	50 (16·9)
50–59	5 (31·3)	46 (15·5)
⩾60	1 (6·3)	53 (17·9)
Gender		
Female, *n* (%)	8 (50)	202 (68·2)
Male, *n* (%)	8 (50)	94 (31·8)

N, Number of subjects; *n*, number of subjects in a given category; S.D., standard deviation.

chain reaction (PCR) was only performed in one patient without serological evidence of pertussis and failed to identify a pathogen. There were 94 (30·1%, 94/312) patients with suspected tuberculosis; all of whom had negative examination results of sputum for acid-fast bacilli. One patient (without serological evidence of pertussis) had pleural tuberculosis confirmed by pleural biopsy (post-enrolment and was included in study analyses).

Contact with a household or workplace member with known or suspected whooping cough was reported by 1/16 (6·3%) patient with serological evidence of pertussis *vs.* 29/296 (9·8%) of subjects without pertussis. Contact with a household or workplace member with persistent cough was reported by 4/16 (25·0%) pertussis patients and 109/296 (36·8%) patients without pertussis, and contact with a household or workplace member who developed a cough subsequently was reported by 6/16 (37·5%) and 106/296 (35·8%) subjects, respectively. Of the 16 patients with serological evidence of recent pertussis infection, three (18·8%) were employed as teachers and one reported having contact with an infant aged <1 year either at home or the workplace.

Of the 16 patients with serological evidence of pertussis, 10 (62·5%) reported not receiving any previous dose of pertussis vaccine, with a further five (31·3%) patients unable to recall their vaccination status. Only one patient reported receiving one dose of pertussis vaccine previously. Of the 296 patients without serological evidence of pertussis, 87 (29·4%) reported not receiving any previous dose of pertussis vaccine while 114 (38·5%) were unable to recall their vaccination status. The remaining 95 (32·1%) patients reported previous pertussis vaccination history: 50 (52·6%) received 4–5 doses, two (2·1%) received 2–3 doses, and 43 (45·3%) received one dose. However none of the patients' vaccination histories could be verified.

In patients with serological evidence of pertussis, the number of days absent from work ranged from 0 to 30, with a median of 0 and a mean of 2·4 (standard deviation 8·0). One patient from Malaysia reported lost income due to missing work, with an average daily income loss >US$97.5. Pertussis infection was associated with a median of 2·5 visits (range 1–10) to healthcare professionals (general practitioner, emergency room, or specialist). The median total direct medical cost of pertussis per episode in public hospitals (including consultations with physicians and/or emergency room visits) was US$13 (range US$13–16) or 40 MYR (range 40–50 MYR) in Malaysia; US$83 (or 2450 NTD) in Taiwan (one patient) and US$26 (range US$12–168) or 800 THB (range 360–5200 THB) in Thailand. The median time spent seeking medical care was 4 h (range 0·25–29 h).

Of subjects with serological evidence of pertussis infection, the overall median EQ-5D index score of cases was 0·72 (range 0·42–1·00). Two patients (2/16, 12·5%) had problems with mobility, 6/16 (37·5%) had problems in performing usual activities, 6/16 (37·5%) suffered from pain/discomfort and 7/16 (43·8%) suffered from anxiety/depression.

DISCUSSION

We found serological evidence of pertussis infection in the last 12 months in 5·13% of adults presenting to hospitals with cough of at least 2 weeks' duration in Malaysia, Taiwan and Thailand. This is comparable with a prevalence of pertussis of 7·2% in Taiwanese adults with cough duration ⩾1 week tested by serology (anti-PT) or PCR [7], and 1–17% of adults with prolonged cough illness in the United States, Denmark and Korea tested for elevated anti-PT levels in non-outbreak settings (reviewed in [19]). In addition, two thirds of the subjects had no evidence of immunity against pertussis meaning they remain at risk of contracting infection.

Pertussis disease in adults is frequently difficult to diagnose because of the absence of classical clinical

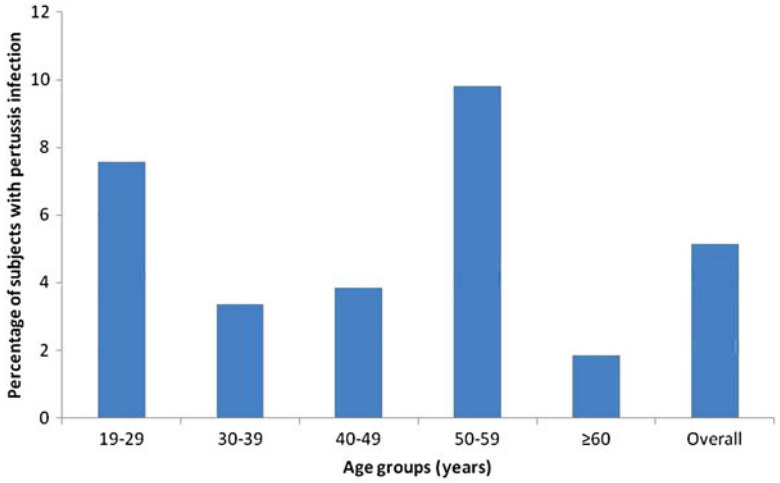

Fig. 2. Proportion of subjects in each age group with serological evidence of pertussis in the previous 12 months (anti-PT IgG $\geqslant$62·5 IU/ml; according-to-protocol cohort).

Table 3. *Clinical signs and symptoms of chronic cough by status of pertussis infection by anti-PT levels (according-to-protocol cohort)*

Clinical symptoms	With serological evidence (anti-PT $\geqslant$65·5 IU/ml) (N = 16)	Without serological evidence (anti-PT <65·5 IU/ml) (N = 296)	P value
Duration of cough, days, median (range)	43 (15–120)	31 (14–1682)	
Cough duration, days, *n* (%)			
14–30	4 (25·0)	142 (48·0)	<0·01†
31–60	7 (43·8)	74 (25·0)	
61–90	2 (12·5)	40 (13·5)	
>90	3 (18·8)	40 (13·5)	
Fever since onset of cough, *n* (%)			
Yes	5 (31·3)	74 (25)	0·56†
Presence of at least one of the following symptoms, *n* (%)			
Yes	13 (81·3)	258 (87·2)	0·45†
Whoop	2 (12·5)	18 (6·1)	0·27†
Paroxysm	12 (75·0)	143 (48·3)	0·04‡
Post-tussive vomiting	6 (37·5)	72 (24·3)	0·24†
Apnoea	0	3 (1·0)	1·00†
Cyanosis	0	0	—
Coughing up phlegm	6 (37·5)	180 (60·8)	0·06‡
Sneezes	6 (37·5)	111 (37·5)	1·00‡
Wheezes	3 (18·8)	34 (11·5)	0·42†
Cough at night	11 (68·8)	211 (71·3)	0·78†
Episodes of being unable to stop coughing	7 (43·8)	140 (47·3)	0·78‡
Breathlessness/chest pain	10 (62·5)	106 (35·8)	0·03‡

N, Number of subjects.
† Fisher's exact test *P* value.
‡ χ^2 test *P* value.

features such as the inspiratory 'whoop' that are typically associated with disease in unvaccinated children. Therefore, raising awareness in healthcare providers to consider pertussis in the differential diagnosis of cough illness in older individuals can help to improve the diagnostics. This may be particularly important as few clinical features were identified in our study that might facilitate differential diagnosis

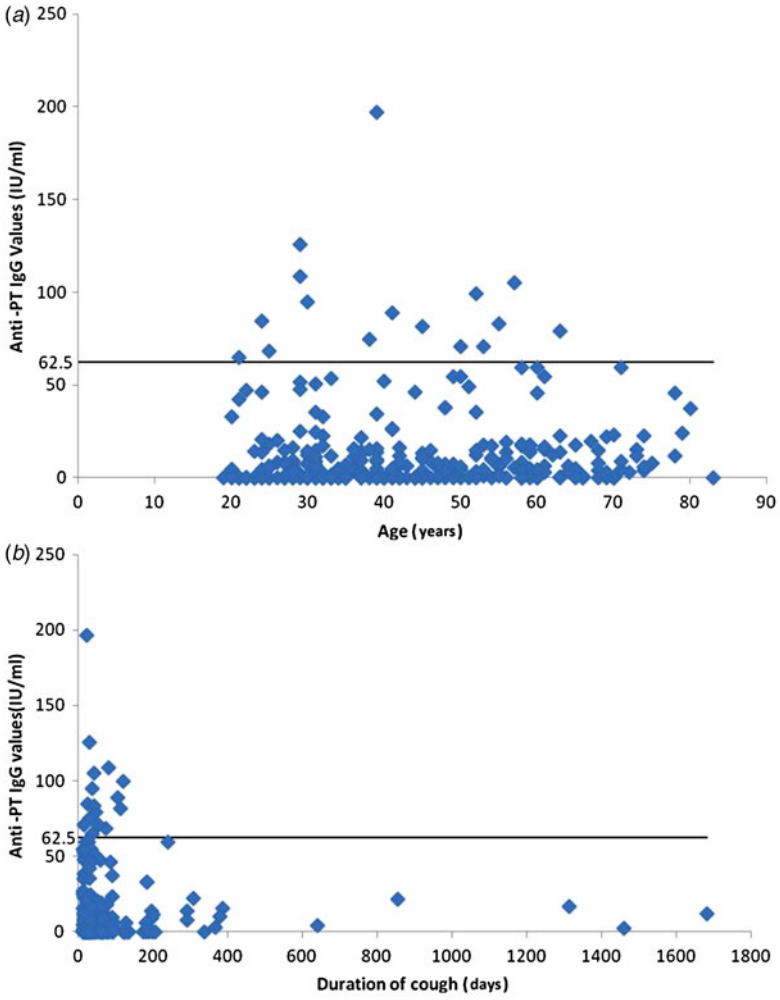

Fig. 3. Distribution of anti-PT IgG concentrations by (*a*) age and (*b*) cough duration (according-to-protocol cohort).

in this age group. *Bordetella pertussis* is a fastidious organism that is difficult to culture, and while PCR improves pertussis detection rates compared to culture [21], these techniques are both expensive and not readily available in many Asian laboratories. In addition, PCR is optimally sensitive during the first 3 weeks of cough, meaning patients in our study may have missed this window for detection. Further difficulty in performing routine testing in Asian countries is represented by the specialist training, experience and specific sample storage and transportation media required for the collection and processing of nasopharyngeal samples for PCR or culture. A single acute-phase serum sample, as used in our study, can reliably diagnose pertussis and has been advocated by the EU Pertstrain group [17]. This method is also supported by kinetic studies showing that anti-PT antibodies decline rapidly in all age groups after infection [15].

None of the patients with serological evidence of pertussis in the previous 12 months in our study received a diagnosis of pertussis. This suggests low awareness of pertussis in healthcare professionals and the potential for transmission of undetected pertussis to vulnerable infants. An increasing number of countries are adopting measures to reduce infant pertussis by vaccinating adults: this includes cocooning strategies and periodic booster doses at defined ages [22]. Of more recent interest is the potential to prevent infant pertussis through maternal immunization [23], with early evidence from the UK suggesting that high uptake and decreases in infant pertussis deaths are possible [24, 25].

Recent pertussis infection was associated with a reduced quality of life in our study, with over one third of subjects reporting pain/discomfort and problems conducting routine activities (e.g. work, study, housework, family or leisure activities). Most marked

was that over 40% of patients reported being 'moderately anxious'. The median EQ-5D score for subjects with recent pertussis infection was 0·72 suggesting that subjects with suspected pertussis perceived an impact on their quality of life.

The direct medical costs associated with pertussis episodes in our study varied between countries and was likely related to individual healthcare systems. The 2012 average monthly wage was US$623 in Malaysia, US$1546 in Taiwan and US$359 in Thailand [26]. This means that pertussis-associated medical costs represented around 2% of the monthly wage in Malaysia, 55% in Taiwan and over 7% in Thailand.

Our study has several limitations. Patients recruited from secondary and tertiary hospitals could possibly have more severe conditions than those seen by primary healthcare physicians. This could result in either over- or under-estimation of the true pertussis burden. Even though the patients were enrolled from primary healthcare centres within the hospitals, these patients may not be representative of patients seeking primary healthcare in general practitioners' or family physicians' clinics.

Another limitation is that the pertussis vaccination history was self-reported by patients. We were not able to verify vaccination status of adult patients via vaccination records. However, both the pertussis positive and negative patients provided the information without the knowledge of the serological test results and thus were not likely to be biased by the diagnosis.

In addition, PCR has not been widely used in laboratories of many Asian countries for the diagnosis of pertussis. The diagnosis of pertussis in this study was based on serology, which could have resulted in an underestimation of the pertussis burden. Furthermore, patients may not be fully aware of government subsidy levels for healthcare expenses, or they could be reluctant to share income information, resulting in an underestimation of the true health economic impact.

In conclusion, approximately 5% of adult patients in Malaysia, Taiwan and Thailand presenting to hospitals with cough of at least 2 weeks' duration showed serological evidence of pertussis infection, while over two-thirds had no evidence of existing immunity. Hence, pertussis should be considered in patients with prolonged or paroxysmal cough in the previous 12 months. Pertussis infection posed a significant health economic burden and moderate impact on the health-related quality of life of the affected patients. Increased awareness of pertussis by physicians and improved capacity of local laboratories is needed to improve early diagnostics and reduce the transmission of pertussis to children especially vulnerable young infants who are at the highest risk of severe disease and death. The need for adult vaccination against pertussis in Asian countries should be reassessed.

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DECLARATION OF INTEREST

M.T.K. reports receiving personal fees from the GSK group of companies. **W.B.** reports receiving grants and personal fees from the GSK group of companies, AstraZeneca and Boehringer Ingelheim, and personal fees from Novartis, MSD, Takeda and Thai Otsuka. **N.A.** reports receiving grants and non-financial support from the GSK group of companies. **X.H.Z., R.D.** and **J.C.** are employees of the GSK group of companies. The remaining authors have nothing to declare.

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