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Review

Pertussis in the Association of Southeast Asian Nations: epidemiology and challenges

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ABSTRACT

Pertussis is a highly infectious respiratory disease caused by *Bordetella pertussis*. Infants and young children are particularly at risk of severe and life-threatening disease. Infectious older individuals may transmit *Bordetella pertussis* to unprotected infants. Pertussis control measures have even failed in some countries with high pertussis vaccination coverage rates, leading to increased incidence rates. In 2014, this caused the World Health Organization to declare pertussis resurgent in some countries and led to recommendations regarding pertussis surveillance and national immunization programs. Despite the resurgence of pertussis, epidemiology of the disease in Southeast Asia has received little attention. In this narrative review, we describe pertussis surveillance systems, control measures, epidemiologic trends, and region-specific pertussis research in Southeast Asia. We also make recommendations for the intensification of pertussis surveillance and research in the region.

Contents

Introduction

Pertussis is a highly contagious infection of the respiratory tract caused by *Bordetella pertussis (B. pertussis)* and is endemic in all countries (World Health Organization, 2015). The most severe cases and mortality occur mainly in unprotected infants (aged <1 year old) and young children (aged 1–4 years old) (Cherry and Paddock, 2014; Kilgore et al., 2016). Although mass vaccination greatly reduced the number of pertussis cases and deaths, epidemic cycles of various intensity are occurring every two to five years, even in some countries with high vaccination coverage rates (Chow et al., 2016; WHO SAGE Pertussis Working Group, 2014).

Routine childhood immunization against pertussis globally has changed pertussis transmission dynamics. Its overall effectiveness

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in reducing pertussis circulation and number of cases also increased the length of the interepidemic period (Broutin et al., 2010). Concerns have been raised about the reactogenicity of whole cell pertussis vaccines (wP) which contain various amounts of whole inactivated bacterial cells expressing large numbers of antigens including the lipooligosaccharide (LOS) which is one of the factors responsible for the adverse reactions in children. As a result many countries have switched to the less reactogenic acellular pertussis vaccines (aP). aP vaccines are a new generation of vaccines that contain between one and five purified antigens (pertussis toxin [PT], filamentous haemagglutinin [FHA], pertactin [PRN], fimbriae [FIM] types two and three) (World Health Organization, 2015; World Health Organization, 2017). A reduced dose version of the aP vaccine is used for booster immunization, in adolescents and adults (World Health Organization, 2017).

A shift in the age distribution of pertussis towards older age groups (older children, adolescents, and adults) has recently been observed, particularly in some high income countries where aP replaced wP vaccines in the primary vaccination series (World Health Organization, 2015). Causative factors for recent changes in trends are multifactorial and are therefore still the cause of much discussion. Besides the naturally occurring cyclic patterns of disease circulation, waning natural immunity or waning vaccine-acquired immunity may also contribute to continued circulation of pertussis; these factors along with the accumulation of susceptible individuals provide favorable conditions for epidemics to occur. Indeed, the duration of immunity developed after natural infection has been estimated at 3.5–30 years (Kilgore et al., 2016). aP vaccines have been estimated to confer a shorter duration of immunity than wP vaccines (4–7 years vs. 5–14 years, respectively) (Kilgore et al., 2016). Other possible contributory factors include improved performance of laboratory diagnostic methods to identify cases (Kaczmarek et al., 2016), disease awareness among healthcare workers and in the general population (Hoffait et al., 2011; Wilder-Smith et al., 2007), adaptation of *B. pertussis* to vaccines or the human host (Hovingh et al., 2018; Breakwell et al., 2016; Hegerle and Guiso, 2014), lower efficacy/effectiveness of some vaccines (Fulton et al., 2016; Chit et al., 2018), and insufficient vaccination coverage. The World Health Organization (WHO) recommends national immunization programs (NIPs) using wP vaccines to continue using it. Countries that consider switching from wP to aP vaccines should have a surveillance system in place as the use of aP vaccines may result in a resurgence of pertussis after several years. Resurgence of pertussis may be associated with an increased risk of death in children who are too young to be vaccinated. NIPs using aP vaccines should consider additional aP boosters and other strategies if resurgence occurs, and surveillance with biological diagnosis, especially for hospitalized infants (World Health Organization, 2015).

Although intensive surveillance and research activities have focused on pertussis epidemiology in Western countries, such efforts have been lacking in Southeast Asia. The Association of Southeast Asian Nations (ASEAN) includes ten countries: Brunei Darussalam, Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand, and Vietnam. The ASEAN population is estimated at 635 million, of which 57.6 million are aged <5 years old (United Nations Population Division, 2017). Estimated mortality rates for those under 5 years old in ASEAN in 2016 indicate great disparity in the health of young children, reflecting wealth inequality between these countries. Mortality rates in those under 5 years old (per 1000 live births) are lowest in Singapore (2.8) and highest in Laos (63.9) (United Nations Inter-agency Group for Child Mortality Estimation, 2017). In their recent pertussis disease burden model, Yeng et al. estimated that out of the 179.5 million individuals below 5 years of age living in Southeast Asia in 2014, a total of 6.3 million (3.5%) of these children would develop pertussis disease leading to approximately 42,500 deaths (Yeung et al., 2017).

To date, no review has focused on the epidemiology of pertussis in ASEAN. Thus, we aim to review the epidemiology of pertussis as well as the current control measures implemented in ASEAN and make recommendations about pertussis surveillance and epidemiologic research.

Data sources and data selection process

Data about surveillance system characteristics were obtained from the websites of ASEAN ministries of health. Epidemiologic trends data from 2000–2017 came from the WHO vaccine-preventable diseases monitoring system (World Health Organization, 2018a) and United Nations population estimates (United Nations Population Division, 2017). We chose these data sources because of the limited specificity of the WHO pertussis clinical case definition for non-infant pertussis presentations (Patriarca et al., 1988), which is commonly used in ASEAN, and unreliability of population census data from some ASEAN countries. The WHO vaccine preventable diseases monitoring system counts cases confirmed by paired serology, culture, and polymerase chain reaction (PCR) (World Health Organization, 2018a). Vaccination schedules and coverage rates were obtained from ASEAN ministries of health websites and WHO estimates (World Health Organization, 2018b), respectively. ASEAN pertussis epidemiologic studies were retrieved from OVID Medline, Web of Science, and Scopus using MeSH and keyword terms for pertussis and ASEAN countries.

Surveillance Systems

All ASEAN countries have passive surveillance by population-based statutory notification of pertussis. Most ASEAN countries use the WHO clinical case definition for all age strata. Low sensitivity of the WHO clinical case definition, which does not account for age-specific differences in clinical manifestations, may contribute to under-recognition of pertussis by healthcare workers (Patriarca et al., 1988). Many ASEAN countries have limited laboratory testing facilities to biologically confirm diagnosis. Thus, most cases reported to statutory notification systems in most ASEAN countries are clinically suspected. For example, only 80 of 285 cases reported to the Filipino statutory notification system in 2017 were laboratory-confirmed while the other cases were clinically suspected (Epidemiology Bureau of the Public Health Surveillance Division, 2017). Improved access to diagnostic laboratories may contribute to higher numbers of overall and laboratory-confirmed cases. For example, implementation of PCR at a national reference laboratory in Malaysia in 2010 was associated with a dramatic increase in case counts reported to the statutory notification system (World Health Organization, 2018a; Ministry of Health, Malaysia, 2010). Therefore, both increased diagnostic laboratory availability and pertussis awareness may contribute to increasing case counts and incidence rate data reliability in ASEAN.

Epidemiologic trends

Pertussis incidence rate trends

Annual incidence rates for ASEAN countries between 2000 and 2017 are shown in Table 1.

Brunei Darussalam. The annual incidence rate ranged from 0–1.20 per 100,000 population. No striking changes in epidemiological trends were observed even when the NIP switched from wP to aP in 2008.

Table 1
Annual incidence rate of pertussis in ASEAN countries between 2000 and 2017 (World Health Organization, 2018a).

Country	Estimated incidence rate (per 100,000 population)																	
	2017	2016	2015	2014	2013	2012	2011	2010	2009	2008	2007	2006	2005	2004	2003	2002	2001	2000
Brunei Darussalam	0.00	0.00	1.20	0.243	-	0.750	0.761	0.257	0.00	0.528	-	-	0.00	0.00	0.00	-	0.00	0.600
Cambodia	0.125	0.0571	0.0644	0.0196	0.00	0.365	-	2.60	3.64	8.73	4.10	3.52	3.48	0.505	2.45	2.53	38.0	-
Indonesia	0.395	0.316	-	0.816	1.18	-	0.790	-	0.407	-	-	1.46	3.92	0.692	1.98	0.818	0.478	0.0671
Laos	1.62	0.133	2.10	-	0.924	6.42	0.600	0.0961	0.195	0.430	0.218	3.11	2.09	3.51	3.58	-	2.05	1.50
Malaysia	1.11	0.955	3.06	1.65	0.747	0.744	0.866	0.146	0.0181	0.0406	0.0563	0.0230	0.0312	0.159	0.113	0.0248	0.110	-
Myanmar	0.00750	0.00378	0.00954	0.00963	0.0272	0.00392	0.00990	0.000	0.00602	0.0101	0.0264	0.0266	0.0227	0.208	0.0399	0.129	-	0.119
Philippines	0.0839	0.0281	0.00492	0.00	0.0234	0.00	-	0.0661	0.00217	0.0507	0.019	0.0467	0.0232	0.0118	0.0108	0.00983	0.0201	0.0295
Singapore	1.38	-	-	-	0.317	0.455	0.56	0.158	0.262	0.68	0.803	0.0434	0.0445	0.00	0.0235	0.00	0.0249	0.0511
Thailand	0.0795	0.122	0.0743	0.0205	0.0352	0.0206	0.0178	0.00892	0.0374	0.0240	0.0347	0.109	0.0352	0.0323	0.0372	0.0234	0.113	0.148
Vietnam	0.580	0.282	0.330	0.0973	0.0590	0.108	0.117	0.0916	0.139	0.323	0.213	0.169	0.230	0.393	0.865	0.808	1.53	1.78

Cambodia. The annual incidence rate ranged from 0–38 per 100,000 population. The dramatic decrease in the number of laboratory-confirmed cases since 2013 coincided with consistent coverage rates of over 90% since 2008 with one dose of a pertussis-containing vaccine (DTP1) and three doses of a pertussis-containing vaccine (DTP3) (World Health Organization, 2018b).

Indonesia. The annual incidence rate ranged from 0.0671–3.92 per 100,000 population with no clear changes in trends.

Laos. The annual incidence rate ranged from 0.0961–6.42 per 100,000 population. Overall the incidence rate dropped dramatically after 2006 but sharp increases were detected in 2012, 2015 and 2017. Whether these peaks reflect a true increase in incidence or are the result of improved surveillance remains unclear.

Malaysia. The annual incidence rate ranged from 0.0181–3.06 per 100,000 population. No changing trend seemed to be associated with the switch from wP to aP by the Malaysian NIP in 2008. But an increase in the reported incidence is noticeable since 2010, which corresponds with the introduction of PCR for biological confirmation of the disease in the same year (Ministry of Health, Malaysia, 2010). Whether the increase in incidence is due to improved laboratory diagnosis or to true resurgence of pertussis is still unclear.

Myanmar. The annual incidence rate ranged from 0–0.208 per 100,000 population. Myanmar has the lowest reported incidence rate between 2000 and 2017 among all ASEAN countries with no visible changes in incidence rate trends over that period. Because the vaccination coverage rates of DTP1 and DTP3 have rarely been ≥90% (World Health Organization, 2018b), the incidence rates of confirmed cases reported are likely to be underestimated.

Philippines. The annual incidence rate ranged from 0–0.0839 per 100,000 population without any clear recent change in trend. These reported incidence rates likely underestimate the true incidence rate because annual vaccination coverage rates of DTP1 and DTP3 are usually <90% (World Health Organization, 2018b).

Singapore. The annual incidence rate ranged from 0–1.39 per 100,000 population. The highest incidence rate was observed in 2017, data based on WHO case counts are missing for 2014–2016. Official Singaporean government reports show incidence rates for 2014, 2015, and 2016 at 0.385, 1.03, and 1.3939 per 100,000 population, respectively (Ministry of Health, Singapore, 2018). The overall trend is towards an increased incidence of the disease since 2007 and especially since 2015. The Singaporean NIP switched from wP to aP in 2008.

Thailand. The annual incidence rate ranged from 0.00892–0.148 per 100,000 population. Although a higher number of cases have been declared since 2015, whether this represents true pertussis resurgence or improved surveillance is unclear.

Vietnam. The annual incidence rate ranged from 0.059–1.78 per 100,000 population. After a drop in 2004, an increasing number of cases have been reported since 2015. Whether this represents a true resurgence or improved surveillance is unclear.

Vaccination schedules, vaccination coverage rates, and type of pertussis vaccine used

Contemporary vaccination schedules and coverage rates between 2008 and 2017 are shown in Table 2.

Four ASEAN countries, Cambodia, Laos, Myanmar and the Philippines, do not offer a booster dose after the primary series of vaccinations. Indonesia, Malaysia, Singapore, Thailand and Vietnam include one booster dose for toddlers. Only Brunei Darussalam and Thailand offer a pre-school age booster. Only Singapore offers an adolescent booster. No ASEAN country schedules an adult booster.

WHO reported estimated national vaccination coverage rates for DTP3 for 2008 to 2017 and showed Laos, Myanmar, Indonesia and the Philippines had consistently low estimated DTP3 coverage

Table 2
Pertussis immunization schedule and estimated national DTP3 vaccination coverage rates by ASEAN country.

Country	Time period of NIP using vaccine type	Current primary series	Current booster doses			DTP3 vaccination coverage rate from 2008–2017 (%, min-max)[b]
			Toddler	Pre-school age	Adolescent	
Brunei Darussalam	From[a] 1984 to 2007	wP				95–99
	Since 2008	aP 2, 4, 6 mo		aP 5 y		
Cambodia	Since 1986	wP 6, 10, 14 wk				91–99
Indonesia	Since 1977	wP 2, 3, 4 mo	wP 18 mo			73–95
Laos	Since 1982	wP 6, 10, 14 wk				61–89
Malaysia	From 1958 to 2007	wP				95–99
	Since 2008	aP 2, 3, 5 mo	aP 18 mo			
Myanmar	Since 1978	wP 2, 4, 6 mo				75–90
Philippines	Since 1976	wP 6, 10, 14 wk				60–96
Singapore	From 1959 to 2007	wP				96–97
	Since 2008	aP 3, 4, 5 mo	aP 18 mo		aP 10-11 y	
Thailand	Since 1977	wP 2, 4, 6 mo	wP 18 mo	wP 4–6 y		99–99
Vietnam	Since 1981	wP 2, 3, 4 mo	wP 18 mo			59–97

Abbreviations: aP, acellular pertussis-containing vaccine; DTP3, third dose of diphtheria, tetanus toxoid, and pertussis vaccine; mo, month; NIP, national immunization program; wP, whole-cell pertussis-containing vaccine; wk, week; y, year.
Available at: http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveragedtp3.html Accessed May 18 2018
[a] Brunei Darussalam became an independent nation in 1984.
[b] National coverage of third dose of diphtheria, tetanus toxoid, and pertussis vaccine between 2008-2017 estimated by WHO/UNICEF.

rates annually. Since 2008, the coverage rate for DTP3 in Vietnam was consistently ≥90%, however there was one exception to this in 2013 when coverage was reported at 59%. This was caused by a well-publicized public health scare involving pertussis-containing vaccine-associated deaths in Vietnam in 2012, the scare was subsequently proven not to be linked to pertussis vaccination and vaccination rates therefore recovered (World Health Organization, 2013).

Currently, the Brunei Darussalam, Malaysian and Singaporean NIPs use aP only, after switching from wP in 2008, while the other ASEAN countries have been using wP only. Among ASEAN countries, only Singapore has introduced recommendations for maternal vaccination against pertussis in 2017.

Epidemiologic studies

Nine studies containing descriptive epidemiology data from ASEAN countries were identified: two hospital-based studies of children with severe pertussis (Kowalzik et al., 2007; Sadiasa et al., 2017), two hospital-based studies of adults with prolonged cough (Siriyakorn et al., 2016; Koh et al., 2016), two seroepidemiology surveys (Wanlapakorn et al. 2016; Son et al. 2018), and three studies of multiple etiologies of respiratory illness (Wertheim et al. 2015; Barger-Kamate et al. 2016; Lau et al. 2018) (Table 3). Pertussis disease in ASEAN countries is poorly characterized, partly demonstrated by the fact that only six out of ten countries are represented by these nine studies.

Hospital-based studies of children with severe pertussis. In Singapore, 13/147 [9% (95%CI: 4–13%)] cases were found among infants aged <1 year old (using the US Centers for Disease Control and Prevention pertussis case definition) in pediatric intensive care units between 2001 and 2004 (Kowalzik et al., 2007). The mean age was 3.1 months (SD: 2.4), the case-fatality rate (CFR) was 0/13 (0%), and the non-participation rate was 68%. In the Philippines, 34/1152 (2.95%) cases were found in hospitalized children aged 8 days to 13 years presenting with severe pneumonia between 2012 and 2015 (Sadiasa et al., 2017). Around two-thirds of the confirmed cases were aged <3 months, and approximately half of them had viral co-infections. The CFR was 15%.

Both studies estimated the burden of severe symptomatic pertussis in children but the high non-participation in the Singaporean study could be a significant source of bias.

Hospital-based studies of adults with prolonged cough. In Thailand, 14/76 (18.4%) pertussis cases were found in adults aged ≥15 years from 2010 to 2011 (Siriyakorn et al., 2016). The investigators of another multinational study conducted between 2012 and 2013 in adults aged ≥19 years used a commercial anti-PT IgG detection ELISA kit recommended by WHO on a single serum specimen and found 9/147 (6.1% [95%CI: 2.84–11.30%]) suspect cases in Thailand and 6/76 (7.9% [95%CI: 2.95–16.40%]) suspect cases in Malaysia (Koh et al., 2016; Riffelmann et al., 2010; World Health Organization, 2014). Four of these 15 subjects had anti-PT antibody titers indicative of active or recent infection, and the other nine individuals had serological evidence of pertussis infection in the last 12 months. Of the cases reported, patient-reported pertussis vaccination statuses were collected; 62.5% said they had no previous vaccination and could therefore be considered as confirmed cases, 31.3% had no recollection of having had a vaccination and one patient said they had received one dose (Koh et al., 2016). The different serology diagnostic cut-off values used in each of the studies precludes direct comparison (Table 3). These hospital-based studies most probably underestimate the incidence of symptomatic pertussis in adults since a number of those with mild symptoms may not seek healthcare.

Seroepidemiology surveys. In Thailand, a 9.4% seroprevalence (84/900 participants) was found by conducting a randomized, national survey among participants in all age strata in 2014 (Wanlapakorn et al., 2016). One-third of the seropositive individuals were children who may have had vaccine-induced antibodies. A multinational serosurvey that included Thailand was performed between 2013 and 2016 among adolescents aged 10–18 years (Son et al., 2019). A 5.26% seroprevalence (11/209 Thai participants) was found. Logistic regression showed no difference in number of cases based on factors such as immunization with aP versus wP vaccine, number of vaccine doses, and age.

Studies of multiple etiologies of respiratory illnesses. A laboratory-based survey analyzed respiratory clinical specimens collected from persons aged ≥1 year hospitalized with influenza-like illness (ILI) in Indonesia, Thailand, and Vietnam from 2008 to 2009 (Wertheim et al., 2015). Out of 1222 patients tested, only one (0.08%) pertussis case was found. No pertussis-specific symptoms or vaccine status was reported. The Pneumonia Etiology Research for Child Health Study was a multinational, prospective, hospital-based and community control study which included Thai infants

Table 3
Selected descriptive epidemiologic research studies from ASEAN.

Country	Study period	Study type	Participants	Diagnostic test used	Case definitions	Main findings	References
Hospital-based studies of children with severe pertussis							
Singapore (one of seven countries)	September 2001–January 2004	Prospective, hospital-based cross-sectional survey	[a]Infants aged <1 y with clinical pertussis (US CDC case definition) admitted to PICUs in Singapore	Culture, IgG anti-PT ELISA serologic test, and PCR[b]	Confirmed case Culture Isolation of *B. pertussis* PCR Positive Single sera Active infection = > 100 IU/mL (for age >6 mo, without vaccination in previous 6 mo)	Singapore Laboratory-evidenced cases[c] = 13 (9% [95%CI 4-13]) Case-fatality ratio = 0%	Kowalzik et al. (2007)
Philippines	August 2012–February 2015	Prospective hospital-based case-comparison study	1152 children aged 8 d-13 y hospitalized with severe pneumonia at two referral hospitals	PCR[b]	PCR Positive	PCR-confirmed cases = 34/1152 (2.95%) Case-fatality ratio = 15%	Sadiasa et al. (2017)
Hospital-based studies of adults with prolonged cough							
Thailand	October 2010–February 2011	Prospective hospital-based cross-sectional survey	76 adults aged ≥15 y with cough >2 wk without chronic lung disease, immunocompromised status, and history of Tdap booster at aged 10-11 years at one referral hospital	IgG anti-PT ELISA serologic test and PCR[d]	Serology 4-fold paired sera, or ≥3 SD single serum from an unreported reference sera PCR Positive	Laboratory-evidenced cases = 14/76 (18.4%) (PCR-confirmed n = 1 and serology-evidenced n = 13)	Siriyakorn et al. (2016)
Malaysia and Thailand (two of three Asian countries)	June 2012– May 2013	Prospective hospital-based cross-sectional survey	Adults aged ≥19 y with cough ≥14 d without chronic lung, immunocompromised status, and pertussis vaccination status within 12 mo: 76 in Malaysia at two referral hospitals and 147 in Thailand at three referral hospitals	IgG anti-PT ELISA serologic test	Single sera Recent infection in the last 12 months = ≥ 62·5 IU/ml; Active or recent infection = ≥100 IU/ml	Thailand Recent infection in the last 12 months, recent or active pertussis infection = 9/147 (6.1% [95%CI 2.84-11.30]) Malaysia Recent infection in the last 12 months, recent or active pertussis infection = 6/76 (7.9% [95%CI 2.95-16.40])	Koh et al. (2016)
Seroepidemiology surveys							
Thailand	March–October 2014	Retrospective cross-sectional serosurvey using residual serum	900 adults and children (any age) without chronic disease, immunocompromised status, and bleeding disorders from seven provinces nationwide in Thailand	IgG anti-PT ELISA serologic test	Single sera Acute pertussis infection or recent vaccination = >100 IU/mL Probable past exposure to pertussis = 40–100 IU/mL	Acute infection or vaccination = 23/900 (2.6%) Probable past exposure to pertussis = 61/900 (6.8%) Pooled probable past exposure to pertussis, acute infection, and recent infection or vaccination = 84/900 (9.4%)	Wanlapakorn et al. (2016)
Thailand (one of seven Asian countries)	July 2013–June 2016	Prospective hospital-based cross-sectional survey	209 adolescents aged 10-18 y attending hospital for other medical reasons without history of Tdap booster in 1 y and immunocompromised status at one referral hospital in Thailand	IgG anti-PT ELISA	Single sera Pertussis infection within 12 mo = ≥62·5 IU/ml	Thailand Probable infection within 6 and 12 mo = 5.26% (11/209)	Son et al. (2019)
Studies of multiple etiologies of respiratory illnesses							
Indonesia, Thailand and Vietnam	July 2008– June 2009	Retrospective laboratory-based cross-sectional survey using stored respiratory specimens	1222 patients age ≥1 y hospitalized with clinically diagnosed ILI ≤10 d at three Indonesian hospitals, four Thai hospitals, and five Vietnamese hospitals	PCR[d]	PCR Positive	PCR-confirmed *B. pertussis* infection = 1/1222 (0.08%)	Wertheim et al. (2015)

Table 3 (*Continued*)

Country	Study period	Study type	Participants	Diagnostic test used	Case definitions	Main findings	References
Thailand (one of seven countries)	August 2011–January 2014	Prospective hospital- and community-based case-control study in two provinces in Thailand	224 hospitalized cases of severe pneumonia in children aged 1-59 mo 659 community controls aged 1-59 mo (Lau et al., 2018)	PCR[d]	PCR Positive	Thailand Pneumonia case group = 0% (0 of 224) Community control group = 0.455% (3/659; WHO case definitions: two clinically and one laboratory-confirmed case)	Barger-Kamate et al. (2016)
Singapore	January 2016–January 2017	Prospective ARI surveillance at one army medical clinic in Singapore	2647 adult Singaporean servicemen with ARI	PCR[d]	PCR Positive	*B. pertussis* cases = 7/2647 (0.264%)	Lau et al. (2019)

Abbreviations: ARI, acute respiratory illness; d, day; ELISA, enzyme-linked immunosorbant assay; ILI, influenza-like illness; m, month; PCR, polymerase chain reaction; PICU, pediatric intensive care unit; PT, pertussis toxin; Tdap, diphtheria toxoid, tetanus toxoid, and acellular pertussis vaccine booster for adolescents and adults; US CDC, United States of America Centers for Disease Control and Prevention; WHO, World Health Organization; wk, week; y, year.
[a] The number of participants in Singapore was not reported.
[b] WHO-recommended *B. pertussis*-specific PCR technique.
[c] The specific biological diagnostic technique for the Singaporean participants was not reported. One of 99 laboratory-evidenced cases from all seven countries participating in the study was diagnosed by serology.
[d] No evidence in the literature of the clinical diagnostic performance of this PCR technique.

aged 1-59 months presenting with pneumonia between 2011 and 2014 (Barger-Kamate et al., 2016). None of the 224 pneumonia cases tested positive for pertussis by PCR while three (0.34%) cases (two clinically and one PCR-confirmed case) were found in the control group. The Singaporean Army performed respiratory disease surveillance of multiple etiologies of acute respiratory illness (ARI) in servicemen at an army clinic (Lau et al., 2018). Seven out of 2647 (0.264%) cases tested positive for pertussis between 2016 and 2017. These studies of multiple etiologies of acute respiratory illness estimate the proportion of pertussis as an etiology for ILI, pneumonia, and ARI. Unfortunately, no study covered one full traditional 3–5 year epidemic cycle. The laboratory-based and Singaporean Army surveillance studies did not report pertussis-specific clinical data. Inferences from these studies may be limited because primary study aims were not specifically designed to identify pertussis cases. In addition, all these studies collected various types of respiratory specimens while only nasopharyngeal swabs and aspirates are recommended for *B. pertussis* diagnosis by PCR (World Health Organization, 2014).

Surveillance and epidemiologic research recommendations

All ASEAN countries have statutory pertussis notification through population-based passive surveillance. No reliable data are currently available to estimate the extent of pertussis underreporting by these population-based passive surveillance systems. Underreporting is caused by various factors such as lack of physician awareness, rare treatment seeking behavior among mild pertussis cases, lack of biological diagnosis testing capacity, and absence of user-friendly reporting infrastructure (Crowcroft et al., 2018; Schielke et al., 2018). Thus, we recommend the following alternative options.

Surveillance of children aged <5 years. Considering the high incidence of disease and the mortality rate observed in young children (especially in infants who are too young to be vaccinated), surveillance of this age group should be prioritized. Severe pertussis disease in children aged <5 years is the easiest to identify because caregivers tend to seek healthcare. Therefore, continuous pediatric hospital-based sentinel surveillance with standardized biological diagnosis for all suspect cases at hospitals throughout each ASEAN country should be established (Tubiana et al., 2015; IMPACT, 2009). It is also probably the most cost-effective way to determine the incidence of the disease in infants and, at the same time, to identify the source of contamination since parents and grandparents who normally bring the child to the consultation represent the source of infant's contamination in approximately 60% of cases (Wiley et al., 2013).

Surveillance of older children, adolescents, and adults. Adults with symptomatic pertussis may not seek healthcare because of the mildness of their symptoms. Therefore, healthcare facility-based surveillance may underestimate their disease burden. Healthcare facility-based surveillance with standardized biological diagnosis for one 3–5 year epidemic cycle could be performed. However, randomized, large community-based surveys in older children, adolescents, and adults with standardized biological diagnosis would be required in the same geographical areas to adjust incidence rate estimates from healthcare facility data (World Health Organization, 2005).

Serosurveillance. Large, randomized serosurveys are a convenient method for estimating the circulation of *B. pertussis*, especially in older age groups (Pebody et al., 2005; De Melker et al., 2006). However, only *B. pertussis*-specific IgG anti-PT serology with external quality assessment should be used (European Centre for Disease Prevention and Control, 2014). Indeed, we excluded two serosurveys from this review that used commercial mixed pertussis antigen ELISA (Wilder-Smith et al., 2006; Lai et al., 2012) and includes filamentous hemagglutinin antigen that is cross-reactive with *B. parapertussis* (European Centre for Disease Prevention and Control, 2014).

Vaccination coverage surveys. Large, detailed vaccination coverage surveys including private healthcare service providers are required to endorse official government reports of pertussis vaccination coverage rates (Brown et al., 2013). These may also assess the detailed performance of NIPs in the timeliness and completeness of immunization schedules among general populations and hard-to-reach populations.

Data collection and diagnosis. Patient and close contact demographic data, pertussis-associated symptoms description, and vaccination status would allow much more detailed interpretation of the findings (World Health Organization, 2008; World Health Organization, 2014). Reporting these data elements and stratifying them by country in multinational studies is essential.

Clinical diagnosis by the WHO clinical case definition is not optimally sensitive for each age strata (Patriarca et al., 1998; Jõgi et al., 2018). Thus, the standardized Global Pertussis Initiative case definitions (World Health Organization, 2008) should be considered instead.

Biological diagnostic methods should be standardized. *B. pertussis* can be isolated from nasopharyngeal swabs, nasopharyngeal aspirates or sputum and quickly transported at room temperature to the microbiology lab for culture, the sensitivity of this technique does not usually exceed 60%. For PCR testing, a Dacron swab with polystyrene stick is preferred to collect the nasopharyngeal specimen (World Health Organization, 2014). PCR is more sensitive than bacterial culture and general good laboratory practices for molecular biology diagnosis should be strictly followed. Multiple genes can be targeted for PCR diagnosis but the method should be wisely selected (World Health Organization, 2014). For instance, the insertion sequence IS481 that is commonly targeted by many diagnostic PCRs is actually not specific of *B. pertussis* and can be also found in *B. holmesii* (Njamkepo et al., 2011; Rodgers et al., 2013).

For direct diagnosis, of *B. pertussis* infection, by bacterial culture and PCR, it is recommended to collect the nasopharyngeal sample within 2–3 weeks after onset of the cough. The serology consists of detecting anti-PT antibodies in the serum of patients after 2-3 weeks of cough using in-house assays developed by reference centers or commercial kits recommended by WHO (Riffelmann et al., 2010; World Health Organization, 2014; Dinu et al., 2014). This indirect diagnosis method cannot be used in infants (as their immune system is still immature and liable to interference by antibodies transferred by the mother during pregnancy) and in patients vaccinated within one year of developing the infection. The serology test cannot differentiate between antibodies present from the vaccine or from natural infection. The serological diagnosis is based on the detection of a significant increase in the concentration of anti-PT antibodies in paired serum samples collected during the early catarrhal stage and then one month later. In a single serum sample, a high antibody concentration in an unvaccinated individual is an indicator of recent infection (World Health Organization, 2015).

Using equipment without clinical diagnostic performance assessment or external quality assessment may preclude comparisons of data. Using *B. pertussis*-specific biological diagnostic methods with external quality assessment and standardizing serology cut-off values at a national level should be considered (European Centre for Disease Prevention and Control, 2014; European Centre for Disease Prevention and Control, 2012). Improving capacities of ASEAN national reference laboratories to confirm diagnoses, to provide reference materials, to assist other laboratories to develop their skills, and to perform external quality control assessments may improve the quality of the study results and allow comparison of the data across the region thanks to standardized biological diagnosis (Mulders et al., 2017). Biological samples should be sent to appropriate laboratories for further characterization of circulating clinical isolates of *B. pertussis* (van Gent et al., 2015; Galit et al., 2015; Moriuchi et al., 2017). Antibiotic resistance of *B. pertussis* strains should also be closely monitored considering the risk of spread of macrolides-resistant strains that have been recently identified, especially in China where up to 91.9% of the clinical isolates are highly resistant to erythromycin (Fu et al., 2019; Liu et al., 2018).

The role of surveillance and epidemiologic research in parameterizing pertussis transmission models

Modeling *B. pertussis* transmission to infants and young children requires estimating the rate at which they become infected from close contacts. Ideal inputs are empirical data from all age strata of close contacts, per contact risk of infection, and the fractional prevalence of pertussis by age strata of close contacts (Campbell et al., 2015). Estimating the fractional prevalence of pertussis also requires data on duration of infectivity in an infected individual, epidemic cycles, vaccination coverage, vaccine effectiveness, and duration of naturally and vaccine-acquired immunity (Campbell et al., 2015). The vaccine effectiveness and duration of vaccine-acquired immunity of contemporary wP vaccine used in ASEAN populations is unknown. Therefore, observational studies, such as nested case-control studies, should be performed in ASEAN (Verani et al., 2017a; Verani et al., 2017b). Improvement of pharmocovigilance infrastructures and activities to monitor the adverse effects and address the potential safety issues associated with wP vaccines in particular should also be considered (Dellepiane and Pagliusi, 2019). To inform vaccination policy-makers, transmission models can identify which age strata to vaccinate and what critical vaccination coverage rate in the age strata is necessary to reduce transmission to infants and young children (Fine et al., 2011; Clark, 2012).

A recent age-stratified compartment transmission model (Domenech de Celles et al., 2018) suggests an explanation for the resurgence of pertussis in some Western countries. Countries with resurgence may have had a "honeymoon period" of low pertussis incidence due to increased vaccination coverage and a high proportion of immune pre-vaccination era adults with long-lasting naturally acquired immunity. Subsequently, resurgence may have occurred because of pre-vaccination adult population turnover and the accumulation of susceptible individuals who were either unimmunized or had waning vaccine-induced immunity without natural immune boosting.

The only ASEAN pertussis transmission models are from Thailand and suggest no resurgence (Blackwood et al., 2013, 2016). However, important parameters such as infant close contacts were not empirical Thai data. Collecting surveillance and research data to parameterize explanatory transmission models is necessary.

Summary

There is a substantial degree of variability in pertussis immunization schedules and vaccination coverage rates across ASEAN countries. The descriptive epidemiologic data show that *B. pertussis* circulates in ASEAN countries, but the true disease burden remains unclear due to lack of reliable and informative data elements. Increased surveillance efforts are required to monitor trends in pertussis incidence. ASEAN country-specific data for pertussis transmission modeling could optimize immunization schedules to protect infants and young children who are most at risk of hospitalization and death resulting from pertussis.

Conflicts of interest and sources of funding

PB is an employee of and holds shares in the GSK group of companies. The opinion presented in this paper is the one of the authors and does not reflect GSK position, no funding was provided by GSK for this review. Ethical approval is not required.

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