

## Pertussis in Children: Problems in Indonesia

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### Abstract

The burden of pertussis cases has dramatically resurged and increased in highly immunized countries. However, in Indonesia those cases are still under diagnosed because of lack of awareness and laboratory support to confirm pertussis diagnoses. This review article will discuss about pertussis in children, the magnitude problems in Indonesia.

We searched databases including Pubmed/MEDLINE database, Elsevier, and also official website for the following keywords: Pertussis, whooping cough, children, diagnosis and treatment, problem, Indonesia.

We reviewed the most recent algorithm, case classification, and guidelines by World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) and also some problems in Indonesia in diagnose and treat children with pertussis.

In Indonesia most cases are diagnosed as having bronchopneumonia while later known as probable pertussis. To understand this disease and its problems in Indonesia, it is important to enhanced awareness of diagnose and treat pertussis in children.

**Keywords:** Pertussis; Whooping cough; Children; Indonesia

### Introduction

Pertussis or whooping cough (also known as 100 days cough or batuk rejan in Indonesian language) has dramatically resurged in the recent years. The burden of the disease has increased in highly immunized countries, particularly in those aged over 10 years and infants less than five months of age [1-6].

Pertussis are generally under-diagnosed in Indonesia. Health personnels in remote area health facility have limited knowledge of pertussis or pertussis like cough. The diagnosis particularly rely on the presence of clinical manifestations because diagnostic tests such as culture and polymerase chain reaction (PCR) are not available. The late recognition often makes the patient come to the hospital with severe complication and respiratory failure. The lack of case reporting might be due, in part, to the demographic characteristic of Indonesia archipelago which consist of thousand islands and has poor communication facility. The purpose of this article is to review the problematic management of pertussis in children in Indonesia.

### Methods

We searched databases including Pubmed/MEDLINE database, Elsevier, and also official website for the following keywords: Pertussis, whooping cough, children, diagnosis and treatment, problem, Indonesia.

We reviewed the most recent algorithm, case classification, and guidelines by World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) and also some problems in Indonesia in diagnose and treat children with pertussis.

### Situation in Indonesia

World Health Organization (WHO) had reported 200,868 cases of pertussis in 2012, 95% of cases occurred in developing countries. Although reliable reports on the incidence rate of pertussis are hampered by misdiagnosis, unavailability of laboratory test confirmation, under-reporting and different case criteria between countries, it is obvious that 90% of estimated 400,000 pertussis related death occur in these countries [3,7]. In Indonesia, laboratory test confirmation is nearly not possible because microbiology culture facility for Bordetella pertussis

is not available except at a limited laboratory center at Bandung, West Java. One study reported two of 61 pertussis cases were laboratory confirmed [8]. Eventhough WHO recommended PCR test for *B. pertussis* laboratory confirmation, it is not available in Indonesia [9].

The notification rate of 9.1 per 100,000 populations was reported in Europe in 2014. The most susceptible infants were those under six months of age which comprised 83% of under one year of age infants suffered from pertussis [10]. Fifty percent of infants less than 1 year of age who had pertussis will require hospitalization, of which 50% will develop pneumonia and 1% will die due to pneumonia [11]. Most deaths attributed to young infants who were either unvaccinated or incompletely vaccinated [3,4,12]. This situation is also happened in Indonesia, where most cases are infant < 1 year old and present with bronchopneumonia and later known as having probable pertussis [13].

After declined incidence of pertussis after immunization circa 1970, case notification in South East Asia noted resurgence of pertussis which increased from 38,510 cases in year 2000 to 52,871 in 2014. Despite DPT3 vaccination coverage of more than 80%, there were 2,970 documented pertussis cases reported in Indonesia in 2013 (Figure 1) [14].

World Health Organization (WHO) and Centre of Disease Control (CDC) guidelines for pertussis diagnosis.

### Classification in Indonesia

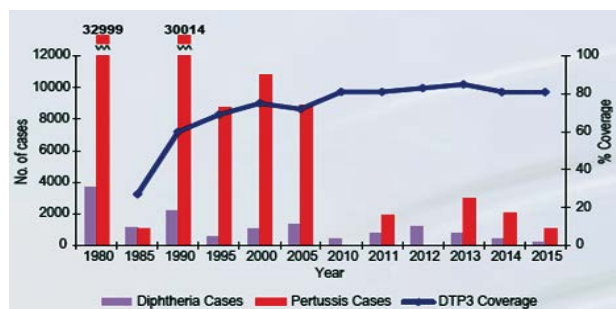
Algorithm for diagnosis of pertussis has been developed by the Global Pertussis Initiative to address the different clinical features between infants and older children, as well as inequality of access to

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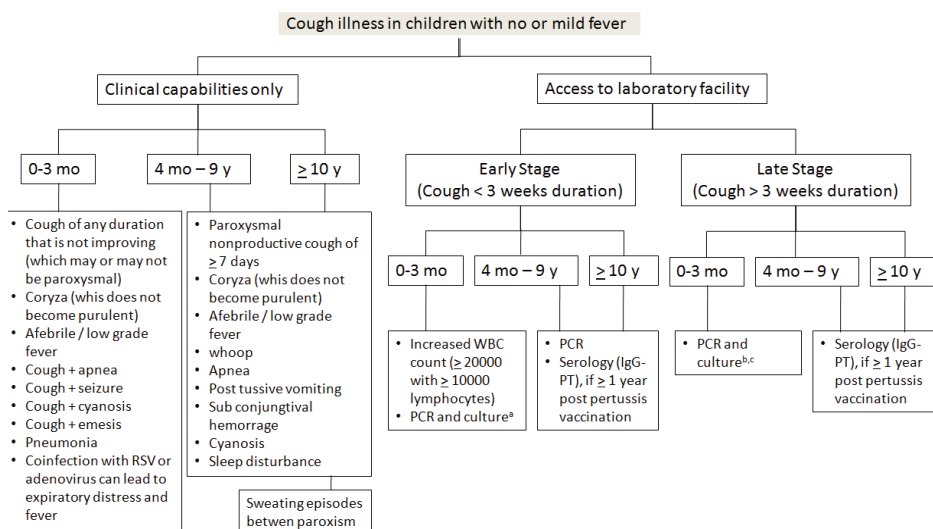
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**Figure 1:** DPT 3 coverage<sup>1</sup>, diphtheria and pertussis cases<sup>2</sup> in Indonesia 1985-2015  
<sup>1</sup>WHO and Unicef estimates of national immunization coverage July 2016 revision  
<sup>2</sup>WHO vaccine preventable disease: monitoring system 2016.

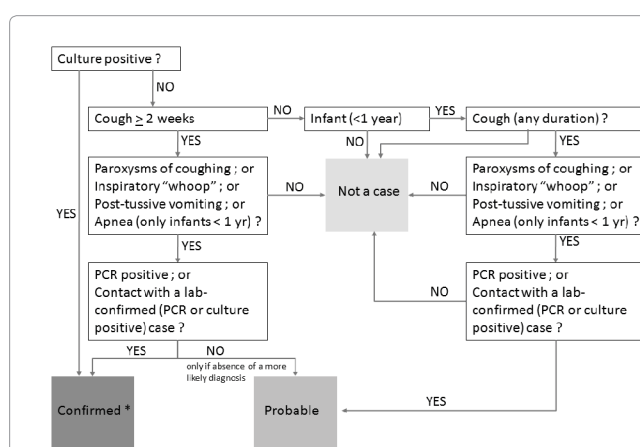


**Note:** Abbreviations: IgG, immunoglobulin G; PCR, polymerase chain reaction; PT, pertussis toxin; RSV, respiratory syncytial virus; WBC, white blood cell. <sup>a</sup>In resource-limited areas where PCR is not available, samples may be sent to a reference laboratory for culture confirmation. <sup>b</sup>False-negatives possible. <sup>c</sup>Serology not useful in this age cohort.

**Figure 2:** Algorithm for the diagnosis of pertussis.

laboratory facilities especially in developing countries (Figure 2) [15]. The WHO and CDC have developed criteria for case definition of pertussis which is applicable in various settings, including in limited sources country. The cases which meet the clinical case definition criteria should be confirmed with either appropriate laboratory testing (i.e, culture or PCR assay) or the presence of contact with laboratory confirmed case [16]. Cases should be classified according to the pertussis clinical case definitions and criteria for laboratory confirmation recommended by WHO and/or CDC (Figure 3) [16,17].

Pertussis case definition by CDC is a case diagnosed as pertussis by a physician or a person with a cough lasting at least two weeks with at least one of the following symptoms: paroxysmal (that is, fits) of coughing, inspiratory whooping, post-tussive vomiting (that is, vomiting immediately after coughing) without other apparent cause. Criteria for laboratory confirmation are isolation of *B. pertussis* or detection of genomic sequences by means of the PCR or positive paired serology. Thus, the pertussis case would be classified as either of the two classifications, first is clinically confirmed: a case that meets the clinical case definition but is not laboratory-confirmed, and the second



**Note:** An illness meeting the clinical case definition should be classified as "probable" rather than "confirmed" if it occurs in a patient who has contact with an infant aged <1 year who is PCR positive for pertussis and has ≥ 1 sign or symptom and cough duration <14 days (classified as "probable" case) [16].

**Figure 3:** Case classification flowchart.

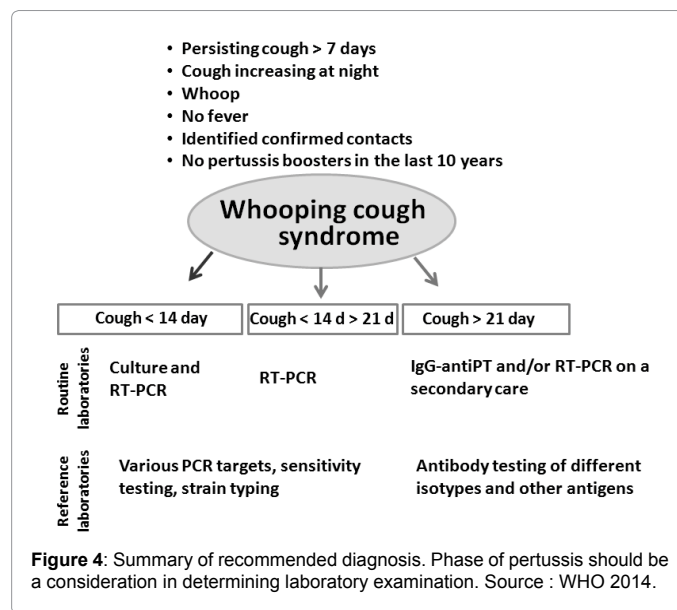
is laboratory-confirmed: a case that meets the clinical case definition and is laboratory-confirmed [18].

Most of pertussis case definition by WHO are similar with CDC, but WHO has some additional criteria for symptom such as apnea (with or without cyanosis) (for infants less than one year of age only), epidemiologic linkage and special consideration for infants less than one year of age. Clinical criteria for pertussis by WHO is a cough illness lasting more than or equal to two weeks with one of the following symptoms paroxysmal of coughing, or inspiratory “whoop” or post-tasie vomiting, or apnoea (with or without cyanosis) (for infants less than one year of age only). Laboratory criteria for diagnosis are isolation of *B. pertussis* from clinical specimen or positive PCR for *B. pertussis*, and epidemiologic linkage is contact with a laboratory-confirmed case of pertussis. Pertussis case classified by WHO as probable and confirmed. The cases is classified as probable if, in the absence of a more likely diagnosis, there is a cough illness lasting more than or equal to two weeks, with at least one of the signs or symptoms above, and absence of laboratory confirmation, and no epidemiologic linkage to a laboratory-confirmed case of pertussis. For infants less than one year of age only if there is acute cough illness of any duration, with at least one of the signs or symptoms above, and PCR positive for pertussis, or those signs or symptoms above, and contact with a laboratory-confirmed case of pertussis. The case is classified as confirmed if there is an acute cough illness of any duration, with isolation of *B. pertussis* from a clinical specimen; or cough illness lasting more than or equal to two weeks, with at least one of the signs or symptoms above, and PCR positive for pertussis; or with those signs or symptoms above, and the presence of contact with a laboratory-confirmed case of pertussis. An illness meeting the clinical case definition should be classified as “probable” rather than “confirmed” if it occurs in a patient who has contact with an infant less than one year of age who is PCR positive for pertussis and has a sign or symptom or more and cough duration <14 days (classified as “probable” case) [16].

However, those guidelines especially WHO criteria is difficult to be implemented in Indonesia, particularly for infant less than one year. If we strictly follow that criteria most of our cases do not meet the case definition of pertussis and finally will classified as not a case. This because PCR for pertussis is not available and culture only available in one centre, so we could not find any cases who have contact with confirmed cases. Additionally, most of our patients are less than one year old with unspecific cough with any duration.

Young infant may present atypical and severe clinical symptoms. This lead to difficulty in diagnosis and the patient frequently diagnosed as pneumonia upon hospital admission. Infant with critical pertussis illness may not all have a paroxysmal cough, nor an inspiratory “whoop”, but they present autonomic instability such as apnea, cyanosis, and bradycardia that may dominate the clinical manifestation [19,20]. Hence, apnea (with or without cyanosis) added to pertussis case definition by WHO for infants aged less than one year only. This symptom is further worsened by pneumonia and complicated to respiratory failure requiring mechanical ventilation. In Indonesia most cases are infant less than one year, come with cough with any duration, and diagnosed as bronchopneumonia. A reported case of unvaccinated infant who presented with respiratory failure and circulation disturbance was previously diagnosed as bronchopneumonia and later known as having probable pertussis [21].

The time to choose laboratory approaches is very important, as shown by Figure 4. If we want to get the best result for diagnostic test according to the clinical stage of pertussis, so that we should do the



PCR and culture in catarrhal stage, PCR and serology in paroxysms stage, and only serology in convalescent stage [12,22]. One study in Indonesia reported only two of 61 pertussis cases were laboratory confirmed because most of the patients were admitted on paroxysmal phase [8]. Culture and RT-PCR is more likely to give positive results in infant, which culture is more specific and RT-PCR is more sensitive [23]. Serologic test is not recommended to do in infant because their immature immune system, maternal antibodies, and in infant who is vaccinated within one year [23].

The gold standard for *B. pertussis* identification is culture because it is 100% specific, and also for strain identification and antibiotic resistance. Culture method has sensitivity ranged 10% to 60% depend on timing of specimen collection relates to symptom onset, and this low sensitivity also influenced by the fastidious nature of the organism, recent antibiotic use, the type of specimen collected, the method of collection, prolonged transport to the laboratory and delayed specimen plating, and the specific collection media. The best specimen for culture should be obtained from nasopharyngeal aspirate or posterior nasopharyngeal swab by dacron swabs or calcium alginate. This specimen site is chosen because this specimen contained the ciliated respiratory epithelial cells for which the organism has an affinity. The medias are Regan-Lowe media and Bordet-Gengou agar which usually growth in 7-10 days. A study found only two cases confirmed pertussis by positive Bordet Gengou media culture, because they all came in paroxysmal phase [8]. The most sensitive and rapid method is PCR, which can detect small number of viable and non-viable organisms and can give results in 1-2 days [24].

In neonates and young infants, PCR and/or culture should be performed on nasopharyngeal samples, nasopharyngeal swabs (NPSs) or nasopharyngeal aspirates (NPAs) as soon as possible post-onset of symptoms. For older children and also including parents and other household members should performed measurement of IgG-anti-PT. The culture and PCR recommended to be performed in vaccinated children, adolescents and adults with less than two weeks of coughing, PCR and the measurement of IgG-anti-PT in adolescents and adults with coughing of less than three weeks, and only the measurement

of IgG-anti-PT if coughing lasted at least 2-3 weeks. In outbreak situations, PCR and culture should be performed from nasopharyngeal samples and IgG-anti-PT should be measured in serum samples [25].

In Indonesia, laboratory confirmation such as culture and PCR are not available in all settings, thus the diagnosis rely mainly on clinical manifestations which made delayed in diagnosis. One study published in Indonesia in 2012 reported eleven patients classified as probable pertussis which initially diagnosed as severe bacterial pneumonia. Although the diagnoses could not be confirmed because all had negative culture result, but the clinical manifestation, good clinical response to clarithromycin, and mostly had no pertussis immunization, made those case classified as probable pertussis [26].

### Treatment of pertussis in Indonesia

Hospital admission was associated with young age <18 weeks. Clinical presentations associated with Pediatric Intensive Care Unit (PICU) admission include heart rate >180 bpm, total WBC count >25 × 10<sup>9</sup> /L and neutrophil to lymphocyte ratio >1 [27,28]. However, HIV infection seems not associated with pertussis infection [29].

The treatment of pertussis purposed to treat the bacterial infection and also the symptoms. Mostly *B. pertussis* spontaneously will be cleared from the nasopharynx within 2-4 weeks of infection, but still remain as carriage for 6 weeks. If antibiotic started early in catarrhal stage, it can be shorten the course and attenuate the severity. But mostly the patient come in paroxysmal stage, and this condition makes antibiotic not effective because the clinical manifestations are due to toxin-mediated effect. However, the administration of appropriate antibiotic is indicated if *B. pertussis* suspected [11,12]. The guideline for treatment and prophylaxis of *B. pertussis* infection recommended by CDC and American Academy of Pediatrics (AAP) (Table 1), and it is the same in regimen and dose of antibiotic [11].

The duration of antibiotic treatment is vary between 5-14 days. A recent Cochrane Review concluded that short-term treatment with macrolides (azithromycin for three to five days, or clarithromycin or erythromycin for seven days) was as effective as long-term treatment in eradication of *B. pertussis*, with fewer side effects [30].

A systematic review by Wang, et al. [31] showed that symptomatic treatment of the whooping cough in pertussis infection did not support sufficient evidence about the effectiveness of intervention. Diphenhydramine, pertussis immunoglobulin, salbutamol, and dexamethasone did not reduce whooping cough, vomiting, cyanosis, length of stay in hospital, and serious complication in pertussis infection [31].

Mostly pertussis cases in Indonesia admitted to the hospital in paroxysmal stage after had several treatment for upper respiratory infection. They already had empirical antibiotic but their specific cough

was not improved and worsening because some of them accompanied with pneumonia. Because our limitation in laboratory support, mostly those cases treated with macrolide because their clinical manifestation and immunization status support to pertussis cases, and their improvement after macrolide therapy made they classified as probable pertussis.

In Indonesia most of our patient insurances are covered by the national health care and social security agency (in Indonesian Language known as Badan Penyelenggara Jaminan Sosial Kesehatan or BPJS Kesehatan). The drugs that listed in their catalogue (known as Formularium Nasional in Indonesian Language) that can be covered in all level of health facility for macrolide is only erythromycin, although in very few area especially third level hospital can provide clarithromycin and azithromycin only in special occasion [32].

Severe paroxysms cough have led to complications and more common in non-immune infants. The complications are including pneumonia, failure to thrive, seizures, encephalopathy, cerebral hypoxia, secondary bacterial infections, pulmonary hypertension, rectal prolapse, apnea and death [11,12]. The course of illness is more severe in young children, with infants under age six months most at risk for hospitalization and severe complications [11]. A case reported by Nataprawira HM, et al. [21] indicated the lack of awareness in diagnosis of pertussis infection may cause misdiagnosis pertussis and leading to severe respiratory failure and septic shock requiring mechanical ventilation and aggressive fluid therapy [21].

### Pertussis prevention in Indonesia

Antibiotic may prevent *B. pertussis* infection in exposed individuals if given 21 days of symptoms onset in the index case [11]. The CDC and AAP currently recommend prophylaxis of high-risk close contacts, as well as who may have contact with high-risk individuals. The recommended antibiotics and dosing regimens for pertussis prophylaxis are the same as for treatment. The previous immunization status may not predict his susceptibility to infection, and this status should not be a factor when determining the need for prophylaxis [11]. Children with confirmed or suspected pertussis should be excluded from school or child care settings, and if not appropriately treated, they should be kept from school or child care settings until 21 days from the onset of cough [15].

Pertussis can be prevented by immunization, about 80-85% effective to prevent infection after completion of the primary series. If the child had already vaccinated, they are more likely to have sub clinical or less severe clinical manifestation if they become infected. The recommendation for immunization schedule from birth to adolescence shown in Table 2 [33]. It is recommended to give passive immunization for infants aged 2-3 months in order to decrease morbidity and mortality by maternal Tdap immunization at the beginning of the third

Agent	Dose and Regimen
Azithromycin*	<ul style="list-style-type: none"> <li>Infants aged &lt;6 mo: 10 mg/kg for 5 days</li> <li>Infants and children aged ≥ 6 mo: 10 mg/kg (maximum 500 mg) on day 1, followed by 5 mg/kg per day (maximum 250 mg) on days 2-5</li> </ul>
Clarithromycin*	<ul style="list-style-type: none"> <li>Infants aged &lt;1 mo: not recommended</li> <li>Infants and children aged &gt;1 mo: 15 mg/kg per day (maximum 1 g/day) in 2 divided doses each day for 7 days</li> </ul>
Erythromycin*	<ul style="list-style-type: none"> <li>Infants aged &lt;1 mo: azithromycin is preferred because of risk for pyloric stenosis with erythromycin. If erythromycin is used, the dose is 40-50 mg/kg per day in 4 divided doses. These infants should be closely monitored for pyloric stenosis.</li> <li>Infants aged &gt;1 mo and older children: 40-50 mg/kg per day (maximum 2 g per day) in 4 divided doses for 14 days.</li> </ul>
TMP-SMX	<ul style="list-style-type: none"> <li>Infants aged &lt;2 mo: contraindicated</li> <li>Infants aged &gt;2 mo and children: TMP 8 mg/kg per day, SMX 40 mg/kg per day in 2 divided doses for 14 days</li> </ul>

TMP: trimethoprim; SMX: sulfamethoxazole,

\*Infant aged less than onemonth should be monitored closely for pyloric stenosis when treated with a macrolide.

Table 1: Agents for pertussis treatment [10].



Age group (vaccine)	Timing
Birth through age 6 y (DTaP)	2, 4, and 6 mo, at 15-18 mo, and at age 4-6 y
Age 7-10 y	Single dose for those not fully immunized <sup>a,b</sup>
Adolescent aged 11-18 y (Tdap)	Single dose for those fully immunized, preferably at age 11 or 12 y <sup>a</sup> If not, then as soon as possible during this period

DTaP: diphtheria-tetanus toxoids, acellular pertussis; Tdap: tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.  
<sup>a</sup>Catch-up schedule should be followed if not fully immunized  
<sup>b</sup>Five doses of DTaP or four doses DTaP if the fourth dose was administered on or after the fourth birthday

**Table 2:** CDC DTaP and Tdap recommendations [30].

or late of second trimester of pregnancy. This is being implemented in many countries to reduce the burden of pertussis in early infancy [27,34,35]. While a study suggested that Tdap administration at 30-32 weeks of gestation give optimum specific antibody level at 34 weeks when placental transport is most efficient, other studies showed earlier vaccination in second semester provide higher level of specific antibody both for term and preterm infants [36]. Unfortunately, Indonesian immunization national programme has not included this vaccination due to financial limitation.

Indonesian national immunization programme had included DTP, but for booster 18-24 month actually started in 2013 only for four provinces (West Java, DI Yogyakarta, Bali, and West Nusa Tenggara), so that before that there was no booster. And then, finally in 2014 all provinces in Indonesia had included booster DTP until now [36].

## Conclusion

Despite of lack laboratory facilities in many settings, and the cases presented in later stage of disease that cannot performed and given laboratory results adequately to support pertussis diagnose in children, WHO and CDC guideline will be helpfull in order to uniformly made pertussis diagnose and classification. But this guideline, especially WHO guideline must be applied wisely in accordance with various settings in Indonesia. Hopely in Indonesia, pertussis can be diagnosed immediately, so that prompt treatment can be given to decrease complication and death. Prevention can be done by antibiotic prophylaxis in exposed individuals, isolate children with confirmed or suspected pertussis from school or child care settings, and increase support on immunization programme.

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## Conflicts of Interest

The authors have no conflicts of interest.

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