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CENTRE FOR RESPIRATORY DISEASES AND MENINGITIS

OUTBREAK RESPONSE, DIVISION OF PUBLIC HEALTH SURVEILLANCE AND RESPONSE

Pertussis:

NICD Recommendations for

Diagnosis, Management

and

Public Health Response

Version 1.0 (July 2017) and Version 2.0 (December 2018):

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Version 2.0 December 2018	Guideline Writing Committee	Update to Category 1 notifiable condition Case definitions updated Treatment guidelines updated to align with EDL Case investigation form updated

Disclaimer:

The information contained in this document, be it guidelines, recommendations, diagnostic algorithms or treatment regimens, is offered in the public interest. To the best of the knowledge of the writing team, the information contained is correct. Implementation of any aspect of these guidelines remains the responsibility of the implementing agency in so far as public health liability resides, or the responsibility of the individual clinician in the case of diagnosis or treatment.

Pertussis case definitions (page 12):

A **suspected case** of pertussis:

Any person with signs and symptoms consistent with pertussis: an acute cough illness lasting ≥14 days (cough illness of any duration for children <1 year), without a more likely diagnosis, plus one or more of the following symptoms: paroxysms of coughing, or inspiratory whoop, or post-tussive vomiting or apnoea in infants <1 year, OR clinical suspicion of pertussis

A **probable (epidemiologically-linked) case** of pertussis:

Any person with signs and symptoms consistent with pertussis OR clinical suspicion of pertussis **AND** epidemiological linkage, by contact, to a laboratory-confirmed case of pertussis in the 21 days before symptom onset.

A **confirmed case** of pertussis:

Any person with signs and symptoms consistent with pertussis OR clinical suspicion of pertussis **AND** laboratory-confirmation (isolation of *Bordetella pertussis* from a clinical respiratory specimen OR polymerase chain reaction (PCR) positive for *B. pertussis* OR pertussis-specific IgG antibody response in older children and adults at least one year after last vaccine dose)

Management of a case of pertussis (page 13):

1. **Isolate:** Prevent transmission of *B. pertussis* by practising contact and droplet precautions
2. **Provide supportive care:** Supportive care aims to monitor the severity of the patient's condition, limit the number of paroxysms and maximise nutrition, rest, and recovery
3. **Treat with antibiotics:** Macrolide or suitable alternative to prevent transmission

Management of contacts of persons with pertussis (page 16):

1. Identify close and vulnerable (at-risk of severe disease) contacts
2. Take nasopharyngeal swabs from symptomatic contacts
3. Administer targeted chemoprophylaxis to close and vulnerable contacts
4. Vaccinate close and vulnerable contacts appropriately (depending on vaccination status).
5. Monitor contacts for at least 21 days for typical signs and symptoms

Laboratory identification of *B. pertussis* (page 9):

Sputum samples and/or nasopharyngeal swab/aspirate transported in (a) Regan-Lowe (RL) or Amies charcoal transport medium (culture and PCR) or (b) universal transport medium (UTM).

1. Samples are streaked onto fresh Regan-Lowe charcoal agar containing cephalexin and 10% defibrinated sheep blood.
    - All plates are incubated aerobically for up to 10 days at 35–37 °C and inspected at day 3 and 7 after inoculation.
    - Typical colonies appear as small mercury-like glistening droplets.
2. Real-time PCR detection of *B. pertussis* (*IS481* and *ptxS1*) conducted on clinical respiratory specimens.
3. Anti-pertussis toxin IgG response in serum in older children and adults, and >1 year after last vaccine dose. Serology should not be used for diagnosis in infants, as (i) their immune system is immature and serology is affected by maternal antibodies, or (ii) in patients vaccinated within one year, since serology does not differentiate between antibodies produced in response to vaccine and natural infection.

Notification of cases and additional support:

Pertussis is a Category 1 notifiable medical condition. Immediate reporting should be done telephonically, followed by written or electronic notification within 24 hours of diagnosing a case.

Please complete the NMC form (available at: http://www.nicd.ac.za/index.php/nmc/) and case investigation form (Appendix 3) and submit to provincial & district CDC coordinators and to the NICD: NMCSurveillanceReport@nicd.ac.za

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1. Introduction

Pertussis (also known as whooping cough) is a highly contagious, vaccine-preventable respiratory tract disease, caused by the bacteria *Bordetella pertussis.* It can affect people of all ages, however young unimmunised or partially immunised infants are the most vulnerable group with the highest rates of complications and death. Transmission occurs person-to-person through respiratory secretions. According to World Health Organization (WHO) estimates, pertussis caused around 63 000 deaths in children aged <5 years in 2013 [1], but the exact burden is unclear due to the lack of reliable surveillance data from developing countries. Pertussis is a Category 1 notifiable medical condition (NMC) in South Africa. Immediate reporting should be done by written or electronic notification within 24 hours of diagnosing a case. All cases should be reported using the NMC form (available at http://www.nicd.ac.za/index.php/nmc/) to infection prevention and control practitioners at healthcare facilities where applicable, district and provincial communicable disease control coordinators, and the NICD (NMCSurveillanceReport@nicd.ac.za) urgently (as per routine notifiable medical condition notification procedures – details can be found on the NICD website: http://www.nicd.ac.za/index.php/nmc/).

2. Epidemiology

2.1. Global epidemiology of pertussis

Prior to the availability of vaccines in the 1950s, pertussis was one of the most common diseases in children <5 years of age, with the highest case-fatality ratios in infancy [1, 2]. Subsequent to the introduction of the pertussis vaccine into the Expanded Programme on Immunisation (EPI), the number of pertussis cases and deaths in children has declined significantly. Despite high vaccine coverage, pertussis remains endemic in all countries and epidemic cycles have been reported every 2 to 5 years. Unimmunised or partially immunised infants remain the most vulnerable to disease-related complications and death.

Two types of vaccines are available: whole-cell pertussis (wP) containing a suspension of killed bacteria, or acellular pertussis (aP) preparations that contain 1–5 components of *B. pertussis*. Currently the wP formulation is still used mainly in low-income countries and the aP vaccines in high-income countries and some middle-income countries (like South Africa). In recent years, a shift in the age distribution of pertussis to older children, adolescents and adults has been noted in some countries, particularly 5-10 years following aP vaccines having replaced wP vaccines in the childhood vaccine programmes [1, 2]. A number of factors may have contributed to these changes, including increased awareness and recognition of atypical disease in older individuals, more sensitive laboratory tests and improved surveillance programmes. In addition, aP vaccine-derived immunity is less robust and an accompanying reduction in natural boosting of immunity by circulating *B. pertussis* can result in waning immunity and an increase in susceptibility of adolescents and adults to disease [3]. Studies comparing wP and aP vaccines in non-human primate models [4, 5] have demonstrated that aP vaccines protect against severe pertussis-associated symptoms but not against infection or colonisation. In addition, the aP-vaccinated baboons did not clear infections quicker than unvaccinated animals, and because they failed to prevent colonisation were able to transmit *B. pertussis* infection to contacts. In contrast, wP-vaccinated animals cleared infection more rapidly, generated a better T-cell response protecting against colonisation and shedding.

Due to the increasing concern of an apparent rise in pertussis cases following the introduction of aP vaccines in some countries, WHO conducted a data review which included information from 19 high- and middle-income countries [6]. This review concluded that there was no evidence of a global resurgence of pertussis and the increase in case numbers was attributed to natural cyclical changes, improved surveillance programmes and disease awareness, as well as the availability of more sensitive diagnostic tests such as the polymerase chain reaction (PCR). Some evidence of a true escalation of case numbers was evident in five of the 19 countries reviewed, of which four exclusively used aP vaccines namely Australia, Portugal, United Kingdom and USA. Increases in disease incidence may be due to decreases in vaccine coverage and/or waning immunity from the aP vaccine, and highlight the importance of timely vaccination and high coverage.

Duration of immunity following a wP vaccine three-dose primary series schedule has been reported to range from 8 to 12 years, with some vaccines having a longer duration of protection [7], while studies with aP vaccine reported protection for 5-6 years post two- (with booster) or three-dose primary series vaccines [8, 9]. There is increasing evidence that protection following booster doses of aP vaccines wanes faster in individuals primed with aP compared to those primed with wP vaccines [8, 10]. Epidemiological data show waning immunity in school-aged children, adolescents and young adults in populations receiving aP vaccine [11].

2.2. Epidemiology of pertussis in South Africa

A combined diphtheria toxoid and pertussis whole-cell vaccine was introduced in South Africa in January 1950. This was combined with tetanus toxoid, to produce a diphtheria, tetanus, and pertussis (DTwP) vaccine in May 1957 [12]. The Expanded Programme on Immunisation in South Africa (EPI-SA) was introduced in 1995 and included the DTwP vaccine. In 2009, South Africa changed from a wP to an aP vaccine (DTaP). Vaccination coverage for the third dose of DTP was reported as 66% in 2016 according to WHO/UNICEF estimates, and 84% according to administrative estimates [13].

Prior to 1950, only pertussis deaths and not cases were notifiable; thereafter pertussis was made a notifiable disease. The Cape Town Health Department reported a pertussis outbreak in 1947 which resulted in 107 deaths. Following the introduction of the wP vaccine there was a significant reduction in pertussis-related deaths [12]. However, despite high vaccination coverage, an outbreak was reported in Cape Town between June 1988 and April 1989 which was thought to be driven by vaccine failures and children too young to be vaccinated [12].

A retrospective review in Bloemfontein of children presenting with clinical features suggestive of pertussis between 2008 and 2015, reported a detection rate of 14% and a case-fatality ratio of 5% [14]. Infants aged <18 weeks constituted 57% of the cases. A study from Cape Town in children <13 years of age hospitalised with lower respiratory tract infections, detected pertussis in 7% of the 460 enrolments from September 2012 to September 2013 [15]. Children with confirmed *B. pertussis* had a median age of 8 months, and the detection rate amongst infants aged <2 months was 15%. Pertussis testing was introduced into the NICD Severe Acute Respiratory Illness (SARI) surveillance programme (now National Pneumonia Surveillance Programme) and Influenza-Like Illness (ILI) surveillance programme in 2012. In 2015, of the 5013 patients enrolled into the programmes, 3602

were tested for pertussis and 105 (3%) tested positive. The highest proportion of cases was in children <5 years of age (73%, 76/104) and the in-hospital case-fatality ratio was 7% (7/101) [16]. The detection rate for pertussis was similar in 2014 (3%, 46/1667) and the highest detection rates were in the <5 year (29%, 13/45) and 25-44 year age groups (29%, 13/45). The Pneumonia Etiology Research for Child Health (PERCH) study explored the characteristics of pertussis among children hospitalised with WHO-defined severe and very severe pneumonia in 7 developing countries, including South Africa, from 2011-2014. This study identified *B. pertussis* in 2.3% (40/1721) of pneumonia cases and in 3.7% (5/137) of the in-hospital deaths in children <6 months of age. The case-fatality ratio of pertussis-infected pneumonia cases in this age group was 12.5% (5/40) [17]. In Soweto, retrospective testing of respiratory samples collected from infants <6 months old with symptoms of respiratory illness during a maternal influenza trial in 2011 revealed an overall pertussis incidence rate of 5.8/1000 child-months: 7.4/1000 in HIV-exposed infants and 5.5/1000 in HIV-unexposed infants (P=0.47) [18]. Among infants <1 year of age hospitalised with respiratory illness at Chris Hani Baragwanath Academic Hospital in Soweto in 2015, 2.3% tested positive for *B. pertussis,* with the majority of pertussis cases (86%) occurring in infants <3 months old [19]. The overall incidence of pertussis hospitalisation was 2.2/1000 infants: 2.9/1000 and 1.9/1000 in the HIV-exposed and HIV-unexposed cases, respectively (P=0.09).

3. Microbiology, pathogenesis and transmission

Bordetella pertussis is an aerobic, fastidious Gram-negative coccobacillus which infects the ciliated epithelial cells of the human respiratory tract. The organism expresses a number of virulence factors including pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), fimbriae (FIM) type 2 and 3, adenylate cyclase toxin (ACT), tracheal toxin (TCT) and lipo-oligosaccharide (LPS), which are responsible for the clinical features of pertussis and immunity by stimulating an immune response [1]. Some changes have been observed in the genomic sequences of virulence factors in circulating strains, but there is no evidence that this has resulted in a reduction of wP vaccine effectiveness [20, 21]. Pertactin-deficient isolates have been detected in regions where aP vaccines are used [22]. Presently there is limited evidence of decreased effectiveness of vaccines against different allelic variants of *B. pertussis*. A study from the USA showed that vaccinated case-patients were more likely to be infected with pertactin-deficient *B. pertussis* strains compared with unvaccinated case-patients [23]. There was no difference in the clinical outcome of patients who were infected with pertactin-deficient strains. Additional studies are required to determine whether effectiveness and duration of protection by the aP vaccine is decreased against pertactin-deficient strains.

A number of *Bordetella* species cause disease in humans, including *B. pertussis, B. parapertussis, B. holmesii* and *B. bronchiseptica* [23-25]. *B. parapertussis* and *B. holmesii* infections result in less severe symptoms than *B. pertussis. B. bronchiseptica* has been identified as a cause of disease in immunocompromised individuals. Other *Bordetella* species rarely isolated in humans include *B. hinzii, B. trematum, B. petrii, B. avium* and *B. ansorpii*.

Pertussis is primarily a toxin-mediated disease. Bacteria attach to the cilia of respiratory epithelial cells, produce toxins that paralyse cilia, and cause inflammation of the respiratory tract allowing invasion [26]. Some studies have shown immunity from pertussis infection to last from 4 to 20 years.

Pertussis is transmitted via respiratory droplets from infected individuals and is most contagious during the early catarrhal stage. During this stage the secondary attack rate may be up to 90% of non-immune household contacts [1]. If patients are untreated they may remain contagious for ≥3 weeks following cough onset, but chronic carriage has not been described. A systematic review which explored the source of *B. pertussis* infection in infants <6 months of age demonstrated that household contacts were the source in 74%–96% of cases, with mothers being the most common source (39%) [27].

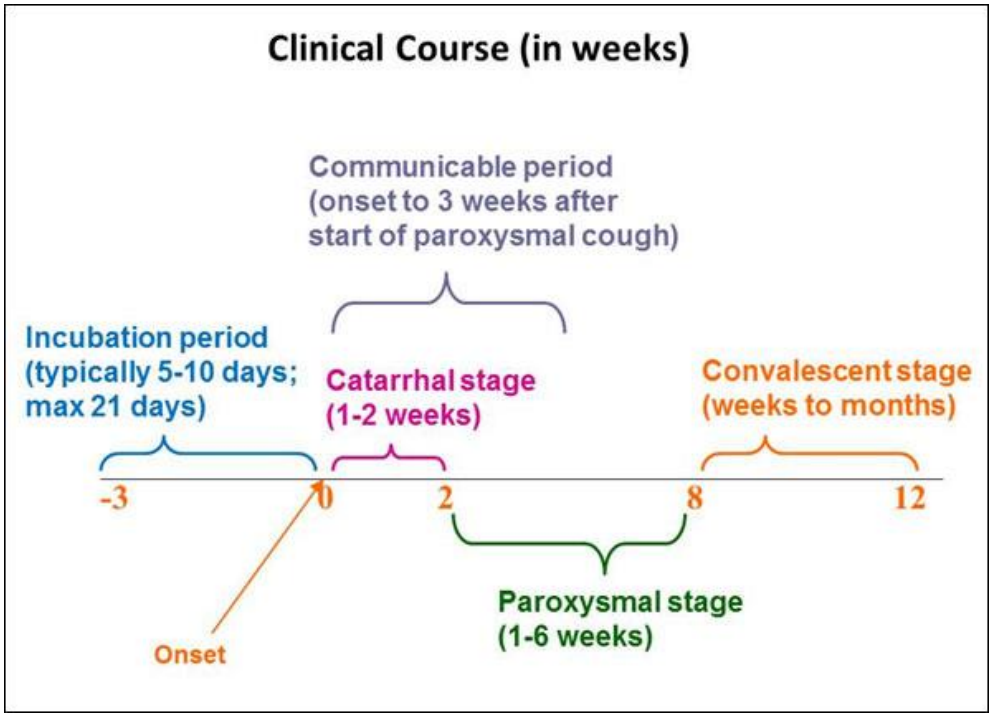
4. Clinical presentation and risk factors for pertussis

The incubation period of pertussis is usually 7–10 days (range 4–21 days). The clinical course of classic pertussis illness is divided into three stages (Figure 1) [26, 28], although many cases, especially young infants, do not present with these features. Disease in older, previously vaccinated, individuals is milder than in infants and young children and some cases of infection may be asymptomatic. The stages of disease are:

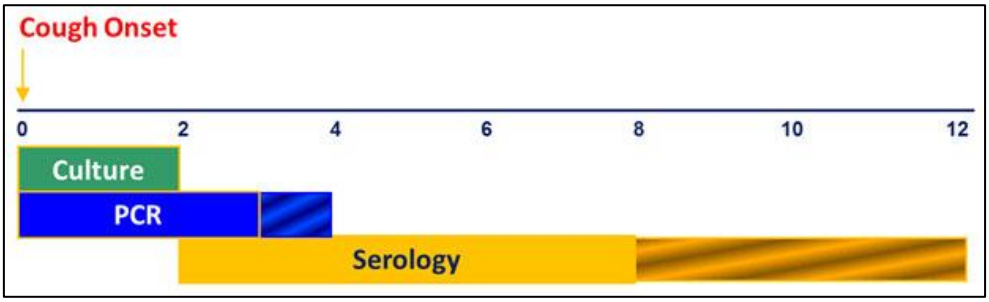
- The first stage of disease is the catarrhal stage, which is associated with rhinorrhoea or nasal congestion, sneezing, conjunctival suffusion, low grade fever (minimal) and a mild, occasional cough. The cough gradually increases in severity to transition into the next stage of the disease.
- The second stage of disease, the paroxysmal stage, is characterised by bursts of rapid coughs followed by a long inspiratory whoop and patients often become cyanosed during these episodes. In typical cases, cough is particularly severe at night and frequently followed by post-tussive vomiting (emesis). In young infants, pertussis may initially present atypically with episodes of apnoea and cyanosis and no cough; while in previously immunised adolescents and adults, persistent cough may be the only feature. This stage usually lasts for 1-6 weeks, but may persist for up to 10 weeks.
- The last stage is the convalescent stage, in which recovery is gradual. The cough becomes less paroxysmal and usually disappears in 2 to 3 weeks. However, paroxysms may recur and this stage may last for several months.

In general, pertussis should be suspected as a diagnosis in patients who are afebrile with increasing cough duration and severity. Young, unimmunised infants (particularly those born prematurely, <3 months of age, or born to unimmunised mothers) are at increased risk of severe or complicated pertussis. Partially immunised infants (<3 doses DTaP) are not fully protected, although disease severity may be attenuated. Signs and symptoms of pertussis may vary slightly between different age groups [29]:

- Children aged 0-3 months: cough (of any duration) and coryza with no or minimal fever. Pertussis is more likely if the child also has one of the following signs: apnoea, post-tussive vomiting (emesis), cyanosis, seizures or pneumonia.
- Children aged 4 months to 9 years: pertussis is suspected with a paroxysmal non-productive cough of ≥7 days' duration (cough of any duration for children <1 year of age) and coryza with no or minimal fever. Whoop, apnoea, post-tussive vomiting (emesis) or cyanosis may also occur. Symptoms are reported to get worse at night.
- Individuals aged ≥10 years: non-productive, paroxysmal cough of ≥7 days' duration with no fever and any of the following: whoop, apnoea, post-tussive vomiting (emesis), sweating episodes between paroxysms. Symptoms are reported to get worse at night.



Source: https://www.cdc.gov/pertussis/clinical/features.html



Source: https://www.cdc.gov/pertussis/clinical/diagnostic-testing/diagnosis-confirmation.html

Figure 1. Clinical course of pertussis infection and appropriate laboratory testing

5. Laboratory diagnosis of pertussis

The diagnosis of pertussis is based on clinical features, combined with laboratory testing of posterior nasopharyngeal specimens obtained during the catarrhal and early paroxysmal stages. Laboratory confirmation can be made using the following methods [26] (Figure 1):

- Culture is considered the gold standard, however the organism is difficult to grow due to its fastidious nature and requires charcoal- and blood-supplemented media. The highest yield is during the first 2 weeks of illness, during the catarrhal phase. A negative culture does not exclude pertussis.
- Polymerase chain reaction (PCR) for *Bordetella* spp. is highly sensitive and can be used to detect *Bordetella* species directly from clinical specimens, but different tests may vary in specificity. A PCR may be useful up to 4 weeks after cough onset and may be used in outbreak situations.

- Serological diagnosis by detection of anti-pertussis toxin IgG antibody levels in serum taken at least 14 days after the onset of cough using an enzyme-linked immunosorbent assay (ELISA) can provide confirmatory evidence of recent infection. Single sample (using a test-specific, validated diagnostic cut-off for IgG-anti-PT of between 50 and 120 IU/ml) or dual-sample (paired sera) serology can be used. Serology can be helpful for adults and adolescents who present late in the course of their illness, when both culture and PCR are likely to be negative. During the first year post-vaccination, serological testing using a single serum sample does not differentiate between antibodies resulting from natural infection and those produced after vaccination and interpretation may be problematic [1, 26, 30]. Serology should not be used in infants, as their immune system is immature and liable to interference by maternal antibodies.

5.1 Specimen collection

B. pertussis can be isolated from nasopharyngeal swabs (NPS), nasopharyngeal aspirates (NPA) or sputum samples [25]. Flocked (Figure 2A), calcium alginate or Dacron swabs should be used to collect specimens as they give a better yield on PCR, while cotton wool-tipped swabs are not recommended [31, 32]. Respiratory specimens should preferably be collected before antibiotic treatment is started. However, if antibiotics have already been started, specimens may still be collected. Every effort must be made to prevent contamination during the collection of the sample.

For culture and PCR: swabs should be placed in Regan-Lowe (Figure 2B) transport medium or Amies charcoal-containing transport medium immediately and transported at ambient (15-30°C) temperature, within 48 hours, to the microbiology laboratory.
For PCR only: swabs should be placed in universal transport medium (UTM) immediately and transported at 2-8°C within 48 hours, to the microbiology laboratory.

Figure 2A. Flocked swab

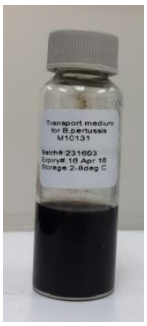


Figure 2B. Regan-Lowe semisolid transport medium

5.1.1 Nasopharyngeal swabs (NPS)

- Gently insert the flocked swab through one nostril beyond the anterior nares along the floor of the nasal cavity, until the pharyngeal wall is reached.
- Force must not be used to overcome any obstruction.
- Rotate the swab three times against the nasopharyngeal wall and then withdraw the swab slowly.
- Place the swab into the transport medium without touching the inside of the tube, and transport the labelled swab to the laboratory.

5.1.2 Nasopharyngeal aspirates (NPA)

- Fill 5ml syringe with saline; attach catheter tubing to syringe tip.
- Slowly insert the catheter into one nostril until the pharyngeal wall is reached.
- Quickly inject saline into nostril and then aspirate the recoverable nasopharyngeal specimen.
- Withdraw the catheter under suction, being careful not to touch the tip.
- Inject the aspirated fluid into a labelled sterile specimen container or Regan-Lowe transport medium and transport to the laboratory.

5.2 Processing of specimens for the detection of *B. pertussis*

5.2.1 Culture

The NPS should be rolled onto the surface of a fresh Regan-Lowe charcoal agar containing 40 µg/mL cephalexin (to inhibit normal flora) and 10% defibrinated sheep blood, as well as a 5% blood agar plate [25]. For NPA samples, approximately 200 µl should be inoculated onto each of the agar plates. For sputum, purulent mucous portions (not saliva) should be inoculated onto each of the agar plates. All plates must be streaked for single colonies and incubated aerobically for seven days at 37 °C and inspected at day 3 and 7 post-inoculation. After 3 days' incubation, examine all plates, carefully comparing growth on the different agar plates. Any colonies which have grown on charcoal agar but not on blood agar are suspicious/presumptive *Bordetella* species, and require further identification by phenotypic identification and/or PCR. Plates should be incubated for seven days before being discarded as negative. If *B. parapertussis* is identified, do not discard plates before day 7 since co-infection with *B. pertussis* can occur. Colony size and morphology change with time. Very young colonies (day 3-5) are small (1mm in diameter) and flat, becoming smooth, convex, iridescent and increase in size with prolonged incubation (Figure 3).

Figure 3. *B. pertussis* on Regan-Lowe charcoal agar

5.2.2 PCR

The most commonly used targets for diagnostic purposes are the insertion element *IS481* and the pertussis toxin S1 (*ptxS1)* gene [25]. Multiplex real-time PCR assays targeting the *IS481* gene, *ptxS1* toxin gene, *pIS1001* gene and the *hIS1001* gene may be used to identify *B. pertussis, B. parapertussis, B. holmesii* and B. *bronchiseptica* [33]. Due to the high copy number of *IS481* (50-200 copies per genome), false-positive results of assays using a single *IS481* target may occur due to contamination. Laboratories should have strict measures in place for prevention and detection of

contamination, and the identification of multiple cases of *Bordetella* spp. on PCR over a short space of time should be investigated. Laboratories performing PCR need to perform external quality assessment (EQA) regularly.

5.3 Transport of specimens to the laboratory

For clinically suspected cases of pertussis requiring laboratory confirmation, or to confirm possible outbreaks, specimens should be transported within 48 hours to the local NHLS, NICD or private laboratory (depending on available capacity). Specimens should be submitted together with an NHLS specimen submission form (Appendix 1).

For referral of specimens to NICD, specimens should be sent to the Centre for Respiratory Diseases and Meningitis (CRDM) bacteriology laboratory, National Institute for Communicable Diseases (NICD), 1 Modderfontein Road, Sandringham, 2131. If you require additional information, please contact: Linda de Gouveia 011-555-0327 lindad@nicd.ac.za or Nicole Wolter 011-555-0352 nicolew@nicd.ac.za, or Mignon du Plessis 011-555-0387 mignond@nicd.ac.za, or after-hours, the NICD doctor-on-call 082 883 9920.

6. Case definition of pertussis

Symptoms of pertussis include an acute cough lasting ≥14 days (cough illness of any duration for children aged <1 year), without an apparent cause plus one or more of the following:

- Paroxysms of coughing
- Inspiratory whoop
- Post-tussive vomiting
- Apnoea (with or without cyanosis) (for infants aged <1 year only)

A case of pertussis is defined as follows [34]:

Suspected case of pertussis:

Any person in whom a clinician suspects pertussis infection OR any person with signs and symptoms consistent with pertussis **AND**

Absence of laboratory confirmation and no epidemiological link to a laboratory-confirmed case

Probable case of pertussis:

Any person in whom a clinician suspects pertussis infection OR any person with signs and symptoms consistent with pertussis **AND**

Epidemiological linkage, by contact, to a laboratory-confirmed case of pertussis in the 21 days before symptom onset

Confirmed case of pertussis:

Any person in whom a clinician suspects pertussis infection OR any person with signs and symptoms consistent with pertussis **AND**

Laboratory confirmation (isolation of *B. pertussis* from a respiratory specimen OR PCR-positive respiratory specimen OR pertussis-specific IgG antibody response in older children and adults at least one year after last vaccine dose)

7. Management and treatment of pertussis

The management of pertussis cases is primarily supportive, with the goal to limit paroxysms, maximise nutrition and rest. Antibiotic therapy (Table 1) is of some value in that it eradicates the organism from secretions and thereby reduces transmission and, if initiated early (during catarrhal stage), may lessen disease severity.

7.1. Infection prevention and control

- Isolate hospitalised patients with suspected pertussis using standard infection control and droplet precautions until the diagnosis is excluded or adequate treatment has been administered (5 days after commencement of recommended antibiotic therapy or until 21 days after the onset of symptoms, if appropriate antimicrobial therapy is not given) [34].
- Where patients are not hospitalised, restrict contact with others, especially with young infants until 5 days after commencement of recommended antibiotic therapy or until 21 days after the onset of symptoms, if appropriate antimicrobial therapy is not given.

7.2 Supportive care

- Supportive therapy is the mainstay of treatment in patients with pertussis disease and aims to monitor the severity of the patient's condition, limit the number of paroxysms and maximise nutrition, rest, and recovery.
- Assistance should be provided in terms of oxygenation, breathing support and mechanical ventilation as necessary. Infants should be monitored for apnoea, cyanosis, or hypoxia.
- Infants and children with frequent paroxysms of cough may have increased fluid and energy needs, which can be difficult to meet if the infant is coughing or vomiting. The child's fluid and nutritional status should be monitored closely, whether the child is admitted to the hospital or cared for at home.
- Recommended indications for inpatient treatment in infants and children with pertussis infection or suspected pertussis infection include:
    - Clinical signs/symptoms
        - Respiratory distress, including tachypnoea, retractions, nasal flaring, grunting, and the use of accessory muscles
        - Requiring supplemental oxygen
        - Evidence of pneumonia
        - Cyanosis or apnoea, with or without coughing
        - Seizures or encephalopathy
        - Persistent nausea and post-tussive vomiting
    - Characteristics of underlying conditions

- Age ≤6 months
- Premature infants
- Underlying pulmonary, cardiac, or neuromuscular disease as at high risk of severe disease
- Preceding failure to thrive

7.3 Antibiotics for treatment of pertussis

- Treatment is aimed at eradicating *B. pertussis* from cases to prevent secondary transmission, however antibiotics have a limited effect on the clinical course of illness, especially if administered beyond 2-3 weeks after the onset of symptoms [24, 34]. Antibiotic treatment to ameliorate pertussis symptoms should only be considered within three weeks of symptom onset. Thereafter antimicrobials are only recommended to reduce transmission.
- Macrolides are highly effective at eradicating *B. pertussis* from the nasopharynx. Recommended antibiotics are azithromycin, clarithromycin or erythromycin. Trimethoprim-sulphamethoxazole can also be used [24, 34, 35].
- Resistance of *B. pertussis* to macrolides is rare [24].

Table 1: Recommended antibiotic treatment and post exposure prophylaxis in patients with pertussis, by age group [34-36]*

	Azithromycin	Clarithromycin	Erythromycin[b]	Cotrimoxazole[c]
Neonates (<1 month)	Preferred in neonates 10mg/kg once a day for 5 days	Not recommended (safety data unavailable)	Not recommended due to association with hypertrophic pyloric stenosis	Not recommended in infants <2 months
Infants (1 – 5 months)	10mg/kg once a day for 5 days	7.5mg/kg twice a day for 7 days (max 1g/day)	10mg/kg every 6 hours for 7 days	Infants 2-5 months: 120mg twice a day for 7 days
Infants ≥6 months and children	10 mg/kg (max 500mg) in single dose on day 1, followed by 5mg/kg (max 250mg) once a day on days 2-5	7.5mg/kg twice a day for 7 days (max 1g/day)	10mg/kg every 6 hours for 7 days	6 months to 5 years: 240mg twice a day for 7 days 6 to 11 years: 480mg twice a day for 7 days 12 to 17 years: 960mg twice a day for 7 days
Adults	500mg in a single dose on day 1, followed by 250mg once a day on days 2-5	500mg twice a day for 7 days	500mg every 6 hours for 7 days	960mg twice a day for 7 days
Pregnant Women[a]	It is the responsibility of the clinician to select the most appropriate antibiotic. Erythromycin is the preferred antibiotic. Human pregnancy studies have indicated that azithromycin is compatible for use in pregnancy.			**Contraindicated in pregnancy and breastfeeding**

*Doses for treatment and prophylaxis are the same for all ages.

[a] For pregnant contacts, a risk assessment would need to be done to look at the risk and benefits of antibiotic therapy/prophylaxis. The aim of treatment/prophylaxis in pregnancy is to prevent transmission to the newborn infant, and should be considered in those who have not received a pertussis-containing vaccine more than one week and less than five years prior. Where possible, pregnant women should begin treatment at least three days prior to delivery

[b] Doses can be doubled in severe infections

[c] Consider if macrolides contraindicated or not tolerated

7.4 Symptomatic treatment of whooping cough

A Cochrane review of 12 studies concluded that there is insufficient evidence to support the use of diphenhydramine, salbutamol, pertussis immunoglobulin, opioids or dexamethasone in the treatment of the cough associated with pertussis [37]. There is a need for a large, well-designed,

randomised controlled trial to identify effective antitussive treatments for the cough associated with pertussis disease. Cough suppressants, e.g. codeine-containing products, are not indicated.

7.5 Contact management

Management of contacts should be performed for all confirmed/probable/suspected pertussis cases [34]. Recommendations for contact management are based on the infectiousness of the patient, the intensity of the exposure, the potential consequences of severe pertussis in the contact, and the possibilities for secondary exposure of persons at high risk from the contact. Persons with pertussis are infectious from the beginning of the catarrhal stage through the third week after the onset of paroxysms or until 5 days after the start of effective antimicrobial treatment.

7.5.1 Contact case definitions

Close contacts

Close contacts are considered people with face-to-face exposure to a confirmed/probable/suspected case, and include family and household members, people who have stayed overnight in the same room as the case and people who have had direct contact with respiratory, oral or nasal secretions from a symptomatic patient.

Vulnerable contacts

This refers to persons who are not necessarily close contacts according to the definition above, but have been exposed to a symptomatic patient and are themselves at increased risk of complications from pertussis **OR** are at risk of transmitting the infection to other vulnerable persons at risk of severe pertussis disease.

- Vulnerable (at risk) persons include:
    - Infants <2 months of age
    - Infants <1 year of age who have received <3 doses of pertussis-containing vaccine
- Transmitters include:
    - Pregnant women in the third trimester of pregnancy
    - Healthcare workers working with infants and pregnant women
    - Individuals of any age working (e.g. child-minders) or sharing a house (e.g. siblings and grandparents) with young infants not fully vaccinated

7.5.2 Post-exposure chemoprophylaxis for contacts

Post-exposure prophylaxis should be administered to close and vulnerable contacts, regardless of age and vaccination status, within 21 days of onset of cough in the index case. The recommended antimicrobial agents and doses are the same for treatment and prophylaxis (Table 1). Exposed individuals, especially those with an incomplete vaccination history, should be closely observed for symptoms and signs of pertussis for three weeks after contact.

Public health resources are limited and extensive contact tracing and widespread use of antibiotics may not be possible and have also not been shown to limit the extent of an outbreak. Antibiotics only prevent pertussis disease if given prior to symptom onset. The overuse of antibiotics can increase resistance rates in the community and should be avoided.

Post-exposure prophylaxis for healthcare workers that may be exposed to pertussis cases on regular basis should be considered on a case-by-case basis, taking into account their risk of exposure (type/duration of contact, use of PPE etc.) and their risk of transmission to vulnerable individuals such as infants. If they are considered to have a high risk of exposure and/or have contact with vulnerable individuals, then PEP should be administered regardless of vaccination status.

7.5.3 Vaccination and post-exposure chemoprophylaxis for contacts

Immunisation should be considered for contacts in addition to chemoprophylaxis as follows:

- Children <7 years of age who are unimmunised or partially immunised should complete their DTaP vaccination schedule.
- Individuals ≥7 years, including pregnant women >32 weeks' gestation, should receive a booster dose of an appropriate pertussis-containing vaccine (Tdap-IPV, currently only available in the private sector) if they have not been vaccinated in the last five years.

8 Control and prevention of pertussis

The main aim of pertussis vaccination is to reduce the risk of severe pertussis in infants and young children. Therefore it is important to vaccinate young infants against *B. pertussis* with at least three doses of vaccine [1]. The vaccine should contain either a suspension of killed bacteria, i.e., whole-cell pertussis (wP), or acellular pertussis (aP) preparations that contain 1–5 different components of *B. pertussis*. Currently the wP formulation is still used mainly in low-income countries and the aP vaccines in high-income countries and some middle-income countries (like South Africa). To control pertussis and prevent outbreaks, it is essential to adhere to the EPI vaccination schedule (Appendix 2) and ensure good vaccine coverage (≥90%) with at least 3 doses of pertussis vaccine. For aP preparations, a fourth booster dose in the second year of life is recommended, with subsequent boosters every 4-6 years.

Although aP and wP vaccines have an equivalent initial effectiveness in preventing disease in the first year of life, there is evidence of more rapid waning of immunity, lack of protection against infection and possibly reduced impact on interrupting transmission with aP vaccines. According to WHO recommendations [1], countries using aP vaccine in the primary infant immunisation schedule, should consider additional boosters and maternal immunisation during pregnancy.

The vaccines currently available in South Africa for different age groups are listed in Table 2.

Table 2: Currently available vaccines that are appropriate for the prevention of pertussis in South Africa

Product name	Vaccine description	Appropriate indications
Hexaxim® (DTaP-IPV-Hib-HBV)*	Diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae type b*, inactivated polio and hepatitis B	Primary vaccination series, and booster at 18 months licenced for use in children aged 6 weeks to 2 years
Infanrix® Hexa (DTaP-IPV-HBV/Hib)	Diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b, inactivated polio and hepatitis B	Primary vaccination series, and booster at 18 months licenced for use in children aged 6 weeks to 7 years**; can only be given at 6 weeks if Hep B given at birth, else commence schedule at 2 months.
Infanrix® (DTaP)	Diphtheria, tetanus, acellular pertussis	Primary vaccination series, and booster at 18 months, licenced for use in children aged 6 weeks to 7 years
Adacel Quadra® Boostrix Tetra® (Tdap-IPV)#	Tetanus, diphtheria (reduced dose), acellular pertussis, inactivated polio	Active immunisation or booster (single dose) in persons aged 11-64 years (Adacel Quadra®) or 10-64 years (Boostrix Tetra®)##

*Replaced Pentaxim® (DTaP-IPV/Hib) in EPI schedule in 2015. Safety not established beyond 2yrs of age

**Safety not established beyond 2yrs of age, should not be given over 7 years due to dose differences of reduced strength formulations

There are no licensed Tdap products in South Africa that do not contain IPV.

Adults aged ≥65 years: Those who have or anticipate having close contact with an infant aged less than 12 months should receive a single dose of Tdap. Other adults aged ≥65 years may be given a single dose of Tdap.
Children aged 7-10 years: Those not fully vaccinated against pertussis and for whom no contraindication to pertussis vaccine exists should receive a single dose of Tdap. Those never vaccinated against tetanus, diphtheria, or pertussis or who have unknown vaccination status should receive a series of three vaccinations containing tetanus and diphtheria toxoids. The first of these three doses should be Tdap.

Because immunity from pertussis disease wanes, children who have recovered from a documented pertussis infection should still be vaccinated with pertussis vaccines according to routine schedules. Countries with demonstrable nosocomial transmission are encouraged to vaccinate health-care workers, particularly maternity and paediatric staff, if economically and logistically feasible. Some countries have introduced maternal pertussis vaccination during pregnancy to protect infants too young to be vaccinated.

9 Recommended public health response to pertussis cases and outbreaks in South Africa

Pertussis is a Category 1 notifiable medical condition in South Africa. Immediate reporting should be done by written or electronic notification within 24 hours of diagnosing a case.

Please complete the NMC form (available at: http://www.nicd.ac.za/index.php/nmc/) and Case Investigation Form (Appendix 3) and submit to provincial & district CDC coordinators and to the NICD (NMCSurveillanceReport@nicd.ac.za).

The objective of public health follow-up of pertussis cases in South Africa is to prevent disease in young infants with particular focus on exposures in household, child-care and health-care settings. No action is required for cases notified >21 days after the onset of paroxysmal cough or >28 days after the onset of any cough unless they are reported to be part of a cluster. If a single case is notified within 21 days they should be followed up and treated according to the guidelines in section 7 and contacts should be given prophylaxis as detailed in section 7. An outbreak is considered when two or more cases are clustered in time (within 42 days of each other) and space (in same location) where transmission is suspected to have occurred in that setting. It is not helpful to test contacts without respiratory symptoms in the context of an outbreak. Culture confirmation for at least one suspected case of pertussis is recommended when there is suspicion of a pertussis outbreak.

On notification of case-patients the following public health actions should be initiated immediately: These actions should be undertaken in conjunction with the relevant local health department and local CDC contact:

Step 1: Conduct a detailed case investigation

- Obtain detailed demographic, clinical and risk factor information
- Compile a case line list and apply case definitions
- Compile a case contact line list

Step 2: Identify contacts

Close and vulnerable (at-risk) contacts are defined as in section 7. For cases who have vulnerable contacts, do active contact tracing and give antibiotic treatment and prophylaxis where necessary. Recommend that contacts' immunisations be updated if appropriate (see step 7). Asymptomatic contacts do not have to be excluded from school/work, etc.

Step 3: Conduct laboratory investigation of symptomatic contacts

- Collect nasopharyngeal samples for PCR/culture from symptomatic contacts; if possible ideally before commencing antibiotics.
- In an outbreak setting, samples may only be required from the first few symptomatic contacts to confirm the diagnosis.

Step 4: Administer chemoprophylaxis to close and vulnerable contacts

- Post-exposure chemoprophylaxis should be targeted (section 7) to persons at high risk of developing severe pertussis and to persons who will have close contact with those at high risk of developing severe pertussis.
- Where disease transmission is widespread (hospital or community outbreak) the benefit of wider chemoprophylaxis is likely to be of limited value.

Step 5: Monitor close and vulnerable contacts

Monitor close and vulnerable contacts for respiratory symptoms for at least 21 days after last exposure. Educate them about the disease and advise them to seek medical care if they develop symptoms.

Step 6: Exclude close contacts in high-risk settings

Exclusion from work, school, preschool, and child care, and restricted attendance from other settings, especially where there are infants, should be recommended for cases or contacts suspected of having pertussis until they are no longer infectious or until suspected cases are proven not to have pertussis (whichever comes first). In hospital settings, suspected symptomatic pertussis cases should be managed with droplet precautions and accommodated in a single room.

Symptomatic individuals are considered to no longer be infectious either:

- 21 days after the onset of any cough, or
- 14 days after the onset of paroxysmal cough (if the onset is known), or
- when they have completed 5 days of an appropriate antibiotic

Step 7: Vaccinate close and eligible at-risk contacts

It is recommended to give pertussis vaccine to all under-immunised close or at-risk contacts:

- Children ≥6 weeks of age who are unimmunised or only partially immunised for age, should initiate or continue their vaccines according to the EPI schedule.
- Children >12 months of age who have received 3 doses of DTaP can be given a fourth dose of DTaP.
- Children 4-6 years of age who have received 4 doses of DTaP and received the fourth dose before their 4th birthday, should be given a fifth dose of DTaP.
- Children 7-10 years of age who did not receive a 4th dose after age 4 years, should be given Tdap
- Individuals >10 years of age should receive a single dose of Tdap if they have not received a pertussis-containing vaccine in the past 5 years.
- Healthcare workers should receive a single dose of Tdap if they have not received a pertussis-containing vaccine in the past 5 years.
- Where possible, pregnant women should get a dose of Tdap during every pregnancy (during the third trimester).

Step 8: Alert other healthcare facilities in the area

- Alert local healthcare practitioners and inform them to maintain a high index of suspicion
- Provide fact sheets about the disease aimed at healthcare professionals

Step 9: Conduct health promotion activities and health education

- Produce and distribute information, education and communication materials that provide basic information about the disease and, importantly, about the vaccine and vaccine schedule
- Cases should be advised to avoid contact with infants and with women in the last month of pregnancy

Step 10: Vaccination campaigns in response to outbreaks

In the event of an outbreak, selective campaigns targeting at-risk groups (including healthcare workers) may be considered.

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11 Appendices

11.1 Appendix 1: Specimen and isolate submission form

Specimen and isolate submission form

Please submit this form when sending any clinical specimen or isolate to the NICD (CRDM Bacteriology laboratory; 011-555-0356) for testing:

Date of sending (dd/mm/yyyy): _____

At the NICD, for the attention of: _____

Sending clinician/laboratory details:

Sending clinician/laboratory name: _____

Sending laboratory contact person: _____

Sending clinician/laboratory contact details (please tick preferred method of contact):

☐ Tel: _____ ☐ Fax: _____ ☐ Email: _____

Specimen/isolate details:

Date of specimen collection (dd/mm/yyyy):

☐ Clinical specimen type: _____

☐ Isolate Suspected organism: _____

Test requested/reason for sending: _____

Previous laboratory results/comments (or attach copy of test results): _____

_____

Patient details:

First name: _____ Surname: _____ Gender: ☐ Male ☐ Female

Birthdate (dd/mm/yyyy): _____/_____/_____ Age: _____ Years ☐ Months ☐ Days ☐

Clinical diagnosis: _____

Date of symptom onset (dd/mm/yyyy): _____ Patient identifier:

_____

Additional comments: _____

11.2 Appendix 2: Routine immunisation schedule

Expanded Programme on Immunisation – EPI (SA) Revised Childhood Immunisation Schedule from December 2015

Age of child	Vaccines needed	How and where it is given
At birth	BCG Bacille Calmette Guerin vaccine	Right arm
	OPV (0) Oral polio vaccine	Drops by mouth
6 weeks	OPV (1) Oral polio vaccine	Drops by mouth
	RV (1) Rotavirus vaccine*	Liquid by mouth
	DTaP-IPV-Hib-HBV (1) (Hexaxim®) Diphtheria, tetanus, acellular pertussis/inactivated polio/ *Haemophilus influenzae* type b and hepatitis B vaccine	Intramuscular left thigh
	PCV (1) Pneumococcal conjugated vaccine	Intramuscular right thigh
10 weeks	DTaP-IPV-Hib-HBV (2) (Hexaxim®) Diphtheria, tetanus, acellular pertussis/inactivated polio/ *Haemophilus influenzae* type b and hepatitis B vaccine	Intramuscular left thigh
14 weeks	RV (2) Rotavirus vaccine*	Liquid by mouth
	DTaP-IPV-Hib-HBV (3) (Hexaxim®) Diphtheria, tetanus, acellular pertussis / inactivated polio / *Haemophilus influenzae* type b and hepatitis B vaccine	Intramuscular left thigh
	PCV (2) Pneumococcal conjugated vaccine	Intramuscular right thigh
6 months	Measles vaccine (1)**	Subcutaneous left thigh
9 months	PCV (3) Pneumococcal conjugated vaccine	Intramuscular right thigh
12 months	Measles vaccine (2)**	Subcutaneous right arm
18 months	DTaP-IPV-Hib-HBV (4) (Hexaxim®) Diphtheria, tetanus, acellular pertussis/inactivated polio/ *Haemophilus influenzae* type b and hepatitis B vaccine	Intramuscular left arm
6 years	Td vaccine (Tetanus & reduced amount of diphtheria vaccine)	Intramuscular left arm
12 years	Td vaccine	Intramuscular left arm
*Rotavirus vaccine should not be administered after 24 weeks **Do not administer with any other vaccine Note: Human papilloma virus vaccine (HPV (1) and HPV (2) - 2 doses 6 months apart) is given to girls aged 9 years through the school health programme.		

11.3 Appendix 3: Case investigation form

Unique Case ID (*Study, Hospital, Lab no.):*

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division in the National Health Laboratory Service

Pertussis Case Investigation Form

Laboratory-confirmed case □ Probable case □ Suspected case □ Asymptomatic contact □

A) Individual Details: *(All cases/contacts)*

1. First Name: _____ Surname: _____
2. Sex: Male □ Female □
3. Date of birth: _____/_____/_____ (dd/mm/yyyy)
4. Age: _____ Years □ Months □ Weeks □ Days □
5. City/town of residence:_____
6. Province of residence:_____
7. If contact of a case,

   a) Name of contact:_____ b) Age of contact:_____

   c) Relationship of contact to case: _____

B) Symptoms: *(All cases/contacts)*

8. Did the individual have any pertussis-related symptoms? Yes □ No □ Not known □
9. If yes, date of first symptom onset: _____/_____/_____ (dd/mm/yyyy)
10. If yes, indicate specific symptoms experienced (mark all that apply):

Cough	Yes □	No □	Not known □
If yes, duration of cough: _____ days			
Paroxysmal cough (rapid and numerous bouts of cough):	Yes □	No □	Not known □
Inspiratory whoop (high pitched gasp for air after bouts of cough):	Yes □	No □	Not known □
Post-tussive vomiting (vomiting after bouts of cough):	Yes □	No □	Not known □
Apnoea (infants aged <1 year only, stopping breathing for short periods):	Yes □	No □	Not known □

Other symptoms-please specify: _____

C) Underlying medical conditions: *(All cases/contacts)*

11. Please indicate if the individual has any underlying medical conditions (mark all that apply):

Chronic respiratory disease (incl. asthma) □ Chronic heart disease □

Diabetes □ Pregnant □

HIV infection□ TB □

Immunosuppression (e.g. chemotherapy, organ transplant) □

Other medical condition- please specify: _____

Unique Case ID (*Study, Hospital, Lab no.):*

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D) Vaccination history *(All cases/contacts)*

12. Was the individual immunised against pertussis? Yes □ No □ Not known □

Vaccine dose	**Was pertussis vaccine received?**	**Date received** (dd/mm/yyyy)
1st Dose	Yes □ No □ Not known □	
2nd Dose	Yes □ No □ Not known □	
3rd Dose	Yes □ No □ Not known □	
4th Dose	Yes □ No □ Not known □	
Booster dose	Yes □ No □ Not known □	

E) Specimen Details *(Symptomatic individuals)*

13. Date of first specimen collection: _____/_____/_____(dd/mm/yyyy)
14. Specimen type: NPS/NPA □ Sputum □ Tracheal aspirate □ Other-please specify_____
15. Specimen laboratory number: _____
16. Testing laboratory:_____

F) Healthcare and Outcome: *(Symptomatic individuals)*

17. Did the individual seek care for the illness? Outpatient □ Inpatient □ No care sought □ Not known □
18. If yes, facility name _____
19. Did the individual receive azithromycin or another macrolide? Yes □ No □ Not known □
20. Outcome of illness: Recovered □ Still sick □ Died □ Not known □
21. Date of outcome: _____/_____/_____ (dd/mm/yyyy)

Form completed by: _____

Contact no: _____

Date of interview: _____(dd/mm/yyyy)