# An outbreak of pertussis in Bloemfontein, South Africa, 2008–2009

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## Abstract

**Background:** In April 2008, the first case of pertussis since 1998 was diagnosed in the Free State province. The outbreak that occurred over a 12-month period is described in this article.

**Method:** This is a case series of 18 children diagnosed with pertussis in Bloemfontein, Free State province, between April 2008 and March 2009. The clinical diagnosis was confirmed by means of a *Bordetella* polymerase chain reaction test done on a nasal swab. Data were collected from every child with a confirmed diagnosis of pertussis.

**Results:** Eighteen cases of pertussis were diagnosed in the 12-month period; 15 in the public sector and three in the private sector. A peak of cases was observed in the autumn and early winter months. Twelve infants were under six months of age and were thus regarded as "pre-vaccinated". Fourteen children required admission to hospital, of whom five required intensive care. No deaths occurred. The cost of managing these children was high.

**Conclusions:** Pertussis is not commonly diagnosed in South Africa. Young children are worst affected by the disease. Ongoing surveillance is needed. A vaccination plan to prevent pertussis in South Africa requires consideration.

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## Introduction

Pertussis or whooping cough, caused by *Bordetella pertussis*, is a highly contagious and vaccine-preventable bacterial infection that affects all susceptible individuals, regardless of age. Although it is a notifiable disease in South Africa, it is believed to be an uncommon condition. According to the World Health Organization (WHO), no cases were reported in South Africa in the period 2004–2008.[1] However, according to another source, three cases were reported in 2007.[2] A recent resurgence of pertussis cases has been reported mainly from developed countries, yet the real burden is believed to be in the developing nations.[3]

Definitive diagnosis of pertussis is challenging. This article describes an outbreak of pertussis in Bloemfontein from April 2008 to March 2009.

## Methods

This is a case series of children diagnosed with pertussis. The clinical case definition included any of the following symptoms: cough of at least two weeks' duration, paroxysms of coughing, inspiratory whoop, post-tussive vomiting, or apnoea in young infants.[4]

Dry nasal swabs were taken with a Dacron® swab and referred by the local National Health Laboratory Services (NHLS) medical microbiology laboratory to the NHLS central referral laboratory in Johannesburg for a *Bordetella* polymerase chain reaction (PCR) test. Specimens obtained from patients in the private sector were analysed by private laboratories. The sensitivity, specificity, positive predictive value and negative predictive value for the PCR have been reported as 93.5%, 97.1%, 84.3% and 98.9%, respectively.[5]

A child with clinical features of pertussis and a positive PCR result was regarded as a definite case of pertussis and notified to the appropriate authorities. Clinical data were collected of each case.

Ethics approval for the study was obtained from the Ethics Committee of the Faculty of Health Sciences, University of the Free State (ETOVS number 143/08).

## Results

In the 12-month period, 97 swabs from the public sector and an unknown number of swabs from the private sector were sent for *Bordetella* PCR analysis. Twelve specimens were

either unsuitable for analysis or the result was equivocal, and 70 had negative results. Fifteen specimens yielded positive results (15 of 85 suitable specimens, 17.6%) for *B. pertussis* and none for *B. parapertussis*. Three confirmed positive results were reported in the private sector cases.

In total, 18 confirmed cases of pertussis were therefore detected. Twelve patients were female and six were male. All patients lived in Bloemfontein or the immediate surrounding areas. All cases were seen by doctors working in the public sector, supervised by a paediatric consultant. The cases diagnosed in the private sector were seen by one paediatrician. A predominance of cases was noted during the autumn and winter months, while three cases occurred during spring or early summer (Figure 1). The ages of the children ranged between five weeks and 31 months (Table I). Twelve (66.7%) children were younger than six months of age.

According to the children's clinical history, the duration of cough ranged from one day up to two weeks. No child had been coughing for longer than two weeks at initial presentation. On examination, post-tussive vomiting, staccato cough, apnoeic episodes, cyanotic episodes and coughing spells were most commonly observed. Only five children presented with an inspiratory whoop, one child had convulsions, and none of the children had subconjunctival haemorrhages.

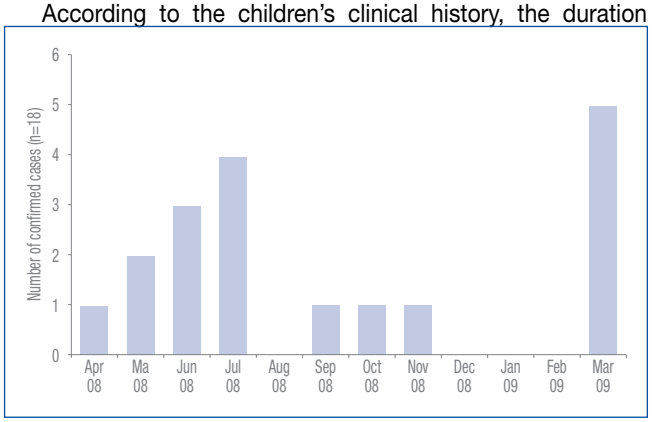


**Figure 1:** Distribution of the monthly incidence of pertussis, April 2008 – March 2009.

**Table I:** Age distribution of pertussis cases

| Age of patients | Number of cases (n = 18) | % |
|---|---|---|
| 5 weeks | 4 | 22.2 |
| 6 weeks | 2 | 11.1 |
| 6–9 weeks | 2 | 11.1 |
| 11–12 weeks | 3 | 16.7 |
| 4 months | 1 | 5.6 |
| 6 months | 3 | 16.7 |
| 11 months | 1 | 5.6 |
| 14 months | 1 | 5.6 |
| 31 months | 1 | 5.6 |

Eight (44.4%) children had total white cell counts above 20.0 x $10^9$/l, of which seven had high lymphocyte counts (either above 17.0 x $10^9$/l or 50% or more of the total white cell count).

Fifteen (83.3%) children required hospitalisation, of whom five had to be admitted to the intensive care unit (ICU). The latter were all aged nine weeks or younger. Complications encountered included pneumonia with hypoxia, pneumothorax, myocarditis and prerenal failure with hypernatraemia. The duration of ventilation, ICU stay and total hospital stay are shown in Table II.

**Table II:** Infants with pertussis requiring admission to intensive care unit (n = 5)

| Case number | Age (weeks) | Ventilation (days) | Total stay in ICU (days) | Total stay in hospital (days) |
|---|---|---|---|---|
| 9 | 6 | 6 | 8 | 12 |
| 10 | 5 | 7 | 11 | 25 |
| 11 | 5½ | 28 | 39 | 74 |
| 16 | 9 | 10 | 13 | 20 |
| 17 | 9 | 12 | 17 | 22 |

All public sector patients were treated with oral erythromycin at a dosage of 15–25 mg/kg per dose in four daily doses for 14 days. All immediate contacts were given erythromycin prophylaxis. Neither clarithromycin nor azithromycin, the preferred antibiotics for the treatment of pertussis, was available in the public sector. Children from the private sector were also treated with erythromycin (the reason for this was not given).

Fourteen (77.8%) of the 18 children had an appropriate vaccination status for their age. Of the other four, one child, aged four and a half months, had never been immunised, while another child of seven months had missed the third diphtheria, pertussis and tetanus (DPT) dose. The vaccination status of two children was unknown.

A "prevaccinated" child is one who has not yet received all three initial doses of the pertussis vaccine (incompletely vaccinated or too young to be fully vaccinated), or who is younger than 18 weeks of age. It takes a month after the last vaccine to reach an adequate antibody level.[6,7] Twelve (66.7%) children were prevaccinated or incompletely vaccinated infants, while six (33.3%) were fully vaccinated. Of the 12 prevaccinated children, five had not yet received any pertussis vaccine, while the other seven had received one or two vaccinations shortly before they became ill. Three of the five babies that had not received any pertussis vaccine required ICU admission. The vaccination coverage

of DPT in the Motheo district of the Free State at the time of the outbreak was just below 90% (personal communication, Expanded Programme on Immunisation officer, Free State Department of Health).

In seven (38.9%) patients, a history of coughing in an adult family member, such as a parent, relative or grandparent, was reported. Owing to cost constraints, we did not investigate any of the contacts.

The cost analysis based on the length of hospital stay (ward and/or ICU) is expounded in Table III. Of the 15 cases diagnosed in the public sector, only two patients received ambulatory care. The other 13 children spent a total of 235 days in the hospital: 147 days in the general wards and 88 days in the ICU. The five infants who required intensive care were ventilated for a total of 63 days. One of the three children in the private sector received ambulatory care, while the other two spent a total of 22 days in a general paediatric ward. The mean total cost for each hospitalised case of pertussis was over R20 000. This amount did not include the laboratory investigations, medication and additional expenses for the parents, such as transport and absence from work. The amounts given have been rounded off to the nearest rand.

A brief summary of the infants treated in the ICU is given below (see also Table II).

**Table III:** Cost analysis of hospitalised cases (n = 15) of pertussis in South African rand, 2008

| Hospitalisation | Number of cases | Total stay | Cost per day* | Total cost | Mean total cost per case |
|---|---|---|---|---|---|
| ***Private sector*** | | | | | |
| General ward | 2 | 22 days | R2 400 | R52 800 | R26 400 |
| ***Public sector*** | | | | | |
| General ward | 8 | 147 days | R678 | R99 666 | R12 458 |
| ICU | 5 | 88 days | R2 200 | R193 600 | R38 720 |
| **Total** | **15** | | | **R346 066** | |

*Information as quoted by private and public hospital administration for 2008 (personal communication).

***Case 9:*** The infant (aged six weeks) had not yet been vaccinated and was not human immunodeficiency virus-(HIV) exposed. The child had a one-day history of cough and apnoeic episodes with cyanosis at home. The father, a paramedic, gave mouth-to-mouth resuscitation and rushed the child 60 km to Bloemfontein. She also had right upper lobe pneumonia.

***Case 10:*** The infant (aged five weeks) had not yet been vaccinated, and was HIV exposed but uninfected. This child was initially admitted to the general ward with a diagnosis of *Pneumocystis* pneumonia, possible pertussis. His total white cell count at admission was 57.99 x $10^9$/l (normal for five weeks 5–19.50 x $10^9$/l), and his lactate dehydrogenase levels (LDH) were 733 U/l (normal range 180–430 U/l). Cyanotic spells were noted after five days of hospitalisation. His condition deteriorated and he was admitted to the ICU on day 9 of his illness. The white cell count increased to 72.49 x $10^9$/l after one week, and he developed myocarditis and right upper lobe collapse.

***Case 11:*** The infant (aged five-and-a-half weeks) had not yet been vaccinated and was not exposed to HIV. This baby was difficult to ventilate, requiring high-frequency oscillation and developing bilateral pneumothoraces, convulsions and nosocomial *Klebsiella* septicaemia. Oxygen dependence persisted for 30 days after ventilation was ended.

***Case 16:*** The infant (aged nine weeks) was HIV exposed, had received nevirapine after birth (local policy at the time), was breastfed and had received supplemental formula feeds, according to information obtained from the mother. The baby was intubated in the emergency department and admitted to ICU. Treatment for presumed *Pneumocystis* pneumonia was started. An increased LDH level of 1 047 U/l was observed. The cue to pertussis was a white cell count of 26.0 x $10^9$/L, with a lymphocyte predominance of 13.8 x $10^9$/l (normal for nine weeks 1.2–3.4 x $10^9$/L). The clinical diagnosis of pertussis was confirmed by PCR testing eight days after admission. Nosocomial infections developed, which included *Klebsiella* from a tracheal aspirate, *Acinetobacter* from a blood culture and *Enterococcus faecium* from a urine specimen. The HIV-PCR test was positive and the child was started on antiretroviral treatment during hospitalisation.

***Case 17:*** This infant (aged nine weeks) was born at 28 weeks' gestation with a birth weight of 1 050 g. He was admitted to the neonatal ICU, ventilated for four days and discharged well at six weeks of age. The baby had not yet been vaccinated. He was readmitted three weeks later with apnoea attacks and convulsions and developed bilateral pneumothoraces. The HIV-PCR was positive and the infant was started on antiretroviral treatment during hospitalisation.

None of the 18 pertussis cases had a fatal outcome. Five children were still coughing for one to two months after the diagnosis. To the authors' knowledge, all the children eventually recovered.

With regard to HIV co-morbidity, five (27.8%) children tested positive with PCR and all required hospitalisation. Three of them were younger than 10 weeks of age and the other two were four and seven months old respectively. Two of the younger infants needed ICU admission. The

older two children presented with a lobar pneumonia. The four-month-old child had never been immunised, while the seven-month-old had received only the first two doses of vaccine.

## Discussion

According to statistics available from the Department of Health, 94 cases of pertussis were reported in South Africa for the period 1999–2005. Most cases were infants younger than one year, and the majority occurred in the Western Cape and Gauteng. Approximately a quarter of the cases were diagnosed during February.[8] No national figures were published after 2005. No cases were reported in the Free State province during 1998–2002, and after this period no records are available (personal communication, Free State Department of Health). A recent Communicable Diseases Communiqué of the National Institute of Communicable Diseases (NICD) and the NHLS reported two cases of infants with pertussis, one six weeks and the other 10 weeks of age, who were part of a cluster of pertussis cases. It was not mentioned in which province these children resided.[9] The vaccination coverage in South Africa has been reported to be 97% for the third pertussis vaccine (DTP).[2]

The WHO recommended that an incidence of pertussis of less than one case per 100 000 population should have been achieved in Europe by 2000. Globally, only Japan has achieved this target. Other developed countries with low national incidences are the USA with 2.7, France with 3.4 and the United Kingdom with 4.0. There has been a resurgence in other developed countries, with reported incidences of 10–30 in Canada, 22–58 in Australia and 180 in Switzerland. More cases occurred in the older age groups in these countries despite high immunisation rates in the paediatric population.[10]

In 2005, the WHO reported a total number of 17.6 million cases of pertussis. It is thought that the worldwide resurgence of pertussis could be attributed to the following:

- Waning of natural and vaccine-induced immunity.
- Lack of natural boosting.[10]
- The emergence of new bacterial toxin variants.[11,12]

It is estimated that 71% of the global burden of pertussis occurs in developing countries.[2] However, no accurate figures are available for Africa, Asia or Latin America.[2,13] A recent study from Argentina reported a rising incidence of pertussis since 1997, with a peak in 2005 of 5.7 per 100 000 population.[11] Although the WHO reports the number of pertussis cases per region of the world, it is estimated that only 5 to 25% of cases are actually reported.[10] In 2001, the Global Pertussis Initiative (GPI) was established to monitor the pertussis problem on a worldwide basis and to advise on control measures.[14]

The incidence of pertussis, for the 12 months studied, for Bloemfontein and surrounding areas was calculated to be 2.1 cases per 100 000 population. This is based on 18 cases in 12 months in an estimated population of 840 000.[15] This is likely to be a small proportion of the total number of people infected with *B. pertussis*. It is estimated that the true incidence is three- to fourfold the reported incidence in developed countries, and globally up to 100-fold the reported incidence.[2,10] This situation is due to the lack of surveillance; underreporting (especially in the older population), and difficulty in making the diagnosis. Because only those children ill enough to present to a hospital were diagnosed, it is certain that many cases have gone undiagnosed.

No confirmed adult case of pertussis was either reported or investigated by the local public and private diagnostic medical microbiology laboratories. It is reported that more than 20% of pertussis cases occur in adolescents and adults, and up to a quarter of adults with a prolonged cough have pertussis.[3,16] In the post-vaccination era in developed countries, pertussis has become a disease of adolescents and adults.[10] We are not sure whether this case series has been an outbreak or whether the disease is at the peak of one of its cyclical (changing incidence over years) or seasonal (changing incidence within a year) phases, or whether it has not been recognised and diagnosed.[17] A seasonal increase has been recorded to occur in South Africa in the first three months of the year.[3,8,10] At the time of this pertussis cluster, there was an acceptable vaccination coverage of just below 90% in the district.

The diagnosis of pertussis is initially based on clinical characteristics, which includes a cough lasting for longer than two weeks.[4] In South Africa, with a very high incidence of tuberculosis and HIV infection, pertussis is easily overlooked. Unless the history of a whoop, post-tussive vomiting or paroxysms of coughing is specifically asked for, or the physician has the opportunity to observe an episode, pertussis may be missed. Tuberculosis and respiratory infections caused by *Mycoplasma, Chlamydia, B. parapertussis* and *B. bronchiseptica* and viral infections, caused by adenovirus, respiratory syncitial virus, human metapneumovirus, parainfluenza and influenza viruses, may also present with coughing of prolonged duration. Other causes also associated with protracted coughing include foreign bodies in the airways, asthma and bronchiectasis, which are common in South Africa. In our series, coughing for two weeks was never present in the younger prevaccinated infants. These are the children most at risk and most severely affected. A history of exposure to

a coughing adolescent or adult contact could be helpful in the diagnosis.

To diagnose more cases of pertussis in the community, it is necessary to have access to resources to confirm a suspected case. The *Bordetella* PCR is available in the public health sector via the NHLS laboratories, from where the specimens are sent to Johannesburg. Specimens need to reach the laboratory within 12 days of collection. The result should be available within three working days of receipt at the testing laboratory. Thus the *Bordetella* PCR is accessible anywhere in South Africa. The cost of a *Bordetella* PCR in 2009 was R458 and R562 in the public and private sectors, respectively.

Thick Dacron® or rayon swabs are generally available in the public sector health facilities. Thinner swabs are easier to use in children, as they can be inserted deeper into the nasopharyngeal cavity, improving the yield of positive results. This justifies the cost of R9 for the thinner swabs as opposed to the standard swabs at 30 cents (based on 2009 information).

A pertussis antibody test, available in only one laboratory in South Africa, is not useful for diagnostic purposes early in the disease.[5] Culture is the gold standard but is not done routinely. *Bordetella* is very difficult to culture and the possibility of isolating this fastidious organism decreases over time. Collection of the specimen should be at the bedside using cough plates, which is technically difficult to perform, especially in children.[3] Furthermore, it is not always feasible to have culture medium available, as it has a short shelf life. The cost of the culture medium is R17.40 per plate, and isolation costs are approximately R80 (based on 2009 information). However, it would be useful to culture existing circulating *Bordetella* organisms to type the strain for surveillance, as well as for future vaccine manufacturing.[11,12]

Laboratory confirmation of pertussis is recommended and is probably cost-effective. A definitive diagnosis always influenced the management of the children in this series, and was helpful in limiting further investigations. Antibiotic therapy was changed to a macrolide, inappropriate treatment was terminated and contacts were given prophylactic treatment to limit the spread of the disease.

This outbreak shows that the main burden of severe disease in pertussis occurs among young infants.[7] All children admitted to the ICU in this series were aged nine weeks or younger, and most children (11 of 18; 61.1%) were younger than three months of age.[11] The female predominance in this series has been documented in other studies, but currently no explanation for this observation has been proposed.[18]

In this small group, HIV-positive cases did not seem to be more common in the children affected by pertussis than in the population of children admitted to hospital, and HIV infection also did not adversely affect the outcome. An unanswered question is whether trimethoprim-sulfamethoxazole used as prophylaxis in HIV-infected children reduces their risk for *B. pertussis* infection or severe illness.

Pertussis is costly. There are direct medical costs (doctors' fees, hospitalisation, laboratory and radiological fees), as well as indirect costs (lost working days, travel costs). In a study among the Dutch population, infants accounted for only 5% of pertussis cases, but generated 50% of the costs pertaining to the management of the disease.[19,20]

Several suggestions have been made in recent medical literature for the prevention of the re-emergence of pertussis. Reduction of the incidence of pertussis in prevaccinated infants is the main objective. These proposals, listed below, should be discussed and considered in order to implement a new pertussis vaccination strategy for South Africa.

- Pre-term infants must be vaccinated according to their chronological age.[21]
- Revaccination at age four to five years is routinely done in North America, and has also been recommended by the GPI.[6,22] However, a Dutch study concluded that a pre-school booster is not a cost-effective strategy.[19]
- Vaccination of adults could be considered.[21–23] Although the cost of the disease is carried mainly by infants, the GPI suggests that the most effective method to reduce the main burden of the disease would be to focus on reducing the disease among the adult population.[20]
- Vaccination of adults in close contact with newborns is regarded as the most effective strategy. This is the so-called cocoon strategy, which involves the vaccination of parents, close household contacts and healthcare workers.[6,22]
- Maternal immunisation in pregnancy would partly protect the infant from the time of birth, except for premature babies.[7] Infants would still be susceptible until their own immunity is induced. There are insufficient data on the safety of vaccination (DTaP in which the pertussis component is acellular) in pregnancy, and it is now advised that mothers be vaccinated in the postpartum period.[6,24]
- Vaccination of adolescents is an important consideration, as they are a significant reservoir of infection. Adolescents could be reached through high school immunisation programmes.[2,6,11,16,25,26]
- Vaccination of newborns has been suggested.[19] However, neonatal vaccination is no longer regarded as

an option, as the acellular pertussis vaccine has been found to interfere with an adequate antibody response to other infant vaccines up to 18 months of age.[27,28]

- Finally, revaccination of HIV-infected children on antiretroviral treatment could be considered in order to boost their antibody levels.[29]

## Conclusion

Awareness of pertussis needs to be rekindled. Data need to be collected nationally, also in older children, adults and the elderly, to determine the true incidence of pertussis. An assessment of pertussis vaccination needs to be formulated to address persistent pertussis infections. Broader vaccine coverage in the general population would probably be cost-effective.

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