AN INVESTIGATION OF A POTENTIAL INCREASE IN PERTUSSIS CASES IDENTIFIED THROUGH SENTINEL SURVEILLANCE IN SOUTH AFRICA, JULY 2012 – SEPTEMBER 2014

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Introduction

It is estimated that *Bordetella pertussis* causes about 16 million cases and 195,000 deaths globally in children every year.[1] Children in developing countries are most affected, especially where vaccination coverage is low.[1] A global increase in pertussis cases has been noted in the last two decades.[2] This has been attributed to various factors including increased clinician awareness and improved diagnostics[2], decreased vaccination coverage, use of acellular pertussis (aP) vaccines instead of the previously used whole-cell vaccines and pathogen adaptation.[3] The relative contribution of these factors may differ between countries and is the subject of ongoing debate. The effectiveness of the aP vaccine has been found to wane after the last scheduled dose but immunity may be reactivated by a booster dose administered to older children.[4, 5]

Confirming a diagnosis of infection with *B. pertussis* in the laboratory is challenging as the organism is fastidious to culture. Although currently there is no satisfactory gold standard technique for laboratory confirmation of a pertussis infection, isolation of *B. pertussis* in culture has nearly 100% specificity.[2] Polymerase chain reaction (PCR) of *B. pertussis* is based on detection of the insertion sequence IS481.[6] Due to the high copy number (~200 copies) of IS481 in *B. pertussis,* the assay is susceptible to contamination and pseudo-outbreaks have been previously reported.[7] A culture-negative result does not exclude the diagnosis of pertussis as other factors such as previous immunization, receipt of antimicrobial therapy or testing late in the clinical course after several weeks of symptoms may affect the sensitivity of diagnosis.[8]

South Africa introduced whole-cell pertussis vaccines in 1950 which led to a marked decline in reported pertussis morbidity and mortality.[9] In order to achieve a triple vaccine comprising diphtheria, tetanus and pertussis (DTP), tetanus toxoid and diphtheria was added in May 1957.[9] The aP vaccines were introduced into the South African national immunisation programme - the Expanded Programme on Immunization (EPI) - in 2009 through a pentavalent combined vaccine.[10] Infants are

immunised with aP vaccines at 6, 10 and 14 weeks followed with a booster dose at 18 months.[11] The pentavalent combined vaccine includes: Bacille Calmette-Guérin (BCG), diphtheria, tetanus, acellular pertussis, inactivated polio vaccine, *Haemophilus influenza* type B and hepatitis B vaccine (DTaP-IPV/Hib/HBV)[12].

Data obtained from the National Institute for Communicable Diseases (NICD) pneumonia Severe Acute Respiratory Illness (SARI) surveillance programme, an active sentinel-site based surveillance programme for severe respiratory infection which was implemented in 2012, suggested an increase in pertussis cases from July-September 2014. The aim of this surveillance project was to conduct an investigation of patients identified though the SARI and Influenza-like Illness (ILI) surveillance programmes testing positive for pertussis from June 2012 to September 2014 in order to establish whether this was a pseudo-outbreak due to environmental and/or laboratory contamination or a true increase in disease. Furthermore, a comparison of the characteristics of patients during the period of increased case numbers against the baseline was conducted. Additionally, this project aimed to establish whether cases identified during the period of increased case numbers presented with classical pertussis symptoms.

Methods

In June 2012, the NICD began conducting enhanced surveillance for an expanded panel of respiratory pathogens (including *Bordetella* spp.) as part of the SARI programme at the Edendale and Klerksdorp-Tshepong Hospital Complex (KTHC) enhanced surveillance sites. In addition, the NICD initiated a programme of systematic ILI surveillance at public health clinics in the catchment area of the surveillance hospitals. Edendale Gateway clinic in Pietermaritzburg and Jouberton Clinic in Klerksdorp began systematically enrolling patients with ILI in June 2012.

The SARI and ILI programmes have been described previously.[12] In brief, dedicated surveillance officers screen all admissions and patients presenting for outpatient consultation Monday to Friday at SARI and ILI surveillance sites respectively. All patients meeting surveillance case definitions (Table 1) are approached for study enrolment and consenting patients are enrolled. Detailed epidemiologic data are collected through patient interview and medical record review and include demographic characteristics, clinical signs and symptoms, presence of underlying conditions, details of clinical management and outcome. Hospitalised patients are followed up until discharge or death to determine in-hospital outcome. Surveillance officers collect nasopharyngeal aspirates from children aged <5 years and nasopharyngeal and oropharyngeal swabs from individuals aged ≥5 years. In addition, induced sputum specimens are collected from all consenting hospitalised patients if not contraindicated.

Detection of *Bordetella* spp. was conducted using a previously published multiplex real-time PCR assay.[13] The assay detects the IS481 gene to determine the presence of *Bordetella* spp., the *pIS1001* gene for *B. parapertussis*, the *hIS1001* gene for *B. holmesii* and the pertussis toxin (*ptx*) gene to confirm *B. pertussis*.

Table 1: Case definitions by age criteria used in the influenza-like illness (ILI) and severe acute respiratory illness (SARI) surveillance systems.

Case	Age criteria	Case definition
ILI	All ages	2012-2014 • Acute fever of >38 degrees Celsius and/or self-reported fever within the last 3 days AND • Either cough or sore throat • The absence of other diagnoses 2014- • Acute fever of ≥38 degrees Celsius and/or self-reported fever within the last 10 days AND • Cough in the absence of other diagnoses
SARI	2days to < 3 months old	Any child with diagnosis of suspected sepsis or physician-diagnosed lower respiratory tract infection (LRTI) irrespective of signs and symptoms. Patient presenting within ≤10 days of the onset of illness
	3 months old to <5 years old	A child with physician-diagnosed acute lower respiratory tract infection (LRTI) including bronchiolitis, pneumonia, bronchitis and pleural effusion. Patient should be presenting within≤10 days of the onset of illness
	≥5 years old	Any person presenting with manifestations of acute lower respiratory infection with: sudden onset of fever (>38ºC) AND, cough or sore throat AND, shortness of breath, or difficulty breathing with or without clinical or radiographic findings of pneumonia), or tachypnea. Patient presenting within 7 days of the onset of illness From May 2014- changed to any person presenting with physician diagnosed LRTI with history of fever/documented fever (≥38^{0}C) and cough and onset within ≤10 days
Severe respiratory infection	All ages	Patient with clinical signs and symptoms meeting the case definitions for SARI or clinician-diagnosed LRTI irrespective of duration of symptoms and patients with suspected or confirmed TB

Investigation of increase in incidence

The baseline was defined as the period from June 2012 through June 2014 and the suspected outbreak defined as the period from July to September 2014. A *B. pertussis* case was defined as any individual with either an NP and/or sputum specimen with an IS481 Ct value <45 who presented during the period July 2012 to September 2014. In order to identify potential laboratory contamination all PCR controls, reagents and equipment were tested for *B. pertussis*. Environmental swabs from surfaces in specimen collection, vaccination and staff rooms from three facilities were collected and tested in order to identify possible environmental contamination with DNA. These surfaces included children's scales, immunization supplies cupboards, oral rehydration boxes, immunization chairs, surveillance officers' supplies cooler boxes, door handles to stock cabinet, isolation room basin, surveillance officer handwashing basin, data capture room basin, patient locker tap and biohazard bins.

For the retrospective case investigations clinical symptoms of pertussis were defined as one or more of the following: a cough of more than two weeks, paroxysmal cough, cough with inspiratory "whoop", post-tussive vomiting and apnoea or cyanosis in infants. A questionnaire was developed and face-to-face retrospective interviews were conducted with cases to determine the presence of typical pertussis symptoms at the time of illness as these were not specifically asked about in the SARI and ILI surveillance questionnaire. In addition to clinical presentation, data on case management, exposure contacts and post-exposure management of cases through the questionnaire were collected.

Chi-square tests were used for statistical analysis of data.

Results

Peaks of *B. pertussis cases* were noted during May-September among patients with both ILI and SARI in all the three years of surveillance (Figures 1 & 2). A mean of 5 *B. pertussis* cases per month from July-September were identified during the baseline period compared to 14 cases per month during the suspected outbreak period (Figure 2). No significant differences in the characteristics of individuals with SRI and ILI testing *B. pertussis* positive during baseline and suspected outbreak periods were identified (Table 2).

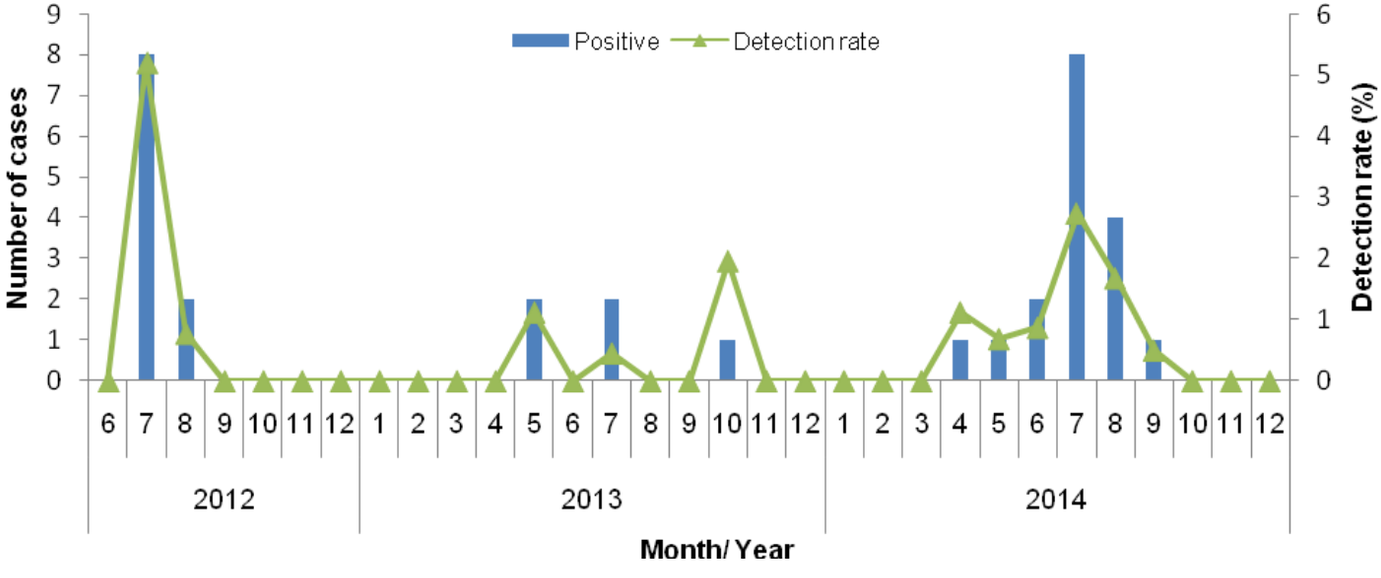

Figure 1: Numbers of positive cases and detection rate of *Bordetella pertussis* among influenza-like illness (ILI) cases in Klerksdorp and Pietermaritzburg, 2012-2014.

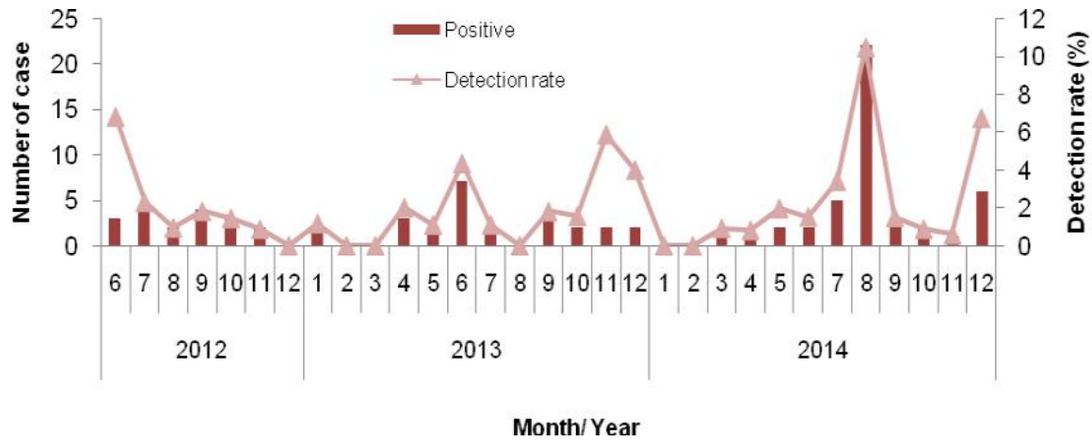

Figure 2: Numbers of positive cases and detection rate of *Bordetella pertussis* among severe acute respiratory illness (SARI) cases in Klerksdorp and Pietermaritzburg, 2012-2014.

Table 2: Comparison of characteristics of patients with influenza-like illness and severe acute respiratory illness testing positive for *Bordetella pertussis* during the baseline and suspected outbreak periods at the Edendale and Klerksdorp-Tshepong Hospital Complex sites, June 2012-Sept 2014

Characteristic		Influenza-like illness			Severe acute respiratory illness		
		Baseline* n/N (%)	Suspected Outbreak** n/N (%)	p-value	Baseline* n/N (%)	Suspected Outbreak** n/N (%)	p-value
Site				0.095			0.271
	Pietermaritzburg	10/19 (53)	3/13 (23)		22/49 (45)	13/39 (33)	
	Klerksdorp	9/19 (47)	10/13 (77)		27/49 (55)	26/39 (67)	
Age				0.575			0.506
	<4months	1 /19 (5)	0/13 (0)		6/49 (12)	3/39 (8)	
	4m - 1year	0/19 (0)	0/13 (0)		8/49 (16)	3/39 (8)	
	1-4y	4/19 (21)	5/13 (39)		4/49 (8)	4/39 (10)	
	5-24y	7/19 (37)	5/13 (39)		2/49 (4)	3/39 (8)	
	25-44y	7/19 (37)	3/13 (23)		17/49 (35)	11/39 (29)	
	45-64y	0/19 (0)	0/13 (0)		11/49 (22)	10/39 (26)	
	65+	0/19 (0)	0/13 (0)		1/49 (2)	4/39 (11)	
Sex				0.567			0.906
	Male	6/19 (31)	5/12 (42)		22/49 (45)	19/39 (46)	
HIV Status				0.191			0.514
	Infected	9/16 (56)	3/10 (30)		23/39 (59)	18/35 (51)	
Symptom duration				0.771			0.140
	<7 days	15/18 (83)	10/12 (83)		28/47 (60)	17/39 (44)	
Death							0.758
	Yes	0/19 (0)	0/13 (0)		4/48 (8)	4/39 (10)	

*Baseline: June 2012-June 2014
**Suspected outbreak: July–September 2014
n=Proportion of cases
N=Total number of cases

Of 32 environmental swabs taken, one (3%) surface from Tshepong hospital tested positive. This swab was taken from a basin in a data entry office used by nurses to wash their hands and also to store the ward rotation supplies cooler bag. Nurses did not take specimens or conduct any procedures in this room. Rooms where patient sample collection took place were not used for vaccination. All laboratory controls and reagents tested were negative for *B. pertussis.*

Epidemiological investigations to determine the presence of classical pertussis symptoms were conducted for 23 of 52 cases identified during the outbreak period (44%). All 23 showed at least one pertussis symptom, the commonest being history of cough more than 2 weeks (83%, 19/23), followed by paroxysmal cough (52%, 12/23). Apnoea was reported in both infants in this group (100%,2/2) and cyanosis in one of them (50%, 1/2). No epidemiologic links were identified between cases. Among children <5 years of age, vaccination data were missing for 30% of cases (7/23) in the baseline and 25% (4/16) in the suspected outbreak period. Of those with available data, 75% (12/16) in the baseline and 36% (4/12) in the suspected outbreak period were fully vaccinated according to the recommended schedule (p=0.027). Of the 23 interviewed cases 9% (2/23) were clinically suspected of pertussis by the attending physician. A mean of 5 (range: 1-7) household contacts for each case was found and none of the contacts reported receiving chemoprophylaxis.

Discussion

This investigation, including the environmental contamination results, suggests that the increase in pertussis cases during July-–September 2014 was unlikely a pseudo-outbreak or due to laboratory contamination. Rigorous laboratory and environmental disinfection practices minimized the likelihood of false-positive results from contaminated clinical specimens.

A seasonal increase in the incidence of pertussis cases was found throughout the surveillance period (2012-2014) with most cases occurring during South Africa's winter season of May to September. This correlation suggests true seasonality of pertussis disease in South Africa which may have, in part, contributed to the observed increase in case numbers that prompted this investigation. However, the observed increase in 2014 was greater than in previous years and could reflect underlying disease periodicity or other factors.[14]

These results are based on data that only go as far back as 2012 when the surveillance system was initiated. Without extensive baseline data it is difficult to determine whether this observed increase is due to pertussis epidemic peaks that occur every 3-5 years as described in other countries.[15] A retrospective review of case clinical presentation showed that cough of >2 weeks duration was the commonest symptom (present in 83% of individuals), consistent with previous findings in other settings.[16]

After the introduction of the acellular pertussis vaccine into the routine immunisation programme in 2009 in South Africa, the estimated coverage for the DTP vaccine according to the South African National Department of Health was 10.3% while UNICEF estimated the coverage to be at 69% in 2012.[17] Better quality data on vaccine coverage for South Africa are needed. The contribution of possible low vaccine coverage to the observed increase in pertussis incidence should be further explored.

A minority of cases identified were clinically suspected by the attending clinician, even though on review all cases had at least once classic pertussis symptom. The commonest symptom was chronic cough which is non-specific and clinicians may be more likely to consider other more common diagnoses such as tuberculosis. Contact follow-up with chemoprophylaxis was also not conducted for any cases, likely related to the low index of clinical suspicion and the fact that availability of surveillance results was delayed. It is important that clinicians consider pertussis in the differential diagnosis of patients with cough and submit specimens for testing. Suspected pertussis cases should be notified and contacts followed up. At sentinel sites, processes for transport, testing and reporting of pertussis results should be streamlined to ensure more rapid reporting of results to clinicians. Efforts are underway to implement this.

This study had several limitations. Cases may have been missed because the surveillance case definitions were not designed to specifically target pertussis for both ILI and SARI. Due to enrolment being restricted to weekdays, cases that presented over weekends were likely missed. Gaps in available data on the vaccination status of children have been identified which limited analysis. In addition, there was a delay in the collection of clinical data from cases which may have resulted in recall bias. It was not possible to collect environmental specimens from the Gateway clinic site. However, only 3 of the 52 cases in the outbreak period were identified from this site.

In conclusion, an increase in the incidence of pertussis cases in South Africa between July and September 2014 occurred. This increase does not appear to be due to environmental or laboratory contamination or a discrete outbreak as no epidemiologic links between cases was identified. The high proportion of children not fully vaccinated according to age should be explored further. Improved collection of complete vaccine histories in all children aged <5 years is needed. Recent data following the conclusion of this outbreak investigation shows a sustained increase in pertussis case numbers in 2015.[18] This suggests that the observed increase in case numbers may have been the start of a period of increased case incidence possibly related to disease periodicity. The possible contribution of waning immunity following the change to acellular pertussis vaccine in the routine immunisation programme since 2009 should be further investigated.

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References

1. CDC. Pertussis in other countries 2015 [updated 8 September 2015; cited 2015 7 October 2015]. Available from: http://www.cdc.gov/pertussis/countries.html. *Centers for Disease Control and Prevention* [Internet].
2. Fisman DN, Tang P, Hauck T, Richardson S, Drews SJ, Low DE, et al. Pertussis resurgence in Toronto, Canada: a population-based study including test-incidence feedback modeling. *BMC public health* 2011; 11: 694.
3. Mooi FR, van Loo IH, van Gent M, He Q, Bart MJ, Heuvelman KJ, et al. *Bordetella pertussis* strains with increased toxin production associated with pertussis resurgence. *Emerg Infect Dis.* 2009; 15(8):1206-13.
4. Winter K, Harriman K, Zipprich J, Schechter R, Talarico J, Watt J, et al. California pertussis epidemic, 2010. *J Pediatr.* 2012;161(6):1091-6.
5. Witt MA, Katz PH, Witt DJ. Unexpectedly limited duarability of immunity following acellular pertussis vaccination in preAdolescents in a North American outbreak. *Clin Infect Dis*. 2012 Jun; 54(12):1730-5.
6. Lievano FA, Reynolds MA, Waring AL, Ackelsberg J, Bisgard KM, Sanden GN, et al. Issues associated with and recommendations for using PCR to detect outbreaks of pertussis. *J Clin Microbiol*. 2002; 40(8):2801-5.
7. Tozzi AE, Celentano LP, Ciofi degli Atti ML, Salmaso S. Diagnosis and management of pertussis. *Can Med Assoc J*. 2005; 172(4):509-15.
8. Crowcroft NS, Pebody RG. Recent developments in pertussis. *The Lancet*. 2006; 367(9526):1926-36.
9. Strebel P, Hussey G, Metcalf C, Smith D, Hanslo D, Simpson J. An outbreak of whooping cough in a highly vaccinated urban community. *J Trop Pediatr* 1991; 37(2):71-6.
10. Madhi SA, Bamford L, Ngcobo N. Effectiveness of pneumococcal conjugate vaccine and rotavirus vaccine introduction into the South African public immunisation programme. *S Afr Med J*. 2014; 104(3):228.
11. Souter J. Vaccines administered at 6, 10 and 14 weeks. *Prof Nurs Today*. 2012; 16(2):24-8.
12. McAnerney JM, Cohen C, Moyes J, Besselaar TG, Buys A, Schoub BD, *et al*. Twenty-five years of outpatient influenza surveillance in South Africa, 1984-2008. *J Infect Dis*. 2012; 206(Suppl 1):S153-8.
13. Loeffelholz M. Towards improved accuracy of Bordetella pertussis nucleic acid amplification tests. *J Clin Microbiol*. 2012; 50(7):2186-90.
14. Broutin H, Viboud C, Grenfell BT, Miller MA, Rohani P. Impact of vaccination and birth rate on the epidemiology of pertussis: a comparative study in 64 countries. *Proc Biol Sci*. 2010; 277(1698):3239-45.
15. Broutin H, Guegan JF, Elguero E, Simondon F, Cazelles B. Large-scale comparative analysis of pertussis population dynamics: periodicity, synchrony, and impact of vaccination. *Am J Epidemiol*. 2005; 161(12):1159-67.
16. Senzilet L, Halperin SA, Spika JS, Alagaratnam M, Morris A, Smith B, et al.Pertussis is a frequent cause of prolonged cough illness in adults and adolescents. *Clin Infect Dis*. 2001 Jun 15; 32(12):1691-7.
17. Van den Heever J [Internet]. What is the South African immunisation coverage? 2012. [cited 2015 Oct 28]. Available from: https://www.google.co.za/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CBwQFjAAahUKEwid1vqVj-fIAhVB2RQKHR3aAQU&url=http%3A%2F%2Fwww.africacheck.org%2Fwp-content%2Fuploads%2F2012%2F11%2FS-Africans-Immunization-Coverage-ppt-EPI-Manager3.pdf&usg=AFQjCNEhtSBZ06kvqmEVTq0bIfXT8undgQ&sig2=FKWVFbay5PqKo4wIfc9EjQ
18. NICD. Increased detection of *Bordetella pertussis* in the pneumonia and influenza-like illness surveillance programmes. Communicable Diseases Communiqué; 14(6): 4-5.