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Trends in Pertussis Incidence in Georgia from 2010 – 2020 Based on the 2020 CSTE/CDC Case Definition

Gina U. Raderalazasoa

ABSTRACT

TRENDS IN PERTUSSIS INCIDENCE IN GEORGIA FROM 2010 – 2020 BASED ON THE 2020 CSTE/CDC CASE DEFINITION

By

GINA URSULA RADERALAZASOA

7/20/2021

INTRODUCTION: Pertussis is a highly contagious respiratory infection transmitted from person to person in close contact. Its burden is high among unvaccinated infants (< 1 year) due to age appropriateness, and the number of cases has been on the rise among adolescents and adults in the past ten years. In 2020, a change in pertussis case definition (CD) was issued by the Council of State and Territorial Epidemiologists (CSTE), classifying PCR-positive cases as confirmed cases regardless of cough duration. This study aims to assess whether the change in pertussis CD affects the number of confirmed and probable pertussis cases reported in Georgia from 2010 -2020 and evaluate its effectiveness.

METHODS: Epidemiologic data were obtained from the State Electronic Notifiable Disease Surveillance System (SendSS). Based on the 2020 CSTE/CDC case definition, reported pertussis cases were re-evaluated as confirmed, probable, and not-a-case (NAC). A cross-sectional study was performed. The characteristics of all reported pertussis cases were first described. Then, the incidence rates were compared under the old and new CDs. Last, sensitivity, specificity, predictive value positive (PVP), and predictive value negative (PVN) of the new CD were estimated.

RESULTS: From 2010 to 2020, there were 3,882 reported pertussis cases in Georgia. About 22% (n=867) of reported pertussis cases were among infants < 1 year. Cough duration was inconsistent across case classification. PCR was ordered in 62.28% (n=2,176), whereas culture in 8.67% (n=303) only. More than half of the laboratory-confirmed cases were obtained from PCR. Between 2010 and 2020, 2,765 (71.23%) reported cases were considered as pertussis cases (confirmed and probable), and 1,117 (28.77%) were NACs, using the previous CDs issued in 2010 and 2014. After reclassification based on the 2020 CSTE/CDC case definition, 3,213 (82.77%) were

considered as cases, whereas 669 (17.23%) were NACs. Fifty-eight percent (n=137, 95% CI: [50.79% – 65.31%] of pertussis cases would have been missed in 2020 if the 2014 CSTE/CDC case definition was still in use. The incidence rate of pertussis cases was 1.16 times higher with the new CD than the old CD. The new CD was estimated to have 83.80% [95%CI: 82.42 – 85.17] sensitivity and 72.11% [95%CI: 70.56% – 73.66%] predictive value positive.

CONCLUSION: Pertussis is a remerging infectious disease that needs better control and surveillance. Changing the clinical criteria of illness of cough ≥ 2 weeks to cough of any duration and accounting PCR-positive cases as laboratory-confirmed cases were found to be effective in capturing more pertussis cases in Georgia. Despite the limitations of this study, it demonstrates the usefulness of updating case definitions with reliable diagnostic tools. These findings can be used to reinforce the capacity of health districts and public health departments to identify pertussis cases accurately and deploy the necessary resources. Standardized and evidence-based tools are essential for notifiable diseases surveillance to monitor trends and stop epidemics on time. Future research could expand on adopting an integrated approach to surveillance of emerging infectious diseases.

KEYWORDS: Bordetella pertussis, case definition, incidence, surveillance.

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APPROVAL PAGE

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AUTHOR'S STATEMENT PAGE

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Gina Ursula Raderalazasoa

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AC: Adenylate Cyclase Toxin

ACIP: Advisory Committee on Immunization Practices

CD: Case Definition

CDC: Centers for Disease Control and Prevention

CI: Confidence Interval

CSTE: Council of State and Territorial Epidemiologists

DFA: Direct Fluorescent-Antibody

DNT: Dermonecrotic Toxin

DPH: Georgia Department of Public Health

DTaP: Diphtheria, Tetanus, and acellular Pertussis Vaccine

FHA: Filamentous Hemagglutinin

FIM: Fimbriae

GSU: Georgia State University

NNDSS: National Notifiable Diseases Surveillance System

OASIS: Online Analytical Statistical Information System

PCR: Polymerase Chain Reaction

PEP: Postexposure Prophylaxis

PHIP: Public Health Information Portal

PRN: Pertactin

PT: Pertussis Toxin

SendSS: State Electronic Notifiable Disease Surveillance System

TC: Tracheal Cytotoxin

Tdap: Tetanus, Diphtheria, and acellular Pertussis Vaccine

U.K.: United Kingdom

U.S.: United States

WHO: World Health Organization

Chapter I – Introduction

Pertussis or whooping cough is a highly contagious respiratory infection caused by *Bordetella pertussis* bacteria. In 2014, the World Health Organization (WHO) estimated 24.1 million pertussis cases and 160,700 deaths occurred globally, where 21% of the cases and 53% of the estimated deaths were found in infants less than 12 months old (Yeung et al., 2017). Symptoms in adolescents and adults are usually mild or atypical, leading to underreported cases, but those with mild illness can still transmit the disease to unvaccinated individuals (Sanstead et al., 2015). Young infants are often incompletely or not vaccinated because the earliest dose of the pertussis vaccine DTaP can be administered at 2 months of age. The five doses recommended for children will not be complete until age 6, according to the Advisory Committee on Immunization Practices (ACIP) recommendations (CDC, 2020b).

In 2010 and 2012, pertussis cases peaked in the United States (U.S.) with more than 27,000 cases and 48,277 cases, respectively (CDC, 2019). About 35% of the cases were among children, mostly under 3 months old (Syed & Bana, 2014). The risk of pertussis-related complications and death is highest among infants < 1 year; about half of these infantile pertussis cases required hospitalization (CDC, 2021a).

Pertussis is preventable through vaccination. Since the implementation of routine childhood vaccination in 1940s, pertussis mortality and morbidity decreased in the U.S. (CSTE, 2019). However, this success was short-lived as the number of reported pertussis cases has increased during the past 40 years despite the widespread vaccination (Syed & Bana, 2014). Moreover, immunity against pertussis does not confer life-long protection, either after natural infection or induced by vaccination, lasting about 5 – 8 years (Chiappini et al., 2013). Thus, pertussis has been the least controlled of all bacterial vaccine-preventable diseases in the U.S. (Masseria et al., 2017).

In 2020, the Council of State and Territorial Epidemiologists (CSTE) issued a change in pertussis case definition (CD), intended to capture the disease across all age groups better and precisely estimate its burden (CSTE, 2019). According to the Centers for Disease Control and Prevention (CDC), a surveillance CD is a set of uniform criteria to define a disease that enables public health officials to classify and count cases consistently across reporting jurisdictions (CDC, 2021d).

Previously, the criteria for confirmed cases included a positive culture and the presence of cough or a positive polymerase chain reaction (PCR) with cough onset of 14 days or more. Although culture was considered the gold standard to diagnose pertussis, PCR is currently the most widely used diagnostic tool for pertussis because it has become more efficient and accurate over time. Thus, the new classification considers PCR-positive cases as confirmed, regardless of cough duration (CSTE, 2019).

Since pertussis is reportable in Georgia, this study aims to measure how this change in CD affects the number of confirmed and probable pertussis cases reported from 2010 -2020 and assess its effectiveness.

Chapter II – Literature Review

1. Epidemiology

Pertussis remains a public health issue worldwide. The first described outbreaks occurred in the 16th century (Kilgore et al., 2016). Bordetella pertussis was first isolated in 1906, and pertussis was one of the most common childhood illnesses of the 20th century (CDC, 2020d). It was also a major cause of childhood mortality in the U.S., with 1 death per 10 cases, and it killed more children annually than polio and measles combined (Clark, 2014). Countries with a large population, such as China, India, Indonesia, Nigeria, and Pakistan, could have underreported pertussis cases (Syed & Bana, 2014). In 1940, a whole-cell vaccine that induced an immune response similar to a natural *B. pertussis* infection became available worldwide and was routinely used for childhood immunization (Clark, 2014). As a result, pertussis incidence has decreased more than 75% than that of the pre-vaccine era (CDC, 2020d). However, the whole-cell vaccines had been reported to be associated with adverse reactions with increasing age and the number of administered doses. In the 1990s, the replacement of these whole-cell vaccines with less reactogenic acellular vaccines resulted in the resurgence of the disease among adolescents and school-aged children (**Figure 1**) (Gabutti et al., 2015). Previous studies suggest that possible reasons for this re-emergence of pertussis include increased reporting due to the increased awareness of the disease, the development of new clinical definitions, and the widespread use of PCR for laboratory confirmation, but also, the waning of immunity after natural infection or vaccination (Chiappini et al., 2013). Pertussis cases in adults are often subsequent, mild, or asymptomatic infections that remain undetected and putting unvaccinated children at risk of transmission (Sanstead et al., 2015). Also, immunity against pertussis is transient, with outbreaks occurring every 3 – 5 years (Gabutti et al., 2015).

In the U.S., state health departments report suspected, probable, and confirmed pertussis cases to the CDC through the National Notifiable Diseases Surveillance System (NNDSS) (CDC, 2021b).

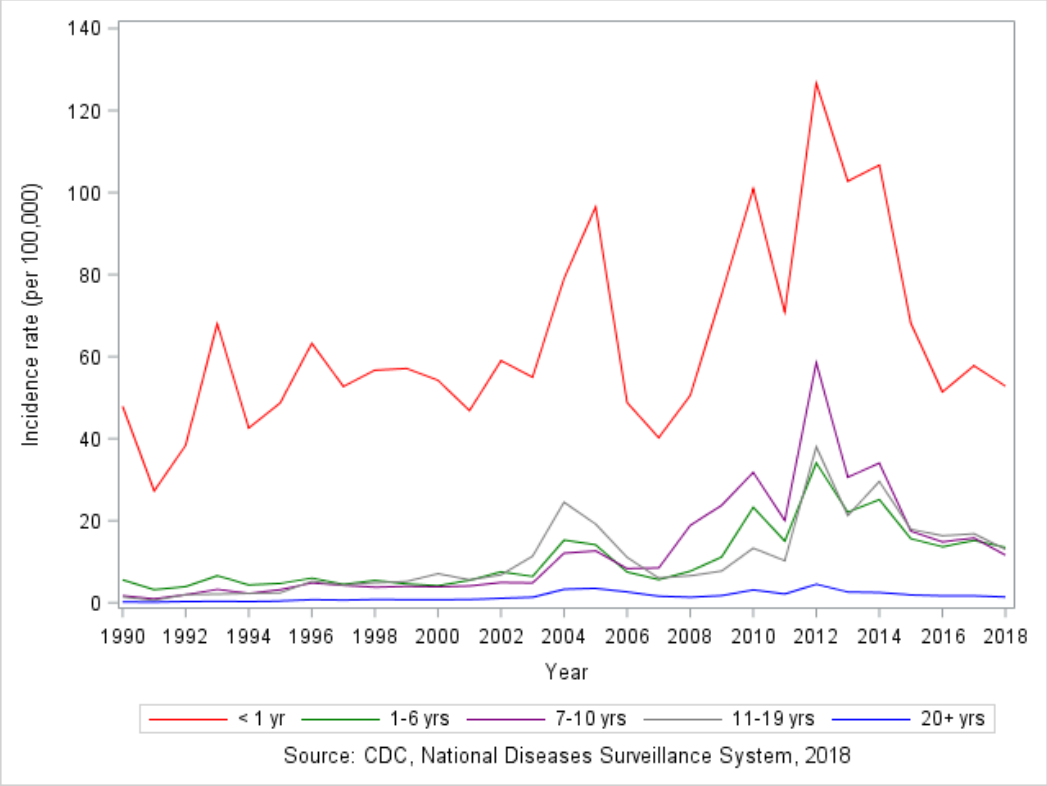

Figure 1. Reported pertussis incidence by age group in the U.S., 1990 – 2018. Source: https://www.cdc.gov/pertussis/surv-reporting.html.

2. Pathogenesis

Pertussis, also known as whooping cough, is an airborne bacterial respiratory infection caused by *Bordetella pertussis*. Other *Bordetella* species (*B. parapertussis* and *B. holmesii*) can cause milder whooping cough-like symptoms in humans and can also infect animals. In contrast, *B. pertussis* is specific to humans (Kilgore et al., 2016). This pathogen is an aerobic, Gram-negative bacterium. It is virulent due to its antigenic and biologically active components such as pertussis toxin (PT), filamentous hemagglutinin (FHA), fimbriae (FIM), pertactin (PRN), agglutinogens, adenylate cyclase toxin (AC), dermonecrotic toxin (DNT), and tracheal cytotoxin (TC) (CDC, 2020d). *B. pertussis* is transmitted from person to person through aerosol droplets. The incubation period is typically 7 – 10 days but can range from 4 – 21 days (CDC, 2020d). The bacteria adhere to the cilia of the tracheal epithelium and lungs of the host via FHA and FIM, multiply locally, and release toxins (Kilgore et al., 2016). Then, the produced toxins cause inflammation, paralyze the cilia, and

interfere with the evacuation of pulmonary secretions (**Figure 2**) (CDC, 2020d). Thus, this cascade of events translates into pertussis clinical features.

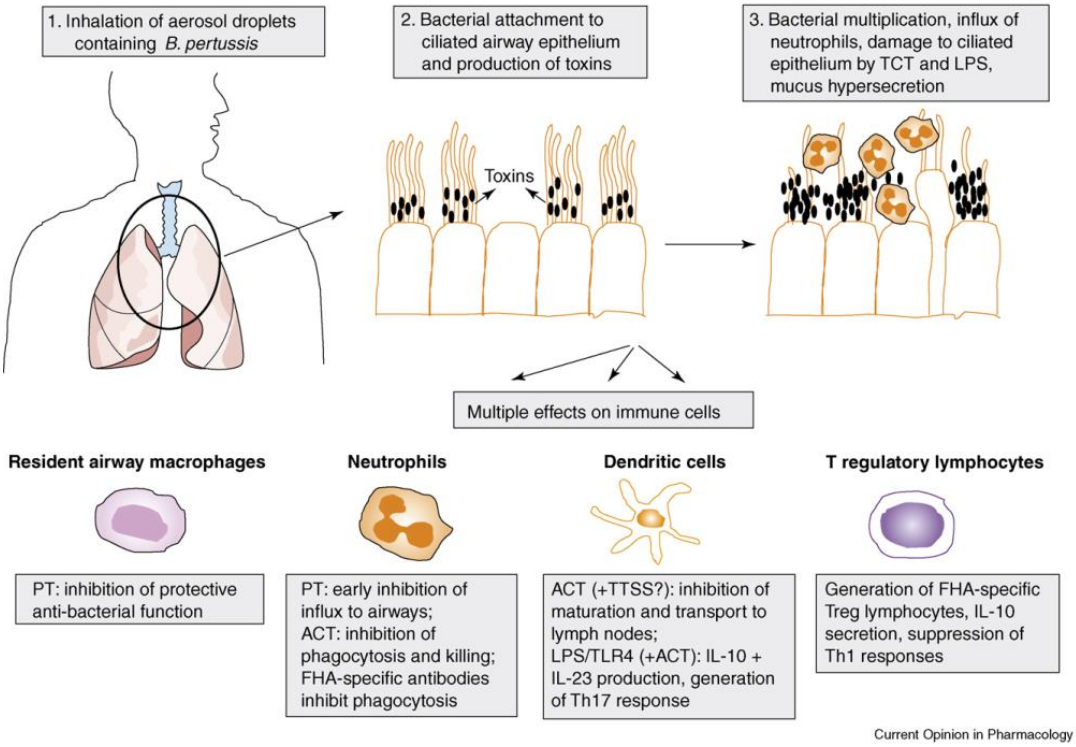

Figure 2. Pathogenesis of *B. pertussis* infection.

Source: Carbonetti, 2007.

3. Clinical features

The clinical course of pertussis is divided into three stages. First, the catarrhal stage (1–2 weeks) is characterized by an insidious onset of cold-like symptoms such as nasal congestion, sneezing, mild cough, and a low-grade fever. During the paroxysmal stage (1–6 weeks), the symptoms persist and become more severe (**Figure 3**). The patient experiences uninterrupted bursts of cough, called paroxysms, due to the difficulty of expelling thick mucus through the swollen airways and followed by a long inspiratory phase characterized by the whooping sound (Mattoo & Cherry, 2005). Complications include vomiting, collapsed lungs, rib fractures, and petechiae as capillaries burst due to the pressure. This stage can manifest with gasping, cyanosis, apnea, and apparent life-threatening events in small infants. The decreased oxygen levels can cause seizures, encephalopathy, and death (Heininger, 2019). The transition to the convalescent stage is gradual

and marked by a decrease in the paroxysms' frequency and severity. Though, it can last up to 6 weeks (Kilgore et al., 2016). Adolescents, adults, and children previously immunized against pertussis through vaccination or natural infection usually have milder symptoms, but they can still infect susceptible persons with no or incomplete immunity (CDC, 2020d). Infants younger than 12 months of age are at higher risks for severe outcomes (**Table 1**) (Kilgore et al., 2016).

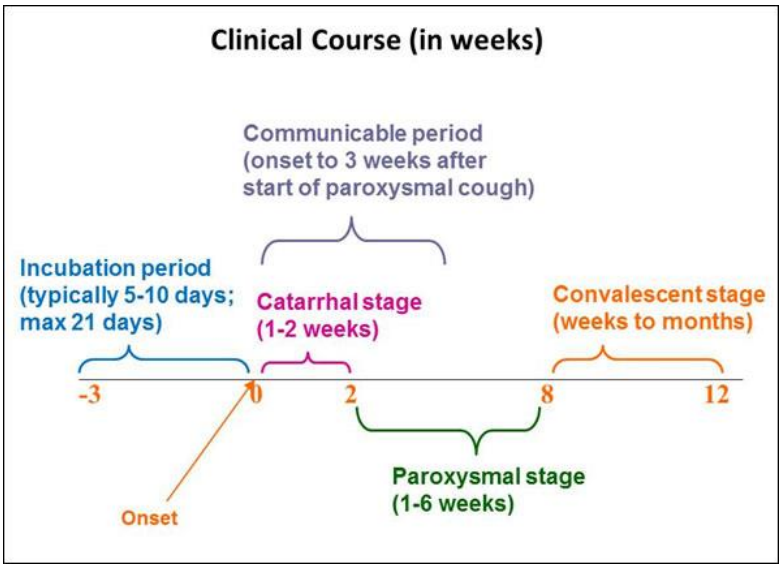

Figure 3. Clinical course of pertussis infection.

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

Table 1. Clinical complications of pertussis among infants, adolescents, and adults from 1981 – 2015.

Source: (Kilgore et al., 2016)

	Frequencies (%) in:	
Clinical complications	**Infants**	**Adolescents and adults**
Hospitalization	~ 50	0 – 12
Apnea	50 – 67	27 – 86
Pneumonia	20 – 23	0.6 – 8
Convulsions	1	0 – 0.6
Death	1 – 1.6	0.01
Insomnia	-[a]	77
Sinusitis	-	13
Otitis media	6	4
Weight loss	12	3 – 33
Urinary incontinence	-	3 – 28
Syncope	-	2 – 6
Rib fracture	-	1 – 4
Loss of consciousness	-	1

[a]*data not available*

4. Transmission

Pertussis is transmitted from person to person through airborne droplets when an infected person coughs, sneezes, or share breathing space with susceptible individuals. Susceptible individuals are unvaccinated infants, immunocompromised people, pregnant women, and the elderly. It is considered highly contagious, far more than polio, smallpox, rubella, mumps, and diphtheria (Kilgore et al., 2016). Pertussis reproduction number (R_0) was estimated to be 5.5, but studies have shown that one infected person can transmit *B. pertussis* to as many as 12 – 17 other susceptible individuals (Kretzschmar et al., 2010).

5. Diagnosis

Pertussis can be diagnosed clinically, as well as with laboratory testing. The specimen is usually collected with a nasopharyngeal swab from all suspected cases (CDC, 2021c). Culture is the gold standard laboratory test. It is highly specific when performed during the first 2 weeks of cough onset (CDC, 2020d). The PCR became widely used in the last 20 years because it is rapid and has a higher sensitivity than conventional culture (CSTE, 2019). It provides accurate results for up to 4 weeks of cough in infants or unvaccinated persons. Moreover, PCR assay protocols can also differentiate *B. pertussis* from other *Bordetella* species (CDC, 2020d). Serology is more useful in the later stage of the disease when both culture and PCR can no longer detect infection (CSTE, 2019). It may be performed on a specimen collected up to 12 weeks following cough onset (CDC, 2020d).

6. Treatment and prevention

Macrolides antibiotics (e.g., erythromycin, clarithromycin, or azithromycin) were proven to be effective against *B. pertussis* infection (Kilgore et al., 2016). In addition, antibiotics may reduce the duration of the infectious period. Close contacts of infected individuals are also recommended to get postexposure prophylaxis (PEP) administration. However, the rise of antibiotic resistance in recent years may have impacted the management of pertussis cases (Kilgore et al., 2016). Vaccination remains a global prevention strategy. In the U.S., a whole-cell vaccine was introduced in the 1940s and abandoned 30 years later due to several reported adverse events (Chiappini et al., 2013). Subsequently, acellular vaccines were demonstrated to be effective and have been routinely used since the 1990s. However, they only protect about 4 – 7 years, whereas whole-cell vaccines can protect up to 5 – 14 years (Kilgore et al., 2016). Currently, DTaP and Tdap are pertussis-containing vaccines recommended by the CDC (**Figure 4**). Children are considered fully vaccinated if they receive 5 doses of DTaP or 4 doses of DTaP if the fourth dose was administered on or after the fourth birthday (CDC, 2020a).

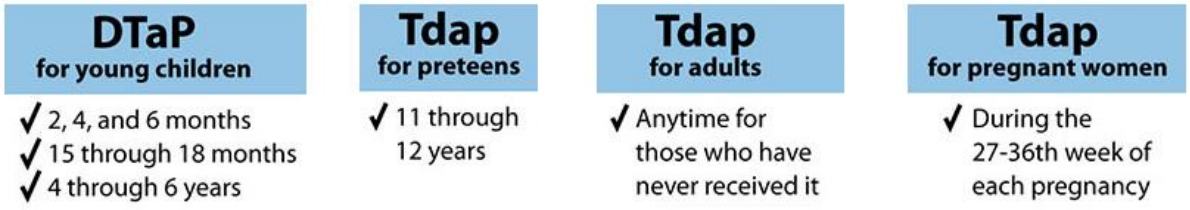

Figure 4. Recommended pertussis vaccination calendar.

Adapted from the CDC (https://www.cdc.gov/vaccines/vpd/pertussis/index.html).

7. Surveillance case definition and classification

Pertussis CD has been updated three times from 2010 – 2020. In 2010, the case classification was reformatted to clarify the wording, but no substantive change was made to the CD used since 1997 (**Table 2**).

Table 2. Pertussis classification based on the 2010 CSTE/CDC case definition.

Adapted from the NNDSS (https://ndc.services.cdc.gov/case-definitions/pertussis-2010/).

Criteria	Probable case	Confirmed case		
Cough duration	≥ 2 weeks	Any	≥ 2 weeks	≥ 2 weeks
Clinical criteria[a]	At least one of the symptoms	-	At least one symptom	At least one symptom
Laboratory confirmation	Absence	Culture +	PCR +	-
Epidemiologic linkage to a laboratory-confirmed case	No	-	-	Yes

[a]Clinical criteria include paroxysms or inspiratory whoop or post-tussive vomiting

In 2014, the CSTE intended to accurately capture the burden of disease in infants < 1 year by including apnea as a defining accessory symptom and removing the requirement for coughs ≥ 2 weeks for this age group (**Table 3**).

Table 3. Pertussis classification based on the 2014 CSTE/CDC case definition.

Adapted from the NNDSS (https://ndc.services.cdc.gov/case-definitions/pertussis-2014/).

Criteria	Probable case	Probable case for infants < 1 year		Confirmed case		
Cough duration	≥ 2 weeks	Any	Any	Any	≥ 2 weeks	≥ 2 weeks
Clinical criteria[a]	At least one of the symptoms	At least one of the symptoms	At least one of the symptoms	-	At least one of the symptoms	At least one of the symptoms
Laboratory confirmation	Absence	PCR +	-	Culture +	PCR +	-
Epidemiologic linkage to a laboratory-confirmed case	No	-	Yes	-	-	Yes

[a]Clinical criteria include paroxysms or inspiratory whoop or post-tussive vomiting or apnea ± cyanosis (for infants < 1 year only)

In 2020, the CSTE updated the 2014 CSTE/CDC case definition by classifying PCR-positive cases as confirmed, regardless of cough duration and presence of pertussis symptoms. Its application limits the confirmed cases to those with laboratory confirmation and removes the age-specific classification (CSTE, 2019) (**Table 4**).

Table 4. Pertussis classification based on the 2020 CSTE/CDC case definition.

Adapted from the NNDSS (https://ndc.services.cdc.gov/case-definitions/pertussis-2020/).

Criteria	Probable case	Confirmed case
Cough duration	Any	Any
Clinical criteria[a]	At least one of the symptoms	-
Laboratory confirmation	-	Culture + or PCR +
Epidemiologic linkage to a laboratory-confirmed case	Yes	-

[a]Clinical criteria include paroxysms or inspiratory whoop or post-tussive vomiting or apnea ± cyanosis

8. Research question

The present study aims to answer whether the application of the new pertussis CD captures more pertussis cases than the previous CDs. Thus, this study assesses whether the number of confirmed and probable pertussis cases reported in Georgia from 2010-2020 increases using the 2020 CSTE/CDC case definition and measures whether the new CD is a more effective surveillance tool than the previous pertussis CDs.

Chapter III – Materials and Methods

1. Ethical consideration

The present study was approved by the Internal Review Board of Georgia State University (GSU) and the Georgia Department of Public Health (DPH). The use of secondary data put it under the exempt category. Deidentified data was requested from DPH through the Public Health Information Portal (PHIP).

2. Data collection

The population data were obtained from the publicly available Online Analytical Statistical Information System (OASIS). Georgia population counts from 2010 to 2020 for all ages, genders, races and ethnicities were extracted by year. Epidemiologic data were obtained from the State Electronic Notifiable Disease Surveillance System (SendSS). Pertussis cases are electronically transmitted to SendSS after a verbal report has been made to the local health department or a filing of a Pertussis Report Form by the districts, forwarded to the Epidemiology Branch. Pertussis-related variables included in patient demographics, signs and symptoms, complications and other symptoms, treatment, laboratory tests, vaccination history, epidemiologic information, patient setting, and maternal TdaP information for mothers of infants < 1 year were used in the analysis.

3. Data cleaning

The SAS 9.4 package was used to re-evaluate the reported pertussis cases as confirmed, probable, and not-a-case (NAC), based on the 2020 CSTE/CDC case definition. The NAC included the deleted, not confirmed, out-of-state, pending cases, and cases from unknown counties. Duplicated data entries were filtered by the unique identifier assigned by state (STATECASEID) and date of onset (DOO) variables, then deleted. The old CD corresponds to the 2010 CSTE/CDC definition for cases reported between 2010 – 2013 and the 2014 CSTE/CDC definition for cases reported between 2014 – 2019. On the other hand, the new CD corresponds to the 2020 CSTE/CDC case definition. Next, dichotomous variables were created for the new CD's clinical, laboratory, and epidemiologic criteria. Then, pertussis cases were reclassified as confirmed,

probable, or NAC. Confirmed and probable cases that met the necessary criteria were grouped as cases, whereas those that did not meet the criteria were NACs.

4. Data analysis

A cross-sectional study was performed. First, the characteristics of all pertussis cases reported from 2010 to 2020 were described. Next, pertussis cases reported during the 2010 – 2013 and 2014 – 2019 periods were compared with the reclassified ones. As the new CD was already used for pertussis cases reported during 2020, these cases were reclassified using the 2014 CSTE/CDC definition, and the differences were calculated. Then, the incidence rates (per 100,000 person-years) of the cases and NACs were compared under the old and new CDs. The sensitivity, specificity, predictive value positive (PVP), and predictive value negative (PVN) were estimated by testing the new CD against the old CD with a two-by-two table. These measures were calculated using the formulas below.

$$Sensitivity = \frac{True\ pertussis\ cases}{Total\ reported\ as\ pertussis\ cases}$$

$$Specificity = \frac{True\ non-pertussis\ cases}{Total\ reported\ as\ non-pertussis\ cases}$$

$$PVP = \frac{True\ pertussis\ cases}{Total\ classified\ as\ pertussis\ cases}$$

$$PVN = \frac{True\ non-pertussis\ cases}{Total\ classified\ as\ non-pertussis\ cases}$$

Chapter IV – Results

There were 3,882 pertussis cases reported in Georgia from 2010 to 2020. Fifty two percent (n=2,032) were confirmed cases, 22.41% (n=870) probable cases, and 25.24% (n=980) NAC. The incidence of pertussis cases was higher in 2014 than in other years, with 60% (n=332) confirmed cases.

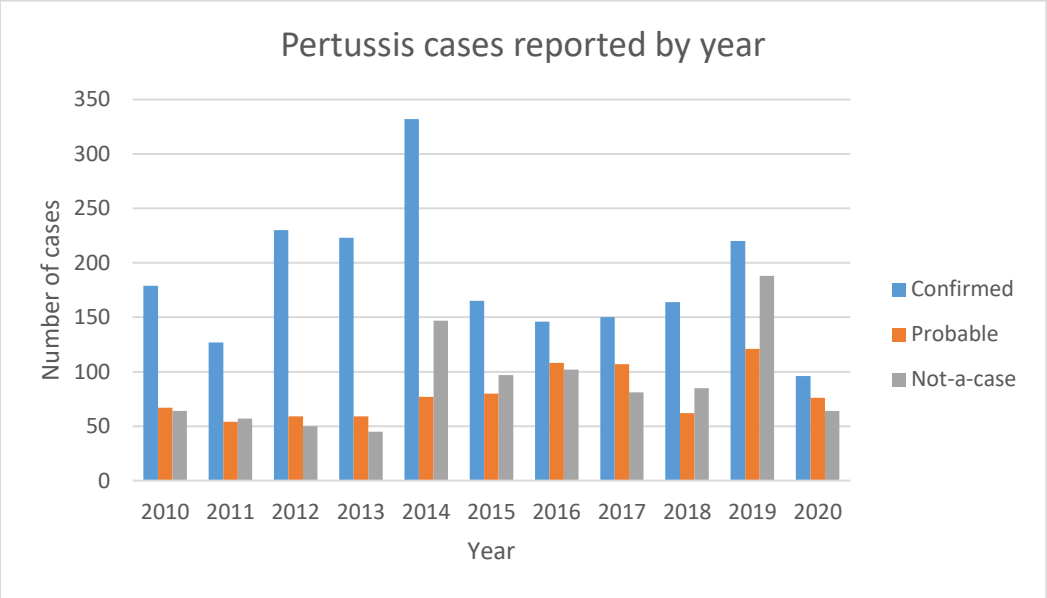

Figure 5. Trends of pertussis cases in Georgia from 2010 – 2020.

1. Characteristics of reported pertussis cases

Description of the population

About 22% (n=867) of reported pertussis cases were among infants < 1 year. More than half (n=2,217) of the pertussis cases were reported in females, and 69% in NH Whites. The characteristics of the overall pertussis cases are summarized in **Table 5**.

Table 5. Demographic characteristics of pertussis cases in Georgia from 2010-2020 (N=3,882).

	Frequency (n)	Percent (%)	Incidence per 100,000 person-years
Age category (years)			
< 1	867	22.37	60.42
1-9	1,082	27.92	7.99
10-19	785	20.25	5.01
20-29	134	3.46	0.84
30-39	201	5.19	1.32
40-49	249	6.42	1.62
50-59	213	5.50	1.45
60-69	191	4.93	1.70
70-79	116	2.99	1.87
80+	38	0.98	1.22
Gender			
Female	2,217	57.11	3.85
Male	1,662	42.81	3.04
Race/Ethnicity			
NH[a] White	2,493	64.22	4.43
NH Black	608	15.66	1.75
Hispanic	438	11.28	0.59
NH Asian	62	1.60	0.14
Other[b]	281	7.24	4.00

[a]*NH: Non-Hispanic*

[b]*Other includes Natives, multiracial and unknown race*

Signs and symptoms

All reported case-patients presented a cough onset (N=3,882). The clinical characteristics of these cases are summarized in **Table 6**.

Table 6. Clinical characteristics by case classification of pertussis cases in Georgia from 2010-2020 (N=3,882).

	Confirmed cases (n=2,032)	Probable cases (n=870)	NACs[a] (n=980)
Signs and symptoms	**n (%)**	**n (%)**	**n (%)**
Cough	2,032 (100)	870 (100)	980 (100)
Cough duration			
< 14 days	22 (1.09)	17 (1.97)	204 (26.60)
≥ 14 days	1,987 (98.17)	833 (96.30)	381 (49.67)
Paroxysms	1,893 (93.25)	795 (91.48)	248 (25.97)
Whoop	751 (37.10)	283 (32.60)	71 (7.47)
Post-tussive vomiting	1,177 (58.01)	381 (43.79)	130 (13.60)
Apnea	361 (18.63)	54 (6.43)	33 (3.71)
Cyanosis	322 (16.86)	35 (4.24)	24 (2.64)
Fever	167 (17.47)	120 (21.13)	113 (19.19)
Complications	**n (%)**	**n (%)**	**n (%)**
Pneumonia	63 (10.90)	62 (16.45)	39 (16.88)
Seizure	16 (0.79)	3 (0.35)	2 (0.21)
Encephalopathy	8 (0.40)	6 (0.69)	3 (0.32)
Hospitalized	397 (19.54)	61 (7.01)	74 (7.55)
Died	1 (0.05)	2 (0.24)	5 (0.52)

[a]NACs: Not-a-cases

Laboratory evidence

Ninety-two percent (n=3,560) of the reported pertussis cases had laboratory testing done. PCR was ordered in 62.28% (n=2,176), whereas culture in 8.67% (n=303) only. More than 50% of the laboratory-confirmed cases were obtained from PCR (**Table 7**).

Table 7. Proportions of laboratory-confirmed pertussis cases in Georgia from 2010 – 2020.

	PCR n (%)	Culture n (%)	Other[a] n (%)
Positive n (%)	1,795 (51.37)	85 (2.43)	928 (26.56)
Negative n (%)	294 (8.41)	100 (2.86)	63 (1.8)

[a]*Other includes DFA, IgA, IgG, IgM, serology, panel, and unknown tests.*

Epidemiology

None of the case-patients reported were previously diagnosed with pertussis. Fifty-nine percent (n=1,455) were completely vaccinated, whereas 39.24% (n=965) were incompletely vaccinated and 1.59% (n=39) were unvaccinated. The vaccination history by case classification is summarized in **Table 8**. Thirty-six percent (n=1,423) of the vaccination status variable were missing values. The main reasons for being unvaccinated were: too young (n=445, 32.74%), unknown (n=423, 31.13%), parent/patient refusal (n=190, 13.98%). About 7% (n=275) cases were associated with a known pertussis outbreak, and 21.22% (n=807) were epidemiologically linked to a laboratory-confirmed case. Five percent (n=198) were employed at or attended a daycare facility, 31.60% (n=879) were at school. The transmission setting was unknown (n=2,316, 65.02%) most of the time, then at home (n=793, 22.26%) and school (n=187, 5.25%). About 78% (n=2,174) of the case-patients reported they did not spread pertussis outside their household. For infant cases, the source of infection identified was more likely from the elderly (68.09%, n=256), children 1 – 9 years (13.30%, n=50), and adolescents 10 – 19 years (6.38%, n=24). Transmission from young adults (20 – 29 years) and adults (30 – 39 years) to infants < 1 year were found in 5.05% (n=19) and 4.26% (n=16), respectively. The mother was the source of infection in 6.99% (n=29) cases.

Table 8. Vaccination history of pertussis case-patients in Georgia from 2010 – 2020 (N=2,459).

	Confirmed cases n (%)	Probable cases n (%)	NACs n (%)
Completely vaccinated	779 (31.68)	356 (14.48)	320 (13.01)
Incompletely vaccinated	584 (23.75)	164 (6.67)	217 (8.82)
Unvaccinated	30 (1.22)	4 (0.16)	5 (0.20)

Maternal TDAP Information - only for mothers of case-patients < 1 year

About 64% (n=464) of mothers have ever received the Tdap vaccine. Sixteen percent (n=117) were vaccinated during pregnancy, and 20.96% (n=96) received the shot during their third trimester. Among the 54.37% (n=249) unvaccinated mothers during pregnancy, the reason for not being vaccinated was unknown in 25.74% (n=140) cases, whereas 23.16% (n=126) did not recall being vaccinated, 21.51% (n=117) got vaccinated after pregnancy, and 10.66% (n=58) declined vaccination.

2. Variability of pertussis incidence using case definitions

From 2010 to 2019, 916 (25.12%) reported cases were classified as NACs. About nine percent (n=311) of these cases were reclassified as cases after using the new CD. Two CDs were used during that period.

First, between 2010 and 2013, 216 (17.79%) reported cases were classified as NACs using the 2010 CSTE/CDC case definition. Seven percent (n=85, 95% CI: [4.23% – 9.77%]) of these cases were reclassified as cases, either confirmed or probable, after using the 2020 CSTE/CDC case definition. This comparison is shown in **Table 9**.

Table 9. Pertussis case classification in Georgia from 2010 – 2013 (N=1,214).

	2010 CD[a] n (%)	**2020 CD n (%)**	**Difference n (%) = 2020 CD – 2010 CD**	**95% CI[b] [%]**
Case[c]	998 (82.21)	1083 (89.21)	-85 (-7.00)	[-9.77 – -4.23]
NAC[d]	216 (17.79)	131 (10.79)	85 (7.00)	[4.23 – 9.77]

[a]CD: Case definition

[b]CI: Confidence interval

[c]Case includes confirmed and probable

[d]NAC: Not-a-case

Then, between 2014 and 2019, 700 (28.78%) reported cases were classified as NACs using the 2014 CSTE/CDC case definition. Nine percent (n=226, 95% CI: [6.90% – 11.68%]) of these cases were reclassified as cases, either confirmed or probable, after using the 2020 CSTE/CDC case definition. This comparison is shown in **Table 10**.

Table 10. Pertussis case classification in Georgia from 2014-2019 (N=2,432).

	2014 CD[a] n (%)	2020 CD n (%)	Difference n (%) = 2020 CD – 2014 CD	95% CI[b] [%]
Case[c]	1,732 (71.22)	1,958 (80.51)	-226 (-9.29)	[-11.68 – -6.90]
NAC[d]	700 (28.78)	474 (19.49)	226 (9.29)	[6.90 – 11.68]

[a]CD: Case definition
[b]CI: Confidence interval
[c]Case includes confirmed and probable
[d]NAC: Not-a-case

In 2020, the new CD classified 96 (40.68%) reported cases as confirmed, 76 (32.20%) as probable, and 64 (27.12%) as NACs. Fifty-eight percent (n=137, 95% CI: [50.79% – 65.31%]) of these cases would have been missed if the 2014 CSTE/CDC case definition was still in use. This comparison is shown in **Table 11**.

Table 11. Reclassification of the 2020 pertussis cases using the 2014 CD (N=236).

	2020 CD[a] n (%)	2014 CD n (%)	Difference n (%) = 2020 CD – 2014	95% CI[b] [%]
Case[c]	172 (72.88)	35 (14.83)	137 (58.05)	[50.79 – 65.31]
NAC[d]	64 (27.12)	201 (85.17)	-137 (-58.05)	[-65.31 – -50.79]

[a]CD: Case definition
[b]CI: Confidence interval
[c]Case includes confirmed and probable
[d]NAC: Not-a-case

Overall, between 2010 and 2020, 2,765 (71.23%) reported cases were considered as pertussis cases (confirmed and probable), and 1,117 (28.77%) were NACs, using the 2010 CSTE/CDC case definition from 2010 – 2013, and the 2014 CSTE/CDC case definition from 2014 – 2019. After reclassification based on the 2020 CSTE/CDC case definition, 3,213 (82.77%) were considered as cases, whereas 669 (17.23%) were NACs (**Figure 6**). There were 448 (11.54%, 95% CI: [9.69% – 13.40%]) cases captured with the new CD.

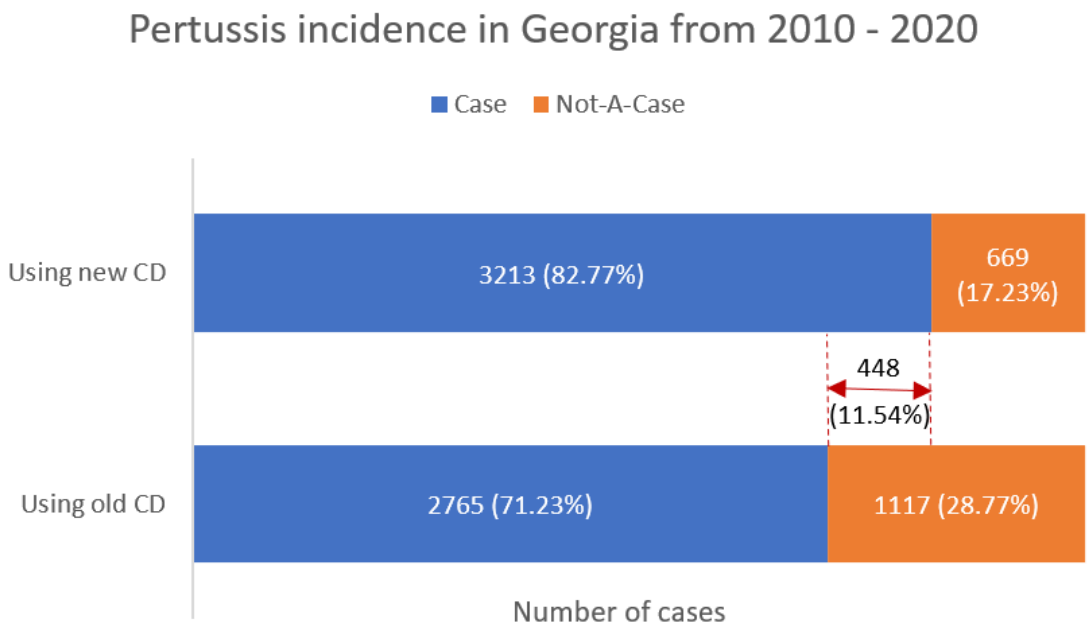

Figure 6. Pertussis incidence in Georgia from 2010 – 2020 using the old and new case definitions.

The incidence rates of these pertussis cases calculated from the total population (N= 112,338,777) in Georgia from 2010 – 2020 are shown in **Table 12**.

Table 12. Incidence rates of pertussis cases in Georgia from 2010 – 2020 based on case definitions (N= 112,338,777).

Incidence rate	Old CD[a]	New CD
Case[b] (per 100,000 person years)	2.46	2.86
NAC[c] (per 100,000 person-years)	0.99	0.60

[a]*CD: Case Definition*
[b]*Case includes confirmed and probable*
[c]*NAC: Not-a-case*

3. Assessment of the 2020 CSTE/CDC case definition

In the two-by-two table below (**Table 13**), 448 is hypothetically false negative or false non-pertussis cases. By deducting it from the total reported as pertussis cases under the old CD, 2,317 would be true positive or true pertussis cases. In the same way, subtracting the false negative from the total reclassified as non-pertussis cases under the new CD would give 221 true negative or true non-pertussis cases. Consequently, 896 would be false positive or false pertussis cases.

Table 13. Two-by-two table comparing the old CD and the new CD.

		Old CD[a]		
		Case (n)	**NAC (n)**	**Total**
New CD	**Case[b] (n)**	2,317	896	3,213
	NAC[c] (n)	448	221	669
	Total	2,765	1,117	3,882

[a]CD: Case Definition
[b]Case includes confirmed and probable
[c]NAC: Not-a-case

As a result, the new CD has an estimated sensitivity of 83.80% (±0.70%, 95% CI: [82.42% – 85.17%]), a specificity of 19.79% (±1.19%, 95% CI: [17.45% – 22.12%]), a predictive value positive of 72.11% (±0.79%, 95% CI: [70.56% – 73.66%]), and a predictive value negative of 33.03% (±1.82%, 95% CI: [29.47% – 736.60%]) (**Table 14**).

Table 14. Measures of validity of the new pertussis case definition.

Measures	**Estimate %**	**Standard Error %**	**95% CI[a] %**
Sensitivity	83.80	0.70	[82.42 – 85.17]
Specificity	19.79	1.19	[17.45 – 22.12]
PVP[b]	72.11	0.79	[70.56 – 73.66]
PVN[c]	33.03	1.82	[29.47 – 36.60]

[a]CI: confidence interval
[b]PVP: predictive value positive
[c]PVN: predictive value negative

Chapter V – Discussion and Conclusions

Pertussis is a remerging infectious disease that needs better control and surveillance.

Our findings show that reported pertussis cases were high in Georgia in 2014. It could be related to the application of the 2014 CSTE/CDC case definition that addressed the significant numbers of infant cases with positive PCR results but not meeting the required clinical criteria. A previous study conducted at the Georgia Department of Public Health (DPH) reported an 11.4% increase in the number of infant cases between 2010 and 2013, using this 2014 CSTE/CDC case definition (Thomas & Tuttle, 2016).

The results show no differences in pertussis incidence across gender and race/ethnicity. However, the disease burden is higher among infants < 1 year, consistent with other studies (Gabutti et al., 2015). In the U.K., the highest pertussis mortality rate occurred in this age group (Billingsley, 2012). More precisely, children under 6 months of age have been reported to present severe and life-threatening disease manifestations (Arehart et al., 2019).

The clinical characteristics pointed out that cough is a constant sign observed in all reported cases. Usually, the cough worsens in both frequency and degree over a 7- to 14-day period (Mattoo & Cherry, 2005). The proportion of patients having a cough duration < 14 days or ≥ 14 days is almost the same between confirmed and probable cases, but nearly half of the NACs had a cough more than 14 days. So, cough duration was inconsistent across case classification. Similarly, the other signs and symptoms were not significantly different between confirmed and probable cases, and they were irregular for NACs.

Regarding the complications, hospitalization was 3 times higher among confirmed than probable cases. However, fewer pertussis-related deaths (0.29%) were reported in Georgia between 2010 and 2020 compared to 58% of estimated deaths in the African region (Yeung et al., 2017). The WHO reported an average range of pertussis mortality rates between 3 and 10 per 1 million births in high-income countries from 2003 – 2012 (Chow et al., 2016).

The present study shows a greater proportion of laboratory-confirmed pertussis cases obtained from PCR than culture or other laboratory tests. Indeed, it aligns with the CSTE's objective to rely on a frequently used diagnostic tool than the inconsistent duration of cough. Although culture is more specific than PCR, it is only sensitive at 60% if the samples are collected within the first 2 –

3 weeks after cough onset (WHO, 2014). Serology was among the earliest confirmation diagnostic tools of pertussis, but previous vaccinations or infections, cross-reactivity with other *Bordetella* species, and variable response to *B. pertussis* antigens can interfere with the serodiagnosis (van der Zee et al., 2015). Nevertheless, it was found that positivity with serological diagnosis (IgA and IgG titers) improved with increasing age and duration of disease (van der Zee et al., 1996).

The missing values in the vaccination status variable did not allow a comprehensive vaccination history by age group. However, children aged 7 – 10 years are considered susceptible to waning immunity despite having completed the DTaP vaccination series because they would have not yet received the Tdap booster recommended at age 11 – 12 years (Winter et al., 2012). Also, being too young was the most frequent (32.74%) reason for not being fully vaccinated against pertussis, as mentioned in other publications (Chow et al., 2016).

Usually, young infants contract pertussis from their mothers, but we found the source of infection was more likely from the elderly (68.09%, n=256), older children (13.30%, n=50), and adolescents (6.38%, n=24). In cases where the mothers were the source of infection, the onset of symptoms occurred in the pregnant women before delivery (de Greeff S. C. et al., 2010). Thus, vaccination of mothers during pregnancy or post-partum has been adopted as a prevention method. Also, the cocooning strategy that consists of vaccinating individuals in close contact with infants too young to receive the vaccine is recommended (Althouse & Scarpino, 2015).

In 2020, we noticed that pertussis incidence in Georgia was lower compared to that of previous years. The COVID-19 pandemic might have impacted the reporting of notifiable diseases in general during that time. Still, fifty-eight percent (n=137) of pertussis cases would have been missed in 2020 if the 2014 CSTE/CDC case definition was still in use. The incidence rate of pertussis cases was 1.16 times higher with the new CD than the old CD. Thus, specifying appropriate case definitions is essential in emerging infectious diseases to identify cases efficiently and limit their spread (Gregg, 2003). Yet, evaluating pertussis incidence is complicated due to the nonuniformity of case definitions across different surveillance systems (Kilgore et al., 2016). During the SARS outbreak in 2003, for example, a centralized assessment of reported cases by a team with clinical and public health expertise was a practical solution for addressing differences in applying case definitions (Timen et al., 2006).

Sensitivity is an essential characteristic of a case definition. It is the capacity of a surveillance system to ascertain the health problem that it is intended to detect (CDC, 2020c). Likewise, predictive value positive (PVP) is the proportion of reported or identified cases that are truly cases (CDC, 2020c). A high PVP is preferred because it permits the allocation of appropriate surveillance resources; false-positive reports may lead to unnecessary investigations and unwarranted concerns in the community (Klaucke et al., 2001). Thus, the present study suggests that the 2020 CSTE/CDC case definition detects pertussis cases at 83.80%, and the identified cases are truly cases at 72.11%.

Limitations

Although the application of the new CD seems to improve the surveillance of pertussis in our analysis, this study has encountered several limitations.

Concerning the burden of pertussis, it was not possible to specify the age of infants < 1 year by months to have a more granular analysis, as seen in other studies. For instance, Masseria et al. reported an overall pertussis incidence rate of 117.7 per 100,000 person-years among infants < 12 months, and the highest incidence rate (247.7/100,000 person-years) was found among 3-month-olds (Masseria et al., 2017).

Also, it was challenging to establish whether the pertussis vaccines received by case-patients were coherent with the recommended calendar. The de-identified data did not contain the date of birth variable to calculate age at vaccination. Thus, those who received 5 doses of pertussis-containing vaccine prior to illness onset were considered fully vaccinated in this analysis, regardless of age-appropriateness.

Next, the responses to pertussis spread outside the household during case investigations may be subject to social desirability bias as individuals would report they remained home during their infectious period. Reporting bias could also apply to the reasons for not being vaccinated. Further, the patient setting variables' low rate of completeness report might have overestimated the epidemiologic linkage of pertussis cases, resulting in more probable cases. Last, the estimated sensitivity of the new CD was limited to the case reporting level, but its ability to detect epidemics has not been evaluated. Validity measures of previous pertussis CDs were not available to compare with those of the new CD; the outcomes only indicate that it is more sensitive than

specific and has a better PVP than PVN. Although our results may not be generalizable across the U.S., they can still be used as benchmarks for future research.

In conclusion, pertussis remains a public health issue with a high burden among infants < 1 year. Changing the clinical criteria of illness of cough ≥ 2 weeks to cough of any duration, and accounting PCR-positive cases as laboratory-confirmed cases were found to be effective in capturing more pertussis cases in Georgia. Despite the limitations of this study, it demonstrates the usefulness of updating case definitions with reliable diagnostic tools. These findings can be used to reinforce the capacity of health districts and public health departments to identify pertussis cases accurately and deploy the necessary resources. Standardized and evidence-based tools are essential for notifiable diseases surveillance to monitor trends and stop epidemics on time. Future research could expand on adopting an integrated approach to surveillance of emerging infectious diseases.

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