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Burden of disease and predictors of clinically diagnosed pertussis within a surveillance system, Guatemala, 2007-2011

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An abstract of
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2012

Abstract

Burden of disease and predictors of clinically diagnosed pertussis within a surveillance system, Guatemala, 2007-2011

By Antoinette Nguyen

Background: Pertussis, or whooping cough, is a highly contagious respiratory infection that remains a cause of severe debilitating illness in young children. Pertussis is often diagnosed based only on clinical signs, symptoms, vitals and basic laboratory values. Since the incidence of pertussis, especially among early infants, within our surveillance system in Guatemala, the aim of this study is to determine the burden of clinical pertussis. Since many pertussis cases are diagnosed clinically without laboratory confirmation, this study also explores the predictors of pertussis.

Methods: We utilized surveillance data from the *Vigilancia Comunitaria* (ViCo) project in Guatemala which collected biological samples, demographic, risk factor and health history information to identify patients admitted with symptoms suggesting diarrhea, respiratory disease or unspecified febrile illness. Incidence rate analyses was calculated for the total ViCo population while vaccine efficacy analyses was only calculated for children <5 years of age. We used multivariate logistic regression to determine the predictors of pertussis.

Results: The total ViCo population included 64,999 persons while sub-analysis for predictor selection and modeling were computed on a population of 9,152 persons. We determined an annual incidence (cases per 100,000 population) of 283 in the total ViCo population and 320 among children <1 year of age. There was an initial peak in incidence among children <2-5 months of age (625) that then declined to a trough among children 2-4 years (119). A second peak (1095) was observed among those ≥65 years of age. The DTP vaccine efficacy among children <5 years of age was 54.97%. The following predictors were significantly associated with pertussis: age, health facility, department, cough duration, vomiting (□=0.05).

Conclusion: In conclusion, diagnosing pertussis in infants is crucial since the burden of disease and rates of complication and death are highest in this population. From our analysis, the burden of disease, especially among early infants, is significant in our surveillance system in Guatemala. Further studies should be completed to examine the relationship between clinical and lab-confirmed diagnosis, which would help elucidate the sensitivity and specificity of a clinical case definition in a non-outbreak setting with limited resources for laboratory confirmation.

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INTRODUCTION

Pertussis, or whooping cough, is a highly contagious respiratory infection that remains a cause of severe debilitating illness in young children. Even after the introduction of large-scale vaccination during the 1950s-1960s, incidence in developed countries has slowly increased since 1976 [1-5].

Estimates from the World Health Organization (WHO) suggest that, in 2008, there were about 16 million cases worldwide and 195,000 deaths, mainly among infants in developing countries [6]. The burden of disease and rates of complication and death – most commonly due to secondary bacterial pneumonia – are highest among infants ≤6 months of age, most too young to have completed their primary series of tetatus toxoid, diphtheria toxoid, and pertussis antigen vaccines (DTP) [1, 4, 7, 8].

The WHO recommends primary DTP doses at the ages of 6, 10, and 14 weeks with the last dose completed by the age of 6 months [9]. In Guatemala, the tetatus and reduced diphtheria (Td) booster vaccine is recommended every 10 years. There are currently no special considerations for pregnant women or recommendations for Td or Tdap vaccination during pregnancy [9]. However, in 2011 in the U.S., the Advisory Committee on Immunization Practices (ACIP) recommended the tetanus, reduced diphtheria, and acellular pertussis antigens vaccine (Tdap) during pregnancy as a means to protect the infant and prevent infant pertussis cases [7, 10, 11].

The Centers for Disease Prevention and Control (CDC) and WHO employ similar definitions for pertussis case definition in the absence of laboratory

confirmation (Appendix A). Both definitions define a clinical pertussis case as a person with cough for 14 days plus one of the following: paroxysmal cough, inspiratory whooping and posttussive vomiting, without other apparent cause [3]. The CDC additionally stipulates that in an outbreak setting, a clinical diagnosis can be made with only an acute cough for 14 days [3, 12].

Multiple factors may complicate diagnosis, including wide heterogeneity in disease expression, modification of disease by immunization, mixed infections and a low index of suspicion among many physicians [13-15]. Pertussis is often diagnosed based only on clinical signs, symptoms, vitals and basic laboratory values [16]. Therefore, case-reporting is likely severely underestimated, especially in developing countries and for mild cases in adults [17].

Since the incidence of pertussis, especially among early infants, among our study population is currently unknown, the aim of this study is to determine the burden of clinical pertussis. Since many pertussis cases are diagnosed clinically without laboratory confirmation, this study also explores the predictors of pertussis within our surveillance system in Guatemala.

METHODS

Study Design.

This study utilized data from the *Vigilancia Comunitaria* (ViCo) project, an active public health surveillance system implemented by the Center for Health Studies of Universidad del Valle de Guatemala (CHS-UVG) and the International Emerging Infectious Program (IEIP) of the Centers for Disease Control and Prevention's regional office for Central America and Panama (CDC-CAP). Starting in June 2007, participants were systematically entered into the ViCo project following surveillance conducted at the national hospitals and of the health centers and health posts of selected municipalities in the departments of Santa Rosa, Quetzaltenango, and Guatemala.

At each site, paid surveillance staff actively searched the emergency room, inpatient logs and laboratory and radiology registers to identify patients admitted with symptoms suggesting diarrhea, respiratory disease or unspecified febrile illness. After obtaining written, informed consent from patients or their caregivers, clinical information was gathered to determine whether patients met inclusion and exclusion criteria (Appendix B).

Data Collection.

The ViCo sites currently have a well-established facility-based surveillance system. The study data was collected primarily using electronic case report forms/data instruments on hand-held personal digital assistants (PDAs) with preprogrammed range and skip patterns. Those who satisfied inclusion and

exclusion criteria were admitted into the project and appropriate biological samples, demographic, risk factor and health history information was taken to assist in the diagnosis of the etiologic agent of their disease. However, none of the biological samples from project participants were tested for pertussis so there is no laboratory confirmation of pertussis disease.

Setting.

The project collected data from patients who presented to the national hospitals and the health centers and health posts of selected municipalities in the departments of Santa Rosa, Quetzaltenango and Guatemala.

Guatemala is divided into 23 administrative departments, each of which is sub-divided into approximately 10-14 municipalities. Each department roughly corresponds to a “health area” that is responsible for all public health activities in its catchment area. There is generally one regional (referral) or departmental hospital per health area; each municipality corresponds to a “health district” and has at least 1 health center and several health posts.

The department of Santa Rosa has an area of 3,164 km^2 has a population of 308,522 and is divided into 14 municipalities. The department of Quetzaltenango has a population of 780,000 living in an area of 2,132 km^2. Located west of Guatemala City, the Quetzaltenango department has 24 municipalities. The departments of Santa Rosa and Quetzaltenango have a combined annual birth cohort of 15,000.

VARIABLES

Dependent Variable.

The main outcome variable was the clinical diagnosis of pertussis based upon WHO and CDC criteria: a cough lasting at least 14 days with at least one of the following symptoms: paroxysmal cough, inspiratory whooping and posttussive vomiting.

Due to the skip pattern of the ViCo questionnaire, the presence of pertussis symptoms – paroxysmal cough, inspiratory whooping and posttussive vomiting – were only asked if the patient or patient's caregiver indicated the presence of an acute cough lasting at least 7 days (ambulatory settings) or 14 days (hospital setting). Therefore, since respondents who did not meet the duration of cough criteria for pertussis diagnosis were not asked any of the symptomatic pertussis questions, there were disproportionately more missing values for those variables amongst the pertussis negative group compared to the pertussis positive group.

Predictors.

Age, gender, health facility[1], department, year, age-appropriate DTP vaccination[2], education[3] and family monthly income (in US dollars) were grouped into demographics. History, signs and symptoms that were analyzed were presence of cough, duration of cough and presence of paroxysmal cough, whoop, posttussive vomit, self-reported fever, vomiting (including posttussive),

[1] Presentation to hospital versus ambulatory site, which combined health centers and health posts
[2] Age-appropriate dosing per WHO recommendations among children <5 years old defined as dose 1 before age 3 months, dose 2 before age 5 months and dose 3 before age 7 months
[3] If patient <18 years of age, answered by patient's parent/tutor

recent use of antibiotics and other respiratory diagnosis upon discharge. Physical findings that were analyzed included measured fever (≥38°C), hypoxia (% oxygen saturation ≤94%) and abnormal breath sounds on exam (crackles/rales, wheezes or rhonchi). Table 4 presents this classification schema.

DATA ANALYSES

All analyses were performed using SAS statistical software, version 6.3 (Cary, NC). Following Kleinbaum's variable specification strategy, statistical significance was set at □=0.25, two-tailed, during the selection of predictors to include in the model [18]. For all other analyses, statistical significance was set a priori at □=0.05, two-tailed.

Incidence Analyses.

We determined the incidence rate of clinical pertussis within our ViCo surveillance population for the time period from June 1, 2008 to July 31, 2011 (43 months or 3.58 years). This was defined as the incidence of new cases of pertussis within our "at risk" population during this given period. Since individual follow-up was unknown for our study population, person-time was calculated by the following: (total population in surveillance project) x (time length of the study period). Therefore, the denominator of our rate included all persons initially surveyed for inclusion into the ViCo surveillance project. The incidence rates were then stratified by age categories (Table 1, Figure 1). This method assumes a stable, dynamic cohort and a small number of new cases.

Vaccine Efficacy Analysis.

The incidence rates of pertussis were stratified by age-appropriate DTP vaccination status[4] (Figure 2). This analysis was only calculated for the population of children <5 years of age since vaccination history was collected only for this sub-population.

DTP vaccine efficacy was measured by calculating the incidence rates (attack rates) of pertussis disease among vaccinated and unvaccinated persons and determining the percentage reduction in the incidence rate of disease among vaccinated persons compared to unvaccinated persons [19]. The basic formula was:

$$VE = \frac{ARU - ARV}{ARU} \times 100$$

where VE = vaccine efficacy, ARU = attack rate in the unvaccinated population, and ARV = attack rate in the vaccinated population. A child was considered vaccinated if s/he had received age-appropriate DTP vaccination[4]. A child was considered unvaccinated if s/he had reported zero DTP doses. Persons of unknown vaccination status or with an incomplete series of vaccinations were excluded from these calculations.

Descriptive and Crude Analyses.

For the first part of this analysis, a contingency table was built exploring the predictor exposure amongst pertussis positive and pertussis negative persons

[4] Age-appropriate dosing per WHO recommendations among children <5 years old defined as dose 1 before age 3 months, dose 2 before age 5 months and dose 3 before age 7 months

confined to the population of persons who met our own study definition for suspected respiratory illness (Appendix C) among all persons initially surveyed for the ViCo project (Table 3).

For the second part of this analysis (Table 4) as well as the stratified and multivariate logistic analyses, we only included persons who met 1) ViCo surveillance system case definition for febrile, respiratory and/or diarrheal illness (Appendix B) and 2) our own study definition for suspected respiratory illness (Appendix C) (Figure 3). The questionnaire only collected basic demographic and clinical information from all persons who were surveyed; more detailed data points, including most of the predictors we were studying, were only asked if the person met the ViCo inclusion and exclusion criteria. As the objective of these analyses was to determine predictors of clinical pertussis cases, we further confined our study to only those who would be deemed "at-risk" for respiratory illness by a physician, either by clinical signs/symptoms and/or physical exam. Therefore, in order to statistically compare exposure to the predictors in the pertussis group to the non-pertussis group, analyses were confined to persons who met both of the above criteria.

A contingency table was built for each predictor and outcome combination in order to calculate the frequency distributions and chi-square statistics along with their associated p-values. This was done in order to assess whether there were significant differences in exposure/predictor frequencies between those who met and those who did not meet the clinical diagnostic criteria for pertussis (Table 4). Unadjusted (crude) odds ratios and 95% confidence intervals were

then calculated to determine the association between each predictor and outcome variable separately (Table 5).

Predictor Selection.

All covariates whose chi-squared p-values (Table 4) were <0.25 and did not have ≥80% missing value were entered into the initial model (Model 1). The predictor of age-appropriate DTP vaccination was not included in Model 1 since the data was only collected of ViCo respondents who were less than 5 years of age. This full model was assessed for collinearity by determining p-values and variance inflation factors (VIF) with a cut-off point of VIF <10 (Table 6). Inflated VIF's were resolved by the removal of the variable.

Due to the large number of covariates included, we selected the eight terms with the smallest p-values for Model 2. A Hosmer-Lemeshow goodness-of-fit (GOF) test was carried out on each model to assess how well the model fit the data.

Stratified Analyses.

Stratified analyses were performed to evaluate the association of the outcome variable (clinical pertussis) with each of the eight selected predictors, controlling separately for each covariate (Tables 7-27). Adjusted odds ratios and 95% confidence intervals were calculated and compared to the unadjusted (crude) odds ratios. A variable was considered a confounder if the two odds ratios were meaningfully different by 10-20%. Any variable found to be a confounder was included in the model.

Multivariate Logistic Analysis.

A logistic regression model was created with the categorical variable of clinical pertussis designated as the outcome. Model 1 included all covariates whose chi-square p-values were <0.25 as well as having <80% missing values (Table 4). This was reduced to Model 2 by only including the eight predictors with the smallest p-values. Potential confounders were then entered into the model, forming Model 3 (Table 27). The final model – Model 4 – was selected using backwards elimination following the removal of 12 variables (Table 28). A Hosmer-Lemeshow goodness-of-fit test was carried out on the final model.

RESULTS

Total Study Population

From June 1, 2007 to July 31, 2011, a total of 64,999 persons were included in the ViCo surveillance project. Of that original population, about 47 percent (n=30,287) met our study definition for suspected respiratory illness. The total ViCo population (n=64,999) was used to analyze incidence rates of pertussis cases.

Incidence Analyses. The annual incidence rate was 283 pertussis cases per 100,000 population among all persons initially included in the ViCo project. When stratified by age categories, there was an initial peak in the incidence rate among children < 2-5 months of age (625 cases per 100,000 population) that then declined to a trough of 119 cases per 100,000 population among children 2-4 years. A second peak (1095 cases per 100,000 population) was then observed among those ≥65 years of age (Table 1, Figure 1). For all children <1 year of age, the incidence was 320 cases per 100,000 population.

Vaccine Efficacy Analysis. DTP vaccine status was known in 7,385 of 33,806 children <5 years of age (21.85%) (Table 2). Numbers of DTP doses received among the age groups <5 years of age are given in Table 2.

Among children <5 years of age who entered the ViCo surveillance project, the incidence of pertussis was 583 cases per 100,000 population. There was a much higher incidence rate of pertussis among those children who had not

received age-appropriate DTP vaccinations: 1058 versus 408 cases per 100,000 population among children <5 years (Figure 2).

The attack rate of pertussis in the unvaccinated population (children who had received zero doses of DTP vaccine) was 906 cases per 100,000 population. The attack rate in the vaccinated population (children who were age-appropriately vaccinated) was 408 cases per 100,000-years. Therefore, the DTP vaccine efficacy among children <5 years of age was 54.97%.

Comparison of Predictors. Six hundred fifty-eight pertussis cases were found among all persons enrolled in the ViCo system between June 2007 to July 2011 (Table 3). Among these cases, the mean age was 27.09 years ± 28 years; 160 persons (24.3%) were younger than 12 months, 322 (48.9%) were male and 452 (68.7%) had presented to a hospital. Of the 658 cases, 110 (16.7%) were from Guatemala department, 212 (32.2%) from Santa Rosa, 192 (29.2%) from Quetzaltenango and 144 (21.9%) were from some other department. No cases were from 2007, 9 (1.4%) from 2008, 109 (16.6%) from 2009, 238 (36.2%) from 2010 and 302 (45.9%) from 2011. Among children <5 years of age with pertussis, 67 (25.7%) had age-appropriate DTP vaccination.

The distribution and frequency of patient characteristics, stratified by pertussis status, among all respondents in the ViCo project with suspected respiratory illness were statistically different according to age, health facility, department, year, and DTP vaccination status (Table 3).

Sub-Population of ViCo cases with suspected respiratory illness.

For the logistic regression analyses, the original ViCo population (n=64,999) was first stratified by ViCo case status, resulting in 12,448 (19.2%) ViCo cases and then further stratified by suspected respiratory illness status. The final study population only included those persons who met both ViCo case definition and study definition of suspected respiratory illness (n=9,152) (Figure 3).

Comparison of Predictors. The distribution and frequency of the predictors of pertussis are presented in Table 4. Using a chi-square p-value of 0.25 (see methods section), those with pertussis versus those without pertussis were statistically different with regards to the predictors of age, health facility, department, year, age-appropriate DTP vaccination, education, family monthly income, cough, cough duration and the presence of paroxysmal cough, whoop, posttussive vomit, self-reported fever, vomiting (including posttussive), recent use of antibiotics, other respiratory diagnosis upon discharge, measured fever (≥38°C), hypoxia (% oxygen saturation ≤94%) and abnormal breath sounds on exam (crackles/rales, wheezes or rhonchi). Therefore, all predictors were significant except for gender.

Those classified as having a clinical diagnosis of pertussis were more likely to be female; have presented to a hospital; be from Guatemala, Quetzaltenango or "other" departments; have no education or secondary education; have family monthly income of $375-625; and have signs and symptoms of cough, cough lasting 14-20 days as well as over 3 weeks; paroxysmal cough; whoop; posttussive

vomit; vomiting (including posttussive); recent use of antibiotics; having a respiratory diagnosis other than pertussis at discharge; and abnormal breath sounds on exam.

Those not classified as having pertussis were more likely to be male; have presented to ambulatory setting; be from Santa Rosa; be age-appropriately vaccinated for DTP; have primary, basic studies or superior studies; have family monthly income of <$125, $125-375 or >$625; cough lasting < 7 days or7-13 days; and self-reported fever.

Bivariate (Crude) Analyses. Table 5 provides the unadjusted odds ratios and their associated 95% confidence intervals. In crude analysis, the following variables were significantly associated with the clinical diagnosis of pertussis at □-level of 0.05: presenting to a hospital (cOR=20.73 [11.65-36.87]), "other" department (cOR=3.35 [2.59-4.34]), diagnosis during the years 2009 (cOR=7.55 [2.76-20.59]), 2010 (cOR=11.16 [4.14-30.09]), and 2011 (cOR=12.33 [4.52-33.66]), family monthly income of $375-625 (cOR=1.68 [1.05-2.69]), cough (cOR=94.32 [5.88-1512]). Strong associations were also noted with paroxysmal cough, whoop, posttussive vomit, vomiting, recent use of antibiotics, hypoxia and abnormal breath sounds.

A significant protective association at this same □ level was also found for age 0-2 months (cOR=0.15 [0.08-0.29]), age 2-5 months (cOR=0.55 [0.39-0.77]), age 6-11 months (cOR=0.68 [0.60-0.77]), age 12-23 months (cOR=0.13 [0.08-0.20]), age 2-4 years (cOR=0.15 [0.09-0.23]), age 5-17 years (cOR=0.20 [0.13-0.32]), the Santa Rosa department (cOR=0.22 [0.16-0.30]), cough lasting

≥21 days (cOR=0.65 [0.47-0.90]). A significant protective association was also seen for the predictors of self-reported fever and measured fever.

We also noted strong associations for no education (cOR=1.41 [0.99-2.01]) and secondary school no education (cOR=1.22 [0.98-1.52]) even though they were not significant at □-level.

Predictor Selection. For each model, all predictors significantly associated with the outcome (pertussis diagnosis) were entered into the model. Collinearity diagnostics were performed on the model that included all predictors with a chi-square p-value <0.25 (Table 6- Model 1), except for paroxysmal cough, whoop and posttussive vomit, which were removed due to the high number of missing values. Age-appropriate DTP vaccination was also removed since this value was only collected of ViCo respondents who were less than 5 years of age. We observed collinearity with the variable for year. Therefore, the subsequent model had year removed and included the eight terms with the smallest chi-square p-values (Table 6- Model 2), with no collinearity observed.

Stratified Analyses. The associations between each predictor in Model 2 (Table 6) and the outcome variable (pertussis diagnosis) were stratified by each of the other predictors from Model 2 (Tables 7-27). All of the variables yielded a summary odds ratio with a difference from the crude odds ratio of >10-20%. Therefore, the data-based method (10-20% guideline) yielded confounders that were included in Model 3 (Table 28).

Multivariate Logistic Analysis. The final logistic model, Model 4, was selected through backward elimination (Table 29). Those with pertussis were 3.02 times more likely to be seen in a hospital, 1.55 times more likely to be seen in Guatemala department; 2.77 times more likely to be seen in a department other than Guatemala, Santa Rosa or Quetzaltenango; 16.38 times more likely to have a cough for ≥21 days and 10.79 times more likely to have a history of vomiting (including posttussive). Those with pertussis were also 0.33 times more likely to be <2 months of age, 0.73 times more likely to be 6-11 months of age, 0.21 times more likely to be 12-23 months of age, and 0.30 times more likely to be 2-4 years of age.

DISCUSSION

Absolute numbers of cases of pertussis depend on a number of factors, including the criteria used to define and diagnose the infection. Case definitions have been established by the WHO and the CDC. However, due to unavailability and/or poorly performed laboratory tests, the lab-based confirmation of *B. pertussis* infection can be difficult, if not impossible, especially in resource-poor settings. Since none of the biological samples from ViCo project participants were tested for pertussis, there was no laboratory confirmation of pertussis disease in our study population. Therefore, we focused on the clinical case definition of pertussis in in order to determine the burden of disease, especially among early infants, in our study population.

There has been very little documented about the epidemiology of pertussis in Latin America. In our ViCo surveillance system, we determined an annual incidence of 283 pertussis cases per 100,000 population, which is notably higher than national incidences (cases per 100,000 population) in developed countries such as Spain (2.3), the United States (2.7), France (3.4), the United Kingdom (4), Australia (22-58) and Switzerland (180) [20].

When stratified by age, there was an initial peak in the incidence (cases per 100,000 population) among children < 2-5 months of age (625) that then declined to a trough of 119 among children 2-4 years. A second peak (1095) was then observed among those ≥65 years of age (Table 1, Figure 1). For all children <1 year of age, the incidence was 320, which is notably higher than previously documented incidences in Spain (118), the United States (65), France (95), Australia (154), and Canada (270) [1, 5, 13, 14, 20]. Several observational studies

suggest that early infants, especially those <6 months of age, may be at a higher risk of disease secondary to limited direct protection from immunization until the receipt of two doses of a pertussis-containing vaccine [21-23]. This high incidence could also be due to waning immunity against pertussis in those able to transmit pertussis to infants: adolescents and adults [20].

When exploring the role of DTP vaccination and clinical pertussis diagnosis, there was a high incidence of pertussis (408 cases per 100,000 population) among children <5 years of age in our study population who had received age-appropriate DTP vaccinations albeit much lower than compared to children who had not (1058 cases per 100,000 population). Therefore, in our population, the DTP vaccine has 54.97% efficacy. Efficacy data from a large trial in the USA (APERT), estimates vaccine protection from culture or PCR proven pertussis disease is 92% although protection against less severe coughing illness is likely to be only 50-60%[14, 24].

Since many pertussis cases are diagnosed clinically without laboratory confirmation, this study also sought to explore the predictors of clinical pertussis. At the demographic level, age, health facility, and department were predictors of pertussis. At the clinical level, cough duration as well as vomiting (including posttussive) were predictors of pertussis. However, it is questionable how clinically useful this data is as studies have shown that while useful in outbreak situations, the clinical case definitions are not useful in non-outbreak illness because of a low level of specificity [13]. Clinical diagnosis is also problematic due to the wide spectrum of disease manifestation and awareness of clinicians.

This surveillance system presents important strengths, including the prospective nature of the surveillance, allowing us to identify all cases that meet clinical diagnostic criteria of pertussis; a specific case definition for suspected respiratory illness that sought to clinically identify cases amongst persons who would be identified as “at-risk” by a clinician; inclusion of all age groups; and the ability to calculate population-based rates within our catchment area.

However, this surveillance system collects data only from persons who present to health facilities. While health care through governmental hospital and clinics is free and universal in Guatemala, previous healthcare utilization studies carried out in Santa Rosa (2006) and Quetzaltenango (2009) indicate that healthcare utilization of these services are 15-33% [25]. Therefore, since our study utilizes data from a health-systems-based surveillance project, this relatively low utilization of government health care services in the surveillance catchment areas likely means that the rates presented here are underestimates of the true rate of disease in the population.

In conclusion, diagnosing pertussis in infants is crucial since the burden of disease and rates of complication and death are highest in this population. From our analysis, the burden of disease, especially among early infants, is significant in our surveillance system in Guatemala. Further studies should be completed to examine the relationship between clinical and lab-confirmed diagnosis, which would help elucidate the sensitivity and specificity of a clinical case definition in a non-outbreak setting with limited resources for laboratory confirmation.

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Table 1. Incidence rate of pertussis stratified by age, among all respondents presenting to all health facilities, 2007-2011

Age	Pertussis Cases	Population	Incidence Rate*
0-2 months	13	4949	73
2-5 months	79	3528	625
6-11 months	68	5485	346
Total <1 year	160	13962	320
12-23 months	52	8342	174
2-4 years	49	11502	119
5-17 years	75	14752	142
18-49 years	150	11439	366
50-64 years	78	2604	837
≥65 years	94	2398	1095
TOTAL	658	64999	**283**

***pertussis cases/100,000 person-year**

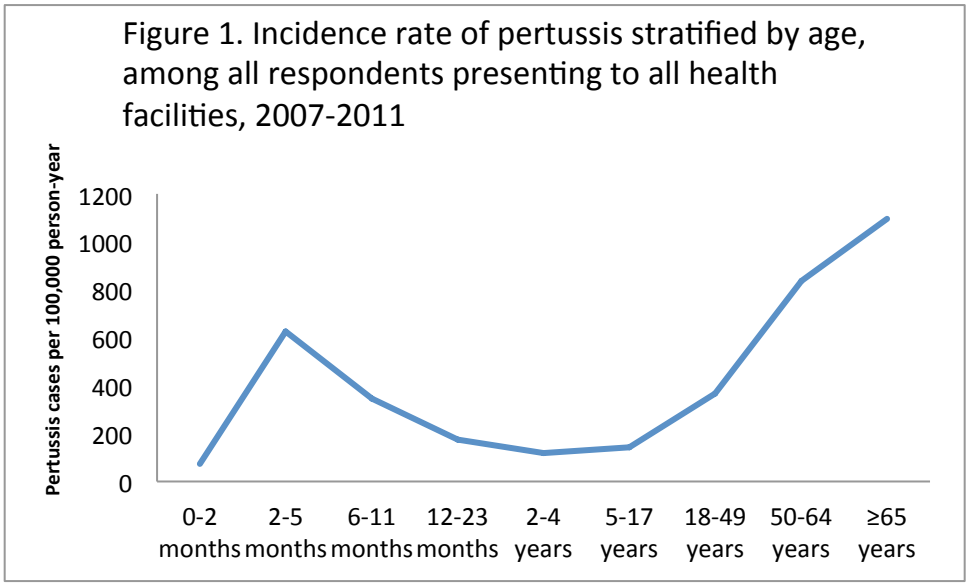
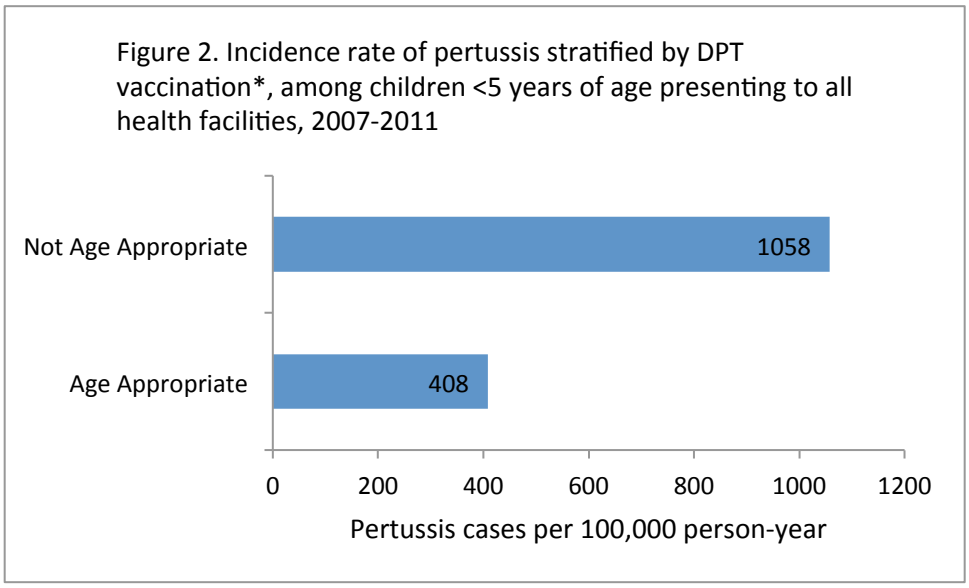


Table 2. DTP vaccination*status of children < 5 years of age presenting to all health facilities, 2007-2011

			No. of DTP doses			
Age	**Population**	**Unknown vaccination status**	**0**	**1**	**2**	**3**
0-2 months	4949	4339	573	28	4	9
2-5 months	3528	2403	299	480	306	39
6-11 months	5485	3797	110	109	387	1065
12-23 months	8342	6253	87	54	109	1824
2-4 years	11502	9587	41	52	54	1755
Total	33806	26379	1110	723	860	4692

*Received as either a part of pentavalent vaccine (DTP/Hib/Hepatitis B) or as DTP alone



*Age-appropriate dosing per WHO recommendations among children <5 years old (n=18370). Defined as dose 1 before age 3 months, dose 2 before age 5 months and dose 3 before age 7 months

Table 3. Distribution of predictors, by pertussis status, among all respondents with suspected respiratory illness presenting to all health facilities, 2007-2011

		Pertussis Positive	%	Pertussis Negative	%	Total	%	p-value
Overall		658	2.17	29629	97.83	**30287**		
								<.0001
Age	**mean +/- SD**	27.09	28.04	11.25	18.18	11.59	18.59	
								<.0001
	0-2 months	13	1.98	1258	4.25	1271	4.20	
	2-5 months	79	12.01	2290	7.73	2369	7.82	
	6-11 months	68	10.33	3492	11.79	3560	11.75	
	12-23 months	52	7.90	4711	15.90	4763	15.73	
	2-4 years	49	7.45	6358	21.46	6407	21.15	
	5-17 years	75	11.40	5712	19.28	5787	19.11	
	18-49 years	150	22.80	3883	13.11	4033	13.32	
	50-64 years	78	11.85	891	3.01	969	3.20	
	≥65 years	94	14.29	1034	3.49	1128	3.72	
	Missing	0	0.00	0	0.00	0	0.00	
Gender								0.199
	Female	336	51.06	15461	52.18	15797	52.16	
	Male	322	48.94	14044	47.40	14366	47.43	
	Missing	0	0.00	124	0.42	124	0.41	
Health Facility								<.0001
	Hospital	452	68.69	7740	26.12	8192	27.05	
	Ambulatory	206	31.31	21889	73.88	22095	72.95	
Department								<.0001
	Guatemala	110	16.72	2211	7.46	2321	7.66	
	Santa Rosa	212	32.22	17595	59.38	17807	58.79	
	Quetzaltenango	192	29.18	8666	29.25	8858	29.25	
	Other	144	21.88	1155	3.90	1299	4.29	
	Missing	0	0.00	2	0.01	2	0.01	
Year								<.0001
	2007	0	0.00	144	0.49	144	0.48	
	2008	9	1.37	1166	3.94	1175	3.88	
	2009	109	16.57	8161	27.54	8270	27.31	
	2010	238	36.17	12328	41.61	12566	41.49	
	2011	302	45.90	7830	26.43	8132	26.85	
Age-appropriate DTP vaccination*								<.0001
	Yes	67	25.67	3420	18.89	3487	18.98	
	No	64	24.52	1341	7.41	1405	7.65	
	Missing	130	49.81	13348	73.71	13478	73.37	
	Total	261		18109		18370		

*Age-appropriate dosing per WHO recommendations among children <5 years old (n=18370). Defined as dose 1 before age 3 months, dose 2 before age 5 months and dose 3 before age 7 months

Figure 3. Study population for multivariate logistic modeling

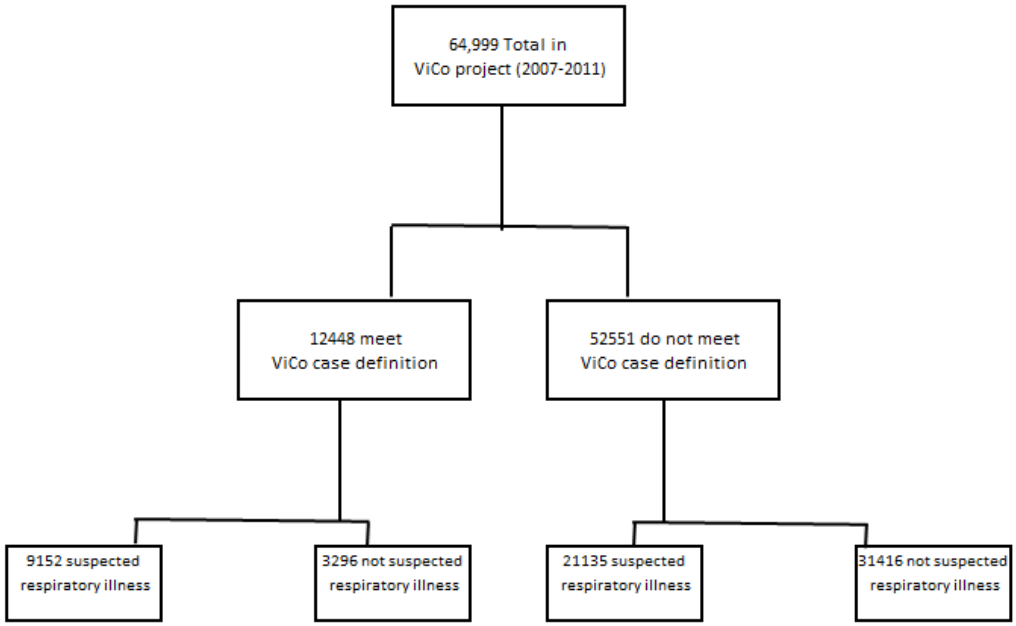


Table 4. Distribution of predictors, by pertussis status, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

		Pertussis Positive	%	Pertussis Negative	%	Total	%	p-value
Overall		409	4.47	8743	95.53	**9152**		
Demographics								
Age								**<.0001**
	mean +/- SD	27.27	29.27	10.55	19.95	11.3	20.75	
								<.0001
	0-2 months	11	2.69	606	6.93	617	6.74	
	2-5 months	65	15.89	984	11.25	1049	11.46	
	6-11 months	53	12.96	1405	16.07	1458	15.93	
	12-23 months	25	6.11	1626	18.60	1651	18.04	
	2-4 years	28	6.85	1596	18.25	1624	17.74	
	5-17 years	26	6.36	1074	12.28	1100	12.02	
	18-49 years	85	20.78	709	8.11	794	8.68	
	50-64 years	49	11.98	310	3.55	359	3.92	
	≥65 years	67	16.38	433	4.95	500	5.46	
	Missing	0	0.00	0	0.00	0	0.00	
Gender								0.6371
	Female	194	47.43	4043	46.24	4237	46.30	
	Male	215	52.57	4700	53.76	4915	53.70	
	Missing	0	0.00	0	0.00	0	0.00	
Health Facility								**<.0001**
	Hospital	397	97.07	5375	61.48	5772	63.07	
	Ambulatory	12	2.93	3368	38.52	3380	36.93	
Department								**<.0001**
	Guatemala	102	24.94	1623	18.56	1725	18.85	
	Santa Rosa	48	11.74	4025	46.04	4073	44.50	
	Quetzaltenango	132	32.27	2405	27.51	2537	27.72	
	Other	127	31.05	690	7.89	817	8.93	
	Missing	0	0.00	0	0.00	0	0.00	
Year								**<.0001**
	2007	0	0.00	117	1.34	117	1.28	
	2008	4	0.98	793	9.07	797	8.71	
	2009	94	22.98	2470	28.25	2564	28.02	
	2010	215	52.57	3820	43.69	4035	44.09	
	2011	96	23.47	1543	17.65	1639	17.91	
Age-appropriate DTP vaccination*								**<.0001**
	Yes	67	36.81	3420	55.01	3487	54.49	
	No	64	35.16	1340	21.55	1404	21.94	
	Missing	51	28.02	1457	23.44	1508	23.57	
	Total	182		6217		6399		
Education**								**0.0206**
	None	106	25.92	1873	21.42	1979	21.62	
	Primary school	207	50.61	4607	52.69	4814	52.60	
	Basic studies	45	11.00	1120	12.81	1165	12.73	
	Secondary school	40	9.78	664	7.59	704	7.69	
	Superior studies	10	2.44	399	4.56	409	4.47	
	Missing	1	0.24	80	0.92	81	0.89	

Family monthly income* **								**<.0001**
	< $125	213	52.08	4975	56.90	5188	56.69	
	$125 - 375	119	29.10	2806	32.09	2925	31.96	
	$375-625	22	5.38	308	3.52	330	3.61	
	> $625	2	0.49	105	1.20	107	1.17	
	Missing	53	12.96	549	6.28	602	6.58	
History, Signs and Symptoms								
Cough								**<.0001**
	Yes	409	100.0	6438	73.64	6847	74.81	
	No	0	0.00	741	8.48	741	8.10	
	Missing	0	0.00	1564	17.89	1564	17.09	
Cough Duration								**<.0001**
	<7 days	0	0.00	3669	41.97	3669	40.09	
	7-13 days	0	0.00	1045	11.95	1045	11.42	
	14-20 days	280	68.46	152	1.74	432	4.72	
	≥21 days	129	31.54	108	1.24	237	2.59	
	Missing	0	0.00	3769	43.11	3769	41.18	
Paroxysmal cough								**<.0001**
	Yes	277	67.73	346	3.96	623	6.81	
	No	132	32.27	812	9.29	944	10.31	
	Missing	0	0.00	7585	86.76	7585	82.88	
Whoop								**<.0001**
	Yes	186	45.48	264	3.02	450	4.92	
	No	222	54.28	889	10.17	1111	12.14	
	Missing	1	0.24	7590	86.81	7591	82.94	
Posttussive vomit								**<.0001**
	Yes	278	67.97	431	4.93	709	7.75	
	No	131	32.03	727	8.32	858	9.38	
	Missing	0	0.00	7585	86.76	7585	82.88	
Fever, self-reported								**<.0001**
	Yes	282	68.95	6303	72.09	6585	71.95	
	No	124	30.32	2005	22.93	2129	23.26	
	Missing	3	0.73	435	4.98	438	4.79	
Vomiting, including posttussive								**<.0001**
	Yes	285	69.68	2368	27.08	2653	28.99	
	No	124	30.32	6375	72.92	6499	71.01	
	Missing	0	0.00	0	0.00	0	0.00	
Recent use of antibiotics								**<.0001**
	Yes	145	35.45	2100	24.02	2245	24.53	
	No	89	21.76	2893	33.09	2982	32.58	
	Missing	175	42.79	3750	42.89	3925	42.89	
Other respiratory diagnosis upon discharge								**0.1368**
	Yes	39	9.54	659	7.54	698	7.63	
	No	370	90.46	8084	92.46	8454	92.37	
	Missing	0	0.00	0	0.00	0	0.00	
Physical Findings								
Fever, Temp ≥38°C								**<.0001**
	Yes	135	33.01	4270	48.84	4405	48.13	
	No	266	65.04	4132	47.26	4398	48.06	
	Missing	8	1.96	341	3.90	349	3.81	

Hypoxia (%O2 saturation ≤94%)							**<.0001**
	Yes	32	7.82	3204	36.65	3236	35.36
	No	377	92.18	5539	63.35	5916	64.64
	Missing	0	0.00	0	0.00	0	0.00
Breath sounds (crackles/rales, wheezes, rhonchi)							**<.0001**
	Yes	344	84.11	4298	49.16	4642	50.72
	No	65	15.89	4445	50.84	4510	49.28
	Missing	0	0.00	0	0.00	0	0.00

*Age-appropriate dosing per WHO recommendations among children <5 years old (n=18370). Defined as dose 1 before age 3 months, dose 2 before age 5 months and dose 3 before age 7 months

**If patient <18 years of age, answered by patient's patient/tutor

***Income in US dollars

Table 5. Predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

		Pertussis Positive	%	Crude OR	(95%CI)	p-value
Demographics						
Age						
	0-2 months	11	2.69	**0.15**	**(0.08 - 0.29)**	<0.0001
	2-5 months	65	15.89	**0.55**	**(0.39 - 0.77)**	0.0005
	6-11 months	53	12.96	**0.68**	**(0.60 - 0.77)**	<0.0001
	12-23 months	25	6.11	**0.13**	**(0.08 - 0.20)**	<0.0001
	2-4 years	28	6.85	**0.15**	**(0.09 - 0.23)**	<0.0001
	5-17 years	26	6.36	**0.20**	**(0.13 - 0.32)**	<0.0001
	18-49 years	85	20.78	referent		
	50-64 years	49	11.98	1.32	(0.91 - 1.92)	0.1496
	≥65 years	67	16.38	1.29	(0.92 - 1.82)	0.1434
Gender	**Female**	194	47.43	1.05	(0.86 - 1.28)	0.6371
Health Facility	**Hospital**	397	97.07	**20.73**	**(11.65 - 36.87)**	<0.0001
Department						
	Guatemala	102	24.94	1.14	(0.88 - 1.49)	0.3182
	Santa Rosa	48	11.74	**0.22**	**(0.16 - 0.30)**	<0.0001
	Quetzaltenango	132	32.27	referent		
	Other	127	31.05	**3.35**	**(2.59 - 4.34)**	<0.0001
Year						
	2007	0	0.00	0.00	(0.00 - 0.00)	0.9992
	2008	4	0.98	referent		
	2009	94	22.98	**7.55**	**(2.76 - 20.59)**	<0.0001
	2010	215	52.57	**11.16**	**(4.14 - 30.09)**	<0.0001
	2011	96	23.47	**12.33**	**(4.52 - 33.66)**	<0.0001
Age-appropriate DPT vaccination*		67	51.15	**0.41**	**(0.29 - 0.58)**	<0.0001
Education**						
	None	106	25.92	**1.41**	**(0.99 - 2.01)**	0.0596
	Primary school	207	50.61	1.12	**(0.80 - 1.55)**	0.5053
	Basic studies	45	11.00	referent		
	Secondary school	40	9.78	**1.22**	**(0.98 - 1.52)**	0.069
	Superior studies	10	2.44	0.79	**(0.56 - 1.12)**	0.183
Family monthly income***						
	< $125	213	52.08	1.01	(0.80 - 1.27)	0.9352
	$125 - 375	119	29.10	referent		
	$375-625	22	5.38	**1.68**	**(1.05 - 2.69)**	0.0296
	> $625	2	0.49	0.44	**(0.11 - 1.81)**	0.2588
History, Signs and Symptoms						
Cough		409	100.00	**94.32**	**(5.88 - 1512)**	<0.0001

Cough Duration									
	<7 days	0	0.00	0.00	(	0.00	-	0.00	)	0.9994
	7-13 days	0	0.00	0.00	(	0.00	-	0.00	)	0.9997
	14-20 days	280	68.46	referent						
	≥21 days	129	31.54	**0.65**	(	**0.47**	-	**0.90**	)	0.0086
Paroxysmal cough		277	67.73	**4.92**	(	**3.86**	-	**6.28**	)	<0.0001
Whoop		186	45.59	**2.82**	(	**2.22**	-	**3.58**	)	<0.0001
Posttussive vomit		278	67.97	**3.58**	(	**2.32**	-	**4.55**	)	<0.0001
Fever, self-reported		282	69.46	**0.72**	(	**0.58**	-	**0.90**	)	0.0033
Vomiting, including posttussive		285	69.68	**6.19**	(	**4.99**	-	**7.68**	)	<0.0001
Recent use of antibiotics		145	61.97	**2.24**	(	**1.71**	-	**2.94**	)	<0.0001
Other respiratory diagnosis upon discharge		39	9.54	1.29	(	0.92	-	1.82	)	0.1368
Physical Findings										
Fever, Temp ≥38°C		135	33.67	**0.49**	(	**0.40**	-	**0.61**	)	<0.0001
Hypoxia (%O2 saturation ≤94%)		284	75.33	**2.28**	(	**1.79**	-	**2.90**	)	<0.0001
Breath sounds (crackles/rales, wheezes, rhonchi)		344	84.11	**5.47**	(	**4.19**	-	**7.16**	)	<0.0001

*age-appropriate dosing per WHO recommendations among children <5 years of age, only analyzed for children <5 years of age (n=6399), defined as: dose 1 before age 3 months, dose 2 before age 5 months and dose 3 before age 7 months

**if patient <18 years of age, answered by patient's patient/tutor

***income in US dollars

Table 6. Chi-square p-values and collinearity diagnostics of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Predictor		Model 1		Model 2	
		p-value	VIF	p-value	VIF
Intercept		<0.0001	0.00	<0.0001	0.00
Age					
	0-2 months vs. 18-49 years	0.81	2.35	0.62	2.02
	2-5 months vs. 18-49 years	0.52	3.56	0.23	2.52
	6-11 months vs. 18-49 years	0.06	3.80	0.00	2.68
	12-23 months vs. 18-49 years	0.34	3.38	0.05	2.53
	2-4 years vs. 18-49 years	0.13	3.55	0.01	2.63
	5-17 years vs. 18-49 years	0.87	1.85	0.71	1.80
	50-64 years vs. 18-49 years	0.51	1.57	0.08	1.54
	≥65 years vs. 18-49 years	<.0001	1.83	<.0001	1.76
Health Facility	**Hospital**	0.55	1.75	0.86	1.96
Department					
	Guatemala vs. Quetzaltenango	0.04	2.71	0.00	2.07
	Santa Rosa vs. Quetzaltenango	0.72	2.18	0.79	1.92
	Other vs. Quetzaltenango	0.01	1.49	0.00	1.44
Year					
	2007 vs. 2008	--	--	--	--
	2009 vs. 2008	0.20	23.94	--	--
	2010 vs. 2008	0.24	32.64	--	--
	2011 vs. 2008	0.06	23.87	--	--
Education*					
	None vs. Basic studies	0.32	2.03	--	--
	Primary school vs. Basic studies	0.85	2.29	--	--
	Secondary school vs. Basic studies	0.54	1.68	--	--
	Superior studies vs. Basic studies	0.56	1.36	--	--
Family monthly income**					
	< $125 vs. $125-375	0.11	1.78	0.15	1.51
	$375-625 vs. $125-375	0.65	1.15	0.89	1.09
	> $625 vs. $125-375	0.63	1.21	0.64	1.07
Cough		0.99	1.01	--	--
Cough Duration					
	<7 days vs. 14-20 days	<0.001	3.42	<.0001	1.51
	7-13 days vs. 14-20 days	<0.001	3.00	<.0001	1.09
	≥21 days vs. 14-20 days	0.08	1.43	0.00	1.07
Fever, self-reported		0.98	1.26	--	--
Vomiting, including posttussive		<.0001	1.14	<0.0001	1.13
Recent use of antibiotics		0.98	1.16	--	--
Other respiratory diagnosis upon discharge		0.92	1.16	--	--
Fever, Temp ≥38°C		0.99	1.26	--	--
Hypoxia (%O2 saturation ≤94%)		0.06	1.38	0.10	1.34
Breath sounds (crackles/rales, wheezes, rhonchi)		0.08	1.94	0.94	1.82

*if patient <18 years of age, answered by patient's patient/tutor
**income in US dollars

Model 1 (2602 observations). Goodness-of-fit: chi-square=6.037, 8 df (chi-square p-value=0.6431)
Model 2 (4263 observations). Goodness-of-fit: chi-square=8.4767, 8 df (chi-square p-value=0..3883)

Table 7. Stratified analysis of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Association between age 0-2 months and pertussis diagnosis, stratified by each of the other predictors

Stratified predictor	Crude OR*	Summary OR	95% CI	Difference from Crude OR (%)
	0.15 (0.08-0.29)			
Health Facility**		0.27	(0.15-0.49)	80.00
Department**		0.35	(0.20-0.67)	133.33
Family monthly income**		0.47	(0.25-0.88)	213.33
Cough Duration**		0.89	(0.34-2.35)	493.33
Vomiting, including posttussive**		0.74	(0.39-1.38)	393.33
Hypoxia (%O2 saturation ≤94%)**		0.24	(0.1- 0.48)	60.00
Breath sounds (crackles/rales, wheezes, rhonchi)**		0.29	(0.16-0.52)	93.33

*Crude $OR_{0\text{-}2 \text{ months of age vs. } 18\text{-}49 \text{ years}}$

**Represents a confounder by the 10-20% rule-of-thumb

Table 8. Stratified analysis of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Association between age 2-5 months and pertussis diagnosis, stratified by each of the other predictors

Stratified predictor	Crude OR*	Summary OR	95% CI	Difference from Crude OR (%)
	0.55 (0.39-0.77)			
Health Facility**		1.07	(0.81-1.40)	94.55
Department**		1.33	(1.00-1.78)	141.82
Family monthly income**		1.81	(1.35-2.41)	229.09
Cough Duration**		1.75	(1.06-2.89)	218.18
Vomiting, including posttussive**		1.42	(1.07-1.87)	158.18
Hypoxia (%O2 saturation ≤94%)**		1.26	(0.94-1.68)	129.09
Breath sounds (crackles/rales, wheezes, rhonchi)**		1.32	(1.00-1.74)	140.00

*Crude $OR_{2\text{-}5 \text{ months of age vs. } 18\text{-}49 \text{ years}}$

**Represents a confounder by the 10-20% rule-of-thumb

Table 9. Stratified analysis of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Association between age 6-11 months and pertussis diagnosis, stratified by each of the other predictors

Stratified predictor	Crude OR*	Summary OR	95% CI	Difference from Crude OR (%)
	0.68 (0.60-0.77)			
Health Facility		0.68	(0.51-0.92)	0.00
Department		0.82	(0.60-1.10)	20.59
Family monthly income		0.78	(0.56-1.06)	14.71
Cough Duration**		0.87	(0.55-1.40)	27.94
Vomiting, including posttussive		0.59	(0.44-0.80)	13.24
Hypoxia (%O2 saturation ≤94%)		0.76	(0.56-1.05)	11.76
Breath sounds (crackles/rales, wheezes, rhonchi)		0.73	(0.55-0.99)	7.35

*Crude $OR_{6\text{-}11 \text{ months of age vs. } 18\text{-}49 \text{ years}}$

**Represents a confounder by the 10-20% rule-of-thumb

Table 10. Stratified analysis of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Association between age 12-23 months and pertussis diagnosis, stratified by each of the other predictors

Stratified predictor	Crude OR*	Summary OR	95% CI	Difference from Crude OR (%)
	0.13 (0.08-0.20)			
Health Facility**		0.38	(0.25-0.58)	192.31
Department**		0.28	(0.19-0.43)	115.38
Family monthly income**		0.41	(0.27-0.62)	215.38
Cough Duration**		1.75	(0.80-3.83)	1246.15
Vomiting, including posttussive**		0.20	(0.13-0.30)	53.85
Hypoxia (%O2 saturation ≤94%)**		0.36	(0.22-0.56)	176.92
Breath sounds (crackles/rales, wheezes, rhonchi)**		0.33	(0.23-0.51)	153.85

*Crude $OR_{12\text{-}23 \text{ months of age vs. } 18\text{-}49 \text{ years}}$

**Represents a confounder by the 10-20% rule-of-thumb

Table 11. Stratified analysis of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Association between age 2-4 years and pertussis diagnosis, stratified by each of the other predictors

Stratified predictor	Crude OR*	Summary OR	95% CI	Difference from Crude OR (%)
	0.15 (0.09, 0.23)			
Health Facility**		0.48	(0.32-0.71)	220.00
Department**		0.58	(0.38-0.87)	286.67
Family monthly income**		0.37	(0.25-0.56)	146.67
Cough Duration**		1.26	(0.63-2.53)	740.00
Vomiting, including posttussive**		0.27	(0.18-0.40)	80.00
Hypoxia (%O2 saturation ≤94%)**		0.38	(0.25-0.57)	153.33
Breath sounds (crackles/rales, wheezes, rhonchi)**		0.46	(0.31-0.68)	206.67

*Crude $OR_{2\text{-}4 \text{ years of age vs. } 18\text{-}49 \text{ years}}$

**Represents a confounder by the 10-20% rule-of-thumb

Table 12. Stratified analysis of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Association between age 5-17 years and pertussis diagnosis, stratified by each of the other predictors

Stratified predictor	Crude OR*	Summary OR	95% CI	Difference from Crude OR (%)
	0.20 (0.13-0.32)			
Health Facility**		1.07	(0.70-1.61)	435.00
Department**		0.71	(0.47-1.08)	255.00
Family monthly income**		0.51	(0.34-0.78)	155.00
Cough Duration**		1.05	(0.54-2.04)	425.00
Vomiting, including posttussive**		1.14	(0.74-1.75)	470.00
Hypoxia (%O2 saturation ≤94%)**		0.62	(0.40-0.94)	210.00
Breath sounds (crackles/rales, wheezes, rhonchi)**		0.92	(0.61-1.39)	360.00

*Crude $OR_{5\text{-}17 \text{ years of age vs. } 18\text{-}49 \text{ years}}$

**Represents a confounder by the 10-20% rule-of-thumb

Table 13. Stratified analysis of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Association between age 50-64 years and pertussis diagnosis, stratified by each of the other predictors

Stratified predictor	Crude OR*	Summary OR	95% CI	Difference from Crude OR (%)
	1.32 (0.90-1.92)			
Health Facility**		2.67	(1.93-3.68)	102.27
Department**		3.11	(2.23-4.33)	135.61
Family monthly income**		4.22	(2.98-5.99)	219.70
Cough Duration**		0.79	(0.50-1.24)	40.15
Vomiting, including posttussive**		5.73	(4.00-8.20)	334.09
Hypoxia (%O2 saturation ≤94%)**		2.91	(2.08-4.06)	120.45
Breath sounds (crackles/rales, wheezes, rhonchi)**		2.72	(1.97-3.77)	106.06

*Crude $OR_{50\text{-}64 \text{ years of age vs. } 18\text{-}49 \text{ years}}$

**Represents a confounder by the 10-20% rule-of-thumb

Table 14. Stratified analysis of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Association between age 65+ years and pertussis diagnosis, stratified by each of the other predictors

Stratified predictor	Crude OR*	Summary OR	95% CI	Difference from Crude OR (%)
	1.29 (0.92-1.82)			
Health Facility**		2.44	(.184-3.22)	89.15
Department**		3.09	(2.30-4.15)	139.53
Family monthly income**		3.40	(2.45-4.73)	163.57
Cough Duration**		0.54	(0.37-0.80)	58.14
Vomiting, including posttussive**		6.42	(4.67-8.83)	397.67
Hypoxia (%O2 saturation ≤94%)**		2.91	(2.09-3.77)	125.58
Breath sounds (crackles/rales, wheezes, rhonchi)**		2.48	(1.87-3.29)	92.25

*Crude $OR_{65+ \text{ years of age vs. } 18\text{-}49 \text{ years}}$

**Represents a confounder by the 10-20% rule-of-thumb

Table 15. Stratified analysis of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Association between health facility and pertussis diagnosis, stratified by each of the other predictors

Stratified predictor	Crude $OR_{hospital}$	Summary OR	95% CI	Difference from Crude OR (%)
	20.73 (11.65-36.87)			
Age*		13.53	(7.78-23.54)	34.73
Department*		9.98	(5.61-17.76)	51.86
Family monthly income*		15.06	(8.51-26.67)	27.35
Cough Duration*		1.62	(0.71-3.71)	92.19
Vomiting, including posttussive		21.89	(12.24-39.14)	5.60
Hypoxia (%O2 saturation ≤94%)*		11.85	(5.21-26.97)	42.84
Breath sounds (crackles/rales, wheezes, rhonchi)*		13.81	(7.35-25.94)	33.38

*Represents a confounder by the 10-20% rule-of-thumb

Table 16. Stratified analysis of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Association between Guatemala department and pertussis diagnosis, stratified by each of the other predictors

Stratified predictor	Crude OR*	Summary OR	95% CI	Difference from Crude OR (%)
	1.14 (0.88-1.49)			
Age**		2.00	(1.54-2.60)	75.44
Health facility**		0.82	(0.65-1.03)	28.07
Family monthly income**		1.74	(1.30-2.32)	52.63
Cough Duration**		5.52	(3.05-10.01)	384.21
Vomiting, including posttussive**		1.62	(1.28-2.05)	42.11
Hypoxia (%O2 saturation ≤94%)**		0.77	(0.60-0.98)	32.46
Breath sounds (crackles/rales, wheezes, rhonchi)		1.21	(0.94-1.55)	6.14

*Crude $OR_{Guatemala\ vs.\ Quetzaltenango}$

**Represents a confounder by the 10-20% rule-of-thumb

Table 17. Stratified analysis of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Association between Santa Rosa department and pertussis diagnosis, stratified by each of the other predictors

Stratified predictor	Crude OR*	Summary OR	95% CI	Difference from Crude OR (%)
	0.22 (0.16-0.30)			
Age		0.20	(0.15-0.27)	9.09
Health facility		0.26	(0.19-0.36)	18.18
Family monthly income**		0.16	(0.11-0.21)	27.27
Cough Duration		0.18	(0.12-0.27)	18.18
Vomiting, including posttussive**		0.15	(0.11-0.20)	31.82
Hypoxia (%O2 saturation ≤94%)**		0.33	(0.23-0.47)	50.00
Breath sounds (crackles/rales, wheezes, rhonchi)		0.25	(0.18-0.33)	13.64

*Crude $OR_{Santa\ Rosa\ vs.\ Quetzaltenango}$

**Represents a confounder by the 10-20% rule-of-thumb

Table 18. Stratified analysis of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Association between "other" department and pertussis diagnosis, stratified by each of the other predictors

Stratified predictor	Crude OR*	Summary OR	95% CI	Difference from Crude OR (%)
	3.35 (2.59-4.34)			
Age		3.86	(3.05-4.89)	15.22
Health facility		3.29	(2.62-4.12)	1.79
Family monthly income**		6.28	(4.88-8.09)	87.46
Cough Duration**		1.55	(1.08-2.22)	53.73
Vomiting, including posttussive**		6.75	(5.30-8.61)	101.49
Hypoxia (%O2 saturation ≤94%)**		4.13	(3.26-5.24)	23.28
Breath sounds (crackles/rales, wheezes, rhonchi)		3.32	(2.63-4.19)	0.90

*Crude $OR_{"Other"\ vs.\ Quetzaltenango}$

**Represents a confounder by the 10-20% rule-of-thumb

Table 19. Stratified analysis of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Association between <$125 income and pertussis diagnosis, stratified by each of the other predictors

Stratified predictor	Crude OR*	Summary OR	95% CI	Difference from Crude OR (%)
	1.01 (0.80-1.27)			
Age		0.85	(0.67-1.07)	15.84
Health facility**		1.25	(1.01-1.56)	23.76
Department		1.20	(0.92-1.57)	18.81
Cough Duration**		0.40	(0.27-0.60)	60.40
Vomiting, including posttussive		0.90	(0.72-1.13)	10.89
Hypoxia (%O2 saturation ≤94%)**		1.28	(1.02-1.61)	26.73
Breath sounds (crackles/rales, wheezes, rhonchi)		1.17	(0.93-1.47)	15.84

*Crude $OR_{<\$125 vs. \$125-375}$

**Represents a confounder by the 10-20% rule-of-thumb

Table 20. Stratified analysis of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Association between $375-$625 income and pertussis diagnosis, stratified by each of the other predictors

Stratified predictor	Crude OR*	Summary OR	95% CI	Difference from Crude OR (%)
	1.68 (1.05-2.69)			
Age**		2.12	(1.35-3.34)	26.19
Health facility		1.41	(0.90-2.22)	16.07
Department**		1.31	(0.83-2.08)	22.02
Cough Duration**		2.80	(1.01-7.77)	66.67
Vomiting, including posttussive		1.73	(1.08-2.74)	2.98
Hypoxia (%O2 saturation ≤94%)**		1.23	(0.78-1.95)	26.79
Breath sounds (crackles/rales, wheezes, rhonchi)**		2.20	(1.39-3.47)	30.95

*Crude $OR_{\$375-625 vs. \$125-375}$

**Represents a confounder by the 10-20% rule-of-thumb

Table 21. Stratified analysis of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Association between >$625 income and pertussis diagnosis, stratified by each of the other predictors

Stratified predictor	Crude OR*	Summary OR	95% CI	Difference from Crude OR (%)
	0.44 (0.11-1.81)			
Age**		1.32	(0.55-3.17)	200.00
Health facility**		0.59	(0.17-2.10)	34.09
Department**		0.72	(0.22-2.32)	63.64
Cough Duration**		3.00	(0.14-62.92)	581.82
Vomiting, including posttussive**		0.74	(0.20-2.71)	68.18
Hypoxia (%O2 saturation ≤94%)		0.42	(0.10-1.73)	4.55
Breath sounds (crackles/rales, wheezes, rhonchi)**		0.58	(0.14-2.38)	31.82

*Crude $OR_{>\$625 \text{ vs. } \$125\text{-}375}$

**Represents a confounder by the 10-20% rule-of-thumb

Table 22. Stratified analysis of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Association between cough <7 days and pertussis diagnosis, stratified by each of the other predictors

Stratified predictor	Crude OR*	Summary OR	95% CI	Difference from Crude OR (%)
	0.00 (0.00-0.00)			
Age		0.00500	(0.00-0.01)	0.50
Health facility		0.00190	(0.00-0.01)	0.19
Department		0.00200	(0.00-0.01)	0.20
Family monthly income		0.00400	(0.00-0.02)	0.40
Vomiting, including posttussive		0.00110	(0.00-0.01)	0.11
Hypoxia (%O2 saturation ≤94%)		0.00110	(0.00-0.01)	0.11
Breath sounds (crackles/rales, wheezes, rhonchi)		0.00120	(0.00-0.01)	0.12

*Crude $OR_{<7 \text{ days vs. } 14\text{-}20 \text{ days}}$

Table 23. Stratified analysis of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Association between cough 7-13 days and pertussis diagnosis, stratified by each of the other predictors

Stratified predictor	Crude OR*	Summary OR	95% CI	Difference from Crude OR (%)
	0.00 (0.00-0.00)			
Age		0.05	(0.02-0.12)	5.00
Health facility		0.03	(0.00-0.23)	3.00
Department		0.02	(0.00-0.08)	2.00
Family monthly income		0.05	(0.01-0.20)	5.00
Vomiting, including posttussive		0.01	(0.00-0.06)	1.00
Hypoxia (%O2 saturation ≤94%)		0.01	(0.00-0.01)	1.00
Breath sounds (crackles/rales, wheezes, rhonchi)		0.01	(0.00-0.01)	1.00

*Crude $OR_{7\text{-}13 \text{ days vs. } 14\text{-}20 \text{ days}}$

Table 24. Stratified analysis of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Association between cough ≥21 days and pertussis diagnosis, stratified by each of the other predictors

Stratified predictor	Crude OR*	Summary OR	95% CI	Difference from Crude OR (%)
	0.65 (0.47-0.90)			
Age**		13.41	(9.96-18.05)	1963.08
Health facility**		20.02	(15.08-26.57)	2980.00
Department**		19.06	(13.93-26.07)	2832.31
Family monthly income**		21.75	(15.96-29.65)	3246.15
Vomiting, including posttussive**		22.30	(15.24-32.62)	3330.77
Hypoxia (%O2 saturation ≤94%)**		23.36	(16.96-32.17)	3493.85
Breath sounds (crackles/rales, wheezes, rhonchi)**		20.51	(15.43-27.28)	3055.38

*Crude $OR_{\geq 21 \text{ days vs. } 14\text{-}20 \text{ days}}$

**Represents a confounder by the 10-20% rule-of-thumb

Table 25. Stratified analysis of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Association between vomiting and pertussis diagnosis, stratified by each of the other predictors

Stratified predictor	Crude OR_{vomit}	Summary OR	95% CI	Difference from Crude OR (%)
	3.58 (2.32-4.55)			
Age**		11.12	(8.84-14.11	210.61
Health facility**		6.90	(5.54-8.61)	92.74
Department**		7.21	(5.77-9.02)	101.40
Family monthly income**		6.35	(5.03-8.01)	77.37
Cough duration**		27.42	(16.57-45.36)	665.92
Hypoxia (%O2 saturation ≤94%)**		6.85	(5.44-8.62)	91.34
Breath sounds (crackles/rales, wheezes, rhonchi)**		7.94	(6.37-9.89)	121.79

*Represents a confounder by the 10-20% rule-of-thumb

Table 26. Stratified analysis of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Association between hypoxia and pertussis diagnosis, stratified by each of the other predictors

Stratified predictor	Crude $OR_{hypoxia}$	Summary OR	95% CI	Difference from Crude OR (%)
	2.28 (1.79-2.90)			
Age		1.86	(1.44-2.39)	18.42
Health facility		1.94	(1.51-2.47)	14.91
Department*		1.73	(1.33-2.25)	24.12
Family monthly income		2.19	(1.70-2.82)	3.95
Cough Duration		2.30	(1.58-3.35)	0.88
Vomit		1.93	(1.50-2.48)	15.35
Breath sounds (crackles/rales, wheezes, rhonchi)		2.03	(1.60-2.59)	10.96

*Represents a confounder by the 10-20% rule-of-thumb

Table 27. Stratified analysis of predictors of pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011

Association between breath sounds and pertussis diagnosis, stratified by each of the other predictors

Stratified predictor	Crude $OR_{breath\ sounds}$	Summary OR	95% CI	Difference from Crude OR (%)
	5.47 (4.19-7.16)			
Age*		3.49	(2.63-4.62)	36.20
Health facility*		1.63	(1.21-2.19)	70.20
Department*		1.88	(1.39-2.54)	65.63
Family monthly income*		3.26	(2.41-4.42)	40.40
Cough Duration*		0.84	(0.53-1.35)	84.64
Vomit*		7.27	(5.54-9.55)	32.91
Hypoxia*		2.61	(1.95-3.50)	52.29

*Represents a confounder by the 10-20% rule-of-thumb

Table 28. Relationship between predictors and clinical pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011[1]

Predictor		Parameter Estimate	Standard Error	Wald x^2	Wald x^2 p-value[2]	Adjusted Odds Ratio (95% CI)	
Intercept		-1.33	1.06	1.59	0.21		
Age	**0-2 months vs. 18-49 years**	0.70	0.97	0.52	0.47	2.01	(0.30-13.42)
	2-5 months vs. 18-49 years	-0.04	0.49	0.01	0.94	0.97	(0.37-2.50)
	6-11 months vs. 18-49 years	-0.50	0.17	8.64	**0.00**	**0.61**	**(0.43-0.85)**
	12-23 months vs. 18-49 years	-0.39	0.83	0.22	0.64	0.68	(0.13-3.47)
	2-4 years vs. 18-49 years	0.11	0.67	0.03	0.87	1.11	(0.30-4.18)
	5-17 years vs. 18-49 years	0.09	0.62	0.02	0.88	1.10	(0.33-3.69)
	50-64 years vs. 18-49 years	-0.02	0.43	0.00	0.96	0.98	(0.42-2.27)
	≥65 years vs. 18-49 years	-0.41	0.40	1.08	0.30	0.66	(0.31-1.44)
Health Facility	**Hospital**	-0.89	1.06	0.71	0.40	0.41	(0.05-3.27)
Department	**Guatemala vs. Quetzaltenango**	2.28	0.63	13.2	**0.00**	**9.81**	**(2.86-33.58)**
	Santa Rosa vs. Quetzaltenango	-0.57	0.39	2.14	0.14	0.57	(0.27-1.21)
	Other vs. Quetzaltenango	0.52	0.32	2.63	0.10	1.69	(0.90-3.19)
Family monthly income*	**< $125 vs. $125-375**	-0.66	0.37	3.21	0.07	0.52	(0.25-3.50)
	$375-625 vs. $125-375	-0.15	0.72	0.05	0.83	0.86	(0.21-3.50)
	> $625 vs. $125-375	20.82	>999	0.00	1.00	>999.999	(<0.001->999)
Cough Duration	**<7 days vs. 14-20 days**	-50.44	>999	0.00	1.00	<0.001	(<0.001->999)
	7-13 days vs. 14-20 days	-50.66	>999	0.00	1.00	<0.001	(<0.001->999)
	≥21 days vs. 14-20 days	-0.14	0.28	0.23	0.63	0.87	(0.50-1.52)
Vomiting, including posttussive		3.84	0.38	99.9	**<.0001**	**46.75**	**(22.00-99.35)**
Hypoxia (%O2 saturation ≤94%)		1.03	0.32	10.3	**0.00**	**2.80**	**(1.49-5.24)**
Breath sounds (crackles/rales, wheezes, rhonchi)		1.55	0.55	7.89	**0.01**	**4.71**	**(1.60-13.91)**

*income in US dollars

[1]**Model 3: full model** (4263 observations)

[2]**Bold p-values** indicate significance at alpha=0.05, two-sided; **Bold CI's** do not pass through null

Table 29. Relationship between predictors and clinical pertussis, among respondents with suspected respiratory illness who met surveillance system case definition presenting to all health facilities, 2007-2011[1]

Predictor		Parameter Estimate	Standard Error	Wald x^2	Wald x^2 p-value[2]	Adjusted Odds Ratio (95% CI)	
Intercept		-4.78	0.33	208.50	**<.0001**		
Age	**0-2 months vs. 18-49 years**	-1.10	0.33	11.28	**0.00**	**0.33**	**(0.17-0.63)**
	6-11 months vs. 18-49 years	-0.32	0.06	29.88	**<.0001**	**0.73**	**(0.65-0.82)**
	12-23 months vs. 18-49 years	-1.54	0.23	43.44	**<.0001**	**0.21**	**(0.14-0.34)**
	2-4 years vs. 18-49 years	-1.21	0.22	30.31	**<.0001**	**0.30**	**(0.19-0.46)**
Health Facility	**Hospital**	1.11	0.32	11.69	**0.00**	**3.02**	**(1.60-5.70)**
Department	**Guatemala vs. Quetzaltenango**	0.44	0.15	8.60	**0.00**	**1.55**	**(1.12-2.09)**
	Other vs. Quetzaltenango	1.02	0.16	42.95	**<.0001**	**2.77**	**(2.04-3.76)**
Cough Duration	**≥21 days vs. 14-20 days**	2.80	0.18	240.12	**<.0001**	**16.38**	**(11.5-23.33)**
Vomiting, including posttussive		2.38	0.13	317.01	**<.0001**	**10.79**	**(8.31-14.02)**

**if patient <18 years of age, answered by patient's patient/tutor

***income in US dollars

[1]**Model 4: final model** determined from backward elimination from Model 3 (full model) (5383 observations)
Goodness-of-fit: chi-square=10.3701, 7 df (chi-square p-value=0.1686)

[2]**Bold p-values** indicate significance at alpha=0.05, two-sided; **Bold CI's** do not pass through null

APPENDIX A: Pertussis case definitions

CDC Recommendations for Pertussis Cases Definitions [3]

Clinical	Acute cough for 14 days plus one of the following: paroxysmal cough, post-tussive emesis, inspiratory "whooping," and no other apparent cause Or In an outbreak setting: acute cough for 14 days
Confirmed	Patient's illness meets criteria for "clinical case" plus one of the following: positive PCR assay or epidemiologic linkage to a laboratory- confirmed (PCR assay or culture) case Or Acute cough illness of any duration and positive Bordetella pertussis culture
Probable	Patient's illness meets criteria for "clinical case" plus all of the following: negative PCR assay, negative B. pertussis culture, no epidemiologic linkage to a laboratory-confirmed (PCR assay or culture) case

WHO Recommendations for Pertussis Case Definitions [12]

Clinically Confirmed	A case diagnosed as pertussis by a physician **or** A person with a cough lasting at least 14 days with at least one of the following: paroxysmsmal cough, inspiratory whooping, post-tussive vomiting Is not laboratory-confirmed
Laboratory Confirmed	A case that meets the clinical case definition and is laboratory-confirmed: • Isolation of *Bordetella pertussis* **or** • Detection of genomic sequences by means of the polymerase chain reaction (PCR) **or** • Positive paired serology

APPENDIX B: ViCo case definitions, inclusion and exclusion criteria

A. DIARRHEA

a. Case Definition

i. Diarrhea: the acute onset of 3 or more loose or liquid stools in a person in a 24-hour period during the last 72 hours
ii. Severe diarrhea: diarrhea as above with one of the following:
    1. Lethargy or unconsciousness
    2. Sunken eyes
    3. Requiring intravenous fluids
    4. Presence of blood

b. Inclusion Criteria

i. Hospital: residents of the project catchment area during the last 30 days before presenting the hospital admitted with a diagnosis of diarrhea;
ii. Health center: residents of the selected *municipos* during the last 30 days before presenting to the health center with complaint of diarrhea;
iii. Health post: residents of the selected *municipos* during the last 30 days before presenting to the health center with complaint of diarrhea.

c. Exclusion Criteria

i. Another episode of diarrhea in the 7 days before the start of this episode

B. RESPIRATORY DISEASE

a. Case Definition

i. **Pneumonia**: a person is considered to have a pneumonia if they are admitted to the hospital and they have either i.a. or i.b.

i.a. IEIP pneumonia case definition

a. Evidence of acute infection during the first 24 hours of admission (at least one of the following):
    i. Fever ≥38°C
    ii. Temperature <35.5°C with chills
    iii. Abnormal white blood cell count (>11,000/cm^3 or <3,000/cm^3) *or* abnormal white blood cell differential

AND

b. Signs or symptoms of respiratory tract disease (at least tachypnea or one symptom):
    i. Tachypnea (defined as):
        1. Age <2 months: ≥60/min
        2. Age 2-12 months: ≥50/min
        3. Age >12 months-5 years: ≥40/min
        4. Age >5 years: ≥20/min

ii. Symptoms: Cough, sputum production, hemoptysis, chest pain or dyspnea, shortness of breath, sore throat, abnormal lung exam,

or for children <2 years old: refusing to eat, drink or breastfeed, repeatedly pausing to breathe while breastfeeding or drinking, nasal flaring, chest indrawing, or grunting

i.b. <u>Pneumonia case definition from WHO Integrated Management of Child Illness program for children <59 months of age</u>

a. Age <2 months with tachypnea or chest indrawing

OR

b. Age <2 months with cough or difficulty breathing and at least one of the following:
    a. Cyanosis
    b. Not drinking or breastfeeding
    c. Vomiting all intake
    d. Convulsions
    e. Lethargy or fainting
    f. Head nodding
    g. Stridor at rest
    h. Hypoxia (O_2 saturation <90%)
    i. No movement or only when stimulated

OR

c. Age 2-59 months with cough or difficulty breathing and at least one of the following:
    a. Tachypnea
    b. Chest indrawing
    c. Cyanosis
    d. Not drinking or breastfeeding
    e. Vomiting all intake
    f. Convulsions
    g. Lethargy or fainting
    h. Head nodding
    i. Stridor at rest
    j. Hypoxia (O_2 saturation <90%)

ii. **Influenza-Like Illness (ILI)**: a person is considered to have ILI if they are seen at the health center, health post, or private physician and have:
    1. A documented acute fever of ≥38°C **AND**
    2. History of cough or sore throat within previous 14 days

b. **Inclusion Criteria**: same as for diarrhea

c. **Exclusion Criteria**: same as for diarrhea

APPENDIX C: Study definition of suspected respiratory illness

A. Inclusion Criteria:

a. Resident of the project catchment area (if presenting to hospital) or resident of the selected *municipos* (if presenting to health post or health center) who had any one of the following:
   i. Denoted as presenting with indications of respiratory disease by surveillance staff
   ii. Cough
   iii. Sputum
   iv. Hemotypisis
   v. Chest pain or dyspnea
   vi. Difficulty breathing
   vii. Shortness of breath
   viii. Sore throat
   ix. Runny nose
   x. Nasal flaring
   xi. Tachypnea(defined as):
      1. Age <2 months: ≥60/min
      2. Age 2-12 months: ≥50/min
      3. Age >12 months-5 years: ≥40/min
      4. Age >5 years: ≥20/min
   xii. Physical findings on exam:
      1. Adenopathy
      2. Stridor
      3. Abnormal lung exam and/or wheezes, rales or rhonci
   xiii. Age <2 years
   xiv. Age <2 or 2-59 months with cough or difficulty breathing and at least one of the following:
      1. Cyanosis
      2. Chest indrawing
      3. Not drinking or breastfeeding
      4. Vomiting all intake
      5. Convulsions
      6. Lethargy or fainting
      7. Head nodding
      8. Stridor at rest
      9. Hypoxia (O_2 saturation <90%)
      10. No movement or only when stimulated

B. Exclusion Criteria:

a. None