Hopf Bifurcation in Models for Pertussis
Epidemiology

Herbert W. Hethcote and Yi Li
Department of Mathematics
University of Iowa
Iowa City, IA 52242
U.S.A.
hethcote@math.uiowa.edu and yli@math.uiowa.edu

Zhujun Jing
Institute of Mathematics
Academia Sinica
Beijing
P.R.China 100080
jingzj@263.net

(Received March, 1999; accepted June, 1999)

Abstract

Pertussis (whooping cough) incidence in the United States has oscillated with a period of about four years since data was first collected in 1922. An infection with pertussis confers immunity for several years, but then the immunity wanes, so that reinfection is possible. A pertussis reinfection is mild after partial loss of immunity, but the reinfection can be severe after complete loss of immunity. Three pertussis transmission models with waning of immunity are examined for periodic solutions. Equilibria and their stability are determined. Hopf bifurcation of periodic solutions around the endemic equilibrium can occur for some parameter values in two of the models. Periods of about four years are found for epidemiologically reasonable parameter values in two of these models.

Key words: pertussis, epidemiology, differential equations, Hopf bifurcation, periodic solutions.

1 Introduction

Because prolonged coughing is a major symptom of the infectious disease pertussis, it is commonly known as whooping cough. In the prevaccine era, the average
age of a typical pertussis attack was about 5 years and nearly all children in the United States were infected. In children under age one year in the prevaccine era, there were three times as many deaths from pertussis complications as from all other childhood diseases combined \[1\] \[2\]. In 1949 killed whole-cell pertussis bacteria were combined with diphtheria and tetanus toxoids to form the DTP vaccine \[3\]. Because of the pertussis vaccination program, the reported incidence of pertussis dropped by a factor of about 100 between the 1940s and the 1970s to a minimum of 1,010 cases in 1976 \[2\] \[4\]. Since it was first recorded in the 1920s, reported pertussis incidence in the United States has oscillated irregularly with a period of about four years \[5\]. Reported pertussis incidence has continued to vary cyclically with 6586 cases reported in 1993, 4617 in 1994, 4315 in 1995, 7796 in 1996, 5957 in 1997, and 6,279 in 1998 \[6\] \[7\] \[8\] \[9\].

Here we investigate a new possible cause of the roughly four year oscillations in pertussis incidence. See \[10\] for a survey of mechanisms leading to periodicity in epidemiology models. Some papers on modeling of pertussis in the United Kingdom are cited in \[11\]. An age-structured epidemiologic model developed for pertussis in the United States consists of 12 classes for individuals who are in epidemiologic states corresponding to being susceptible, infectious, immune, or vaccinated \[11\]. It also includes waning of both infection-acquired and vaccine-induced immunity, and vaccination of children corresponding to the vaccination coverage since 1940. Pertussis data were used to estimate parameter values in that model. Computer simulations of that mathematical model suggested that the upward trend in reported pertussis cases since 1976 may be due to some factor such as an increase in the percentage of cases reported rather than an increase in actual cases. The adult reservoir of infection found in those simulations before the vaccination program started in the 1940s continued to exist through 2040. Continuation of the current vaccination program in those simulations led to a continued pertussis incidence at about the current level, so that no significant future changes are expected \[11\].

Acellular pertussis vaccines (aP) have recently been developed which cause fewer adverse reactions and can be used safely in adults \[12\]. Epidemiologists have suggested that the new acellular pertussis vaccines be combined with the tetanus-diphtheria (Td) booster, which is now recommended for adolescents and adults every 10 years. An expanded pertussis vaccination program which includes adult boosters has been studied using computer simulations \[13\]. In the simulations the addition of adult pertussis booster vaccinations every ten years was beneficial in reducing adult incidence, but caused only modest reductions in the incidence in infants and young children, who have high complication rates \[14\].

For many diseases, the contact rate goes up in the winter as children gather in closed classrooms and adults work in confined areas. Thus it is natural to expect corresponding oscillations in the incidence of these diseases. In some geographic regions disease incidences oscillate seasonally with a period of one year. For measles, the incidence in many cities has a roughly biennial oscillation pattern with alternating years of high and low incidences. For other diseases such as pertussis, mumps, rubella, poliomyelitis, chickenpox, and diphtheria,
the inter-epidemic period is often several years [15, p. 129]. The reasons for these oscillations in disease incidences with multiple year periods are not known, but there are several possible causes [10]. The numerical solutions of a basic endemic SEIR model with yearly seasonal oscillations in the contact rate had yearly oscillations for parameter values appropriate for many diseases such as chickenpox, but there were biennial oscillations for diseases such as measles with higher basic reproduction numbers [16]. The two year period for measles seems to be due to a subharmonic resonance, where the one year variations in the contact rate reinforce the natural two-year period for the damping of the oscillations in the model without seasonality. Further investigations of these models with periodic contact rates has revealed period-doubling bifurcations to chaos and many multiyear periodic solutions [17] [18]. The search for chaos in epidemiologic data [19] [20] has been countered with other explanations [21] [22].

Since cases in the United States were first reported in 1922, the reported incidence of pertussis has been cyclical with a period of about four years. This cyclic phenomenon has been investigated using an epidemiologic-demographic pertussis model [5]. When adult booster vaccinations were suddenly added in the year 2000 in the simulations, there was a perturbation from the equilibrium and a damped oscillation with a four year period to the new equilibrium [13]. This suggested that the age-structured pertussis model had a natural damping period of about four years. Because a measles model has damped oscillations to an equilibrium with a two year period and seasonal (i.e. one year period) contact rates in models for measles led to subharmonic oscillations with a period of two years [16], it was expected that a seasonal contact rate in the pertussis model would lead to similar multiyear oscillations. But this did not occur, since the oscillations in the pertussis incidence in the computer simulations always had a period of one year for any size of one-year oscillations in the contact rate. Thus the usual explanation of subharmonic resonance for the multiyear inter-epidemic period did not work for the age-structured pertussis model. However, 2% yearly stochasticity in the contact rate in the pertussis simulation model did lead to irregular oscillations with a period and a magnitude consistent with the reported pertussis data [5]. Thus a yearly random contact rate factor in the interval [0.98,1.02] due to weather, imported cases, or other causes is a possible explanation for the observed cyclic pertussis incidence.

Another possible explanation for the fluctuations in the pertussis incidence with a period of about four years is the cyclic nature of the process where people are susceptible, infectious, immune and then susceptible again. It has been shown that periodic solutions can occur in \( SIR_n \ldots R_3 R_1 S \) models, which use ordinary differential equations, for certain parameter regions when \( n \geq 3 \) [23]. These models are called cyclic, since individuals start as susceptibles, then become infectious, then move through a sequence of removed classes, and finally become susceptible again. The age-structured pertussis model in [11] [5] has four removed classes before individuals return to the susceptible class. This pertussis model differs from the cyclic \( SIR_4 R_3 R_2 R_1 S \) model in [23], which has only one infectious class, because the pertussis model has three infectious
classes for those with full, mild and weak pertussis infections. Here we look for periodic solutions in three ordinary-differential-equation, pertussis models with two, three, and four removed classes. These pertussis models differ from the age-structured, partial-differential-equation pertussis model in [11] [5], since they have neither an age-structure nor a birth-death process.

The pertussis model here with four removed classes is the ordinary-differential-equations analog of the age-structured pertussis model in [11] [5]. The other two pertussis models here with two and three removed classes are simplifications of the pertussis model with four removed classes. We analyze these pertussis models with two, three, and four removed classes in Sections 2, 3, and 4, respectively. Our goal is to determine which of these models have periodic solutions arising by Hopf bifurcations around the endemic equilibrium. We find that the pertussis model with two removed classes does not have such periodic solutions, but the pertussis models with three and four removed classes do have periodic solutions arising through Hopf bifurcation. Moreover, these models have periodic solutions with periods of about four years for some epidemiologically reasonable parameter values. These periodic solutions are consistent with the roughly four year period in reported pertussis incidence. Section 5 contains a discussion of the main results.

2 The Pertussis Model with Two Removed Classes

The five distinct epidemiologic classes in the first model as shown in Figure 1 are the susceptible class $S$, the two infective classes $I$ and $I_m$, and the two recovered classes $R_2$ and $R_1$. The class $S$ consists of susceptible people with no immunity to pertussis. When there is an adequate contact of a susceptible with an infective, the susceptible becomes infected and leaves the class $S$. Because the latent period in which a person is infected, but not yet infectious, is only about one week for pertussis [3], it is neglected in this model. Hence infected individuals enter the class $I$ of infectious people and have a full-disease case of pertussis with high infectivity. Upon recovery they enter the class $R_2$ with high immunity. The infection-acquired pertussis immunity lasts for several years, but then immunity wanes, so that a pertussis infection can occur. The severity of the disease and the degree of infectivity depends on the elapsed time since the last infection [24] [25] [26].

As shown in Figure 1, the waning of immunity is modeled by moving people down through the sequence $R_2R_1S$, where $R_2$ and $R_1$ are the recovered classes with high and low immunity, respectively. People in $R_1$ with low immunity who have an adequate contact with an infective enter the class $I_m$ for infectious people with mild-disease symptoms and medium infectivity and then return to $R_2$ after the infectious period. Let $S(t)$, $I(t)$, $I_m(t)$, $R_2(t)$, and $R_1(t)$ denote the fractions of the population in each class at time $t$. Those in the medium infectivity class $I_m$ are less infectious than those in the high infectivity class $I$. 


Figure 1: Transfer diagram for the pertussis model with two removed classes.

so that their relative infectivity $\rho$ is in the interval $[0,1]$. The force of infection $\lambda(t)$ for the population at time $t$ is the product of the contact rate $\beta$ and the sum of the infectious class fraction $I(t)$ plus $\rho$ times the medium infectious class fraction $I_m(t)$. The incidence (number of new cases per unit time) is the product of the infectivity $\lambda(t)$ and the susceptible fraction $S(t)$. The formulation in terms of fractions in the classes makes the force of infection $\lambda(t)$ independent of the population size, which is consistent with numerous studies [27].

The transfers out of some epidemiologic classes are given by $\gamma I$, $\gamma I_m$, $\alpha R_1$, and $\alpha R_2$, so that the mean infectious period is $1/\gamma$, and the mean period of temporary immunity for those in classes $R_1$ and $R_2$ is $1/\alpha$ [28]. The contact rate $\beta$ and the transfer rates $\gamma$ and $\alpha$ are assumed to be positive. The basic reproduction number $R_0$ is defined as the average number of secondary cases in a completely susceptible population produced by a typical infective during the infectious period. Here $R_0 = \beta/\gamma$, since $\beta$ is the average number of contacts per day and $1/\gamma$ is the average infectious period in days.

The pertussis model as summarized in Figure 1 consists of ordinary differential equations for the changes in the class sizes and initial conditions at time 0. Because the dependent variables are the fractions of the population in the epidemiological classes,

$$S + I + I_m + R_2 + R_1 = 1. \quad (1)$$

If this equation is used to eliminate the variable $S$, then the four differential equations corresponding to the transfers in Figure 1 are:

$$\begin{align*}
\frac{dI}{dt} &= \beta(I + \rho I_m)(1 - I - I_m - R_2 - R_1) - \gamma I \\
\frac{dI_m}{dt} &= \beta(I + \rho I_m)R_1 - \gamma I_m \\
\frac{dR_2}{dt} &= \gamma(I + I_m) - \alpha R_2 \\
\frac{dR_1}{dt} &= \alpha R_2 - \beta(I + \rho I_m)R_1 - \alpha R_1 \quad (2)
\end{align*}$$

The initial conditions are the values of the class fractions at time 0. Consider the region

$$D = \{(I, I_m, R_2, R_1) | I \geq 0, I_m \geq 0, R_i \geq 0, I + I_m + R_2 + R_1 \leq 1\}. \quad (3)$$
This region can be shown to be positively invariant for the system (2), since no paths leave through any boundary. The right side of (2) is $C^\infty$, so unique solutions exist on maximal time intervals. Paths are bounded, since they stay in the region $D$, so solutions to (2) exist for all $t \geq 0$ [29, pp. 18-27]. Thus the model (2) is mathematically well-posed and is epidemiologically reasonable, since all of the fractions remain between 0 and 1.

2.1 Equilibria

Equilibria for the system (2) are found by setting the right sides equal to zero. The origin is an equilibrium of (2) in $D$ for all values of $R_0$; it is called the infection-free equilibrium. For $R_0 = \beta/\gamma > 1$, we now show that there is also a positive (endemic) equilibrium in $D$. All of the other variables can be solved in terms of $R_1$ to obtain

$$S = \alpha R_1/\lambda, \ I = \alpha R_1/\gamma, \ I_m = \lambda R_1/\gamma, \ R_2 = (1 + \lambda/\alpha) R_1,$$

where the force of infection $\lambda = \beta(I + \rho I_m)$ satisfies $\lambda = \beta \alpha R_1/(\gamma - \beta \rho R_1)$. If these are substituted into the equation (1), then $R_1$ satisfies the following quadratic equation

$$R_1^2 [\beta(1 - \rho)^2 + \beta \alpha (1 - \rho)/\gamma] + R_1 [\beta \rho + \alpha + 2\gamma (1 - \rho)] + \gamma (\gamma/\beta - 1) = 0.$$  \hspace{1cm} (5)

For $0 \leq \rho \leq 1$, the coefficient of $R_1^2$ is nonnegative and the coefficient of $R_1$ is positive; the constant term is nonnegative if $R_0 = \beta/\gamma \leq 1$ and is negative if $R_0 = \beta/\gamma > 1$. By the Descartes rule of signs, there is a positive root of this quadratic if and only if the basic reproduction number satisfies $R_0 > 1$. Thus for $R_0 \leq 1$, the infection-free equilibrium is the only equilibrium in $D$. But for $R_0 > 1$, the two equilibria are the infection-free equilibrium and the endemic equilibrium corresponding to a positive solution $R_1$ of (5).

2.2 Stability of the infection-free equilibrium

A local linearization of the system (2) at the origin reveals that the origin is locally asymptotically stable if $R_0 < 1$ and is unstable with a one dimensional unstable manifold tangent to the $I$ direction if $R_0 > 1$. We now use a Liapunov function to prove global stability below the threshold.

If $R_0 \leq 1$, then all solutions of (2) in the region $D$ approach the infection-free equilibrium at the origin.

Proof. Consider the Liapunov function $V = I + I_m$ with Liapunov derivative given by

$$V' = \beta(I + \rho I_m)(1 - I - I_m - R_2) - \gamma (I + I_m)$$

$$\leq [\beta(1 - I - I_m - R_2) - \gamma](I + I_m) \leq 0.$$

The last inequality holds because $R_0 = \beta/\gamma \leq 1$. The Liapunov-Lasalle theorem [29, pp. 296-7] implies that all paths in $D$ approach the largest positively


invariant subset of the set $E$ where $V' = 0$. Here $E$ is the set where $I = I_m = 0$. On the boundary of $D$ where $I = I_m = 0$, we have $R'_2 = -\alpha R_2$, so $R_2(t) = R_2(0)e^{-\alpha t} \to 0$ as $t \to \infty$. Also $R'_1 = \alpha R_2(0)e^{-\alpha t} - \alpha R_1$, so $R_1(t) = [R_1(0) + \alpha R_2(0)t]e^{-\alpha t} \to 0$ as $t \to \infty$. Thus the origin is the only positively invariant subset of $E$. Hence all solution paths in $D$ approach the origin.  

2.3 Stability of the endemic equilibrium

For $R_0 > 1$, the endemic equilibrium is given by (4) where $R_1$ is the positive root of (5). If the equations in (2) are divided by $\gamma$ and the new time variable is $\tau = \gamma t$, then the unit time becomes $1/\gamma$, $\beta$ is replaced by $\beta/\gamma$, and $\alpha$ is replaced by $\alpha/\gamma$. This rescaling and replacement of parameters is equivalent to setting $\gamma = 1$ in (2), so that the Jacobian of the rescaled system at the endemic equilibrium is

$$
J = \begin{bmatrix}
\beta S - \lambda - 1 & \beta \rho S - \lambda & -\lambda & -\lambda \\
\beta R_1 & \rho R_1 - 1 & 0 & \lambda \\
1 & 1 & -\alpha & 0 \\
-\beta R_1 & -\rho R_1 & \alpha & -\lambda - \alpha \\
\end{bmatrix},
$$

where $S = 1 - I - I_m - R_2 - R_1$, and $\lambda = \beta(1 + \rho I_m)$. At the endemic equilibrium (4) for the rescaled system, we have the identities $\beta S = 1 - \rho R_1$, and $\beta R_1 = \lambda/(\rho \alpha + \alpha)$, so that the Jacobian becomes

$$
J = \begin{bmatrix}
-\rho \lambda/(\rho \alpha + \alpha) - \lambda & \alpha \rho/(\rho \alpha + \alpha) - \lambda & -\lambda & -\lambda \\
\lambda/(\rho \alpha + \alpha) & -\alpha/(\rho \alpha + \alpha) & 0 & \lambda \\
1 & 1 & -\alpha & 0 \\
-\lambda/(\rho \alpha + \alpha) & -\rho \lambda/(\rho \alpha + \alpha) & \alpha & -\lambda - \alpha \\
\end{bmatrix},
$$

which depends on the three parameters $\lambda$, $\alpha$, and $\rho$. From these three parameters, $R_1$ and the basic reproduction number $R_0$ can be recovered using $R_1 = \lambda \alpha/[(\lambda + \alpha)(\lambda + \alpha + \alpha)]$, and $R_0 = \lambda/[R_1(\rho \alpha + \alpha)]$.

The characteristic equation for the eigenvalues of the Jacobian at this endemic equilibrium is a fourth degree polynomial given by $P_4(z) = z^4 + c_1 z^3 + c_2 z^2 + c_3 z + c_4 = 0$, where the coefficients are

$$
c_1 = 2\alpha + 1 + 2\lambda, \\
c_2 = \alpha^2 + 2\alpha + 3\alpha \lambda + 3\lambda + \lambda^2, \\
c_3 = [\alpha^2(1 + \lambda) + \alpha^2(\lambda(4 + \rho) + \lambda^2(1 + \rho)) + \alpha \lambda(1 + 3\lambda(1 + \rho) + \rho \lambda^2) + \rho \lambda^2 + 2\rho \lambda^3]/(\rho \lambda + \alpha), \\
c_4 = \lambda[\alpha^3 + \alpha^2(2\lambda + 2 + \rho) + \alpha \lambda(2 + \rho \lambda) + \rho \lambda^2]/(\rho \lambda + \alpha).
$$

The Routh-Hurwitz criteria [30] for the local asymptotic stability of the endemic equilibrium are $c_1 > 0$, $c_3 > 0$, $c_4 > 0$, and $c_1 c_2 c_3 - c_2^2 c_4 > 0$. The first three conditions are true by examining the coefficients above. The last condition is satisfied, because all terms remaining in the expansion after cancellation are
positive. Thus the endemic equilibrium is always locally asymptotically stable, so that periodic solutions never arise by Hopf bifurcation in this pertussis model. Hence we expect this model to have the same threshold behavior as the basic SIRS model \[31\], where the disease dies out when \( R_0 \leq 1 \) and goes to the endemic equilibrium when \( R_0 > 1 \). This is consistent with the behavior of the \( SIR_2R_1S \) model considered in \[23\].

3 The Pertussis Model with Three Removed Classes

This pertussis model shown in Figure 2 is similar to the pertussis model with two removed classes in the previous section, but this model has one more removed class \( R_3 \). The definitions of the classes, the transfers between classes, and the notation for this model are similar to those for the previous model. As shown in Figure 2, people move down through the sequence \( R_3R_2R_1S \) as immunity wanes, where \( R_3 \), \( R_2 \), and \( R_1 \) are the recovered classes with high, medium and low immunity, respectively. When people in \( R_1 \) with low immunity have an adequate contact with an infective, they enter the class \( I_m \) of infectious people with mild-disease and medium infectivity and then return to \( R_3 \) after the infectious period. As in the previous model, the relative infectivity is \( \rho \), and the force of infection is \( \lambda(t) = \beta(I + \rho I_m) \). The contact rate \( \beta \) and the transfer rates \( \gamma \) and \( \alpha \) are assumed to be positive. As before, the basic reproduction number \( R_0 = \beta/\gamma \) is the average number of secondary cases in a completely susceptible population produced by a typical infective during the infectious period.

The pertussis model here is an initial value problem corresponding to Figure 2. Here \( S(t) \), \( I(t) \), \( I_m(t) \), \( R_3(t) \), \( R_2(t) \), and \( R_1(t) \) denote the fractions of the population in each class at time \( t \), so that

\[
S + I + I_m + R_3 + R_2 + R_1 = 1. \tag{6}
\]

If this equation is used to eliminate the variable \( S \), then the five differential equations corresponding to the transfers in Figure 2 are:

\[
\begin{align*}
\frac{dI}{dt} & = \beta(I + \rho I_m)(1 - I - I_m - R_3 - R_2 - R_1) - \gamma I \\
\frac{dI_m}{dt} & = \beta(I + \rho I_m)R_1 - \gamma I_m \\
\frac{dR_3}{dt} & = \gamma(I + I_m) - \alpha R_3 \\
\frac{dR_2}{dt} & = \alpha R_3 - \alpha R_2 \\
\frac{dR_1}{dt} & = \alpha R_2 - \beta(I + \rho I_m)R_1 - \alpha R_1
\end{align*}
\tag{7}
\]

Here the relevant region is

\[
D = \{(I, I_m, R_3, R_2, R_1) | I \geq 0, I_m \geq 0, R_i \geq 0, I + I_m + R_3 + R_2 + R_1 \leq 1 \}. \tag{8}
\]

This region \( D \) is positively invariant for the system (7). Since the right side of (7) is \( C^\infty \), unique solutions exist on maximal time intervals. Paths stay in the region \( D \), so they are bounded and solutions to (7) exist for all \( t \geq 0 \) \[29, pp. 18-27\]. Thus the model (7) is also mathematically well-posed and is epidemiologically reasonable.
3.1 Equilibria

The equilibrium of (7) at the origin is called the infection-free equilibrium. For $R_0 = \beta/\gamma > 1$, there is also a positive (endemic) equilibrium in $D$. All of the other variables can be solved in terms of $R_1$ to obtain

$$S = \alpha R_1/\lambda, I = \alpha R_1/\gamma, I_m = \lambda R_1/\gamma, R_3 = R_2 = (1 + \lambda/\alpha) R_1,$$

where the force of infection $\lambda = \beta(I + \rho I_m)$ satisfies $\lambda = \beta \alpha R_1/(\gamma - \beta \rho R_1)$. If these are substituted into the equation (6), then $R_1$ satisfies the following quadratic equation

$$R_1^2[\beta(1-\rho)(2-\rho) + \beta \alpha(1-\rho)/\gamma] + R_1[\beta \rho + \alpha + \gamma(3-\rho)] + \gamma(\gamma/\beta - 1) = 0. \quad (10)$$

For $0 \leq \rho \leq 1$, the coefficient of the $R_1^2$ is nonnegative and the coefficient of $R_1$ is positive. The constant term is nonnegative if $R_0 = \beta/\gamma \leq 1$ and is negative if $R_0 = \beta/\gamma > 1$. By the Descartes rule of signs, there is a positive root of this quadratic if and only if the basic reproduction number satisfies $R_0 > 1$. Thus the infection-free equilibrium is the only equilibrium in $D$ when $R_0 \leq 1$; however, there is also the endemic equilibrium corresponding to a positive solution $R_1$ of (10) when $R_0 > 1$.

3.2 Stability of the infection-free equilibrium

A local stability analysis of (7) shows that the origin is locally asymptotically stable if $R_0 < 1$ and is unstable with a one dimensional unstable manifold if $R_0 > 1$. We use the same Liapunov function as in the previous model to prove global stability below the threshold.

If $R_0 \leq 1$, then all solutions of (7) in the region $D$ approach the infection-free equilibrium at the origin.

Proof. For the Liapunov function $V = I + I_m$, the Liapunov derivative is
For $R_0 > 1$, the endemic equilibrium is given by (9) where $R_1$ is the positive root of (10). Using the same rescaling and substitutions that were used in the previous model, the Jacobian here is

$$J = \begin{bmatrix}
-\rho \lambda/(\rho \lambda + \alpha) - \lambda & \alpha \rho/(\rho \lambda + \alpha) - \lambda & -\lambda & -\lambda & -\lambda \\
\lambda/(\rho \lambda + \alpha) & -\alpha/(\rho \lambda + \alpha) & 0 & 0 & \lambda \\
1 & 1 & -\alpha & 0 & 0 \\
0 & 0 & \alpha & -\alpha & 0 \\
-\lambda/(\rho \lambda + \alpha) & -\rho \lambda/(\rho \lambda + \alpha) & 0 & \alpha & -\lambda - \alpha
\end{bmatrix},$$

which depends on the three parameters $\lambda$, $\rho$, and $\alpha$. The equilibrium value $R_1$ and the basic reproduction number $R_0$ can be recovered from these parameter values using $R_1 = \alpha \lambda / [(\lambda + \alpha)(2\lambda + \alpha \lambda + \alpha)]$, and $R_0 = \lambda / [R_1(\rho \lambda + \alpha)]$.

Here the characteristic equation at the endemic equilibrium is a fifth degree polynomial given by $P_5(z) = z^5 + c_1 z^4 + c_2 z^3 + c_3 z^2 + c_4 z + c_5 = 0$, where the coefficients are

$$\begin{align*}
c_1 &= 3\alpha + 1 + 2\lambda, \\
c_2 &= 3\alpha^2 + 3\alpha + 5\alpha \lambda + 3\lambda + \lambda^2, \\
c_3 &= (\alpha^4 + \alpha^3(3 + \lambda + 4 + \rho)) + \alpha^2 \lambda(8 + 3\rho + \lambda^2(2 + 4\rho)) + \alpha \lambda(1 + \lambda(3 + 7\rho) + 2\rho \lambda^2 + 2\rho \lambda^3)/(\rho \lambda + \alpha), \\
c_4 &= (\alpha^4(1 + \lambda) + \alpha^3 \lambda(6 + \rho) + \lambda(1 + \rho)) + \alpha^2 \lambda(3 + \lambda(6 + 4\rho) + \rho \lambda^2) + \alpha \lambda^2(2 + 2\rho + 4\rho \lambda) + \rho \lambda^3)/(\rho \lambda + \alpha), \\
c_5 &= \alpha \lambda \alpha^2(\lambda + 3 - \rho) + \alpha \lambda(4 + \rho \lambda) + 2\rho \lambda^2)/(\rho \lambda + \alpha).
\end{align*}$$

All of the coefficients $c_i$ are positive. The Routh-Hurwitz criteria that are necessary and sufficient for the local asymptotic stability of the endemic equilibrium are that the Hurwitz determinants $H_i$ are all positive [30]. For a fifth degree polynomial these criteria are $H_1 = c_1 > 0$,

$$H_2 = c_1 c_2 - c_3 > 0,$$

$$H_3 = c_1 c_2 c_3 + c_1 c_5 - c_1^2 c_4 - c_3^2 > 0,$$

$$H_4 = (c_3 c_4 - c_2 c_5)(c_1 c_2 - c_3) - (c_1 c_4 - c_5)^2 > 0.$$
The following theorem gives criteria that guarantee that the first two conditions for Hopf bifurcation are satisfied [33, 34].

Let \( \alpha \) be the Jacobian. Thus condition 3) for Hopf bifurcation is also satisfied.

Substituting \( \mu \) into \( P(z) \) yields \( \omega = \omega(\mu) \). This Hopf surface can also be plotted in the three dimensional space of the parameters \( \alpha \), \( \rho \), and \( \lambda \); recall that rescaling time is equivalent to setting \( \gamma = 1 \). The Hopf surface in \( \alpha \rho R_0 \) space is intractable analytically, but we have plotted this Hopf surface using Mathematica in Figure 3. Figure 4 is a contour plot of the Hopf bifurcation surface. As part of the numerical calculations, we have verified transversality by showing that \( \frac{dH_3}{d\rho} > 0 \) at all points on the Hopf surface; that is, the real parts of the complex conjugate pair of eigenvalues do change sign as the Hopf bifurcation surface is crossed. Thus the first two conditions for Hopf bifurcation are satisfied by Theorem 3. Substituting \( z = i\omega \) into \( P_5(z) = 0 \) yields \( \omega = [(c_1c_4 - c_5)/(c_1c_2 - c_3)]^{1/2} \), so that the oscillation frequencies of the bifurcating periodic solutions near a point on the Hopf bifurcation surface are approximately equal to this \( \omega \). Zero is not a root and the pure imaginary roots \( \pm i\omega \) are not repeated roots, since \( P_5(i\omega) = 0 \) leads to a contradiction when the expressions for the coefficients are substituted. Thus condition 3) for Hopf bifurcation is also satisfied.

The existence of attracting periodic solutions of the rescaled system for parameter values inside the Hopf surface has been confirmed by finding some of them numerically using WINPP (a differential equations package produced and distributed free by Bard Ermentrout at the University of Pittsburgh).
Figure 3: Hopf bifurcation surface for the pertussis model with three removed classes. Level surfaces are shown for 0.01 increments of $\rho$. 

\[\begin{array}{c}
\end{array}\]
Figure 4: Contour plot of the Hopf bifurcation surface for the pertussis model with three removed classes. Level surfaces are shown for 0.01 increments of $\rho$. 

\[ R_0 \]
The periods for the bifurcating periodic solutions are about four years for a part of the Hopf bifurcation surface with $\alpha \in (0.02, 0.033)$, $\rho \in (0, 0.01)$, and $R_0 = \beta \in (1.7, 2.4)$. Hence this model with three removed classes does yield a possible explanation for the roughly four year period in the reported pertussis incidence data.

4 The Pertussis Model with Four Removed Classes

This third pertussis model shown in Figure 5 is similar to the two previous pertussis models, but it has four removed classes. This pertussis model is the ordinary-differential-equations analog without the birth-death process of the age-structured pertussis model used in [11, 13, 5]. The definitions, formulation, and notation are the same as those for the previous models. As shown in Figure 6, people move down through the sequence $R_4 R_3 R_2 R_1 S$ as immunity wanes, where $R_4$, $R_3$, $R_2$, and $R_1$ are the recovered classes with highest, high, medium and low immunity, respectively. As before, when people in $R_1$ have a contact with an infective, they enter the class $I_m$ infectious people with mild-disease and medium infectivity and then return to $R_3$ after the infectious period. When people in $R_2$ have a contact with an infective, they enter the class $I_w$ infectious people with weak-disease and low infectivity and then return to $R_3$. Here the relative infectivities are $\rho_m$ for those in $I_m$, and a lower value $\rho_w$ for those in $I_w$.

The equation for the sum of the fractions in the classes is

$$S + I + I_m + I_w + R_4 + R_3 + R_2 + R_1 = 1.$$  \hfill (11)

When this equation is used to eliminate the variable $S$, then the seven differential equations for the other classes in Figure 5 are:

$$dI/dt = \beta((I + \rho_m I_m + \rho_w I_w)(1 - I - I_m - I_w - R_4 - R_3 - R_2 - R_1) - \gamma I)$$
$$dI_m/dt = \beta(I + \rho_m I_m + \rho_w I_w)R_3 - \gamma I_m$$
$$dI_w/dt = \beta(I + \rho_m I_m + \rho_w I_w)R_2 - \gamma I_w$$
$$dR_4/dt = \gamma(I + I_m + I_w) - \alpha R_4$$
$$dR_3/dt = \alpha R_4 - \alpha R_3$$
$$dR_2/dt = \alpha R_3 - \beta(I + \rho_m I_m + \rho_w I_w)R_2 - \alpha R_2$$
$$dR_1/dt = \alpha R_2 - \beta(I + \rho_m I_m + \rho_w I_w)R_1 - \alpha R_1$$ \hfill (12)

The initial conditions are the values of the class sizes at time 0. Here the domain for the seven variables is

$$D = \{ \text{region in positive orthant } | I + I_m + I_w + R_4 + R_3 + R_2 + R_1 \leq 1 \}.$$  \hfill (13)

As before, this region $D$ is positively invariant, unique solutions exist on maximal time intervals, and paths are bounded, so the model (12) is mathematically and epidemiologically well-posed.
4.1 Equilibria

As before, the equilibrium of (12) at the origin is called the infection-free equilibrium. There is also a positive (endemic) equilibrium in $D$ when $R_0 = \beta/\gamma > 1$. All of the other variables can be solved in terms of $R_1$ to obtain

$$S = \frac{\alpha R_1}{\lambda}, \quad I = \frac{\alpha R_1}{\gamma}, \quad I_m = \frac{\lambda R_1}{\gamma}, \quad I_w = L(\lambda + \alpha)R_1/\alpha \gamma, \quad R_4 = R_3 = (\lambda + \alpha)^2 R_1/\alpha^2, \quad R_2 = (1 + \lambda/\alpha)R_1. \quad (14)$$

If these are substituted into the equation (11), then $R_1$ satisfies

$$R_1 = \frac{\lambda \alpha^2 \gamma / [(\lambda + \alpha)^2(2\lambda + \lambda \alpha + \alpha \gamma)]}{1 + 2 \alpha / \alpha} = 0. \quad (15)$$

and the force of infection satisfies

$$\lambda = \frac{(\beta/\gamma)}{\alpha + \rho_m \lambda + \rho_w \lambda(1 + \lambda/\alpha)}R_1. \quad (16)$$

In the previous two models, we solved the second equation for $\lambda$ and substituted into the first equation. Here the second equation is a quadratic in $\lambda$, so we reverse the procedure and substitute the first equation into the second to get the following cubic equation for $\lambda$.

$$\lambda^3(1 + 2/\alpha) + \lambda^2(2\alpha + 5\gamma - \beta \rho_w) + \lambda(\alpha^2 + 4\alpha \gamma - \alpha \beta(\rho_m + \rho_w)] + \alpha^2 \gamma(1 - \beta/\gamma) = 0. \quad (17)$$

Recall that $\rho_m$ and $\rho_w$ are between 0 and 1. For $R_0 = \beta/\gamma \leq 1$, all of the coefficients are nonnegative, so that there are no sign changes and hence no positive root by the Descartes rules of signs. Now consider the case when $R_0 = \beta/\gamma > 1$. The coefficient of $\lambda^3$ is positive, and the constant term is negative. If the coefficient of $\lambda^2$ is positive, then there is exactly one sign change. If the
coefficient of $\lambda^2$ is non-positive, then $\alpha + 4\gamma - \beta w < 0$, so that the coefficient of $\lambda$ is negative and there is only one sign change. Thus in both cases there is only one positive root $\lambda$, which is equivalent to the existence of a positive equilibrium value for $R_1$. The infection-free equilibrium is the only equilibrium in $D$ when $R_0 \leq 1$, but there is also the endemic equilibrium corresponding to a positive $\lambda$ and $R_1$ when $R_0 > 1$.

4.2 Stability of the infection-free equilibrium

As for the other two models, a local stability analysis of (12) shows that the origin is locally asymptotically stable if $R_0 < 1$ and is unstable if $R_0 > 1$. For this model we use a similar Liapunov function to show that below the threshold $D$ is the asymptotic stability region for the origin.

If $R_0 \leq 1$, then all solutions of (12) in the region $D$ approach the infection-free equilibrium at the origin.

Proof. For the Liapunov function $V = I + I_m + I_w$, the Liapunov derivative is given by

$$V' = \beta(I + \rho I_m + \rho w I_w)(1 - I - I_m - I_w - R_4 - R_3 - R_2 - R_1)$$

$$- \gamma(I + I_m + I_w) \leq 0,$$

where the last inequality holds because $R_0 = \beta/\gamma \leq 1$. Here the set $E$ where $V' = 0$ is the set where $I = I_m = I_w = 0$. As in the previous proofs, the differential equations for the $R_i$ can be solved successively to show that $R_4(t)$, $R_3(t)$, $R_2(t)$, and $R_1(t)$ approach 0 as $t \to \infty$. Thus the origin is the only positively invariant subset of $E$, so that all solution paths in $D$ approach the origin [29, pp. 296-7].

4.3 Stability of the endemic equilibrium and Hopf bifurcation

For $R_0 > 1$, the endemic equilibrium is given by (14) where $R_1$ corresponds to the positive root $\lambda$ of (17). Using the same rescaling so that $\gamma$ is replaced by 1, the Jacobian of the rescaled system at the endemic equilibrium is

$$J = \begin{bmatrix}
\beta S - \lambda - 1 & \rho_m \beta S - \lambda & \rho_w \beta S - \lambda & -\lambda & -\lambda & -\lambda & -\lambda \\
\beta R_1 & \rho_m \beta R_1 - 1 & \rho_w \beta R_3 & 0 & 0 & 0 & \lambda \\
\beta R_2 & \rho_m \beta R_2 & \rho_w \beta R_2 - 1 & 0 & 0 & \lambda & 0 \\
1 & 1 & 1 & -\alpha & 0 & 0 & 0 \\
0 & 0 & 0 & \alpha & -\alpha & 0 & 0 \\
-\beta R_2 & -\rho_m \beta R_2 & -\rho_w \beta R_2 & 0 & \alpha & -\lambda & -\alpha \\
-\beta R_1 & -\rho_m \beta R_1 & -\rho_w \beta R_1 & 0 & 0 & \alpha & -\lambda - \alpha
\end{bmatrix}.$$  

Here we use the substitutions

$$\beta S = \alpha^2/denom, \beta R_1 = \lambda \alpha/denom, \beta R_2 = \lambda (\lambda + \alpha)/denom,$$
also satisfied, so that Hopf bifurcation does occur. 

\[ P_r(z) = (z + 1)P_b(z) = (z + 1)(z^6 + c_1z^5 + c_2z^4 + c_3z^3 + c_4z^2 + c_5z + c_6), \]

Since one eigenvalue is -1, we can consider the polynomial equation \( P_b(z) = 0 \) in our Hopf bifurcation analysis. The expressions for the coefficients \( c_i \) are found to be positive. The Hurwitz determinants \( H_1, H_2, \) and \( H_3 \) are all positive, because all terms in their expansions have positive coefficients. The determinant \( H_4 \) is also found to be positive after combining a few terms. The determinant \( H_5 \) has some terms with negative coefficients and can be negative for certain parameter values, so the Routh-Hurwitz conditions that the Hurwitz determinants are all positive are not satisfied. The Hopf bifurcation surface where \( H_5 = 0 \) is found using Mathematica and the transversality condition \( \frac{dH_5}{d\omega} > 0 \) is satisfied everywhere on this surface, so that by Theorem 3 in the previous section, the first two conditions for Hopf bifurcation are satisfied. Algebraic combination of the real and imaginary parts of \( P_b(\omega) = 0 \) yields \( \omega = [(c_3c_5 + c_1^2c_4 - c_1c_2c_5)/H_3]^{1/2} \) with \( H_3 = c_1c_2c_3 - c_2^2 - c_4^2 + c_1c_5 \). Near a point on the Hopf bifurcation surface, the oscillation frequencies of the bifurcated periodic solutions are approximately equal to \( \omega \). Zero is not a root, since \( c_6 > 0 \). The imaginary roots \( \pm i\omega \) are not repeated roots, since \( P_b'(\omega) = 0 \) leads to a contradiction. Thus condition 3) is also satisfied, so that Hopf bifurcation does occur.

If the differential equations are rescaled so that \( \gamma = 1 \), then this Hopf bifurcation surface defined by \( H_5 = 0 \) lies in a four dimensional space of the parameters \( \alpha, \rho_w, \rho_m, \) and \( \lambda \). For various ratios \( \rho_w/\rho_m \) with \( \rho_w < \rho_m \), the plots of the Hopf bifurcation surface and the contour plots found using Mathematica are similar to those for the model with three removed classes as shown in Figures 3 and 4. Figure 6 shows this Hopf surface in the three dimensional space of the parameters \( \lambda, \rho_m, \) and \( \alpha \), with \( \rho_w = \rho_m/2 \). For this model it is not
Figure 6: Hopf bifurcation surface with $\rho_w = \rho_m/2$ for the pertussis model with four removed classes. Level surfaces are shown for 0.01 increments of $\rho_m$. 
Figure 7: Asymptotically stable periodic solution for the pertussis model with four removed classes with parameter values $R_0 = 5.4$, $\alpha = 0.011$, $\rho_m = 0.41$, $\rho_w = 0.001$, and $\lambda = 0.0077$.

feasible to convert to the parameters $\alpha$, $\rho_w$, $\rho_m$, and $R_0 = \beta$, since the equation for $\lambda$ in terms of $\beta$ is a cubic equation. Periodic solutions of the rescaled system have been found for different parameter values inside the Hopf surface using the differential equations package WINPP. Parameter values can be chosen to give periodic solutions with a period of about 4 years. For example, Figure 7 shows the unstable equilibrium point and the attracting periodic solution found using WINPP with the parameter values $R_0 = 5.4$, $\alpha = 0.011$, $\rho_m = 0.41$, $\rho_w = 0.001$, and $\lambda = 0.0077$. Corresponding to a 21 day infectious period with $\gamma = 1/21$ before the rescaling, the period of the periodic solution is $74 \times 21 = 1554$ days = 4.25 years.

5 Discussion

For the past seventy years, reported pertussis incidence in the United States has oscillated irregularly with a period of about four years [5]. What are possible explanations for these oscillations? An age-structured model for pertussis with four removed classes has been developed and used to study the current pertussis vaccination program in the United States and the effects of the addition of an adult booster program using the new acellular pertussis vaccine [11, 13]. Birth and death data were used to estimate the demographic parameters and pertussis data were used to estimate the epidemiological parameters in this model with both time and age dependence. Although this model had a damped 4 year period after the start of an adult booster vaccination program in the year 2000, it did not have any undamped periodic solutions. When the contact rates among the age groups were varied seasonally, the solutions of this pertussis model were periodic with a period of 1 year [5]. Thus periodic solutions with a period of 4 years did not arise through subharmonic resonance. However, multiplying...
all contact rates in the pertussis simulation model by a random factor in the
interval $[0.98, 1.02]$ each year did lead to irregular oscillations with a 4 year
average period and a magnitude consistent with the reported pertussis data [5].
Thus this yearly random contact rate factor corresponding to a 2\% stochasticity
is one possible explanation for the observed cyclic pertussis incidence. One can
hypothesize that this stochasticity could be due to randomness in the contacts
or due to yearly differences in the weather or in imported cases.

In this paper we have investigated three ordinary-differential-equations mod-
ells that are analogous to the compartmental pattern in the age-structured,
partial-differential-equations pertussis model [11]. The model with four removed
classes shown in Figure 5 is the direct analog. In Section 4 we find that this
model has periodic solutions for some parameter values. The periodic solution
shown in Figure 7 has a period of 4.25 years, so that periodic solutions with
periods of about 4 years occur for this model. Moreover, the parameter values
with $R_0 = 5.4$, $\alpha = 0.011$, $\rho_m = 0.41$, and $\rho_w = 0.001$ for the example in Figure
7 are plausible. An unpublished estimate of $R_0$ for the age-structured pertussis
model in [11] is 5.4. The baseline estimates used in [11] were a mean infec-
tious period of 21 days, a mean waiting time in the removed classes of 5 years,
and relative infectivities of $\rho_m = 0.5$ and $\rho_w = 0.25$. These lead to
$\gamma = 1/21$
(before rescaling) and $\alpha = [1/(5 \times 365)]/(1/21) = 0.011$ (after rescaling). The
infectivities $\rho_m = 0.41$, and $\rho_w = 0.001$ used in the calculations in Figure 7 are
lower than those used in the age-structured pertussis model, but it would not
be unreasonable to have the mildly infectious people be 0.41 times as infectious
as the full disease infectives and the weakly infectious people be a thousand
times less infectious. Thus periodic solutions with periods of about 4 years can
be obtained for this ordinary-differential-equations pertussis model with four
removed classes using plausible parameter values.

Do simpler ordinary-differential-equations pertussis models have periodic so-
lutions and if so, are the periods approximately four years and the parameter
values plausible? The pertussis model with two removed classes studied in
Section 2 does not have periodic solutions arising by Hopf bifurcation for any
parameter values. The pertussis model with three removed classes considered in
Section 3 does have periodic solutions for some parameter values. The Hopf bi-
furcation surface in this model occurs within the parameter region $0 < \rho < 1/3,$
$0 < \alpha < 0.035,$ and $1 < R_0 < 3$, and these parameter ranges are plausible. The
parameter region given in Section 3 with periods of about 4 years has $R_0$ in
$(1.7, 2.4)$, which is a realistic range. The range for the removal rate constant
$\alpha$ corresponds to mean waiting times in the removed periods between 1.7 and
2.9 years. These mean waiting times are short, but possible. The range with
$\rho < 0.01$ for the relative infectivity of the infectives with mild-disease is quite
low, but these values are not impossible. Thus the parameter region with pe-
riods of about 4 years for the pertussis model with three removed classes has
some extreme, but possible values.

In summary, periodic solutions with periods of about 4 years occur for the
pertussis models with three and four removed classes, so they both could explain
the observed 4 year periodicity in the pertussis incidence data, but the
parameters leading to these periodic solutions are more realistic for the model with four removed classes.

References


