

# How Should We Approach Adolescent and Adult Pertussis?

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## ABSTRACT

Previously considered a disease of childhood, pertussis is now also recognized as a significant problem for adolescents and adults; however, diagnosing pertussis remains problematic due to its nonspecific clinical presentation and the time delay, sensitivity/specificity, and expense of testing. To be effective, therapy is best started very early in the illness, when the illness is seldom recognized. Other than chemoprophylaxis in families with a non-immune infant, antibiotic therapy is controversial due to the ubiquitous nature of pertussis, its similarity to other respiratory infections, increased prevalence, prolonged outbreaks, and difficulties in determining true exposures in the general community. If antimicrobial therapy is used extensively for whooping cough prevention, drug reactions and increased bacterial resistance are expected. Likewise, without laboratory confirmation of infection, isolation of individuals is difficult and expensive. Fortunately, 2 new Food and Drug Administration-approved vaccines, 1 for adolescents and 1 for adolescents/adults, are now available. Both have been shown to be safe and to produce protective antibody responses. As vaccination of adolescent and adult groups is expanded, the rising incidence of pertussis in all age groups can be curtailed.

## INTRODUCTION

A recent public health perspective, "Adults Are Whooping, But Are Internists Listening?"<sup>1</sup> asks the question: "Why are internists [and other primary care physicians] not more aggressive in pursuing pertussis testing, treatment, isolation, and reporting of adolescents and adults with prolonged cough illness?" We be-

lieve there are practical, economic, and biologic reasons for this current reticence.

The first problem is that unlike non-immune infants with whooping cough, adolescents and adults with pertussis often do not whoop, and may not have a paroxysmal cough.<sup>2,3</sup> Therefore, without specific knowledge of a recent pertussis exposure, deciding who to test is problematic.

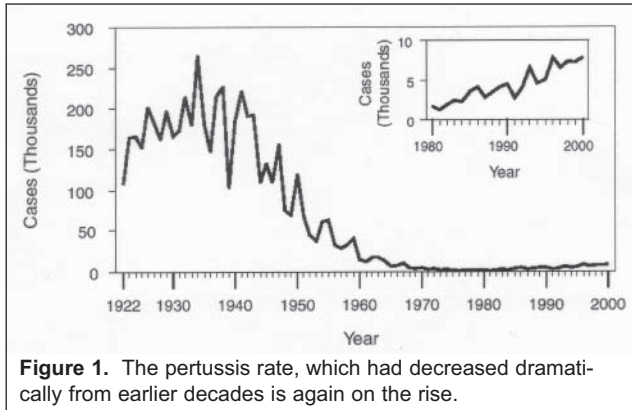
How to test is also problematic. Current serologic tests are cumbersome, must be timed appropriately to detect elevated titers, and a standardized test is not yet commercially available. In a referral laboratory, the pertussis direct fluorescent antibody (DFA) test has a sensitivity of 52% and a specificity of 98%.<sup>4</sup> However, DFA specificity is lower in general use, secondary to cross-reactivity to nasopharyngeal flora. Culture requires special media, and results may not be available for approximately 7 days and have a sensitivity of only 15%. A considerably more sensitive (95%) and faster test, the pertussis polymerase chain reaction (PCR), is now available.<sup>4</sup> Increased pertussis PCR testing has contributed to the rising recognition of pertussis in adolescents and adults.<sup>5</sup>

But does spending approximately \$75 for a pertussis PCR help a coughing patient? Once pertussis has progressed through the initial catarrhal phase, when it is seldom recognized, and past the very early paroxysmal coughing phase, antibiotic therapy reduces neither the length nor the severity of the illness.<sup>6,7</sup>

## EPIDEMIOLOGY

Pertussis occurs in approximately 3- to 4-year cycles,<sup>5</sup> with a peak incidence in mid to late summer. The true burden of pertussis is unknown. Reported pertussis cases represent only a fraction of actual cases. Reported cases peaked in the 1930s, and then declined after the introduction of routine childhood vaccination in the 1940s, but have started to rise again over the last 2 decades (Figure 1).<sup>8</sup> The percent distribution of reported pertussis has increased most significantly in older children (>10 years), adolescents, and adults (11.9% of cases from 1978-1981

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**Figure 1.** The pertussis rate, which had decreased dramatically from earlier decades is again on the rise.

compared to 49.8% of cases from 1997-2000).<sup>9</sup> Waning immunity from childhood vaccination, greater awareness of adolescent/adult disease, and wider availability of diagnostic tests such as PCR all contribute to the rise in reported pertussis in recent years.<sup>9</sup> In the United States, the estimated annual incidence is 800,000-3.3 million cases per year<sup>10</sup> with adolescent/adult incidence of 150-500 per 100,000.<sup>11,12</sup> The annual adolescent/adult attack rate is approximately 2%, and 12%-20% of prolonged coughs in adolescents and adults are pertussis-related.<sup>13</sup> The reported cases of pertussis in Wisconsin markedly increased from a 20-year average of <150 cases to 697 cases in 2003 and 5644 cases in 2004.

**ANTIBIOTICS TO TREAT PERTUSSIS**

In the general population, it would appear that to attempt to control pertussis with antibiotic therapy of patients and their contacts is akin to treating the tip of an iceberg. In institutions for the mentally disabled, hospital wards, or the Armed Forces, where all (exposed, carriers, and the ill) can receive prophylaxis over a short period, antimicrobials have reduced the secondary attack rate.<sup>14-17</sup> However, in these studies, drug-drug interactions occurred,<sup>14</sup> and patients who were reluctant to take antibacterials due to fear of side effects had to be coerced.<sup>17</sup> In more open groups, reductions in secondary attacks by antimicrobials have not been consistent. Retrospective and/or observational studies of household contacts have shown reductions of new *Bordetella pertussis* infection or of severity of the disease with prophylaxis. These studies indicate that secondary transmission of pertussis appeared to be reduced if therapy was given before secondary cases or before the end of the second week of a household index case.<sup>18-21</sup> However, even then the benefits of antibiotics were modest<sup>21</sup> and were applied when the epidemic was on the decline.<sup>20</sup> These cohort studies are offset by randomized, prospective studies (some blinded) that

have shown no or marginal benefit of antibiotic chemoprophylaxis.<sup>22-27</sup>

Erythromycin is approved by the Food and Drug Administration (FDA) for pertussis, and both the standard 7- and 14-day course are effective in eradicating carriage of *Bordetella pertussis*.<sup>28</sup> While not FDA-approved or well-studied, clarithromycin and azithromycin are the currently favored therapy due to better tolerability.<sup>29,30</sup> However, heavy use of macrolides or the alternative, trimethoprim sulfamethoxazole, would have consequences. For example, the disadvantages of azithromycin include cost (approximately \$60 for a 5-day course), common gastrointestinal side effects, and potential for drug-drug interactions with amiodarone, carbamazepine, phenytoin, cyclosporin, warfarin, and others. Furthermore, with widespread chemoprophylaxis, a few cases of serious adverse reactions would be expected (such as torsades, central nervous system dysfunction, liver dysfunction, ototoxicity, and severe skin reactions). Also, increased antibiotic use will trigger a concomitant increase in the already widespread multi-drug resistance of community pathogens.<sup>31</sup> Antibiotics are already inappropriately prescribed for acute viral bronchitis. Advocating antibiotics for either chemoprophylaxis or possible pertussis cases, which has not been demonstrated to shorten an outbreak, will further open the floodgates of antibiotic misuse.

**DILEMMAS WITH THE PUBLIC HEALTH RECOMMENDATIONS**

The Public Health pertussis case definitions (clinical, confirmed, probable, or suspect) are complex.<sup>32</sup> Clinicians are requested to test, isolate, treat, and report not only confirmed cases but also probable cases before test results are available. Probable cases are defined as patients with cough of longer than 2 weeks with paroxysms, whoop, or post-tussive vomiting without confirmatory testing. The latter 2 clinical findings are unusual in adolescent and adult pertussis, and paroxysms, which are poorly defined and nonspecific, occur in approximately 60%. How many health care professionals remember and have the time to report patients with the unproven diagnosis of “probable pertussis” to Public Health before the results of testing are available, when other contagious diseases verified by positive tests are increasingly reported electronically by laboratories? And how many health care professionals would, themselves, remain isolated for 5-7 days of antibiotic therapy if their pertussis test was positive, let alone for 3-7 days pending test results?

Furthermore, for patients manifesting a prolonged cough with or without paroxysms after exposure to a confirmed case, Public Health advocates testing, isolating, treating, and reporting before test results are available. What constitutes an exposure is difficult to determine, and cough illnesses are common due to respiratory viral infections.<sup>33</sup> Even at the peak of a pertussis epidemic, only approximately 25% of those tested are PCR positive. In addition, close contacts, definitions of which are problematic and vary with the situation, are recommended to receive antibacterials. As clinicians who take calls when local schools have pertussis cases, we can attest to the difficulties in attempting to apply contact guidelines. And logistically, how does one prescribe antibacterials to large numbers of persons? In Wisconsin, it is illegal to prescribe to persons who have not been established with the physician. Such laws help protect the public and clinicians from problems that can lead to medicolegal issues. Finally, outbreaks of whooping cough can last as long as 6 months. Many are reluctant to accept repeated courses of antibiotics after each repeat exposure. In summary, the current Public Health recommendations are impractical and expensive.

### **COSTS OF PERTUSSIS**

In the United States, the morbidity of severe pertussis accounts for approximately 1400 hospitalizations per year. Mortality is rare, with approximately 16 deaths per year, primarily in non-immune infants.<sup>34</sup> Unfortunately, there has been a small but significant rise in infant pertussis-related mortality in recent years,<sup>35</sup> and adolescents and adults are often the source of infection for non-immune infants who are most vulnerable to morbidity and mortality.<sup>26,36,37</sup>

Morbidity in adolescents and adults is significant as well. Adolescent and adult pertussis causes 80% to cough >21 days, and 27% to cough >90 days.<sup>13</sup> Other symptoms include sleep disturbance (50%-80%), pharyngeal pain (37%), flu-like illness (30%), and headaches (14%). Rare, severe complications include pneumothorax, inguinal herniation, pneumonia, fractured rib, carotid artery dissection, and seizures. Direct medical expense is estimated at \$326 per adolescent/adult case, and indirect cost, such as loss of work and school, is substantial.<sup>38</sup> By the time of the diagnosis of adolescent/adult pertussis, an average of 3.7 physician visits have occurred, and 1.2 courses of antibiotics have been given.<sup>39</sup> Resistance in human bacterial flora must result from attempts to treat this annoying cough.

In more than 50% of cases, the source of adolescent/adult pertussis is nonhousehold environments.<sup>20</sup> Once established in a medical institution, pertussis can be difficult and expensive to control due to the slow spread of infection between patients and staff. For example, pertussis in one pediatric hospital led to \$85,400 in total control cost.<sup>40</sup> A nursing home outbreak led to a 27% attack rate in the 70-79 year age group,<sup>41</sup> presumably due to declining natural immunity, which is estimated to last approximately 15 years.<sup>42</sup> Thus, pertussis is costly.

### **TIME FOR A VACCINE APPROACH**

So how should we approach pertussis? We believe that focused screening and chemoprophylaxis of close contacts of a non-immune infant, if done before 2-3 weeks of the primary case, may be cost effective. However, whooping cough will be best controlled with communitywide immunization.

Two non-child pertussis vaccines (Tdap) are now available, 1 for adolescents only, with 3 components; and a second, 5-component vaccine for adolescent and adult pertussis. Both are combined with adult formulation tetanus-diphtheria (Td).<sup>43</sup> Both are effective in creating protective antibody levels significantly higher than those generated by the primary 3 doses in infants. Neither vaccine has reaction rates significantly different from the standard Td.<sup>43</sup> Reactions include local pain, erythema, short-lived fevers (1%-5%), and extensive but short-lived limb edema (1 in 3000). Such edema reactions have been seen with multiple other vaccines, such as pneumococcal, influenza, Td, and DTaP (33% after fourth dose, 20% after fifth dose).<sup>44</sup>

Adolescent and adult pertussis vaccine has now been used in Europe and Canada for more than 5 years. Epidemiologic data have demonstrated the availability of adolescent/adult pertussis vaccine to decrease pertussis cases in Canadian provinces and territories.<sup>45-46</sup> For example, Tdap vaccine was introduced in Newfoundland in 1999, including a school-based program for those aged 14-16 years. Reported pertussis from 2000-2004 declined more than 5-fold compared with that from 1991-1999, and in an epidemic year (2003), cases were almost exclusively confined to those who did not receive the Tdap vaccine.<sup>47</sup> In 2003, Canada recommended that Tdap be used as a single booster dose in place of Td for adolescents and adults to protect against pertussis.<sup>48</sup> In the United States, the results of the first prospective, randomized clinical efficacy trial of Tdap vaccine were recently published and demonstrated the ability of Tdap to protect adolescents and adults from pertussis.<sup>49</sup> Overall, scientific and epide-

miologic data have shown Tdap to be safe, immunogenic, and effective for pertussis.

Following FDA approval of the new Tdap vaccines in the United States, the Advisory Committee on Immunization Practices (ACIP) unanimously recommended that Tdap be used instead of Td for both adolescents and adults <65 years who are due for Td booster vaccines. Experts agree that vaccinating this susceptible population is the best way to reduce the spread of pertussis, including the spread to non-immune infants.<sup>50,51</sup> Further studies will be needed to assess safety, efficacy, and cost effectiveness of recurrent boosters—and the ability of the new vaccines to control recognized outbreaks, including in the elderly—in lieu of repeated and questionable courses of antibiotics.

At this time, public and private sectors should combine their efforts to improve community immunity against pertussis. As safety and efficacy studies of the recently FDA-approved adolescent/adult pertussis vaccines are confirmed by extended experience, immunization—not widespread antibiotic use of marginal public health benefit—should become the global health approach to pertussis control.

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