Pertussis, Still a Formidable Foe

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Pertussis disease remains a major global health problem. Both the public and health care professionals remain poorly informed about the disease caused by *Bordetella pertussis*. Control is possible. There are now many publications highlighting important immunization strategies to enable significant control of the mortality and morbidity caused by pertussis.

Ask family physicians about pertussis, and the likely response will be threefold: that it is a condition of infancy or childhood, that pertussis has been conquered by immunization, and that diagnosis of pertussis disease is too difficult or cannot be determined by laboratory diagnostics. Ask internal medicine physicians, or even respiratory physicians, and similar responses are frequently offered. But is this perspective correct? Ask pediatricians, and they will respond by saying that pertussis is a significant problem in childhood, even though immunization is available and has high coverage in many places, so, yes, pertussis disease is a problem for childhood, and, no, this has not been eliminated as a medical problem, in spite of immunization. Ask infectious diseases physicians, and they will likely respond by highlighting that pertussis disease is around, but there is an uncertainty of incidence, because considering pertussis disease clinically or testing for *Bordetella pertussis* is not routine. What, then, is the situation regarding pertussis disease? There are data, there are opportunities for intervention, there is urgent need for better understanding of this important disease, and there is urgent need for better public health policy for pertussis disease prevention.

EPIDEMIOLOGY

From a public health perspective, pertussis disease is a problem in developed, urbanized, apparently immunized communities, as well as in the developing world. Globally, it is estimated that 50 million cases occur annually, 90% of which are in developing countries, which result in >400,000 deaths each year [1]. Many of these deaths are likely to be during infancy. Global reported pertussis incidence rates (some based on clinical confirmation only in those countries with limited access to laboratory services), which, of course, greatly underrepresent actual cases, are given in table 1, which shows that there is extensive disease occurring globally.

In the prevaccine era, pertussis was a universally present disease, with cyclic peaks every 2–5 years. Reported cases averaged 157 per 100,000 persons in the United States and occurred almost exclusively in unvaccinated children [2, 3]. The early use of whole-cell vaccines and the US vaccination schedule were highly effective and reduced the incidence of reported pertussis to <1 case per 100,000 persons during the 1970s. Since 1984, there has been a modest increase (although some would call it a resurgence) in the reported incidence of pertussis, to 8 cases per 100,000 persons, with cyclic peaks still occurring at 2–5-year intervals [4, 5]. It is believed that endemic adolescent and adult disease is responsible for the cyclic pattern still seen in unvaccinated children.

Reported incidences have a range of 0.1–200 cases per 100,000 [2, 3]. Within the United States, it is estimated that there are between 800,000 and 3.3 million cases per year [2]. A recent review of the situation in the United States [6] amplifies the call for the medical community to adhere to the Advisory Committee on Immunization's pertussis control policy. In 1990, Australia—a developed country of 20 million people with high vaccination rates—instituted the National Notifiable Diseases Surveillance System (NNDSS) active surveillance. There were 19,815 notifications of pertussis to the NNDSS during 1991–1996. This yields a pertussis rate of 22–57.6 notifiable cases per 100,000 Australian population for this period [7]. Given that this rate is for notifiable cases only, it will be a conservative estimate; the real figure is considerably higher (suggested "true" vs. notified cases is on the order of 3–100-fold higher). It should also be noted that >60% of notifications involved persons aged ⩾10 years [8]. In 1998, for

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Table 1. World Health Organization regional and global summaries of pertussis incidence, 1980, 1990, and 1996–2005.

	Year											
Location	1980	1990	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Africa	367,961	89,515	35,382	12,101	38,961	11,066	52,008	50,386	19,452	16,418	26,335	22,139
Americas	123,763	38,009	17,901	16,496	23,375	22,089	18,144	12,811	15,162	12,756	26,194	8747
Eastern Mediterranean	171,631	27,437	2823	3210	4367	2840	2112	4257	2650	1161	81,987	5164
Europe	90,546	129,735	54,745	67,307	56,317	48,897	53,675	31,084	25,176	25,530	42,220	26,425
Southeast Asia	399,310	156,028	22,479	41,940	46,666	127,76	34,930	37,813	43,250	39,371	39,002	37,764
Western Pacific	829,173	35,653	8009	25,953	15,875	17947	25,282	32,182	30,682	11,348	21,106	21,560
Global	1,982,384	476,377	141,339	167,007	185,561	115,615	186,151	168,533	13,6372	106,584	236,844	121,799
No. of countries	151	164	155	163	151	156	159	162	162	150	165	156

NOTE. Data are no. of reported cases, unless otherwise stated. Data are available at http://www.who.int/immunization_monitoring/diseases/GS_Pertussis.pdf.

example, there were 2260 pertussis notifications for people aged ⩾20 years. This was associated with ~15,200 lost work days, ~8400 general practitioner visits, and ~4300 prescriptions [9].

Thus, pertussis is an active disease, is costly, and has much variance globally and locally, likely due to differences in diagnosis, case definitions, surveillance, vaccination strategies, and herd immunity, factors that underlie some of the confusion about pertussis as a disease.

PERTUSSIS DISEASE IN ADULTS AND ADOLESCENTS

Although *B. pertussis* infection is not generally perceived to be as serious a problem among adolescents and adults as it is among neonates and infants, it does represent a significant health burden in these older age groups, including elderly persons [7]. Clinical manifestations are often atypical, especially in previously vaccinated individuals, ranging from upper respiratory infection symptoms with mild cough to severe, persistent cough [5]. However a significant number of adults do have typical symptoms of paroxysmal cough, whoop, and posttussive vomiting, which can be severe [10]. Studies indicate that 12%–32% of adolescents and adults with a coughing illness lasting at least 1–2 weeks are infected with *B. pertussis* [10]; the percentage is dependent on which antigens were used in the serological tests. Most adolescents and adults (80%) with pertussis disease have a cough that lasts ⩾21 days [11], and many (27%) are still coughing at 90 days [10, 12].

Pertussis-related complications, some of which may be serious [13], also occur fairly frequently in adolescents and adults [14]. Although hospitalization due to pertussis disease is highest for infants, it is not an infrequent occurrence among adolescents and adults [15]. However, mortality among hospitalized patients with pertussis is rare for those aged >10 years; in reported cases—likely, therefore, to be more severe—it has been cited as 0.1% [16, 17].

Although disease burden remains highest among infants aged <1 year, the reported incidence of pertussis disease in adolescents and adults is increasing in many countries [12, 18]. The increase in pertussis among adolescents and adults may be due to multiple factors, including waning vaccine-induced immunity and increased disease recognition, diagnosis, and reporting. Although it is not certain to what extent the change in reported pertussis epidemiology in the postvaccination era is real, it is clear that adolescents and adults are commonly and regularly infected with *B. pertussis* and, therefore, are potentially a major source of pediatric infection [5].

In a Swedish household study [19], 41% of adults exposed to study children with pertussis disease showed laboratory signs of pertussis infection; however, 44% of those adults were asymptomatic. Older vaccinated children are also commonly infected; nevertheless, they are less likely to have cough symptoms and are thus less likely to transmit *B. pertussis* infection to infants.

There is widespread agreement that parents are a common source of *B. pertussis* infection for infants [20, 21]. Siblings, grandparents, aunts, and uncles are also potential sources of infection [22, 23]. Although German data have indicated a very similar level of antipertussis toxin and other pertussis-related antibodies in pediatric health care workers and non–health care workers [24], it is parents' increased risk of coming into contact with unprotected newborns that also makes this adult subgroup a risk to the young [25]. One serological study reported annual incidences of *B. pertussis* infection as high as 4%–16% among health care workers [26]. Furthermore, it was shown that the annual incidence of *B. pertussis* infection among physicians in training and among emergency department staff is higher than for any disease against which health care workers are vaccinated, with the exception of influenza [27]. Adolescents are also an important reservoir of infection for infants and other household members [20].

PERTUSSIS DISEASE IN INFANTS

Infants remain the group most vulnerable to *B. pertussis* infection. During 1997–2000, in the United States, 20% of all

pertussis cases required hospitalization; 90% of patients were infants aged <1 year [4]. Infant disease is somewhat different from that in older children and adults. Apnea may be a key presenting symptom, as may be pulmonary hypertension or overwhelming multiorgan failure, with minimal respiratory symptoms. Compared with older patients, infants are much sicker for much longer.

Incidence rates vary widely, but the general resurgence of pertussis is greater in the infant population than in the general population [28]. There is also evidence that death certificates underestimate pertussis death rates, particularly in those aged <4 months [29]. This group is highly susceptible to pertussis, with outbreaks occurring in neonatal intensive care units [30].

The difficulty is that infants aged <6 months are inadequately protected, because it takes 3 doses of vaccine to provide adequate protection. In most international schedules, this does not occur until age 6 months. The conundrum for this group is that they are not only inadequately protected but also have high rates of exposure to older family members and health care workers and experience the most-serious consequences of disease.

DIAGNOSIS

Clearly, pertussis disease is poorly recognized. The classic phenotype of the whooping infant is well known, but adolescents and adults with a nagging, persistent cough rarely present to the family physician; if they do, the majority of clinicians do not usually consider the disease to be due to *B. pertussis.* There are at least 2 reasons for this: confusion over the clinical phenotype of pertussis disease and inconsistent and poorly standardized laboratory diagnostics.

There are at least 2 different standards for the clinical diagnosis of pertussis—one used in the evaluation of vaccine efficacy and another promulgated by the World Health Organization as a clinical standard—and neither has been reinterpreted in the context of newer diagnostics, such as PCR of single-serum pertussis toxin IgG. The World Health Organization–recommended case definition is a case diagnosed as pertussis by a physician or a person with a cough lasting at least 2 weeks with at least 1 of the following symptoms: paroxysms of coughing, inspiratory whooping, and/or posttussive vomiting without other apparent cause. Criteria for laboratory confirmation are: isolation of *B. pertussis,* detection of genomic sequences by PCR, or positive paired serology.

It is likely that neither clinical standard is particularly useful for the adult in the developed world who presents to the local family doctor with persistent cough [4]. Therefore, newer clinical criteria for such situations need to be articulated, although perhaps the single-most-important issue is awareness—awareness that pertussis is an adult disease that occurs regularly in those previously immunized. Once the possibility is considered, then application of an appropriate laboratory diagnostic is recommended.

Laboratory diagnostics have come a long way since culture on Bordet-Gengou medium. For diagnosis of acute cases in a medical setting, where there is access to nasopharyngeal aspirates or throat swabs, real-time PCR will provide rapid definitive diagnosis. Standardization is, however, a problem. The European Research Programme for Improved Pertussis Strain Characterization and Surveillance published a consensus report in 2005 that addressed the methodology and the application of real-time PCR for detecting *Bordetella* DNA [31]. It concluded that real-time PCR is more sensitive than culture for the detection of *B. pertussis* and *Bordetella parapertussis,* especially after the first 3–4 weeks of coughing and after antibiotic therapy has been started.

Although PCR is particularly useful in children and during outbreak situations, there is now sufficient experience to recommend single-specimen IgG to pertussis toxin. However, there are difficulties with standardization. A new PT reference

Table 2. Control options.

Intervention	Purpose		References
	Primary	Secondary	
Universal adolescent immunization	Reduce pertussis incidence in adolescents; promote herd immunity	Reduce transmission to infants	[35]
Universal adult immunization	Reduce pertussis incidence in adults; promote herd immunity	Reduce transmission to others, particularly young infants	[36, 37]
Selective immunization of family around a newborn	Reduce transmission to infants	Reduce morbidity in family	[38, 34]
Selective immunization of health care workers	Reduce transmission to patients	Reduce morbidity in health care workers	[39, 40]
Selective immunization of child care workers	Reduce transmission to children	Reduce morbidity in child care workers	[33, 41]
Immunization of newborns at birth[a]	Reduce pertussis disease in infants	Reduce pertussis morbidity in childhood	…
Immunization of mothers during pregnancy[a]	Reduce pertussis disease in newborns	Reduce pertussis morbidity in mothers	…

[a] Insufficient evidence of efficacy.

serum is being developed; once this is standardized, there will be greater reliability in this assay.

PREVENTION

Because this disease can be difficult to recognize clinically, with variable and poorly standardized laboratory diagnostics, another strategy is necessary for control; indeed, the only strategy currently available for control of *B. pertussis* is immunization.

Since 2001, a multidisciplinary group of international experts in *B. pertussis* and pertussis disease have met as the Global Pertussis Initiative, to examine all the issues involving pertussis disease. Their findings have been summarized elsewhere [32–34]. Given all the known epidemiologic data, the Global Pertussis Initiative examined options for disease control. An outcome of such deliberations was the systematic examination of the options of universal vaccination of adults every 10 years; universal immunization of adolescents; selective immunization of new mothers, family, and close contacts of newborns (the cocoon strategy); selective immunization of health care workers; selective immunization of child care workers; immunization of newborns at birth; and immunization of mothers during pregnancy. The options for control are summarized in table 2.

Using best available evidence, the Global Pertussis Initiative strongly endorsed the policy that regular schedules of immunization against pertussis, which is available in most countries, need to be endorsed and adhered to, with systematic and routinized delivery infrastructure and surveillance to monitor effectiveness.

There is now sufficient evidence to recommend routine adolescent immunization to boost childhood immunizations, that targeted immunization to the close family around a newborn be provided (the cocoon strategy), and that health care and child care staff be immunized. There is still insufficient evidence to recommend, at this time, immunization of the newborn at birth or of pregnant mothers. Regarding regular (every 10 years) vaccination of adults, there is sufficient evidence that this intervention is likely to reduce the morbidity of pertussis disease in adults. Doubts, however, remain about the overall likely effectiveness of regular adult immunization. There is such low awareness of pertussis in adults that it is highly unlikely that either the medical profession or the public will, at this time, seek regular immunization. Such lack of awareness indicates that stronger public health policy for regular pertussis immunization needs to be endorsed and communicated. Given the low awareness of pertussis among the medical community as well as the general public, targeted campaigns to those most at risk is at least an acceptable "patch" at this time.

CONCLUSIONS

We discussed at the beginning of this report the fact that many medical professionals are insufficiently aware of the morbidity/mortality of pertussis disease and of the prevention strategies available. Certainly, pertussis immunization has drastically reduced disease incidence, but pertussis continues to be a serious problem for infants and a significant cause of respiratory morbidity for adolescents and adults. Greater awareness of the public health morbidity and mortality of pertussis, thinking of pertussis as a possible cause of coughing illness in adults, intensive immunization adherence for all those in contact with infants, and adherence to routine immunization schedules will go a long way to reducing the burden of disease due to *B. pertussis*.

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