The Re-Emergence of Pertussis in Israel

Larisa Moerman MD MPH[1], Alex Leventhal MD MPH MPA[2], Paul E. Slater MD MPH[1], Emilia Anis MD MPH[1], Ruth Yishai PhD[3] and Esther Marva PhD[3]

[1]Department of Epidemiology, [2]Public Health Services, and [3]Central Laboratories, Ministry of Health, Jerusalem, Israel

Key words: pertussis, epidemiology, Israel, incidence, re-emergence

Abstract

Background: Pertussis is the only vaccine-preventable disease that has re-emerged in Israel. The reported crude incidence of the disease increased 16-fold since 1998.

Objectives: To describe the epidemiology of pertussis and explain the substantial increase in reported pertussis incidence in Israel in recent years.

Methods: Crude and specific pertussis incidence by age, patient immunization status, hospitalization rate, and national immunization coverage rate were calculated from information provided by the public health offices of the Ministry of Health.

Results: The reported crude incidence of pertussis increased from 1–2/100,000 in 1994–98 to 23/100,000 in 2004. The trend was observed in all age groups, being most prominent in infants under age 1 year and in children aged 5–14. The incidence of pertussis was substantially higher in unvaccinated and partly vaccinated compared to fully vaccinated persons. Fifteen percent of notified cases were hospitalized, but in infants under age 1 year the hospitalization rate was 50%. National pertussis immunization coverage by age 2 years was stable during the last 10 years.

Conclusions: There are several possible explanations for the re-emergence of pertussis in Israel. The most plausible reason seems to be the waning of vaccine-induced immunity in face of infrequent natural exposure to the infectious agent and lack of a pertussis vaccine booster dose after age 1.

IMAJ 2006;8:308–311

Pertussis is an endemic worldwide disease that affects about 40 million people annually [1]. Susceptibility in unvaccinated individuals is universal. The disease is common in young children, but also occurs in adolescents and adults despite prior disease or active immunization [2-4]. The introduction of pertussis vaccine to the routine immunization program in Israel in 1957 resulted in a 100-fold decline in pertussis incidence in the 1960s and 1970s. For 40 years pertussis containment was satisfactory, with a stable 1–2/100,000 annual incidence rate and outbreaks of modest magnitude every 3–4 years.

Since 1999, pertussis seems to have re-emerged in Israel, showing a consistent increase in reported annual incidence. Similar trends were reported in the last 10 years in many countries with high immunization coverage rates, including the United States, Canada, the Netherlands and France [5-8]. Although immunization coverage with killed whole-cell pertussis vaccine was high and stable during the past 10 years, both the medical community and the public demanded the change to acellular pertussis vaccine. This pressure influenced the Israel Ministry of Health to introduce the acellular pertussis vaccine in 2002 with the hope of increasing pertussis immunization compliance still further. In this report, we assess and analyze pertussis morbidity in Israel and suggest possible explanations for its resurgence.

Methods

Pertussis has been notifiable in Israel since the early 1950s. Practitioners are required to notify all new cases to the local public health office. The 15 public health offices and the Army Health Branch (since 2004) report new cases to the Department of Epidemiology of the Ministry of Health on a weekly basis. Each notification includes: age, gender, nationality, address, date of disease onset, laboratory method of pertussis diagnosis, and the number of pertussis vaccine doses received by the patient in the past.

Any clinical case reported by a physician is considered to be pertussis, and no laboratory confirmation is required for the case to be included in Health Ministry statistics. In fact, serologic or polymerase chain reaction confirmation is sought in most cases in various government, hospital and community laboratories. These laboratory methods are not standardized nationally, and the Ministry of Health has not issued laboratory criteria for confirmation of pertussis diagnosis. Nevertheless, we will indicate the proportion of pertussis cases notified in recent years for which laboratory support was provided.

Public health office epidemiologic nurses investigate each reported case and obtain demographic information as well as information on the immunization status of the patient and his/her family from available immunization records. National immunization coverage is calculated every year by the public health offices and submitted to the Department of Epidemiology, which prepares an annual national summary. The calculation is based on a representative sample of children born in each health district and registered in the public Mother and Child Health Services.

Results

National incidence

In the 1950s, before the introduction of pertussis vaccine, about 10,000 cases of pertussis were reported annually to the Ministry of Health. In the early 1960s, following the implementation of routine pertussis immunization, the annual incidence declined to a few hundred cases per year, and for about four decades remained at 1–2 per 100,000, punctuated by small outbreaks every 3–4 years. The reported crude incidence of the disease started to increase in 1999 and reached 23 per 100,000 in 2004 [Figure 1].

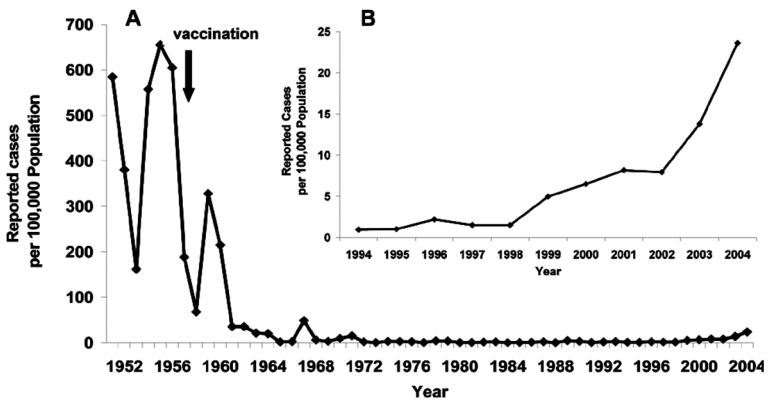

Figure 1. Annual reported cases of pertussis per 100,000 population, Israel. **[A]** 1951–2004, **[B]** 1994–2004.

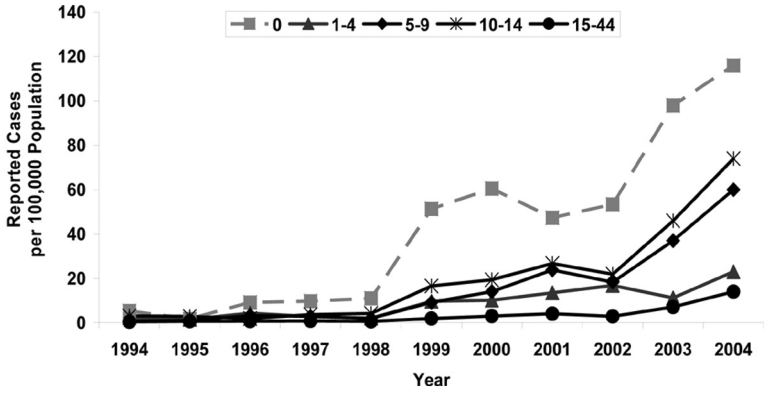

Figure 2. Reported cases of pertussis per 100,000 population by age and year, Israel, 1994–2004.

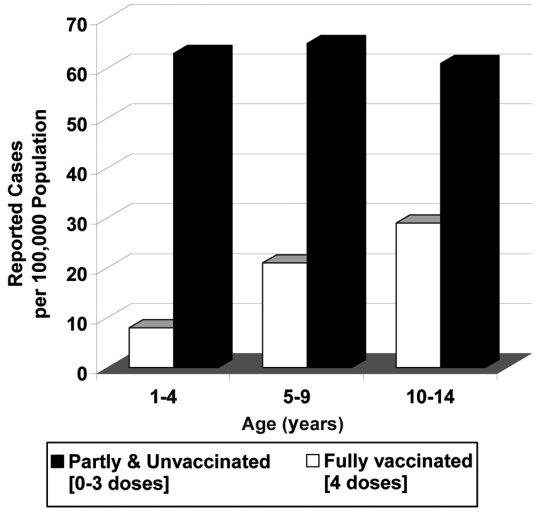

Figure 3. Reported cases of pertussis per 100,000 population by pertussis vaccination status, Israel, 2000–2004.

Age-specific pertussis incidence

Increased pertussis incidence was observed in all age groups in 1999–2004; it rose from 11 per 100,000 in 1998 to 116 per 100,000 in 2004 in infants under age 1 year; from 2 to 23 per 100,000 in 1–4 year olds; from 1.9 to 60 per 100,000 population in children aged 5–9; 4.2 to 74 per 100,000 in youngsters 10–14; and 0.6 to 14 per 100,000 in persons aged 15–44 [Figure 2].

Although during 1999–2004, the highest age-specific incidence rate occurred in infants under age 1 year, the most prominent rise in incidence, about 30-fold, was observed in children 5–9 years of age.

Pertussis incidence by vaccination status

The estimated incidence in unvaccinated and partly vaccinated children aged 1–15 years old in 2000–2004 was considerably higher than in fully vaccinated children (four doses). The highest ratio of incidence in unvaccinated and partly vaccinated children compared with those vaccinated, about 8:1, was in children aged 1–4 years [Figure 3].

Pertussis diagnosis supported by the laboratory

Table 1 shows the proportion of notified cases of pertussis supported by laboratory methods. This proportion has remained stable and high (85–93%) throughout the period of pertussis re-emergence.

Hospitalization rate

Fifteen percent of pertussis cases in the years 2000–2004 were hospitalized. The hospitalization rate was inversely related to age: about 50% of infants and only 2–3% of adolescents and adults were treated in hospitals, reflecting the variable severity of the disease in the different age groups.

Deaths attributed to pertussis

There were 16 deaths attributed to pertussis during 1970–2004, three of them in the last 4 years. All deaths were in young unvaccinated babies.

Immunization coverage rate

No changes in annual immunization coverage in 2 year old children were observed during the last decade and the rate remained stable: 92–93% of 2 year olds had received four doses of pertussis vaccine, and 94–95% had received three doses.

Discussion

The incidence of pertussis in Israel increased from a few cases reported each year in the 1970s and 1980s to over 1600 cases in 2004, despite excellent immunization coverage. Even though there were small year-to-year variations in immunization coverage in each district, there was no consistent pattern of changes of pertussis incidence corresponding to immunization coverage.

The highest incidence occurred in infants, the lowest in 1–4 year olds, and the most striking increases in incidence were in children aged 5–9 years. Cases from the military sector were

Table 1. Case distribution of pertussis by diagnostic methods and year, Israel, 2000–2004

Year	No. of cases	Isolation of *B. pertussis* (%)	Serology confirmation (%)	PCR (%)	Clinical only (%)	Total (%)
2000	410	7	79	11	3	100
2001	531	3	81	7	9	100
2002	528	1	69	19	11	100
2003	942	0	74	12	14	100
2004	1653	1	74	11	14	100

unavailable to the Ministry of Health until 2004. This fact may result in underestimation of pertussis morbidity in 15–44 year olds, particularly since small outbreaks of pertussis in military personal were reported [9]. As expected, the incidence in unvaccinated and partly vaccinated children was higher than in fully vaccinated persons.

In Israel, the new acellular pertussis vaccine was introduced in 2002 into the routine immunization schedule in order to increase public acceptance of an apparently safer vaccine. Without question, compliance to pertussis vaccination in the last 3 years did increase slightly, but pertussis incidence is still climbing. The phenomenon of increased reported pertussis incidence since 1999 has the following possible explanations:

- *Non-specific case definition*: The case definition for reported pertussis in Israel is clinical pertussis as diagnosed by a physician, with or without laboratory confirmation. The disadvantage of this case definition is its low specificity in comparison with the more specific but less sensitive case definitions used by the U.S. Centers for Disease Control and the World Health Organization [10,11]. The advantage of this definition is that it has not changed in 55 years. Therefore, the increase in pertussis in the last 6 years cannot be explained by simply the addition of false positive cases resulting from a low specificity case definition.
- *Increasing physician awareness and improved notification*: The incidence of pertussis started to rise in 1999, when a study was conducted in the Haifa district to seek pertussis cases among children with prolonged cough. Moreover, in the same year a new computerized reporting network was introduced by the Ministry of Health to simplify and improve reporting. These two parallel changes could explain partially the temporal rise of reported pertussis in 1999–2000, but not the continued rise in incidence in 2003–2004.
- *Availability of highly sensitive laboratory methods*: Although the clinical picture is officially sufficient for case reporting, most clinicians are reluctant to notify pertussis without laboratory support, either by PCR, where it is available, or single-point serology. These methods have relatively high sensitivity for pertussis diagnosis and their use might have artificially increased the reported incidence of pertussis [12]. Nevertheless, as we have shown, the proportion of notified cases of pertussis supported by laboratory methods, particularly PCR, has been stable over the past 5 years and it is unlikely to have influenced the continued rise in reported incidence since 1999.
- *Genetic divergence of circulating pertussis strain*: The genetic divergence of circulating pertussis strains from vaccine strains were studied in the Netherlands, Japan, Canada, Poland, France and other countries [13-17]. Whereas in some countries (Japan, Canada, Poland) polymorphism between circulating pertussis and vaccine strains was noted [14-16], there are no Israeli data regarding genetic divergence.
- *Waning of vaccine-induced immunity*: The incidence of pertussis was 23 per 100,000 in children aged 1–4, and 60 per 100,000 in children aged 5–9 years. Sixty-nine percent of pertussis patients aged 5–9 years had received four doses of vaccine in infancy. These findings suggest waning immunity over time in an environment of minimal circulation of the agent and little opportunity for natural boosting of vaccine-induced immunity. Since this observation has been noticed in many countries, it is the most reasonable explanation for the current epidemiologic trend of pertussis in Israel.

PCR = polymerase chain reaction

Achieving better pertussis control in Israel

Today, most developed countries, in accordance with the Global Pertussis Initiative, have five or even six dose schedules for pertussis immunization, and a number of them prescribe a booster dose in the adolescent years [18-21].

In Israel, beginning in 2006, a fifth dose of pertussis vaccine was introduced for the first time among 7 year old schoolchildren. The plan is to continue to monitor the pattern of pertussis occurrence in the coming years, as successive cohorts of 7 year olds receive the fifth dose, to observe whether the additional dose has the intended effect of diminishing pertussis incidence in older schoolchildren as well as in their infant siblings. The data will be used to determine the need for changing the timing of the additional dose or for adding a sixth dose of pertussis vaccine.

Conclusions

There appear to be several reasons for the re-emergence of pertussis in Israel, of which the most feasible is the waning of vaccine-induced immunity in an environment of infrequent exposure to the infectious agent and the lack of additional doses of pertussis vaccine after age 1 year. Increased physician awareness and reporting and the availability of more sensitive diagnostic aids may also have contributed to the rise in incidence. The next step towards re-establishing pertussis containment in Israel must be a second booster dose of pertussis vaccine for schoolchildren to minimize disease risk in adolescents and adults and to interrupt the spread of pertussis from older children and young adults to small babies.

Acknowledgments. The authors wish to thank Dr. Dan Gandacu and Ruslan Gusinov for editorial and statistical help.

References

1. World Health Organization. Department of Vaccines and Biologicals. Pertussis surveillance. A global meeting. WHO/V&B/01.19 Geneva, 2001.
2. Hewlett EL, Edwards KM. Pertussis – not just for kids. N Engl J Med 2005;352:1215–22.
3. Campins-Marti M, Cheng HK, Forsyth K, et al. Recommendations are needed for adolescent and adult pertussis immunisation: rationale and strategies for consideration. Vaccine 2001;20:641–6.
4. Yih WK, Lett SM, des Vignes FN, Garrison KM, Sipe PL, Marchant CD. The increasing incidence of pertussis in Massachusetts adolescents and adults, 1989-1998. J Infect Dis 2000;182:1409–16.
5. CDC. Pertussis – United States, 1997-2000. MMWR 2002;51:73–6.
6. CCDR. Statement on adult/adolescent formulation of combined acellular pertussis, tetanus and diphtheria vaccine. Can Commun Dis Rep 2000:26 (ACS-1).
7. de Melker HE, Schellekens JF, Neppelenbroek SE, Mooi FR, Rumke HC, Conyn-van Spaendonck MA. Reemergence of pertussis in the highly vaccinated population of the Netherlands: observations on surveillance data. Emerg Infect Dis 2000;6:348–57.
8. Baron S, Njamkepo E, Grimprel E, et al. Epidemiology of pertussis in French hospitals in 1993 and 1994: thirty years after a routine use of vaccination. Pediatr Infect Dis J 1998;17:412–8.
9. Klement E, Uliel L, Engel I, et al. An outbreak of pertussis among young Israeli soldiers. Epidemiol Infect 2003;131:1049–54.
10. CDC. Guidelines for the control of pertussis outbreaks. Atlanta, GA: US Department of Health and Human Services, CDC, 2000.
11. World Health Organization. Vaccines, Immunization and Biologicals. Geneva: WHO, 2003.
12. Van der Zee A, Agterberg C, Peeters M, Mooi F, Schellekens J. A clinical validation of Bordetella pertussis and Bordetella parapertussis polymerase chain reaction: comparison with culture and serology using samples of patients with suspected whooping cough from a highly immunized population. J Infect Dis 1996;174:89–96.
13. van Loo IH, van der Heide HG, Nagelkerke NJ, Verhoef J, Mooi FR. Temporal trends in the population structure of Bordetella pertussis during 1949-1996 in a highly vaccinated population. J Infect Dis 1999;179:915–23.
14. Kodama A, Kamachi K, Horiuchi Y, Konda T, Arakawa Y. Antigenic divergence suggested by correlation between antigenic variation and pulsed-field gel electrophoresis profiles of Bordetella pertussis isolates in Japan. J Clin Microbiol 2004;42:5453–7.
15. Tsang RS, Lau AK, Sill ML, et al. Polymorphisms of the fimbria fim3 gene of Bordetella pertussis strains isolated in Canada. J Clin Microbiol 2004;42:5364–7.
16. Gzyl A, Augustynowicz E, van Loo I, Slusarczyk J. Temporal nucleotide changes in pertactin and pertussis toxin genes in Bordetella pertussis strains isolated from clinical cases in Poland. Vaccine 2001;20:299–303.
17. Njamkepo E, Rimlinger F, Thiberge S, Guiso N. Thirty-five years experience with the whole-cell pertussis vaccine in France: vaccine strains analysis and immunogenicity. Vaccine 2002;20:1290–4.
18. Forsyth KD, Campins-Marti M, Caro J, et al. New pertussis vaccination strategies beyond infancy: recommendations by the global pertussis initiative. Clin Infect Dis 2004;39:1802–9.
19. Halperin SA. Canadian experience with implementation of an acellular pertussis vaccine booster-dose program in adolescents: implications for the United States. Pediatr Infect Dis J 2005;24: S141–6.
20. CDC. Recommended Childhood and Adolescent Immunization schedule – United States, 2006. MMWR 2006,54(52):Q1–4.
21. Halperin SA. Pertussis – A disease and vaccine for all ages. N Engl J Med 2005;353:1615–17.

Correspondence: Dr. L. Moerman, Dept. of Epidemiology, Ministry of Health, P.O. Box 1176, Jerusalem, Israel.
Phone: (972-2) 670-6814
Fax: (972-2) 6706876
email: larisa.moerman@moh.health.gov.il