Epidemiol. Infect. (1998), **120**, 143–149. Printed in the United Kingdom

Review of the evidence for the use of erythromycin in the management of persons exposed to pertussis

H. DODHIA[1] AND E. MILLER[2]*

[1] *Public Health Medicine, Bromley Health Authority, Global House, 10 Station Approach, Hayes, Kent BR2 7EH*
[2] *Communicable Disease Surveillance Centre, Public Health Laboratory Service, 61 Colindale Avenue, Colindale, London NW9 5EQ*

(*Accepted 28 October 1997*)

SUMMARY

We assessed the quality of evidence for the use of erythromycin in preventing secondary transmission of pertussis to close contacts of primary cases. A literature search was undertaken and identified papers were reviewed critically. Thirteen original papers and 1 manuscript met the inclusion criteria for review (3 randomized controlled trials, 4 analytical studies and 7 descriptive studies). Evidence from both experimental and analytical studies showed little effect of the use of erythromycin in preventing secondary transmission. Its effect is at best modest when compared with the protection conferred by use of good quality whole cell vaccine. Three studies reported adverse events with erythromycin prophylaxis; these were mainly nausea, vomiting and abdominal pain. In countries where effective pertussis vaccines are in use, erythromycin use should be confined to close contacts of cases, particularly unimmunized children or partially immunized infants who would be most susceptible to the complications of pertussis, or adults who come into close contact with vulnerable children.

INTRODUCTION

Whooping cough is a re-emerging disease in some developed countries despite high uptake of pertussis vaccine [1–5], and remains a major public health problem in developing countries [6, 7]. In the UK, pertussis is well controlled [8] although 3 small clusters of cases were reported in 1996 [9]. Erythromycin prophylaxis has been advocated to prevent transmission of *Bordetella pertussis* infection [10, 11] but the evidence to support its use has not been reviewed systematically. While erythromycin treatment of cases has little effect on the clinical course of illness, it does render the individual culture negative [12]. Recommendations for its use as a prophylactic measure require evidence of clinical benefit in contacts. We report the outcome of a systematic review of the evidence for the use of erythromycin for prevention of secondary transmission of pertussis.

* Author for correspondence.

METHODS

A 'Medicine' search was undertaken for the period 1980–96. Key words used included: 'whooping cough', '*Bordetella pertussis*', 'treatment', 'prophylaxis', 'erythromycin', 'controlled trials', 'case-control' and 'cohort studies'. A manual search of the references of key review articles on prophylaxis against pertussis was also undertaken and the articles gathered over 20 years on pertussis by one of the authors (EM) were search manually. This included papers published prior to 1980. Finally, some international experts were contacted to see if there were any other studies currently in progress. The initial plan was to review only randomized controlled trials

Table 1. *Assessing the quality of the evidence* (*adapted from reference 13*)

I	Evidence obtained from at least one properly randomized controlled trial
II-1	Evidence obtained from well designed controlled trials without randomization
II-2	Evidence obtained from well designed cohort or case controlled analytical studies preferably from more than one centre or research group
II-3	Evidence obtained from multiple time series with or without the interventions, or from dramatic results in uncontrolled experiments
III	Opinions of well respected authorities based on clinical experience, descriptive studies or reports of expert committees
IV	Evidence inadequate owing to problems of methodology, e.g. sample size, length or comprehensiveness of follow-up, or conflict in evidence

but this was extended to analytical studies (case control and cohort outbreak investigations) and uncontrolled descriptive reports (case series and clinical reports) as there were very few published controlled trials. The criteria for inclusion in the review were the use of erythromycin as treatment of primary cases (i.e. to prevent spread and reduce infectivity) or as prophylaxis only in secondary contacts, or both. For experimental and analytical studies this included appropriate primary and secondary case definitions and outcome measures. Studies were then classified to assess the overall quality of the evidence according to the scheme adapted from Stevens and Raftery [13] (Table 1).

RESULTS

Thirteen original papers were identified that met the inclusion criteria. Two were randomized controlled trials [14, 15], 4 were analytical studies [16–19] and 7 were uncontrolled case reports or outbreak investigations with descriptive findings [20–26]. In addition, contact with international experts yielded one trial recently submitted for publication which was also reviewed [27].

Experimental studies

Two small double-blind, placebo-controlled, randomized trials were published in the early 1980s; 1 evaluated the efficacy of erythromycin in preventing secondary attacks of pertussis in unvaccinated household contacts and the other in all household contacts [14, 15].

In both trials it was concluded that erythromycin was not effective as a prophylactic measure. However, sample size calculations were not performed in either trial and the numbers of subjects recruited into each study were small (91 contacts in 1 trial and 20 in the other). It was not clear how randomization was undertaken and whether this worked. With such small numbers there are likely to be problems in randomization. In one of the trials more contacts in the treatment group were experiencing symptoms at the start of treatment compared with the control group. Also, randomization in this trial was by family unit but the analysis was carried out in terms of individual contacts [15]. Neither trial could support any detailed analysis and both were published as letters.

Recently, a larger, randomized, double-blind, placebo-controlled clinical trial has been undertaken in Canada. The use of erythromycin prophylaxis in household contacts of children with pertussis was studied [27]. A total of 152 households with a total of 362 contacts were recruited (73 households with 170 contacts received erythromycin and 79 households with 192 contacts received an identically appearing placebo). Baseline characteristics of the 2 groups were comparable and randomization was appropriate. The presence and duration of symptoms in the index cases were similar in both groups prior to administration of chemoprophylaxis to contacts. The primary outcome measure was bacteriological culture of *B. pertussis* from nasopharyngeal aspirates and secondary outcome measures included compliance with medication, adverse events, clinical symptoms and antibody response. The main findings were a significant difference in secondary cases as measured by positive cultures (6·6% in the erythromycin group compared with 20·3% in the placebo group; efficacy 67·5%, 95% confidence intervals (CI): 7·6–88·7%). However, apart from post-tussive vomiting being less common ($P = 0{\cdot}02$) and a trend for fewer whoops in the erythromycin group ($P = 0{\cdot}09$), there was no evidence of other clinical benefit in those families who received prophylaxis compared with the placebo group. In addition there was no difference in serological response between treatment and placebo groups. The

authors concluded that erythromycin may have more effect in eradicating the organism from the nasopharynx than in preventing infection. Compliance was lower in the erythromycin than the placebo group ($P = 0{\cdot}025$) and this group also had significantly more adverse events with 34·3% *vs.* 15·9% ($P = 0{\cdot}0003$) complaining of any adverse event. These were mainly diarrhoea (20·3%) and nausea (12·6%).

Analytical studies

The 4 analytical studies are summarized in Table 2. The main objective of the 3 retrospective cohort studies was to evaluate the effectiveness of erythromycin as a prophylactic measure. In 2 cohorts, study households were ascertained by identifying culture-confirmed or clinically suspect cases of pertussis. Both of these studies gave reference to the sensitivity and specificity of the clinical case definitions used and defined in detail primary, co-primary and secondary cases [15, 16]. The third cohort was defined by ascertaining culture or serology positive residents with respiratory symptoms in an institution for mentally handicapped people during an outbreak of pertussis [18].

'Risk' factors considered in each study included age, sex and immunization status. In addition one study considered household size, crowding, income, race and source of children's healthcare as potential confounding factors [17]. Each study clearly described the statistical methods used and the outcomes being measured. One study used a multivariable model to assess the independent effects of different risk factors and also the type and dose of erythromycin used [16].

The study by de Serres and colleagues [16] was the largest, with 246 families participating, a response rate of 89%. The overall reduction in attack rate was modest but clinically important. The protection induced by prophylaxis did not vary with age. Subgroup analysis showed that when prophylaxis was used before the onset of a secondary case, the risk of pertussis was considerably lower than when it was used after the occurrence of a secondary case (4% compared with 35%; $P < 0{\cdot}001$; relative risk (RR) = 0·11, 95% CI: 0·06–0·22). The attack rate was lower if chemoprophylaxis was given within 21 days after onset in a primary case (11% compared with 29%) with attack rates being similar in contacts given prophylaxis after 21 days compared with families without prophylaxis (29% compared to 25%). A logistic regression model (which included vaccination status, age, use of prophylaxis before or after the onset of secondary cases and delay before prophylaxis) showed that only increasing age ($P < 0{\cdot}001$) and use of prophylaxis before onset of secondary case ($P = 0{\cdot}001$) were independently associated with protection against pertussis. Further analysis of culture-proven cases only did not alter these findings.

The study by Sprauer and colleagues [17] looked at the effect of treatment of the index case as well as prophylaxis for household contacts in preventing secondary cases. Although relatively small with a total of 37 households participating (17 with secondary spread and 20 without spread), the 2 comparison groups were similar in respect of a number of potentially confounding characteristics. A standardized questionnaire was used to ascertain exposures reducing the chance of information biases. However, the potential to use a multivariable model was not explored. A higher proportion of patients received erythromycin in households with no secondary spread and the proportion given prophylaxis within 3 weeks of onset in a primary case was also higher. There was also an association between delay in initiating treatment in primary cases and prophylaxis in contacts, and secondary spread (see Table 2).

In the study by Steketee and colleagues [18], erythromycin was given as treatment or prophylaxis to 219 residents in exposed wards. Different sources were used to gather data including the memories of staff members. It was not clear whether the questionnaire used was standardized, thus the potential for information recall biases was increased. The timing between onset of a first case on a ward and the start of erythromycin treatment or prophylaxis differed between wards as the intervention was instituted in the 17th week of the outbreak. A significant difference in attack rates was found in those residents who were given erythromycin late compared with those who were given it early (Table 2). However, it was not clear how comparable these 2 groups were in terms of age, sex, exposure risk and immunization status. The findings of this study which showed a nearly fivefold reduction in attack rate with early use of prophylaxis should thus be treated with some caution.

Adverse effects of erythromycin were considered in two cohort studies. In one study 84% of subjects ($n = 309$) who received prophylaxis completed all their medication, 6% had to stop because of adverse effects (mainly abdominal pain, nausea, vomiting and diarrhoea) and 10% interrupted prophylaxis without any stated reason [16]. In the other study carbam-

https://doi.org/10.1017/S0950268897008571 Published online by Cambridge University Press

Table 2. *Summary of analytical studies reviewed*

Study [Reference]	Setting	Design	Case definition	Outcomes measured	Main effect with regard to erythromycin treatment of prophylaxis
de Serres et al. [16]	Households Quebec, Canada	Cohort $n = 246$, families (940 individuals)	Culture confirmed or a cough $\geqslant 2$ weeks without other apparent causes and at least one of the following symptoms: paroxysms, post-tussive vomiting, apnoea or whoop. Primary and secondary case definitions*	Attack rates in 'families' given prophylaxis compared with 'families' not given prophylaxis	Attack rate 17% (with prophylaxis) and 25% (without prophylaxis). Relative Risk (RR): 0·69; 95% Confidence Intervals (CI): 0·52 to 0·93
Sprauer et al. [17]	Households Maricopa County, Arizona, USA	Cohort $n = 37$ households (184 individuals)	Case of pertussis was defined as one of the following: (1) a positive nasopharyngeal culture; (2) an acute cough lasting $\geqslant 14$ days; (3) a paroxysmal cough of $\geqslant 7$ days; Primary, co-primary, second primary and secondary case definitions†	Households without secondary spread compared with households with secondary spread	(1) Treated %: 100% *vs.* 76%; $P = 0{\cdot}04$; (2) Delay in initiating treatment in primary case; median of 11 days *vs.* 21 days; $P = 0{\cdot}057$); (3) Given prophylaxis % within 3 weeks of onset in primary case: 97% *vs.* 47%; $P < 0{\cdot}0001$; (4) Delay in initiating prophylaxis in secondary contacts: median of 16 days *vs.* 22 days; $P < 0{\cdot}001$
Steketee et al. [18]	Residential institution for the handicapped, Wisconsin, USA	Cohort $n = 278$ residents	Case of pertussis was defined as a person with respiratory illness with one of the following: (1) positive culture; (2) direct fluorescent antibody; (3) serological evidence of pertussis infection; No classification of cases as primary or secondary	Attack rate for late use ($\geqslant 4$ weeks after onset in primary case) of erythromycin prophylaxis compared with early use (< 2 weeks after onset in primary care)	Attack rate: 75% (late use) compared with 16% (early use) (RR: 4·70; 95% CI: 3·36 to 6·57)
Beillik et al. [19]	Households, Central Wisconsin, USA	Case-control $n =$ 181 households (685 individuals)	(1) Cough lasting $\geqslant 14$ days; (2) Cough + paroxysms lasting for $\geqslant 7$; (3) Paroxysmal cough + sleep disturbance on two or more consecutive days. Primary, co-primary, second primary and secondary case definitions†	Households without secondary cases compared with households with secondary cases, in the initiation of therapy and prophylaxis	Interval between onset of illness in the first primary case and initiation of therapy (10·9 days without secondary cases *vs.* 23·6 days with secondary cases; $P < 0{\cdot}001$). Interval between onset of illness in first primary case and initiation of prophylaxis (14·4 days without secondary cases *vs.* 22·6 days with secondary cases; $P < 0{\cdot}02$)

* Reference 16. Primary case: first case in 'study families'; secondary cases: other cases in 'study families' who had coughed for $\geqslant 2$ weeks.

† References 17 and 19. Primary case: household member with earliest date of cough onset; co-primary case: patient with cough onset within 1–6 days of primary case; secondary case: patient with cough onset between 7–28 days after onset in primary case; second primary case: patient with cough onset more than 28 days after a primary case, co-primary or secondary case in the same household.

azepine toxicity was observed in 7 out of 37 mentally handicapped residents who were treated concurrently with carbamazepine and erythromycin [18].

Biellik and colleagues [19] compared 61 'case households' with 62 randomly selected community 'control households' and 58 neighbourhood 'control households' in a case control study. Case households were ascertained by identifying culture-confirmed cases using an active laboratory-based surveillance covering over 90% of residents in the study area in a defined time period. A detailed description of how control households were selected is given clearly. Cases identified in the study households were defined according to the presence of clinical syndromes or laboratory confirmation. The sensitivity and specificity of the clinical case definitions used was referenced. Cases were also classified into primary, co-primary, second primary and secondary cases. Both the type and duration of erythromycin were given. Its use as prophylaxis was based on a subgroup analysis of 61 case households which were stratified into 2 groups, those in which secondary transmission occurred after exposure to a primary case ($n = 15$) and those with no secondary cases ($n = 34$). Case households with co-primary or secondary primary cases were excluded ($n = 12$). The 2 groups were comparable in respect of a number of potential confounders. There were significant associations between early initiation of erythromycin therapy and prophylaxis and households without secondary spread (Table 2).

Descriptive studies

Six of 7 studies suggested that erythromycin was an effective prophylactic agent. Of these, 3 gave microbiological evidence of colonization in secondary contacts [20–22]. Prophylaxis eliminated colonization and prevented development of clinical symptoms in 29 of 30 culture-confirmed contacts. However, it is not possible to say that this was due to prophylaxis. In one study, undertaken over 10 years, 35 pregnant mothers with serology or culture confirmed pertussis at delivery were followed up [23]. All the women received treatment with erythromycin a few days prior to delivery and 28/35 new-born infants received prophylaxis (22 new-borns for 10 days and 6 for 5 days, all at 40 mg/kg body weight) starting at birth. The infants were nursed by their mothers and none developed symptoms of whooping cough. One study that suggested erythromycin to be ineffective was based on a single colonized contact. Following prophylaxis for 5 days, eradication did not occur and symptoms of infection developed [24].

DISCUSSION

Reviewing the available evidence enables clinicians to make informed decisions and public health authorities to formulate appropriate guidelines. We found very few published experimental and analytical studies. Only one large, well-designed trial (awaiting publication) assessing the protective effect of erythromycin prophylaxis in preventing secondary cases of pertussis after contact with primary cases, has been undertaken recently. The primary outcome measured used was bacteriological culture. However it may have been more appropriate to use a clinical case definition (e.g. WHO case definitions for pertussis) [28] in combination with culture or serology as primary outcome measures. This trial produced little evidence of clinical benefit in the families who received prophylaxis compared with placebo. However, if the effect of erythromycin is at best modest then even this trial may not have had sufficient power to detect a difference. We calculated that with 80% power and 5% significance, 317 households would be required in each arm to detect a reduction in attack rate of 10%.

All 4 analytical and 6 of 7 descriptive studies reviewed favoured the use of erythromycin as prophylaxis for close contacts. The most convincing evidence came from a recent well-designed, large cohort study [16]. The analytical studies consistently suggested that early initiation of prophylaxis was an important factor in preventing secondary cases. Two studies also gave evidence of early initiation of therapy in primary cases as an important factor in preventing transmission. The studies which stated the dose and duration of erythromycin prophylaxis used a dose of 40–50 mg/kg/day for children and 250–500 mg for adults in three divided doses for 10–14 days duration.

In this review studies in languages other than English and other unpublished studies were excluded from the search routine and thus some studies may have been missed. However, we believe that most important published studies have been reviewed. We were unable to undertake a meta-analysis and derive summary statistics as the studies reviewed were of different designs and had slightly different case definitions. None of the analytical studies reviewed were carried out in the UK. However, since a

biological effect was being observed the findings reported should be applicable to the UK population. Although there may be serotype variations in pertussis these are unlikely to be related to antimicrobial sensitivity.

Erythromycin appears to be modestly efficacious in preventing secondary cases of pertussis although the effect appears to increase with decreasing vigour of the study design. A number of other issues need to be considered when formulating guidelines to ensure effectiveness in outbreak control. Pertussis is most infectious during the early catarrhal phase when it may not be recognized. By the time the infection is recognized it may be too late to give prophylaxis. Our review indicates that the best time to give prophylaxis is before 21 days (preferably 14 days) of onset of paroxysmal cough in the primary case and preferably before a secondary case has occurred. This means that clinicians would have to rely on a clinical diagnosis to treat contacts. In targeting prophylaxis effectively 2 problems may arise; first, not all cases of paroxysmal coughing are due to pertussis and reliance on a clinical case definition could lead to overuse of erythromycin; secondly adults or children who have been immunized may not have a typical clinical presentation, which could lead to underuse of erythromycin.

Compared with the effectiveness of the whole cell vaccines used in Europe, and some of the new acellular products [29–31], the efficacy of erythromycin in protecting contacts appears modest. Infants have higher death rates (particularly under 3 months) and hospital admissions (particularly under 11 months) [32]. Unvaccinated children have more severe illness and are also more likely to be admitted to hospital (particularly those under 5 years) [33]. This suggests that erythromycin prophylaxis would be most beneficial in households or closed institutions with unimmunized children or partially immunized infants who are at increased risk of the complications of pertussis. In the USA and Canada, erythromycin prophylaxis has been recommended for all contacts irrespective of vaccination status [10, 11]. This policy was developed prior to the publication of the large cohort study and clinical trial undertaken in Canada which show the efficacy of erythromycin prophylaxis to be modest [16, 27]. Furthermore the evidence on which the Canadian and American recommendations were based was not presented as a systematic review. The use of erythromycin prophylaxis for all contacts irrespective of vaccination status may increase the risk benefit ratio for older children and adults in the UK where the efficacy and uptake of whole cell vaccine is good. Recent evidence suggests that the efficacy of one US whole cell pertussis vaccine is poor [34].

The adverse effects of the use of erythromycin need to be balanced against the potential benefits. Adverse effects assessed by three of the papers reviewed were mostly due to gastrointestinal disturbances and compliance was fairly good. However, the newer generation of macrolides (clarithromycin and azithromycin) may have several advantages over erythromycin, including improved oral bioavailability, longer half-life, allowing once or twice daily administration, higher tissue concentrations, enhanced antimicrobial activity and fewer gastrointestinal adverse effects [35]. Although there have been no specific studies of prevention of secondary transmission of pertussis using these newer macrolides, their biological effect is considered to be similar to erythromycin. They may be considerably more expensive to use.

In conclusion, there is only weak evidence to support the use of erythromycin prophylaxis. The overall quality of this evidence was judged to be II-2 (Table 1). The effect is at best modest when compared with the protection conferred by an effective whole cell vaccine. There is no evidence of any benefit to contacts other than household-type contacts (i.e. living under the same roof). Prophylaxis needs to be given before 21 days of onset of a primary case, both as therapy to the primary case and prophylaxis to contacts, in adequate dosage (40–50 mg/kg for children and 250–500 mg for adults in three divided doses) and duration (10–14 days) and restricted to households where there are vulnerable contacts.

ACKNOWLEDGEMENTS

We would like to acknowledge all the PHLS Regional Epidemiologists and members of the PHLS Standing Scientific Committee on Vaccines and Immunisation for their helpful comments on this paper.

REFERENCES

1. de Serres G, Boulianne N, Douville FM, Duval B. Pertussis in Quebec: ongoing epidemic since the late 1980s. Can Commun Dis Rep 1995; **21**: 45–8.
2. Anonymous. Resurgence of pertussis-United States, MMWR 1993; **42**: 952–3, 959–60.
3. Howell F, Jennings S. The epidemiology of pertussis in the Republic of Ireland. CDR Rev 1992; **2**: R31–3.
4. MacIntyre R, Hogg G. Surveillance for *Bordetella pertussis* infection in Victoria. Aust J Public Health 1994; **18**: 21–4.

5. de Melker HE, Conyn-van Spaendonck MAE, Rumke HC, van Wijngaarden JK, Mooi FR, Schellekens JFP. Pertussis in the Netherlands: an outbreak despite high levels of immunisation with whole-cell vaccine. Emerg Infect Dis 1997; **3**: 175–8.
6. Hodder SL, Mortimer EA. Epidemiology of pertussis and reactions to pertussis vaccine. Epidemiol Rev 1992; **14**: 243–67.
7. Muller AS, Leeuwenburg J, Pratt DS. Pertussis: epidemiology and control. Bull WHO 1986; **64**: 321–31.
8. White JM, Fairley CK, Owen D, Matthews RC, Miller E. The effect of an accelerated immunisation schedule on pertussis in England and Wales. CDR Rev 1996; **6**: R86–91.
9. Anonymous. Vaccine preventable diseases of childhood: weeks 34–38/96. CDR Wkly 1996; **6**: 340.
10. Joint Statement by the National Advisory Committee on Immunisation, the Advisory Committee on Epidemiology and the Canadian Pediatric Society. Statement on management of persons exposed to pertussis and pertussis outbreak control. Can CDR 1994; **20**: 193–9.
11. American Academy of Pediatrics. Pertussis. In: Peter G, ed. 1994 Red Book: Report on the Committee on Infectious Diseases, 23rd ed. Elk Grove Village, IL: American Academy of Pediatrics, 1994; 355–75.
12. Bergquist S, Sverkr B, Dahnsjo H, Sundelof BO. Erythromycin in the treatment of pertussis: a study of bacteriological and clinical effects. Pediatr Infect Dis J 1987; **6**: 458–61.
13. Stevens A, Raftery J. The epidemiological approach to needs assessment. In: Stevens A, Raftery J, eds. Health care needs assessment. Oxford: Radcliffe Medical Press, 1994; **1**: 21–30.
14. Grob PR. Prophylactic erythromycin for whooping-cough contacts. Lancet 1981; **1**: 772.
15. Spencely M, Lambert HP. Prophylactic erythromycin for whooping-cough contacts. Lancet 1981; **1**: 772–3.
16. de Serres G, Boulianne N, Duval B. Field effectiveness of erythromycin prophylaxis to prevent pertussis within families. Pediatr Infect Dis J 1995; **14**: 969–75.
17. Sprauer MA, Cochi SL, Zell ER, et al. Prevention of secondary transmission of pertussis in households with early use of erythromycin. Am J Dis Child 1992; **146**: 177–81.
18. Steketee RW, Wassilak SGF, Adkins WN Jr. et al. Evidence for a high attack rate and efficiacy of erythromycin prophylaxis in a pertussis outbreak in a facility for the developmentally disabled. J Infect Dis 1988; **157**: 434–40.
19. Biellik RJ, Patriarca PA, Mullen JR, et al. Risk factors for community- and household-acquired pertussis during a large-scale outbreak in Central Wisconsin. J Infect Dis 1988; **157**: 1134–41.
20. Linnemann CC Jr, Ramundo N, Perlstein PH, Minton SD, Englender GS. Use of pertussis vaccine in an epidemic involving hospital staff. Lancet 1975; ii: 540–3.
21. Altemeier WA III, Ayoub Em. Erythromycin prophylaxis for pertussis. Pediatrics 1977; **59**: 623–5.
22. Fisher MC, Long SS, McGowan KL, Kaselis E, Smith DG. Outbreak of pertussis in a residential facility for handicapped people. J Pediatr 1989; **114**: 934–9.
23. Grastrom G, Sterner G, Nord CE, Granstrom M. Use of erythromycin to prevent pertussis in newborns of mothers with pertussis. J Infect Dis 1987; **155**: 1210–4.
24. Halsey NA, Welling MA, Lehman RM. Nosocomial pertussis: a failure of erythromycin treatment and prophylaxis. Am J Dis Child 1980; **134**: 521–2.
25. Christie CDC, Glover AM, Wilkie MJ, Marx ML, Reising SF, Hutchinson NM. Containment of pertussis in the regional pediatric hospital during the Greater Cincinnati Epidemic of 1993. Infect Control Hosp Epidemiol 1995; **16**: 556–63.
26. Kelly H, Donelly J, Waycott D, Meadows K. Possible successful intervention in a localised pertussis outbreak. Commun Dis Intell 1995; **19**: 290–1.
27. Halperin SA, Bortolussi R, Langley JM, Miller B, Eastwood BJ. Erythromycin chemoprophylaxis in household contacts of children with pertussis. Dalhousie University and the IWK-Grace Health Centre, Halifax, Nova Scotia, Canada and the University of Auckland, New Zealand. ICAAC, April 1996.
28. Report of the WHO meeting on case definition of pertussis. WHO: Geneva, 1991; 2–6.
29. Report from the PHLS Epidemiological Research Laboratory and 21 Area Health Authorities. Efficacy of pertussis vaccination in England. BMJ 1982; **285**: 357–9.
30. Fine PEM, Clarkson JA, Miller E. The efficacy of pertussis vaccines under conditions of household exposure. Int J Epidemiol 1988; **17**: 635–42.
31. Schmitt HJ, von Konig W, Neiss A, et al. Efficacy of acellular pertussis vaccine in early childhood after household exposure. JAMA 1996; **275**: 37–41.
32. Pollock TM, Miller E, Lobb J. Severity of whooping cough in England before and after the decline of pertussis immunisation. Arch Dis Child 1984; **59**: 162–5.
33. Ramsey MEB, Farrington CP, Miller E. Age-specific efficacy of pertussis vaccine during epidemic and non-epidemic periods. Epidemiol Infect 1993; **111**: 41–8.
34. Edwards KM, Decker MD. Acellular pertussis vaccines for infants. N Engl J Med 1996; **334**: 391–2.
35. Zukerman JM, Kaye KM. The newer macrolides: azithromycin and clarithromycin. Infect Dis Clin North Am 1995; **9**: 731–45.