Summary
Pertussis is well controlled in the UK as a result of an effective vaccination programme. Nevertheless, the disease has not been eliminated, and cases still occur in the most vulnerable group of young infants. Erythromycin chemoprophylaxis has been advocated for use in contacts to prevent secondary cases but the evidence for its use is weak. These guidelines are based on a review of the evidence and aim to help clinicians make more rational decisions on the use of erythromycin chemoprophylaxis for pertussis. Erythromycin has well-established side effects and so its use should be limited to situations where it is likely to be of greatest benefit. If a clinically suspected or confirmed case of pertussis is identified who is also in household contact with someone at greatest risk from pertussis – young infants, especially neonates – then erythromycin chemoprophylaxis should be considered. The aim is to protect those at greatest risk from pertussis by offering chemoprophylaxis to them, to all their household contacts who are unimmunized and to contacts who are 5 years or older if they did not receive a pre-school pertussis booster (not given to those born before 1996 in the United Kingdom). There is no evidence of any benefit from chemoprophylaxis given more than 21 days from the date of onset of the primary case. Unimmunized or partially immunized cases and contacts should complete their course of vaccine.

Keywords: whooping cough, erythromycin chemoprophylaxis, guidelines, pertussis vaccine

Introduction
Bordetella pertussis causes an acute bacterial infection involving the respiratory tract. Transmission of the organism occurs as a result of close direct contact with an infected person. It is highly contagious, especially in the first week of illness, with up to 90 per cent of susceptible household contacts developing the disease. The incubation period varies from 7 to 13 days. Clinically, three phases are recognized as part of the syndrome: the early catarrhal phase, the paroxysmal phase and the convalescent phase. Symptoms in very young infants, adolescents and adults may be atypical. Complications of pertussis include bronchopneumonia and cerebral complications such as seizures, stupor, weakness, cranial nerve abnormalities and encephalopathy. Age is an important determinant of disease severity and prognosis. Infants under the age of 1 year have the highest mortality rate and are also more likely to be hospitalized and suffer complications such as pneumonia and cerebral complications. Epidemiology
In the United Kingdom the incidence of pertussis rose dramatically in the late 1970s and early 1980s when vaccine coverage declined from about 80 per cent (in 1969) to only 30 per cent (in 1978) because of fears about potential side effects of vaccination. Since then, vaccine coverage at 2 years has improved steadily to 95.2 per cent and the number of notifications has fallen dramatically from 70,868 in 1982 to 3,669 in 1997. Despite good vaccination coverage, epidemic cycles continue to be observed in the United Kingdom. Cases and clusters of pertussis still occur, including adults and infants too young to be vaccinated, although the diagnosis can be missed. In other developed countries pertussis may be a re-emerging problem despite high uptake of pertussis vaccine and it remains a major public health problem in developing countries.

Erythromycin chemoprophylaxis
Literature search
Details of the literature search assessing the evidence for the use of erythromycin in preventing secondary transmission were...
highlighted in a review paper published in 1998.\textsuperscript{12} A summary of the papers reviewed was tabulated in that paper. In developing these guidelines an additional electronic and manual search of the literature was carried out using similar methods. This identified a large clinical trial that was only available in manuscript form at the time of the review.\textsuperscript{13} Other descriptive studies were also identified.\textsuperscript{14,15} The Scottish Intercollegiate Guidelines Network (SIGN) grading system for the levels of evidence and grade of recommendation was used (see Table) in formulating these guidelines.\textsuperscript{16}

**Summary and grading of evidence**

The review identified 13 original papers and one manuscript that met the inclusion criteria for review (three randomized controlled trials, four analytical studies and seven descriptive studies).\textsuperscript{12} Evidence from both experimental (evidence level 1+) and analytical studies (evidence level 2+) showed little effect of the use of erythromycin in preventing secondary transmission. The authors concluded that its effect was at best modest. It is therefore more important to ensure high vaccine uptake, which in addition to providing individual protection may also prevent secondary transmission. There is no evidence of any benefit to contacts other than close prolonged ‘household type’ contact (evidence level 3). The authors also advocated that infants, particularly neonates, would probably benefit with chemoprophylaxis. Although a recent large randomized controlled trial showed no evidence of clinical benefit, infants under 6 months (those most at risk) were excluded.\textsuperscript{13} Other studies have shown significant benefits in neonates (evidence level 2+).\textsuperscript{14,15} A review of pertussis disease in England and Wales between 1995 and 1997 provided some evidence that use of chemoprophylaxis reduced severity of outcome in vulnerable groups. This study showed that infants who had received chemoprophylaxis were approximately half as likely to be admitted to hospital (evidence level 3).\textsuperscript{13}

To be at all effective, chemoprophylaxis has to be given within 21 days of onset of the primary case, in adequate dosage and for the correct duration (evidence level 2+).\textsuperscript{12} It should be restricted to households where there are vulnerable contacts (evidence level 3). There is no evidence that erythromycin has any additional effect in reducing likelihood of transmission to or from contacts who are fully vaccinated and within 5 years of primary immunization (evidence level 3). Furthermore, adverse effects of erythromycin are well established (evidence level 1+).\textsuperscript{12,13} Halperin et al. found the incidence of adverse events to be significantly higher in the treatment group compared with the placebo group for ‘any adverse reaction’ (34 per cent compared with 15.7 per cent, \(p = 0.0004\)), ‘nausea’ (12.6 per cent compared with 4.9 per cent, \(p = 0.04\)), ‘diarrhoea’ (20.3 per cent compared with 8.5 per cent, \(p = 0.004\)) and ‘abdominal cramps’ (5.6 per cent compared with 0.6 per cent, \(p = 0.04\)). These adverse events led to significantly reduced compliance rates in the treatment groups.\textsuperscript{13} In addition, two recent retrospective cohort studies have reported that neonates receiving

### Table Revised Scottish Intercollegiate Guidelines Network (SIGN) grading system\textsuperscript{16}

<table>
<thead>
<tr>
<th>Levels of evidence</th>
<th>Grades of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</td>
<td>A At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results</td>
</tr>
<tr>
<td>1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias</td>
<td>B A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+</td>
</tr>
<tr>
<td>1– Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias</td>
<td>C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++</td>
</tr>
<tr>
<td>2++ High-quality systematic reviews of case–control or cohort studies</td>
<td>D Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+</td>
</tr>
<tr>
<td>2+ High-quality case–control or cohort studies with a very low risk of confounding, bias or chance, and a high probability that the relationship is causal</td>
<td></td>
</tr>
<tr>
<td>2– Case–control or cohort studies with a high risk of confounding, bias or chance, and a significant risk that the relationship is not causal</td>
<td></td>
</tr>
<tr>
<td>3 Non-analytic studies, e.g. case reports, case series</td>
<td></td>
</tr>
<tr>
<td>4 Expert opinion</td>
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RCT, randomized controlled trial.
systemic erythromycin were at increased risk of developing infantile hypertrophic pyloric stenosis (IHPS) (evidence level 2+). The first study found an increased relative risk of 6.8 (95 per cent confidence interval (CI) 3.0–15.7) with an increased absolute risk of 4.5 per cent. The second study found that infants prescribed systemic erythromycin had increased risk of IHPS (relative risk 10.51 for erythromycin in first 2 weeks of age, 95 per cent CI 4.48–24.66). The authors calculated that in the first 2 weeks of life 42 infants would need to be treated to cause one extra case of IHPS, rising to 98 for those aged 2 weeks to 3 months. Maternal macrolide antibiotics within 10 weeks of delivery may have been associated with higher risk of IHPS but the data were not conclusive. The authors cautioned against the use of erythromycin if alternatives were available. However, this is not the case with pertussis and thus we endorse the authors’ recommendation that if erythromycin is prescribed for any infant, parents should be informed of the risk and symptoms of IHPS. This can be conveyed to parents as a risk of IHPS developing in an infant treated with systemic erythromycin is highest in the first few weeks of life and ranges from around 1 in 20 to 1 in 100. Clinicians caring for these infants should maintain a high index of suspicion for the condition.

Pertussis vaccine efficacy shows a significant drop between early childhood (1–4 years) and later childhood (5–14 years) (evidence level 2++). Fully vaccinated older children and adults can become infected with pertussis. However, the infection is generally mild and may not be recognized. They are thus more likely to transmit to vulnerable contacts. For this reason, we advocate offering chemoprophylaxis to adults and children after reaching the age of 5 years if they did not receive a pre-school pertussis booster and if they are in close household contact with both a case (suspected or confirmed) and a vulnerable person. This 5-year age cut-off is arbitrary but based on the best data available at present on waning of vaccine-derived immunity. Information on waning of immunity in individuals who receive four doses of pertussis vaccine including a pre-school booster is not yet available. This should be considered at a future review of these guidelines in order to decide at which age erythromycin prophylaxis should be given to this group. Exclusion is a further intervention that is relevant in schools. Recent guidance advises exclusion of 5 days for children with pertussis who are also on treatment (evidence level 3). In hospitals, cases should be in respiratory isolation.

Guidelines

The following guidance on use of chemoprophylaxis was formulated following a review of the evidence. In addition, earlier drafts of these guidelines were extensively peer reviewed by a number of Regional Epidemiologists, Consultants in Communicable Disease Control in England and Wales, and Consultants in Public Health Medicine (Communicable Diseases and Environmental Health) in Scotland as well as the PHLS Scientific Advisory Committee on Vaccination and Immunization. The Figure outlines the management for close vulnerable contacts. In considering whether or not chemoprophylaxis is required several aspects should be considered, which are described in detail below.

A detailed history is required when a case of pertussis is suspected. This includes the date of onset and nature of symptoms, the vaccination history and details of household contacts. A per-nasal swab or nasopharyngeal aspirate (npa) should ideally be obtained to confirm the diagnosis but this may prove impossible in primary care. Where there is potential for a neonate to be exposed, general practitioners (GPs) may be encouraged to seek a definitive diagnosis with the assistance of local microbiologists and/or paediatricians. However, to identify vulnerable contacts and institute control measures in good time, the clinician will have to rely on a clinical diagnosis. The case should be notified on clinical suspicion to the Consultant in Communicable Disease Control in England and Wales and Northern Ireland, or the Consultant in Public Health Medicine (Communicable Diseases and Environmental Health) in Scotland. The following may assist in the identification of cases of pertussis.

Clinically suspected case

A clinical case is defined as follows: an acute cough lasting 14 days or more with at least one of the following symptoms: post-tussive vomiting, apnoea or whoop (recommendation level D). In addition, someone who is coughing for any duration and is also linked epidemiologically to a confirmed case of pertussis can be considered a suspect case.

Confirmed case

Laboratory confirmation is recommended for most sporadic cases and a sufficient number of cases to establish the diagnosis in an outbreak (recommendation level B). A case can be confirmed by per-nasal culture, serology or PCR. Culture from per-nasal swabs or npa is the ‘gold standard’ highly specific technique for diagnosis of pertussis but the method is not sensitive and results may take 3–5 days. Samples should be obtained as soon as possible after onset of coughing for maximum sensitivity and plated out immediately onto a suitable selective medium. If this is not possible, specimens should be transported as quickly as possible – within hours – to the laboratory. Swabs should be transported in a charcoal transport medium. PCR is more sensitive and rapid than culture but is not yet widely available. In older and/or previously vaccinated individuals, for whom positive cultures are more difficult to obtain, serological testing, available from a few specialized laboratories, may be appropriate.

Close contact

Family members or people living within a single house would qualify as close ‘household contacts’. Contacts in institutions with overnight stay in the same room (e.g. facilities for the learning disabled, hospital wards) should also be considered close
GUIDELINES FOR USE OF ERYTHROMYCIN CHEMOPROPHYLAXIS

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ERECTHROMYCIN CHEMOPROPHYLAXIS

DEFINITIONS

- **Close ‘household’ contact**: person living within the same household or institutional setting (e.g., ward, residential home).
- **Vulnerable contact**: newborn infants born to symptomatic mothers; neonates, infants and children with no or incomplete protection from vaccine (see below); presence of other chronic illness: asthma, congenital heart disease; immunocompromised when not fully or partially vaccinated.
- **No/incomplete protection from vaccination**: fewer than 3 doses of vaccine or ≥5 years old and not received a pre-school booster. Anyone born before November 1996 will not routinely have received a pre-school booster, nor some born up to May 1998.
- **Suspect case**: an acute cough lasting 14 days (with at least one of the following symptoms: post-tussive vomiting, apnoea or whoop) or a paroxysmal cough lasting 7 days.
- **Confirmed case**: a symptomatic case with positive laboratory result by culture, PCR or serology where available.
- **Erythromycin chemoprophylaxis**: the dose and duration of erythromycin chemoprophylaxis should be 125 mg 6 hourly for children up to 2 years age; 250 mg 6 hourly for children 2–8 years of age; and 250–500 mg 6 hourly for children over 8 years of age and adults. The duration of treatment and chemoprophylaxis should be for 7 days.

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**Guidelines for Use of Erythromycin Chemoprophylaxis**

Contact (recommendation level B). ‘Household-type’ contacts may include those who have stayed overnight in the same room, but only if they are vulnerable themselves or if they form part of a continuing household-type contact group for another identified vulnerable individual. The rationale differs here from that used for control of meningococcal disease. For meningococcal disease antibiotic prophylaxis protects susceptible members of a social group by eliminating carriage from non-susceptible individuals. The carriers and susceptibles are not identified. For pertussis prophylaxis, vulnerable contacts are the equivalent to susceptibles. However, as they are identified, it is easier to define the close contacts who should be given prophylaxis. Prophylaxis should not be extended to household-type contacts (e.g., other children at a ‘sleepover’, kissing contacts) unless they will continue to be in household-type contact with the vulnerable individual (recommendation level B). Other type of contact (e.g., contact at work, in school or casual contact) would not be considered close contact but each situation would need to be
considered on its own merit, particularly where vulnerable contacts are involved (recommendation level D).

**Vulnerable contacts**

Infants, particularly under 3 months, should be considered vulnerable contacts (recommendation level B). They have the highest death rates and hospital admissions as a result of pertussis. A recent analysis of Scottish morbidity records showed that for the years 1995–1998, 79 per cent of infants hospitalized with a diagnosis of pertussis were under 3 months of age (C. Bramley, personal communication). For England and Wales this figure was 37 per cent of infants in 1995. More recent Hospital Episode Statistics (HES) data from 1999 showed an increase to 52 per cent of infants under 3 months age group (A. Nardone, personal communication). Children (particularly those under 5 years) with more severe illness and those admitted to hospital were more likely to be unvaccinated. Other contacts who may be vulnerable include those with moderate to severe asthma and congenital heart disease if unvaccinated (recommendation level C).

**Dose and timing of chemoprophylaxis**

The dose and duration of erythromycin chemoprophylaxis should be 125 mg 6 hourly for children up to 2 years age; 250 mg 6 hourly for children 2–8 years of age; and 250–500 mg 6 hourly for children over 8 years of age and adults. The duration of chemoprophylaxis should be for 7 days (recommendation level B). Chemoprophylaxis should be given within 21 days (preferably 14 days) of onset of paroxysmal cough in the primary case and preferably before a secondary case has occurred (recommendation level B). The newer macrolides clarithromycin and azithromycin may have fewer adverse effects and may be equally effective for chemoprophylaxis although currently they are not licensed for this indication.

**Treatment of cases**

To reduce transmission risk, treat primary and other clinically suspected or confirmed case(s) with onset <21 days with erythromycin for 7 days in the doses stated for chemoprophylaxis (recommendation level B). There is no evidence of benefit in cases with onset ≥21 days (recommendation level B). Pregnant women with suspected or confirmed pertussis should be given treatment for at least 3 days before delivery for 7 days (recommendation level C).

**Pertussis vaccine**

The current UK pertussis vaccination programme consists of a series of primary immunizations at 2, 3 and 4 months with whole-cell pertussis vaccine (in combination with the diphtheria and tetanus vaccines) and a pre-school booster immunization with acellular pertussis vaccine (introduced in November 2001). Close contacts in this eligible age group should be given a booster dose if they have not already had one. Adults and children born before November 1996 and some children born 1996 to May 1998 will not have had the pre-school acellular pertussis booster. We recommend chemoprophylaxis for anyone who has not received a pre-school booster and is 5 years old or above if in close contact with vulnerable contacts.

**Criteria for action**

The criteria for action would be a clinically suspected or a confirmed case with vulnerable close contacts present. It is important that cases or contacts who remain unvaccinated or partially vaccinated complete their course of primary immunization and booster vaccine. The impact of booster immunization on waning immunity is unclear at present. We thus recommend that children who are fully immunized including a pre-school booster more than 2 weeks before do not require erythromycin prophylaxis. Adults and children who have not received a pre-school booster and who are 5 years old or above should be given prophylaxis. Children 3.5–6 years who have not received a pre-school booster should be given Diphtheria, Tetanus, acellular Pertussis vaccine (DTaP), including children with confirmed pertussis once they are well.

Treatment should be given to the primary case and chemoprophylaxis to all close contacts, including the vulnerable one(s) but excluding those below age 5 years who have completed their primary immunization, in the dose and for the duration stated above. There is no evidence of clinical benefit in giving chemoprophylaxis after 21 days of onset in the primary case. The case studies below illustrate the principles for using this guidance.

**Case study 1**

A case of pertussis is suspected clinically in an infant aged 6 months with a 2-week history of chronic cough and post-tussive vomiting. He has not been vaccinated. Other family contacts include two older siblings aged 2 and 6 years, who have not been fully vaccinated, and the parents of the family. All contacts are currently asymptomatic although the mother had a bout of chronic coughing about 2 weeks ago that is now resolving. Neither of the parents have contact with other vulnerable contacts.

**Action**

All three children should have the complete course of pertussis vaccine provided there are no recognized contraindications. The primary case should have a per-nasal swab or npa taken to confirm diagnosis. All household members including the primary case should be given chemoprophylaxis. There is no indication to exclude the older child from nursery.

**Case study 2**

A child of 6 years has been confirmed microbiologically to have pertussis following a 2½-week history of chronic cough and vomiting. The child has a full history of primary pertussis immunization. Other contacts in the household include the par-
ents and a 1-year-old sibling who is also fully immunized. The primary case goes to the local infants school. Her mother looks after learning disabled children aged 5–15 years in a local residential home for learning disabled.

**Action**
The primary case needs to be treated symptomatically. The 1-year-old child is fully immunized and thus does not require chemoprophylaxis. Neither parent requires chemoprophylaxis. The primary case should be excluded from school for 5 days while taking erythromycin.

**Case study 3**
A child of 12 is suspected to have pertussis following a 2-week history of acute cough with a mild whoop. She has a full history of vaccination. She lives with her parents and two siblings aged 1 month and 4 years and attends a local school. The 4-year-old also has a full history of primary vaccination but has not had a booster as yet.

**Action**
Both parents and the 1-month-old child should be offered chemoprophylaxis. The 4-year-old does not need chemoprophylaxis as s/he is fully vaccinated but should be offered booster immunization. The primary case should also be treated with erythromycin and excluded from school for 5 days as per PHLS guidance. None of the schoolchildren who have contact with the primary case require chemoprophylaxis.

**Case study 4**
A case of pertussis has been microbiologically confirmed in a 3-month-old infant following a 3-week history of paroxysmal cough, post-tussive vomiting and whoop. The infant has only been partially vaccinated. One older sibling 4 years has a full primary vaccination and booster history. A third older sibling of 8 years, although fully vaccinated with primary immunization, is recovering from a 3-week history of acute cough with no other symptoms with onset 2 weeks before the infant. Both the parents are well.

**Action**
The primary case needs to be treated symptomatically and vaccination completed. Chemoprophylaxis is not indicated for any household members as there are no other vulnerable contacts. It is also unlikely to benefit any close contacts as more than 21 days have elapsed since onset in the primary case. There is no indication for excluding the 8-year-old child from school as s/he is out of the infective period.

**Case study 5**
A 39-week pregnant woman presents to her GP with her 7-year-old son who has had paroxysms of coughing and vomiting for 3 weeks. The mother started coughing 2 days ago. Her fully vaccinated 2-year-old is well.

**Action**
The 7-year-old and the mother need to be investigated further to confirm diagnosis. If pertussis is clinically suspected both the mother and the 7-year-old sibling need treatment and the father or partner should be given chemoprophylaxis. The newborn infant will also require chemoprophylaxis. The 2-year-old sibling who is fully vaccinated does not require chemoprophylaxis but should be offered booster vaccine when reaching the eligible age. There is no indication for excluding the 7-year-old child from school as he is out of the infective period.

**Case study 6**
A 7-year-old child was admitted to a general paediatric hospital ward with a ‘chesty’ cough and a preliminary diagnosis of pneumonia. The cough had been persistent for 2 weeks, paroxysmal in nature and with occasional bouts of vomiting. A detailed history led to a suspected diagnosis of whooping cough and the child was put into isolation and started on treatment. A perinasal swab was taken and serology performed. A full history of primary immunization was confirmed by the child health records. The ward is open plan with 24 beds, admitting children of all ages.

**Action**
The hospital infection control team and the CCDC/CPHM should be notified. A risk assessment should be carried out to identify the level of contact of all the children on the ward (in terms of proximity and duration of contact) with the primary case, their vaccination status and their vulnerability. Should there be close contacts present and the onset of symptoms in the primary case is within the last 21 days then follow-up should be arranged and chemoprophylaxis considered for vulnerable contacts who have been discharged before chemoprophylaxis could be arranged. Contacts who are not in a vulnerable group and who have already been discharged or are shortly to be discharged do not require chemoprophylaxis. The primary case should be isolated for 5 days on treatment with erythromycin.

**Conclusion**
Erythromycin chemoprophylaxis is of limited value, diagnostic laboratory methods are insensitive and pertussis is often diagnosed too late for chemoprophylaxis to be of significant benefit. For this reason a certain amount of judgement has to be used in deciding whether to give chemoprophylaxis, and it is not possible to be prescriptive. This guidance aims to reduce the inappropriate use of erythromycin chemoprophylaxis. For neonates, however, it has been found to be underused, and erythromycin chemoprophylaxis should be promoted to protect this group in particular. However, clinicians need to weigh up the benefits and risks of giving erythromycin chemoprophylaxis
and should inform parents of the possible risks of infantile hypertrophic pyloric stenosis in this age group.

Acknowledgements

We would like to acknowledge Dr K. Cann, Dr P. Van Buynder and Dr D. Fleming for their helpful comments. We would also like to acknowledge all the CCDCs, CPHMs, Regional Epidemiologists and hospital clinicians who made useful suggestions about the use of these guidelines. The PHLS Scientific Advisory Committee on Vaccination and Immunisation has endorsed these guidelines.

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5 Statutory notifications for England and Wales, Northern Ireland and Scotland from PHLS CDSC Colindale and Northern Ireland and SCIEH.


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