Do delayed prescriptions reduce antibiotic use in respiratory tract infections? A systematic review

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SUMMARY

Background: *There is concern about the increasing resistance of antibiotics to common bacteria. Delayed prescribing for respiratory tract infections is a strategy that may reduce the use of antibiotics.*

Aim: *To systematically review controlled trials of delayed prescriptions to establish their capacity to reduce antibiotic intake.*

Design of study: *A systematic review of the literature.*

Setting: *Four studies were conducted in the United Kingdom and one in New Zealand.*

Methods: *We searched MEDLINE from 1966 to April 2003, EMBASE, and the Cochrane Controlled Trials Register using the following terms: 'delayed', 'antibiotics', 'prescriptions', and 'back-up' (as in back-up prescription). We included controlled trials of studies in which the intervention was a delayed prescription compared to an immediate prescription for patients with upper respiratory tract infections. The studies were selected independently and the results compared. Disagreements were resolved by discussion. The data and quality of the studies were extracted and assessed independently by two of the authors.*

Results: *Four randomised controlled trials and one before–after controlled trial contributed to the review. The relative risk in the randomised trials for lower antibiotic usage when a delayed prescription was given ranged from 0.54 for the common cold to 0.25 for otitis media.*

Conclusion: *The consistent reduction in antibiotic usage in the five controlled trials included in this review suggests that delayed prescription is an effective means of reducing antibiotic usage for acute respiratory infections. The duration of delay for prescriptions ranged widely, from 1 to 7 days.*

Keywords: *respiratory tract infections; delayed prescriptions; antibiotics.*

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Introduction

THERE is evidence that the majority of patients feel that antibiotics are an appropriate treatment for a wide range of respiratory tract symptoms, and that doctors will prescribe antibiotics for them.[1] This is in spite of systematic reviews suggesting minimal or no benefit from antibiotics for sore throat,[2] acute bronchitis,[3] the common cold,[4] acute cough[5] and otitis media (with the proviso that antibiotic treatment may play an important role in reducing the risk of mastoiditis in populations where it is more common).[6] While there appears to be some reduction in the rate of antibiotic prescribing in the United States (US), the absolute levels (750 per 1000 visits for bronchitis in 1999–2000) are still high.[7] This situation of potentially 'inappropriate' prescribing prompted one commentator to suggest the use of delayed prescriptions.[8] Delayed prescriptions (i.e. prescriptions to be used later if symptoms persist) have been used for purposes other than respiratory tract infection for many years. These include oral steroids for serious asthma[9] and anti-malarial drugs for acute malaria.[10]

The first evidence of benefit from a randomised trial of delayed prescriptions for respiratory symptoms came from a trial of antibiotics for acute sore throat carried out by Little *et al* (1997), who gave either a prescription for antibiotics to be filled immediately, or one to be filled after 3 days, or no prescription for antibiotics.[11] The immediate group consumed 99% of the antibiotic prescriptions, while the delayed group used only 31% with no apparent serious harm.

The aim of this study was to conduct a systematic review of the controlled trials of delayed antibiotic prescription for upper respiratory tract infections. We also explored the differences found between the studies, the potential for harm, and offer advice to clinicians for use in everyday practice. We felt that the techniques of delayed prescription used were sufficiently similar to make generalisations, even though they were applied to different respiratory tract symptoms or diseases.

Methods

Inclusion criteria

We included controlled trials of studies in which the intervention was a delayed prescription compared to an immediate prescription for patients with upper respiratory tract infections. These included acute cough, sore throats, otitis media, the common cold, and sinusitis. The patients could be seen in any general practice setting (i.e. they could self-refer). We did not limit the age of participants.

HOW THIS FITS IN

What do we know?

Some studies show a reduction in antibiotic use when delayed prescriptions are given for upper respiratory tract infections. Antibiotics are not always needed for acute upper respiratory tract infections.

What does this paper add?

There is a consistent reduction in antibiotic use for otitis media, the common cold, and acute cough when delayed prescriptions are used. Asking the patient to return to the clinic to collect the prescription is more effective than giving the prescription to the patient. Patients are less likely to think that antibiotics are effective for their condition when given a delayed prescription. Patients may be less satisfied with the consultation when given a delayed prescription.
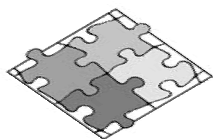
Literature search

We searched MEDLINE from 1966 to April 2003, EMBASE, and the Cochrane Controlled Trials Register using the following terms: 'delayed', 'antibiotics', 'prescriptions', and 'back-up' (as in back-up prescription). We contacted the authors of published controlled trials of delayed prescriptions to see if they were aware of any unpublished articles. There was no language restriction and one study, published in Dutch, was translated in to English by one of the authors.[12] The papers were chosen independently and disagreements resolved by discussion.

Validity and quality assessment

One of the authors assessed the abstracts and titles of potential papers and the chosen papers were confirmed by a second author. Two of the authors assessed the trials independently for the quality of randomisation, concealment of allocation, co-interventions, losses to follow-up (intention-to-treat analysis), degree of blinding, and extraction of data. Disagreements among the reviewers were resolved by discussion and consensus. The quality of the four randomised controlled trials (RCTs) was assessed using the Jadad scale.[13] This is one of a few validated quality assessment tools for clinical trials.

Analysis

The pooled relative risks (RRs) and 95% confidence intervals were calculated with Revman 4 (Update Software 2000) using both fixed and random effects models.[14] The authors were concerned about pooling such different clinical entities. The primary outcomes of interest were the use of, or filling of, the prescription, and any reported side effects. The secondary outcomes were satisfaction with the consultation, a sense that the doctor had dealt with worries, belief that antibiotics are effective, and belief that antibiotics can legitimate an illness to work or school colleagues and to friends and family.

Results

Studies identified

A flow chart showing the study selection process, from the initial search to those finally assessed, is shown in Figure 1. Five published controlled trials were reported (Table 1).[11,15–18] No unpublished studies were found. One of the included studies was a controlled before–after study[16] and four were RCTs.[11,15,17,18] There were differences in the conditions that the delayed prescriptions were used for; two studies used delayed prescriptions for otitis media,[16,17] one for the common cold,[18] one for cough,[15] and one for sore throat.[11] Eligibility criteria for age differed between studies. For otitis media the children in one study were between 6 months and 10 years of age,[17] whereas in the other otitis media study the entry criteria was any child.[16] In the sore throat study, participants were aged over 4 years of age, and in the acute cough study they had to be older than 16 years. In the common cold study the patients could be of any age.

Methodological issues

Concealment of allocation was achieved by the use of opaque envelopes opened in front of the patient in the four RCTs (Table 2). Completion of follow-up ranged from 78% to 95% of participants. All four of the RCTs stated that they used an intention-to-treat analysis, but three of them did not state how they dealt with missing data.[11,15,17] Details on the blinding of the patients and the diaries were obtained directly from two of the authors (see Table 2).

Outcomes

Reduction in prescriptions consumed or collected. There was significant heterogeneity among the five studies and hence statistical pooling was not conducted. The RR for lower antibiotic use (consumed or collected) when a delayed prescription was given ranged from 0.25 to 0.77
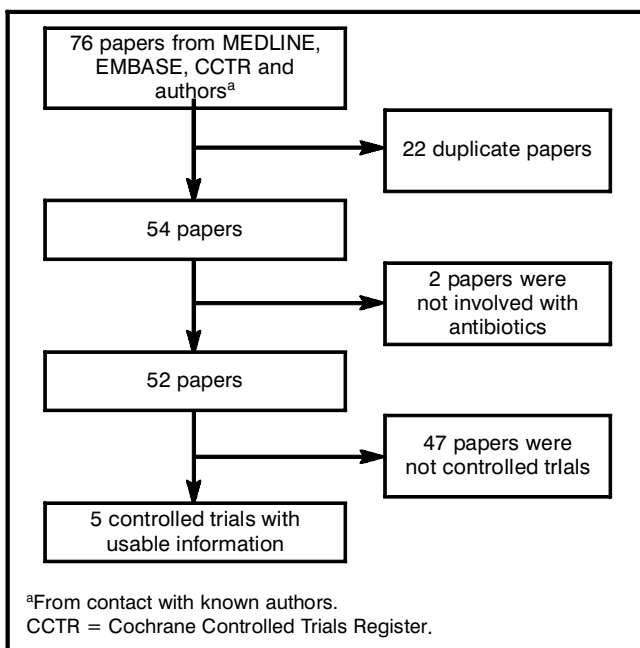

*From contact with known authors.
CCTR = Cochrane Controlled Trials Register.

Figure 1. Flow chart showing the study selection process.

Table 1. Criteria for review participants, interventions, barriers, and outcomes for the controlled studies.

Study (first author, date, type, reference)	Participants	Interventions	Barriers in addition to delayed prescription	Outcomes
Arroll, 2002, RCT[18]	Patients of any age who asked for antibiotics or whose general practitioner thought they wanted them. Patients had common cold by ICHPPC-2	Delayed prescription versus immediate. If delayed they were asked to wait at least 3 days	None. Both intervention and control given prescription at time of consultation	Antibiotic consumed by 32/67 of delayed group and 55/62 of immediate group.[a] No difference in symptoms. Diarrhoea in 3/63 of delayed group and 3/66 of immediate group
Dowell, 2001, RCT[15]	Patients 16 years and over with acute cough with or without coryza, shortness of breath, sputum, fever, sore throat or tightness in chest. Excluding strong preference for antibiotics and toxic patients	Delayed prescription or an immediate prescription. Delayed to collect after one week if required	Patients had to return to the surgery to collect the prescription	Antibiotic collected by 43/95 of delayed group and 92/92 of immediate group.[a] No difference in repeat visits after one
Little, 2001, RCT[17]	Patients aged 6 months to 10 years with acute otalgia and acute inflammation of the ear drum. Excluded if they had OME[b], CSOM[c], serious chronic disease, antibiotics in previous 2 weeks, previous septic complications, hearing impairment or were looking too unwell	Delayed or immediate prescription of amoxycillin or erythromycin (if allergic to penicillin). Delayed to collect prescription after 72 hours if otalgia or fever not getting better or if the child had a discharge of more than 10 days duration	Patient had to return to surgery to collect the prescription	Antibiotic consumption by 36/150 of delayed group and 132/135 of immediate group.[a] More symptoms and more paracetamol consumed in the delayed group.[a] No difference in time off school, distress, and daily pain score. Harms: diarrhoea in 9% (14/150) of delayed group and 19% (25/135) of immediate group
Cates, 1999, BACT[16]	Children with otitis media who were not particularly ill	Given a handout that summarised the limited benefit of antibiotics, and a delayed prescription for amoxycillin. Parents asked to keep it for 1 or 2 days	Parents given a prescription	Antibiotic use by 639/988 of intervention delayed practice group and 835/991 of control practice group[a]
Little, 1997, RCT[11]	Patients aged 4 years and over with sore throat as primary complaint and an abnormal sign in throat. If <12 years of age, abnormal throat signs sufficient	Delayed prescription for antibiotics, no antibiotics, or an immediate prescription to be collected from reception if symptoms not settling within 3 days	Patient had to return to surgery to collect the prescription	Antibiotic use by 55/176 in the delayed group, 210/211 in the immediate group and 23/184 in the no antibiotic group.[a] Diarrhoea in 23/237 of delayed group and 23/246 of immediate antibiotic group. There were more symptoms and signs in the delayed group[a]

[a]P< 005. [b]Otitis media with effusion. [c]Chronic suppurative otitis media. RCT = randomised controlled trial; BACT = before–after controlled trial.

(Table 3). There was a difference in the barriers to collecting or the use of prescriptions. In three studies, patients had to return to the physician's office to collect their prescription.[11,15,17] The RR for these three studies ranged from 0.25 (95% confidence interval [CI] = 0.19 to 0.34) to 0.45 (95% CI = 0.36 to 0.56). In the remaining two studies, patients were given the prescription at the time of consultation.[16,18] For these studies the RR was 0.54 (95% CI = 0.41 to 0.7) and 0.77 (95% CI = 0.73 to 0.81). There was a difference in the RRs for the before–after controlled trial in children with otitis media and the RCT for the same condition (0.77 versus 0.25, respectively).

Symptoms and signs. Three of the studies reported an increase in symptoms and signs in patients who received a delayed prescription,[11,15,17] one reported a decrease,[18]

and one did not report on symptoms.[16] The study on sore throat found a significant difference in fever >37°C in terms of a median of 5 days versus 4 days for delayed the versus the immediate antibiotic.[11] The RCT of delayed prescriptions in otitis media found a number of significant differences. The children who had delayed antibiotics had a longer illness by 1.1 days, more disturbed nights, and more paracetamol consumed, but less diarrhoea than the immediate group (9% versus 19% for diarrhoea). There was a significant reduction of diarrhoea in one study:[17] RR = 0.45 (95% CI = 0.22 to 0.91), and a non-significant reduction in the others.[11,18] There was a non-significant higher level of cough in the delayed prescription study of acute cough,[15] and in the common cold study there was a significantly lower temperature (0.2°C) in the delayed antibiotic group.[18]

Table 2. Methodological issues.

Study (first author, date, type)	Concealment of allocation	Method of randomisation	Follow-up	Blinding	ITT
Arroll, 2002, RCT	Sealed, numbered envelope opened in front of patient	Generated from Excel spreadsheet	123/129 (95%)	Control and intervention group unaware of what the other group were given	Assumed drop-outs took antibiotics and for continuous variables took last recorded value
Dowell, 2001, RCT	Sealed, numbered envelope opened in front of patient[a]	Randomised in balanced blocks of four using random number tables	95/99 (96%) in delayed arm antibiotic taking verified. 78% of questionnaires returned	Patients aware of other arm of study. Assessment of diary not blind to intervention[a]	Stated ITT but no information given on how they accounted for missing values
Little, 2001, RCT	Sealed, numbered envelope opened in front of patient	Randomised but no details	285/315 (90%)	Patients unaware[b] of other arm of study. Assessment of diary probably blind to intervention	Said ITT but no information on how they accounted for missing values
Cates, 1999, BACT	N/A	N/A	N/A	Control practice not using patient information sheet	N/A
Little, 1997, RCT	Sealed, numbered envelope opened in front of patient	Randomised but no details	81% of diaries. 80% of antibiotic usage known.	Control and intervention group unaware of what other group given. Patient diary completed with lack of awareness of other group	Stated ITT but no information given on how they accounted for missing values

[a]Not reported in the article but confirmed through contact with the second author (MP). [b]Not reported in the article but confirmed through contact with the first author (PL). ITT = intention-to-treat analysis; N/A = not assessable; RCT = randomised controlled trial; BACT = before–after controlled trial.

Satisfaction with the consultation and beliefs about antibiotics

Two of the randomised trials showed a significant decrease in satisfaction with the consultation when delayed antibiotics were given (RR = 0.84 [95% CI = 0.76 to 0.93][15] and RR = 0.76 [95% CI = 0.66 to 0.88]).[17] Neither of the two randomised trials that reported the belief that the doctor dealt with their worries was significant.[11,18] Two of three studies reported a significant reduction in the belief that antibiotics were effective in the delayed group compared to the immediate group (RR= 0.69 [95% CI = 0.6 to 0.79][11] and RR = 0.6 [95% CI = 0.49 to -0.73])[17] (Table 3).

Co-interventions

Analgesic use was the same for both groups in the sore throat RCT,[11] but there was higher paracetamol use reported in the delayed antibiotic group in the otitis media RCT,[17] and no results reported in the cough and common cold RCTs.[15,18]

Quality of studies

All four RCTs studies had Jadad scores greater than three.[13]

Heterogeneity

Significant heterogeneity was found when the five controlled trials were pooled for antibiotics consumed or collected. The heterogeneity persisted when different studies were combined and was even present when any two studies were pooled.

Descriptive studies

We identified three descriptive studies that were not included in the analysis. In one US descriptive study, 50.2% of 'back-up' (delayed) prescriptions were given for a variety of upper respiratory tract symptoms.[1] The proportion of patients who received a delayed prescription was 63% for respiratory congestion/head cold, 55% for cough, 11% for chest congestion, 11% for sinus congestion, 11% for ear-related complaint, 2% for sore throat and 6% for fever. Two other descriptive studies were from the United Kingdom (UK)[19] and The Netherlands.[12] The UK study found that 55% of prescriptions for upper or lower respiratory tract infections were dispensed and taken, whereas 31% of prescriptions were not dispensed and 14% were dispensed but not taken. In the Dutch study, out of 2891 prescriptions given for upper respiratory tract infection, 117 were 'postponed' (delayed) prescriptions and of these, 62% were filled.

Discussion

Summary of the main findings

Our results show a consistent reduction in the use of antibiotics in all five controlled trials. The statistical heterogeneity was not unexpected given the different conditions and interventions. However, all four RCTs had significant RRs, with the highest limit of the confidence intervals being for the common cold study (95% CI = 0.41 to 0.70), which would still be regarded as clinically significant.[18] The RR of 0.77, with an upper limit of the confidence interval being 0.81 for the

Table 3. Satisfaction with consultation and other patient opinions.

Study (first author, date)	Patients satisfied with consultation	Patients felt GP dealt with worries	Patients thought antibiotics to be effective	Patients felt antibiotics legitimised illness to work/school	Patients felt antibiotics legitimised illness to friends or family	RR (95% CI random)
Arroll, 2002	Delayed group: 64/67, immediate group: 58/62[a]	Delayed group: 64/67, immediate group: 58/62[a]	Delayed group: 51/67, immediate group: 47/62[a]	Delayed group: 13/54, immediate group: 19/62[a]	Delayed group: 7/60, immediate group: 6/62[a]	0.54 (0.41 to 0.70)
Dowell, 2001	Delayed group: 54/73, immediate group: 73/75[b,c]	Patients in delayed group were less enabled: 2.4 versus 3.3 ($P = 0.04$)				0.77 (0.73 to 0.81)
Little, 2001	Delayed group: 115/150, immediate group: 123/135[d,c]	Delayed group: 64/140, immediate group: 100/131[d,c]				0.45 (0.36 to 0.56)
Cates, 1999	N/A	N/A	N/A	N/A	N/A	0.31 (0.25 to 0.39)
Little, 1997	Delayed group: 165/177, immediate group: 202/211[a]	Delayed group: 164/177, immediate group: 201/211[a,c]	Delayed group: 99/165, immediate group 181/207[a,c]	Delayed group: 96/177, immediate group: 128/209[a,c]	Delayed group: 67/176, immediate group: 75/210[a,c]	0.25 (0.19 to 0.34)

[a]Very or moderately compared to slightly or not at all. [b]Very or moderately compared with not very or not at all satisfied. [c]$P < 0.05$. [d]Very effective compared with not very effective. N/A = not applicable; RR = relative risk (for lower antibiotic use [consumed or collected] when a delayed prescription was given).

before–after controlled trial,[16] would also be regarded as clinically significant. It is more difficult to explain why this was so different from the RR in the RCT for otitis media (RR = 0.25), especially as parents reported a significant excess of symptoms and paracetamol consumption in the delayed group (Table 3). We speculate that parents may be more concerned that their children avoid antibiotics, but less concerned when taking them for themselves. This has been reported in a qualitative study of patients with sore throat.[20] The before–after controlled trial for otitis media may reflect what is possible in everyday practice, while the RCT study for otitis media may reflect what is possible when doctors and patients are trying hard to avoid antibiotics, and may represent the lower limit of antibiotic usage through using delayed prescriptions. The other explanation is that the three studies that required patients to return to the physician's office to collect the prescription had lower RRs than the common cold RCT[18] and the otitis media before–after study[16] (Table 1). The routine use of such a barrier or the use of post-dated prescriptions may result in lower usage in everyday practice.

An additional insight relates to the time of waiting for collection or consumption of the antibiotics. One of the papers suggested collection after 1 day, while another made it 7 days. This suggests that waiting 1–3 days may be too conservative for some conditions and that additional delaying time barriers may be warranted.

There was less consistency for patient satisfaction and other opinions (Table 3). Two of the four RCTs found that patients were less satisfied if they were given delayed antibiotic prescriptions. The fact that patients were less likely to feel that the doctor had dealt with their worries when given the delayed prescription implies that doctors may need to explain more clearly to the patient why they are being given a delayed prescription. The belief that antibiotics are less effective for the delayed antibiotic groups is consistent with

the medicalisation of the respiratory symptoms. This shows that a delayed prescription can change patients' beliefs. This is consistent with a second study by Little *et al* (1997), where patients were less likely to consult for a sore throat within the subsequent year if they had received a delayed antibiotic.[21] The study by Dowell *et al* found no difference in consulting rate after 15 months.[15] Three of the four RCTs found more symptoms in the delayed group than in the immediate group, suggesting that delayed prescriptions are not entirely risk free. Targeting of patients may be possible if higher risk patients can be identified, as was demonstrated in a study of otitis media.[22]

Strengths and weaknesses

The four RCTs had a Jadad score of at least three or more out of five and hence were of satisfactory quality.[13] We believe that our search for papers is as comprehensive as is possible for a technique that is applied to a wide range of diseases or symptoms. We cannot exclude publication bias, as all four RCTs (and the three descriptive studies) reported reductions in antibiotics consumed or collected. A funnel plot analysis with the four RCTs did not find any asymmetry in the findings, although this is difficult to assess with only four studies.

RCTs are not the best method of assessing rare adverse effects such as meningitis. The safety issues of using delayed prescriptions with acute otitis media are not clear. In the before–after study, Cates gave the patients a pamphlet that explained what to do. This is important, as in a RCT of antibiotics versus placebo in children under the age of 2 years, one child in the placebo group developed meningitis.[23] While it is clear that all patients do not need antibiotics for acute otitis media, it is not clear how to distinguish those who may need antibiotics from those who do not. Similarly, it is not clear which patients with sore throats should get

antibiotics. Obviously, some of those patients will have streptococcal tonsillitis and will be at a small (but not zero) risk of rheumatic fever and complications such as quinsy.[24] For patients with a cough or uncomplicated common cold, it is clear that patients can be given delayed prescriptions without any risk of harm.

None of the studies described their patients sufficiently to enable stratification by severity. However, in general they excluded very sick patients.

Existing literature

The reduction in the use of antibiotics in the four RCTs compares well to other methods of reducing antibiotics. There have been a number of RCTs of interventions to change either doctor or patient practice. One US study intervened with parents of children aged less than 4 years. The intervention for parents involved the distribution of materials and presentations, and for doctors the interventions were formal presentations and small group meetings. This was accompanied by a reduction in the proportion of parents who expected antibiotics for their child from 14% to 9%, while there was an increase in the control area from 7% to 10%.[25] There was a decrease in the intervention group in the number of parents taking their child to another doctor because they did not receive an antibiotic from 5% to 2%, whereas there was an increase in the control group from 2% to 4%. RCTs of educational interventions (prescriber feedback and management guidelines, and a visit to high prescribers) found a significant RR reduction of 0.21 in Australian general practice trainees compared to an intervention on an unrelated topic,[26] and a UK study of general practitioners who gave an information leaflet to the intervention arm and delayed prescriptions to both had a RR of 0.76 (95% CI = 0.59 to 0.97) for antibiotic usage.[27] A US prospective controlled trial found that an intervention consisting of education, practice profiling, and academic detailing resulted in a reduction of antibiotic usage for acute uncomplicated bronchitis, from 74% to 48% (RR = 0.64, $P = 0.003$) but not in the control group (78% to 76% [$P = 0.81$]).[28] A review of methods of reducing antibiotic usage suggested that this was an under-researched topic and that enhanced consulting skills, guidelines, monitoring strategies, patient education, and anti-inflammatory drugs all hold the promise of reducing antibiotic usage for respiratory tract symptoms in primary care.[29]

Future research and clinical implications

Generalisability is difficult in all RCTs, whether they are in general practice or in other settings. Including consecutive patients would give the ideal situation for generalisation, but this was not possible in the four RCTs. The fact that the studies were conducted in a general practice situation assists considerably the generalisability compared to if the studies had been conducted in an emergency room or hospital outpatient clinic. Four of the studies were conducted in the UK and one in New Zealand. The case could be made that delayed prescriptions may increase the rate of use compared to a policy of giving no prescriptions. Qualitative research suggests that general practice physicians are concerned that if patients want antibiotics for respiratory

tract infections they will seek out other physicians if this need is not met.[30] This is where the delayed prescription has a place, and it represents a gentle form of education. Long-term monitoring and larger trials of patients obtaining delayed prescriptions is needed to ensure that complications, such as meningitis or a resurgence of mastoiditis do not occur, as these sorts of complications are rare in clinical trials.[23] Future research should examine delayed prescriptions for other conditions, such as acute sinusitis and acute bronchitis. More work, such as that by Little *et al* (2002),[22] is needed to identify patients at higher risk and those in whom antibiotics may be effective. This review will be of interest to clinicians, policy makers, public health advisors, microbiologists, and infectious disease physicians.

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