Clostridium difficile infection: risk with broad-spectrum antibiotics

Evidence summary

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Key points from the evidence

> The content of this evidence summary was up-to-date in March 2015. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

Use of broad-spectrum antibiotics is associated with an increased incidence of *Clostridium difficile* infection. This briefing reviews the evidence assessing the risk of *C. difficile* infection associated with individual broad-spectrum antibiotics based on the highest quality published evidence.

Both antibiotic prescribing practice and the epidemiology of *C. difficile* infections are changing. *C. difficile* has been reported with clindamycin since 1978 (Bartlett et al. 1978). Subsequently, since the early 1990s, the antibiotics most commonly reported as being associated with *C. difficile* infection were cephalosporins and quinolones. Antibiotic guidelines steadily adopted that evidence and prescribing of cephalosporins and quinolones decreased over the decade to 2013/14 in primary and secondary care in England. However, over the same period, the prescribing of combination penicillins increased: co-amoxiclav prescribing increased in primary and secondary care and piperacillin-tazobactam prescribing increased in secondary care. With further clarification of the epidemiology following the establishment of the C. difficile ribotyping network service, these combination penicillins have become the antibiotics most frequently reported as being associated

with *C. difficile* infections. These data should be interpreted with caution and should not be considered to indicate conclusively which antibiotics have the highest risks of *C. difficile* infection.

Three meta-analyses in people with hospital-associated and community-associated *C. difficile* infection confirmed that the antibiotics most strongly associated with the infection were clindamycin, cephalosporins and quinolones. However, the interpretation of data on the risk of *C. difficile* with different antibiotics is extremely difficult. Such data should be interpreted with caution and should not be considered to definitively show which antibiotics or subgroups of antibiotic classes carry higher risks of *C. difficile* infection.

Although the data have limitations that prevent firm conclusions, the evidence shows the importance of following antibiotic guidelines that recommend that all broad-spectrum antibiotics are prescribed appropriately and with careful stewardship.

Introduction and current guidance

C. difficile are bacteria that exist widely in the environment, notably in soil, and may become established in the colon of healthy people. *C. difficile* produces spores, which are passed out in the faeces and may survive for months or years in the environment (for example, on clothes or bedding). Spores that get into the gut then develop into mature bacteria. *C. difficile* infection occurs when the other harmless bacteria in the gut are disrupted (for example, by taking antibiotics) or when the immune system is compromised, allowing the numbers of *C. difficile* bacteria to increase to high levels. Certain *C. difficile* strains produce toxins that damage the lining of the colon, causing symptoms ranging from mild, self-limiting diarrhoea to pseudomembranous colitis, toxic megacolon, perforation of the colon, sepsis and death (NICE clinical knowledge summary: diarrhoea - antibiotic associated; Brown et al. 2013).

As well as broad-spectrum antibiotics, other factors increase the risk of *C. difficile* infection. These include advanced age, underlying morbidity, hospitalisation, exposure to other people with the infection, long duration of antibiotic treatment, taking multiple antibiotics concurrently or taking multiple antibiotic courses, and inflammatory bowel disease (NICE clinical knowledge summary: diarrhoea - antibiotic associated; Public Health England and Department of Health guidance: Clostridium difficile infection: how to deal with the problem).

The number of *C. difficile* infections in the NHS in England has decreased substantially, from 55,498 cases in 2007/08 to 13,361 cases in 2013/14 (Public Health England annual epidemiological commentary: MRSA, MSSA and E. coli bacteraemia and C. difficile infection data, 2013/14). This decrease has occurred in conjunction with mandatory surveillance and

target-setting, additional measures to control of antibiotic prescribing, and increased compliance with isolation, hand-washing and hygiene protocols (Department of Health: annual report of the Chief Medical Officer 2011, volume 2).

In 2008, the Department of Health and Public Health England's report on Clostridium difficile infection: how to deal with the problem recommended that trusts should develop restrictive antibiotic guidelines that use narrow-spectrum agents alone or in combination as appropriate. These guidelines should avoid recommending clindamycin and second- and third-generation cephalosporins (especially in older people) and should recommend minimising the use of quinolones, carbapenems (for example, imipenem and meropenem) and prolonged courses of aminopenicillins (for example, ampicillin and amoxicillin). Broad-spectrum antibiotics should be used only when indicated by the person's clinical condition, and their use should be reviewed after the results of microbiological testing or based on the sensitivities of causative bacteria. The Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI) recommends the Start smart – then focus approach. This recommends that, if immediate antibiotic treatment is necessary, the clinical diagnosis and continuing need for antibiotics should be reviewed within 48–72 hours.

When antibiotics are considered necessary to treat common infections in primary care, Public Health England's guidance on managing common infections recommends suitable options and advises that broad-spectrum antibiotics should be used only when narrow-spectrum antibiotics are ineffective.

Appropriate use of antimicrobials is also important to reduce the serious threat of antimicrobial resistance. A cross-governmental UK 5 year antimicrobial resistance strategy was launched in 2013.

Full text of introduction and current guidance.

Evidence review

- This evidence review outlines 1 meta-analysis of hospital-associated *C. difficile* infection (Slimings and Riley 2014) and 2 of community-associated *C. difficile* infection (Brown et al. 2013 and Deshpande et al. 2013).

- The results of the 3 meta-analyses are similar. Slimings and Riley (2014) concluded that cephalosporins and clindamycin are the antibiotics most strongly associated with hospital-associated *C. difficile* infection. Brown et al. (2013) and Deshpande et al. (2013) found that, for community-associated infection, the strongest association was seen with clindamycin,

cephalosporins and quinolones. Trimethoprim and sulfonamides were also associated with an increased risk of infection in all 3 meta-analyses but data were not reported for trimethoprim alone. See table 1 for details.

- Slimings and Riley (2014) also considered subgroups of antibiotic classes. They found that penicillin combination antibiotics, such as co-amoxiclav and piperacillin-tazobactam, were associated with a statistically significant (1.5 times) increase in the risk of hospital-associated *C. difficile* infection. Second-, third- and fourth-generation cephalosporins were associated with 2 to 3 times the risk of infection, but the increased risk seen with first-generation cephalosporins was not statistically significant. However, the 95% confidence intervals, which give a measure of the results' precision, overlapped.

- The associations seen in the meta-analyses of community-associated infection are generally stronger than in the meta-analysis of hospital-associated infection. This may be because antimicrobial-associated risk factors for community-associated *C. difficile* infection are less likely to be confounded by other (hospital-associated) risks.

- The studies included in the 3 meta-analyses are observational studies and are, therefore, prone to confounding and bias. Possible confounding factors include comorbidities, polypharmacy, duration and dose of antibiotic, and use of multiple antibiotics. Possible sources of bias include sampling bias (commonly prescribed antibiotics will be more often reported as being associated with cases), clinical susceptibility bias (patients with illnesses requiring antibiotics may have inherent increased risks of developing *C. difficile*, and cases may be falsely attributed solely to the clinically-indicated use of antibiotics in such people), selection of inappropriate controls, and misclassification of *C. difficile* and exposures to antibiotics. Heterogeneity was commonly seen in the meta-analyses because of, for example, differences in study populations and methodologies, definitions of cases, and strains of *C. difficile*. Also, there is the potential for publication bias and a lack of consensus regarding the appropriate time window to measure antibiotic exposure.

Table 1 Summary of risk of *C. difficile* infection associated with antibiotics

	Slimings and Riley (2014) Hospital-associated	Brown et al. (2013) Community-associated	Deshpande et al. (2013) Community-associated

	13 case-control studies and 1 cohort study 3202 cases 15,938 people in total	6 case-control studies and 1 cohort study 2578 cases Total number of people not reported	8 case-control studies Number of cases not reported 30,184 people in total
All antibiotics	13 studies OR 1.57 95% CI 1.31 to 1.87	5 studies OR 3.55 95% CI 2.56 to 4.94	8 studies OR 6.91 95% CI 4.17 to 11.44
Clindamycin	6 studies OR 2.86 95% CI 2.04 to 4.02	3 studies OR 16.80 95% CI 7.48 to 37.76	2 studies OR 20.43 95% CI 8.50 to 49.09
Cephalosporins	8 studies OR 1.97 95% CI 1.21 to 3.23 Subgroup analyses 1st generation: no significant association seen OR 1.36 95% CI 0.92 to 2.00 2nd generation: 6 studies OR 2.23 95% CI 1.47 to 3.37 3rd generation: 6 studies OR 3.20 95% CI 1.80 to 5.71 4th generation: 2 studies OR 2.14 95% CI 1.30 to 3.52	5 studies OR 5.68 95% CI 2.12 to 15.23 Also includes monobactams and carbapenems	3 studies OR 4.47 95% CI 1.60 to 12.50

Quinolones	10 studies OR 1.66 95% CI 1.17 to 2.35	5 studies OR 5.50 95% CI 4.26 to 7.11	3 studies OR 5.65 95% CI 4.38 to 7.28
Penicillins	No significant association seen overall<hr>Subgroup analysis penicillin combination antibiotics (e.g. co-amoxiclav and piperacillin-tazobactam) 6 studies OR 1.54 95% CI 1.05 to 2.24	5 studies OR 2.71 95% CI 1.75 to 4.21	4 studies OR 3.25 95% CI 1.89 to 5.57
Macrolides	No significant association seen	4 studies OR 2.65 95% CI 1.92 to 3.64	3 studies OR 2.55 95% CI 1.91 to 3.39
Trimethoprim and sulfonamides	5 studies OR 1.78 95% CI 1.04 to 3.05	4 studies OR 1.81 95% CI 1.34 to 2.43	3 studies OR 1.84 95% CI 1.48 to 2.29
Carbapenems	6 studies OR 1.84 95% CI 1.26 to 2.68	Assessed with cephalosporins and monobactams	Not assessed
Tetracyclines	No significant association seen	No significant association seen	No significant association seen
Aminoglycosides	No significant association seen	Not assessed	Not assessed
Abbreviations: CI, confidence interval; OR, odds ratio.			

Full text of evidence review.

Context

Reducing inappropriate use of cephalosporins and quinolones to reduce *C. difficile* infection (and MRSA infection) has been prioritised in both primary and secondary care since the late 1900s and early 2000s. Although there has been a marked decline in their use in the past decade, the use of other broad-spectrum antibiotics has increased.

According to Public Health England's English surveillance programme antimicrobial utilisation and resistance (ESPAUR) report, in general practice, use of cephalosporins and quinolones decreased, but use of co-amoxiclav significantly increased between 2010 and 2013. In hospitals, the use of narrow-spectrum antibiotics (phenoxymethylpenicillin, flucloxacillin and erythromycin) decreased and the use of broad-spectrum antibiotics such as co-amoxiclav, piperacillin-tazobactam and meropenem significantly increased during the same period.

According to Public Health England's C. difficile ribotyping network (CDRN) report, since 2007 the strains of *C. difficile* identified and the antibiotics most frequently reported as being associated with *C. difficile* infections referred to the CDRN have changed markedly. In 2007/08, cephalosporins and quinolones were the most commonly cited antibiotics, but they were superseded by co-amoxiclav and piperacillin-tazobactam in 2011/12 and 2012/13. These data should be interpreted with caution and should not be considered to indicate conclusively that these antibiotics have a higher risk of *C. difficile* infection. The CDRN states that the data probably reflect changes in antibiotic prescribing as one of the control measures for *C. difficile* infection.

Full text of context.

Estimated impact for the NHS

Because of the limitations of the data there is too much uncertainty to definitively assign levels of risk of *C. difficile* infection to different antibiotics or subgroups of antibiotic classes. Identifying the cephalosporin and quinolone classes as 'high-risk' may have driven the increased prescribing of co-amoxiclav and other broad-spectrum antibiotics such as piperacillin-tazobactam.

Without clear evidence showing that 1 particular antibiotic or class of antibiotic is 'low-risk', only general recommendations are possible. Broad-spectrum antibiotics should be used only in limited circumstances and when clinical need is greatest. Organisations should follow national guidance, support local antimicrobial stewardship programmes and follow local antimicrobial guidelines. These should be evidence based, relevant to the local healthcare setting and take into account local antibiotic resistance patterns.

Healthcare professionals should review and, if appropriate, revise current prescribing practice and ensure prescribing is in line with Public Health England's guidance for primary care on managing common infections, the Department of Health's guidance Start smart – then focus, and local trust antimicrobial guidelines. The total volume of all antibiotic prescribing and broad-spectrum antibiotic prescribing should be reviewed against local and national data.

See the estimated impact for the NHS section of this medicines and prescribing briefing for information on resources to help reduce inappropriate antibiotic prescribing.

NICE has produced several guidelines relating to healthcare-associated infections and antibiotic prescribing, which are listed in the relevance to NICE guidance programmes section of this medicines and prescribing briefing. NICE is also developing guidelines on antimicrobial stewardship (publication expected July 2015) and antimicrobial stewardship – changing risk-related behaviours (publication expected March 2016).

Full text of estimated impact for the NHS.

About this evidence summary: medicines and prescribing briefing

'Evidence summaries: medicines and prescribing briefings' aim to review the evidence for the clinical effectiveness of medicines within a therapeutic class or indication to provide advice on the relative position of different medicines as therapeutic options. This will assist localities in their planning on medicines optimisation priorities as well as providing individual prescribers with information to help informed decision making. The strengths and weaknesses of the relevant evidence are critically reviewed to provide useful information, **but this medicines and prescribing briefing is not NICE guidance.**

Full evidence summary: medicines and prescribing briefing

Introduction and current guidance

Clostridium difficile infection

Diarrhoea is a common side effect of antibiotic treatment, occurring in 2–25% of people taking antibiotics, and depends on a range of factors including the antibiotic. The most common cause of antibiotic-associated diarrhoea is disruption of the usual gut flora; around 20–30% of cases are caused by *Clostridium difficile* infection.

Although no particular antibiotics can be ruled out, those most commonly implicated in *C. difficile* infection are clindamycin, cephalosporins (in particular second- and third-generation cephalosporins), quinolones, co-amoxiclav and aminopenicillins (for example, ampicillin and amoxicillin, which may be related to their volume of use rather than being 'high risk') (NICE clinical knowledge summary: diarrhoea - antibiotic associated). Compared with narrow-spectrum antibiotics, broad-spectrum antibiotics are more likely to significantly change the gut flora, potentially allowing other bacteria, such as *C. difficile*, to become established.

C. difficile may be found in the gut of people with no symptoms: up to 3% of healthy adults, 7% of residents in long-term care facilities, 14–20% of older people on hospital wards and about 66% of healthy children aged under 2 years. When the normal bacteria in the gut are disrupted (for example, by antibiotics), the numbers of *C. difficile* bacteria may increase to unusually high levels, particularly in people whose immune system is compromised. *C. difficile* diarrhoea is not caused by overgrowth of *C. difficile* alone; certain strains may produce toxins, which damage the lining of the colon. Symptoms vary from mild, self-limiting diarrhoea to severe complications, including pseudomembranous colitis, toxic megacolon, perforation of the colon, sepsis and death (NICE clinical knowledge summary: diarrhoea - antibiotic associated).

Ribotyping has identified over 600 strain types of *C. difficile*. Ribotype 027 is 1 strain that is associated with higher morbidity and mortality in *C. difficile* infection; in vitro data suggest that this strain may produce high levels of toxin. Ribotype 027 has been implicated in outbreaks in the UK and contributed to a rise in the rate of *C. difficile* infection after 2003, although more recently the incidence decreased and a wider variety of strains has been found. Circulating strains of *C. difficile* vary in their susceptibility to antibiotics, and some strains are difficult to treat (NICE clinical knowledge summary: diarrhoea - antibiotic associated; Public Health England and Department of Health guidance: Clostridium difficile infection: how to deal with the problem; Public Health England's Clostridium difficile ribotyping network report 2011–13).

As well as antibiotics, factors that increase the risk of *C. difficile* infection include advanced age, frailty, underlying morbidity such as abdominal surgery, cancer, chronic renal disease and tube feeding. Other risk factors include hospitalisation, exposure to other people with *C. difficile* infection, long duration of antibiotic treatment, taking multiple antibiotics concurrently or multiple antibiotic courses, and inflammatory bowel disease. Concurrent therapy with a proton pump inhibitor or other acid-suppressing drug has also been associated with an increased risk of *C. difficile* infection. The mortality associated with *C. difficile* infection can be up to 25% in frail older people in hospitals (NICE clinical knowledge summary: diarrhoea - antibiotic associated).

Most of the information on risk factors is from data from people with hospital-associated *C. difficile* infection and risk factors for community-associated *C. difficile* infection are less clear. A UK study found that more than a third of cases had not been admitted to hospital or received antibiotics (Wilcox et al. 2008; Public Health England and Department of Health guidance: Clostridium difficile infection: how to deal with the problem). This is reinforced by other studies (Kutty PK et al. 2010; Bauer MP et al. 2009).

The recurrence rate of *C. difficile* infection is high in hospitalised patients; around 20% after the first episode and 45–60% after the second episode. Few data are available for community-associated *C. difficile* infection. Between 20 and 50% of recurrences are reported to have been reinfections, not relapses caused by the same strain of *C. difficile* (NICE clinical knowledge summary: diarrhoea - antibiotic associated).

The number of *C. difficile* infections has been decreasing in the NHS in England since April 2007 when acute trusts were required to report all cases in people aged 2 years and over through Public Health England's mandatory surveillance scheme. A total of 13,361 cases were reported in 2013/14, compared with 55,498 cases in 2007/08, a reduction of 76% (Public Health England's annual epidemiological commentary: MRSA, MSSA and E. coli bacteraemia and C. difficile infection data, 2013/14). However, the fall in cases has levelled off recently (Public Health England's C. difficile infection counts by NHS acute trust and month [from December 2013 to December 2014]). In England and Wales, the number of deaths involving *C. difficile* decreased from 8324 in 2007 to 1646 in 2012 (Office for National Statistics report on deaths involving Clostridium difficile, England and Wales, 2012). Success in reducing *C. difficile* infections has been associated with the increased focus of healthcare organisations through mandatory surveillance and target-setting, additional measures to control of antibiotic prescribing, and isolation, hand-washing and hygiene protocols (Department of Health: annual report of the Chief Medical Officer 2011, volume 2).

More information on the epidemiology of *C. difficile* infection, and guidance on its diagnosis and reporting and prevention, control and treatment is available on the Public Health England website. A NICE clinical knowledge summary provides a general overview of the management of antibiotic-associated diarrhoea.

Prudent antibiotic prescribing

A Cochrane review (Davey et al. 2013) found evidence from 5 studies that restricting the use of broad-spectrum antibiotics (mainly cephalosporins or clindamycin) can reduce *C. difficile* infection. However, only 2 of the studies were at low risk of bias and these reported the smallest effect on *C. difficile* infection.

The Department of Health and Public Health England report Clostridium difficile infection: how to deal with the problem includes a section on preventing *C. difficile* infection through prudent antibiotic prescribing. It recommends that trusts should develop restrictive antibiotic guidelines that recommend narrow-spectrum agents alone or in combination for empirical and definitive treatment where appropriate. These guidelines should recommend avoiding the use of clindamycin and second- and third-generation cephalosporins whenever possible (especially in older people) and minimising the use of quinolones, carbapenems and prolonged courses of aminopenicillins. The guidelines should also specifically recommend reducing the use of repeated courses of antibiotics in hospitals. Restricted broad-spectrum antibiotics should be used only when indicated by the person's clinical condition, and should be reviewed after the results of microbiological testing or based on the local sensitivities of causative bacteria.

The Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI) recommends the Start smart – then focus approach. 'Start Smart' states thatantibiotic treatment should be started within 1 hour of diagnosis (or as soon as possible) in people with life-threatening infections, in line with local antibiotic prescribing guidance. Microbiological cultures should be obtained before starting treatment if possible. The importance of documentation (for example the indication, route, dose, duration and review date for the antibiotic) is stressed. 'Then Focus' states thatthe clinical diagnosis and continuing need for antibiotics should be reviewed within 48–72 hours, with 5 options to consider:

- stop antibiotics if there is no evidence of infection

- switch antibiotic formulation from intravenous to oral

- change antibiotic – ideally to a narrower spectrum, but broader if required

- continue antibiotics and document next review date

- outpatient parenteral antibiotic therapy.

When antibiotics are considered necessary to treat common infections in primary care, guidance from Public Health England recommends suitable options and advises that generic antibiotics should be used if possible. Broad-spectrum antibiotics (for example, co-amoxiclav, quinolones and cephalosporins) should generally be used only when narrow-spectrum antibiotics are ineffective, because they increase the risk of meticillin-resistant *Staphylococcus aureus* (MRSA) infection, *C. difficile* infection and antibiotic-resistant urinary tract infections.

Evidence review

This evidence review considers the risk of *C. difficile* infection associated with individual broad-spectrum antibiotics based on the highest quality published evidence. It outlines 1 meta-analysis of hospital-associated infection (Slimings and Riley 2014) and 2 of community-associated infection (Brown et al. 2013 and Deshpande et al. 2013). The 2 meta-analyses on community-associated *C. difficile* infection included some different studies but had similar results.

Hospital-associated *C. difficile* infection

- Design: the systematic review and meta-analysis by Slimings and Riley (2014) included controlled observational studies published between 2002 and 2012 measuring associations between antibiotic classes and *C. difficile* infection in hospital inpatients. One cohort study and 13 case–control studies undertaken in the USA, Europe and Australia between 1996 and 2009 met the inclusion criteria.

- Population: the studies included between 15 and 1142 symptomatic cases of *C. difficile* infection with a positive test result and 15,938 people in total. Hospital-acquired *C. difficile* infection was defined as infection occurring more than 2 days, 3 days and 5 days after admission in 6 studies, 7 studies and 1 study respectively.

- Intervention and comparator: 12 studies used asymptomatic controls. Controls with symptoms and a negative test for *C. difficile* infection were used in some studies. The antibiotic classes considered were penicillins, cephalosporins, tetracyclines, trimethoprim and sulfonamides, macrolides, quinolones, aminoglycosides, lincosamides (clindamycin) and carbapenems. Eleven studies measured antibiotic use before and during admission (28 days to 3 months); 3 studies measured antibiotic exposure during admission only.

The meta-analysis by Slimings and Riley (2014) found that, in the case–control studies using asymptomatic controls, overall exposure to antibiotics was associated with a statistically significant 60% relative increase in the risk of *C. difficile* infection (13 studies; odds ratio [OR] 1.57, 95% confidence interval [CI] 1.31 to 1.87). This varied between the antibiotic classes. Associations were seen with:

- clindamycin (6 studies; OR 2.86, 95% CI 2.04 to 4.02)

- cephalosporins (8 studies; OR 1.97, 95% CI 1.21 to 3.23)

- carbapenems (6 studies; OR 1.84, 95% CI 1.26 to 2.68)

- trimethoprim and sulfonamides (5 studies; OR 1.78, 95% CI 1.04 to 3.05)

- quinolones (10 studies; OR 1.66, 95% CI 1.17 to 2.35).

However, the 95% confidence intervals, which give a measure of the results' precision, overlap substantially and it is not appropriate to rank the antibiotic classes.

No statistically significant association was seen with penicillins, aminoglycosides, tetracyclines or macrolides. Evidence of heterogeneity was identified for all classes except clindamycin, carbapenems and tetracyclines. Stated sources of heterogeneity included differing study populations, timings of antibiotic exposure and definitions of hospital-acquired infection.

When subgroups of antibiotic classes were considered, penicillin combination antibiotics, such as co-amoxiclav and piperacillin-tazobactam, were associated with a statistically significant 50% relative increase in the risk of *C. difficile* infection (6 studies; OR 1.54, 95% CI 1.05 to 2.24). No statistically significant increase was seen with other penicillin subgroups (beta-lactamase-sensitive penicillins, beta-lactamase-resistant penicillins and extended-spectrum penicillins).

Second-, third- and fourth-generation cephalosporins were associated with 2 to 3 times the risk of *C. difficile* infection (6 studies; OR 2.23, 95% CI 1.47 to 3.37: 6 studies; OR 3.20, 95% CI 1.80 to 5.71: and 2 studies; OR 2.14, 95% CI 1.30 to 3.52 respectively). However, there was heterogeneity, particularly for third-generation cephalosporins. The increased risk of *C. difficile* infection with first-generation cephalosporins was not statistically significant (OR 1.36, 95% CI 0.92 to 2.00).

The cohort study identified by Slimings and Riley (2014) (n=7792) found that quinolones (hazard ratio [HR] 4.05, 95% CI 2.75 to 5.97) third- and fourth-generation cephalosporins (HR 3.12, 95% CI 1.85 to 5.25), combination penicillins (HR 2.25, 95% CI 1.46 to 3.48) and trimethoprim and sulfonamides (HR 2.03, 95% CI 1.19 to 3.47) were associated with an increased risk of *C. difficile* infection. Increases in risk with clindamycin (HR 1.92, 95% CI 0.84 to 4.40) and macrolides (HR 1.56, 95% CI. 0.75 to 3.25) were not significant, and no increase in risk was seen with aminoglycosides.

Community-associated *C. difficile* infection

Meta-analysis by Brown et al. (2013)

- Design: the systematic review and meta-analysis by Brown et al. (2013) included population-based studies up to March 2012 that considered the association between antibiotics and *C. difficile* infection in people with little or no contact with the healthcare

system before infection. One cohort study and 6 case–control studies done in the UK, USA and Canada between 1988 and 2007 were eligible for inclusion.

- Population: the studies included between 40 and 1233 cases of *C. difficile* infection (total number of people not reported). In 5 studies, infection was confirmed by testing, in 1 study hospital coding was used, and in the final study diagnosis on an insurance claim was considered. Participants in 5 studies had not been in hospital 42 days to 1 year before infection, but information was unclear for the other 2 studies.

- Intervention and comparator: 5 studies included controls who had not been exposed to antibiotics and were included in the meta-analysis. The antibiotic classes considered were tetracyclines, trimethoprim and sulfonamides, penicillins, macrolides, quinolones, clindamycin, and cephalosporins, monobactams and carbapenems. The duration of antibiotic exposure ranged from 28 to 180 days before the infection.

In the 5 studies using asymptomatic controls, Brown et al. (2013) found that exposure to antibiotics was associated with 3 times the risk of *C. difficile* infection (OR 3.55, 95% CI 2.56 to 4.94). Of the 7 classes of antibiotics, 6 were associated with a statistically significant increased risk of infection compared with asymptomatic controls. Clindamycin; cephalosporins, monobactams and carbapenems; and quinolones showed the strongest association:

- clindamycin (3 studies; OR 16.80, 95% CI 7.48 to 37.76)

- cephalosporins, monobactams and carbapenems (5 studies; OR 5.68, 95% CI 2.12 to 15.23)

- quinolones (5 studies; OR 5.50, 95% CI 4.26 to 7.11)

- penicillins (5 studies; OR 2.71, 95% CI 1.75 to 4.21)

- macrolides (4 studies; OR 2.65, 95% CI 1.92 to 3.64)

- trimethoprim and sulfonamides (4 studies; OR 1.81, 95% CI 1.34 to 2.43).

No statistically significant difference was seen with tetracyclines. There was significant heterogeneity between the studies for cephalosporins, monobactams and carbapenems; penicillins; and clindamycin. This heterogeneity was possibly because of differences in strain susceptibility, individual antibiotics and different study methods.

Meta-analysis by Deshpande et al. (2013)

- Design: the systematic review and meta-analysis by Deshpande et al. (2013) included controlled observational studies up to December 2012 that considered the association between antibiotics and *C. difficile* infection in adults who had not been hospitalised in the period before the infection. Eight case–control studies undertaken in the UK, USA and Canada between 1999 and 2007 were included.

- Population: the studies included between 121 and 13,563 people (total 30,184: number of cases not reported). For identifying cases, 4 studies used a positive *C. difficile* test result, 2 studies used *C. difficile* testing and/or a clinical diagnosis, and 2 studies used hospital coding. Participants in 6 studies had not been hospitalised 8 weeks to 1 year before infection, but information was unclear for the other study.

- Intervention and comparator: the antibiotic classes considered were tetracyclines, trimethoprim and sulfonamides, penicillins, macrolides, quinolones, clindamycin and cephalosporins. The duration of antibiotic exposure before the infection ranged from 30 to 180 days.

Deshpande et al. (2013) found that about 53% of people with community-associated *C. difficile* infection had received antibiotics in the previous 30–180 days. Antibiotic exposure was associated with a statistically significant 7 times increased risk of infection (OR 6.91, 95% CI 4.17 to 11.44). The risk varied between the antibiotic classes:

- clindamycin (2 studies; OR 20.43, 95% CI 8.50 to 49.09)

- quinolones (3 studies; OR 5.65, 95% CI 4.38 to 7.28)

- cephalosporins (3 studies; OR 4.47, 95% CI 1.60 to 12.50)

- penicillins (4 studies; OR 3.25, 95% CI 1.89 to 5.57)

- macrolides (3 studies; OR 2.55, 95% CI 1.91 to 3.39)

- trimethoprim and sulfonamides (3 studies; OR 1.84, 95% CI 1.48 to 2.29).

Tetracyclines were not associated with a statistically significant increased risk of *C. difficile* infection. There was high heterogeneity between the studies overall, possibly because of differing patient characteristics, comorbid conditions, and duration and dose of antibiotic. However, heterogeneity was only seen for cephalosporins and penicillins when considering individual antibiotic classes.

Evidence strengths and limitations

The results of the meta-analyses have many limitations and should be interpreted cautiously. It would be unethical to perform randomised controlled trials (RCTs) comparing the risk of *C. difficile* infection with different antibiotics. Therefore, the studies included in the meta-analyses are observational studies, which are prone to confounding and bias (for example, through selection of controls and misclassification of outcomes and exposures) and the results can only show association and do not prove causation. Some specialists involved in producing this evidence summary had concerns that the meta-analyses may not have considered all of the available evidence from different study designs in the absence of RCTs.

The interpretation of data on the risk of *C. difficile* infection with individual antibiotics is difficult. For example, commonly used antibiotics may be reported as being associated with *C. difficile* infection more often than rarely used antibiotics. Also, the duration of antibiotic exposure and polypharmacy are often not considered, and the data may be confounded by other risks, such as age and comorbidities.

The studies included in the meta-analyses covered a period of considerable change in the epidemiology of *C. difficile* infections, including the rise and fall of the incidence of ribotype 027, and the emergence of quinolone-resistant strains of *C. difficile*, which were not identified before ribotype 027 but which are now common.

Heterogeneity was often seen in the meta-analyses and some sources of heterogeneity were not investigated. Heterogeneity in strain variation is particularly important because bacteria that are relatively antibiotic resistant will have a selective advantage when exposed to some antibiotics. For example, some strains of *C. difficile* are relatively resistant to clindamycin or quinolones and, if these agents are used in an outbreak, a strong association between these antibiotics and *C. difficile* infection may or may not be found, depending on the strain.

Hospital-associated C. difficile infection

The quality of the studies included in Slimings and Riley (2014) was rated as high for 7 studies, moderate for 6 studies and low for 1 study. Details of sample size calculations were often not reported and 6 studies either had insufficient power to detect differences or did not report sufficient information to allow calculation. Some analyses were based on small numbers of studies and subgroup analyses included relatively smaller numbers of cases than the primary analyses.

Four studies included people with recent antibiotic exposure, who are not representative of all cases of hospital-associated *C. difficile* infection. For controls, 1 study used people who tested

negative for *C. difficile* who are, therefore, not comparable with the case population. Paediatric studies were excluded, although 1 study included people aged over 2 years.

The Department of Health guidance on Clostridium difficile: updated guidance on diagnosis and reporting advises that all people with diarrhoea that is not clearly attributable to an underlying condition should be tested for *C. difficile* infection. However, it is possible that in the studies, people exposed to antibiotics were more likely to be tested for *C. difficile*, which may have introduced bias. The study authors note that the definition of hospital-acquired *C. difficile* infection varied, with only a small number of studies including recent contact with healthcare facilities.

Many outcomes were heterogeneous. There is no consensus about the appropriate time window to measure antibiotic exposure giving rise to heterogeneity. Also, the number of antibiotics, dosage and duration of antibiotic exposure have all been identified as risk factors for *C. difficile* infection and these potential confounders may not have been adequately considered. Only 6 studies addressed 4 or more confounders. Age, sex, length of hospital stay and exposure to other antibiotics were most commonly considered. Only 5 studies considered comorbidities.

Community-associated C. difficile infection

Only 3 studies were included in both meta-analyses of community-associated *C. difficile* infections and it is unclear why the 2 meta-analyses include different studies. However, the results are similar. Of the 5 studies included in the meta-analysis by Brown et al. (2013), the quality was reported as high for 2 studies, moderate for 2 studies and low for 1 study. In Deshpande et al. (2013), the quality of all studies was reportedly high, which conflicts with the study quality assessment in Brown et al. (2013) for some studies because of the different rating scales used by the assessors. Some outcomes were based on only 2 or 3 studies, and confidence intervals were wide for many results.

There may be a risk of a number of selection biases affecting the data: populations, definitions of cases, matching of controls and ways of determining antibiotic exposure varied across the studies included in the meta-analyses. Not all studies adequately excluded people exposed to hospital settings during the risk period, and some may have included people with hospital-associated *C. difficile* infection. Also, some studies were restricted to people who were tested for *C. difficile* infection. Depending on the diagnostic method used, asymptomatic carriers may have been included or cases of *C. difficile* infection may have been missed. In people who were not tested, diarrhoea may have been caused by another organism and been misclassified as *C. difficile* infection. In other studies, hospital-diagnosed cases with onset of symptoms 48 hours after admission could

not be separated from those with onset within 48 hours. Therefore, unmeasured inpatient antibiotic exposures may have caused the infection.

Heterogeneity between the included studies was seen in both meta-analyses. There were differences in the strains of *C. difficile*, the dose and duration of antibiotic treatment before diagnosis of infection, concomitant illness and other medications. The most common confounders adjusted for in the studies included in Deshpande et al. (2013) were age, use of acid-suppressing drugs and comorbidities. Confounders were not reported by Brown et al. (2013) but it is possible that some confounding variables were not fully identified and recorded in studies in both meta-analyses.

Other potential sources of bias include the lack of consensus about the appropriate time window for identifying antibiotic exposure and using more than 1 antibiotic for an infection. Also, there is a risk of clinical susceptibility bias - people receiving antibiotics may have underlying health conditions placing them at greater risk for *C. difficile* infection. Publication bias could not be excluded because of the small numbers of studies in the meta-analyses.

The associations seen in the meta-analyses of community-associated *C. difficile* infection are generally stronger than in the meta-analysis of hospital-associated infection. This may be because antibiotic-associated risk factors for community-associated *C. difficile* infection are less likely to be confounded by other (hospital-associated) risks. It could also be because of differences in, for example, the populations, study methods, antibiotic prescribing practice and strains of *C. difficile*. Also, hospital-associated *C. difficile* infectionhas been the focus of Department of Health guidance since the 1990s, resulting in significant changes in hospital practice, but community-associated *C. difficile* infection has only been recognised more recently.

Context

Antibiotic prescribing trends

Reducing inappropriate use of cephalosporins and quinolones to reduce *C. difficile* infection (and MRSA infection) has been prioritised in both primary and secondary care since the turn of the century (see the NICE key therapeutic topic: antibiotic prescribing – especially broad spectrum antibiotics). Although there has been a marked decline in their use in the past decade, use of other broad-spectrum antibiotics has increased.

Ashiru-Oredope et al. (2012) found that, in secondary care between 2004 and 2009, there was a decrease in the use of quinolones and second- and third-generation cephalosporins, but an increase

in the use of co-amoxiclav, carbapenems and piperacillin-tazobactam. Cooke et al. (2014) considered hospital data between 2009 and 2013 and found a reduction in the use of first- and second-generation cephalosporins but little change in the use of third-generation cephalosporins and quinolones. By contrast, use of co-amoxiclav, carbapenems and piperacillin-tazobactam increased. The total and relative amounts of antibiotics used varied widely between individual hospitals.

In primary care, Ashiru-Oredope et al. (2012) found that antibiotic prescribing decreased between 1995 and 2000, but then rose steadily. However, prescribing of quinolones and cephalosporins decreased. There was a 2-fold variation in antibiotic prescribing among general practices in England. In 2010, the NHS Atlas of Variation documented a 3-fold variation in prescribing of quinolones and an 18-fold variation in prescribing of cephalosporins across primary care trusts in England. The Health and Social Care Information Centre's prescribing comparator data to support the NICE key therapeutic topic on antibiotic prescribing – especially broad spectrum antibiotics show a 6-fold variation in prescribing of quinolones and cephalosporins combined across clinical commissioning groups in 2013/14.

Public Health England's English surveillance programme antimicrobial utilisation and resistance (ESPAUR) report includes detailed national data on antibiotic prescribing from 2010 to 2013. During that period, total antibiotic consumption increased by 6% in primary and secondary care in England; penicillins, tetracyclines and macrolides were the most frequently used antibiotics.

Between 2010 and 2013, cephalosporin use decreased by 55% in general practice, from 0.8 to 0.4 defined daily doses (DDD) per 1000 population/day. Use of cephalosporins was largely unchanged in hospitals over this period, following the reduction already seen in the previous decade after the introduction of prescribing policies. Overall, quinolone use decreased from 0.61 to 0.58 DDD per 1000 population/day between 2010 and 2013. This reduction occurred in only general practice, where there was a 6% decrease. Increases of 10% and 5% were seen hospital inpatients and outpatients respectively over this period.

During the past 4 years, co-amoxiclav use increased by 13%, from 1.9 to 2.2 DDD per 1000 population/day in primary and secondary care. In 2013, 59% of co-amoxiclav use was in general practice, and this antibiotic was the most commonly prescribed in hospitals (21% of total consumption in inpatients). The NICE key therapeutic topic on antibiotic prescribing – especially broad spectrum antibiotics was updated in 2015 to include co-amoxiclav. Piperacillin-tazobactam use, although low overall, increased by 46%, from 0.06 to 0.09 DDD per population/day. Over 99% of use was in hospitals because this parenteral antibiotic was rarely used in primary care at the time of the report. A similar increase was seen for carbapenems (mainly meropenem) in hospitals.

Public Health England's ESPAUR report notes that national guidance to limit the use of cephalosporins and quinolones to minimise the risk of *C. difficile* infection appears to have been followed in trust antibiotic guidelines. In a survey, the top 5 antibiotics recommended in guidelines for 10 common infections were: amoxicillin, clarithromycin, co-amoxiclav, gentamicin, and piperacillin-tazobactam. Cephalosporins and quinolones were recommended in less than 6% of empiric guidelines and only for catheter-associated and upper urinary tract infections.

Rates of *C. difficile* infection and association with antibiotics

Separate from Public Health England's mandatory surveillance scheme, in England and Northern Ireland 9 *C. difficile* Ribotyping Network (CDRN) laboratories provide *C. difficile* culture and ribotyping according to certain criteria. This service is used to investigate clusters of cases and optimise the management of *C. difficile* infections locally. It also provides national information about *C. difficile* infection.

According to Public Health England's CDRN 2011–13 report, since the service began in 2007, the strains of *C. difficile* identified have changed markedly. There was a large decrease in ribotype 027 prevalence (from about 64% to about 5%) and smaller decreases in ribotypes 001 and 106, with increases in some other ribotypes and a wider variety overall. The CDRN report notes that these findings may reflect the success of control measures in hospitals to reduce cross-infection caused by formerly predominant epidemic strains, especially ribotype 027. It is unknown whether the decrease in ribotype 027 is directly related to changes in antibiotic prescribing practice. However, quinolones have been particularly associated with the ribotype 027 strain of *C. difficile* (Vardakas et al. 2012) and it is noted that the incidence of this strain has decreased with a decline in quinolone (and cephalosporin) prescribing.

The CDRN report notes that the antibiotics most frequently reported as being associated with *C. difficile* infections referred to the CDRN have changed markedly over the 6-year period since the service was established. In 2007/08, cephalosporins and quinolones were the most commonly cited antibiotics, but they were superseded by co-amoxiclav and piperacillin-tazobactam in 2011/12 and 2012/13. It is interesting that the changes in antibiotic prescribing discussed in the ESPAUR report are associated with similar changes in the antibiotics reportedly associated with *C. difficile* infections in the CDRN report. The CDRN report states that the data probably reflect real changes in prescribing of antibiotics as one of the control measures for *C. difficile* infection, but this should be interpreted with caution and should not be considered to show which antibiotics were associated with *C. difficile* infection.

Estimated impact for the NHS

The 3 meta-analyses in this medicines and prescribing briefing have many limitations and, because of those limitations and the observational nature of the studies, cannot definitively establish a causal relationship between particular antibiotics and *C. difficile* infection. Changes in antibiotic prescribing practice, the frequent use of multiple antibiotics and other potential confounding factors make it difficult to determine the relative risk for individual antibiotics. However, the results of the meta-analyses are similar and some antibiotics do seem to be associated with a higher risk of *C. difficile* infection. Slimings and Riley (2014) concluded that cephalosporins and clindamycin are most strongly linked with hospital-associated *C. difficile* infection. They state that the association seen with quinolones is not surprising because quinolones have been associated with the ribotype 027 *C. difficile* strain, the incidence of which is decreasing. Brown et al. (2013) and Deshpande et al. (2013) found that, for community-associated infection, the strongest association was seen with clindamycin, cephalosporins and quinolones. Trimethoprim and sulfonamides were associated with an increased risk of infection in all 3 meta-analyses but data were not reported for trimethoprim alone, which is most commonly used in England.

Data from the ESPAUR report show that prescribing of cephalosporins and quinolones decreased between 2010 and 2013, but prescribing of co-amoxiclav and piperacillin-tazobactam increased. The CDRN report notes that, in 2007/08, cephalosporins and quinolones were the antibiotics most commonly associated with *C. difficile* infection, but these have been superseded by co-amoxiclav and piperacillin-tazobactam. Subgroup analyses by Slimings and Riley (2014) found that co-amoxiclav and piperacillin-tazobactam were associated with an increase in the risk of hospital-associated *C. difficile* infection.

Although the data have limitations and should be interpreted cautiously, they show that antibiotic prescribing practice and the epidemiology of *C. difficile* infections are changing,and show the importance of ensuring all broad-spectrum antibiotics are prescribed appropriately.

It is important to remember that other factors have contributed to the decrease in cases of *C. difficile* infection, as well as changes in antibiotic prescribing practice. For example, there has been a substantial change in infection prevention and control practice. Although there are fewer cases of *C. difficile* infection associated with co-amoxiclav and piperacillin-tazobactam, compared with the number of cases previously associated with antibiotics such as cephalosporins and quinolones, there is also less environmental contamination.

In summary, after considering the data's limitations, it is not possible to definitively assign relative risks to antibiotics or subgroups of antibiotic classes.

Although identifying the cephalosporin and quinolone classes as 'high-risk' may have been an important control measure in reducing the risk of *C. difficile* infection, an unintended consequence of this may have been a recent increase in clinically inappropriate prescribing of co-amoxiclav and other broad-spectrum antibiotics, such as piperacillin-tazobactam. These antibiotics have a very limited set of recommended clinical indications. For example, according to Public Health England's guidance for primary care, co-amoxiclav is recommended only for persistent acute rhinosinusitis, upper urinary tract infections in children, acute pyelonephritis, facial cellulitis, and the prophylaxis and treatment of infection after bites. It is also a second-line recommendation in acute exacerbations of chronic obstructive pulmonary disease if infection is resistant to first-line options.

In the absence of clear evidence showing that 1 particular antibiotic or class of antibiotic is 'low-risk', only general recommendations are possible. Broad-spectrum antibiotics should be used only in limited circumstances and organisations should support local antimicrobial stewardship programmes and prescribers should carefully follow local antimicrobial guidelines based on national guidance. These should be evidence based, relevant to the local healthcare setting and take into account local antibiotic resistance patterns.

Healthcare professionals should review and, if appropriate, revise current prescribing practice and ensure prescribing is in line with Public Health England guidance and local trust antibiotic guidelines. To help healthcare professionals inprimary care and commissioners use antibiotics responsibly, the TARGET antibiotics toolkit was developed by the Royal College of General Practitioners, Public Health England and the Antimicrobial Stewardship in Primary Care collaboration. In secondary care, the Department of Health's Start smart – then focus is recommended. The Public Health England website has information on antibiotic resistance and resources to help reduce inappropriate antibiotic prescribing. Patient information on *C. difficile* infection is available on NHS Choices and leaflets are available on the TARGET website.

The total volume of all antibiotic prescribing and broad-spectrum antibiotic prescribing should be reviewed against local and national data. The Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI), which provides advice to the government on minimising the risk of healthcare associated infections, has agreed antimicrobial prescribing quality measures for primary and secondary care. The Health and Social Care Information Centre's prescribing measures for primary care are to reduce total antibiotic consumption and the proportion of cephalosporin, quinolone and co-amoxiclav antibiotics used. The prescribing measures for secondary care are reducing total antibiotic consumption and carbapenem consumption. NHS England's Planning guidance for 2015/16 for NHS foundation trusts includes a national quality premium measure on antibiotics for clinical commissioning groups.

Relevance to NICE guidance programmes

NICE has produced several guidelines relating to healthcare-associated infections and antibiotic prescribing. The NICE guideline on prevention and control of healthcare-associated infections is a quality improvement guide for board members working in or with hospitals. It aims to reduce the risk of harm from healthcare-associated infections for patients, staff and visitors, and to reduce the costs associated with preventable infection. The NICE guideline on infection: prevention and control of healthcare-associated infections in primary and community care aims to help build on advice given in the Department of Health code of practice on preventing and controlling infections to improve the quality of care and practice in these areas. A NICE pathway on prevention and control of health-care associated infections and the NICE quality standard on infection prevention and control are also available.

The NICE guideline on respiratory tract infections – antibiotic prescribing and a the NICE pathway on self-limiting respiratory tract infections – antibiotic prescribing provide guidance on managing common infections in adults and children in primary care. The NICE guideline on pneumonia and the NICE pathway on pneumonia cover the diagnosis and management of community- and hospital-acquired pneumonia in adults.

NICE has issued the following guidance relating to the management of *C. difficile* infections:

- Faecal microbiota transplant for recurrent Clostridium difficile infection (2014) NICE interventional procedure guidance 485

- Diarrhoea and vomiting in children (2009) NICE guideline CG84.

Three related NICE guidelines are in development:

- Antimicrobial stewardship (NICE guideline: publication expected July 2015)

- Antimicrobial stewardship - changing risk-related behaviours (NICE guideline: publication expected March 2016).

- Sepsis (NICE guideline: publication expected July 2016).

As well as guidance, NICE produces advice publications which do not constitute formal NICE guidance but critically appraise the evidence to help decision-making. Three NICE key therapeutic topics consider antibiotic prescribing, including antibiotic prescribing – especially broad spectrum antibiotics. A NICE evidence summary: new medicine assessed fidaxomicin for Clostridium difficile infection when fidaxomicin was launched in 2012.

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Development of this evidence summary: medicines and prescribing briefing

This evidence summary: medicines and prescribing briefing has been developed using the processes described in the integrated process statement for evidence summaries: new medicines. This statement sets out the process NICE uses to select topics for the evidence summaries, and explains how they are developed, quality assured and approved for publication.

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Declarations of interest

Professor Mark Wilcox has received consulting fees from Abbott Laboratories, Actelion, Astellas, AstraZeneca, Cerexa, Cubist, Durata, The European Tissue Symposium, The Medicines Company, Merck, Nabriva, Novacta, Novartis, Optimer, Paratek, Pfizer, Roche, Sanofi-Pasteur, Summit, Synthetic Biologics and VH Squared. He has received lecture fees from Abbott, Alere, Astellas,

AstraZeneca and Pfizer; grant support from Abbott, Actelion, Astellas, bioMerieux, Cubist, Da Volterra, The European Tissue Symposium, Merck and Summit.

Dr Philippa Moore has received remuneration from Novartis for advice on developing an educational module on skin and soft tissue infection and input into an orthopaedic infection focus group. She has also been contracted by Public Health England Primary Care Research Unit (PHE PRCU) to help with developing national guidelines (for example, stool sampling guidance, primary care antibiotic guidance) and is the Director of Clinical Microbiology Consultancy Ltd through which she has been employed by PHE PRCU and Gloucestershire Clinical Commissioning Group to deliver TARGET antibiotic workshops.

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Professor Michael Moore had no relevant declarations of interest.

Richard Seal is a member of the PHE English Surveillance Programme for Antimicrobial Utilisation and Resistance oversight group, and the lead for the Birmingham and Solihull local practice forum of the Royal Pharmaceutical Society. He occasionally speaks at national and regional events on medicines optimisation in connection with his role as Chief Pharmacist at the NHS Trust Development Authority. He receives no personal financial recompense for such activities; however, some of the meetings may be sponsored by third parties.

In the past few years, Magnus Hird has been paid by Chiesi (to prepare and deliver educational workshops on asthma and COPD) and Lilly (to prepare and deliver educational workshops on type 2 diabetes). He has also been paid to participate in a number of interviews and focus groups in the past few years, but none with specific relevance to infections or treatments for infection. He has received hospitality in the context of educational meetings from a number of pharmaceutical

companies over the past few years, including some that manufacture antimicrobial drugs. He peer reviewed the HPA management of infection guideline.

Michael Wilcock has attended advisory boards for AbbVie, AstraZeneca and Scope Ophthalmics. He is on the editorial board of the Drug & Therapeutics Bulletin.

About this evidence summary: medicines and prescribing briefing

'Evidence summaries: medicines and prescribing briefings' aim to review the evidence for the clinical effectiveness of medicines within a therapeutic class or indication to provide advice on the relative position of each medicine. This will assist localities in their planning on key new and existing medicines as well as providing individual prescribers and their patients with information to assist informed decision making. The strengths and weaknesses of the relevant evidence are critically reviewed to provide useful information, **but this medicines and prescribing briefing is not NICE guidance.**

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