NICE National Institute for Health and Care Excellence

Antimicrobial prescribing: delafloxacin for community-acquired pneumonia

Evidence review

Publication date August 2021

This evidence review sets out the best available evidence on delafloxacin for treating community-acquired pneumonia in adults when it is considered inappropriate to use other antimicrobial agents that are commonly recommended for the initial treatment of community-acquired pneumonia. It should be read in conjunction with the evidence summary, which gives the likely place in therapy and factors for decision making.

Disclaimer

The content of this evidence review was up to date in August 2021 See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites for up-to-date information.

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Background

This evidence review considers delafloxacin for treating community-acquired pneumonia in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment. Delafloxacin, a fluoroquinolone antibiotic, was launched in the UK in July 2020 for acute bacterial skin and skin structure infections (ABSSSI) in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections. A NICE evidence review on delafloxacin for the treatment of ABSSSI was published in January 2021. Delafloxacin was licensed in the UK for the community-acquired pneumonia indication in March 2021.

Community-acquired pneumonia is pneumonia that is acquired outside hospital and is most commonly caused by bacterial infection. *Streptococcus pneumoniae* is the main cause of community-acquired pneumonia worldwide, independent of age. However, other pathogens including *Haemophilus influenzae*, *Staphylococcus aureus* and *Legionella pneumophila* have also been isolated in people with community-acquired pneumonia treated in the community in the UK. *Mycoplasma pneumoniae* also occurs in outbreaks approximately every 4 years in the UK. However, this is much more common in school-aged children and young adults (see the NICE antimicrobial prescribing guideline on community-acquired pneumonia).

In adults, the NICE antimicrobial prescribing guideline recommends amoxicillin as the first-choice oral antibiotic for moderate severity community-acquired pneumonia, with clarithromycin or erythromycin (in pregnancy) added if atypical pathogens are suspected. Doxycycline or clarithromycin are given as alternative treatment options for moderate severity community-acquired pneumonia in adults who have penicillin allergy. For high severity community-acquired pneumonia in adults co-amoxiclav with clarithromycin or erythromycin (in pregnancy) is recommended as the first-choice antibiotic treatment. Levofloxacin is as an alternative treatment option for high severity community-acquired pneumonia in adults who have penicillin allergy. The guideline highlights the need to consider safety issues with fluoroquinolone treatment.

The NICE rapid guideline on the management of COVID-19 recommends that antibiotics should not be used for preventing secondary bacterial pneumonia in people with COVID-19. If a person has suspected or confirmed secondary bacterial pneumonia, antibiotic treatment should be started as soon as possible. For antibiotic choices to treat community-acquired pneumonia caused by a secondary bacterial infection, see the NICE antimicrobial prescribing guideline on community-acquired pneumonia.

Product overview

Mode of action

Delafloxacin is a fluoroquinolone antibiotic. It inhibits bacterial enzymes (topoisomerase IV and DNA gyrase [topoisomerase II]) that are needed for bacterial DNA replication, transcription, repair and recombination (see the summary of product characteristics [SPC] for delafloxacin).

Regulatory status

Delafloxacin (Quofenix) has a marketing authorisation for treating community-acquired pneumonia in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment. It also has a marketing authorisation for treating acute bacterial skin and skin structural infections in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections (see the SPC for delafloxacin)

Dosing information

Delafloxacin is available as a 300 mg (Quofenix) powder for concentrate for solution for infusion and as a 450 mg oral tablet. The 300 mg infusion and 450 mg tablet formulations are bioequivalent.

The recommended dosage of delafloxacin infusion for the treatment of community-acquired pneumonia is 300 mg intravenously every 12 hours, administered over 1 hour. The SPC states that treatment may be switched to delafloxacin tablets (450 mg every 12 hours) at the prescriber's discretion. The recommended total

duration of treatment with delafloxacin for the treatment of community-acquired pneumonia is 5 to 10 days (see the SPC for delafloxacin). The recommended antibiotic treatment duration in the NICE antimicrobial prescribing guideline on community-acquired pneumonia is 5 days.

See the person-centred factors section of this evidence review for more information on using delafloxacin and, in particular, switching between intravenous and oral treatment.

Follow the SPC for delafloxacin for all dosing information.

Antimicrobial resistance

Resistance to fluoroquinolones, including delafloxacin, can occur because of mutations in defined regions of the target bacterial enzymes topoisomerase IV and DNA gyrase, referred to as Quinolone-Resistance Determining Regions, or through other resistance mechanisms such as efflux mechanisms. There may be cross-resistance between delafloxacin and other fluoroquinolones, although some isolates resistant to other fluoroquinolone may retain susceptibility to delafloxacin (see the SPC for delafloxacin).

Objective

This evidence summary aims to review the best available evidence on the effectiveness and safety of delafloxacin for the treatment of community-acquired pneumonia in adults.

Review questions

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see appendix A for more information). The review questions for this evidence review are:

1. What is the effectiveness of delafloxacin for the treatment of community-acquired pneumonia in adults?

2. What is the safety of delafloxacin for the treatment of community-acquired pneumonia in adults?

Summary of included studies

A literature search for delafloxacin for the treatment of community-acquired pneumonia in adults when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of community-acquired pneumonia identified 143 references (see appendix E for full details). These references were screened using their titles and abstracts and 7 full text references were obtained and assessed for relevance.

One study is included in this evidence summary. A summary of the included study is shown in appendix B. Quality assessment of the included study is in appendix C.

Horcajada et al. 2019 is a double-blinded, randomised controlled trial (RCT) in adults with community-acquired bacterial pneumonia (n=859). It compared intravenous delafloxacin with intravenous moxifloxacin. In participants who met clinical criteria, treatment could be changed to the oral route after a minimum of 6 intravenous doses. The total duration of treatment in the study was from 5 to 10 days. The median total duration of treatment in each group was 9 days. The median duration of intravenous treatment was 6 days and of oral treatment was 2 days.

Six studies were excluded. Details of these excluded studies are in appendix F.

Effectiveness and safety

Full details of the results are in appendix D.

Review question 1: What is the effectiveness of delafloxacin for the treatment of community-acquired pneumonia in adults?

Early clinical response

In adults with community-acquired bacterial pneumonia and a Pneumonia Patient Outcomes Research Team (PORT) risk class of II to V, intravenous delafloxacin was shown to be non-inferior to intravenous moxifloxacin for the outcome of early clinical response, assessed 96 hours (±24 hours) after the start of treatment (Horcajada et al. 2019, primary outcome and US Food and Drug Administration primary outcome). For the intention-to-treat (ITT) population, in the delafloxacin group 383/431 (88.9%)

participants had an early clinical response compared with 381/428 (89.0%) in the moxifloxacin group (difference −0.2%, 95% confidence interval [CI] − 4.4% to 4.1%, non-inferiority margin −12.5%). Similar results were found for this outcome in the clinically evaluable population. In the delafloxacin group, 52.7% of participants had an early clinical response together with an improvement in vital signs compared with 43.0% in the moxifloxacin group (difference 9.7%, 95% CI 3.0% to 16.3%, secondary outcome). Only percentages for each group were provided for this outcome in the study, numbers in each group were not provided.

Clinical response at test of cure

Clinical response at test of cure (5 to 10 days after the last dose of study drug) was the European Medicines Agency primary outcome (secondary outcome in the Horcajada et al. 2019 study). The European public assessment report (EPAR) variation for delafloxacin concluded that delafloxacin was non-inferior to moxifloxacin for clinical response at test of cure (non-inferiority margin −10%) in the modified ITT population (including people in PORT risk class III or more who received at least 1 dose of study drug). In the study, assessment of this outcome was categorised as success, failure or indeterminate. In the ITT population, 390/431 (90.5%) participants in the delafloxacin group had clinical success compared with 384/428 (89.7%) in the moxifloxacin group (difference 0.8%, 95% CI −3.3% to 4.8%).

Clinical response by baseline pathogen

In Horcajada et al. 2019, 520/859 (60.5%) participants had at least 1 pathogen identified at baseline. *Streptococcus pneumoniae* was the most commonly identified pathogen (226/520, 43.5%). *Haemophilus influenzae* and *Legionella pneumophila* were both identified in 62/520 (11.9%) and *Staphylococcus aureus* was identified in 57/520 (11.0%). Clinical success rates at test of cure in these different baseline pathogen groups were similar for delafloxacin and moxifloxacin. No statistical analysis were presented for these comparisons.

Review question 2: What is the safety of delafloxacin for the treatment of community-acquired pneumonia in adults?

Treatment-emergent adverse events were seen in 131/429 (30.5%) of participants given delafloxacin and 112/427 (26.2%) of participants given moxifloxacin in Horcajada et al. 2019. In the delafloxacin group, 15/429 (3.5%) of participants stopped treatment due to a treatment-emergent adverse event compared with 7/427 (1.6%) in the moxifloxacin group. Serious treatment-emergent adverse events occurred in 23/429 (5.4%) of participants in the delafloxacin group and 20/427 (4.7%) in the moxifloxacin group. In the delafloxacin group 9/429 (2.1%) had a treatment-emergent adverse event that led to death compared with 7/427 (1.6%) in the moxifloxacin group. No deaths were considered to be related to the study drug. No statistical analyses were presented for safety data.

The summary of product characteristics (SPC) for delafloxacin lists the following common adverse reactions (seen in between 1 in 10 and 1 in 100 people): fungal infection, headache, diarrhoea, vomiting, nausea, pruritis, infusion site reaction and hypertransaminasaemia (raised liver transaminases). The EPAR variation for delafloxacin states that the safety data assessed was 'mostly consistent with the known safety profile of delafloxacin, indicating no major safety advantage or disadvantage compared with moxifloxacin.'

There are safety concerns associated with fluoroquinolone treatment. In March 2019, the MHRA recommended prescribing restrictions and precautions for fluoroquinolone antibiotics because disabling, long-lasting or potentially irreversible adverse reactions affecting musculoskeletal and nervous systems have been reported very rarely. Warnings include stopping treatment at first signs of a serious adverse reaction (such as tendonitis), prescribing with special caution for people older than 60 and those with renal impairment, and avoiding coadministration with a corticosteroid (see the MHRA Drug Safety Update on fluoroquinolone antibiotics: new restrictions and precautions for use due to very rare reports of disabling and potentially long-lasting or irreversible side effects).

In addition, in November 2018 the MHRA issued a safety alert highlighting that systemic and inhaled fluoroquinolones may be associated with a small increased risk of aortic aneurysm and dissection, particularly in older people. The MHRA recommended that fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in people at risk for

aortic aneurysm and dissection (see the MHRA Drug Safety Update systemic and inhaled fluoroquinolones: small increased risk of aortic aneurysm and dissection; advice for prescribing in high-risk patients).

The MHRA also recommended in December 2020 that fluoroquinolones should be used only after careful benefit-risk assessment and after consideration of other therapeutic options in people at risk for heart valve regurgitation (incompetence). Systemic and inhaled fluoroquinolones have been associated with a small increased risk of heart valve regurgitation, with one retrospective case-control study suggesting a 2-fold increased relative risk with current oral fluoroquinolone use compared with amoxicillin or azithromycin use (see the MHRA Drug Safety Update on systemic and inhaled fluoroquinolones: small risk of heart valve regurgitation; consider other therapeutic options first in patients at risk).

Horcajada et al. 2019 assessed adverse events of special interest that reflected the safety profile of the fluoroquinolone antimicrobial drug class. These included potential myopathy, *Clostridium difficile* diarrhoea, convulsions, potential peripheral neuropathy, tendon disorders, potential QT-prolongation, phototoxicity, allergic reactions, abnormal blood glucose levels and hepatic-related events. Overall these adverse events of special interest occurred in 34/429 (7.9%) of participants in the delafloxacin group and 32/427 (7.5%) in the moxifloxacin group. Hepatic-related events occurred in 22/429 (5.1%) of participants in the delafloxacin group and 12/427 (2.8%) in the moxifloxacin group, increased transaminases were the most frequently reported hepatic-related event. *Clostridium difficile* diarrhoea occurred in 2/429 (0.5%) in the delafloxacin group and 1/427 (0.2%) in the moxifloxacin group. No participants in either treatment group had a potential peripheral neuropathy, tendon disorder, phototoxicity or potential aortic rupture or dissection. However, some of these adverse events of special interest only occur as rare events. The EPAR variation for delafloxacin states that ‘not all known fluoroquinolone class adverse effects were observed with delafloxacin use which is to be expected given that some occur with very rare or unknown frequencies’. Suspected adverse reactions associated with delafloxacin should be reported via the Yellow Card Scheme.

The SPC includes several warnings and precautions for use which reflects the safety profile of the fluoroquinolones. See the SPC for delafloxacin for full details on contraindications, warnings and precautions for use.

Limitations of the evidence

Horcajada et al. 2019 was a double-blind randomised study. The study did not provide any information on allocation sequence, leading to some concerns regarding potential risk of bias. However, the baseline characteristics of the 2 treatment groups were similar and did not suggest that there were any issues with the randomisation process.

The participants in the Horcajada et al. 2019 study had a mean age of 60, with approximately 45% of participants 65 years and older. There were slightly more participants 65 years and older in the delafloxacin group than the moxifloxacin group (47.1% compared with 41.8%). PORT risk class was used in the study to define the severity of pneumonia, approximately 60% of the population had a PORT risk class of III and approximately 25% had a PORT risk class of IV. PORT risk has 5 classes (I to V, with V being the highest risk of mortality).

The summary of product characteristics (SPC) for delafloxacin states that 90.7% of participants in the study had a CURB-65 score of less than or equal to 2 (scale range 0 to 5). This would suggest that the majority of the study population had pneumonia with a low to intermediate risk of mortality. The NICE antimicrobial prescribing guideline on community-acquired pneumonia recommends a fluoroquinolone antibiotic (levofloxacin) only as a treatment option for high severity community-acquired pneumonia (CURB-65 score 3 to 5) in adults who have penicillin allergy. In addition, the European public assessment report variation for delafloxacin states that 'most participants had community-acquired pneumonia of relatively mild to moderate severity.' Therefore, the study population may not be representative of people with high severity community-acquired pneumonia.

The study was conducted in 88 study centres in 18 countries. However, no study centres were in the UK and it's unclear if the study population compares with the UK population.

Delafloxacin was compared with moxifloxacin (a fluoroquinolone) in the Horcajada et al. 2019 study. There are no published clinical studies which compare delafloxacin to any other fluoroquinolones or to other classes of antimicrobials. All participants in the study had intravenous antibiotic treatment. This could be switched to oral treatment if clinical criteria were met. The NICE guideline on antimicrobial prescribing for community-acquired pneumonia recommends that oral antibiotics should be given first-line if the person can take oral medicines, and the severity of their condition does not require intravenous antibiotics. There is currently no published evidence using oral delafloxacin alone for community-acquired pneumonia. However, the 300 mg infusion and 450 mg tablet formulations are bioequivalent and the SPC states that delafloxacin infusion may be switched to delafloxacin tablets at the prescriber's discretion (see the SPC for delafloxacin). The NICE guideline recommends that if intravenous antibiotics are given for community-acquired pneumonia there should be a review by 48 hours and consideration given to switching to oral antibiotics if possible. The median duration of intravenous treatment in the study was 6 days and for oral treatment was 2 days. Specialists who commented on this evidence review raised that it was unclear why study participants with mild to moderate community-acquired pneumonia had intravenous treatment when an oral preparation is available. They also noted that the duration of intravenous treatment was longer than it would usually be in UK practice.

The primary outcome in the Horcajada et al. 2019 study was early clinical response, which was the US Food and Drug Administration approved primary outcome. The European Medicines Agency approved primary outcome was clinical response at test of cure, this was only included as a secondary outcome in the study.

Person-centred factors

Delafloxacin infusion is administered intravenously every 12 hours, over 1 hour. The NICE guideline on antimicrobial prescribing for community-acquired pneumonia recommends that oral antibiotics should be given first-line if the person can take oral medicines, and the severity of their condition does not require intravenous antibiotics. If intravenous antibiotics are given there should be a review by 48 hours and consideration given to switching to oral antibiotics if possible. Also, Public Health England's guidance start smart then focus and the NICE guideline on antimicrobial

stewardship: systems and processes recommend that intravenous antibiotic prescriptions should be reviewed at 48 to 72 hours, documenting response to treatment and any available microbiology results to determine whether the antibiotic should be continued or switched to a narrower spectrum or an oral antibiotic.

The SPC states that delafloxacin infusion may be switched to delafloxacin tablets at the prescriber's discretion. The 300 mg infusion and 450 mg tablet formulations are bioequivalent. Switching to oral treatment is likely to be preferable to people in terms of ease of administration and convenience compared with ongoing intravenous treatment.

Resource implications

The cost of delafloxacin 300 mg powder for concentrate for solution for infusion is £61.50 for 1 vial. The cost of 1 delafloxacin 450 mg oral tablet is also £61.50 (see the BNF information on delafloxacin).

Delafloxacin is given every 12 hours and the recommended total duration of treatment is 5 to 10 days. The recommended antimicrobial treatment duration in the NICE antimicrobial prescribing guideline on community-acquired pneumonia is 5 days, which would cost £615.

Specialists who commented on this evidence review indicated that, when treatment with a fluoroquinolone antibiotic is required for community-acquired pneumonia, levofloxacin is most commonly used in the UK. The cost of 1 levofloxacin 500 mg tablet is £2.09 (see the Drug Tariff; July 2021) and the cost of levofloxacin 500 mg in 100 ml intravenous infusion is £4.00 for 1 bag (see the BNF information on levofloxacin). The recommended dosage of levofloxacin in the NICE antimicrobial prescribing guideline on community-acquired pneumonia is 500 mg twice a day orally or intravenously for 5 days. This would cost £20.86 for oral treatment and £40.00 for intravenous treatment.

References

Horcajada J P, Salata R A, Alvarez-Sala R et al (2019) A phase 3 study to compare delafloxacin with moxifloxacin for the treatment of adults with community-acquired bacterial pneumonia (DEFINE-CABP). Open forum infectious diseases 7(1)

Development of the evidence review

Process

The evidence summary: process guide sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

Expert advisers

Details of expert advisers and any declarations of interest

Name, job title and organisation	Declaration of interest
Colin Brown, Deputy Director (Interim), Healthcare-associated Infections and Antimicrobial Resistance, National Infection Service, Public Health England	Microbiology support to a private charitable hospital with onsite hospice (Financial interest, January 2020 – ongoing) Ad hoc one-off market research advisory, no long-term engagements or direct communication with pharmaceutical companies (though some relate to antibiotics) (Financial interest, 2012 - ongoing) Occasional contact with companies promoting novel antimicrobial therapies through role with AMRHAI (antimicrobial resistance and healthcare associated infections) as the national reference laboratory for investigating AMR in healthcare-associated bacteria (Non-financial interest, April 2019 – ongoing) Attend Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection (APRHAI) and the Antimicrobial Programme Board on behalf of Public Health England (Indirect interest, April 2019 – ongoing)
Anastasios Lekkas, Consultant Respiratory Physician, University Hospital Southampton NHS Foundation Trust	Private practice (Financial interest, 2007 - ongoing)
Natasha Ratnaraja, Consultant Microbiologist, University Hospitals Coventry and Warwickshire NHS Trust	Contract with BMI Meriden for clinical advice (Financial interest, October 2018 – ongoing) Co-Chair of Clinical Services Committee for infection in British Infection Association (Non-financial interest, September 2016 – ongoing)

Name, job title and organisation	Declaration of interest
	Deputy Chair Medical Microbiology & Virology SAC, RCPath (Non-financial interest, April 2021 – ongoing) Member of RCPath COVID Action Group (Non-financial interest, November 2020 – ongoing) British Infection Association representative on the UK Standards for Microbiology Investigations bacteriology working group (Non-financial interest, June 2021 – ongoing)
Rowland Bright-Thomas, Consultant Respiratory Physician, Wythenshawe Hospital	No relevant interests declared

Terms used in this evidence review

CURB-65 score

This is a 6-point score based on confusion, urea, respiratory rate, blood pressure, and age to stratify the severity of community-acquired pneumonia (see Lim et al 2003 Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study). People with a score of 0 or 1 are classed as having a low risk of mortality, people with a score of 2 an intermediate risk, and people with a score greater than 2 a high risk.

PORT risk class

The PORT (Pneumonia patient Outcomes Research Team) risk class is an assessment algorithm that estimates the morbidity risk for adults with community-acquired pneumonia. There are 5 risk classes (I to V, with V being the highest risk).

Appendices

Appendix A: PICO table

Population, intervention, control, and outcomes (PICO) table

Criteria	Details
P – Population and indication	Adults aged 18 years and over who have community-acquired pneumonia.
I – Intervention	Delafloxacin (Quofenix) 450 mg oral tablets recommended dose for community-acquired pneumonia 450 mg every 12 hours for 5 to 10 days. 300 mg powder for concentrate for solution for infusion recommended dose for community-acquired pneumonia 300 mg every 12 hours. Line of treatment: licensed to be used when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of community-acquired pneumonia.
C – Comparator(s)	Any comparator including: other oral and intravenous fluoroquinolones.
O – Outcomes	Clinical response Microbiological response Adverse events
Inclusion criteria	-
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials. If no higher-level quality evidence is found observational studies including case series can be considered.
Language	English
Patients	Human studies only
Age	Adults 18 years and over
Date limits	None
Exclusion criteria	-
Publication type	Pre-prints prior to peer review, conference abstracts or studies that have not been published in full.
Study design	Case reports

Appendix B: Summary of included studies

Summary of included studies

Study	Number of participants	Population	Intervention	Comparison	Outcomes
Horcajada et al. 2019 RCT, 86 centres across 18 countries (there were no centres in the UK, information taken from the EPAR variation for delafloxacin).	n=859 (ITT population)	Adults 18 years and over (mean age 60 years) with community-acquired bacterial pneumonia and a PORT risk class of II, III, IV or V. 91.5% of participants were white, 85.7% were from Europe.117 participants (13.6%) had asthma or chronic obstructive pulmonary disease.	Delafloxacin 300 mg intravenous infusion every 12 hours. Participants who met the clinical criteria could switch to oral treatment after a minimum of 6 intravenous doses. Total duration of treatment was 5 to 10 days (n=431).	Moxifloxacin 400 mg intravenous infusion every 24 hours plus placebo infusion to maintain blinding and every-12-hours infusion schedule. Participants who met the clinical criteria could switch to oral treatment after a minimum of 6 intravenous doses. Total duration of treatment was 5 to 10 days. If MRSA was confirmed, participants in the moxifloxacin group could have their treatment switched to intravenous linezolid 600 mg every 12 hours (n=428).	Primary outcome: • early clinical response (US Food and Drug Administration primary endpoint). Secondary outcomes: • early clinical response with improvement in vital signs • clinical response at test of cure (European Medical Agency primary endpoint) • clinical response at test of cure by baseline pathogen • adverse events.

Abbreviations: COPD, chronic obstructive pulmonary disease; EMA, European Medicines Agency; EPAR, European public assessment report; FDA, US Food and Drug Administration; ITT, intention-to-treat; MRSA, methicillin-resistant *Staphylococcus aureus*; PORT, Pneumonia patient Outcomes Research Team; RCT, randomised controlled trial

Appendix C: Quality assessment of included studies

Quality assessment of Horcajada et al. 2019

Question	Horcajada et al. 2019
Domain 1: Risk of bias arising from the randomisation process	-
1.1 Was the allocation sequence random?	No information
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	No information
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No
Risk of bias judgement	Some concerns
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	-
2.1. Were participants aware of their assigned intervention during the trial?	No
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	-
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	-
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	-
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	-
Risk of bias judgement	Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	-
2.1. Were participants aware of their assigned intervention during the trial?	No
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	-
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?	-

Question	Horcajada et al. 2019
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	-
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	-
Risk of bias judgement	Low
Domain 3: Missing outcome data	-
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	Yes
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	-
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	-
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	-
Risk of bias judgement	Low
Domain 4: Risk of bias in measurement of the outcome	-
4.1 Was the method of measuring the outcome inappropriate?	No
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Probably no
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	-
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	-
Risk of bias judgement	Low
Domain 5: Risk of bias in selection of the reported result	-
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalised before unblinded outcome data were available for analysis?	Yes
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (for example, scales, definitions, time points) within the outcome domain?	No
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	No
Risk of bias judgement	Low
Overall risk of bias judgement	Some concerns

Checklist used: Cochrane risk of bias 2 tool.

Abbreviations: Y, Yes; PY, Probably yes; PN, Probably no; N, No; NI, No information.

Appendix D: Results table

Results table for Horcajada et al. (2019)

Outcome	Delafloxacin	Moxifloxacin	Analysis
Primary outcome	**n=431**	**n=428**	**-**
Early clinical response (FDA primary endpoint)	383/431 (88.9%)	381/428 (89.0%)	−0.2% (95% CI −4.4% to 4.1%) Non-inferiority of delafloxacin to moxifloxacin shown (non-inferiority margin −12.5%)
Secondary outcomes	**n=431**	**n=428**	**-**
Early clinical response (clinically evaluable population)	381/418 (91.1%)	380/414 (91.8%)	−0.6% (95% CI −4.5% to 3.2%)
Early clinical response with improvement in vital signs (ITT population)	52.7% (number of participants not reported)	43.0% (number of participants not reported)	9.7% (95% CI 3.0% to 16.3%)
Clinical success at test of cure in the ITT population (EMA primary endpoint)	390/431 (90.5%)	384/428 (89.7%)	0.8% (95% CI −3.3 to 4.8%)
Subgroup analysis by baseline pathogen	**-**	**-**	**-**
Clinical success at test of cure –*Streptococcus pneumoniae*	103/110 (93.6%)	94/99 (94.9%)	No statistical analysis
Clinical success at test of cure –*Legionella pneumophila*	27/29 (93.1%)	32/32 (100%)	No statistical analysis
Clinical success at test of cure –*Staphylococcus aureus*	25/27 (92.6%)	28/30 (93.3%)	No statistical analysis
Clinical success at test of cure –*Haemophilus influenzae*	23/24 (95.8%)	31/35 (88.6%)	No statistical analysis
Safety outcomes	**n=429**	**n=427**	**-**
Any treatment-emergent adverse events	131/429 (30.5%)	112/427 (26.2%)	No statistical analysis
Serious treatment-emergent adverse events	23/429 (5.4%)	20/427 (4.7%)	No statistical analysis
Treatment-emergent adverse events resulting in stopping treatment	15/429 (3.5%)	7/427 (1.6%)	No statistical analysis
Treatment-emergent adverse events of special interest	34/429 (7.9%)	32/427 (7.5%)	No statistical analysis
Treatment-emergent deaths	9/429 (2.1%)	7/427 (1.6%)	No statistical analysis

Treatment-emergent hepatic-related events	22/429 (5.1%)	12/427 (2.8%)	No statistical analysis
Treatment-emergent *Clostridium difficile* diarrhoea	2/429 (0.5%)	1/427 (0.2%)	No statistical analysis

Abbreviations: CI, confidence interval; EMA, European Medicines Agency; FDA, US Food and Drug Administration; ITT, intention-to-treat population

The ITT population included all randomised participants with a signed informed consent form. The clinically evaluable population included the ITT population who received the study drug based on randomisation; had evidence of acute onset community-acquired pneumonia; received at least 80% of expected doses of study drug in the treatment period; had assessments of community-acquired pneumonia being treated within the appropriate timeframe, or had a clinical failure and had a minimum of 4 doses of study drug by end of day 3; did not receive other potentially effective antibiotics before assessment, except for lack of efficacy and had no protocol deviations. The safety population included all randomised participants who received at least 1 dose of the study drug.

Early clinical response was defined as improvement in at least 2 of the following symptoms: chest pain, frequency or severity of cough, amount and quality of productive sputum, dyspnoea and no worsening of the other symptoms in the ITT population. It was assessed 96 hours (plus or minus 24 hours) after the start of the first dose of study drug. For the secondary outcome of early clinical response with improvement in vital signs, in addition to meeting the criteria for the primary outcome there also had to be an improvement and no worsening in all vital sign assessments.

Clinical response at test of cure (5 to 10 days after the last dose of study drug) was based on the assessment of the participants signs and symptoms of infection and categorised as success, failure or indeterminate.

Adverse events of special interest included potential myopathy, *Clostridium difficile* diarrhoea, convulsions, potential peripheral neuropathy, tendon disorders, potential QT-prolongation, phototoxicity, allergic reactions, abnormal blood glucose levels and hepatic-related events.

Appendix E: Literature search strategy

Database search strategies

Database: Medline

Platform: Ovid
Version: 1946 to May 21 2021
Search date: 24/05/2021
Number of results retrieved: 36
Search strategy:
Database: Ovid MEDLINE(R) <1946 to May 21, 2021>
Search Strategy:
---
1 (delafloxacin or quofenix or baxdela* or ABT-492 or ABT492 or RX-3341* or RX3341* or WQ-3034 or WQ3034).tw. (107)
2 exp Pneumonia/ (173699)
3 (pneumon* or bronchopneumon* or pleuropneumon* or tracheobronchit*).tw. (181201)
4 Cough/ (16737)
5 cough*.tw. (46659)
6 ((postnasal* or post nasal*) adj3 drip*).tw. (549)
7 Bronchitis/ (20533)
8 (bronchit* or tracheobronchit*).tw. (21603)
9 (bronchial adj2 infect*).tw. (768)
10 Respiratory Tract Infections/ (39732)
11 Respiratory Syncytial Virus Infections/ (7366)
12 ((pulmonary or lung* or airway* or airflow* or bronch* or respirat*) adj3 syncytial virus*).tw. (12790)
13 Pneumovirus*.tw. (340)
14 (("respiratory tract*" or "acute respiratory" or "lower respiratory" or chest) adj3 (infect* or cough*)).tw. (31883)
15 LRTI.tw. (1060)
16 or/2-15 (404091)
17 1 and 16 (38)
18 limit 17 to english language/ (36)

Database: Medline in-process

Platform: Ovid
Version: 1946 to May 21 2021
Search date: 24/05/2021
Number of results retrieved: 2
Search strategy:
Database: Ovid MEDLINE(R) In-Process & In-Data-Review Citations <1946 to May 21, 2021>
Search Strategy:
---
1 (delafloxacin or quofenix or baxdela* or ABT-492 or ABT492 or RX-3341* or RX3341* or WQ-3034 or WQ3034).tw. (11)

2 exp Pneumonia/ (0)
3 (pneumon* or bronchopneumon* or pleuropneumon* or tracheobronchit*).tw. (4207)
4 Cough/ (0)
5 cough*.tw. (1105)
6 ((postnasal* or post nasal*) adj3 drip*).tw. (12)
7 Bronchitis/ (0)
8 (bronchit* or tracheobronchit*).tw. (242)
9 (bronchial adj2 infect*).tw. (9)
10 Respiratory Tract Infections/ (0)
11 Respiratory Syncytial Virus Infections/ (0)
12 ((pulmonary or lung* or airway* or airflow* or bronch* or respirat*) adj3 syncytial virus*).tw. (310)
13 Pneumovirus*.tw. (5)
14 (("respiratory tract*" or "acute respiratory" or "lower respiratory" or chest) adj3 (infect* or cough*)).tw. (851)
15 LRTI.tw. (47)
16 or/2-15 (6120)
17 1 and 16 (2)
18 limit 17 to english language/ (2)

Database: Medline epubs ahead of print

Platform: Ovid
Version: May 21 2021
Search date: 24/05/2021
Number of results retrieved: 4
Search strategy:

Database: Ovid MEDLINE(R) Epub Ahead of Print <May 21, 2021>
Search Strategy:
---
1 (delafloxacin or quofenix or baxdela* or ABT-492 or ABT492 or RX-3341* or RX3341* or WQ-3034 or WQ3034).tw. (7)
2 exp Pneumonia/ (0)
3 (pneumon* or bronchopneumon* or pleuropneumon* or tracheobronchit*).tw. (3211)
4 Cough/ (0)
5 cough*.tw. (981)
6 ((postnasal* or post nasal*) adj3 drip*).tw. (9)
7 Bronchitis/ (0)
8 (bronchit* or tracheobronchit*).tw. (159)
9 (bronchial adj2 infect*).tw. (10)
10 Respiratory Tract Infections/ (0)
11 Respiratory Syncytial Virus Infections/ (0)
12 ((pulmonary or lung* or airway* or airflow* or bronch* or respirat*) adj3 syncytial virus*).tw. (188)
13 Pneumovirus*.tw. (3)
14 (("respiratory tract*" or "acute respiratory" or "lower respiratory" or chest) adj3 (infect* or cough*)).tw. (722)

15 LRTI.tw. (51)
16 or/2-15 (4804)
17 1 and 16 (4)
18 limit 17 to english language/ (4)

Database: Medline daily update

Platform: Ovid
Version: May 21 2021
Search date: 24/05/2021
Number of results retrieved: 0
Search strategy
As above

Database: Embase

Platform: Ovid
Version: 1974 to 2021 May 21
Search date: 24/05/2021
Number of results retrieved: 90
Search strategy:
Database: Embase <1974 to 2021 May 21>
Search Strategy:
---
1 delafloxacin/ (327)
2 (delafloxacin or quofenix or baxdela* or ABT-492 or ABT492 or RX-3341* or RX3341* or WQ-3034 or WQ3034).tw. (261)
3 1 or 2 (393)
4 pneumonia/ (180915)
5 (pneumon* or bronchopneumon* or pleuropneumon* or tracheobronchit*).tw. (285365)
6 coughing/ (118444)
7 cough*.tw. (89825)
8 ((postnasal* or post nasal*) adj3 drip*).tw. (1031)
9 bronchitis/ (26477)
10 (bronchit* or tracheobronchit*).tw. (28974)
11 (bronchial adj2 infect*).tw. (1150)
12 respiratory tract infection/ (59945)
13 respiratory syncytial virus infection/ (5872)
14 ((pulmonary or lung* or airway* or airflow* or bronch* or respirat*) adj3 syncytial virus*).tw. (17176)
15 Pneumovirus*.tw. (409)
16 (("respiratory tract*" or "acute respiratory" or "lower respiratory" or chest) adj3 (infect* or cough*)).tw. (54939)
17 LRTI.tw. (2117)
18 or/4-17 (596242)
19 3 and 18 (118)
20 limit 19 to (books or chapter or conference abstract or conference paper or "conference review" or letter) (27)
21 19 not 20 (91)
22 limit 21 to english language (90)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL

Platform: Wiley
Version:
CDSR –5 of 12, May 2021
CENTRAL – Issue 4 of 12, April 2021
Search date: 24/05/2021
Number of results retrieved: CDSR 0; CENTRAL 51

Date Run: 24/05/2021 05:22:13
Comment:

ID Search Hits
#1 (delafloxacin or quofenix or baxdela* or ABT-492 or ABT492 or RX-3341* or RX3341* or WQ-3034 or WQ3034):ti,ab,kw (Word variations have been searched) 54
#2 MeSH descriptor: [Pneumonia] explode all trees 4154
#3 (pneumon* or bronchopneumon* or pleuropneumon* or tracheobronchit*):ti,ab,kw 20312
#4 MeSH descriptor: [Cough] this term only 1358
#5 (cough*):ti,ab,kw 14699
#6 ((postnasal* or post nasal*) near/3 drip*):ti,ab,kw 238
#7 MeSH descriptor: [Bronchitis] this term only 1243
#8 (bronchit* or tracheobronchit*):ti,ab,kw 4439
#9 (bronchial near/2 infect*):ti,ab,kw 62
#10 MeSH descriptor: [Respiratory Tract Infections] this term only 2313
#11 MeSH descriptor: [Respiratory Syncytial Virus Infections] this term only 327
#12 ((pulmonary or lung* or airway* or airflow* or bronch* or respirat*) near/3 syncytial virus*):ti,ab,kw 983
#13 (Pneumovirus*):ti,ab,kw 41
#14 (("respiratory tract*" or "acute respiratory" or "lower respiratory" or chest) near/3 (infect* or cough*)):ti,ab,kw 11116
#15 (LRTI):ti,ab,kw 316
#16 {OR #2 -#15} 1690342
#17 #1 and #16 51

Database: INAHTA database

Platform: INAHTA
Version:
Search date: 24/0/2021
Number of results retrieved: 8
Search strategy:
delafloxacin or quofenix or baxdela* or ABT-492 or ABT492 or RX-3341* or RX3341* or WQ-3034 or WQ3034

Trials registry search strategies

Clinicaltrials.gov

Search date:21/05/2021
Number of results retrieved: 1
Search strategy: Community-acquired Pneumonia | Delafloxacin OR quofenix

Clinicaltrialsregister.eu

Search date:21/05/2021
Number of results retrieved: 1
Search strategy: delafloxacin AND pneumonia

Excluded registry results

None

Appendix F: Excluded studies

Study reference	Reason for exclusion
Kaidashev I, Nitu M, Popescu, M et al. (2019) Treatment of community-acquired bacterial pneumonia (CABP) in patients with diabetes: outcomes from a global phase 3 study of delafloxacin (DLX). Open forum infectious diseases 6, S761	Abstract only
Madej A, Pullman J, Popescu M et al. (2019) Outcomes by age and gender from a global phase 3 study of delafloxacin (DLX) in community-acquired bacterial pneumonia (CABP). Open forum infectious diseases 6, S763	Abstract only
McCurdy S, Keedy K, Lawrence L et al. (2020) Efficacy of Delafloxacin versus Moxifloxacin against Bacterial Respiratory Pathogens in Adults with Community-Acquired Bacterial Pneumonia (CABP): Microbiology Results from the Delafloxacin Phase 3 CABP Trial. Antimicrobial agents and chemotherapy 64, 3	Outcomes either not in-line with PICO or duplicate outcomes to main study
McCurdy S, Nenninger A, Sheets A et al. (2020) Efficacy of delafloxacin versus moxifloxacin against atypical bacterial respiratory pathogens in adults with community-acquired bacterial pneumonia (CABP): Data from the Delafloxacin Phase 3 CABP Trial. International journal of infectious diseases: official publication of the International Society for Infectious Diseases 97, 374-79	Outcomes either not in-line with PICO or duplicate outcomes to main study
Salata R, Alvarez-Sala R, Horcajada JP et al. (2019) A global phase 3 study of delafloxacin (DLX) compared with moxifloxacin (MOX) in patients with community-acquired bacterial pneumonia (CABP). Open forum infectious diseases 6, S762	Abstract only
Zinzi D, Horcajada JP, Madej A et al. (2020) Outcomes in treatment of European patients with community acquired bacterial pneumonia comparing delafloxacin and moxifloxacin. Chest 157, 6, A76	Abstract only