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Duration of antibiotherapy for diabetic foot osteomyelitis patients without amputation: a protocol for a systematic review and network meta-analysis

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Duration of antibiotherapy for diabetic foot osteomyelitis patients without amputation: a protocol for a systematic review and network meta-analysis

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ABSTRACT

Introduction Diabetic foot osteomyelitis (DFO) poses a serious threat to the quality of life and survival of patients, and systemic antibiotherapy is effective and plays a pivotal role for DFO patients without amputation. However, the optimum duration of systemic antibiotherapy is not clear. We aim to perform a network meta-analysis to assess the efficacy and safety of different duration of antibiotherapy for DFO patients without amputation.

Methods and analysis We will search multiple databases, including the China National Knowledge Infrastructure (CNKI), VIP database, Wanfang database, ScienceDirect, EBSCO, EMBASE, Web of Science, Cochrane Library, and PubMed. The outcome indicators are remission rate, time needed for a complete wound healing, rates of major amputation, and antibiotic-related adverse events rate. The risk of bias will be assessed using the Cochrane risk of bias tool. Network meta-analysis will be performed using STATA/MP 15.0. The surface under the cumulative ranking area (SUCRA) will be calculated to rank each treatment.

Ethics and dissemination This study is a systematic review protocol collecting data from published literature and does not require approval from an institutional review board. Results from this systematic review will be published in a peer-reviewed journal.

PROSPERO registration number CRD42023486089.

Keywords: Diabetic foot, Anti-bacterial agents, Systematic review, Network meta-analysis

Article Summary: Strengths and limitations of this study

- This systematic review will evaluate all available evidence from randomised controlled trials to determine the optimum duration of systemic antibiotherapy for DFO without amputation.
- The adherence to the PRISMA for network meta-analysis guidelines in the reporting of the study will give credence to the study methodology.
- Data will be analysed using pairwise meta-analysis and network meta-analysis that will give insights into the comparative efficacy and safety of interventions across the included studies.
- The confidence of evidence for the outcomes will be assessed using the GRADE approach.
- We anticipate that not all the included studies have reported all the outcomes of interest in this review and the number of randomized controlled trials available in some comparisons may be relatively small.

1. Introduction

Diabetes mellitus is increasingly prevalent around the globe. The global diabetes prevalence in 2021 was estimated to be 10.5% (536.6 million people), rising to 12.2% (783.2 million) in 2045 [1]. The lifetime incidence of foot ulcers has previously been estimated to be 19 to 34% among persons with diabetes, and more than half of diabetic foot ulcers become infected [2]. About 20% of infected ulcers will spread to the bone causing diabetic foot osteomyelitis (DFO), which will increase the mortality, risk of amputation, and healthcare expenditure [3 4]. There is no doubt that DFO has posed a tremendous threat to individual health and society.

Currently, DFO is presently treated primarily with systemic antibiotics, and may require limb amputation to control the infection in extreme cases. However, amputation leads to a permanent disability, which can significantly reduce quality of life of patients [5]. Fortunately, it was found that systemic antibiotherapy (SAT) had exerted reliable curative effects for DFO patients and could avoid a major amputation [6 7]. The renewed IWGDF/IDSA guidelines recommend that empirical systemic antibiotherapy should be started as early as possible in order to control the infection, and could be switched to targeted antibiotherapy based on bacterial culture and susceptibility test results [8]. Many clinicians treat DFOs with systemic antibiotherapy for more than six weeks or even months intending to improving the therapeutic effect [9 10], despite the recommendation of the guidelines to limit it to six weeks [8]. However, long-term administration of antibacterial agents contributes to a rise in antimicrobial resistance and adverse drug reactions, which may make the treatment of DFO more difficult. The studies revealed that, for DFO without amputation, shorter systemic antibiotherapy yielded no enhanced risk of clinical failure or microbiological failure [11], remission rates were similar between 6-week and 12-week duration systemic antibiotherapy [12], and a systemic antibiotherapy course of three weeks gave similar incidences of remission and adverse events to a course of six weeks [13]. Nevertheless, the small sample size of these studies limited their results. Thus, it is not known whether the duration can be shortened to three weeks. There is currently insufficient evidence to determine the ideal duration of systemic antibiotherapy for DFO without amputation.

The network meta-analysis (NMA), an extension of pairwise meta-analysis (PMA), combines direct and indirect comparisons to compare and rank various interventions. In this study, we will conduct both PMA and NMA to compare and rank the efficacy and safety of different durations of systemic antibiotherapy

for DFO patients without amputation to evaluate the most suitable duration of systemic antibiotherapy. The results of this study will offer valuable evidence to inform recommendations for DFO therapy.

2. Methods

The study protocol was registered in PROSPERO (CRD42023486089). This manuscript was written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols (PRISMA-P) statement [14]. (see *Supplementary Table S1*).

2.1. Criteria for inclusion and exclusion

2.1.1. Participants

Participants must meet the following inclusion criteria: (1) Age ≥18 years; (2) Diagnosed with diabetes mellitus; (3) Diagnosed with DFO, which is defined as a bone infection with any positive microbiological, histological and/or radiological evidence of bone involvement.[8] The exclusion criteria encompass the following: Participants required amputation due to severe peri-osteoarticular damage when DFO was diagnosed [8 15].

2.1.2. Interventions

Patients in the experimental group should be treated with systemic antibiotherapy, which may be administered via injection or oral route. In the absence of definitive culture and susceptibility test results, empirical antibiotic treatment can be administered. However, antibiotics adapted to culture results should be initiated as soon as the results of the tests are definitive. Patients could have undergone appropriate debridement of nonviable infected soft tissues and bones, off-loading, and arterial re-vascularization if clinically indicated. The therapeutic interventions that incorporate amputation surgery will be excluded.

2.1.3. Controls

The control group should have followed the same regime as the intervention group with the sole exception of the duration of antibiotherapy.

2.1.4. Outcomes measures

To be included, studies must have reported at least one of the outcome indicators, such as remission rate which is defined as the percentage of patients achieving remission from the diabetic foot osteomyelitis at the end of follow-up (remission is defined as the absence of recurrent, persistent or new infection at the original site and having no need for surgery or amputation at the initial site), the time needed for a complete wound healing, rates of major amputation which is defined as the percentage of patients who

required and underwent major amputation during follow-up, and antibiotic-related adverse events rate.

2.1.5. Study type

Only randomized controlled trials (RCTs) will be included. Observational, case series, qualitative and laboratory studies, and uncontrolled trials will be excluded.

2.2. Literature searches

We will conduct a comprehensive search of relevant publications up to 1 January 2027 in Chinese- and English-language databases such as the China National Knowledge Infrastructure (CNKI), VIP database, Wanfang database, ScienceDirect, EBSCO, EMBASE, Web of Science, Cochrane Library, and PubMed. Our search strategy will be tailored for each database, utilizing a combination of Mesh, title, abstract, keywords, or free-text words. The retrieval terms include diabetic foot, osteomyelitis, anti-bacterial agents, antibacterial agents, bacteriocidal agents, bacteriocide(s), and antibiotic(s). The search strategy is available in *Supplementary Table S2*. All the records will be concurrently collected and processed in NoteExpress software.

2.3. Study selection

Two researchers will import the retrieved literature into NoteExpress, and duplicates will be removed. They will independently read the titles and abstracts for initial screening, and then assess the full texts of all relevant studies according to our inclusion and exclusion criteria. The number of included, and excluded studies and reasons for study exclusion will be recorded. If multiple reports of the same study exist, the RCT with the richest baseline and outcome data will be included. Disagreements will be resolved through discussions with a third researcher. As shown in *Figure 1*, the screening and selection process will be presented in a PRISMA flow chart.

2.4. Data extraction

Two researchers will independently extract data using a preset data extraction form. Disagreements will be resolved through discussions with a third researcher. The following information will be extracted: (1) general information (name of the first author, year of publication, study site); (2) baseline characteristics of participants (sample size, age, sex, diagnosis, location of osteomyelitis, wound score or surface at admission, and microbiology of bone sample cultures); (3) interventions and controls: (medication, dose, route, duration); (4) outcome indicator data and quality of the RCTs.

2.5. Assessment of risk bias in included studies

The risk of bias in the included studies will be assessed using the Cochrane risk of bias tool [16 17], including the adequate method for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The possible risk-of-bias judgments are as follows: (1) low risk of bias; (2) some concerns for bias; and (3) high risk of bias. Two researchers will independently assess the risk of bias, and any disagreement will be resolved by discussion with a third researcher.

2.6. Data analysis plan

We plan to perform a pairwise meta-analysis and network meta-analysis for every outcome indicator. However, it has to be noted that the findings will be summarized and discussed if a quantitative synthesis is not appropriate.

2.6.1. Pairwise meta-analysis

Pairwise meta-analysis (PMA) will be conducted using Rev Man 5.3 software to compare two interventions at a time. Continuous variables will be analyzed using mean difference (MD) with 95% confidence intervals (CI). Relative risk (RR) with 95% confidence interval (CI) will be calculated for the dichotomous outcomes. Using the I^2 statistic, we will evaluate the heterogeneity between the included studies. Substantial heterogeneity, defined as I^2 statistics exceeding 50%, will prompt the utilization of the random-effects model for pairwise meta-analysis, while the fixed-effects model will be employed in other instances. In case of significant heterogeneity, sensitivity analyses will be performed by excluding the studies with potential clinical heterogeneity or likely bias based on the Cochrane Risk of Bias Tool.

2.6.2. Network meta-analysis

The network meta-analysis (NMA) will be conducted using the network package in STATA/MP 15.0, wherein continuous variables will be analyzed using mean difference (MD) with 95% confidence intervals (CI) and relative risk (RR) with 95% confidence interval (CI) will be calculated for the dichotomous outcomes. The surface under the cumulative ranking area (SUCRA) will be calculated to rank each treatment [18]. The cluster analysis will be utilized to evaluate the effectiveness and safety of the interventions and determine the optimal duration of antibiotherapy.

Network plots will be constructed to visualize the comparisons. The size of each node will be determined by the number of subjects participating in that intervention. Connecting lines will be thicker if there are more studies included [18]. In the case of closed loops in the intervention structure, it is necessary to assess the inconsistency of the evidence [19].

In the NMA, uncertainty in the estimated effect size will be evaluated using the 95% predictive interval (95% PI) results that incorporate heterogeneity. Uncertainty stemming from heterogeneity will be characterized by discrepancies between the 95% CIs and their corresponding 95% PI [18 20]. In instances of substantial heterogeneity, sensitivity analyses will be performed by excluding the studies with potential clinical heterogeneity or which are likely to be biased based on the Cochrane Risk of Bias Tool. We will evaluate transitivity by assessing the distributions of potential effect modifiers across comparisons. These effect modifiers encompass the following items: age, sex, location of osteomyelitis, wound score or surface at admission, microbiology of bone sample cultures, and the selection of the antimicrobial agent and their administration route. Additionally, publication bias will be assessed using a funnel plot, in which a symmetrical funnel indicates little bias.

2.7. Certainty of the Evidence

The grading of recommendations, assessment, development, and evaluation (GRADE) will be utilized to assess the confidence of evidence for the outcomes of the NMA [21-23]. The certainty of the NMA estimates will be rated as “high”, “moderate”, “low”, or “very low” based on considerations of risk of bias, inconsistency, indirectness, imprecision, and publication bias.

2.8. Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

3. Discussion

DFO, one of the severe complications of diabetic foot disease, poses a serious threat to the life and health of patients. Bone and/or joint resection may be required to treat DFO successfully [8 15]. However, patients with DFO are often resistant to amputation [24], because maintaining limb function is critical for maintaining independence and quality of life. In addition, SAT is successful in a large proportion of DFO patients without amputation [25]. Thus, a conservative approach with limited resection and without amputation should be chosen if possible. In this study, the NMA approach facilitates the incorporation of both direct and indirect evidence, enabling comparisons for the efficacy and safety of different durations of SAT for DFO without amputation. The results of this study will provide insights toward optimizing clinical decision-making strategies.

However, it is essential to recognise the potential limitations of this study. First, it was known that factors

such as wound surface at admission [25], locations of osteomyelitis [26], microbiology of bone sample cultures, and the choice of antimicrobial drugs [27] could be identified as the effect modifiers, which could lead to potential heterogeneity. Second, the limited number of included studies and small sample sizes may introduce bias in the research results. Thus, subsequent research should perform three crucial assumptions, including heterogeneity, transitivity, and consistency to achieve valid results. Moreover, to ensure the reliability and objectivity of our research conclusions, the search scope should be expanded by reading the retrieved studies and their references, and eligible RCTs should be retrieved as comprehensively as possible.

Supplementary Materials

Supplementary Table S1 PRISMA-P Checklist; Supplementary Table S2 Details of the search strategy for 9 databases.

Data availability statement

All data relevant to the study are included in the article or uploaded as online supplemental material.

Author contributions:

Zhenyu Jiang and Jing Hu conceptualised and designed this protocol of network meta-analysis. Zhenyu Jiang and Zhijun Yu developed and ran the search strategy. Haiying Deng and Yajun Chen developed the initial data extraction template. Zhenyu Jiang was the major contributor in writing the initial draft of this protocol. All authors reviewed and revised the manuscript, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

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Patient consent for publication: Not applicable.

Ethics approval: Not applicable.

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Figure legends

Figure 1 PRISMA flow chart of the study. CNKI, China National Knowledge Infrastructure database; WFD, Wan fang database; VIP, VIP database; WOS, web of science.

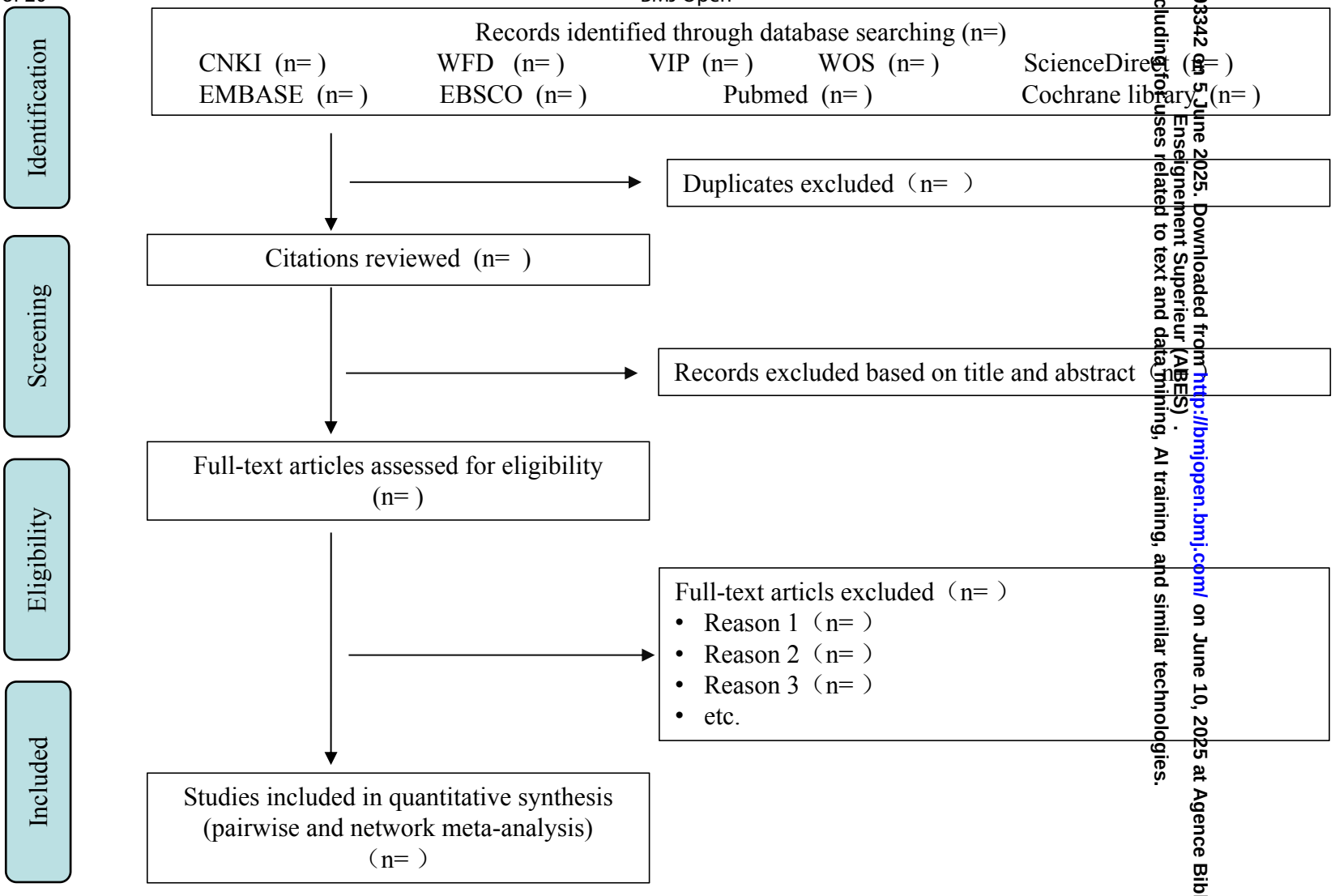

Figure 1 PRISMA flow chart of the study. CNKI, China National Knowledge Infrastructure database; WFD, Wan fang database; VIP, VIP database; WOS, web of science.

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Supplemental Material

TABLE OF CONTENTS

Supplementary Table S1 PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 10
Sponsor	5b	Provide name for the review funder and/or sponsor	Not applicable
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Not applicable
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 5, Page 6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 6, Supplementary Table S2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 6, Page 7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 6
Data collection	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for	Page 6

process		obtaining and confirming data from investigators	
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 6, Page 7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 5, Page 6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Page 7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 7, Page 8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplementary Table S2 Details of the search strategy for 9 databases

Database	search strategy	
PubMed	**#1**	diabetic foot
	#2	osteomyelitis
	#3	anti-bacterial agents
	#4	antibacterial
	#5	bacteriocidal
	#6	bacteriocide
	#7	antibiotic
	#8	#3 OR #4 OR #5 OR #6 OR #7
	#9	#1 AND #2 AND #8
WOS-890	**#1**	TS=(diabetic foot)
	#2	TS=(osteomyelitis)
	#3	TS=("anti-bacterial agents" or antibacterial or bacteriocidal or bacteriocide or bacteriocides or antibiotic or antibiotics)
	#4	#1 AND #2 AND #3
EMBASE-1828	**#1**	('diabetic'/exp OR diabetic) AND ('foot'/exp OR foot)
	#2	'osteomyelitis'/exp
	#3	osteomyelitis
	#4	#2 OR #3
	#5	'antiinfective agent'/exp OR 'antiinfective agent'
	#6	'antibacterial'/exp OR antibacterial
	#7	'anti-bacterial agents'
	#8	bacteriocid*
	#9	antibiotic*
	#10	#5 OR #6 OR #7 OR #8 OR #9
	#11	#1 AND #4 AND #10

Cochrane Library-81	#1	(diabetic foot):ti,ab,kw
	#2	MeSH descriptor: [Diabetic Foot]
	#3	#1 OR #2
	#4	osteomyelitis
	#5	MeSH descriptor: [Osteomyelitis]
	#6	#4 OR #5
	#7	MeSH descriptor: [Anti-Bacterial Agents]
	#8	("anti-bacterial agents" OR antibacterial OR bacteriocidal OR bacteriocide OR bacteriocides OR antibiotic OR antibiotics) in All Text
	#9	#7 OR #8
	#10	#3 AND #6 AND #9
EBSCO-827	"diabetic foot" AND osteomyelitis AND ("anti-bacterial agents" OR antibacterial OR bacteriocidal OR bacteriocide OR bacteriocides OR antibiotic OR antibiotics)	
ScienceDirect-2448	Find articles with these terms: "diabetic foot" AND osteomyelitis AND ("anti-bacterial agents" OR antibacterial OR bacteriocidal OR bacteriocide OR bacteriocides OR antibiotic OR antibiotics)	
CNKI	TKA%=糖尿病足骨髓炎 AND FT%=(抗感染 + 抗菌 + 抗生素 + 霉素 + 西林 + 头孢 + 菌素 + 环素 + 沙星 + 磺胺)	
Wanfang database	全部:(糖尿病足骨髓炎) and 全部:(抗感染 or 抗菌 or 抗生素 or 霉素 or 西林 or 头孢 or 菌素 or 环素 or 沙星 or 磺胺)	
VIP database	U=(糖尿病足骨髓炎) AND (抗感染 OR 抗菌 OR 抗生素 OR 霉素 OR 西林 OR 头孢 OR 菌素 OR 环素 OR 沙星 OR 磺胺)	

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Duration of antibiotherapy for diabetic foot osteomyelitis patients without amputation: a protocol for a systematic review and network meta-analysis

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ABSTRACT

Introduction Diabetic foot osteomyelitis (DFO) poses a serious threat to the quality of life and survival of patients, and systemic antibiotic therapy is effective and plays a pivotal role in the management of patients with DFO without amputation. However, the optimal duration of systemic antibiotic therapy is not clear. We aim to perform a network meta-analysis to assess the efficacy and safety of different durations of antibiotic therapy for patients with DFO without amputation.

Methods and analysis We will search multiple databases, including the China National Knowledge Infrastructure (CNKI), VIP database, Wanfang database, ScienceDirect, EBSCO, EMBASE, Web of Science, Cochrane Library, and PubMed. The outcome indicators are remission rate, time needed for a complete wound healing, major amputation rates, and the rate of antibiotic-related adverse events. The risk of bias will be evaluated using the Cochrane risk of bias tool. Network meta-analysis will be performed using STATA/MP 15.0. The surface under the cumulative ranking area (SUCRA) will be calculated to rank each treatment.

Ethics and dissemination This study is a systematic review protocol collecting data from published literature and does not require approval from an institutional review board. Results from this systematic review will be published in a peer-reviewed journal.

PROSPERO registration number CRD42023486089.

Keywords: Diabetic foot, Anti-bacterial agents, Systematic review, Network meta-analysis

Article Summary: Strengths and limitations of this study

- This systematic review will evaluate all available evidence from randomised controlled trials to determine the optimal duration of systemic antibiotic therapy for DFO without amputation.
- Adherence to the PRISMA guidelines for network meta-analyses will strengthen the methodological rigor of this study.
- Data will be analysed using pairwise meta-analysis and network meta-analysis that will give insights into the comparative efficacy and safety of interventions across the included studies.
- The confidence of evidence for the outcomes will be assessed using the GRADE approach.
- We anticipate that not all the included studies have reported all the outcomes of interest in this review and the number of randomized controlled trials available in some comparisons may be relatively small.

1. Introduction

Diabetes mellitus is increasingly prevalent around the globe. The global diabetes prevalence in 2021 was estimated to be 10.5% (536.6 million people), rising to 12.2% (783.2 million) in 2045 [1]. The lifetime incidence of foot ulcers has previously been estimated to be 19 to 34% among persons with diabetes, and more than half of diabetic foot ulcers become infected [2]. About 20% of infected ulcers will spread to the bone causing diabetic foot osteomyelitis (DFO), which will increase the mortality, risk of amputation, and healthcare expenditure [3 4]. There is no doubt that DFO has posed a tremendous threat to individual health and society.

Currently, DFO is primarily treated with systemic antibiotics, and may require limb amputation to control the infection in extreme cases. However, amputation leads to a permanent disability, which can significantly reduce quality of life of patients [5]. Fortunately, it was found that systemic antibiotic therapy (SAT) has demonstrated reliable therapeutic effects in patients with DFO and could avoid a major amputation [6 7]. The renewed IWGDF/IDSA guidelines recommend that empirical systemic antibiotic therapy should be started as early as possible in order to control the infection, and could be switched to targeted antibiotherapy based on bacterial culture and susceptibility test results [8]. Many clinicians treat DFOs with systemic antibiotic therapy for more than six weeks or even months with the intention of improving therapeutic outcomes [9 10], despite the recommendation of the guidelines to limit it to six weeks [8]. However, long-term administration of antibacterial agents contributes to a rise in antimicrobial resistance and adverse drug reactions, which may make the treatment of DFO more difficult. The studies revealed that, for DFO without amputation, shorter systemic antibiotic therapy did not increase the risk of clinical or microbiological failure [11], remission rates were similar between 6-week and 12-week duration systemic antibiotic therapy [12], and a systemic antibiotic therapy course of three weeks resulted in similar remission rates and adverse events to a course of six weeks [13]. Nevertheless, the small sample size of these studies limited their results. Thus, it is not known whether the duration can be shortened to three weeks. There is currently insufficient evidence to determine the ideal duration of systemic antibiotic therapy for DFO without amputation.

The network meta-analysis (NMA), an extension of pairwise meta-analysis (PMA), combines direct and indirect comparisons to compare and rank various interventions. In this study, we will conduct both PMA and NMA to compare and rank the efficacy and safety of different durations of systemic antibiotic

therapy for patients with DFO without amputation to evaluate the most suitable duration of systemic antibiotic therapy. The results of this study will offer valuable evidence to inform recommendations for DFO therapy.

2. Methods

The study protocol was registered in PROSPERO (CRD42023486089). This manuscript was written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols (PRISMA-P) statement [14]. (see *Supplementary Table S1*).

2.1. Criteria for inclusion and exclusion

2.1.1. Participants

Participants must meet the following inclusion criteria: (1) Age ≥18 years; (2) Diagnosed with diabetes mellitus; (3) Diagnosed with DFO. DFO diagnosis is confirmed when at least two out of the following three criteria are satisfied: positive microbiological evidence, histological confirmation, and radiological indications of bone involvement. The exclusion criteria encompass the following: Participants required amputation due to severe peri-osteoarticular damage when DFO was diagnosed [8 15].

2.1.2. Interventions

Patients in the experimental group should be treated with systemic antibiotic therapy, which may be administered via injection or oral route. In the absence of definitive culture and susceptibility test results, empirical antibiotic treatment can be administered. However, antibiotics adapted to culture results should be initiated as soon as the results of the tests are definitive. Patients may have undergone appropriate debridement of nonviable infected soft tissues and bones, off-loading, and arterial re-vascularization if clinically indicated. The therapeutic interventions that incorporate amputation surgery (including both minor and major amputation) will be excluded.

2.1.3. Controls

The control group should have followed the same regime as the intervention group with the sole exception of the duration of antibiotherapy.

2.1.4. Outcomes measures

To be included, studies must have reported at least one of the outcome indicators, such as remission rate which is defined as the percentage of patients achieving remission from DFO at the end of follow-up, the time needed for a complete wound healing defined as complete epithelialization of the wound, major

amputation rates which is defined as the percentage of patients who required and underwent major amputation during follow-up, and the rate of antibiotic-related adverse events.

Remission is characterized by: 1) the absence of recurrent, persistent, or new infections at the original site, confirmed by the stabilization or improvement of radiographic abnormalities on plain X-rays and the absence of local or systemic infection signs at the conclusion of follow-up; and 2) the absence of necessity for surgical intervention or amputation at the initial site by the end of follow-up. According to the guidelines [8, 15], following antibiotic treatment, surgical consultation should be sought in cases of exacerbations, such as more severe infection or DFO complicated by extensive gangrene, necrotising infection, signs suggesting deep (below the fascia) abscess, compartment syndrome, or severe lower limb ischaemia.

2.1.5. Study type

Only randomized controlled trials (RCTs) will be considered for inclusion. Observational, case series, qualitative and laboratory studies, and uncontrolled trials will be excluded.

2.2. Literature searches

We will conduct a comprehensive search of relevant publications up to 1 January 2027 in Chinese- and English-language databases such as the China National Knowledge Infrastructure (CNKI), VIP database, Wanfang database, ScienceDirect, EBSCO, EMBASE, Web of Science, Cochrane Library, and PubMed. Our search strategy will be tailored for each database, utilizing a combination of Mesh, title, abstract, keywords, or free-text words. The retrieval terms include diabetic foot, osteomyelitis, anti-bacterial agents, antibacterial agents, bacteriocidal agents, bacteriocide(s), and antibiotic(s). The search strategy is available in *Supplementary Table S2*. All the records will be concurrently collected and processed in NoteExpress software.

2.3. Study selection

Two researchers will import the retrieved literature into NoteExpress, and duplicates will be removed. They will independently read the titles and abstracts for initial screening, and then assess the full texts of all relevant studies according to our inclusion and exclusion criteria. The number of included, and excluded studies and reasons for study exclusion will be recorded. If multiple reports of the same study exist, the RCT with the richest baseline and outcome data will be included. Disagreements will be resolved through discussions with a third researcher. As shown in *Figure 1*, the screening and selection process will be presented in a PRISMA flow chart.

2.4. Data extraction

Two researchers will independently extract data using a preset data extraction form. Disagreements will be resolved through discussions with a third researcher. The following data will be extracted: (1) general information (name of the first author, year of publication, study site); (2) baseline characteristics of participants (sample size, age, sex, diagnosis, location of osteomyelitis, wound score or surface at admission, and microbiology of bone sample cultures); (3) interventions and controls: (medication, dose, route, duration); (4) outcome indicator data and quality of the RCTs.

2.5. Assessment of risk bias in included studies

The risk of bias in the included studies will be evaluated using the Cochrane risk of bias tool [16 17], including the adequate method for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The possible risk-of-bias judgments are as follows: (1) low risk of bias; (2) some concerns for bias; and (3) high risk of bias. Two researchers will independently assess the risk of bias, and any disagreement will be resolved by discussion with a third researcher.

2.6. Data analysis plan

We plan to perform a pairwise meta-analysis and network meta-analysis for every outcome indicator. However, it has to be noted that the findings will be summarized and discussed if a quantitative synthesis is not appropriate.

2.6.1. Pairwise meta-analysis

Pairwise meta-analysis (PMA) will be conducted using Rev Man 5.3 software to compare two interventions at a time. Continuous variables will be analyzed using mean difference (MD) with 95% confidence intervals (CI). Relative risk (RR) with 95% confidence interval (CI) will be calculated for the dichotomous outcomes. Using the I^2 statistic, we will evaluate the heterogeneity between the included studies. Substantial heterogeneity, defined as I^2 statistics exceeding 50%, will prompt the utilization of the random-effects model for pairwise meta-analysis, while the fixed-effects model will be employed in other instances. In case of significant heterogeneity, sensitivity analyses will be performed by excluding the studies with potential clinical heterogeneity or likely bias based on the Cochrane Risk of Bias Tool.

2.6.2. Network meta-analysis

The network meta-analysis (NMA) will be conducted using the network package in STATA/MP 15.0,

wherein continuous variables will be analyzed using mean difference (MD) with 95% confidence intervals (CI) and relative risk (RR) with 95% confidence interval (CI) will be calculated for the dichotomous outcomes. The surface under the cumulative ranking area (SUCRA) will be calculated to rank each treatment [18]. The cluster analysis will be utilized to evaluate the effectiveness and safety of the interventions and determine the optimal duration of antibiotherapy.

Network plots will be constructed to visualize the comparisons. The size of each node will be determined by the number of subjects participating in that intervention. Connecting lines will be thicker if there are more studies included [18]. In the case of closed loops in the intervention structure, it is necessary to assess the inconsistency of the evidence [19].

In the NMA, uncertainty in effect size estimates will be assessed using 95% predictive intervals (95% PI), which account for heterogeneity. Uncertainty stemming from heterogeneity will be characterized by discrepancies between the 95% CIs and their corresponding 95% PI [18 20]. In instances of substantial heterogeneity, sensitivity analyses will be performed by excluding the studies with potential clinical heterogeneity or which are likely to be biased based on the Cochrane Risk of Bias Tool. We will evaluate transitivity by assessing the distributions of potential effect modifiers across comparisons. These effect modifiers encompass the following items: age, sex, location of osteomyelitis, wound score or surface at admission, microbiology of bone sample cultures, and the selection of the antimicrobial agent and their administration route. Additionally, publication bias will be evaluated using a funnel plot, in which a symmetrical funnel indicates little bias.

2.7. Certainty of the Evidence

The grading of recommendations, assessment, development, and evaluation (GRADE) will be utilized to assess the confidence of evidence for the outcomes of the NMA [21-23]. The certainty of the NMA estimates will be rated as “high”, “moderate”, “low”, or “very low” based on considerations of risk of bias, inconsistency, indirectness, imprecision, and publication bias.

2.8. Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

3. Discussion

DFO, one of the severe complications of diabetic foot disease, poses a serious threat to the life and health

of patients. Bone and/or joint resection may be required to treat DFO successfully [8 15]. However, patients with DFO are often reluctant to undergo amputation [24], because maintaining limb function is critical for maintaining independence and quality of life. In addition, SAT is successful in a large proportion of patients with DFO without amputation [25]. Thus, a conservative approach with limited resection and without amputation should be chosen if possible. In this study, the NMA approach facilitates the incorporation of both direct and indirect evidence, enabling comparisons of the efficacy and safety of different durations of systemic antibiotic therapy for DFO without amputation. The results of this study will provide insights toward optimizing clinical decision-making strategies.

However, it is essential to recognise the potential limitations of this study. First, it was known that factors such as wound surface at admission [25], locations of osteomyelitis [26], microbiology of bone sample cultures, the types of wounds (including neuropathic, ischemic, and neuro-ischemic types) [27], with or without chronic kidney disease [28], and the choice of antimicrobial drugs [29], could be identified as the effect modifiers, which could lead to potential heterogeneity. Therefore, there is a need to carefully analyze and discuss before conclusions. Second, the limited number of included studies and small sample sizes may introduce bias in the research results. Thus, subsequent research should perform three crucial assumptions, including heterogeneity, transitivity, and consistency to achieve valid results. Moreover, to ensure the reliability and objectivity of our research conclusions, the search scope should be expanded by reading the retrieved studies and their references, and eligible RCTs should be retrieved as comprehensively as possible.

Supplementary Materials

Supplementary Table S1 PRISMA-P Checklist; Supplementary Table S2 Details of the search strategy for 9 databases.

Data availability statement

All data relevant to the study are included in the article or uploaded as online supplemental material.

Author contributions:

Jing Hu and Zhenyu Jiang conceptualised and designed this protocol of network meta-analysis. Zhenyu Jiang and Zhijun Yu developed and ran the search strategy. Haiying Deng and Yajun Chen developed the initial data extraction template. Jing Hu and Zhenyu Jiang were the major contributors in writing the draft of this protocol. All authors reviewed and revised the manuscript, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work. Jing Hu is the guarantor.

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Competing interests: None declared.

Patient and public involvement: Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication: Not applicable.

Ethics approval: Not applicable.

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Figure legends

Figure 1 PRISMA flow chart of the study. CNKI, China National Knowledge Infrastructure database; WFD, Wan fang database; VIP, VIP database; WOS, web of science.

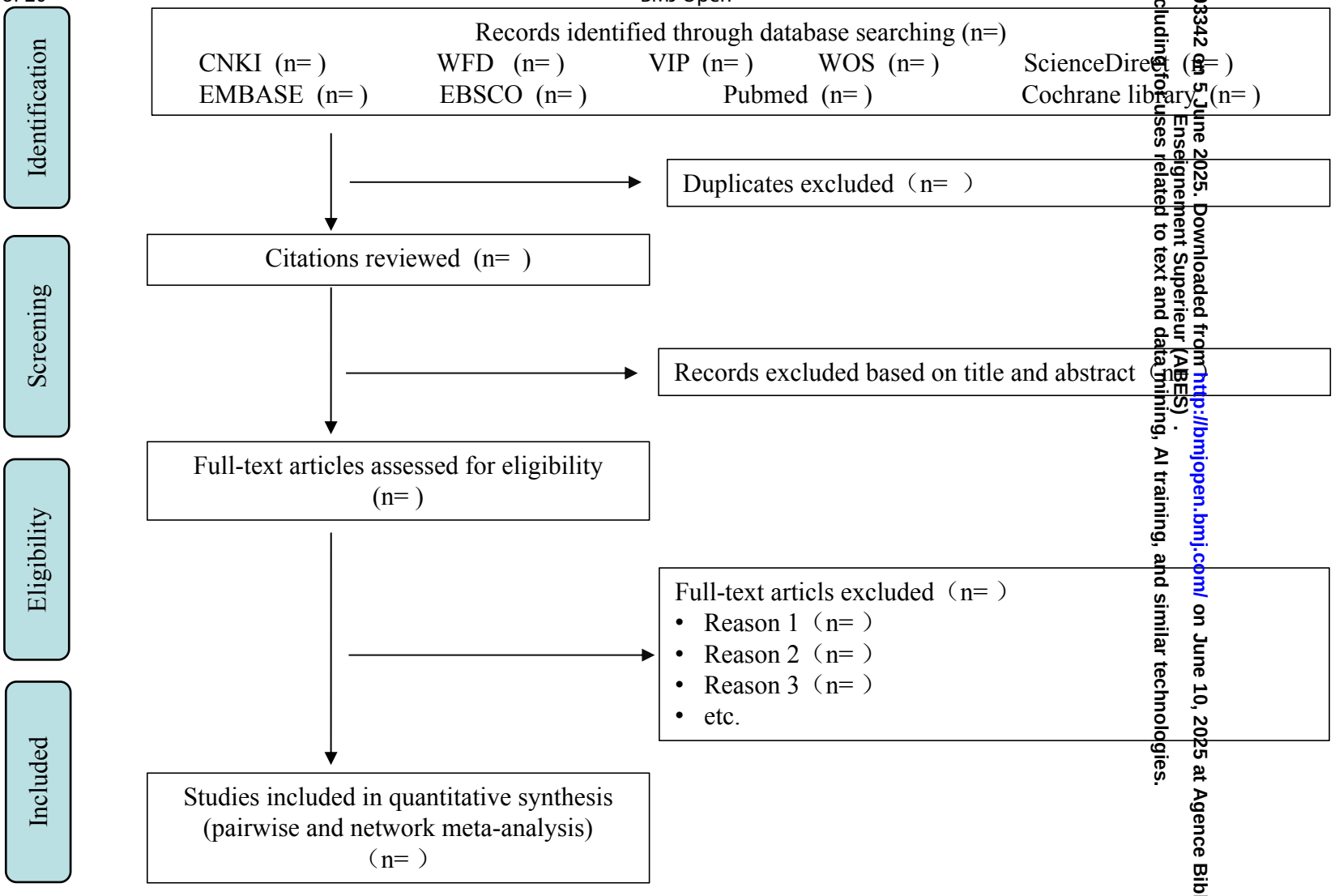

Figure 1 PRISMA flow chart of the study. CNKI, China National Knowledge Infrastructure database; WFD, Wan fang database; VIP, VIP database; WOS, web of science.

Duration of antibiotherapy for diabetic foot osteomyelitis patients without amputation: a protocol for a systematic review and network meta-analysis

Supplemental Material

TABLE OF CONTENTS

Supplementary Table S1 PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 10
Sponsor	5b	Provide name for the review funder and/or sponsor	Not applicable
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Not applicable
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 5, Page 6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 6, Supplementary Table S2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 6
Data collection	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for	Page 7

process		obtaining and confirming data from investigators	
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Pages 5~7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Pages 7~8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Pages 7~8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplementary Table S2 Details of the search strategy for 9 databases

Database	search strategy	
PubMed	#1	diabetic foot
	#2	osteomyelitis
	#3	anti-bacterial agents
	#4	antibacterial
	#5	bacteriocidal
	#6	bacteriocide
	#7	antibiotic
	#8	#3 OR #4 OR #5 OR #6 OR #7
	#9	#1 AND #2 AND #8
WOS	#1	TS=(diabetic foot)
	#2	TS=(osteomyelitis)
	#3	TS=("anti-bacterial agents" or antibacterial or bacteriocidal or bacteriocide or bacteriocides or antibiotic or antibiotics)
	#4	#1 AND #2 AND #3
EMBASE	#1	('diabetic'/exp OR diabetic) AND ('foot'/exp OR foot)
	#2	'osteomyelitis'/exp
	#3	osteomyelitis
	#4	#2 OR #3
	#5	'antiinfective agent'/exp OR 'antiinfective agent'
	#6	'antibacterial'/exp OR antibacterial
	#7	'anti-bacterial agents'
	#8	bacteriocid*
	#9	antibiotic*
	#10	#5 OR #6 OR #7 OR #8 OR #9
	#11	#1 AND #4 AND #10

Cochrane Library	#1	(diabetic foot):ti,ab,kw
	#2	MeSH descriptor: [Diabetic Foot]
	#3	#1 OR #2
	#4	osteomyelitis
	#5	MeSH descriptor: [Osteomyelitis]
	#6	#4 OR #5
	#7	MeSH descriptor: [Anti-Bacterial Agents]
	#8	("anti-bacterial agents" OR antibacterial OR bacteriocidal OR bacteriocide OR bacteriocides OR antibiotic OR antibiotics) in All Text
	#9	#7 OR #8
	#10	#3 AND #6 AND #9
EBSCO	"diabetic foot" AND osteomyelitis AND ("anti-bacterial agents" OR antibacterial OR bacteriocidal OR bacteriocide OR bacteriocides OR antibiotic OR antibiotics)	
ScienceDirect-	Find articles with these terms: "diabetic foot" AND osteomyelitis AND ("anti-bacterial agents" OR antibacterial OR bacteriocidal OR bacteriocide OR bacteriocides OR antibiotic OR antibiotics)	
CNKI	TKA%=(糖尿病足 * 骨髓炎) AND FT%=(抗感染 + 抗菌 + 抗生素 + 霉素 + 西林+ 头孢 + 菌素 + 环素 + 沙星 + 磺胺)	
Wanfang database	全部:(糖尿病足 and 骨髓炎) and 全部:(抗感染 or 抗菌 or 抗生素 or 霉素 or 西林 or 头孢 or 菌素 or 环素 or 沙星 or 磺胺)	
VIP database	U=(糖尿病足 AND 骨髓炎) AND (抗感染 OR 抗菌 OR 抗生素 OR 霉素 OR 西林 OR 头孢 OR 菌素 OR 环素 OR 沙星 OR 磺胺)	