Natural Resources for Human Health
eISSN: 2583-1194

Original Research

Received 21 May 2026
Revised 30 June 2026
Accepted 23 July 2026

Natural Resources for Human Health 2026, Vol. 6 (10s): 869–881

KEYWORDS:
Pharmacoeconomic burden; costs; diabetic foot ulcer; antibiotic cost; systematic review; antibiotics usage in DFU management

Pharmacoeconomic Burden of Antibiotic usage in Diabetic Foot Ulcer (DFU) Management among Diabetics

Running Title: Antibiotics burden and DFU

Muhammad Shahid Iqbal[1]*, Abdullah K Alahmari[1], Muhammad Zahid Iqbal[2], Salah-Ud-Din Khan[3], Mohd Faiyaz Khan[1]

[1]Department of Clinical Pharmacy, College of Pharmacy, Prince Sattam bin Abdulaziz University, Al-Kharj 11942, Saudi Arabia.
[2]Department of Clinical Pharmacy, College of Pharmacy, King Khalid University, Abha 61421, Saudi Arabia
[3]Department of Medical Education, College of Medicine, Imam Mohammad Ibn Saud Islamic University (IMSIU), Riyadh 11432, Saudi Arabia.
Corresponding Author: Department of Clinical Pharmacy, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-Kharj 11942, Saudi Arabia
profdrmsi@gmail.com

ABSTRACT: Diabetic foot ulcer (DFU) has been reported as a severe medical complication that occurs due to poor management of diabetes mellitus (DM). About 3%-8% of DM patients suffer from DFU infection once in their lifetime. A wide range of antibiotics are used for longer time periods for the management of DFU infection depending upon type and severity of the infection. As DFUs impose pharmacoeconomic burden on the healthcare systems across the entire globe, the economic importance of antibiotics usage in the treatment of DFUs among DM patients can't be ignored. This systematic review was conducted by following "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" guidelines to evaluate the pharmacoeconomic burden of antibiotic usage in the management of DFUs among DM patients. Five databases were used for data search, collection, and extraction including PubMed, MEDLINE, EMBSE, Cochrane Library, and PsycInfo, on 13 October 2025. To search data, we used MeSH keywords of "diabetic foot ulcer", "diabetic foot", "pharmacoeconomic burden", "economic cost", "costs of antibiotics in diabetic foot", "antibiotic usage in foot infections in diabetes", "antibiotic resistance in DFUs management" and "outcomes of antibiotics usage in foot infections of diabetics" among all databases. A total of 12 out of total searched papers met the study criteria and were included in the study. Among 12 selected studies, 13930 DM patients with DFU were analyzed in a recent study. Quality assessment of the included studies was done by using a 24-item Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist. It was observed that pharmacoeconomic burden of antibiotics usage among DFU patients has been tremendously increased in recent years due to high prevalence of DM, delayed healing process, multiple antibiotics usage, antibiotics resistance and complicated comorbidities among DM patients. Though parenteral antibiotic therapy has replaced traditional drug therapy and somehow has reduced the DFU infection-linked antibiotic usage cost. However, there is a great need to manage the high prevalence of DM in order to reduce DFU infection rate which directly imposes an economic burden

on the diabetes care budget of healthcare systems of developed as well as developing countries.

1. INTRODUCTION

Diabetic foot ulcer (DFU) is a common, severe, and long-lasting medical complication that occurs due to poorly managed diabetes mellitus (DM) among diabetic patients. DFU has been accounted as the most serious complication of DM that leads to increased rates of hospital admissions, lower limb damage, and lower limb amputations [1,2]. DFU is an infection that occurs in soft (feet) tissues and is categorized based on the infection type, area and severity of the lesions caused [3]. There are high chances of developing DFU infections among 15% of diabetic population and in 2010, the annual incidence rate of DFU ranged from 0.2% to 11% among DM patients in the US [4]. According to the reports from the International Diabetes Foundation (IDF), around 40% of DM patients annually suffer from DFU infection across the globe and this ratio is continuously mounting [4,5]. Another study reported that >15 million DM patients are diagnosed with DFU due to high prevalence of DM and its poor management [5].

The rate of DFU incidence among the DM patients also varies with the type of DFU, type of treatment, severity of the infection, variation in follow-up, patient age, and comorbidities present among DM patients [6]. It is also reported in literature that the annual occurrence rate of DFUs among developed countries is 2-4% with two third recoveries with one-year follow-up [7]. On the other side, 40% of cases of DFUs do not have recovery of wounds and are accounted as major medical complications among DM patients [7]. Among those who suffer from DFUs, about 20% experience lower extremity amputation, either major or minor, and 10% experience mortality risks after the first DFU infection diagnosis [8]. Overall, DFU has been reported as a major risk factor of lower limb amputation (surgical removal) which occurs among 8% of total reported DFU cases among DM patients. Among DFU infected diabetic patients, around 74% have high mortality risks which exist within first 5 years of DFU diagnosis due to severe complications and poor management [9]. Moreover, several scientific evidences suggest that data on DFU epidemiology among type 1 DM patients significantly differs from the type 2 diabetic population [7-9]. Major risk factors of DFUs include peripheral arterial wounds, foot deformity, peripheral sensory neuropathy, and foot trauma among the DM patients [10,11]. These risks are determined by total DM duration, its complications, comorbidities and the age of the sufferers [8-11].

Usually, DFU patients are extensively treated with antibiotics, but sometimes surgical intervention becomes crucial i.e., depending upon the severity of the DFU infection. The antibiotics route of administration to treat DFUs among DM patients is oral, parenteral, or topical. [12] Inappropriate use of antibiotics among DM patients to treat uncontrolled DFU often leads to initiation of antibiotic-resistive response which enhances the overall treatment cost of DFU infections [13]. Antibiotic resistance is directly linked to an increased economic burden among DM patients to treat DFU infections [11-13]. According to statistical estimations, about 58% of the budget of diabetic care in the US (245 billion USDs) usually been spent on peripheral, vascular and neurological complications of DFUs among the DM patients [16]. The study of Rice *et al.,* [17] reported that the US spends >10 billion USDs on DFU treatment (as a medical complication of poorly managed diabetes) per annum. The indirect cost of diabetic care in the US has been reported around 90 billion USDs and the direct cost is 273 billion USDs annually [18]. DM patients who experience DFU problems bear additional costs that are 50% to 100% higher than the usual price of diabetes-related care each year due to a greater frequency of hospitalization, emergency room visits, inpatient stays and home healthcare utilization [19]. Moderate to advanced-stage DFUs can cost more than 50,000 USDs per recurrence of the infection, whereas severe-staged DFUs or amputations cost even higher than the usual expenses [20]. Non-medical costs like productivity losses, and absenteeism from work among DFU infected diabetic patients are also higher as compared with non-DFU patients.

Medical complications related to DFUs severity and antibiotic resistance often result in increased pharmacoeconomic burden to DM patients as well as on diabetic healthcare budgets of the countries [18-20]. This increased healthcare budgets are estimated to be doubled in 2050 due to the higher prevalence of DM among the general population of the world [21]. The economic burden of DFUs not only increase patient expenditures but also affects the overall healthcare expenditures of the countries [22]. According to a study, about 6-7 years of income of a middle-incomed person may be spent on the treatment of DFU infection depending on the type and severity (complications) of the infection [22]. It is also estimated that the treatment cost of non-diabetic foot ulcers is lower than the DFUs as reported to be 0.13 billion USDs and 1.38 billion USDs, respectively.

According to a study finding, DFUs impose an additional and direct burden on the overall budget of diabetic care in different countries [23]. Another study reported that the hospital admission cost of DFU infected diabetic patients was significantly high as compared to non-infected DFU diabetic patients, estimated nearly 11,290 USDs versus 8,145 USDs, respectively [24].

In literature, few studies are evident that evaluated the cost-effectiveness of DFU interventions but nothing is present regarding the evaluation of pharmacoeconomic burden of antibiotics usage in the treatment of DFU among DM patients [25-28]. In the context of high DFU infection prevalence and their related economic burden, it was crucial to evaluate the pharmacoeconomic burden of antibiotics usage in the management of DFU infection among DM patients [28-30]. Hence, a systematic review of cohort-based studies was designed and performed to evaluate the pharmacoeconomic burden of antibiotics use in treatment of DFU infection among the diabetic population.

2. MATERIALS AND METHODS

2.1. Studies selection according to PRISMA guidelines

To fulfill the aim of the study, we conducted a systematic review by following "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" [28] guidelines to evaluate the pharmacoeconomic burden of antibiotic usage in DFU management among DM patients. For the selection and screening of collected research articles, the PRISMA flowchart, [29] was used as shown in figure 1.

2.2. Search strategy

For this systematic review, a comprehensive search strategy was designed and implemented for data collection and extraction. Five databases were searched for data search, collection, and extraction including PubMed, MEDLINE, EMBSE, Cochrane Library, and PsycInfo, on 2 April 2025. To search data, we used MeSH keywords of “diabetic foot ulcer”, “diabetic foot”, “pharmacoeconomic burden”, “economic cost”, “costs of antibiotics in diabetic foot”, “antibiotic usage in foot infections in diabetes”, “antibiotic resistance in DFUs management” and “outcomes of antibiotics usage in foot infections of diabetics” among all databases. Only those research articles were extracted that have been published from January 2010 to October 2025.

2.3. Study selection

The study selection criteria (including both inclusion and exclusion criteria) were designed for the screening and selection of the data. To pursue PRISMA guidelines, the PRISMA flowchart was used for the screening and selection of collected research articles/studies. The selected articles were related to research aim “the evaluation of the pharmacoeconomic burden of antibiotic usage in the management of DFUs among DM patients”.

The inclusion criteria for the systematic review included (1) cohort studies, report data, and economic evaluations (2) the study population were diabetic patients with DFU (3) evaluation or assessment of the pharmacoeconomic burden of antibiotics (4) economic burden of antibiotic used in DFU management as intervention (5) research articles published in the English language.

The exclusion criteria for this study comprised (1) case studies, narrative reviews, and systematic reviews or meta-analyses (2) research articles discussing other types of interventions rather than antibiotics usage (3) studies dealt with non-diabetic populations (4) articles published in languages other than English.

2.4. Data extraction

After following PRISMA guidelines for screening and selection, we extracted necessary data including authors, year of publication, study location, study population (size), study design, study aim, pharmacoeconomic burden, and study finding as shown in table 1.

2.5. Assessment of study quality and data synthesis

The quality assessment of the included studies was conducted by using a 24-item Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [30]. For further quality assessment, two reviewers independently assessed the included studies according to the study aim, criteria and set scores out of 24. Each component received one point, and if any study partially met the requirements i.e., by not explaining why it chose a particular perspective, then partial marks were given. Both of the reviewers examined discrepancies (if any) in the grades given and came to a consensus. It was done to calculate a precise percentage score. Due to the lack of a widely used approach for evaluating quality, predetermined categories were based

on available literature. Studies with scores of 85% or above were deemed to be of "outstanding" quality, studies with scores of 70–85% were deemed to be of "very good" quality, studies with scores of 55–70% were deemed to be of "better" quality and studies with scores of less than 55% were deemed to be of "poor" quality.

3. RESULTS

3.1. Identified studies

For this systematic review, we found 1267 studies related to the pharmacoeconomic burden of antibiotic usage for the management of DFUs among DM patients. According to the inclusion criteria, 80 papers were found to be related and reputable, as well as met the study's aim and objectives. Due to duplication, around 68 studies were removed from 80 studies using exclusion criteria. About 12 out of the remaining papers were up to the standard and met the study inclusion criteria.

3.2. Descriptive analysis of identified studies

Among 12 selected studies, 13930 DFU infected diabetic patients were analyzed in the recent systematic review. These 12 studies were cohort, retrospective, and longitudinal studies conducted in Saudi Arabia, Canada, Malaysia, the United States, the Caribbeans, United Kingdom, Australia, Chile, China, India, Tanzania, Singapore and Syria [31-42]. These studies represent different regions of the world with high, low, and moderate economies.

3.3. Quality assessment

The quality assessment of the included studies was conducted by using the CHEERS checklist and the results are mentioned in figure 2.

3.4. Key results

Each included study discussed the economic burden imposed by antibiotic usage for DFU infection management among DM patients (from different regions of the world). Among all of the 12 included studies, most of them reported direct, indirect, medical and non-medical costs as well as other interventional costs such as foot amputation, lower limb or leg amputations or comorbidities management etc, but we only evaluated/reviewed the pharmacoeconomic burden of antibiotics usage in treatment of DFU infections. Few studies also evaluated pharmacoeconomic burden related to the high prevalence of DFU infection and related comorbidities. Among the total 12 included studies, only 2 studies, Prince *et al.,* [36] and Morley *et al.,* [42] evaluated the percentage increase in pharmacoeconomic burden by antibiotics usage among DFU patients, as 33.1% and 24.1%, respectively. Among the remaining 10 studies, four studies reported per year cost of antibiotic usage in DFU infected patients [38-41] and six studies reported overall burden of DFU infection among DM patients for a particular/defined study period [31-37].

In almost all of the studied studies, it was found that the intervention of antibiotic usage was either cost-effective or cost-saving. This suggested that in majority of the cases, treatments given had offered greater health benefits at lower incremental costs. Usually, economic evaluation comparisons are difficult to be performed because of the different analyses types and methodologies used, but the interventions outperformed the comparison in the nine studies because it offered better health outcomes at a cheaper cost. Due to the adjunct's higher unit cost, the comparator in one study outperformed the intervention. Three of the studies found that the antibiotics used were cost-saving because their medical advantages were comparable. In six included studies overall therapy was found to be cost-effective. The intervention was economical for greater-risk patients across all age categories, whereas the treatment was cost-effective for the least-risk group, according to findings of the studies included.

4. DISCUSSION

The treatment cost of antibiotics used in DFUs impose a significant economic burden on healthcare budgets as compared to simple diabetic care without DFU infection among DM patients [43, 44]. The high prevalence rate of diabetes has been triggering high incidence rates of DFU infection due to its poor management along with altered glycemic control [45-47]. Hence, economic burden of the DM with DFU or without DFU on the healthcare systems can be managed through appropriate preventive practices, better glycemic control, and precise patient awareness among diabetic patients. Moreover, an early diagnosis of DFU and effective treatment plans would play a vital role in reducing overall pharmacoeconomic burden (of antibiotics used in DFUs) on healthcare systems as well as on patient families [47-49].

In this systematic review, the goal of the study was to evaluate the pharmacoeconomic burden of antibiotic usage in DFU infection management among DM patients. The economic burden in terms of antibiotic usage and other allied costs (direct, indirect, medical and non-medical) enormously affect overall healthcare expenditure of diabetic foot care across the globe. The potential economic burden of DFU infection can be managed by adopting preventative measures and improving healthcare education which result in overall improvement in glycemic control, quality of life and lowering related expenditures. Uncontrolled HbA1c, length of antibiotic therapy, type and severity of DFU infection, existence of comorbidities, and therapy complications are well-known risk factors which often result in prolonged and expensive DFU treatment among DM patients. Peripheral artery disease, which develops in almost half of the DM patients is another paramount risk factor for development of DFUs. Other major risk factors of developing DFUs among DM patients include advanced age, poor glycemic control, unhygienic lifestyle, non-adherence to DM medications, and various comorbidities. [50]

The economic cost or pharmacoeconomic burden per DFU-infected patient has been tremendously increased due to multiple factors. These days, apart from the average price of antibiotics use, and overall diabetic foot care costs, [46] new biological therapies costs and peripheral surgical procedures to improve blood circulation to the affected foot have also been added to the treatment choices for patients with DFU. These changes aim to save the affected foot or the lower limb and avoid worse amputation. Though these two variables have raised the intensity and quality of care in DFU therapy but simultaneously they have also lengthened the total time spent in providing optimum care [47]. Along with more effective treatment options, there has been a greater emphasis on treating Wager wounds' first or second-degree infections for further interventions in the management of DFU infections and its complications. Moreover, patients with DFUs have a compromised health related quality of life, higher rate of permanent disabilities and even death, which further increase the intensity of overall resources used in DFUs care. [48]

Twelve studies were evaluated based on model-based approach and the aim and objectives of the study. This analysis relied on published data regarding pharmacoeconomic burden of antibiotics usage in DFUs treatment among diabetic patients. All evaluations were assessed to elaborate the ratio and cost of antibiotics usage in DFUs management strategy. The CHEERS checklist [30] was used for assessment of the quality of included studies. This checklist found few studies to be "excellent" [31, 33, 35, 36, 38], and a few as "good" [32, 34, 38,], contributing to the authenticity of the systematic review. This highlights that this systematic review includes high quality studies with recent publications dates.

Pharmacoeconomic evaluation of antibiotic usage in treatment of DFU in diabetic patients is very important in order to know the exact costs or burden on healthcare systems. Pharmacoeconomic burden of DM has been determined in various countries across the globe like the US, UK, Saudi Arabia, Australia, Singapore, Chile, China, Syria, India, Malaysia and Canada. According to a study done in Saudi Arabia, it was observed that about 30% of the overall expenditure of the DM management i.e., 529389.804 USDs (5347 USDs per 'person) was spent on antibiotic usage especially among patients suffering from DFU infections [31]. In Canada, another study reported that per day per patient cost of antibiotics in severe DFU infection was 65 USDs and per person burden was approx. 23725 USD [32]. In that study most of the antibiotics were administered orally and fewer were IV antibiotics [32]. A study from Malaysia reported that per person daily cost of antibiotics usage was 52 USDs among DM patients suffering from DFUs [33]. In the US, antibiotic usage cost to treat DFU was 2760 USDs in 2005 and 3315 USDs in 2013 among DM patients [34]. A study done in the Caribbean states/countries, the estimated cost of antibiotic usage was 31,216 USDs among DM patients suffering from different types and severity of DFUs in hospitals [35].

In a study done in United Kingdom, it was reported that about 33% cost of DFU infection was taken up by antibiotics usage in the management of DFUs among DM patients [36]. According to another study reported in Australia, it was determined that about 16334·76 ASDs were spent on the treatment of DFU optimal care at an average age of 45-65 years for infection treatment [37]. A study from UK, reported that overall cost of healing DFU by antibiotics ranged from £2140 to £8800 among DM patients [38]. Another study compared pharmacoeconomic burden of antibiotic usage for DFUs treatment among DM patients from different parts of the world [39]. This study was done on five different countries; Chile, China, India, Tanzania, and the United States. This study reported that approximately 124000 USD per annum cost increased for antibiotics usage in the management of DFUs due to the high prevalence of DFU infection rate among DM patients [39].

A study performed among DM patients suffering from DFUs in Singapore reported that the estimated cost for the antibiotics used to treat a single DFU infected case was approx. 3368 USDs per annum [40]. In Syria, a study done among DM patients stated that about 400 USDs were increased each year for antibiotics usage in treating DFUs among DM patients suffering from complicated DFU infections [41]. Another study from the United States, reported that the cost of antibiotics used to treat

DFUs among DM patients is 24.1% less than the overall cost for affected limb amputation [42]. These all studies highlighted the importance of knowing the pharmacoeconomic burden of antibiotic used in the management of DFUs among DM patients in different parts of the world.

Due to rising demand of pharmacoeconomic studies, the majority of the DFU therapies undergo financial assessment comparisons. All of the included studies in this systematic review, observed whether antibiotic usage in DFU treatment in a clinical setting was cost-effective or not. In summary, it can be said that implementing precise treatment approaches with appropriate antibiotic usage over the short- and long-term time spans have lessened the pharmacoeconomic burden of antibiotics usage in DFU infections while ensuring the best possible patient care [43]. The average level of care for DFUs and related expenses were included in the included studies evaluations along with some other factors were also taken into account. These factors include evaluations of the effectiveness of antibiotics, the method and environment in which they were administered, and adaptation of the strategies which were reflected in various guidelines and suggestions to reduce overall costs in DFUs [44]. In most of the studies, the analysis collectively evaluated the financial costs associated with antibiotic use among DFU infected patients. It was also observed that such financial evaluations are varied and difficult to compare since the antibiotics used for DFUs varied in type, dose, and brands together with various antimicrobial and antifungal agents and numerous conventional wound care methods. [45].

Strength and limitations of the study

This study has some shortcomings. The findings of this systematic review are solely based on articles written in English, which might not be a complete representation of all research or available data. Due to time restrictions, we did not look for secret or published but not publicly accessible gray literature. Only full texts articles available through the online library could be obtained. The bulk of studies were model-based, hence results mainly relied on the prediction of the impact of intervention rather than actual application, even if few studies were comparable to clinical studies. The healthcare expenditures of antibiotics used in DFU management were high due risks of surgical procedures and highest rates of hospital admission among diabetic population. Proper awareness and precise management of both types of DM can result in reduction of DFU incidence rates as well as other complications of high blood sugar levels. Thus, the cost of DFU management would also reduce.

5. CONCLUSIONS

Overall, pharmacoeconomic burden of antibiotic usage in management of DFUs have tremendously increased in the last few years due to the high prevalence DM, the delayed healing process, antibiotic resistance and several comorbidities among DM patients. Although the IV antibiotic treatment has replaced traditional oral drug therapy in numerous DFU infections and somehow reduced the DFU infection-linked antibiotic usage cost. However, there is a great need to manage the high prevalence of DM in order to reduce DFU infection rate which directly imposes an economic burden on the diabetes care budget of healthcare systems of developed as well as developing countries.

Funding

"The authors extend their appreciation to Prince Sattam bin Abdulaziz University for funding this research work through the project number (PSAU/2025/03/36938)."

Acknowledgment

"The authors extend their appreciation to Prince Sattam bin Abdulaziz University for funding this research work through the project number (PSAU/2025/03/36938)."

Institutional Review Board Statement

Not applicable

Informed Consent Statement

Not applicable

Conflicts of Interest

The authors declare no conflict of interest.

REFERENCES

[1] Boulton AJM, Vileikyte L, et al. The global burden of diabetic foot disease. Lancet. 2005;366(9498):1719–24. pmid:16291066

[2] Lin C-W, Armstrong DG, et al. Nationwide trends in the epidemiology of diabetic foot complications and lower-extremity amputation over 8 years. BMJ Open Diabetes Res Care. 2019;7(1):e000795. pmid:31749971

[3] Rasmussen A, Almdal T, Nielsen AA, Nielsen KE, Jørgensen ME, Hangaard S, Siersma V, Holstein PE. Decreasing incidence of foot ulcers among patients with type 1 and type 2 diabetes in the period 2001–2014. Diabetes Research and Clinical Practice. 2017 Aug 1;130:221-8.

[4] International Diabetes Federation. The Diabetic Foot. Brussels, Belgium, International Diabetes Federation, 2020. Accessed 1 August 2022. Available from https://www.idf.org/our-activities/care-prevention/diabetic-foot.html

[5] Armstrong DG, Boulton AJ, Bus SA. Diabetic foot ulcers and their recurrence. New England Journal of Medicine. 2017 Jun 15;376(24):2367-75.

[6] Iwase M, Fujii H, Nakamura U, Ohkuma T, Ide H, Jodai-Kitamura T, Sumi A, Komorita Y, Yoshinari M, Kitazono T. Incidence of diabetic foot ulcer in Japanese patients with type 2 diabetes mellitus: the Fukuoka diabetes registry. Diabetes research and clinical practice. 2018 Mar 1;137:183-9.

[7] Hoffstad O, Mitra N, Walsh J, Margolis DJ. Diabetes, lower-extremity amputation, and death. Diabetes care. 2015 Oct 1;38(10):1852-7.

[8] Meloni M, Izzo V, Giurato L, Lázaro-Martínez JL, Uccioli L. Prevalence, clinical aspects and outcomes in a large cohort of persons with diabetic foot disease: comparison between neuropathic and ischemic ulcers. Journal of clinical medicine. 2020 Jun 8;9(6):1780

[9] Jeffcoate WJ, Chipchase SY, et al. Assessing the outcome of the management of diabetic foot ulcers using ulcer-related and person-related measures. Diabetes Care. 2006;29(8):1784. pmid:16873780

[10] Jia L, Parker CN, et al. Incidence and risk factors for developing an infection in patients presenting with uninfected diabetic foot ulcers. PLoS One. 2017;12(5):e0177916. pmid:28545120

[11] Robbins JM, Strauss G, et al. Mortality rates and diabetic foot ulcers is it time to communicate mortality risk to patients with diabetic foot ulceration? J Am Podiatr Med Assoc. 2008;98(6):489–93. pmid:19017860

[12] Cavanagh P, Attinger C, et al. Cost of treating diabetic foot ulcers in five different countries. Diabetes Metab Res Rev. 2012;28(S1):107–11.

[13] Hicks CW, Selvarajah S, et al. The burden of infected diabetic foot ulcers on hospital admissions and costs. Ann Vasc Surg 2016;33:149–58. pmid:26907372

[14] Health Quality Ontario. Hyperbaric oxygen therapy for the treatment of diabetic foot ulcers: a health technology assessment. Ont Health Technol Assess Ser 2017;17(5):1–142. pmid:28572866

[15] Health Quality Ontario. Fibreglass total contact casting, removable cast walkers, and irremovable cast walkers to treat diabetic neuropathic foot ulcers: a health technology assessment. Ont Health Technol Assess Ser 2017;17(12):1–124. pmid:28989556

[16] Liu S, He C-z, et al. Evaluation of negative-pressure wound therapy for patients with diabetic foot ulcers: systematic review and meta-analysis. Ther Clin Risk Manag. 2017;13:533–44. pmid:28458556

[17] Rice JB, Desai U, Cummings AK, Birnbaum HG, Skornicki M, Parsons NB. The burden of diabetic foot ulcers for Medicare and private insurers. Diabetes care. 2014 Mar 1;37(3):651-8.

[18] Chamberlain RC, Fleetwood K, Wild SH, Colhoun HM, Lindsay RS, Petrie JR, McCrimmon RJ, Gibb F, Philip S, Sattar N, Kennon B. Foot ulcer and risk of lower limb amputation or death in people with diabetes: a national population-based retrospective cohort study. Diabetes Care. 2022 Jan 5;45(1):83-91.

[19] Paisey RB, Abbott A, Paisey CF, Walker D, Birch R, Bowen B, Brown R, Clark C, Collings R, Cutts S, Davies J. Diabetic foot ulcer incidence and survival with improved diabetic foot services: an 18-year study. Diabetic Medicine. 2019 Nov;36(11):1424-30.

[20] Tan TW, Calhoun EA, Knapp SM, Lane AI, Marrero DG, Kwoh CK, Zhou W, Armstrong DG. Rates of diabetes-related major amputations among racial and ethnic minority adults following Medicaid expansion under the Patient Protection and Affordable Care Act. JAMA Network Open. 2022 Mar 1;5(3):e223991-.

[21] Jodheea-Jutton A, Hindocha S, Bhaw-Luximon A. Health economics of diabetic foot ulcer and recent trends to accelerate treatment. The Foot. 2022 Feb 4:101909.

[22] Hicks CW, Selvarajah S, Mathioudakis N, Perler BA, Freischlag JA, Black III JH, Abularrage CJ. Trends and determinants of costs associated with the inpatient care of diabetic foot ulcers. Journal of vascular surgery. 2014 Nov 1;60(5):1247-54.

[23] Cavanagh P, Attinger C, Abbas Z, Bal A, Rojas N, Xu ZR. Cost of treating diabetic foot ulcers in five different countries. Diabetes/metabolism research and reviews. 2012 Feb;28:107-11.

[24] Price N. Routine fluorescence imaging to detect wound bacteria reduces antibiotic use and antimicrobial dressing expenditure while improving healing rates: Retrospective analysis of 229-foot ulcers. Diagnostics. 2020 Nov 10;10(11):927.

[25] Nelson EA, O'meara S, Golder S, Dalton J, Craig D, Iglesias C, DASIDU Steering Group. A systematic review of antimicrobial treatments for diabetic foot ulcers. Diabetic Medicine. 2006 Apr;23(4):348-59.

[26] Nelson EA, O'meara S, Craig D, Iglesias C, Golder S, Dalton J, Claxton K, Bell-Syer SE, Jude E, Dowson C, Gadsby R. A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers. Health technology assessment (Winchester, England). 2006 Jan 1;10(12):iii-v.

[27] Stoekenbroek RM, Santema TB, Legemate DA, Ubbink DT, Van Den Brink A, Koelemay MJ. Hyperbaric oxygen for the treatment of diabetic foot ulcers: a systematic review. European Journal of vascular and endovascular surgery. 2014 Jun 1;47(6):647-55.

[28] Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, Koffel JB. PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. Systematic reviews. 2021 Dec;10(1):1-9.

[29] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group* T. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine. 2009 Aug 18;151(4):264-9.

[30] Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, Augustovski F, Briggs AH, Mauskopf J, Loder E, ISPOR Health Economic Evaluation Publication Guidelines-CHEERS Good Reporting Practices Task Force. Consolidated health economic evaluation reporting standards (CHEERS)—explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. Value in health. 2013 Mar 1;16(2):231-50.

[31] Alshammary S, Othman SA, Alshammari E, Alarfaj MA, Lardhi HA, Amer NM, Elsaid AS, Alghamdi HM. Economic impact of diabetic foot ulcers on healthcare in Saudi Arabia: a retrospective study. Annals of Saudi medicine. 2020 Sep;40(5):425-35.

[32] Hopkins RB, Burke N, Harlock J, Jegathisawaran J, Goeree R. Economic burden of illness associated with diabetic foot ulcers in Canada. BMC health services research. 2015 Dec;15:1-9.

[33] Lam AW, Zaim MR, Helmy HH, Ramdhan IM. Economic impact of managing acute diabetic foot infection in a tertiary hospital in Malaysia. Malaysian Orthopaedic Journal. 2014 Mar;8(1):46.

[34] Wolcott R. Economic aspects of biofilm-based wound care in diabetic foot ulcers. Journal of wound care. 2015 May 2;24(5):189-94.

[35] Cawich SO, Islam S, Hariharan S, Harnarayan P, Budhooram S, Ramsewak S, Naraynsingh V. The economic impact of hospitalization for diabetic foot infections in a Caribbean nation. Permanente Journal. 2014 Jan 1;18(1).

[36] Price N. Routine fluorescence imaging to detect wound bacteria reduces antibiotic use and antimicrobial dressing expenditure while improving healing rates: Retrospective analysis of 229 foot ulcers. Diagnostics. 2020 Nov 10;10(11):927.

[37] Cheng Q, Lazzarini PA, Gibb M, Derhy PH, Kinnear EM, Burn E, Graves N, Norman RE. A cost-effectiveness analysis of optimal care for diabetic foot ulcers in Australia. International wound journal. 2017 Aug;14(4):616-28.

[38] Guest JF, Fuller GW, Vowden P. Diabetic foot ulcer management in clinical practice in the UK: costs and outcomes. International wound journal. 2018 Feb;15(1):43-52.

[39] Cavanagh P, Attinger C, Abbas Z, Bal A, Rojas N, Xu ZR. Cost of treating diabetic foot ulcers in five different countries. Diabetes/metabolism research and reviews. 2012 Feb;28:107-11

[40] Lo ZJ, Surendra NK, Saxena A, Car J. Clinical and economic burden of diabetic foot ulcers: a 5-year longitudinal multi-ethnic cohort study from the tropics. International wound journal. 2021 Jun;18(3):375-86.

[41] Alsabek MB, Abdul Aziz AR. Diabetic foot ulcer, the effect of resource-poor environments on healing time and direct cost: A cohort study during Syrian crisis. International Wound Journal. 2022 Mar;19(3):531-7.

[42] Morley R, Rothwell M, Stephenson J, McIlvenny L, Webb F, Barber A. Complex Foot Infection Treated With Surgical Debridement and Antibiotic Loaded Calcium Sulfate—A Retrospective Cohort Study of 137 Cases. The Journal of Foot and Ankle Surgery. 2022 Mar 1;61(2):239-47.

[43] Jodheea-Jutton A, Hindocha S, Bhaw-Luximon A. Health economics of diabetic foot ulcer and recent trends to accelerate treatment. The Foot. 2022 Feb 4:10190

[44] Iwase M, Fujii H, Nakamura U, Ohkuma T, Ide H, Jodai-Kitamura T, Sumi A, Komorita Y, Yoshinari M, Kitazono T. Incidence of diabetic foot ulcer in Japanese patients with type 2 diabetes mellitus: the Fukuoka diabetes registry. Diabetes research and clinical practice. 2018 Mar 1;137:183-9.

[45] Arrieta F, Piñera M, Iglesias P, Nogales P, Salinero-Fort MA, Abanades JC, Botella-Carretero JI, Calañas A, Balsa JA, Zamarrón I, Rovira A. Metabolic control and chronic complications during a 3-year follow-up period in a cohort of type 2 diabetic patients attended in primary care in the Community of Madrid (Spain). Endocrinología y Nutrición (English Edition). 2014 Jan 1;61(1):11-7.

[46] Rasmussen A, Almdal T, Nielsen AA, Nielsen KE, Jørgensen ME, Hangaard S, Siersma V, Holstein PE. Decreasing incidence of foot ulcer among patients with type 1 and type 2 diabetes in the period 2001–2014. Diabetes Research and Clinical Practice. 2017 Aug 1;130:221-8.

[47] Iwase M, Fujii H, Nakamura U, Ohkuma T, Ide H, Jodai-Kitamura T, Sumi A, Komorita Y, Yoshinari M, Kitazono T. Incidence of diabetic foot ulcer in Japanese patients with type 2 diabetes mellitus: the Fukuoka diabetes registry. Diabetes research and clinical practice. 2018 Mar 1;137:183-9.

[48] Margolis DJ, Jeffcoate W. Epidemiology of foot ulceration and amputation: can global variation be explained?. Medical Clinics. 2013 Sep 1;97(5):791-805.

[49] Lipsky BA, Senneville É, Abbas ZG, Aragón-Sánchez J, Diggle M, Embil JM, Kono S, Lavery LA, Malone M, van Asten SA, Urbančič-Rovan V. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update). Diabetes/metabolism research and reviews. 2020 Mar;36:e3280.

[50] Wu WX, Liu D, Wang YW, Wang C, Yang C, Liu XZ, Mai LF, Ren M, Yan L. Empirical antibiotic treatment in diabetic foot infection: a study focusing on the culture and antibiotic sensitivity in a population from southern China. The international journal of lower extremity wounds. 2017 Sep;16(3):173-82.

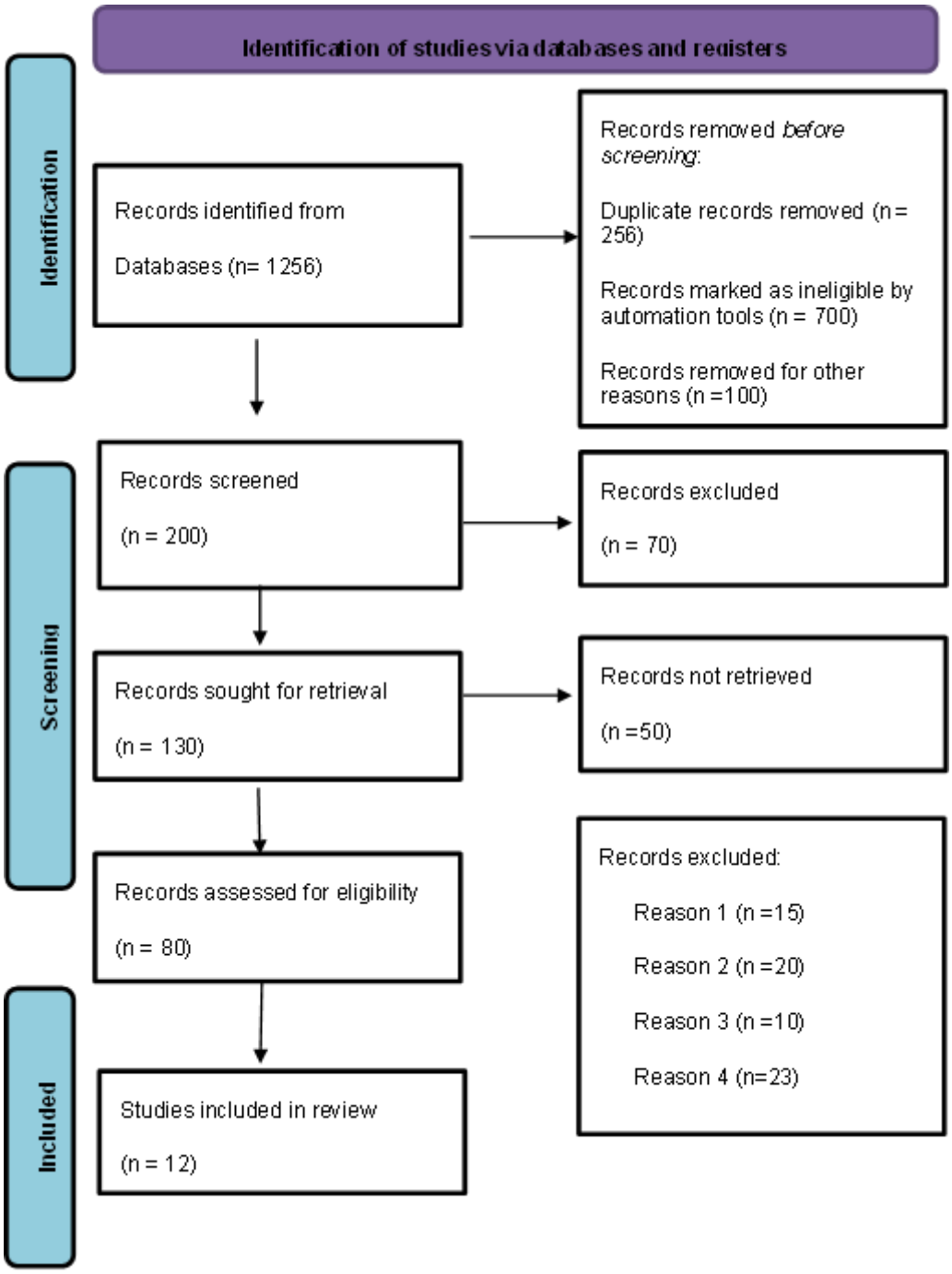

Figure 1: PRISMA flow chart of the systematic review

CHEERS Checklist	Title identified as economic evaluation	Structured Abstract	Intro provide the context and research question	Population	Settings and location	Study Perspective	Comparators	Time horizon	Discount rate	Outcomes and relevance	Preference based outcomes	Measurement of effectiveness	Resources and cost estimation	Currency date and conversion	Model justifications	Model Assumption	Parameters of value	Analysis method	Incremental cost	Heterogeneity explanation	Model sensitivity analysis	Conflict of interests	Funding sources	Total
Alshammary *et al.*, [31]	Y	N	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Hopkins *et al.*, [32]	N	Y	Y	N	N	Y	N	N	Y	Y	N	N	N	Y	N	N	N	Y	N	N	N	Y	N	N
Lam *et al.*, [33]	Y	Y	N/D	Y	N	N	Y	Y	Y	N	Y	Y	N	N/D	Y	N	Y	Y	Y	Y	Y	N/D	Y	Y
Walcott *et al.*, [34]	N/D	Y	N	Y	Y	Y	Y	N/D	N/D	Y	Y	N/D	Y	N	Y	Y	N/D	N/D	N/D	N/D	N/D	N	Y	N/D
Cawich *et al.*, [35]	Y	N	N/D	N	Y	N	N	Y	Y	N	N	Y	Y	N/D	N	Y	Y	Y	Y	Y	Y	N/D	N	Y
Prince *et al.*, [36]	Y	Y	Y	N	N/D	Y	N	Y	Y	Y	N	Y	N/D	Y	N	N/D	Y	Y	Y	Y	Y	Y	N	Y
Cheng *et al.*, [37]	N	Y	N	N/D	Y	N/D	N/D	N	N/D	Y	N/D	N	Y	N	N/D	Y	N	N/D	N	N	N	N	N/D	N
Guest *et al.*, [38]	Y	N	N/D	N/D	Y	Y	N/D	Y	N/D	N	N/D	Y	Y	N/D	N/D	Y	Y	N/D	Y	Y	Y	N/D	N/D	Y
Cavanagh *et al.*, [39]	N	N/D	N/D	N	N	Y	N	N	N	N/D	N	N	N	N/D	N	N	N	N	N	N	N	N/D	N	N
Lo *et al.*, [40]	Y	N	N/D	Y	N/D	Y	Y	Y	N	Y	Y	Y	N/D	N/D	Y	N/D	Y	N	Y	Y	Y	N/D	Y	Y
Alsabek *et al.*, [41]	Y	N/D	Y	N	Y	N/D	N	Y	Y	N/D	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y
Morley *et al.*, [42]	Y	Y	Y	N/D	Y	N/D	N/D	Y	N	Y	N/D	Y	Y	Y	N/D	Y	Y	N	Y	Y	Y	Y	N/D	Y

N/D NOT determined, Y= Yes, and N= No

Figure 2. Quality assessment of included studies using the CHEERS checklist

Table 1. Characteristics of the included studies

Authors, year	Study location	Study population	Study design	Study aim & objectives	Pharmacoeconomic burden of antibiotics	Study findings
Alshammary *et al.,* [31]	Saudi Arabia	99	Retrospective study	To evaluate and determine the medical costs associated with DFU infection in King Fahad Hospital	About 30% of the overall cost of the healthcare program was spent on antibiotic usage 529389.804 USD (5347 USD per person) among DFU patients	The cost of antibiotics, surgical amputation and hospital admission was high among all expenditures
Hopkins *et al.,* [32]	Canada	461	Cohort study	To evaluate the national burden caused by diabetic foot ulcer illness in Canada	The evaluation reported per day per patient cost of antibiotics in severe DFU infection was 65 USDs for oral IV antibiotics. (23725 USDs per person)	The costs were increased due to higher readmission rates by diabetic patients in Canada over the last five years
Lam *et al.,* [33]	Malaysia	182	Cohort study	To identify the cost burden of treatment of DFU infection patients in Malaysia	Per person daily cost of antibiotics was 52 USDs among DFU patients	The increase in antibiotic usage and related antibiotic resistance have increased overall DFU management costs
Wolcott *et al.,* [34]	United States	215	Retrospective analysis	To identify the cost of antibiotics used to cure wound microbiota among DFU patients	Antibiotic usage cost in 2005 was 2760 USDs and in 2013 it was 3315 USDs among DFU patients	The IV antibiotics reduced the cost than traditional antibiotic usage
Cawich *et al.,* [35]	Caribbean countries	446	Cohort study	To identify the treatment cost of DFU infection	The estimated cost of antibiotic usage was 31,216 USDs among DFU patients in hospital	The increased prevalence of DFU infection-impose significant burden on the healthcare system
Prince *et al.,* [36]	United Kingdom	229	Cohort study	To evaluate the antibiotic perception cost for complex DFU infection within two years follow up	About 33% of total cost of DFU infection was taken up only by antibiotics	The higher healing rate of DFU infection leads to reduction in overall DFU infection cost
Cheng *et al.,* [37]	Australia	1864	Retrospective study	To evaluate the cost-effectiveness of treatment and	About 16334·76 ASD spent on treatment of DFU optimal care	The optimal care of DFUs reduced the total burden of

				optimal care in DFU patients		DFUs on the healthcare system
Guest *et al.,* [38]	United Kingdom	6000	Retrospective cohort study	To estimate the annual care cost of DFU among DM patients in the UK	The overall healing cost of antibiotics ranged from 2140 to £8800 among DFU infected patients	The expenditures on wound care and related antibiotics increased due to delays in healing and antibiotic resistance
Cavanagh *et al.,* [39]	Chile, China, India, Tanzania, and the United States	821	Cohort study	To evaluate the cost of treatment of DFU infection among five different countries	Approximately 124000 USDs per annum cost increased for antibiotics usage due to the high prevalence of DFU infection	The cost of treatment for DFU infections took 6-7 years of income in the United States and 2 years of income in India
Lo *et al.,* [40]	Singapore	1729	Longitudinal study	To evaluate the economic burden of DFU in five-years follow up in Singapore	The estimated cost for the antibiotics given per annum for a single DFU-infected case was 3368 USDs	The cost ratio per individual wound healing increased by double folds during the last five years
Alsabek *et al.,* [41]	Syria	1747	Longitudinal study	To evaluate the economic crisis and wound healing among DFU infected patients	About 400 USDs increased each year among DFU patients as cost of antibiotic usage	DFU infected patients face multiple factors which delay the healing and increase the antibiotic cost among them
Morley *et al.,* [42]	United States	137	Cohort study	To compare the cost burden of surgical amputation and antibiotic usage	The cost of antibiotic usage was 24.1% less than the overall amputation cost	Antibiotic usage is cost-effective as compared to surgical interventions among DFU patients