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SHORT REPORT

Fixed-dose combination antibiotics: The search for evidence using the example of ampicillin–cloxacillin

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High consumption of irrational fixed-dose combination (FDC) antibiotics may pose a threat of antimicrobial resistance. In India, ampicillin–cloxacillin was the second highest sold FDC antibiotic behind amoxicillin and clavulanic acid. There remain, however, questions about its efficacy and safety and a lack of regulatory approval. We undertook a literature review for ampicillin–cloxacillin to identify available data on the safety and efficacy of its used as FDC. We identified 1071 studies for screening and 81 studies were considered for inclusion. Only 12 studies in English language were accessible full texts for final review. None of the studies identified provided strong evidence that ampicillin–cloxacillin differed in safety or efficacy to other treatments used, and in particular to the component antibiotics used alone. To fully assess the efficacy and safety of ampicillin–cloxacillin and other FDCs, a standardised search format would be required. This should include broad international collaboration, including contacting the relevant regulatory authorities to facilitate a more evidence-based approach to their use.

KEYWORDS
antibiotics, antimicrobial resistance, fixed-dose combination, literature review

1 | INTRODUCTION

Emerging antimicrobial resistance (AMR) is a global public health crisis. One major concern is high consumption of clinically irrational fixed-dose combination (FDC) antibiotics, as it may potentially pose a threat to tackling AMR,[1] an issue identified as early as the 1960s.[2] However, there remain limited data on FDC antibiotic use at an international level. Determining the evidence for the use of FDC antibiotics will be important for policy makers to strengthen regulations for manufacturing these drugs. For example, India is 1 of the largest consumers of antibiotics,[3] and ampicillin–cloxacillin is the second highest sold FDC antibiotic in this country.[1] It is second only to co-amoxiclav, 1 of the most commonly used FDC antibiotics worldwide,[4] an FDC comprising the penicillin class antibiotic amoxicillin and clavulanic acid, a β-lactam class drug that combats AMR by inhibiting bacterial β-lactamases.[5] In contrast, ampicillin–cloxacillin, when sold as an FDC contains 2 different functional antibiotics, and has not been approved by the Central Drugs Standard Control Organization (CDSCO) in India, the UK Medicines and Healthcare Products Regulatory Agency, the European Medicines Agency or the US Food and Drug Administration.[1] Although ampicillin–cloxacillin as FDC formulation has not been granted approval by many regulatory agencies, ampicillin and cloxacillin are listed separately in the World Health Organization Model List of Essential Drugs. In India, ampicillin and cloxacillin were approved by CDSCO in August 1965. Dicloxacillin was approved by CDSCO in July 1978. In December 2006, CDSCO granted approval for ampicillin (250 mg) and dicloxacillin (250 mg) as FDC formulation in India. It also needs to be addressed that many FDCs are granted approvals by local authorities not CDSCO in India. Although there is not a clear clinical

reason for using ampicillin–cloxacillin as an FDC, its continued use may be also related to the unavailability of cloxacillin independently in India.[6] In India and Nigeria, the use of this FDC has been reported for intravenous antibiotic prophylaxis in surgery and by oral or parenteral administration as empiric antibiotic therapy for infectious diseases in adults and children.[7,8] There remain, however, questions about its efficacy and safety.

We undertook a literature review of papers for ampicillin–cloxacillin with the primary objective of summarising available data on the safety and efficacy of ampicillin–cloxacillin used as an FDC. A secondary objective was to explore the feasibility and potential challenges of systematically reviewing the safety and efficacy of FDC antibiotics generally.

What is already known about this subject

- Fixed-dose combination (FDC) antibiotics are being consumed in large quantities in India, 1 of the highest consumers of antibiotics worldwide.
- The inappropriate use of FDC antibiotics may be contributing to antimicrobial resistance.
- There is a lack of summarised international evidence to support the use of FDC antibiotics.

What this study adds

- An insight into the lack of efficacy and safety evidence for 1 of the most consumed FDC antibiotics in India, ampicillin–cloxacillin.
- An overview of the difficulties such a search entails and potential solutions for FDC antibiotic evaluation at national and global level.

2 | METHODS

We searched the PubMed database in November 2018, without language or date restrictions, using the terms "ampicillin AND cloxacillin" for clinical studies of ampicillin–cloxacillin FDCs administered to humans. Our broad search strategy aimed to be as inclusive as possible. We aimed to identify studies presenting data on efficacy or toxicity of ampicillin–cloxacillin as an FDC in any population. We excluded studies where ampicillin and cloxacillin were not used in FDCs, reviews, news articles, pharmacokinetic studies, in vitro studies and animal studies. We also searched ClinicalTrials.gov, the ISRCTN registry and the World Health Organization International Clinical Trials Registry to identify any ongoing clinical trials for this FDC. Single screening of titles, abstracts and full text articles was carried out by B.S., B.B. and Y.H.; if a reviewer was unsure of a study's eligibility, another reviewer was consulted.

3 | RESULTS

We identified 15 studies with accessible full texts (open access or available through our institutional library) with 1 further available study identified from the reference list (Figure 1). A total of 12 papers with accessible full texts were published in English. Ten papers were published before 1980 and 2 after 2000.

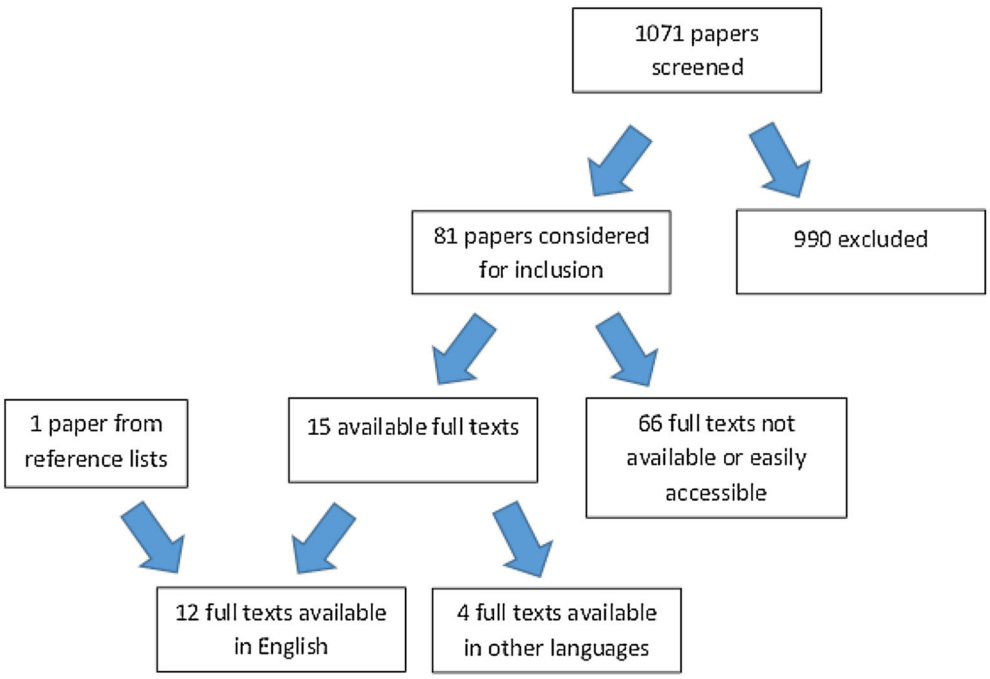

FIGURE 1 Flow chart for numbers of accessible abstracts and full texts from PubMed search for ampicillin–cloxacillin

One double-blind clinical trial from 1973 assessed ampicillin and cloxacillin prophylactic use in oral, pharyngeal and laryngeal cancer surgery.[9] The double-blind study from 1973 compared ampicillin and cloxacillin with a placebo in patients undergoing oral, laryngeal or pharyngeal surgery for neoplastic lesions.[9] The study reported the frequency of postoperative wound and respiratory infections to be higher among the placebo-treated patients (36 *vs*. 17%, $P < .05$ [no further statistical details given]) and did not report any untoward effects from the FDC therapy. There were 2 randomised clinical trials that utilised ampicillin–cloxacillin FDCs as prophylaxis in elective caesarean sections, both published in the 2000s.[10,11] There were limited data from the 2 most recent studies looking at its use as prophylaxis in caesarean sections, carried out in Nigeria[10] and Sudan.[11] The Nigerian study compared a single dose of ceftriaxone with multiple doses of a regimen comprising ampicillin–cloxacillin, gentamicin and metronidazole,[10] so the relative efficacy of ampicillin–cloxacillin used alone could not be calculated. The study in Sudan compared a single dose of ceftriaxone with 3 doses of ampicillin–cloxacillin and did not find evidence of a difference in efficacy in preventing postoperative infection; however, the number of events recorded was small.

There was also a single-blind randomised trial comparing trimethoprim–sulfamethoxazole and ampiclox (ampicillin–cloxacillin in FDC) in older patients with severe exacerbations of chronic bronchitis that required hospitalization in 1970.[12] The study included only 25 patients (12 receiving ampiclox and 13 receiving trimethoprim–sulfamethoxazole); treatment failed for 1 patient in each group. One case of sensitivity dermatitis was reported in the ampiclox group but no further side effects were reported.[12]

A case series of children with septic arthritis in 1975 reported good outcomes with a treatment regimen including oral ampicillin–cloxacillin but did not include comparisons with other treatments and did not specify whether it was used in an FDC.[13] A separate case series looked at the side effects of different antibiotic therapies and the subsequent reported colitis and diarrhoea as a potential side effect of their use in orthopaedic inpatients in London during a 19-month period in 1973–1974.[14] Of 145 courses of ampicillin–cloxacillin prescribed, 25 (17.2%) were associated with diarrhoea. This was higher than reported for most of the other antibiotics and combinations, including ampicillin alone (4/42, 9.5%). Four of the full texts accessed were case reports[15–18]; these papers looked at the use of ampicillin and cloxacillin in a series of different contexts and for different populations, with some unclear as to whether it was used as an FDC so it is very difficult to draw firm conclusions from these.

One additional paper was identified from the reference lists of the screened studies.[19] This randomized, prospective study compared the efficacy of cefamandole naftate with a combination of ampicillin and cloxacillin as prophylaxis in cardiac surgery in 1982.[20] They reported the overall rate of infection to be lower for the group given cefamandole instead of ampicillin and cloxacillin (total infections equal to 1.7% for the group given cefamandole and 13.7% for the group given ampicillin plus cloxacillin).[20]

None of these studies provided strong evidence that ampicillin–cloxacillin differed in safety or efficacy to the other treatments used, and in particular to the component antibiotics used alone. However, difficulties interpreting the results of these studies include a lack of clarity as to whether ampicillin–cloxacillin was administered as an FDC or as separate drugs[13]; presentation of data for the ampicillin–cloxacillin group combined with other treatments[10]; publication before the development of reporting standards for trials and observational studies; and lack of comparison groups in case series and case reports.

Of the 66 papers considered for full text screening but not available as full text, 40 had abstracts available (30 in English and 10 in other languages: 4 in Japanese, 3 in French, 1 in German, 1 in Italian and 1 in Norwegian). A further 8 studies in Japanese did not have abstracts available and were mostly published in the *Japanese Journal of Antibiotics*. A further 6 potentially informative studies were in Italian, of which neither abstract nor full text were available in English, 4 German, 3 French (2 only abstracts and 1 unavailable) amongst several others including Norwegian, Thai and Russian. None of these papers appeared to report randomized–controlled trials.

Our search of clinical trials registries identified 1 potentially relevant ongoing study: an open label trial comparing ampicillin–cloxacillin and ceftriaxone for empirical treatment of infective endocarditis in a hospital in Japan, although it is not explicitly stated that ampicillin–cloxacillin is given as an FDC.[21]

4 | DISCUSSION

Given the high levels of use of antibiotic FDCs such as ampicillin–cloxacillin, including in the absence of relevant regulatory approvals,[3] it is critical to evaluate their efficacy and safety. Our literature review highlights the paucity of the literature in 1 of the most commonly used FDCs. It is unclear from the available data for which indications most FDCs are being used.

Although we did not aim to review the use of ampicillin–cloxacillin in routine practice, the studies identified were conducted in very specific indications, such as surgical prophylaxis and may not reflect the indications for which this FDC is used more generally (e.g. more common clinical scenarios such as skin and soft tissue infections). There are also very limited data in the older studies of the rationale for the dosing regimen used, while a range of dosing regimens may be available for the FDC in different countries. Most commonly, no formal safety data have been submitted for registration to the relevant competent authorities and, as no summary of product characteristics is available, this has not been updated regularly as new data have been published.

This literature review also highlights difficulties in accessing some potentially informative literature, particularly older studies and those published in non-English language journals. Searching of other databases may also have yielded further results. In addition, national regulatory agencies may have access to further efficacy and safety data submitted by manufacturers applying for regulatory approval, which must also be considered in any assessment of the utility of antibiotic FDCs.

Despite the lack of evidence on FDC antibiotics, there is a need for appropriate FDC formulation for treatment. In 2018, the Indian

government took a courageous decision to ban 328 FDCs in the Indian market. Their determination to tighten regulation on inappropriate FDC formulations is a role model for other countries to follow.[22] It is important to strengthen regulatory system to manufacture appropriate FDCs for clinical treatment.

5 | CONCLUSION

To fully assess the efficacy and safety of ampicillin–cloxacillin and other FDCs, a standardised search format, including data on current use, efficacy, dosing and safety, would be required for both national and international approaches. In addition, prospective and retrospective evaluation of evidence is needed at each national level. The rationale for using FDC antibiotics should be further explored and require studies to assess their efficacy, safety, and potential to accelerate antimicrobial resistant. This should include broad international collaboration, including contacting the relevant international regulatory authorities. Furthermore, international initiatives are needed to regulate the manufacturing and sales of these antibiotics. The next step would be an assessment of the most frequently used FDCs internationally and the development of a common protocol for their formal assessment.

COMPETING INTERESTS

The authors declare no conflict of interest.

CONTRIBUTORS

Y.F. and M.S. contributed to the concept. B.S., B.B. and Y.F. designed the search strategy and selection criteria. All authors contributed to the interpretation of the data. B.S. wrote the first draft of the manuscript. All authors reviewed and contributed to subsequent drafts and essential revisions of the manuscript. The corresponding author confirms that she had full access to all the data in the data and had final responsibility for the decision to submit the manuscript for publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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