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Review article

Current antibiotics for leptospirosis: Are still effective?

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ABSTRACT

Leptospirosis is a recurring zoonotic disease of global significance. Leptospirosis is curable, and antibiotics are available for its treatment. However, little is known about the effectiveness of the currently used antibiotics against different *Leptospira* species, serovars, and strains. This review aimed to give insight into the anti-leptospiral activities of the currently available antibiotics towards *Leptospira* strains and their effectiveness in treating and preventing leptospirosis. Anti-leptospiral activities from natural resources were also reviewed. The literature search was conducted using several databases. The majority of *Leptospira* strains were sensitive to the current antibiotics. Antibiotics can accelerate the defervescence and reduced the occurrence of leptospirosis cases, nevertheless, there is no affirmative evidence on the beneficial effects of the antibiotics compared to placebo in preventing death. Adverse reactions like Jarisch-Herxheimer reactions (JHR) in patients treated with the current antibiotics were also reported. Plants, marine actinobacteria and propolis are shown as potential sources of new anti-leptospiral compounds. Although leptospirosis can still be adequately treated with current antibiotics, continuous susceptibility testing and the development of novel antibiotics especially from natural resources are highly encouraged.

1. Introduction

Leptospirosis is an infectious and re-emerging zoonotic disease of global importance. Based on the systemic review of morbidity and mortality studies conducted in 2015, the global estimate of annual leptospirosis cases and deaths is 1.03 million and 58,900, respectively [1]. Leptospirosis is globally prevalent; however, it is more common in regions with humid subtropical and tropical climates. Several countries reported fewer leptospirosis cases during the COVID-19 pandemic, particularly in 2020 [2–4]. This could be due to the changes in the population's behavior and low surveillance activities. However, the number was shown to increase in 2021 [2] with cases of severe disease [5] and death [6]. A leptospirosis outbreak was also reported in Australia in early 2021 [7]. Studies in Maceio, Alagoas [8] and Probolinggo, Indonesia [9] also show a rise in number of cases in 2022.

Leptospirosis is curable; however, the non-specific clinical presentations at the early stage of the disease and the rapid progression from mild to severe challenge the accurate diagnosis and administration of appropriate treatment [10,11]. While mild disease is self-limited with a non-specific flu-like illness, which could resolve without treatment, severe disease requires appropriate treatment and could be fatal [12]. The broad spectrum of clinical presentations in leptospirosis is associated with the host's immune status as well as the different infecting *Leptospira* species, serovars and strains [13–15]. Currently, the genus *Leptospira,* the causative agent of

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leptospirosis, comprises 73 species and over 300 serovars [16–22]. It is inarguable that *Leptospira* species, serovars and strains exhibit varying levels of virulence and disease severity not only in humans but also in animals [23,24]. The different *Leptospira* species and strains have implications in the variable clinical presentations and diagnosis regime. The most commonly used test for diagnosing leptospirosis is the microscopic agglutination test (MAT) assay [25], which needs a panel of serovars representing international and local serovars. The list of *Leptospira* panels could differ from one setting to another, mainly depending on the seroprevalence patterns in the community in specific geographical locations [26,27].

It is known that the diversity of *Leptospira* species, serovars, and strains influence disease severity and diagnosis regime. However, not much is known about the effectiveness of the currently available antibiotics against different *Leptospira* species, serovars and strains. Therefore, this review intends to elucidate the present status of the susceptibility of *Leptospira* strains against the commonly used antibiotics and their effectiveness in treating and preventing human leptospirosis. Moreover, it explores the efforts performed to search for new anti-leptospiral drugs from natural resources.

2. Literature search

A literature search on leptospirosis and antibiotics was performed using the terms "Leptospirosis," "*Leptospira*," "Drug," "Antibiotic," "Treatment," "Prophylaxis," "Adverse reaction," "Plant," and "Antileptospiral" in Web of Sciences (WOS), PubMed, Cochrane Library, and Google Scholar databases. The literature was searched without limiting the language or publication date. Other publications, wherever appropriate, such as non-indexed local journals, bulletins, newspapers, and clinical cases, were also included. Further relevant publications that may not have been found during the initial search were identified in the reference lists of the retrieved articles.

3. Result

3.1. Current treatment options for leptospirosis

Generally, patients with leptospirosis are treated with antibiotics that act directly against the infecting *Leptospira,* along with supportive therapies to mediate the effect of infection. For antibiotic therapy, a range of broad-spectrum antibiotics such as doxycycline, azithromycin, erythromycin, penicillin G, cefotaxime, ceftriaxone, ampicillin, and amoxicillin are used [28–32]. These antibiotics were originally developed to treat other bacteria and act by either inhibiting their growth (bacteriostatic) or directly killing them (bactericidal).

The bacteriostatic antibiotics are erythromycin, doxycycline and azithromycin, which inhibit bacterial protein synthesis. Erythromycin, a natural antibiotic discovered in 1952, binds to the 23S rRNA of the bacterial 50S ribosomal subunit [33]. Doxycycline is a semisynthetic compound under the tetracycline group that has been available since 1967 [34]. Doxycycline binds to the 16S rRNA molecule of the bacterial ribosome and inhibits the binding of aminoacyl-tRNA to the mRNA-ribosome complex [35,36]. Besides its bacteriostatic action, doxycycline was also reported to possess immunoregulatory activity as it was able to decrease the expression of IL-1β in mouse macrophages infected with *L. interrogans* serovar Lai strain Lai (56601) through the suppression of p38, JNK, p65, and NLRP3 inflammasome priming [37]. Severe leptospirosis in the hamster model had been associated with high-level expression of IL-1β [38]. Azithromycin, a semisynthetic antibiotic, was approved for medical use in 1988. Similar to erythromycin, it inhibits bacterial protein synthesis by targeting the 50S subunit of bacterial ribosome [39]. Azithromycin was also reported to have anti-inflammatory properties by reducing the expression of several cytokines, such as TNF-α [40] and IL-1β [41].

Penicillin, ampicillin, amoxicillin, cefotaxime and ceftriaxone are bactericidal antibiotics. These antibiotics bind to penicillin-binding proteins (PBPs), which are enzymes responsible for constructing the bacterial cell wall. This binding leads to cell wall lysis and the destruction of the bacterial cell [42,43]. Penicillin, the first natural antibiotic, was discovered in 1928 [44]. Ampicillin and amoxicillin were discovered in 1958 [45,46]. Both are semisynthetic antibiotics and were developed to overcome the issue of antibiotic resistance. Cefotaxime and ceftriaxone are both semisynthetic antibiotics in the third-generation class of cephalosporins [47,48]

Table 1
Treatment regimen for human leptospirosis.

	Mild disease	Severe disease
Clinical signs and symptoms	Non-specific flu-like illness with fever, chills, myalgia and headache	Fever, renal failure, jaundice, hemorrhage, respiratory distress
Cytokine level	Low	High, "cytokine storm"
Treatments	**Antibiotic therapy**	**Antibiotic therapy**
	- Doxycycline - Ampicillin - Amoxicillin - Azithromycin - Erythromycin	- Intravenous penicillin - Ceftriaxone - Cefotaxime **Supportive care** - Renal replacement therapy - Ventilatory support - Fluid and electrolyte therapy

and were commercially approved for use in 1980 [49] and 1984 [50].

The choice of antibiotics for the treatment of leptospirosis depends on the disease severity (Table 1) [28,51–53]. Patients with mild symptoms are usually treated with doxycycline and other alternative options such as ampicillin, amoxicillin, azithromycin, or erythromycin. For severe disease, intravenous penicillin, ceftriaxone and cefotaxime are the drugs of choice. It is critical to administer the antibiotics early as their usage after the appropriate treatment period can worsen the disease [54]. Supportive care, such as renal replacement therapy, ventilatory support, fluid and electrolyte therapy are also used to manage severe disease [28,51].

3.2. *In-vitro susceptibility of Leptospira spp. against current antibiotics*

The currently used antibiotics are not specifically developed for the treatment of leptospirosis; hence, it is important to review the ability of these antibiotics to inhibit the *in-vitro* growth of *Leptospira*. A total of 20 studies (Table 2) conducted from 1945 to 2022 reported the anti-leptospiral activities of the currently used antibiotics against *Leptospira* strains. The most frequently tested antibiotics were penicillin and doxycycline. All of these studies showed that most of the *Leptospira* strains tested were susceptible to the current antibiotics used to treat leptospirosis (Table 2). Cefriaxone, cefotaxime, and erythromycin showed excellent anti-leptospiral activity as the tested *Leptospira* strains were highly susceptible with a minimum inhibitory concentration (MIC) value of less than 2 μg/mL [55–57,59,63–65,67,68,70]. Penicillin, ampicillin, and doxycycline were also able to inhibit the growth of the tested *Leptospira* strains with high MIC values (12.5–250 μg/mL) in some studies [60,61,67]. Among the tested *Leptospira* species, *L. kirschneri* had high MICs (12.5–25 μg/mL) for penicillin [60,67] and ampicillin [60]. In one earlier study, serovars Icterohaemorrhagiae (strain Buckland) and Samarang were reportedly resistant to penicillin [72].

3.3. *Efficacy and safety of antibiotics in treatment and prevention of leptospirosis*

3.3.1. *Effectiveness of antibiotics to treat and prevent leptospirosis*

A powerful drug for human treatment should not only based on the ability of the antibiotic to inhibit the leptospiral growth *in-vitro*, but also effective in treating and preventing disease in human. Hence, it is crucial to do a continuous investigation and monitoring on the efficacy of antibiotics in human leptospirosis. Several studies have investigated the effectiveness of antibiotics in treating leptospirosis (Table 3). Most of these studies specifically examined their effects on patients with severe forms of the disease. Penicillin was the most commonly tested antibiotic. Some studies [32,75,82,83,86] reported that it reduced the duration of illness; however, other studies [78,79] found no significant difference between treated and untreated groups. In terms of recovery, few patients still died despite penicillin treatment [31,75–78,81]. Similar to penicillin, although studies reported total recovery [85,86] and reduced duration of illness of patients [86], one study also reported death [77] in patients treated with doxycycline. Treatment with ceftriaxone also did not successfully ensure the recovery of all patients [31,84]. In contrast, treatment with cefotaxime [77] and azithromycin [85] resulted in complete recovery for all patients.

Nine studies (Table 4) assessed the effectiveness of antibiotics in preventing leptospirosis after exposure to different risk factors of leptospirosis. Prophylaxis antibiotics did not prevent the occurrence of leptospirosis, but some studies showed a reduction in number of cases. Doxycycline reduced the occurrence of leptospirosis in six studies [88,90,91,93,95], with statistically significant differences in three studies [88,91,95]. Doxycycline was also reported to reduce disease severity in one study [87]. However, other studies showed no difference between the two groups, with some even reporting a higher occurrence of leptospirosis in the group that took prophylaxis [89]. Despite not being statistically significant, the group of people who took prophylaxis penicillin also had a low number of leptospirosis occurrences [92,96].

3.3.2. *Adverse reaction*

Besides the ability to kill or inhibit the growth of harmful pathogens in various sites of infection, an ideal antibiotic should also exhibit little or no toxicity and side effects on the host cells. In leptospirosis, studies have reported that some patients experienced adverse reactions after treatment with antibiotics (Table 5). Penicillin was the most frequently reported antibiotic that caused adverse reactions (Table 5). Most patients have Jarisch_Herxheimer reactions (JHR) characterized as rashes, chills, a rise in temperature, headaches, and gastrointestinal reactions (diarrhea, vomiting, nausea, and abdominal discomfort) after a few hours of antibiotics administration. Tachycardia and tachypnea were also observed in some patients [97,99,112]. Majority of the patients with JHR recovered after days of treatment; however, two patients treated with penicillin [101] and ceftriaxone [111] died.

3.4. *Effort to discover new anti-leptospiral drugs from natural resources*

3.4.1. *Plants*

Plants have been studied for their medicinal properties, including anti-microbial, antioxidant, and anti-inflammatory properties. Plants are equipped with an array of effective defense mechanisms. The search for anti-leptospiral drugs from natural compounds has been performed for over a decade (Table 6). Most of the studies were performed in India (10 studies) and Malaysia (four studies), where leptospirosis is endemic [132]. Each of these studied plants was selected for its history of use in treating human diseases and ailments, as well as its availability or abundance in specific regions. Most of these plants exhibit activities against *Leptospira* with MIC ranging between 50 and 800 μg/mL (Table 6). *Phyllanthus amarus* [56,117,123,128] and *Eclipta alba* [123,128,130] were the most frequently studied plants. Several studies have identified and performed the anti-leptospiral activities of the purified compound from *Phyllanthus amarus*, *Caesalpinia bonducella, Glyptopetalum calocarpum*, and *Garcinia mangostana*. The purified compounds have lower

Table 2
Susceptibility of leptospires to the currently available antibiotics for treatment of leptospirosis.

No.	*Leptospira* species/serovars	Penicillin G (μg/mL)	Penicillin V (μg/mL)	Ampicillin (μg/mL)	Amoxicillin (μg/mL)	Cefriaxone (μg/mL)	Cefotaxime (μg/mL)	Azithromycin (μg/mL)	Doxycycline (μg/mL)	Erythromycin (μg/mL)	Countries	References
1.	*L. interrogans* (Australis, Bataviae, Canicola, Javanica)	0.01–0.88	–	–	0.03–1.22	0.06–0.77	–	0.43–4.12	0.41–4.02	–	Nigeria	[55]
2.	*L. interrogans* (Australis, Bataviae, Canicola, Javanica)	<0.01–0.78	–	–	–	0.05–0.78	–	–	0.39–3.13	–	Malaysia	[56]
3.	*L. interrogans* (Australis, Bataviae, Canicola and Javanica)	0.39	–	–	–	0.20	–	–	3.13	–	Malaysia	[57]
4.	*L. santarosai* (Shermani, Sejroe, Tarassovi, Grippotyphosa, Sarmin)	0.01–0.78	–	–	–	–	–	–	0.39–6.25	–	Brazil	[58]
	L. noguchii (Australis, Autumnalis, Panama)	0.01–0.1	–	–	–	–	–	–	0.2–12.5	–		
	L. interrogans (Sejroe)	0.02	–	–	–	–	–	–	0.2–0.39	–		
5.	*L. borgpetersenii* (Tarrassovi, Sejroe)	0.8–1.2	–	–	1–1.1	0.6–1.1	–	–	0.6–1.7	–	France	[59]
	L. interrogans (Pomona, Sejroe, Australis)	0.9–1.3	–	–	1–1.1	0.7–1.2	–	–	0.6–1.5	–		
	L. noguchii (Panama, Australis, Pyrogenes)	0.9–1.4	–	–	1–1.1	0.7–1.3	–	–	0.5–1.5	–		
6.	*L. borgpetersenii* (Javanica)	0.1–0.2	–	0.05–0.2	–	–	–	–	0.39–1.56	–	Malaysia	[60]
	L. interrogans (Bataviae, Canicola, Pomona, Ricardi)	≤0.01–0.39	–	0.02–0.2	–	–	–	–	>0.2–3.13	–		
	L. kmetyi	0.2	–	0.1	–	–	–	–	3.13	–		
	L. kirschneri	25	–	25	–	–	–	–	3.13	–		
7.	Manhao, Australis, Akiyami, Bangkinang, Bataviae, Canicola, Hebdomadis, Icterohaemorrhagiae, Copenhageni, Pomona, Pyrogenes, Grippotyphosa, Cynopteri, Ballum, Javanica, Sejroe, Lousiana, Celledoni, Andamana, Semaranga, G3, RIR, RR5U, Autumnalis N2	31.7–62.5	–	–	–	–	–	–	250	–	India	[61]
8.	*L. interrogans* (Copenhageni, Canicola, Pomona)	0.13	–	0.25	–	–	–	–	–	–	Brazil	[62]
	L. santarosai (Bananal)	0.13	–	0.25	–	–	–	–	–	–		
	L. borgpetersenii	0.13	–	0.25	–	–	–	–	–	–		
	L. meyeri	1	–	0.5–1	–	–	–	–	–	–		
9.	*L. interrrogans* (Copehenhageni, Mankarso, Icterohaemorrhagiae)	0.05–0.1	–	–	0.05–0.1	0.05–0.20	–	–	0.01–6.25	0.01–0.39	Trinidad	[63]
10.	*L. interrrogans* (Australis, Bankinang I, Canicola, Icterohaemorrhagiae, Hebdomadis, Pomona, Pyrogenes, Bataviae, Djasiman, Hardjo)	≤0.02	–	≤0.02	≤0.02	≤0.02	≤0.02	≤0.02	6.25	≤0.02	India	[64]

(*continued on next page*)

Table 2 (*continued*)

No.	*Leptospira* species/serovars	Penicillin G (μg/mL)	Penicillin V (μg/mL)	Ampicillin (μg/mL)	Amoxicillin (μg/mL)	Cefriaxone (μg/mL)	Cefotaxime (μg/mL)	Azithromycin (μg/mL)	Doxycycline (μg/mL)	Erythromycin (μg/mL)	Countries	References
	L. borgpetersenii (Ballum, Mini, Tarassovi)	≤0.02	–	≤0.02	≤0.02	≤0.02	≤0.02	≤0.02	6.25	≤0.02		
	L. noguchii (Louisiana, Panama)	≤0.02	–	≤0.02	≤0.02	≤0.02	≤0.02	≤0.02	6.25	≤0.02		
	L. weilii (Celledoni, Sarmin)	≤0.02	–	≤0.02	≤0.02	≤0.02	≤0.02	≤0.02	6.25	≤0.02		
	L. kirschneri (Cynopetri, Grippotyphosa)	≤0.02	–	≤0.02	≤0.02	≤0.02	≤0.02	≤0.02	6.25	≤0.02		
	L. santarosai (Manhao, Shermani)	≤0.02	–	≤0.02	≤0.02	≤0.02	≤0.02	≤0.02	6.25	≤0.02		
	L. fainei (Hurstbridge)	≤0.02	–	≤0.02	≤0.02	≤0.02	≤0.02	≤0.02	6.25	≤0.02		
	L. biflexa (Patoc)	≤0.02	–	≤0.02	≤0.02	≤0.02	≤0.02	≤0.02	6.25	≤0.02		
11.	*L. interrrogans* (Bataviae, Grippotyphosa, Icterohaemorrhagiae, Pomona, Pyrogenes)	<0.016–0.06	–	<0.016	–	<0.016–0.06	<0.016–0.03	<0.016	1–2	–	Egypt	[65]
	L.interrrogans	0.06	–	<0.016	–	0.06	0.03	<0.016	0.25	–	Thailand	[65]
	L. weilii	0.03–0.06	–	<0.016	–	0.06–0.03	0.03	<0.016	0.50	–		
	L. interrrogans (Icterohaemorrhagiae)	<0.016	–	<0.016	–	<0.016	<0.016	<0.016	0.25–0.50	–	Hawaii	[65]
12.	*L. kirchneri* (Grippotyphosa)	–	–	–	3.13	–	–	–	–	–	North America	[66]
	L. interogans (Pomona, Canicola, Icterohaemorrhagiae)	–	–	–	0.78–1.56	–	–	–	–	–		
13.	*L. biflexa* (Andamana, Patoc)	6.25	–	0.78	3.13	≤0.01–0.1	≤0.01–0.1	≤0.01	0.05–0.78	≤0.01	United States	[67]
	L. borgpetersenii (Ballum)	0.78	–	0.39	0.39	0.1	≤0.01	≤0.01	0.39	≤0.01		
	L. interrogans (Australis, Autumnalis, Bataviae, Bratislava, Canicola, Copenhageni, Djasiman, Grippotyphosa, Hardjo, Hebdomadis, Icterohaemorrhagiae, Mankarso, Pomona, Pyrogenes, Wolfii)	0.1–6.25	–	≤0.01–0.78	≤0.01–1.56	≤0.01–0.39	≤0.01–0.05	≤0.01–0.05	0.1–0.78	≤0.01		
	L. kirschneri (Butembo, Cynopteri)	12.5–25	–	1.56–3.13	3.13	0.2–0.78	0.1	≤0.01–0.05	0.2–1.56	≤0.01		
	L. noguchii (Fortbragg)	0.1	–	0.05	0.1	≤0.01	≤0.01	≤0.01	0.39	≤0.01		
	L. santarosai (Alexi, Borincana, Georgia, Shermani)	0.1–3.13	–	0.05–0.78	0.02–0.78	0.1–0.39	≤0.01–0.05	≤0.01	0.2–3.13	≤0.01		
	L. weilii (Celledoni)	1.56	–	0.78	0.78	0.1	0.05	≤0.01	0.2	≤0.01		
14.	*L. biflexa* (Patoc)	0.20	–	0.10	0.20	≤0.01	0.05	≤0.01	0.78	≤0.01	United States	[68]
	L. borgpetersenii (Ballum, Sejroe)	0.05–0.39	–	0.05–0.20	≤0.01–0.20	0.02–0.05	≤0.01	≤0.01–0.02	0.78	≤0.01		
	L. interrogans (Copenhageni, Grippotyphosa, Icterohaemorrhagiae, Pomona)	0.39–3.13	–	0.05–0.20	0.05–0.20	≤0.01–0.02	≤0.01–0.02	≤0.01–0.05	0.78–3.13	≤0.01		

(*continued on next page*)

Table 2 (*continued*)

No.	*Leptospira* species/serovars	Penicillin G (μg/mL)	Penicillin V (μg/mL)	Ampicillin (μg/mL)	Amoxicillin (μg/mL)	Cefriaxone (μg/mL)	Cefotaxime (μg/mL)	Azithromycin (μg/mL)	Doxycycline (μg/mL)	Erythromycin (μg/mL)	Countries	References
	L. kirschneri (Butembo)	0.78	–	0.10	0.02	0.20	0.05	≤0.01	0.10	≤0.01		
	L. noguchi (Fortbragg)	0.20	–	0.05	0.05	≤0.01	≤0.01	≤0.01	1.56	≤0.01		
	L. santarosai (Alexi)	3.13	–	0.78	0.10	0.20	0.01	≤0.01	3.13	≤0.01		
	L. weilii (Celledoni)	0.20	–	0.02	0.02	0.10	0.05	≤0.01	0.39	≤0.01		
15.	18 isolates of *Leptospira* hardjo	≤0.78	–	≤0.01	–	–	–	–	–	≤0.78	Canada	[69]
16.	Copenhageni, Canicola, Autumnalis, Illni, *L. biflexa,*	0.2–3.13	0.2–6.25	0.025–0.78	–	–	0.05–1.56	–	–	–	Japan	[70]
17.	Icterohaemorrhagiae, Canicola, Zanoni	2 x $l0^3$–2 x $l0^4$ g/mL[a]	–	–	–	–	–	–	–	2×10^{11} g/mL[a]	Australia	[71]
	Robinsoni, Australis, Esposito, Pomona, Grippotyphosa, Medanensis, Kremastos, Mini, Hyos	2 x $l0^7$–2 x $l0^8$ g/mL[a]	–	–	–	–	–	–	–	2×10^{11} g/mL[a]		
18.	Icterohaemorrhagiae (A, AB, Vady, Cockburn, Wijnberg) Grippotyphosa, Canicola, Sejroe, Djasiman, Batavice, Pomona, Australis a, Poi, Sari, Pyrogenes, Hebdomadis, L. Hc, 3705, Autumnalis, Rachmat, Sentot, Australis b, Naam, Benjamin, Javanica, 90 c, Andarnana	0.5 unit per mL	–	–	–	–	–	–	–	–	England	[72]
	Icterohaemorrhagiae (Buckland), Samarang	Resistant	–	–	–	–	–	–	–	–		
19.	Icterohaemorrhagiae	5000 o.u. per mL	–	–	–	–	–	–	–	–	United States	[73]
20.	Icterohaemorrhagiae, Canicola, Sejroe, Saxkoebing	≥0.25 p.D. U/c. c.	–	–	–	–	–	–	–	–	Denmark	[74]

Note.

[a] The highest dilution of the antibiotics that inhibit the growth of leptospires.

Table 3
The outcome of antibiotics treatment in human leptospirosis.

No.	Antibiotic	Type of leptospirosis	Treatment groups	Outcomes	Recovery period/ Hospital stay	Countries	References
1.	Penicillin	Acute renal failure	6 million units/ day vs. placebo	– 88.4 % of patients survived and recovered (11.6 % deaths) in the treated group – 86.3 % of patients survived and recovered (13.7 % deaths) in the placebo group *Penicillin treatment decreased the duration of hospitalization and minimized complications.	8·4 ± 5·0 (1–24) 1 ± 7·7 (1–38)	Brazil	[75]
		Icteric	12 million units/ day	– 68.7 % of patients recovered without any complication – 25 % of patients died of hepatic and/ or renal failure – 6.25 % of patients had chronic renal failure and underwent regular hemodialysis	15 ± 9 (1–26)	Turkey	[76]
		Severe	1.5 million units/ 6 h	– 96.2 % of patients recovered – 3.8 % died of multiorgan and respiratory failures	3 (1–10)	Thailand	[77]
		Severe and late stage (after at least 4 days of symptoms)	6 million units/ day (1 million units/4h) vs. no antibiotic	– 88 % of patients survived (12 % deaths) in penicillin treated group – 93.7 % of patients survived (6.3 % deaths) in the non-treated group *Penicillin at the late stage of leptospirosis was not beneficial. *Death was due to respiratory, acute renal, and multiple organ failures	9.4 ± 3.5 9.0 ± 3.4	Brazil	[78]
		Severe	1.5 million units/ 6 h	94.2 % of patients survived (5.8 % deaths) - Death was due to pulmonary hemorrhage, multiorgan failure, severe hyperkalemia, uremic encephalopathy, and acute respiratory distress syndrome	Unclear	Thailand	[31]
		Acute renal failure and icteric	6 million units/ day vs. no antibiotic	– 93.8 % of patients survived (6.2 % deaths) in penicillin treated group – 100 % survived in non-treated group *Penicillin therapy did not yield improved clinical results in patients with leptospirosis.	12 ± 6 (2–16) 11 ± 5 (2–16)	Brazil	[79]
		Acute renal failure and icteric	100,000 units/kg of body weight/ day vs. no antibiotic	Antibiotics benefit children with late, severe leptospirosis	Unclear	Brazil	[80]
		Icteric	2 million units/ 6h vs. placebo	– 97.4 % of patients survived (2.6 % deaths) in penicillin treated group – 92.7 % of patients survived (7.3 % deaths) in the placebo group *Penicillin exerts minimal influence on clinical outcomes in icteric leptospirosis	Unclear	West Indies	[81]
		Severe and late	1.5 million units/ 6 h v. placebo	- All patients in the treated group recovered - All patients in the placebo group recovered *Intravenous penicillin must be administered to patients with severe leptospirosis, regardless of whether treatment can commence late in the progression of their illness	4.7 ± 4.19 11.6 ± 8.34	Philippines	[32]
		Mild and severe	600,000 units/6 h vs. no antibiotic	- All patients in the treated group recovered - All patients in the placebo group recovered * No substantial difference exists between the treated group and the untreated group	9.7 10.8	Malaya	[82]

(*continued on next page*)

Table 3 (*continued*)

No.	Antibiotic	Type of leptospirosis	Treatment groups	Outcomes	Recovery period/ Hospital stay	Countries	References
		Unclear	100,000 units/3 h; 500,000 units/ 3 h vs. no antibiotic	A shorter duration of fever in patients given with a larger dosage of penicillin	5.2	Australia	[83]
2.	Cefotaxime	Severe	1 g/6 h	All patients recovered	3 (1–8)	Thailand	[77]
3.	Ceftriaxone	Severe and late	2 g/day	– 95.5 % of patients recovered – 4.5 % of patients died due to respiratory complications	14	Greece	[84]
		Severe	1 g/day	– 94.3 % of patients survived – 5.7 % deaths	Unclear	Thailand	[31]
4.	Azithromycin	Mild/late	1 g initially followed by 500 mg/day	All patients recovered	0.3–5.6	Thailand	[85]
5.	Doxycycline	Mild/late	200 mg as the first dose, followed by 100 mg/12 h	All patients recovered	0.3–5	Thailand	[85]
		Severe	200 mg first dose followed by 100 mg/12 h	– 96 % of patients recovered – 3.8 % died of multiorgan and respiratory failures	3 (1–11)	Thailand	[77]
		Unclear	100 mg/12 h vs. placebo	All patients recovered	2 days of illness reduction in the treated group	United States	[86]

Table 4
The outcome of prophylaxis antibiotics in human leptospirosis.

No.	Reference	Countries	Group of people	Antibiotics	Dosage	Outcomes	
						New Symptomatic Cases (%)	Seroconversion (%)
1.	[87]	Japan	US marines involved in training exercise	Doxycyline	200 mg/week	100	NA
				No antibiotic	–	100	NA
2.	[88]	India	People exposed to flood	Doxycycline	NA	2.6	NA
				No antibiotic	NA	23.4 (p = 0.023)	NA
3.	[89]	Iran	Paddy field workers (from 18 to 65 years)	Azithromycin	500 mg/week	3	IgM: 3 IgG: 7.6
				Doxycycline	200 mg/week	12.6	IgM: 12.6 IgG: 11.3
				Placebo	–	4	IgM: 4 IgG: 24 (p = 0.03)
4.	[90]	Thailand	People exposed to flood water (18 years and above)	Doxycycline	200 mg single dose	0.7	2.8
				No antibiotic	–	4.9	12.2
5.	[91]	India	Paddy field farmers	Doxycycline	200 mg/week	0	NA
				No antibiotic	–	7.29 (p = 0.0167)	NA
6.	[92]	Sri Lanka	Healthy persons (male farmers, 20–80 years)	Oral Penicillin	500 mg/bid	0	NA
				Placebo	–	1	NA
7.	[93]	India	Healthy persons (>10 years old)	Doxycycline	200/week	3.1	29
				Placebo	–	6.82	25.5
8.	[94]	Brazil	People living in area at high risk for flooding	Doxycycline	200 mg single dose	5	IgM: 32.5
				Placebo	–	11.9	IgM: 26.2
9.	[95]	Panama	Healthy volunteers from two U.S. Army units	Doxycycline	200 mg weekly	0.2	NA
				Placebo	–	4.2 (p = 0.001)	NA
10.	[96]	Spain	Rice reapers	Penicillin procain	100,000 U/12 h vo	0	NA
				Control	–	1.3	NA

MIC values [117,118,124,129] compared to the crude extracts. The scanning electron microscope (SEM) analysis revealed that the plants' extracts caused significant structural changes in the morphology of *Leptospira,* such as less coiling and irregular shape [55,56, 120], the disintegration of the hooked ends and several breaks at different locations along the lengthy cell of leptospires [126]. An *in-vivo* study reported that the pre-treatment of Astragalus polysaccharides (APS), a natural molecular compound extracted from *Astragalus membranaceus* roots, enhanced the survival rate of hamsters infected with *L. interrogans* serovar Lai strain Lai (56601), underscoring the potential of this compound as a therapeutic agent for leptospirosis [133].

Table 5
Adverse reaction of antibiotics treatment in human leptospirosis.

No.	Antibiotics	Adverse effect	Study design	Delay before adverse reactions (h)	Outcome	Country	References
1.	Penicillin	Unconsciousness, fever, rigor, increasing tachycardia, hypotension, tachypnea	Case report (n = 1)	2.5	Discharged	China	[97]
		Increase in fever, rigors, severe headache	Case report (n = 1)	1	Discharged	American Samoa	[98]
		Tachypnea, tachnycardia, hypertension, severe rigors	Case report (n = 1)	2	Discharged	Australia	[99]
		Headache, photobia, nuchal rigidity	Case report (n = 1)	8	Unknown	France	[100]
		Increase in fever, hypotension	Case series (n = 2)	4–5	Died (n = 1)	Ireland	[101]
		Fever, chills, hypotension, respiratory distress	Case report (n = 1)	Few hours	Discharged	USA	[102]
		Severe rigor, hypotension, abdominal pain, headache, fever, profuse vomiting	Case series (n = 2)	4–5	Discharged	UK	[103]
		Sharp rise in temperature, rigor	Case series (n = 3)	Unknown	Discharged	UK	[104]
		Fever, aggravation of classic symptoms, hypotension, oligo-anuric	Case series (n = 70)	Unknown	Discharged	Malaysia	[105]
		Rigor, fever, weakness, low blood pressure	Case report (n = 1)	2.5	Discharged	Scotland	[106]
2.	Ampicillin	Rigors, hypotension	Case series (n = 6)	Unknown	Unknown	Japan	[107]
3.	Amoxicillin	Shivering/rigors with the rise in temperature, fall in blood pressure, rise in blood pressure, an increase in respiratory rate	Observational retrospective study (n = 55/262)	2–5	Unknown	France	[108]
		Headache, hypotension, tachycardia, fever, nuchal rigidity	Case report (n = 1)	4	Discharged	France	[109]
4.	Ceftriaxone	Nausea, vomiting, hypotension,	Case report (n = 1)	2	Discharged	Singapore	[110]
		Hypotension, disorientation, shivering chills	Case report (n = 1)	3	Died	Japan	[111]
		Tachycardia, hypotension, tachypnea	Case report (n = 1)	1–2	Discharged	USA	[112]
		Rigors, chills, fever, skin rash	Case report (n = 1)	2	Discharged	Japan	[113]
		Tachycardia, tachypnea, hypertension, severe rigors	Case report (n = 1)	2	Discharged	Australia	[99]
		Pulmonary deterioration	Case report (n = 1)	2	Discharged	Japan	[114]
5.	Doxycycline	Tachycardia, hypotension, tachypnea	Case report (n = 1)	1–2	Discharged	USA	[112]
		Nausea, vomiting, diarrhea, abdominal pain, skin rash, dizziness	Randomized control trial (n = 40)	NA	Discharged	Thailand	[85]
6.	Azithromycin	Nausea, vomiting, diarrhea, skin rash	Randomized control trial (n = 16)	NA	Discharged	Thailand	[85]

3.4.2. Marine actinobacteria

Marine microorganisms are a valuable source of novel and potential bioactive metabolites of considerable interest. Marine actinobacteria are Gram-positive bacteria that fulfill crucial roles in several ecological and medicinal settings [134,135]. Filamentous actinobacteria, particularly *Streptomyces* species, are prevalent makers of bioactive chemicals, generating 39 % of all microbial metabolites [136]. Marine *Streptomyces* are prominent producers of numerous bioactive chemicals utilized in the medical and pharmaceutical sectors as potent therapeutics for various ailments [137]. Actinomycetes have been a rich source of novel antibiotics, including major anti-microbial classes like tetracyclines, β-lactams, rifamycins, macrolides, aminoglycosides, and glycopeptides [138].

The crude extract of marine actinomycetes, *Streptomyces indiaensis* strain MSU5, was reported to have anti-leptospiral activity against leptospires with MIC values varying between 125 and 500 μg/mL [61,131] (Table 6). The active compound isolated from the crude extract, MSU5-1, had a remarkable anti-leptospiral activity against *L. interrogans* serovar Autumnalis strain N2 with MIC as low as 62.5 μg/mL [61]. An *in-vivo* investigation using mice infected with *L. interrogans* serovar Autumnalis strain N2 demonstrated that MSU5-1 might reduce leptospiral proliferation, resulting in an 80 % survival rate [61]. According to the spectrum analysis, the active anti-leptospiral compound MSU5-1 was identified as leptomycin B and possesses a fatty acid functional group [61]. Fatty acids function as mild surfactants that disrupt bacterial cell membranes, leading to partial solubilization that might hinder metabolic control and cellular energy production, reducing bacterial growth [139].

3.4.3. Propolis

Propolis is a resin-like material made by honey bees, and the resinous and aromatic substances are collected from leaf buds and cracks in tree barks. Propolis is a powerful natural product as it has been proven to contain a broad spectrum of biological activities, such as antiseptic, anti-inflammatory, antitumor, anti-microbial, antifungal, and antiviral properties [140,141]. One study from Malaysia investigated the anti-leptospiral activity of *Trigona thoracica* propolis [57] (Table 6) and found that it could inhibit the growth of leptospires with MIC ranging from 790 to 6250 μg/mL. SEM analysis showed significant structural changes, such as flattened and shortened cells, less spiral and the absent hooks at both ends of the treated *L. interrogans* serovar Australis.

Table 6
Antimicrobial activity from natural resources against leptospires.

No.	Reference	Countries	*Leptospira* sp./serovars	Type of plants	Type of compound	MIC value (μg/mL)
1.	[115]	Philippines	*L. interrogans* (Manilae strain k64)	*Cassia alata* *Momordica charantia*	Crude extract Crude extract	2500 1250
2.	[55]	Nigeria	*L. interrogans* (Australis, Bataviae, Canicola, Javanica)	*Annona senegalensis*	Crude extract	100–800
3.	[116]	Malaysia	*L. interogans* (Bataviae, Canicola, Australis), *L. biflexa* (Patoc)	*Zingiber zerumbet*	Crude extract	3.91–500 (IC_{50})
4.	[56]	Malaysia	*L. interrogans* (Australis, Bataviae, Canicola, Javanica)	*Phyllanthus amarus*	Crude extract	100–800
5.	[117]	India	Icterohaemorrhagiae, Canicola Pomona, Autumnalis, Javanica, Pyrogenes, Australis, Hardjo	*Phyllanthus amarus*	Isolated compound	25 & 100
6.	[118]	India	Pomona, Javanica, Pyrogenes, Australis, Hardjo	*Caesalpinia bonducella*	Isolated compound (β-Sitosterol & Pent-4-enoate)	75
7.	[119]	Malaysia	*L. interrogans* (Bataviae), *L. borgpetersenii* (Javanica)	*Canarium odontophyllum Miq.*	Crude extract	4600 & 2250 (IC_{50})
8.	[120]	Malaysia	*L. interrogans* (Javanica, Icterohaemorrhagiae)	*Quercus infectoria*	Crude extract	125
9.	[121]	India	*L. interrogans* (Australis, Autumnalis, Pomona, Icterohaemorrhagiae), *L. borgpetersenii* (Javanica)	*Andrographis paniculata* Nees	Crude extract	200–800
10.	[122]	India	Ballico, Bankinang 1, Paidjain, Hond utrech-IV, Djasiman, Moskva V, CH-31, Hebdomadis, Pomona, RGA, Salinem, Hardjoprajtno, Poi, Sari, Perepelician, CZ-214-K, 507, 1343-K, Nicalaeva, 3522 C, But-6, Peludo, L-14, Patoc-1	*Boesenbergia rotunda*	Crude extract	62.5–125
11.	[123]	India	*L. interrogans* (autumnalis)	*Phyllanthus amarus* *Eclipta alba*	Crude extract Crude extract	160 320
11.	[124]	India	*L. borgpetersenii* (Poi), *L. interrogans* (Canicola)	*Glyptopetalum calocarpum*	Isolated compound (Lupenone & stigmasterol)	100–200
12.	[125]	India	Australis, Autumnalis, Canicola, Grippotyphosa, Hebdomadis, Icterohaemorrhagiae, Javanica, Pomona, Sejroe, Patoc	*Piper betle* L	Crude extract	200–800
13.	[126]	India	*L. interrogans* (Louisiana)	*Adhatoda vasica*	Crude extract	5000
14.	[127]	Thailand	*L. biflexa* (Patoc), *L. interrogans* (Bataviae, Autumnalis, Saigon, Javanica)	*Garcinia mangostana*	Crude extract Purified xanthones	200– ≥ 800 100– ≥ 800
15.	[128]	Brazil	Icterohaemorrhagiae, Canicola, Pomona, Autumnalis, Javanica, Pyrogenes, Australis, Hardjo	*Eclipta alba* *Phyllanthus amarus*	Crude extract Crude extract	25–100 * No inhibition on the growth of *L. australis* 25–100
16.	[129]	India	Australis, Autumnalis, Ballum, Bataviae, Canicola, Cynopteri, Grippotyphosa, Icterohaemorrhagiae, Javanica, Manhao, Pomona, Pyrogenes, Tarassovi, *L. borgpetersenii* (Javanica) 11 isolates recovered from rodents	*Asparagopsis taxiformis*	Isolated compound	100–400
17.	[130]	India	*L. interrogans* (Australis, Autumnalis, Grippotyphosa, Canicola, Icterohaemorrhagiae)	*Eclipta alba*	Crude extract	50–250
18.	[61]	India	Manhao, Australis, Akiyami, Bangkinang, Bataviae, Canicola, Hebdomadis, Icterohaemorrhagiae, Copenhageni, Pomona, Pyrogenes, Grippotyphosa, Cynopteri, Ballum, Javanica, Sejroe, Lousiana, Celledoni, Andamana, Semaranga, G3, RIR, RR5U, Autumnalis N2 *L. interrogans* (Autumnalis strain N2)	Marine actinobacterial compound from *Streptomyces indiaensis* MSU5	Crude extract Isolated compound (MSU5-1)	125–500 62.5
19.	[131]	India	*L. interrogans* (Autumnalis strain N2)	Marine actinobacterial compound from *Streptomyces indiaensis* MSU5	Crude extract	125
20.	[57]	Malaysia	*L. interrogans* (Australis, Bataviae, Canicola and Javanica)	Propolis from *Trigona thoracica*	Crude extract	790–6250

4. Discussion

Leptospirosis is of global public health significance. The endemicity of this disease in humid subtropical and tropical regions and the continuous discovery of new *Leptospira* strains isolated from various ecological niches and animal species urge the need to constantly monitor the efficiency and effectiveness of the current treatment regimes. The emergence of anti-microbial resistance

(AMR), as seen in some bacterial species [142,143], is a serious global public health problem. It affects treatment strategies by reducing the effectiveness of antibiotics and is linked to longer hospital stays, increased deaths, and higher healthcare costs [143]. Currently, there is little understanding and knowledge of AMR in *Leptospira*. Hence, it is important to have insight into the current susceptibility of leptospires toward the currently available antibiotics. In general, evidence from *in-vitro* susceptibility studies showed that leptospires were susceptible to the antibiotics currently used to treat leptospirosis. Only one study reported the resistance of *L. interrogans* serovar Icterohaemorrhagiae strain Buckland and serovar Samarang toward penicillin G [72]. Some studies showed that a high concentration of penicillin G and ampicillin was required to inhibit the growth of *L. kirschneri* [60,67]. However, other antibiotics such as cefriaxone, cefotaxime, azithromycin, doxycycline and erythromycin were able to inhibit the growth of *L. kirschneri* with MIC lower than 2 μg/mL [67]. The findings from these studies [60,67,72] proposed that different *Leptospira* species, serovars and strains have different susceptibilities toward different type of antibiotics. Although continuous studies are being conducted to evaluate the susceptibility of leptospires against the currently used antibiotics, one limitation was observed: the studies only cover a small number of *Leptospira* species, serovars and strains. Most of the studies used *L. interrogans.* Other *Leptospira* species could also infect humans, so it is crucial to conduct a continuous study to identify the infecting *Leptospira* species among patients. Anti-leptospiral studies can be performed against the frequently detected *Leptospira* species, serovars and strains.

Besides the *in-vitro* study*, in-silico* analysis of the presence of resistance genes in the leptospiral genomes can also be performed. A recent study revealed that several strains in *L. interrogans* serovars (Autumnalis, Australis, Batavie, Copenhageni, Canicola, Grippotyphosa, Icterohaemorrhagiae, Pomona, Manilae, and Pyrogenes) were reported to contain several crucial AMR genes in their genomes [144]. Among the discovered AMR genes are *alr, ddl, and murA,* which encode enzymes involved in bacterial peptidoglycan synthesis [144]. The *alr* and *ddl* are targeted by the antibiotic d-cycloserine [145], while the anti-microbial agent Fosfomycin targets *murA* [146]. Genes crucial for *Leptospira* to develop AMR include those involved in regulation, transport, membrane structure, stress response, and DNA damage repair [147]. It is imperative to comprehend the genetic variables in *Leptospira* to clarify the mechanisms underlying their adaptations to toxic substances and the possible pathways that lead to antibiotic resistance in pathogenic *Leptospira*.

The obvious benefits of the current antibiotics in treatment and prevention of leptospirosis observed from the several previous studies are they can shorten the time of patients' recovery and reduce the number of cases and disease severity. However, it can be concluded that there is no affirmative evidence of the effectiveness of the antibiotics in preventing death. The effectiveness of either antibiotics or placebo treatment for leptospirosis showed no substantial differences in the prevention of mortality [148,149]. The died patients were already in their severe state with organs failures, emphasizing the crucial need to administer the antibiotics in early course of the disease. One study reported persistent leptospiruria in patients despite antibiotic treatment (penicillin, amoxicillin, vibramycin, and doxycycline) [150]. However, more studies are needed to be conducted to confirm this finding and also to evaluate the conditions of the patients with persistant leptospiruria. Antibiotic prophylaxis against leptospirosis did not prevent the occurrence of leptospirosis infection; it only reduced the number of cases in high-risk populations, particularly those who took doxycycline [151]. A recent study [87] demonstrated that pre-exposure prophylaxis (200 mg doxycycline weekly) did not prevent the occurrence of leptospirosis outbreak; however, less severe disease manifestation was observed in patients who took the antibiotics. This emphasizes that although prophylaxis antibiotics did not prevent the occurrence of leptospirosis, they are still useful as they can reduce the disease severity.

The effectiveness of antibiotics used for leptospirosis treatment could be affected by several factors such as the species or strains of the infecting leptospires and antibiotic doses. Understanding the factors influencing antibiotics' action to determine the prescription doses and achieve the best treatment result is crucial. Inefficient use of antibiotics leads to various negative consequences, including escalated adverse effects, therapeutic failures, elevated morbidity and death rates, heightened healthcare expenditures, and AMR [152–154]. In relation to those issues, addressing and optimizing prescribing practices is vital to mitigate the adverse effects of antibiotic use on individual patients and the healthcare system. Inappropriate antibiotics significantly impact *Leptospira* resistance by promoting biofilm formation, which exhibits a six to sevenfold increase [155]. In a recent study, transposon mutants were used to demonstrate that diguanylate cyclases (DGCs) and phosphodiesterases (PDEs) control intracellular bis-(3′-5′)-cyclic dimeric guanosine monophosphate (c-di-GMP), which regulates motility and biofilm production in *Leptospira interrogans*. This suggests that the species has a greater ability to withstand environmental stresses [156]. Another study also proves that sub-minimal inhibitory concentration (sub-MIC) levels of antibiotics (doxycycline and tetracycline) are capable of inducing biofilm formation in *Leptospira*, potentially leading to treatment failure and chronic infections [157].

Although the current antibiotics show excellent *in-vitro* activity against several *Leptospira* strains, they also cause adverse reactions in patients treated with the antibiotics. According to several reports, the incidence of JHR in leptospirosis patients was approximately 9 % [108,158]. Recently, patients with pulmonary alveolar hemorrhage (PAH) also developed JHR after penicillin treatment [97]. The JHR was formerly believed to result exclusively from the release of endotoxins due to spirochete lysis induced by antibiotics; however, recent studies have shown that the cytokine cascade is also activated during spirochete degeneration [112]. The mechanisms PAH induced by JHR were believed to stem from damage to and abnormalities in the basement membrane of pulmonary capillaries, resulting from the acute and substantial release of harmful bacterial chemicals due to antibiotic-mediated bacterial lysis [114].

Currently, the therapeutic options for leptospirosis are constrained. The existing antibiotics cause adverse reactions; hence, alternative spirocidal agents that are less toxic, more potent, and exhibit a lower resistance rate are needed [52]. Exploring alternative drugs, especially from natural sources, such as plants, is imperative and worth investigating to deal with the potential of antibiotic resistance due to the continuous discovery of new *Leptospira* strains, the potential of AMR development and the occurrence of adverse reactions. Studies have highlighted the anti-microbial properties of several plants against leptospires (Table 6). However, a limited range of *Leptospira* strains, mostly Australis, were used. To confirm these plants' usefulness, more studies are necessary to test many *Leptospira* strains in different geographical locations. Plants that confer anti-leptospiral activity must be further assessed to identify the

bioactive compounds for drug development.

5. Conclusion

In general, the findings from this review shows that *Leptospira* strains are susceptible to the current antibiotics. However, more *in-vitro* susceptibility studies must be conducted on more *Leptospira* strains in different geographical locations. To understand the AMR mechanisms in the leptospiral genome, it is critical to perform more *in-silico* screening on resistant genes and associate it with the *in-vitro* study. Although there is no solid evidence that antibiotics are beneficial in preventing the occurrence of adverse reactions and death, they can still be used as a current treatment option as can they shorten the duration of illness and reduce the number of leptospirosis cases. More studies are needed to investigate the efficacy and safety of the current antibiotics in the treatment and prevention of leptospirosis to further substantiate their usefulness in the management of leptospirosis. The continuous search and development of new drugs is imperative to manage leptospirosis efficiently.

CRediT authorship contribution statement

Celyne Mendu: Writing – original draft, Conceptualization. **Syarifah Ab Rashid:** Conceptualization. **Wan Siti Nur Atirah Wan Mohd Azemin:** Conceptualization. **Noraini Philip:** Writing – review & editing, Writing – original draft, Conceptualization.

Ethical approval

Review and/or approval by an ethics committee was not needed for this study because this is a review article and no human or animals were involved.

Data availability statement

Data can be found in the manuscripts.

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Declaration of competing interest

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