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SYSTEMATIC REVIEW

Systematic review: Yellow fever control through environmental management mechanisms

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Abstract

Objective: Recent research on mosquito vector-borne diseases points to the possibility for a re-emergence of yellow fever. This study investigated attempts at utilising environmental methods and their efficacy for the control of yellow fever and its main vector, *Aedes aegypti*.

Methods: Potentially eligible studies were searched in Cochrane Library (Reviews and Trials), the Global Index Medicus (encompassing thus the African Index Medicus, the Index Medicus for the Eastern Mediterranean Region, the Index Medicus for the South-East Asia Region, the Latin America and the Caribbean Literature on Health Sciences and the Western Pacific Region Index Medicus), Google Scholar, PubMed and Science Direct.

Results: Of a total number of 172 eligible studies, 20 met the pre-defined inclusion criteria. Two of them provided quantitative assessment on the efficacy of the described water management and house screening methods with a reduction of cases of 98%, and of a reduction of larvae of 100%, respectively. The remaining 18 studies described or recommended the elimination of breeding sites (through water or waste management, unspecified, or house destruction), the use of screens for houses and the improvement of air circulation without providing any data to evidence control effectiveness.

Conclusion: This systematic review provides evidence on the historical use and the perceived effectiveness of environmental management methods for combatting yellow fever. However, these methods would benefit from further investigation via controlled trials to provide data for efficacy, costs, acceptability and feasibility.

KEYWORDS
environmental policy, history, mosquito control, prevention and control, systematic review, Yellow fever

INTRODUCTION

Over the past few decades, there has been a growing number of infections with arboviruses, with yellow fever becoming an evermore significant threat to global health security [1]. Yellow fever is caused by a flavivirus (Flaviviridae family) which is mainly transmitted by *Aedes aegypti* (also known as 'yellow fever mosquito') [2]. As mosquitoes do not only feed on human beings (thus resulting in an urban transmission cycle) but also on monkeys, there is always a pathogenic reservoir besides mankind (fostering a sylvatic and an intermediate transmission cycle, respectively) [2, 3]. Clinically, yellow fever may present with a variety of symptoms, including fever, muscle pain or nausea, as well as, in more severe cases, jaundice or haemorrhagic fever [2, 3]. High fatality rates have been reported for outbreaks during the 18th, 19th and 20th centuries, and even for the 21st century with unvaccinated travellers being at high risk [1, 3–5]. There are an estimated 200,000 cases worldwide, resulting in around 30,000 deaths and of which the vast majority is recorded in Africa [1, 5, 6]. Although vaccination is the key intervention for control, vaccine availability remains a major obstacle [3, 5]. As new methods such as reverse-genetics techniques are still subject to scientific research, the production method has not changed much since its development in the 1930s: embryonated chicken eggs are inoculated and need to be cultured over a certain period, before the live-attenuated vaccine can be manufactured, thus limiting the amount of vaccine that can be produced quickly [3, 5]. Furthermore, there is still no cure for a yellow fever infection and treatment options only include supportive treatment such as antipyretics or fluid intake [2, 3, 5].

Due to climate change, changes in human behaviour such as increased travel activity and the suspension of previously performed control measures, yellow fever has re-emerged over the past 50 years and is now even spreading to new habitats and regions in Africa and tropical South America [1, 3–11]. This has been attributed to a more permissive climate for the vector coupled with rapidly growing urbanisation [5, 8].

In areas where yellow fever is endemic, current vector control approaches are usually holistic, striving to include chemical, biological, environmental methods as well as, if available, vaccinations [8, 12]. While chemical and biological applications, that is the use of insecticides, larvicides or biological agents such as predatory fish, are particularly important in the case of an outbreak [13], vaccines are also often relied on during these emergencies; and, due to shortages, fractioned dosing has had to be used despite not being supported by the International Health Regulations [2, 3, 5, 9, 10]. Further, concerns have emerged that mutations may evolve leading to the vaccine losing its high efficacy [3, 13].

Environmental management was defined by the WHO in 1979 as 'activities for the modifications and/or manipulation of environmental factors or their interaction with man with a view to preventing or minimising vector propagation and reducing man-vector-pathogen contact' [14]. Examples for such methods comprise the elimination of breeding sites, coverage of water containers and the use of screens. For those environmental management methods, beneficial effects have been reported in the past, for example, in Havana, Cuba [13–15], but there is a lack of summary evidence concerning their efficacy and utilisation. These data may be helpful for healthcare policymakers as well as for local communities to decide on their choice of approach to control yellow fever.

The aim of the present study is therefore to investigate environmental methods and their efficacy for the control of yellow fever and its main vector, *Aedes aegypti*.

MATERIALS AND METHODS

This systematic review follows the PRISMA guidelines, with searches performed up to 10th of April 2020. No institutional review board approval was required as this study is based on already published material. The literature search was conducted using a combination of the search terms 'yellow fever', 'environment*' and either 'waste or container or water storage or house or screen or source reduction or habitat or elimination or breeding site' in the following databases: Cochrane Library (Reviews and Trials), the Global Index Medicus (encompassing thus the African Index Medicus, the Index Medicus for the Eastern Mediterranean Region, the Index Medicus for the South-East Asia Region, the Latin America and the Caribbean Literature on Health Sciences and the Western Pacific Region Index Medicus), Google Scholar, PubMed and Science Direct.

The steps for the inclusion process were as follows: (1) each database was searched for eligible articles with a combination of the aforementioned search terms, for example 'yellow fever environment* waste'; (2) the results were screened based on their titles, articles meeting the pre-defined criteria were included, and duplicates of articles were removed; (3) articles were re-screened based on their abstract by two reviewers (SH and AK) for relevance; (4) further selection based on the whole text; (5) the reference section of each included article was examined for additional relevant articles; (6) additional relevant articles were screened, and articles meeting the pre-defined criteria were included; (7) the selected articles were categorised according to their quality and the environmental method mentioned.

In the first step, the search was conducted on the whole text for Pubmed, the Cochrane Library and Google Scholar. As this was not possible for the remaining databases (Global Index Medicus and Science Direct), the search was done in the 'Title, abstract, keyword' mode. The second search term 'environment*' was used as a wildcard term in all databases except for Science Direct which does not support this search mode. For the second step, an article was excluded based on its title if the title indicated solely the use of a chemical or a biological method, if it only referred to the elimination of *Aedes* as those are not the only vectors for yellow fever, if the article only examined the usefulness of vaccination, if the title did mention solely another disease transmitted by *Aedes* (e.g. dengue, Zika or chikungunya), and if the method described was the use of repellents as the latter are a form of individual prophylaxis. The selection process of articles in step four was based on the following pre-determined inclusion criteria: the article had to deal solely with yellow fever, and it had to investigate an environmental method. Screening of the reference section of the preliminary included articles was done based on the title, and, where available, on the abstract according to the procedure in step three. The categorisation in the last step was a twofold division: category 1 included all articles providing numbers to prove the efficacy of the environmental method described; and category 2 included all articles in which an environmental method was mentioned, but not evaluated and/or supported by numerical values. Within each of these categories, the studies were further divided into studies concerning the time before and those after the development of the yellow fever vaccine in 1937, as this invention greatly influenced disease prevention approaches [5, 6, 9]. Information retrieved from each article in category 1 included the following: study type, description of the environmental method, country where the study was located, quantitative indicator used, results and conclusion as given by the article itself. For studies in category 2, the following information was extracted: description of the environmental method, whether it was a description of a performed procedure or whether it was a recommendation to perform this method, country where the study was located, results, and conclusion as given by the article itself. Furthermore, the described methods were classified in elimination of breeding sites (by house destruction, unspecified description, waste management or water management), use of screens and improvement of air circulation. Quality appraisal was done using on the one hand the Mixed Methods Appraisal Tool (MMAT) [16], and on the other hand based on the recommendations made in the *WHO Handbook for Guideline Development* [17]. Results were tabulated.

RESULTS

Data acquisition

A total number of 172 potentially relevant records were identified in all databases searched. After removal of duplicates and application of all inclusion and exclusion criteria, 18 articles were included. The search of the reference sections of the included articles led to an additional two articles (Figure 1). A total number of 20 articles were included in this systematic review.

Quality appraisal

An assessment using the MMAT was initiated with the screening questions ('Are there clear research questions?' and 'Do the collected data allow to address the research question?'). 11 of the 20 included studies did not have a clear research question as they were methodologically historical reports not following the present-day study designs with a designated population, an intervention, a comparison group or an outcome. Thus, no assessment could be performed using the MMAT. The GRADE scoring system of the WHO Handbook for Guidelines also proved not to be applicable for the present body of literature [17].

Category 1 – Studies with a quantitative assessment

Two studies by Freeman [18] and by Wermelinger [19] met the pre-defined inclusion criteria for category 1. Both studies were historical reviews concerning the pre-vaccination era, were published in 2011 and 2016, respectively, and they were located in the Americas.

The study by Freeman [18] focussed on the application of screens to houses of infected patients by using a fine-meshed copper gauze on the windows, on rendering water containers mosquito-proof by fastening a cloth on top of it, and on the creation of a sewerage system. No index was presented to record the efficacy of these methods, but a reduction of cases and fatalities from 62 cases and 19 fatalities in June 1905 to 1 non-fatal case in December 1905 was reported, that is a reduction in cases by 98%, and a reduction of fatalities by 100% [18]. Wermelinger [19] described the efficacy of the elimination of breeding sites, and also of water management methods. The elimination of breeding sites was partially based on water management methods, that is checking on flowerpots and on bromeliads for stagnant water, ensuring the flow of water in streams and making use of the Aculex device in galleries [19]. Removal of containers and cleaning wasteland were also described to contribute to the elimination of breeding sites [19]. Without mentioning key parameters of the study, for example the area actually under surveillance, Wermelinger [19] reported the results based on the house larval index for which a reduction from almost 100% to 0% was indicated (Table 1).

Category 2 – Studies with no supportive quantitative assessment

Eighteen studies were categorised as studies without any quantitative assessment supporting the efficacy of the mentioned environmental method. Four studies were not limited to a specific country, but aiming to present a more general, worldwide vision [20–23]. A slight majority of the included studies (n = 11) were pre-vaccination era [20, 21, 24–32] (Table 2). Eight of these were descriptive [20, 25–27, 29–32], making up the majority of all descriptive studies in category 2 (n = 9) [20, 22, 25–27, 29–32,]. Two studies described the environmental methods employed and also made recommendations for their application [28, 33]. Kuecker [28] stated that the setup of a sewerage system and the introduction of drinkable water were recommended by the local doctors. The study by Carmo Cupertino [33] described water drainage from the streets and the application of screens to windows, recommending the latter as an alternative way to protect oneself from being bitten by a potentially infected mosquito. The recommendation of an environmental method in the remaining seven studies [21, 23, 24, 34–37] was based on the personal opinion of the authors.

The studies included in this category were organised according to the environmental method they presented (Table 2). The majority of studies focussed on the elimination of breeding sites (n = 17), with a focus on water management methods (n = 13). More studies investigated the pre-vaccine era (n = 11) than the post-vaccine era (n = 7), and the methods of improving the air circulation in towns

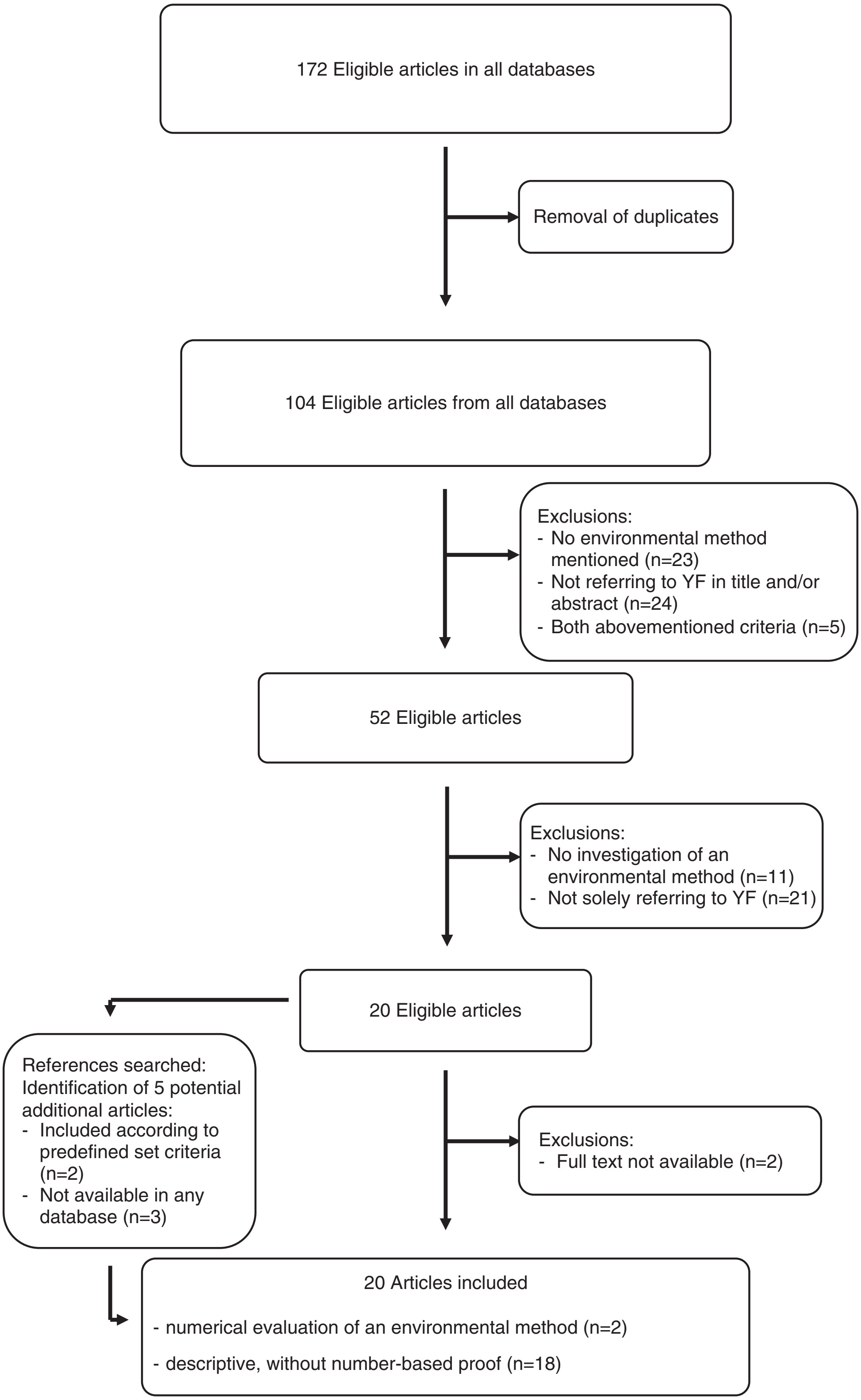

FIGURE 1 Flowchart of data acquisition according to the PRISMA guidelines

('some observers argued for the destruction of the town's fortified perimeter, as this would allow purifying breezes to sweep alleys and narrow passageways […]' [26]) and elimination of breeding sites by destroying houses ('The new techniques included […] evacuating and razing houses' [25]) were only mentioned for the time before 1937. No rationale on the selection criteria of houses to be destroyed was given in the study [25]. The water management methods before 1937 focussed on the creation or improvement of sewerage systems (including water closets) or gutters [20, 26–30], the provision of drinking water and a water supply system [20, 26–28], coverage of storage tanks, wells, and domestic water receptacles [20, 24, 25, 30], drainage [20, 24, 26, 27] or the regular cleaning of water receptacles [25, 29, 30]. Goals of waste management included cleaning out privies and cleaning up around citizens' premises [31], to clean the streets [26], and to clean-up trash [30]. For the time before 1937, screens were recommended to be used in dwellings and other buildings [24, 31] and sanitary workers were also asked to construct mosquito covering and netting [27]. Unspecified descriptions of environmental methods for the elimination of breeding sites were given by Havard [32], White [21], and Pearce [31] with a strong rhetorical focus on top-down wording such as 'given full power to make a steady, insistent, and minutely exact fight on all Stegomyia breeding places' [21] or 'urged people to wage relentless warfare against the infected mosquitoes' [31].

Such a wording could not be observed for the post-1937 studies which did not describe a specific method. Anderson [36] presented a strategy in which the premises needed to be inspected and the breeding places needed to be eliminated, whereas Hargett [22] stated that 'squads of expertly trained men are utilized to search out and destroy those hidden breeding foci'. The most frequently mentioned control method was also water management: provision of adequate water supplies [34, 35], control of water containers [22, 34], coverage of water tanks [23, 35], destruction of water receptacles that may harbour stagnant water [22, 23], drainage [33, 35] and avoidance of leaving stagnant water [33, 35]. Waste management methods were only described by Tauil [35] with the request for a regular garbage collection and for a regular clean-up of the land and the yards. The application of screens was recommended after 1937 by Khan [37] and Carmo Cupertino [33] with it being used also on windows. More detailed information can be found in Table S1.

DISCUSSION

The results of the present systematic review summarise the evidence for the benefit of applying environmental methods to control yellow fever. Quantitative data are scant, but the limited numbers illustrate good levels of efficacy: a reduction of 100% in home larval index and an associated reduction in cases by 98% was reported by Freeman [18]. The methods used to achieve these reductions could be classified into two categories: (i) the elimination of breeding sites, mainly through water management in the form of covering water containers and the creation and monitoring of a sewerage system with no stagnant water, and (ii) the application of screens to houses. Several articles strongly supported the use of screens in particular [20, 23–31, 33, 37].

Knowledge of both categories of methods originates over a century ago as Guiteras [24] indicates when stating that 'The details of the two latter [i.e. use of screens and water management, author's note] are so well known and, in fact, so simple that it seems unnecessary to take up the reader's time with a discussion of them'. It could be hypothesized that the development of the yellow fever vaccine, even more with it being propagated at that time as being able to lead to the elimination of yellow fever [5, 38], and the invention and application of new chemical agents such as dichlorodiphenyltrichloroethane [3, 8] may have led simultaneously to a loss in knowledge concerning the efficacy and to a reduced application of environmental methods for controlling yellow fever and its main vector, *Aedes aegypti*. In contrast, other environmental measures used during the pre-vaccine era seem, by today's standards, to be excessive and hardly compatible with being supported or even tolerated by the local populace. Cueto et al. [25] described the destruction of houses as not being conducted on a large scale because of the public arousal it caused.

One of the principal findings of this systematic review is that, despite a century or more of use, the impact of environmental methods on yellow fever is scarcely reported. Buhler et al. [39] reviewed the use of environmental methods for dengue vector control and reported good effectiveness (i.e. reduced entomological indices) after several interventions such as container covers, waste management and clean-up campaigns, and elimination of breeding sites on larval populations. However, they also demonstrate considerable discrepancies in effectiveness between studies [39]. Another systematic review by Bowman et al. [40] shows that the dengue risk could be reduced significantly through the application of screens (odds ratio [OR] 0.22, $p = 0.04$), and through a combined community-based environmental management and water covering approach (OR 0.22, $p < 0.001$). However, they also point out that the studies reviewed were of poor quality, thus providing only a weak evidence base [40]. Thus, for both dengue and yellow fever, there remains poor understanding of which of the available methods work and what reasons are there for a good or bad performance. Interestingly, a group of researchers from Malaysia and Singapore [41] are intending to review environmental methods for dengue control. It remains to be seen which results may be gained from this. In another study conducted in Singapore, a community-integrative approach against dengue is reported by Sim et al. [42], also including a number of environmental methods such as waste management and water management. Communities are asked to get involved by giving feedback on mosquito numbers, and to learn more on how they can contribute by avoiding the build-up of stagnant water [42]. However, no impact of environmental management on the transmission of other diseases has been reported by Sim et al. [42], even more, a request to investigate this for malaria is put forward.

While it might be tempting to consider all *Aedes*-borne infections together in an assessment of environmental management for their control, there are idiosyncrasies of each disease that might be missed by this grouping. Infection dynamics and distributions of yellow fever and dengue can differ markedly [43] distinguishing their epidemiologies. Therefore, even where these diseases may be transmitted by the same vector, it remains unclear whether the

TABLE 1 Studies with numerical evidence on the therein described environmental methods' efficacy

References	Authors	Year	Study type	Method	Country	Indices
[18]	Freeman AH	2011	Retrospective literature review	Application of screens to houses, mosquito-proofing of water containers with covers and creation of a sewerage system	Panama	No index; reduction of cases and fatalities
[19]	Wermelinger ED, Carvalho RW	2016	Retrospective literature review	Elimination of breeding sites, water management (checking on potential breeding sites and cleaning them)	Brazil	Home larval index

TABLE 2 Overview of the described environmental methods in category 2, divided into two groups (before and after the development of the yellow fever vaccine in 1937)[a]

Before 1937	After 1937
Elimination of breeding sites	Elimination of breeding sites
Water management	Water management
Guiteras, 1909 [24]	Findlay, 1941 [34]
Gorgas, 1920 [20]	Hargett, 1944 [22]
Cueto, 1992 [25]	Tauil, 2010 [35]
Knaut, 1997 [26]	World Health Organization, 2016 [23]
Stern, 2007 [27]	Carmo Cupertino, 2019 [33]
Kuecker, 2008 [28]	
Costa, 2011 [29]	
Sutter, 2016 [30]	
Waste management	Waste management
Pearce, 1978 [31]	Tauil, 2010 [35]
Knaut, 1997 [26]	
Sutter, 2016 [30]	
Unspecified	Unspecified
Havard, 1901 [32]	Hargett, 1944 [22]
White, 1910 [21]	Anderson, 1957 [36]
Pearce, 1978 [31]	
House destruction	
Cueto, 1992 [25]	
Use of screens	Use of screens
Guiteras, 1909 [24]	Khan, 2017 [37]
Pearce, 1978 [31]	Carmo Cupertino, 2019 [33]
Stern, 2007 [27]	
Improvement of air circulation	
Knaut, 1997 [26]	

[a]Note that one article may describe more than one method, hence being mentioned in different categories. Thus, the total number is also not equal to the total number of articles included.

results reported for one pathogen necessarily translate to the other. The comparison becomes even more complicated when acknowledging the existence of multiple, alternative, non-shared vector species with differing habitats and biting behaviour [44]. In addition, due to the spreading COVID-19 pandemic, vaccination programmes had to be halted, and there are reports on a shortage of the vaccine itself, too [1, 3, 6]. As the vaccine is not always available and as there may be more vectors than the commonly combated *Aedes aegypti*, there is a need to investigate the efficacy and applicability of environmental management methods to fight against yellow fever. This need is in line with the request of the global strategy to Eliminate Yellow fever Epidemics (EYE) to investigate vector control methods [45]. The EYE strategy aims furthermore to prevent international spread [45], an aim to which environmental methods may contribute considerably, because these methods can be used by local communities and are not affected by a limited fabrication or even a loss of production of the vaccine. Methodologically, randomised trials encompassing all mosquito species and targeting yellow fever may lead to the most reliable and generalisable results. There are several forms of randomised trials to consider, depending on which environmental management method should be applied and investigated. For dengue, investigations in waste and water management were for example done in form of randomised cluster trials [39, 40] which may also be an applicable study design for yellow fever too.

This study had several limitations. First, the data set of studies included in this systematic review was limited. This may have been due to the pre-defined criterion of focussing solely on yellow fever, thus excluding studies which were also investigating the effects of similar methods on dengue, chikungunya and Zika, among others. Second, being descriptive to the point of almost narrative, the quality of some of the included articles is questionable. Third, some studies were not available in any database, a fact which applies especially to older studies. However, given the paucity of data typically provided by these studies, it is unlikely they will have influenced the overall findings of this review.

In conclusion, this systematic review provides evidence on the historical use and the perceived effectiveness of environmental management methods for combatting yellow fever. However, these methods would benefit from further investigation via controlled trials to provide data for efficacy, costs, acceptability and feasibility.

Results	Conclusion	Comment
Reduction from 62 cases and 19 fatalities in June 1905 to 1 non-fatal case in December 1905	Separating infected people by applying screens to their houses and by using bed-nets as well as the reduction and elimination of breeding sites by water management proved effective and successful in eradicating yellow fever.	Although this historical study is not based on an index, it proves to be a valuable asset for supporting the significance of environmental methods as the efficacy of the environmental methods used is underlined by the reduction of cases and fatalities.
Reduction of the home larval index from almost 100% to almost always below, in many areas to 0%	The success of the 1928–1929 campaign which was achieved by eliminating all possible breeding sites confirms the relevance of environmental management measures	Although this study is only an historical approach, the then newly upcoming use of an index already gives valuable and objective data. However, a disadvantage is that there are no raw numbers mentioned

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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