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Environmental Evidence

SYSTEMATIC REVIEW PROTOCOL

What are the effective solutions to control the dissemination of antibiotic resistance in the environment? A systematic review protocol

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Abstract

Background: Antibiotic treatments are indispensable for human and animal health. However, the heavy usage of antibiotics has led to the emergence of resistance. Antibiotic residues, antibiotic-resistant bacteria and genes are introduced into the terrestrial and aquatic environments via application of human and animal wastes. The emergence and the spread of antibiotic resistance in environmental reservoirs (i.e., soil, water, wildlife) threatens the efficacy of all antibiotics. Therefore, there is an urgent need to determine what effective solutions exist to minimize the dissemination of antibiotic resistance in the environment. The aim of this article is to describe the protocol of a systematic review of the literature considering these solutions.

Methods: The primary questions addressed by the systematic review protocol are: how antibiotic resistance in the environment is impacted by changes in practice concerning (i) the use of antibiotics, (ii) the management of wastes or (iii) the management of the natural compartment. Bibliographic searches will be made in eleven publication databases as well as in specialist databases. Grey literature will also be searched. Articles will be screened regarding the inclusion and exclusion criteria at title, abstract and full-text levels. Studies where a causal relationship between the intervention and the outcome is made will be retained. After critical appraisal, data from the selected articles will be extracted and saved in a database validated by the expert panel. Study quality will be assessed by critical appraisal. Data will be compiled into a qualitative synthesis. If data availability and quality allow it, a quantitative synthesis will be carried out.

Keywords: Antimicrobial, Bacteria, Genes, Management, Contamination, Soil, Aquatic compartment, Wastes, Resistome, One-health

Background

Antibiotics refer to natural substances produced by microorganisms and acting against bacteria [1]. However, the term 'antibiotic' is commonly used to designate medicines for the prevention and the treatment of bacterial infections [2]. The antibiotics comprise many different classes, e.g., beta-lactams, sulfonamides, quinolones [3]. A molecular structure shared between the compounds within an antibiotic family confers their mechanism of action and their physicochemical properties [4]. Antibiotics are widely used in human and animal health to prevent and treat bacterial infections [5]. In livestock industries, the use of antibiotics as growth promoters is prohibited in Europe since 2006 but still relevant in many developing countries [6]. In Canada and United States, the regulations tend to phase out the use of medically important antibiotics as growth promoters [7]. Moreover, antibiotics are used in aquaculture [8] and can also be

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applied on high-value fruits, vegetables and ornamental plants to control bacterial infections [9].

Antibiotic residues, defined as any parent compound or metabolite or transformation product [10], antibiotic-resistant bacteria (ARB) and genes (ARGs) are concomitantly released in wastes, mainly in wastewater and sludge for humans and in livestock manure for animals in agriculture. Different biological and physicochemical treatments can be applied to these wastes, e.g., aerobic or anaerobic treatments, storage, composting, liming, drying, ozonation. These treatments can contribute to decrease the concentrations of antibiotic residues and other pollutants by degradation (biotic or abiotic), dilution and/or bound residues formation [4, 11], and also to decrease the levels of ARB and ARGs [12]. Persistent antibiotic residues can be preferentially sorbed into the sludge; this suggests different risks between sludge application on agricultural soils and discharge of sewage effluent into aquatic environment [13]. The waste management can contribute to minimize the dissemination of antibiotic resistance before their discharge in the natural compartments [14], e.g., treated wastewater in the aquatic environment, sludge or livestock manure in agricultural soil [13, 15]. Diffuse sources such as surface runoff, leaching, could also be considered in the dissemination of antibiotic resistance in the environment [16, 17]. Simultaneously, ARGs can be transferred to autochthonous bacteria, depending on the characteristics of the receiving environment [18, 19]. For example, biofilms may be beneficial for the acquisition and spread of antibiotic resistance [20].

Anthropogenic activities largely contribute to the enrichment of the resistome of different ecosystems: the aquatic and terrestrial environments, also the atmosphere (aerosols, particles, dust) and the wildlife; exposing the bacteria, humans and animals to ARB and ARGs [13, 18, 21–25]. As a serious concern, the environmental reservoirs are a source of emergence and transfer of ARGs from environmental to introduced bacteria into those pathogenic to humans and animals [26, 27]. Consequently, the environmental contamination by antibiotic resistance is potentially associated with impacts on human and animal health. Nowadays, the worldwide presence of ARB and ARGs due to antibiotic misuse and overuse in agricultural and healthcare sectors threatens the efficacy of existing and future antibiotics [13, 28].

Hence, there is an urgent need to find effective solutions and implement them to reduce the dissemination of antibiotic resistance in the environment. Several management options can be proposed to reduce the antibiotic use and to treat the organic wastes before their release in the natural compartments [13, 29]. Recently, a systematic review showed that the restriction of antibiotic use in livestock can be associated with a decrease of antibiotic resistance in the animals and in farmers in contact with them [30].

Antibiotic resistance being maintained at environmental and health interfaces [15], it is highly relevant to tackle the antibiotic resistance issue in a One-Health approach [25, 31] via global, regional and national action plans [13, 32, 33].

This systematic review was commissioned by the French Ministry for the Ecological and Inclusive Transition as a part of the 2015 road map for ecological transition and then included in the third national action plan for health and environment (2015–2019). Multiple stakeholders from governmental agencies, research institutes, nongovernmental organizations, businesses and consultancies are informed and consulted by the project manager several times a year. This systematic review is also integrated into the One-Health approach [27] and could be valuable to determine the effectiveness of different solutions aimed at minimizing the dissemination of antibiotic resistance in the environment. Some of these solutions may contribute to control selection, co-selection and/or transfer of ARGs by decreasing the exposure of environmental bacteria to antibiotic residues, other pollutants (e.g., metals, biocides) and ARGs, respectively. Yet, there is no evidence that such a decrease may be accompanied by a decline in antibiotic resistance in the environment.

This review aims to assess the effectiveness and conditions of effectiveness of interventions implemented at different stages, from the use of antibiotics to the environmental management. To the author's best knowledge, a systematic review on this topic has never been done. This protocol presents the key elements for the conduct of this systematic review, in accordance with the Collaboration for Environmental Evidence guidelines for systematic reviews in environmental sciences [34].

Objective of the review

The occurrence and dissemination of antibiotic resistance in the environment has previously been reviewed [13, 15] and management options to reduce the spread of antibiotic residues and resistances have been proposed [21, 29, 35]. However, none of these reviews were systematic, and it is worth updating the analysis of publications on effective solutions to limit the environmental contamination by antibiotic resistance. The objective of this review is to systematically review and synthesize existing solutions to control the environmental dissemination of antibiotic resistance.

The contamination of the environment could be limited by applying solutions at different levels, from antibiotic use up to the discharge of wastes containing ARB and ARGs in the environment (Fig. 1). Therefore, in this systematic review, the solutions aiming to reduce the environmental contamination by antibiotic resistance will be considered at three different levels:

1. The reduction of the antibiotic use in human, animal and plant health;
2. The waste management, i.e., wastes containing ARB and ARGs (industrial, urban, hospital, agricultural; liquid and solid wastes).
3. The management of the contaminated environment (soil, aquatic environment, wildlife) or the possible role of the natural compartments in buffering the burden of antibiotic resistance.

Each intervention type is supposed to trigger a reduction of antibiotic resistance in the environment (i) directly, by acting on ARB and/or (ii) indirectly, by preventing the selection, the co-selection and the transfer of ARGs, e.g., by decreasing concentrations of antibiotic residues and other pollutants that may co-select for antibiotic resistance.

Primary question: What are the effective solutions to minimize the dissemination of antibiotic resistance in the environment?

With regard to the level of management options (Fig. 1), three sub-questions appear in this systematic review, with respective components for each search question (S1, S2, S3) detailed below with the PICO/PECO (population, intervention/exposure, comparator, and outcomes) format.

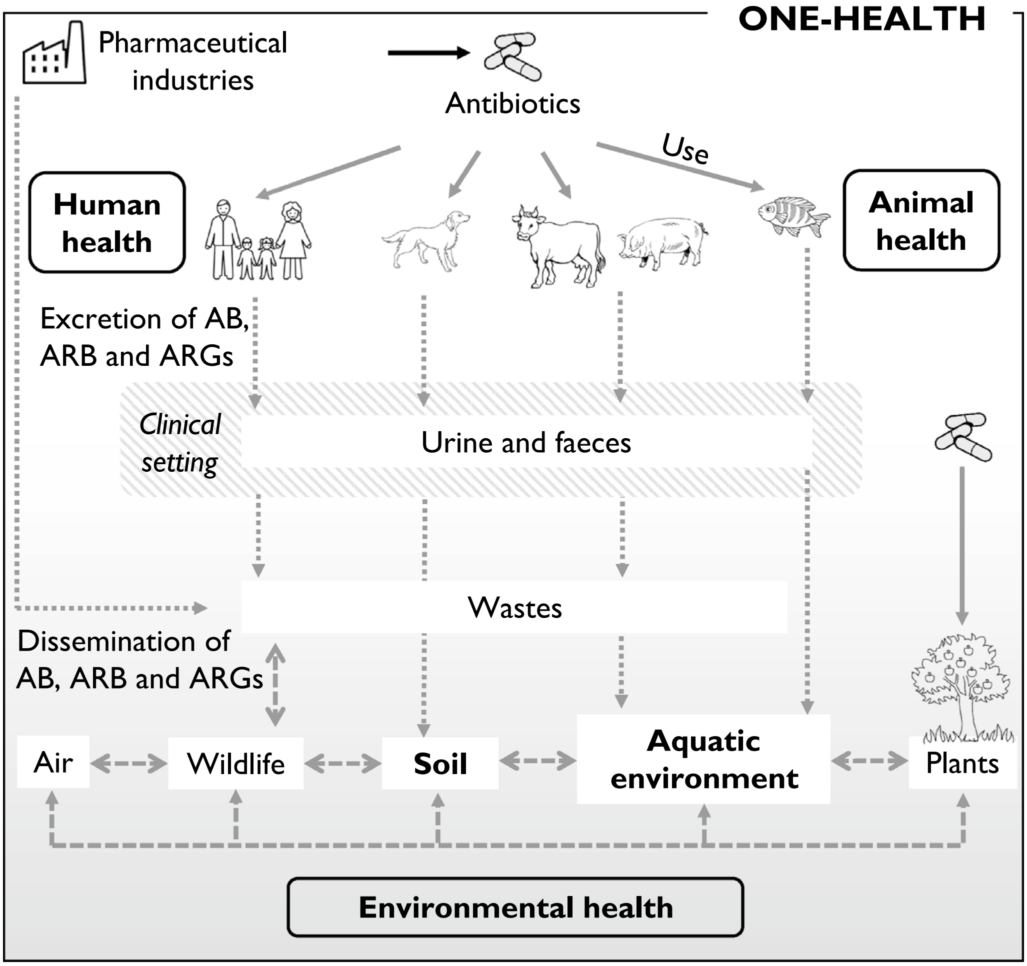

Fig. 1 Dissemination pathways of antibiotic residues (AB), antibiotic-resistant bacteria (ARB) and genes (ARGs) in the environment

***S1*: What are the effects of measures reducing the antibiotic use on the contamination of, and the occurrence/prevalence of antibiotic resistance, in the environment?**

Population	The population receiving or susceptible to receive antibiotics, i.e., humans (household, hospital), animals (pets, farming, aquaculture), cultivated plants
Intervention	Any described measure to reduce the use of antibiotic, including ban, reduction or replacement of the antibiotic, alternative treatments and preventive measures (e.g., hygiene)
Comparator	Usual use of antibiotics (no change), between practices, before the intervention
Outcomes	Changes of concentration, abundance or prevalence of ARB/ARGs in the wastes or in the natural compartments

***S2:* What are the effects of waste management options on the environmental contamination by antibiotic resistance?**

Population	All wastes containing ARB and ARGs, including urban, hospital, livestock or industrial origins
Intervention	Any described waste management, including wastewater treatment, sludge or manure management
Comparator	No management, between managements, before the management.
Outcomes	Changes of concentration, abundance or prevalence of ARB/ARGs in the treated wastes or in the natural compartments

***S3:* What are the effects of various environment management options on the environmental contamination by antibiotic resistance?**

Population	Environmental reservoirs of ARB and ARGs, i.e., soil, aquatic environment (including biofilm and sediment), wildlife
Intervention	Any described environmental management, including any natural process potentially responsible for the attenuation of ARB/ARGs (e.g., bioaccumulation)
or Exposure	Any event leading to the contamination of the natural compartment by ARB/ARGs (e.g., soil fertilization with livestock manure)
Comparator	No management, before the exposure or the management; between exposure levels or managements
Outcomes	Changes of concentration, abundance or prevalence of ARB/ARGs in the natural compartments

Methods

Expert Panel

The Expert Panel was consulted to suggest relevant search terms, literature (scientific publications and grey literature) and specialist websites for searches, as well as eligibility criteria for article screening. Experts belong to the following research institutes: National Institute of Health and Medical Research (INSERM), National Institute of Research in Agronomy (INRA), National Center of Scientific Research (CNRS), National Institute of Research in Sciences and Technologies for Environment and Agriculture (IRSTEA), Agriculture and Agri-Food Canada (AAFC).

Searches

Search terms

A list of search terms (Additional File 1: Table S1) was generated and validated by the Expert Panel. Search terms were organized in columns related to the components "Population", "Intervention" and "Outcome" for each sub-question. In order to capture relevant studies that do not contain the broad search terms "bacteria" or "gene", names of bacteria listed as antibiotic-resistant "priority pathogens" by WHO in 2017, bacteria and genes proposed as antibiotic resistance indicators in the environment by Berendonk et al. [7] were added in the search string. Considering the broad search term "antibiotic", names of antibiotics were included in the search string and searched only in the title to limit the collect of irrelevant studies (e.g., organic synthesis, clinical studies), according to the recovery rates of references included in the test list.

The terms within each category "Population", "Intervention", "Outcome" will be combined using the Boolean operator 'OR', while the Boolean operator 'AND' will be used to combine the terms of the three categories. Truncation and wildcards will be used and adapted to each database as appropriate, in order to take into consideration variants of the search terms.

Language

The systematic review will be limited to studies published in English and in French, a large body of literature being indeed in English and a lot of research reports being available in French.

Testing for performance of the search

To evaluate the performance of the search strategy, a test list of 28 articles was collected from experts and from previous reviews. The number of articles of the test list that will be retrieved by the search will be reported in the review report [36].

Publication databases

Publications will be collected from the following databases, without any limitation on the years of publication:

- PubMed.
- Web of Science.

The following databases will be used depending on the number of publications collected from the first databases and the rate of identification of new articles not previously retrieved:

- Agricola.
- AGRIS (Agricultural database of FAO).
- BioOne.
- Directory of Open Access Journals.
- Drug Resistance Updates.
- IngentaConnect.
- JSTOR.
- Scopus.
- Wiley Online Library.

Internet searches

- Google Scholar.

Specialist searches for grey literature

When the complete search strings cannot be used in the previous publication databases, a broad search will be made with the following terms: (antibiotic OR antimicrobial OR "antimicrobial resistance" OR "antibiotic resistance") AND environment. Specialist organization websites that will be searched are listed below (not exhaustive):

- Alliance for the Prudent Use of Antibiotics.
- Bielefeld Academic Search Engine.
- BIVI database of AFNOR.
- Centre for Antibiotic Resistance Research.
- Centers for Disease Control and Prevention.
- EFFORT against antimicrobial resistance.
- European Antimicrobial Resistance Surveillance Network (EARS-Net) of European Centre for Disease Prevention and Control.
- European Commission Environment.
- European Committee on Antimicrobial Susceptibility Testing.
- European Food Safety Authority.
- Food and Agriculture Organization.
- French Ministry for the Ecological and Inclusive Transition.
- French Ministry for Solidarity and Health.
- Grey Literature Network Service.
- Hyper Articles in Line.
- Open grey literature in Europe.
- National Public Health Agency.
- National Agency of Drug and Health Products Safety.
- National Agency for Sanitary Safety of Food, Environment and Work.
- Portal for information and promotion of fair use of antibiotics.
- World Alliance Against Antibiotic Resistance.
- World Organization for Animal Health.
- World Health Organization.

Supplementary searches

The citation chasing will be used as a method of identifying potentially relevant studies. If not accessible by usual retrieval of articles, authors will be directly contacted to request full texts of publications. Otherwise, members of the Expert Panel will be contacted to know if they have unpublished data or if in their professional network, they know researchers working on solutions to reduce the contamination of the environment by antibiotic resistance. Websites of governmental departments in various countries who might be conducting or be aware of research relevant to this systematic review can be consulted.

With the help of an information manager (INRA), a monitoring tool (Digimind®) is implemented and will allow us to receive alerts from the scientific publication database (Web of Science) and from different websites. The use of this tool will start once the bibliographic search on Web of Science is conducted and will end once the screening by full text is done. Alerts from Web of Science will be screened by title and abstract. If included, the corresponding references will be exported in a separate collection of the database (Search record database section), and then will be screened by full text as for articles collected from the searches in the different publication databases. Alerts from different websites (e.g., press, institutions, governmental) will be screened by title as additional source of grey literature.

Search record database

All articles and documents will be exported into separate collections using the reference management software Zotero®. After all searches have been carried out, references from each search will be merged into one database, and identified duplicates will be removed.

Article screening and study inclusion criteria

Screening process

The articles found by searches in databases will be evaluated for inclusion at three levels, i.e., by title, then by abstract and finally by the full text. For the screening at title level, a subset of 40 articles will be screened by several reviewers. Screening consistency will be evaluated by using Kappa tests and a score ≥ 0.6 will indicate an acceptable agreement between reviewers. Discrepancies will be discussed between reviewers and refine inclusion/exclusion criteria. A second subset of 40 different articles will be screened again for evidence of improvement of consistency. The same method will be used for the screening at abstract level, with two different subsets of 25 articles, screened by several reviewers.

For the screening of articles at full text level, rejection of an article will be decided by the review team upon suggestion of the first reader. Details regarding the final decision of inclusion/exclusion of articles will be clarified and archived in a database. In cases of uncertainty for the decision to include or exclude an article, the reviewer will include this article for the next level of screening. The documents without abstracts will be screened at the full text level. A list of articles excluded at full text level will be provided in the systematic review, accompanied by reasons for exclusion.

Eligibility criteria were developed in consultation with the Expert Panel, for each sub-question and are presented below for each sub-question S1, S2 and S3.

Inclusion criteria

Relevant subjects *S1* Any living organism receiving antibiotics, including humans, animals or plants.

S2 Any waste containing ARB and ARGs, including solid or liquid wastes of human or animal origin.

S3 Any natural compartment contaminated by ARB and ARGs, including soil, aquatic environments. Wildlife will be included given they are considered as environmental reservoir of antibiotic resistance. Contaminated environment after an event such as soil fertilization by sludge or manure, wastewater reuse, rejection of effluent in the aquatic environment, will be included.

Relevant interventions All interventions aiming to reduce the contamination of the environment by antibiotic resistance (i) directly, by acting on the concentration, abundance or prevalence of ABR and/or ARGs; or (ii) indirectly, by acting on the concentrations of antibiotic residues or other pollutants that can co-select for antibiotic resistance (e.g., metals, biocides). Regarding the sub-questions, relevant interventions include:

S1 Solutions to reduce the consumption of antibiotics, e.g., optimization of antibiotic treatments, alternative treatments, better hygiene conditions.

S2 Solutions to manage human and animal wastes, e.g., wastewater treatment, composting, disinfection. The processes such as adsorption or (bio) degradation occurring during the waste management and potentially leading to the decrease of extractable antibiotic residues or other pollutants will be also included.

S3 Solutions to avoid or reduce the contamination of the environment by antibiotic resistance, e.g., regulation of sludge application, protection of drinking water catchment areas, soil management, bioremediation. The natural processes describing the fate of antibiotic residues or other pollutants in the environment (e.g., adsorption, (bio) degradation, runoff, leaching) will be included, but also the transfer of compounds, ARB and ARGs into living organisms and the resilience capacity of the environment.

Relevant comparators For each search sub-question (S1, S2, S3), relevant comparators will include: (1) no intervention, i.e., control experiments, monitoring, natural attenuation; (2) before the intervention for a same population; (3) another intervention for a same population; and (4) another intervention for a different population.

Relevant outcomes The changes of concentration, prevalence/occurrence of ARB and ARGs will be the main focus. Antibiotic resistance markers include ARB, ARGs and mobile genetic elements such as integrons. They can be measured as concentration or prevalence. Abundance of resistant bacteria will be relevant only if abundance of total bacteria is measured to give proportion/prevalence of ARB. Antibiotic resistance of bacteria can be determined by measuring their susceptibility to antibiotics and the minimum inhibitory concentrations. Studies in which the concentrations of antibiotic residues or other pollutants (e.g., metals, biocides) are measured in parallel to the antibiotic resistance monitoring will be included. The antibiotic/pollutant residues include the parent molecule, metabolites, transformation products and the possible different chemical forms of molecules (e.g., ionic, dissolved, associated, complexed or bound molecules). Residues can be measured as mass and/or concentration.

In included studies, the relevant matrices in which antibiotic resistance is measured will be wastes and/or natural compartments for the three sub-questions (S1, S2, S3). Also, for the sub-question on the reduction of antibiotic use (S1), livestock faeces will be included as relevant matrices, considering their more or less direct discharge in the environment. Human or animal matrices (e.g., blood, nasal or rectal swabs) will be excluded as they are relevant of clinical studies (Fig. 1). Moreover, according to [30], the decrease of the antibiotic resistance in animal matrices has already be linked to the reduction of antibiotic use in livestock.

Relevant types of study design Only studies aiming at highlighting the causal relationship between intervention and outcome will be retained. Study designs with appropriate comparators including before/after, control/treatment, different interventions, as well as studies including both these types of comparisons will be included.

Literature reviews will not be taken into account in the systematic review as such, but they will be used to access more literature if needed, to increase the test list using cited references, and to put into perspective the conclusions of the systematic review.

Potential effect modifiers and sources of heterogeneity

Potential effect modifiers will be identified to better understand the variations of effects among studies. Indeed, several factors such as the study location (e.g., regulations for antibiotic use), the climate conditions, the considered antibiotic, can result in heterogeneity of results. The Expert Panel will extract data on potential effect modifiers from studies included at the full text screening. The factors will be recorded in the database. A non-exhaustive list of potential effect modifiers is given hereafter:

- Study location.
- Environmental conditions, i.e., physicochemical properties and characteristics of the environmental matrices.
- History of the environment.
- Physicochemical properties of the antibiotic residue.
- Type of antibiotic-resistant marker, i.e., bacteria or gene or mobile genetic element.
- Study design.
- Monitoring duration.
- Intervention type.
- Comparator type.
- Sampling and analytical methods.

Study quality assessment

The risk that reviewers who authored articles considered within the review influence decisions regarding inclusion or critical appraisal of their own work will be taken into account at two stages: (1) all articles rejected during screening will be double-checked by the project leader; (2) during critical appraisal, reasons for rejection will be examined by all members of the review team.

Studies in this field either assess change over time in antibiotic resistance, or compare it before and after the intervention. Research designed expected in retained studies should be either “BA” (before/after), “CI” (control/intervention), “BACI” (before/after/control/intervention), although observational studies may also be extracted by the search. Replication and randomisation are also possible within this field of research (e.g., when selecting samples). As a result of these differences in study quality and susceptibility to bias, all studies selected at full text level will be described and categorized in “low”, “medium” and “high” risk of bias by considering the following parameters:

- Study setting (field or laboratory experiment).
- Study design.
- Temporal extent of the study (before monitoring, after monitoring, total duration).
- Replication (in time, in space).
- Distance between sampling sites.
- Presence of controls.
- Sampling (method, location, depth).
- Number of samples.
- Analytical methods.
- Statistical methods and statistical power.
- Accounting for potential effect modifiers (see above).
- Type of environmental matrix.
- Type of antibiotic, influencing its environmental dissipation.
- Type of antibiotic-resistant maker, i.e., bacteria or gene or genetic element.
- Type of chemical method to measure the concentration of antibiotic residues or other pollutants.
- Type of biological method to measure the antibiotic resistance.

Data extraction strategy

All data from included studies will be extracted and recorded in an Excel database by using a predefined spreadsheet and validated by the Expert Panel. The extracted data records will be available as Additional file 1: Table S1 of the systematic review. The extracted information will be based on the PICO elements and recorded outcomes will be: outcome means, sample sizes and measures of variation such as standard deviation, standard error, confidence intervals. The extracted information will be used to measure the effects of interventions on the change of antibiotic resistance in the environment. If good quality data exist and is in sufficient number, a meta-analysis will be carried out.

To ensure that data is correctly extracted, two reviewers of the Expert Panel will extract information from a subset of 10% of all articles. Inconsistencies will be discussed between the two reviewers and the entire Expert Panel will be consulted if any disagreement occurs. This will allow the members of the Expert Panel to ensure that information is extracted and interpreted following the same method.

Data synthesis and presentation

A narrative synthesis of data from all documents included in the systematic review will be generated. The results will be summarized into tables or figures as much as possible. A quantitative analysis is the ultimate objective of the systematic review to quantitatively highlight the effects of interventions on the antibiotic-resistance burden in the environment. The quantitative study will be possible only after assessing the content and the quality of full texts. Meta-analyses would be carried out and reported if several studies allow for the calculation of effect sizes. If conducted, heterogeneity or publication bias will be assessed quantitatively in meta-analyses.

Additional file

Additional file 1: Table S1. List of search terms. Key search terms used in scientific publication databases.

Authors' contributions

This systematic review protocol is based on a draft written by AG. The draft was discussed with all authors at a meeting on 2017-06-26. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interest.

Availability of data and material

Not applicable.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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