A systematic review of rodent control as part of infectious disease control programs.

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Conflict of Interest

No conflicts of interest to declare

Abstract

We investigated the empirical evidence supporting chemical rodent control as a public health program via a systematic search of the scientific databases PubMed and Web of Science, searching for term-strings for the concepts: "rodent control" and "zoonotic disease". Retrieved results were screened by title and abstract to eliminate studies that i) do not involve rodents, ii) do not contain a zoonotic component, iii) involve rodents and zoonosis, but no rodent control. Remaining articles were read full-text, eliminating studies that lack direct assessment of rodent control effects, with pre-/post-control measures of epidemiological outcomes. 957 entries were recovered and only 5 passed all elimination criteria. Studies were concentrated in Iran, focusing on zoonotic cutaneous leishmaniasis control. The studies found significant effects in zoonotic incidence post-control, but achieved low scores in quality-of-report assessment. The effectiveness of chemical rodent control as a measure against zoonotic disease is in its infancy, and more studies are necessary to allow an adequate assessment of the method. It is strongly recommended that future studies in the subject should adopt standardized guidelines to report studies.

Keywords: rodent-borne zoonosis, public health, pest control, commensal rodents

Introduction

Rodents and man have doubtless been at odds since the dawn of civilization, with evidence of rodents as both health and economic pests, and evidence of control measures going as far back as the Bronze Age (3300 BCE to 1200 BCE) (Borojevic et al. 2010). Today, rodent control – aiming to control and eradicate invasive rodent species (especially from the genera *Rattus* and *Mus*) – is a global effort and an industry evaluated at over USD 18.2 billion (16.25 billion Euro at 2019 exchange rates) (OECD 2022, Yeware 2019).

Rodent control is relevant in several different spheres, such as conservation biology in areas with invasive rodent species (Duron et al. 2017), agricultural sciences and crop pest management (Capizzi et al. 2014, Swanepoel et al. 2017), and public health, as rodents are common reservoirs of zoonotic diseases (Meerburg et al. 2009). Rodents are also of more general public interest, given their association with large economic losses due to property damage, infrastructure and incidental fires, particularly in urban contexts, with an estimated global financial damage over 23 billion Euros per year (41.65 billion dollars at 2018 exchange rates (OECD 2022)) (Jacob and Buckle 2018).

Today, rodent control is well-understood and established as a matter of public health (Babolin et al. 2016, Combs et al. 2019), with control programs being carried out as part of governmental public health policies both in urban and rural contexts (Colombe et al. 2019), with rodenticide application as the main modality of rodent control applied worldwide (Jacob and Buckle 2018). In spite of this, the efficacy and size of effect of the control programs on reducing or eliminating the incidence of rodent-borne zoonoses is largely unknown and is often not reported as part of the results of rodent control programs. Hence, the translation of the efforts and resources spent on control programs into public health benefits cannot be evaluated, and thus cannot inform the control programs' planning. In this review, we address this issue by performing a systematic review of the published evidence on the impact of rodent control measures on human zoonotic outcomes.

Materials and Methods

Systematic search protocol

In December 2020, we performed systematic searches using the electronic databases Web of Science (https://www.webofknowledge.com) and PubMed (https://pubmed.ncbi.nlm.nih.gov). Keywords strings relating to the main concept of rodent control and eradication were used to find studies of rodent management for zoonosis control. (The search strategies used are shown in Table 1.). The search covered the last 50 years of the periodical literature (1970-2020). Only peer-reviewed articles with full text in English were considered. The search protocol has been indexed in the International Prospective Register of Systematic Reviews (PROSPERO) under number CRD42020199140 (2020).

Processing the search results

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement and checklist) guidelines (Moher et al. 2009) and the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS guidelines) (Moons et al. 2014). Results were imported to a reference management software, followed by an exclusion of duplicates. A manual check of the search results was performed by examining the title and abstract of each entry, excluding studies related to rodent control with no clear link to zoonosis control (e.g., studies on genetics of rodenticide resistance, knowledge, attitudes and practices studies, or rodent control for crop protection and food safety). Remaining entries were then examined by reading the full manuscript to check 1) whether they actually evaluate the impact of rodent control on zoonosis cases in humans; 2) the zoonotic agent(s) involved; 3) the study design; 4) the methods applied for rodent control; 5) the methods applied to measure the efficacy of rodent control; 6) the zoonotic outcome measured (e.g. transmission rate, incidence, prevalence); 7) the method for outcome measurement; 8) the effect (positive or negative) of rodent control on the measured outcome; 9) the quality of the reported study, assessed using the Checklist for Quasi-experimental Studies (non-randomized experimental studies) developed by the Joanna Briggs Institute (2020), where items that fulfilled the criteria presented by the instrument were awarded a point, while incomplete/insufficient/absent items were not.

Entry classification was performed independently and asynchronously by two researchers. Classification agreement was evaluated using Cohen’s Kappa, calculated using the Vassar Stats online tool (Lowry 2001).

Results

The overall search retrieved 957 results (Fig. 1). After title and abstract evaluation 382 records were removed for being out of scope of rodent studies, 69 were removed for being studies on rodent-borne zoonosis but without any rodent control measure, and 478 were removed for being non-zoonosis-related rodent control activity (e.g., crop protection, conservation-related rodent control, studies on effectivity of rodenticides). Thus, 28 full documents were evaluated, of which 22 did not report any evaluation of the effect of rodent control in zoonotic outcomes in humans, and another one had no rodent control as part of the zoonosis control study, resulting in five articles fulfilling the criteria. Cohen’s Kappa indicated adequate agreement between evaluators (unweighted kappa = 0.712; 95% CI 0.4427-0.9817).

The five articles included were classified as Non-Randomized Controlled Cluster Trials (*sensu* Schmidt (2017)), evaluating the effect of rodent control campaigns using rodenticide on incidence of cutaneous case-control leishmaniasis in Iran (Akhavan et al. 2014, Ershadi et al. 2005, Veysi et al. 2012, Veysi et al. 2016, Yaghoobi-Ershadi et al. 2000). All studies used a design with two intervention areas (testing one control method in one area, and another in the second) and one control area (Akhavan et al. 2014, Veysi et al. 2012, Veysi et al. 2016), or two interventions areas and one control area (Ershadi et al. 2005, Yaghoobi-Ershadi et al. 2000) (Supplementary material 1). All studies followed a standardized rodent control routine involving: i) a census of all rodent burrows in a 500-meter radius around each household, ii) the destruction of identified rodent burrows, iii) application of poison baits 48 hours after the destruction of burrows, iv) reassessment of the rodent situation and re-baiting of active burrows; with the activities starting as early as April and normally being finished by September, with the exception of Ershadi et al. 2005 where rodenticide application was performed once a month. Zinc Phosphide was used as rodenticide mixed to foodstuffs in all studies, while Veysi et al. 2012 also applied Coumavec® (composed of the rodenticide coumatetralyl and the insecticide etofenprox. Composition not informed in the manuscript). Akhavan et al. 2014 applied phostoxin (aluminum phosphide) as well, and Veysi et al. 2016 also used Klerat® (a commercial rodenticide with Brodifacoum as active component. Composition not informed in the manuscript). All studies used visual census of active burrows to assess the efficacy of the control method chosen on reducing rodent numbers.

Human cases of leishmaniasis were surveyed through home visits, where people with active cutaneous lesions in conformity with the clinic symptoms of cutaneous leishmaniasis were identified, and the survey data was used to calculate the incidence rate of infection and observe if incidence changed after rodent control. All studies found statistically significant differences in the incidence of leishmaniasis after rodent control.

Quality assessment

Based on the Joanna Briggs Institute criteria, the articles had modest quality scores (4 out of 9 points) (Table 2). The description of the study design (i.e., characterization of areas and populations, field procedures) was often laid out in sparse detail and gave little explanation on criteria such as: i) similarity criteria to assess whether the intervention and control populations are comparable; ii) outcome measurement and reliability mechanisms. The statistical analysis plans were extremely brief (e.g. five lines of text in Akhavan et al. 2014), and lacked useful context to provide information about the adequacy and explanatory power of the analysis plan proposed. Bias control was also not addressed. The sparse characterization of the populations in the studied areas was partially addressed using an outcome measurement expressed in relative numbers (incidence per thousand individuals).

Discussion

The surprisingly low number of studies evaluating the effects of rodent control on zoonosis transmission hinders any further discussion on the merits of the practice. Although the articles found present positive results (Akhavan et al. 2014, Ershadi et al. 2005, Veysi et al. 2012, Veysi et al. 2016, Yaghoobi-Ershadi et al. 2000), they allow little generalization. This hinderance is due to: 1) the small number of control and experimental sites used; 2) being focused on single control events (instead of a rodent control program with systematic implementation as a continuous service); 3) a single zoonotic system and localized context is involved in the studies. Leishmaniasis is a vector-borne zoonosis, transmitted by sand fly (Diptera:Psychodidae, genus *Lutzomyia*) bites (Roque and Jansen 2014). The studies above fail to provide information on whether some manner of vector control is taking place, and do not account for the possibility of variations in vector density affecting the measured outcome (Roche et al. 2013). This contrasts with other zoonotic control subjects such as sand flies (Barata et al. 2011, Dinesh et al. 2017), and ticks (Brei et al. 2009, Schulze et al. 2017), for which there are studies that also assess effects on the target population size although through indirect measures (parasite burden on captured hosts). Mosquito control has been subject of a recent systematic review (Oliver et al. 2021) also identifying a small number of studies evaluating control programs (N= 8).

Despite the consistent trend of rodent control measures having a positive zoonotic disease outcome change, the studies have a very simple study design, with a single instance of rodenticide application as rodent control activities were limited to the period between April and September, following the dipteran vector life cycle previously reported in the area (Veysi et al. 2012), and only one study carried out new interventions when the proxy used to estimate rodent population (number or burrows with signs of active occupation) reached a certain threshold (Ershadi et al. 2005). Studies also used few independent test sites for the interventions ($N \leq 2$), and only two studies (Ershadi et al. 2005, Yaghoobi-Ershadi et al. 2000) characterized the human populations of the areas studied, both in population numbers (villages with 300-400 inhabitants in desert environment) and epidemiological indicators (incidence of leishmaniasis per 1000 people); all other papers lacked this information. The use of non-randomized clustered trials with very little information on the selection criteria and a focus on comparing the effect of different rodenticide treatments (instead of testing the base premise that “rodenticide treatment is effective on controlling rodent-borne zoonosis”) also weakens any conclusions on its efficacy as a health program. The lack of variety of pathogens, reservoir systems, and environments, coupled with the limitations of the study designs, hinder any possible generalization or putative claim that there is solid evidence that rodenticide baiting campaigns or any other kind of rodent control program is effective in reducing human zoonotic health risk. Small arid-climate villages have limited translation to highly anthropized environments with high demographic density (Costa et al. 2017, Himsworth et al. 2013).

This presents a serious problem with regards to the design and implementation of interventions. It has become evident that rodent control programs should become evidence-based, taking into account the ecology of the target species and their environment, in order to achieve their goals (Parsons et al. 2017). Unfortunately, rodent management practices often lack basic information being reported with standardized methodologies. The size of the effect of the control program should also be reported to inform future interventions regarding remaining target size. It is also worth noting that evaluations of a population control program to control a zoonosis are necessary to certify that the effects are actually positive. For example, the population control of stray dogs in areas with leishmaniasis has been questioned on whether the reduction of reservoir dog numbers actually diminishes the incidence of cases (Costa and Vieira 2001, Desjeux 2004).

The idea of controlling the populations of zoonotic reservoir species reducing the impacts of zoonotic disease in humans seems intuitive, as it reduces the chance of vector infection by reducing the possibilities of a contaminating contact (also called dilution effect) (Roche et al. 2013). An opposite effect, however, could be seen as the vacuum left by the removed individuals (or species, in multispecies reservoir systems) can cause a migration influx, reseeding the transmission cycle (Himsworth et al. 2013, Johnson et al. 2015, Zeppelini et al. 2016).

Rodent control programs have focused on suppressing and/or reducing the resident rodent population of a given area by means of systematic rodenticide application (BRAZIL 2002, Centers for Disease Control and Prevention 2006), with secondary implementation of environmental manipulation (such as rat proofing buildings or remove available burrow terrain). However, this reliance on chemical control faces issues such as i) population rebound (as it does not affect the ecological support that the environment can provide to the remaining population, or addressing the possibility of repopulation through migration); ii) unequal effect and reach within the population due to neophobia and differences on movement and exploratory/foraging behavior within the social structure of the population (and the subsequent selection of neophobic and/or chemical resistance traits within the surviving population) and; iii) limited success, effectivity and reduced confidence in the method (Byers et al. 2019, Desvars-Larrive et al. 2017, Macdonald et al. 1999, Parsons et al. 2017, Schweinfurth 2020, Zeppelini et al. 2020). On certain cases, it is possible that rodent control produces the opposite effect on zoonotic transmission (Himsworth et al. 2013, Murray and Sanchez 2021). Rodent control commonly lacks the adequate ecological information to inform the design of the intervention, especially in urban settings, which represent important areas for the activity, and the historical evidence that supports the current understanding on the practice is skewed towards northern temperate regions with a somewhat high degree of urban planning (when compared to fast growing cities in the developing world (Combs et al. 2018, Zeppelini et al. 2020). This lack of properly contextualized supporting information for current rodent control programs presents another issue to be taken into account in potential evaluation efforts.

The quality of the scientific reports was a hinderance in this review, as indicated by the Joanna Briggs Institute assessment tool (Table 2). The analyzed studies still present substantial room for improvement in design presentation, analysis and methods, and as of now do not compose enough evidence to risk any extrapolation or generalization. Future studies need to take into account the importance of standardization in study reports, especially in studies of public health concern such as zoonosis control, in order to maximize the informativity of studies conducted (von Elm et al. 2007). The adoption of a well-established and widely adopted standardization protocol, such as the PRISMA statement (Moher et al. 2009) could greatly benefit both researchers reporting their findings and the audience of such literature. Standardized protocols present and contextualize the fundamental items that must be reported in a well-informative and reproducible study, with guidelines specific for each type of study design; thus, facilitating the assessment of study quality, the accessibility of the information, and the reliability of decisions and meta-analyses. This study identified the need for improvement in the statement of aspects such as data relating to the follow-up of human participants, the definition of human infection outcomes, and the appropriate statistical analysis plan on published papers in the field of rodent control.

Finally, it is important to address potential sources of bias in our results. Publication of research results is naturally biased on itself, as positive results tend to be more readily published in peer-reviewed journals (Mlinaric et al. 2017). Publication of negative results in the field of zoonotic rodent control represents important information about the (in)effectivity of the control methods, and could indicate the need to divert attention to other control methods, or that the method needs to be optimized to achieve suitable performance. It is necessary to also address the limitations on the raw data pool used in this review. Only two databases were searched due to time constraints and people power to process entries. However, the databases were consciously chosen as to cover a solid array of public health, epidemiology and applied ecology journals that would likely report our target studies.

Conclusions

The effectivity of rodent control intervention programs on controlling zoonotic risk for human populations is a field of study in its infancy. Our results make clear the urgency for studies evaluating the impact of the various modalities of rodent control (trapping, poison baits, fertility control, landscape management, etc.) on the transmission cycle of (several) zoonotic diseases. The empirical testing and comparison of the efficacy of different rodent control methods on zoonotic risk mitigation is fundamental to designing the most efficient, cost-effective, bioethical and environmentally safe control programs that will work at short and long term. In other fields of rodent control (e.g., crop protection, ecological conservation, development of control methods) studies similar to the ones necessary for zoonosis control are a well-established research field that can serve as a guide to the endeavor ahead (Jakel et al. 2017, Jakel et al. 2015, Tabak et al. 2015, Vadell et al. 2017). It is also clear that designing and reporting health-related studies can benefit from standardization of parameters to increase the public health benefit yielded from the studies.

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Table 1: Search strategies applied in the review.

Database	Keyword string
PubMed	("Rodent Control"[Mesh] OR “rodent control” OR “control rodent” OR “rat eradication”)
Web of Science	“rodent control” OR “control rodent” OR “rodent eradication” OR (“rodent-borne zoonotic diseases” AND control)

Table 2: Quality Assessment scores for the studies analyzed in the review based in the Joanna Briggs Institute Checklist for Quasi-experimental Studies (non-randomized studies) (2020). Question marks represent categories where the classification of the manuscripts was uncertain or not applicable.

	Yaghoobi-Ershadi et al. 2000	**Ershadi et al. 2005**	**Veysi et al. 2012**	**Akhavan et al. 2014**	**Veysi et al. 2016**
Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	Y	Y	Y	Y	Y
Were the participants included in any comparisons similar?	?	?	?	?	?
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	Y	Y	Y	Y	Y
Was there a control group?	Y	Y	Y	Y	Y
Were there multiple measurements of the outcome both pre and post the intervention/exposure?					
Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	?	?	?	?	?
Were the outcomes of participants included in any comparisons measured in the same way?	Y	Y	Y	Y	Y
Were outcomes measured in a reliable way?	N	N	N	N	N
Was appropriate statistical analysis used?	N	N	N	N	N

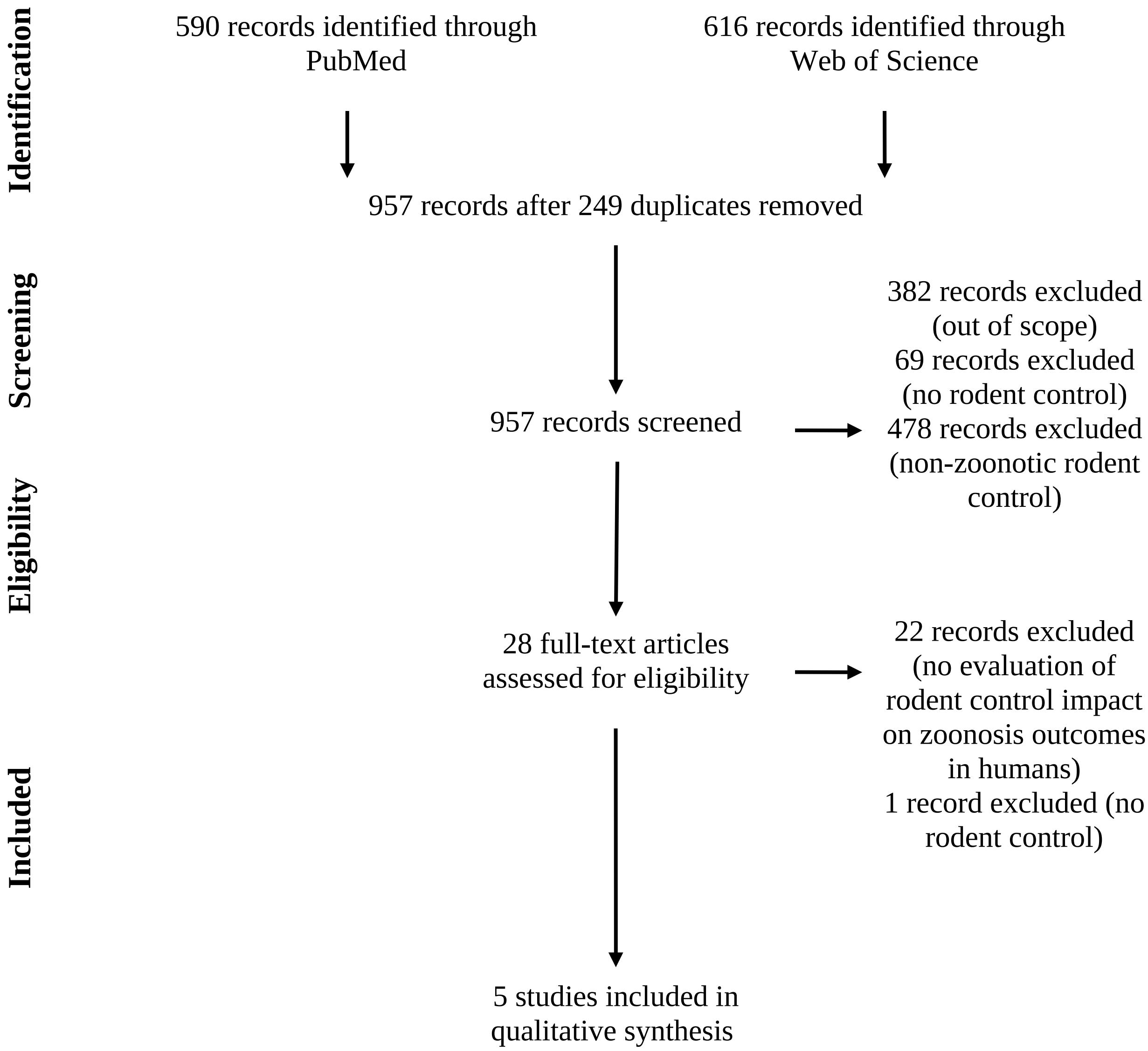

Figure 1: Flowchart summary of the screening process of articles included in the synthesis.

Supplemental material 1: Study design, pre- and post-treatment outcome measures for human zoonotic incidence and rodent infestation, and observed results of the five studies analyzed in the review. ZCL = Zoonotic Cutaneous Leishmaniasis.