zoonotic diseases

Perspective

Chemical-Based Rodent Control Programs as a Zoonosis Control Measure: Proposal of Guidelines for Empirical Proof Studies

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Simple Summary: Diseases spread by rodents are a serious problem, especially in poor urban areas. While many programs use rodenticides to control the diseases they carry, we lack solid proof that they work. This study suggests better ways to test whether rodenticides help protect public health. Key recommendations include the following: Refining methods to obtain reliable results; using urban slums as study sites, given their disproportionate impacts; teamwork with pest control and communities to ensure longer-lasting solutions; studying diseases that spread easily (through contact or the environment) for clearer results; monitor people's health to see if rodent control reduces disease; improving recordkeeping for better analysis; set short and long-term goals; understanding the phenomena behind rodent control; sharing findings in a clear, consistent way. The goal is to improve how we study rodent control so we can better protect people's health.

Abstract: Rodent-borne diseases threaten global public health, impacting the urban poor. Despite widespread application of rodenticide in rodent/rodent-borne disease control programs, empirical evidence demonstrating their effectiveness is lacking. This review proposed guidelines for designing and implementing empirical studies on rodenticides as public health measures. The recommendations include: (i) the importance of the type of quasi-experimental design adopted, and how it creates robust evidence; (ii) how urban slums present both challenges for control and ideal settings for studies; (iii) partnering with pest control authorities and community engagement for long-term viability; (iv) leveraging zoonotic systems with direct/environmental transmission, reliable diagnosis, and high prevalence for effectivity assessment; (v) pairing human cohort studies to observe epidemiological links; (vi) systematic data collection and management protocols; (vii) short- and long-term goals for critical evaluation and course-correction; (viii) focus on mechanistic approach; (ix) the need for standardized reporting of the findings.

Keywords: *Rattus*; zoonotic disease; public health; research method

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1. Introduction

Rats are among the oldest and most impactful pests humankind has faced throughout history. Infestations can destroy crops and food stocks, damage infrastructure, cause domestic accidents like fires, and affect human well-being and safety [1–3]. Economically, rats cause millions of USD in damages every year [4], and the control industry built in response was evaluated to cost 24 billion USD in 2022 [5]. Yet, their gravest threat is rodent-borne diseases, including *Leptospira* spp., *Borrelia* spp., Seoul Hantavirus, Hepatitis E virus, *Toxoplasma gondii*, *Salmonella* spp., and *Angiostrongylus cantonensis* (the rat lungworm, a causative agent of meningitis). Rodent-borne pathogens generate impacts of over 23 billion Euro per year [3,6–9]. Beyond communicable diseases, rat infestations also profoundly impact mental health [1,10,11].

Humans have likely been battling the threat posed by rats for millennia, with the earliest records of rodent-control measures dating back to the Bronze Age [12]. Today, some type of rodent control program is being carried out in most urban and rural areas [3]. Despite increased prevalence of integrated pest management (IPM) [13], anticoagulant rodenticides remain the predominant method for rodent control worldwide, including as part of IPM [2]. Empirical evidence indicates that rodenticide-based control alone is effective in reducing populations in the short term, but fail in long-term or permanent reduction, as populations recover within a few months after control is relaxed or interrupted [14–16]. Rodent control programs are often not based on evidence and knowledge on the ecology of the target species, their relationship with the environment, and the dynamics of rat–people–environment systems [17].

Low- and Middle-Income Countries (LMICs) are experiencing the highest and fastest rates of urbanization in the world [18], a phenomenon associated with disorganized growth and urban poverty due to mass migration of rural populations to city centers in search of better economic prospects [19]. This growth is concentrated in urban slums, the "informal" part of the city, that are often deprived of basic infrastructure and urban services (solid and water waste management, reliable clean water provision, adequate stormwater drainage systems, pavements, housing security, etc.), which, compounded with poor access to formal employment and/or living wages, reduces environmental health and consequently leads to a higher disease burden—infectious or otherwise [20]. Poor urban communities are highly conducive for rodent infestation and disease transmission, normally facing the brunt of the burden of infectious disease [21–24].

Evidence supporting the efficacy of rodenticide-based rodent control programs is minimal, with only six studies published to date. While these studies present some evidence of a reduction in human disease cases, their study designs severely limit their power of evidence, do not represent systematic rodent control programs, and often focus on other objectives such as comparing the efficacy of different rodenticide baits [25,26]. These studies were conducted in a single territory (Iran), examining a single zoonotic pathogen (*Leishmania* sp.). The lack of empirical evidence on the effectiveness of rodenticide programs is concerning, given existing evidence that the opposite effect, an increased risk of disease transmission, is also possible [27,28].

The gravity of the issue requires high-quality, well-designed, and well-reported empirical studies to inform public health practice and policy, potentially saving significant resources and lives. In this context, I present a set of recommendations for the design of real-world field studies aimed at evaluating the effects and potential efficacy of rodenticide-based rodent control programs targeting zoonotic disease control.

2. Consider a Before–After Control–Intervention (BACI) Design

The fundamental design of a study aiming to evaluate the effects of rodenticide as a public health intervention against rodent-borne zoonosis requires a quasi-experimental (as in real-life settings, random application of the treatment is not feasible) control–intervention (where a group remains untreated while another receives some intervention or treatment) design [29,30]. However, when possible, researchers should consider adopting a BACI (Before–After Control–Impact) design. BACI is widely regarded as the most robust framework for environmental impact studies, as it not only compares treated and untreated groups (control–intervention) but also tracks changes in the same population before and after intervention [29].

An ideal design would include a set of intervention–control replicates, first sampled right before beginning the rodenticide intervention to establish a baseline. Follow-ups should occur at regular time intervals (e.g., every three or six months, as this is the estimated period necessary for recovery of rodent populations after control; see [14]). Timing and periodicity of follow-ups should be organized to capture environmental variability (rainy–dry seasonality, any large-scale demographic change that might occur in the study area with predictable periodicity). Control areas should be paired with their intervention counterparts based on similar territory (size of area, topography, vegetation, and buildings), population (similar human occupancy), and infestation (similar history of reports of rodent complaints) characteristics. This requires working in areas not currently covered by pest/zoonosis control services but expected to be included in the near future, guaranteeing long-term provision of rodenticide control in the intervention areas, at least during the study period. While possible, working together with the pest/zoonosis control authority to know where and when they will extend their coverage.

3. The Urban (Slum) Expansion of the Global South: An Opportunity and Call for Action

The importance—and urgency—of addressing zoonotic and vector-borne disease (including rat-borne) in LMIC urban slums is already recognized as a key opportunity for transformative research [20]. These environments offer opportunities for conducting robust studies on rodent control and disease transmission due to the following factors: (I) chronic rat infestations with high animal density, which increases the odds of contact with humans, individuals reaching baits and overcoming neophobia, and the detectability of the effects of control; (II) high human population density and transmission risk; (III) large urban centers often present multiple slum communities, allowing the selection of comparable yet sufficiently spatially distant study sites to ensure analytical independence.

For example, the city of Salvador (Brazil) is a large (2.5 million inhabitants) urban center with over 240 slum communities [31]. It has a long and well-documented history of rodent-borne disease, mainly leptospirosis [32]. Jakarta (Indonesia), with over 10 million inhabitants, is home to approximately 200 slum communities [33] and presents endemic leptospirosis issues [34] as well as Hantavirus circulation [35].

Although an argument should be made for the uniqueness of each "slum system" given the confluence of ecological, historical, economic, and sociological factors to compose the reality of each locality, there are common phenomenological threads among these communities that allow for reasonable comparisons to be made.

It should be noted that the 'informal city' status of slums, the sociopolitical–economic marginalization, and the challenges inherent in working with vulnerable populations require special consideration. While the next section addresses the aspect of collaborating with rather than working on local communities, it does not exhaust the matter. Partnering with vulnerable populations is a complex process, and the power dynamics should be considered—and leveraged—when advocating for these communities (see [36–38]). The bioethics of working in fragilized environments like slums lack clear and unique answers. Studies should be conducted under significant ethical scrutiny to avoid further ecosystem degradation, biodiversity impacts (e.g., rodenticide pollution and bycatch [39]), and unethical vivisectionist practices [40].

4. Team Up with Public Rodent Control Services and Local Communities

Collaborating with a public rodent/zoonosis control service operating at municipal, provincial, or state levels represent the ideal conditions for conducting efficacy assessments. Rodent control programs are usually implemented at the municipality level, targeting either rodent population reduction, zoonosis, or both [13]. The support of a public agency performing systematic rodent control campaigns allows us to build a reliable baseline given the standardized nature of the programs, as well as possibly providing historical data through the records kept by the agency. The records facilitate the defining of study sites based on the history of complaints and/or incidence of disease per community, as well as identifying areas not covered by the service that could serve as controls.

Developing a case–control study by leveraging the limitations of existing control programs, often underfunded and uncapable of covering all affected areas [3], provides an ethical option to develop a case–control study design. The other option (denying the rodent control service to the communities chosen as controls) would deprive residents of potentially life-saving protection against zoonotic transmission, however flawed it might be.

The involvement and engagement of the local population is fundamental for the success of intervention programs, whether in conception, feasibility, maintenance, or long-term success [3,13,41]. Engaging residents in the study areas is crucial for assessing the realities of the communities at a level usually not measurable by conventional methodologies (infestation indexes, surveys and other current standardized approaches), understanding the nature of human–rat conflicts, and empowers this disenfranchised population to address the challenges posed by rodent infestation and their physical, social, and mental health impacts [10,11,42]. This process is also essential for increasing acceptance of the program, which can be perceived as the incursion of "foreign forces" (the rodent control authorities) in their territory, as well as bringing the locals into the control efforts.

Community engagement is a multifaceted process with no clear roadmap to achieving success, as each community's conditions and challenges emerge from complex physical and historical processes. The task requires understanding the relationships between people and their reality. Knowledge, Attitudes, and Practices (KAP) studies are valuable initial tools to assess the symbolic and practical dimensions permeating their relationship with significant real-life issues, also providing insights to identify potentialities and points of attrition that might influence their interface with control programs (e.g., [43,44]).

However, engagement cannot stop at top-down or 'extractivist' (i.e., university/researchers performing research and the community acting as a "research subject", with research outputs created within academic boundaries) approaches; these should be a preparatory step. The process must involve the residents as proactive agents in the production of knowledge, co-responsible for directing the process, and foster ownership of the decisions that affect their reality. Several participatory methodologies are possible and allow local participation and input (e.g., [45,46]), providing both deeper insight and creating stronger bonds with the communities.

5. Choose a Simple, Strong Zoonotic System

The goal of rodenticide application is rodent population reduction and, consequently, reduced rat-to-human transmission of zoonotic pathogens. Although there is some weak evidence indicating that rodenticide control might reduce zoonotic transmission [25,26], there is contrasting evidence indicating that culling reservoir species does not affect the risk of transmission to humans [47,48]; there is also the risk of lethal control aggravating risk of transmission by increasing pathogen prevalence in reservoir populations [28]. Given the uncertain evidence and the potential negative outcomes of lethal control, the choice of zoonotic system is important to provide the clearest possible signal and best detect the type and size of effect derived from the lethal control program, clarify the potential role that lethal control might have in Integrated Pest Management (IPM) scenarios, and ultimately inform studies on more complex systems. Since rodenticide control is unlikely to be eliminated from IPM programs, particularly in resource-strained settings, the selection of the system for this proof of concept must be thoroughly considered.

Ideal target rodent-borne diseases for a study should have the following:

5.1. High Incidence/Prevalence, Both in Asymptomatic/Subclinical Infections and Severe Etiologies

This usually characterizes a disease with significant human impact (e.g., leptospirosis [49]). In proof of concept studies, the high prevalence of asymptomatic infections enhances statistical power of detection of even small effects of rodenticide control. This provides robust power for exposure and morbimortality risk analysis [50].

5.2. Direct or Environmental Transmission

Choosing a pathogen transmitted by direct contact, fomites, and aerosols (e.g., Hantavirus, [51]) or through contaminated water, soil, or foods (e.g., leptospirosis, [52]) provides the simplest system possible and reduces the amount of non-controllable variables that can alter the relationship between the effects of control and human epidemiological parameters. Leishmaniasis, an example where lethal control of reservoirs did not result in positive human outcomes, is a vector-borne disease. The lack of reduction in human incidence could be due to the vector maintaining transmission despite a decrease in the reservoir population [48]. A simple reservoir–host pathogen transmission system, such as leptospirosis, is advantageous for the proof of concept given the relative ease of modeling all components of the system [53].

5.3. Fast and Reliable Diagnostics

Reliable, unambiguous, quick, and cheap diagnostic methods are essential for proper population characterization and accurate epidemiological assessment of incidence and risk. Highly sensitive diagnostics, such as microagglutination tests for leptospirosis [52] and antibody tests for Hantavirus [51], provide dependable results without the need for very large population sizes to achieve adequate epidemiological resolution for risk assessment.

6. Epidemiology: Cohorts and Surveillance

This proof of concept requires a two-pronged approach to epidemiological characterization and effect size evaluation of rodent control programs. As previously stated, it is necessary to assess both risk of exposure and of developing severe etiologies.

A serosurvey cohort study of the populations in the study areas will be necessary for the following steps: (I) characterize spatiotemporal patterns of infection risk exposure and (II) measure the effects of the control program. Following the design and periodicity proposed in "Consider BACI design", serological cohorts enable monitoring incidence/prevalence patterns in time (e.g., [54]), detecting changes, and identifying potential associations with control efforts.

Hospital surveillance should be implemented to assess the effects of control on severe cases, as well as the impacts on healthcare systems. Surveillance could occur at a primary stage, collaborating with the hospital system to actively identify target cases, geolocate their origin, and evaluate changes in distribution over time. Alternatively, secondary surveillance may utilize historical databases of hospital admissions (e.g., [55]).

7. Collect Solid, Systematic Data

Having a solid and systematic data collection protocol with standardized instruments allows for uniformity in sampling. The quality of evidence relies significantly on high-quality datasets, with poor study design and data collection being responsible for reducing reliability of evidence [25]. Nowadays, computer tools are available to help with data gathering, curation, and quality control. For example, REDCap (https://www.project-redcap.org/) is a secure web application for data collection through questionnaires and instruments tailor-made by the researchers and depositing data into a central server controlled locally by the research team. REDCap allows for the highest standards of data quality control and has been applied in projects of over 7500 institutions (e.g., [56,57]). If REDCap is not feasible for any reason, there are other free systematic data collection tools, such as EpiCollect (https://five.epicollect.net/). If the use of electronic solutions is unfeasible, producing standardized comprehensive forms should be applied.

Rodent sampling should provide a reliable portrait of the target populations. This is necessary to assess the effectivity of the control campaign (e.g., [15]), and the effect on pathogen circulation within hosts, as lethal control could unexpectedly increase prevalence in reservoir hosts [28]. The area should be well covered by a distribution of randomized points sampled for several consecutive days. This accounts for neophobia [58] and better characterizes within-population variations [59]. Several studies on rodent populations in urban poor areas are available to serve as a guide for designing studies that consider detection of adequate ecological and epidemiological data (e.g., [7,60]). While rat trapping (either lethal using snap-traps or live-trapping with cages) is fundamental for obtaining certain physio–ecological data (e.g., infection/parasite load, body condition, genetics), trappability is not uniform within populations and is affected by several environmental factors [59]. Other dimensions of rat presence/activity data are important for proper characterization of demography and ecological dynamics, improving the understanding of rat infestations (for an example of a method combining different sources of rodent data, see [61,62]).

Data collected should not be limited to captures alone. At the sampling point, it is important to have an instrument for environmental characterization, including a description of the landscape components and how they are distributed. Give emphasis on resources important for rodent infestation (such as garbage, soil, water), vegetation, presence of other animals (dogs, cats, opossums, etc.), situation of nearby buildings (Is it abandoned? Are its walls plastered? What is the material of its fences? Does it have points of entry for rats?), and the presence of accumulated materials, debris, or rubble. For examples of applied data collection protocols, please check [41,63,64].

8. Short- and Long-Term Goals for Effectivity Evaluation

The proposed study design should characterize both short- and long-term effects of rodent control in the zoonotic system. Rodent control is financially and labor-intensive, while also involving public health risk. The practice could represent an ecological hazard as poison baits will degrade when exposed to the sun and rain, can be ingested by non-target species, or seep into the soil. While longer-term studies would provide more robust evidence and better justify the maintenance or suspension of rodenticide programs, shorter-term evaluations are important for assessing the continuity of the study. Should short-term evaluations indicate significant negative effects or no appreciable effects on human risk, it is worth evaluating the discontinuation of the rodenticide program.

The definition of what would constitute short- and long-term is an issue that has no single, hard-set answer. The minimum time interval to observe demographic effects of rodent control on populations is arguably three to six months. This, corresponding to the time for female sexual maturation and recruitment of a new generation [65], also considers the average time in which population rebound happens after control [14]. Current evidence, however, does not allow for solid links between control effects and epidemiological parameters in rodent populations, although it is expected that the effects on demography should be reflected on pathogens circulation [28,60,66,67]. Defining the time for short-term goals should consider these factors and span at least a few repetitions of the reproductive cycle mentioned above. Two years is possibly a good compromise between quickness of response and sufficient time of observation, as observed in short-span ecological studies [56,68]. This duration also allows for the coverage of two complete seasonal cycles (wet and dry seasons). Under extreme time and resource constraints, one year might be used to observe at least two reproductive cycles [14,41,69], although the limitations on ecological variation should be kept in mind. Long-term observations reflect a the-more-the-better situation to a certain degree, where the final timespan of the study should be decided in relation to practical and methodological aspects of the project (e.g., viability of fieldwork, statistical requirements of the final analysis, legal limits of ethical permits).

9. Mechanistic Understanding

A robust study should accomplish more than detecting effects and test significance. It is important to understand causal and feedback relationships between rodent control and human zoonotic risk within their ecological context, thereby adopting a mechanistic approach (for detailed discussion of mechanistic approaches in ecology, see [70,71]).

At the reservoir (rodent) level, demographic patterns (age, sex, body condition) and environmental dynamics modulate to individual pathogen positivity. These factors affect susceptibility, mediate risk of exposure through environment and social interactions, as well as indicate environmental and sociodemographic drivers of risk [60,66,72–74]. Rodenticide control becomes another ecological pressure present in the environment, affecting demographic patterns (e.g., unequal removal of individuals), activity (neophobia, avoidance), and potential pathogen positivity (altering behavior and physiology, among others) [16,17,27,28,75].

The local population is not equally exposed to risk. Social, racial, economic, educational, and laboral factors determine the odds and magnitude of zoonotic risk they experience as well as the outcomes of infection [42,54,76–78]. To capture these dimensions, it is necessary to collect systematic and robust environmental/ecological data (Section 7) associated with epidemiological data (Section 6).

A study that considers the present recommendations can better evaluate how environmental, human, and spatial factors affect disease transmission/risk. It can also help develop a model to characterize the zoonotic system dynamics (e.g., [53]) and, ultimately, holistically inform the viability of rodenticide-based zoonosis control programs based on the interplay of the system's components.

10. Standards for Reporting

The adoption of a reporting standard statement, such as STROBE for observational studies [79] or JARS–Quant proposed by the American Psychological Association for general quantitative research [80] allows uniformity in the reporting of research methods and findings, reducing bias as well as increasing comparability and future meta-analyses. Bias and quality of reporting assessment should be performed after writing the manuscript to evaluate adequacy to the proposed standards by (I) critically appraising the manuscript in comparison with the guidelines of the adopted statement, or (II) through standardized tools such as Joanna Briggs's tool for risk-of-bias assessment for quasi-experimental studies [81], for example.

11. Conclusions

Zoonotic disease poses a significant threat to humankind, with rodent-borne pathogens being of particular relevance to a world with an increasing portion of anthropic environments and growing urban populations. Evidence-based zoonosis control and prevention programs are urgently needed in a world recently made aware of its response limitations by a pandemic pathogen. The research program proposed in this paper aims to provide the best possible level of empirical evidence for a widespread public health practice with potential for large-scale economic, health, and environmental impacts.

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