



A framework for One Health research



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ABSTRACT

The need for multidisciplinary research to address today's complex health and environmental challenges has never been greater. The One Health (OH) approach to research ensures that human, animal, and environmental health questions are evaluated in an integrated and holistic manner to provide a more comprehensive understanding of the problem and potential solutions than would be possible with siloed approaches. However, the OH approach is complex, and there is limited guidance available for investigators regarding the practical design and implementation of OH research. In this paper we provide a framework to guide researchers through conceptualizing and planning an OH study. We discuss key steps in designing an OH study, including conceptualization of hypotheses and study aims, identification of collaborators for a multi-disciplinary research team, study design options, data sources and collection methods, and analytical methods. We illustrate these concepts through the presentation of a case study of health impacts associated with land application of biosolids. Finally, we discuss opportunities for applying an OH approach to identify solutions to current global health issues, and the need for cross-disciplinary funding sources to foster an OH approach to research.

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1. Introduction

The need for multidisciplinary research to solve today's complex health and environmental challenges has never been greater. The One Health (OH) approach to research addresses questions at the intersections of human, animal, and environmental health by utilizing the expert knowledge of researchers, including public health practitioners and clinicians, from multiple disciplines and at local, national, and global levels. While the need for multidisciplinary research is not new, the concept of OH has gained momentum as researchers from human medicine, public health, veterinary medicine, urban planning, and environmental science increasingly focus on holistic, integrated approaches to complex questions that address human health in conjunction with animal and environmental health [1].

The OH approach to research provides an opportunity for enhanced understanding of a range of health impacts and solutions. By looking at multiple dimensions of the problem through the lens of environmental, animal, and human health, researchers may discover influencing factors that they would not have otherwise seen, which can facilitate more informed intervention design. In 2015, the World Health Organization designated 11 diseases as high risk for severe outbreak, ten of which have a zoonotic reservoir or transmission vector [2]. An OH approach to studying these diseases may be able to provide more complete information about opportunities for outbreak prevention than a traditional one-dimensional approach. For example, a Lassa fever prevention intervention which targets the environmental (e.g. improved household sanitation) and animal (e.g. rodent removal) domains may show promise, but omission of the human domain (e.g. education of nurses on disposal of contaminated material in hospitals) may result in a missed opportunity to achieve optimum results. At worst, siloed approaches may lead to unforeseen detrimental effects. In the Lassa fever example, removal of rodent populations may result in increased malnutrition among humans if rodents were a significant direct or indirect (i.e. prey for larger food source animals) source of protein for families living in affected communities. The ultimate goal of OH research is to identify opportunities for health improvement and optimize risk mitigation simultaneously across all three domains [3].

Though many publications describe the benefits and individual applications of an OH approach [1,4–7], additional guidance for operationalizing the OH approach during the early phase of study design is needed. We address this need by providing a framework for the OH approach to conducting research, with a focus on conceptualization and planning. We illustrate this framework with a case study of the health impacts associated with land application of biosolids.

2. Framework

2.1. Conceptualization phase

To successfully develop a research project using an OH approach, investigators must consider incorporating elements from human, animal, and environmental health and the multiple intersections between each of these (Fig. 1).

2.1.1. Hypothesis and study aims

First, researchers must determine the precise questions they aim to answer and what relationships are known or theoretically exist between various exposure sources and outcomes. In this phase, it may be helpful to draw upon the expertise of research collaborators and

relevant literature to inform the development of a diagram or chart of these relationships. For example, a Directed Acyclic Graph could be used to visualize exposure-outcome pathways and identify important covariables and confounders [8]. Or, a logic model or similar multi-pathway visualization matrix may also be helpful for deciding where in the pathway to intervene and for brainstorming the potential impacts of the intervention on animal, human, and environmental health. For example, a graphing exercise may help the research team anticipate downstream factors of a vector control program that should be measured to both determine the program's effectiveness (e.g. reduced number of vector-borne illnesses) and to evaluate any adverse outcomes associated with the intervention (e.g. impact of mosquito fumigation on local flora and fauna or human respiratory illness associated with exposure to fumigation). Hypotheses and study aims can be based on the findings of this graphing process.

2.1.2. Collaborators and stakeholders

Building a multi-disciplinary team is crucial to the development of research projects which aim to use an OH approach. Researchers may look inside their own institutions or externally for relevant expertise. In the team-building phase, it is important to present the research question to a wide and varied audience to uncover perspectives far outside one's own field that may be unexpectedly relevant to the question at hand. Given the diversity of topics covered in the OH approach, study teams may benefit from involvement of, for example, epidemiologists, veterinarians, ecologists, urban planners, structural and environmental engineers, geologists, hydrologists, climatologists, geospatial scientists, botanists, parasitologists, and microbiologists, among others. Early involvement of specialists from each domain will encourage broader thinking in the planning process and will facilitate the aggregation of resources available in each domain, such as funding, staff, and data. Researchers may also consider involvement of community members who have on-the-ground experience with the issue in question, such as farmers, fisherman, park rangers, scuba divers, wildfire firefighters, plant workers, and community members who live near potential exposure sites. Involvement of community members is likely to enhance the research team's ability to collect new data and to understand the context of the data.

2.2. Planning phase

Having considered which topics from each domain to include in a study using an OH approach, the next steps are to determine the appropriate study design, and identify data sources, analytical methods, and data components required to adequately evaluate the research question(s).

2.2.1. Study design

Determining the study design informs the selection of data collection and data analysis methods. The OH approach may draw from a range of study designs which are utilized in multiple disciplines, including, for example, prospective and retrospective cohort, case-control, genome-wide association, randomized control trial, case series, natural experiments, twin studies, risk assessment or risk analyses, experimental studies, and ecological studies. Due to the complexity of the OH research approach, the overall study design may be a combination of these. For example, a retrospective ecological evaluation of arboviral disease incidence in relation to deforestation patterns could be combined with a prospective natural experiment to assess changes in

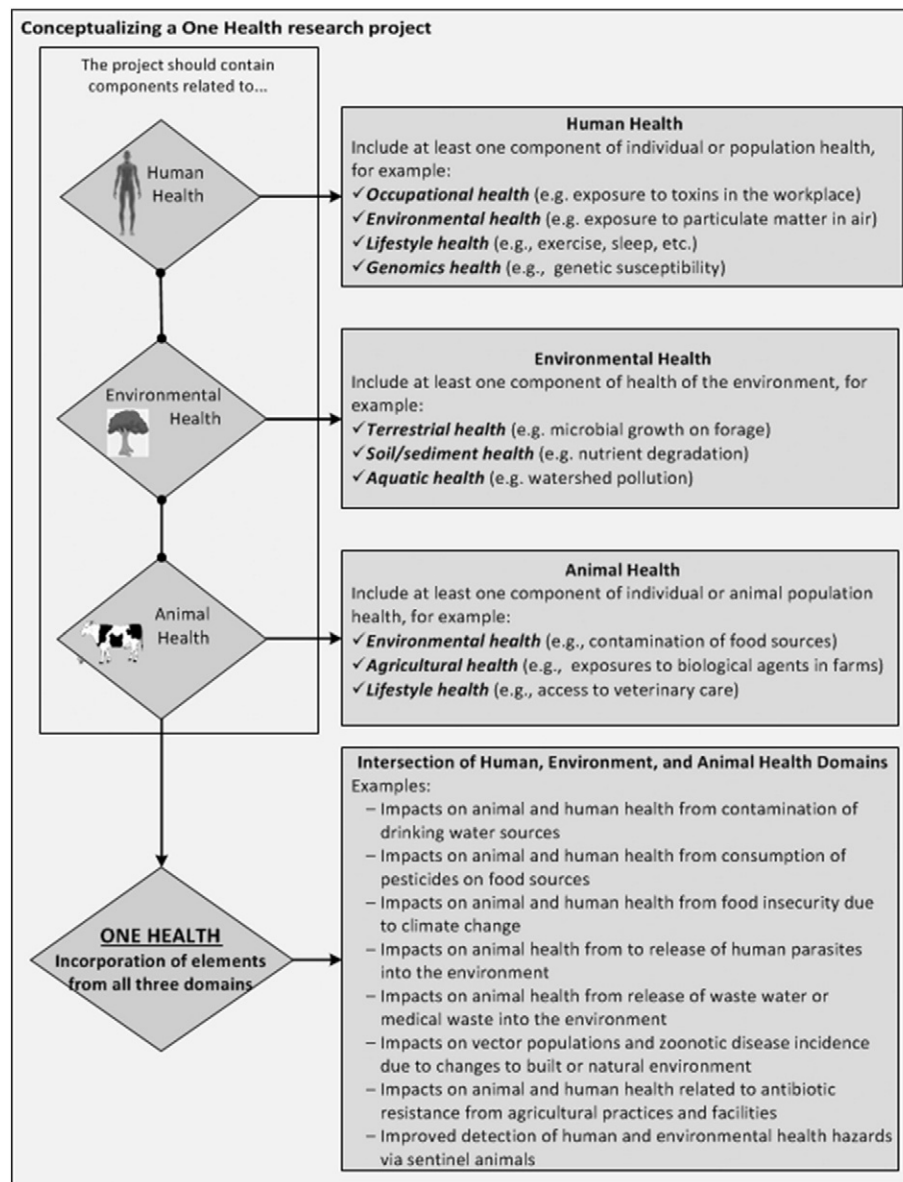


Fig. 1. Conceptualization of a One Health research project.

arboviral disease trends in reforested areas compared to those with continued deforestation. The integrated nature of the OH approach to research also lends itself to mixed data collection methodologies, including qualitative and quantitative human data, environmental samples, and animal behavior observational records. For example, a study of the impacts of groundwater contamination may combine serial readings from groundwater monitoring wells, geospatial modeling of contaminant plumes, evaluation of toxin concentration levels in fish, interviews with residents about perceived drinking water quality, aerial satellite imagery, and longitudinal surveys of residents or health registry data to evaluate health impacts associated with groundwater contamination.

In conjunction with the study design and planning, OH researchers should conduct (at least) preliminary power and sample size computations to address primary or most fundamental research questions. While some OH studies may be exploratory in nature, even a preliminary power and sample size computation may suggest modification or enhancements to the study design, including: 1) increase the breadth of sampling due to insufficient power to address the most important questions; 2) enhance outcome data collection to include more quantitative measures (rather than qualitative) to increase power;

and 3) modify study design (e.g., augment design with follow up of same individuals) to enhance ability to address key questions and increase statistical power. Power computation at an early phase may help avert decisions which would otherwise result in collection of insufficient data to adequately address the most important questions. Power may also be computed mid-study (interim power) to incorporate existing data and trends, and to ensure that the existing data collection plan is sufficient to address the OH questions in light of interim trends.

2.2.2. Data sources

Data may come from existing databases, such as those managed by regulatory agencies (e.g. Environmental Protection Agency and United States Department of Agriculture databases) and human and animal health organizations (e.g. WHO's Global Health Observatory data repository [9] and the World Animal Health Information Database [10]), or from new data collection efforts (e.g. soil and water sample collection, health questionnaires), or a combination of these. Geo-coded data, such as the Gridded Livestock of the World database from the Food and Agriculture Organization of the United Nations [11], provide complementary information to augment analyses. Data collected at frequent intervals (e.g. hourly or daily) and/or in small, specific environments

(e.g. household or watershed) are useful for evaluating local and time-sensitive interactions between animal, human, and environmental factors, while broader datasets (e.g. annual or national) may be used for evaluating health trends associated with more broad-reaching changes in, for example, national policies (e.g. emissions requirements), multi-national corporate strategies (e.g. a decision to cut energy use), or climate patterns. It is important to review and assess the costs and benefits of incorporating various data sources before beginning to develop an OH study design.

2.2.3. Analytical methods

Because data sources used in an OH research approach are likely to be collected and obtained through multiple sources and mixed methodologies, researchers may need to choose analytical methods that accommodate complex data structures and relationships in order to adequately interpret study data. Depending on the research question and the data sources available, a variety of analytical methods and models are useful for the One Health research. We describe two examples here, log-linear models and principal component analysis, but other methods may be more appropriate, such as structural equation modeling, multi-level modeling, and multivariate regression depending on the data context [12], as well as dose-response curves and the derivation of lethal dose (LD) or lethal concentration (LC) values used in health and ecological risk assessments.

2.2.4. Log-linear models

Log-linear models can be used to go beyond the familiar independent-dependent variable relationship to examine three or more variables and their inter-dependencies [13]. Additionally, log-linear models permit more than one outcome which can be especially useful for the complex questions addressed through the OH approach. Using Zika virus research as an example, environmental (e.g. rainfall, sanitation standards), animal (type of mosquito species present in the region), and human (e.g. household hygiene practices, immunological conditions) factors may all impinge upon the prevalence of viral infection, and log-linear models may be useful in parsing out the inter-dependencies among these three sets of factors.

2.2.5. Principal component analysis

Using dozens (or even hundreds) of outcome variables (or many explanatory variables) is sometimes intractable, and a more parsimonious method is desired. Principal component (PC) analysis allows researchers to take advantage of correlations that exist among the variables through the construction of linear combinations of variables. In this way, many variables that are potentially correlated (e.g., poverty, household sanitation, household structure, access to insecticide), may be condensed into a single variable representing “generalized household risk”. As a result, parsimony is more readily achieved [12].

3. Case study

To help illustrate the conceptualization and planning processes of a One Health research study, we present a project completed by researchers from the Research Triangle Institute (RTI) International in 2003 for the US EPA [14]. The multi-media, multi-pathway, multi-receptor methodology that was applied reflects a One Health approach to evaluate the potential human, environmental, and animal health impacts associated with the beneficial application of biosolids (i.e. treated sewage sludge) as an agricultural soil amendment under two farming scenarios: one for the production of crops and the other for pasturing dairy and beef cattle.

3.1. Conceptualization phase

3.1.1. Hypotheses and aims

Drawing upon cross-disciplinary expertise from EPA, EPA stakeholders, and within RTI, the research team developed a complex multi-domain multi-pathway conceptual framework (Fig. 2) to visualize how pollutants in biosolids can be released in the environment and transported through various ecological compartments (e.g. water, fish, livestock) to human and ecological receptors via contact with or consumption of polluted media.

Using the conceptual model, the research team developed the following aims:

- Simulate the potential release of pollutants to the environment from farm field application.
- Estimate pollutant concentrations in ambient air, drinking water, soil, produce, beef, dairy, and fish.
- Estimate pathway-specific exposure levels for farm animals, wildlife, and humans exposed to pollutants in ambient air, groundwater, surface water, soil, produce, beef, dairy, and fish.
- Estimate cancer and non-cancer (e.g. neurological and reproductive) risks to humans and hazards to ecological receptors associated with potential exposures.

3.1.2. Collaborators and stakeholders

The multi-disciplinary team consisted of engineers, geologists, hydrogeologists, statisticians, risk assessors, environmental scientists, and soil scientists working closely with the EPA. Input from agricultural experts was obtained throughout the assessment process to ensure that the predictive modeling parameters accurately reflected the relationships between release mechanisms, media, and receptors. As a final step, the assessment was subjected to EPA review. In response to these reviews and comments, the assessment was modified to refine assumptions and to consider any newly identified data.

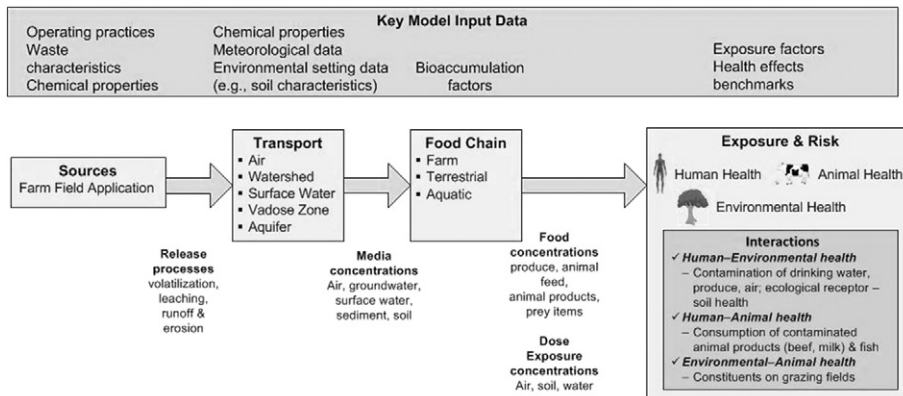


Fig. 2. Schematic of study design for case study (application of biosolids as an agricultural soil amendment).

3.2. Planning phase

3.2.1. Study design

The study used a multi-media, multi-pathway, multi-risk modeling framework to predict potential chemical releases to the environment and the fate and transport of these releases, and to estimate the potential health impacts posed to humans and animals through direct contact (e.g., soil and water) and indirect exposures through the food chain. Simulation methods were selected to evaluate a range of possible exposure and transport scenarios.

3.2.2. Data sources

Simulations were performed to estimate exposures to humans, wildlife, and farm animals. Human exposures can occur through the inhalation of contaminated air (i.e., dust, particles, vapors); ingestion of contaminated groundwater or surface water; inhalation of organic pollutants during showering; incidental ingestion of soil; and ingestion of contaminated farm products, including produce, meat, milk, and fish caught in the farm pond. Wildlife and farm animals may be exposed to pollutants through contact with water, soil, and sediment and through ingestion of contaminated aquatic and terrestrial species. Simulation of these exposures and estimation of health impacts require extensive data collection defining thousands of input parameters. Parameter data were obtained to define modeling scenarios, including the following: physical and chemical composition of biosolids; characteristics of agricultural and field practices (e.g. application frequency); environmental setting and climate characteristics (e.g. daily windspeed, precipitation, etc.); behavior of chemical components in terms of fate and transport; pollutant receptors and rates of uptake; health risks associated with varying levels of chemical toxicity, exposure route, and exposure duration. These data were obtained from EPA reports and databases of the United States Geological Service and the United States Department of Agriculture databases, among other sources [14].

3.2.3. Analytical methods

Chemical release, fate and transport, exposure, and risk models were developed to estimate the risks to human, environmental, and animal health associated with traditional biosolid management practices. Monte Carlo simulations were performed to estimate distributions of non-cancer and cancer effects. Results from the analysis were compared to the human and environmental hazard management thresholds at the 95th percentile of the probability distribution of risk. To enhance model input processing, GIS technology was used to develop data layers and overlays, capture environmental variability, and facilitate subsequent geospatial analyses.

By applying the OH approach to this body of research, investigators were able to assess risk from individual exposure pathways as well as total risk from all pathways (i.e. cumulative exposures). This study was able to determine cumulative ingestion exposure from consumption of pollutants in drinking water, as well as through ingesting exposed fish, crops, and livestock. In addition, risks associated with other exposure pathways, i.e. via air or contact with soil, could be evaluated in conjunction with ingestion-related risk to estimate total risk. This case study illustrates that consideration of connections among environmental, animal and human health facilitates a more comprehensive health risk assessment which has the ability to reflect cumulative exposures.

4. Discussion

The OH approach to research is becoming an increasingly valuable method to frame the ways in which humans, animals, and the environment interact and to embrace the continuous evolution of these interactions. There is a need for more collaboration and synergism across sectors to prevent and respond to emerging threats. Because a critical component of collaborative work takes place in the conceptualization

and planning stage, we have presented guidance and a framework that promotes integration of expertise and resources across all three health domains in the early phases of research development.

The case study we present in this paper highlights the value of applying an OH paradigm to address complex research questions related to agricultural practices. Scientific expertise across multiple disciplines informed the development of diagrams describing the pathways through which the agricultural use of biosolids could impact the health of the environment, animals, and humans. Using these diagrams, the research team generated hypotheses about the possible contamination pathways and associations between biosolid use and human and environmental risk which were tested using simulation models, a methodology that transcends disciplines. In our example, model parameters were obtained from a variety of sources across all three domains of animal, human, and environmental health. Because the study evaluated human impact from exposure via contamination of environmental media, produce, and animal components, the research team was able to interpret results from multi-pathway models to assess total potential hazard to humans. By incorporating information from the animal, human, and environmental domains into the study design, this research generated far more information about exposure routes and hazard levels than would have been observed using a siloed or even two-domain (e.g. human-environment) approach.

The framework we present in this paper can also be used to study emerging health threats and their interrelatedness with climate change using an OH approach. Table 1 shows examples of environmental, disease vector/reservoir, and human behavior/susceptibility factors to be considered when evaluating transmission risk of several diseases considered by the WHO to be high outbreak risk [2].

As others have noted, the use of an OH approach to emerging infectious disease research, which accounts for social and ecological contributing factors, may yield more nuanced results and inform more comprehensive prevention and control measures than traditional epidemiological approaches [7,24,25]. In a rapidly industrializing world, vector-borne disease prevention and control cannot be addressed without consideration of the impact of natural and man-made environmental changes on patterns of disease vector proliferation. The field of climate change research represents an excellent opportunity for researchers to work across disciplines to integrate diverse data sources, develop cross-cutting methodologies, and answer questions about the broader effects of environmental health on human health and animal welfare. Another emerging field of multidisciplinary health and scientific research is Planetary Health [26]. The Planetary Health discipline acknowledges that the preservation of natural systems are an integral part of human survival and prosperity. This same philosophy underlies the One Health approach, and promotes growth and innovation in processes, policies, and technologies that promote conservation and informed stewardship of the natural environment.

5. Conclusions

While we provide a framework that promotes an OH study design covering all three health domains, we also recognize that there are indeed significant challenges and obstacles to implementing OH research in practice. These challenges include, but are not limited to, the need for improved collaborations across disciplines and administrative barriers, improved science-based risk management policies, and improved manpower and research infrastructure capacity in developing countries in particular [27]. In addition, significant challenges to conducting OH research may also arise if funding agencies do not provide effective mechanisms to support interdisciplinary OH research [1]. Though many have argued in favor of trans-disciplinary research [24,28–32], ecological and veterinary science remain largely segregated from human health research [33]. The OH approach to research will continue to advance through demonstration of effective collaboration with key stakeholders. Although progress has been made to foster OH research networks [3,

Table 1
One Health approach to researching diseases of high outbreak risk.

Health threat	Environment	Animal (Vector or reservoir)	Human (Behavior or susceptibility factors)
Zika infection during pregnancy	- Mosquito breeding grounds - Outdoor and household exposure to mosquito bites	Mosquitoes	- Unplanned or planned pregnancy - Use of mosquito repellent/protective clothing
Crimean-Congo haemorrhagic fever	- Tick habitat – bushes and tall grasses	Ticks	- Use of insect repellent
Ebola virus [15,16] and Marburg virus	- Climatic conditions associated with outbreaks	Livestock infections Fruit bats are reservoirs Seroprevalence in dogs as sentinels Impacts on animal populations	- Contact with livestock - Cultural practices in caring for the sick - Treatment of the deceased
Lassa fever [17,18]	- Household conditions - Poor sanitation	Rodent urine or feces	- Grain storage practices - Hygiene - Disposal of contaminated materials in hospitals
Middle East Respiratory Syndrome (MERS) Coronavirus	- Persistence of MERS on environmental surfaces [19] and air	Dromedary camels	- Early diagnosis - Medical countermeasures (such as isolation) to prevent transmission - Personal protective equipment for healthcare staff
Severe Acute Respiratory Syndrome (SARS) [20]	- Removal of reservoir animals from habitat and mingling with other species and humans	Bats are reservoirs Civets were amplifying reservoirs in the 2003 outbreak	- Practice of live animal trade - Medical countermeasures to prevent transmission
Nipah virus	- Haze, deforestation [21], and drought forced bats to migrate to areas where pig farming was common	Pigs affected and may be hosts Bats are reservoirs	- Pig slaughtering methods - Consumption of raw date palm sap (liquor) - Prevention of nosocomial infection [22]
Rift Valley Fever [23]	- Heavy rainfall affected by ocean temperatures - Land use degradation (crop irrigation providing mosquito breeding sites)	Mosquitoes Livestock	- Contact with animal fluids, e.g. birth or slaughter - Irrigation practices

34–36], funding agencies in various sectors should do more to encourage collaborative work across the disciplines of human and ecological health. Encouraging these multidisciplinary research efforts, especially at the conception and planning phases, will help scientists develop innovative solutions to complex and inter-related human, animal, and environmental health threats.

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