

Title: Systematic Review of Antibiotic Resistance of Public Health Importance in Environments near Swine Operations, **NPB Project #13-260**

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Scientific Abstract

A systematic review was conducted to examine the evidence on whether point sources are associated with an increase in antibiotic resistance in the adjacent environment. The review question was based on the Population, Exposure, Comparator, Outcome (PECO) framework as follows: *Is the prevalence or concentration of antibiotic resistant bacteria or resistance genes (O) in soil, water, air or free-living wildlife (P) higher in close proximity to, or downstream from, known or suspected sources (E) compared to areas more distant from or upstream from these sources (C)?* A comprehensive search strategy was created to capture all relevant, published literature. Criteria for two stages of eligibility screening were developed to exclude publications that were not relevant to the question, and determine if the study evaluated the association between a source and levels of resistance using an appropriate comparison group. A decision matrix was created which will permit consistent assessment of risk of bias due to sample selection bias, information bias, and confounding. A data extraction tool was developed for the project with the capacity to efficiently extract data on multiple outcomes from a single study. The systematic review found a large number of studies presenting qualitative evidence that proximity to or direction from point sources, particularly waste water treatment plants, may be associated with higher levels of antibiotic resistance; however, very few studies quantitatively characterize this effect or provide statistical inference to aid in interpretation. Some studies reported no effect of point sources on resistance measures, even qualitatively. Due to a lack of quantitative effect estimates, we are not able to assess possible impacts of publication bias using visual or other methods such as funnel plots. Therefore, we cannot rule out the possibility that some studies found to have null effects were not published in the scientific literature. As such, it is not possible to conclude whether or not point sources are associated with increases in resistance measures in the environment. However, these findings do support the plausibility of such an effect and indicate the appropriateness of further study on this issue. This systematic review provides a strong imperative to improve research methods in order to provide interpretable, quantitative information about the effect of point sources on resistance in the environment. We make the following recommendations for future research:

- Design more longitudinal studies (versus cross-sectional studies), to study changes over time
- Plan study design and data analysis to control for the effect of confounding due to other sources of resistant bacteria or resistance genes
- Quantify the association between point sources and outcomes using effect measures and report with appropriate statistical inference
- Enhance collaborative work between epidemiologists, microbiologists, ecologists, and other scientists, to provide expertise where needed

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