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Pivotal role of environmental toxicants on developing infectious diseases in LMICs: a protocol for a systematic review and meta-analysis

Rehnuma Haque Sarah ,[1,2] Md Shariful Islam ,[1] Md Zamiur Rahaman,[1] Sadia Afrin,[3] Mahbubur Rahman,[1] K M Saif-Ur-Rahman [3,4,5]

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For numbered affiliations see end of article.

Correspondence to
Dr Rehnuma Haque Sarah; rehnuma.haque@icddrb.org

ABSTRACT

Introduction Environmental toxicants such as chemical pollution have an enormous impact on the health of people and the planet. Emerging findings suggest that non-communicable diseases are linked to early and chronic environmental exposures. However, the rapid globalisation in developing countries, environmental change and the emergence, spread, persistence and severity of infectious diseases are not yet well understood. The aim of this study is to understand which environmental toxicants are commonly associated with infectious diseases in low-income and middle-income countries (LMICs).

Methods and analysis A total of four electronic databases, MEDLINE through PubMed, Scopus, Web of Science and CENTRAL (the Cochrane Library) be searched to identify relevant studies and will be screened by two independent reviewers. The Cochrane risk of bias (ROB) tool for randomised control trials (RCTs) and ROB assessment tool for non-randomised studies for non-RCTs will be used to assess the ROB. A meta-analysis will be used to determine the pooled effect if we find out the included articles have similar environmental exposure, participant groups, study design and outcome measures. A narrative synthesis of the findings will be provided, along with summaries of the intervention effect. Heterogeneity between the studies will be assessed, and sensitivity analysis will be conducted based on study quality.

Ethics and dissemination Findings will be summarised in a single manuscript. This review attempts to explore the pivotal role of environmental toxicants in predisposing, developing, persistent and severity of infectious diseases in LMICs. Findings from this study will highlight the effects of individual environmental toxicants' role on infectious disease outcomes for the early prevention and limit toxic exposure to guide individual, community, and occupational health policy for future strategies.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first systematic review and meta-analysis on the role of environmental toxicants in developing infectious diseases in limited-resource settings.
⇒ We will follow PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines, the gold standard tools, to conduct this systematic review.
⇒ Our main limitation is that only articles published in the English language will be included in this review.

BACKGROUND

Infectious diseases are among the top five leading causes of death globally. Even before the COVID-19 pandemic, infectious diseases accounted for 6 of the leading 10 causes of death among low-income populations.[1] Major infectious diseases in LMICs are lower respiratory infections, tuberculosis (TB), malaria, HIV/AIDS, neonatal infection and diarrhoea.[1 2] Poverty, inadequate nutrition, lack of access to clean water, low sanitation and poor hygiene practices lead to infection vulnerability in the developing regions. Scientists have long known that the environment plays a significant role in the spread of infectious diseases. Emerging findings suggest that environmental toxicants such as airborne particulate matter, pesticides and heavy metals may weaken the immune system.[3 4] In addition, exposure to some pollutants may reduce vaccine effectiveness against communicable diseases.[5] Exposure to environmental toxicants also contributes to non-communicable diseases such as endocrine, reproductive, metabolic and neurodegenerative diseases.[6 7]

Environmental toxicants such as air pollutants and suspended particles play essential roles in developing TB.[8] In 2017, 10 million new cases of TB occurred worldwide, which constitute a major health burden straining LMICs. Exposure to environmental pollutants destroys epithelial cells of the respiratory tracts, so they no longer act as a defence mechanism for TB.[9] Pesticide exposure causes varying immune system changes, such as modifications in well-regulated immune responses to allergens, self-antigens and

microbial antigens, increasing the organism's susceptibility to autoimmune and infectious diseases.[5 10] Additionally, lead from industrial sources and adulterated turmeric spice contribute to elevated blood lead levels in pregnant women and children.[11] Arsenic may also contribute to topsoil and drinking water contamination, weakening the immune systems and increasing susceptibility to invading pathogens.[3 4] While environmental pollutants contribute to disease, the specific routes of exposure, the particular toxicants and the resulting patterns of disease vary considerably from country to country. In developing countries, chemical and pesticide contamination and hazardous waste, particularly electronic waste, are increasing.[12] It is crucial to understand current evidence of the role of environmental toxins in developing infectious diseases for designing interventions to mitigate exposure and reduce the disease burden.

Although a few research studies explore cardinal factors relevant to transmissible diseases such as TB, malaria, Lyme disease and hantavirus pulmonary syndrome, there is little research related to the effects of the environment on infectious diseases. Environmental health researchers predominantly focus on chemical and physical agents of environmental toxicants despite findings on the pivotal role of the environment in pathogen dynamics and host response.[13] Thus, in this systematic review, we aim to understand which environmental toxicants are associated with infectious diseases in LMICs. Research on the interplay between these fields could inform new health interventions, public health research and public health policy.

METHODOLOGY

Study registration

This systematic review has been registered with PROSPERO. To perform this research, we will use the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).[14] We started the study in November 2021 and plan to complete it by October 2022.

Search strategy

We will search online databases of MEDLINE through PubMed, Scopus, Web of Science and CENTRAL (the Cochrane Library). Both keywords and subject heading terms related to inclusion and exclusion criteria will be applied to search in the selected databases. The search strategy for PubMed is described in table 1. We will also track references of selected articles to identify relevant articles. Eligible studies will be analytical published papers with an available full text. We will upload all search results to the Rayyan software website to conduct further screening and article selection. We will check for duplicates and remove them from our results.

Inclusion criteria

The studies will be selected based on study design, population, exposure, comparators and outcomes described below.

Type of study

We will include any primary studies on infectious diseases, including bacterial, viral and parasitic pathogenic activities, from observational and experimental studies. Also,

Table 1 Search strategy for PubMed

Serial no.	Search queries
1	LMICs*
2	("Environmental Exposure" OR Environmental Exposure* OR Environmental toxin* OR environment pollutant* OR Chemical toxin* OR "chemical exposure" OR "toxic substance*" OR "poison*" OR "toxin*" OR "contamination*" OR "Heavy metals" OR "Pesticides" OR "Phthalates" OR "Phenols" OR "Parabens" OR "Organochlorine Compounds" OR OCPs OR "Perfluoroalkylated Substances" OR PFAS OR "Polycyclic Aromatic Hydrocarbons" OR "PAHS" OR "Bisphenol A" OR "Air pollution" OR PM2.5 OR PM10 OR NO2)
3	("Communicable Diseases" OR "Blood-Borne Infections" OR "Communicable Diseases, Emerging" OR "Communicable Diseases, Imported" OR "enteric disease" OR "food poisoning" OR Amebiasis OR "athlete's foot" OR "Bacterial Diseases" OR "Bacterial Pneumonia" OR "body lice" OR campylobacteriosis OR cellulitis OR Chickenpox OR cholera OR "Chronic Sinusitis" OR "Common cold" OR "Covid 19" OR Cryptosporidiosis OR Cyclosporiasis OR "Fungal Diseases" OR Giardiasis OR "Haemophilus influenza" OR "head lice" OR "Hepatitis A" OR impetigo OR Influenza OR flu OR Legionellosis OR Listeriosis OR "Meningococcal disease" OR MERS OR "Moraxella catarrhalis" OR Mucormycosis OR Norovirus OR "Parasitic Diseases" OR Pneumonia OR "Infectious Respiratory Diseases" OR Salmonellosis OR SARS OR scabies OR Shigellosis OR shingles OR "Infectious Skin Diseases" OR "staphylococcal infections" OR "Streptococcus pneumonia" OR "Swine flu" OR Trichinellosis OR Trichinosis OR Tuberculosis OR "Typhoid Fever" OR "Typhoid" OR Vibriosis OR "Viral diseases" OR warts OR "Whooping Cough" OR "yeast infections" OR yersiniosis)
4	Human (mh)
5	Animal (mh)
6	#1 AND #2 AND #3 AND #4 NOT #5

*LMICs, the name of low-income and middle-income countries, are based on The World Bank country classification[15] (online supplemental file 1).

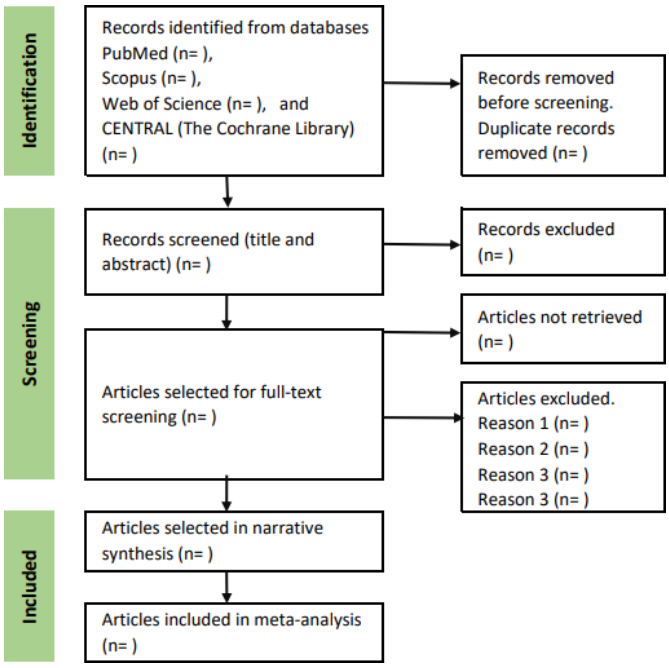

Figure 1 Flowchart of article selection in this systematic review.[14]

we will select studies that include environmental toxicological impacts on developing such diseases and studies where environmental toxicants play an active role in disease severity or transmission. In our primary search, the selected articles will be published in peer-reviewed journals any time before the search date. Only studies published in the English language will be included.

Type of participants

All studies involving adults and children conducted in clinical and non-clinical populations will be included. We will exclusively include studies conducted among human. There will be no limitations on sex, race, religion, ethnicity or socioeconomic status.

Study setting

We will only include studies that were carried out in LMICs as defined by the World Bank.[15] We will not limit our study selection based on study settings. We will include both studies conducted in communities and hospitals.

Exposure

We will include both interventional and observational studies. Interventions that investigated the role or effect of any environmental toxicants exposure in developing any infectious diseases will be included. Studies examining the association between infectious diseases and environmental toxicants will also be included. Environmental toxicants will be any chemical, heavy metals (As, Pb, Cd, Hg, Cr, Mn, Ni), pesticides (organophosphorus compounds; non-persistent organic pollutants including phthalates, phenols and parabens; persistent organic pollutants like organochlorine compounds and perfluoro alkylated substances, polycyclic aromatic hydrocarbons, bisphenol A and PM_{10} (PM10 are particulate matter with diameters of 10 µm and smaller).

Comparators

Comparator groups will be arms that are not exposed to environmental toxicants.

Outcomes

The primary outcome of this systematic review will be identifying the critical infectious diseases with compelling links to environmental pollution in LMICs. We will include any relevant infectious diseases and persistent and emerging environmental pollutants. If any studies are conducted to measure the effect of environmental toxicants on developing all types of diseases, only finding describing the effect of environmental toxicants on developing infectious diseases will be included.

Screening and data extraction

Two independent reviewers will initially screen titles and abstracts to identify articles for full-text assessment based on predetermined eligibility criteria. Then, two independent reviewers will review full texts applying the inclusion and exclusion criteria to select studies to include in the review. In case of potential conflicts, a third review author will be consulted, and a decision will be made. All causes of exclusion will be reported. A PRISMA flow diagram will be used to describe the stages involved in selecting articles (figure 1). Independently, two team members will extract data from the selected studies on study details, study population, intervention and results in a prespecified format. The following items will be included during data extraction: general information, published studies, title, authors, source, country, urban/rural, year of publication, setting; trial characteristics: design, duration, randomisation (and method), blinding (participants, people administering treatment, outcome assessors), check of blinding; intervention(s). Both members will double-check the data's consistency after it has been extracted. Any discrepancies will be assessed by a third researcher and resolved through discussion.

Risk of bias assessment

We will use the Cochrane risk of bias (ROB) tool[16] for randomised control trials (RCTs) and the ROB assessment tool for non-randomised studies[17] for non-RCTs to assess the ROB in the selected research. Two reviewers will independently conduct the bias assessment. Two different researchers will document the ROB assessment on a separate sheet. A third researcher will assess the data discrepancies and agree on how to resolve them.

Data synthesis

A meta-analysis will be used to assess the pooled effect if we find out the included articles have similar environmental exposure, participant groups, study design and outcome measure. In addition, statistic I^2 will be used to determine the degree of heterogeneity among the studies. If relevant, the sensitivity analysis will be conducted. If a

meta-analysis is not feasible due to the heterogeneity of the included articles, summaries of the intervention effect will be provided using a narrative synthesis approach. In addition, a funnel plot will be constructed for each paper using review manager software (RevMan) to analyse potential publication bias. Egger's test will also be used to investigate publication bias.

Certainty of the evidence

Two team members will grade the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool.[18] We will judge certainty based on the ROB, impression, heterogeneity, indirectness and publication bias. According to GRADE recommendations, the certainty of evidence will be classified as very low quality, low, moderate and high quality.

Patient and public involvement

The patient and the public were not involved during the conceptualisation and development of the review protocol.

DISCUSSION

LMICs are overburdened with infectious diseases and environmental pollution. However, the interface of toxicants to developing various infections is indistinct. Findings from this study will support researchers in discovering infectious disease exposure pathways and environmental modelling approaches to understand the biology and transmission dynamics of pathogens and provide early alerts before any outbreak. There is a need to address critical data gaps at the environment–infectious disease interface. This review will provide insight into the predominant infectious diseases that need to be taken into account and examine the pivotal relationship between pollution and the disease burden by integrating mechanisms used in environmental health and infectious disease research. These analyses will support experts from the government, academia and private sector working in infectious diseases, environmental health and data science to analyse current knowledge about the environment–infectious disease interface and explore how this knowledge can shape public health decisions.

Author affiliations
[1]Environmental Interventions Unit, Infectious Diseases Division, icddr,b: International Centre for Diarrhoeal Disease Research, Mohakhali, Dhaka, Bangladesh
[2]School of Medicine, Stanford University, Stanford, California, USA
[3]Health Systems and Population Studies Division, ICDDRB, Dhaka, Bangladesh
[4]College of Medicine, Nursing and Health Sciences, National University of Ireland, Galway, Ireland
[5]Evidence Synthesis Ireland and Cochrane Ireland, Galway, Ireland

Twitter Rehnuma Haque Sarah @Rehnuma_H and Md Zamiur Rahaman @UrZami

Contributors RHS conceptualised and designed the study. RHS and MSI drafted the initial manuscript. MZR, SA, MR and KMS-U-R developed the search strategy. KMS-U-R critically appraised and edited the manuscript. All authors reviewed the manuscript and approved the final manuscript before submission. RHS is the guarantor of this review.

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ORCID iDs
Rehnuma Haque Sarah http://orcid.org/0000-0002-4712-7709
Md Shariful Islam http://orcid.org/0000-0002-3015-0830
K M Saif-Ur-Rahman http://orcid.org/0000-0001-8702-7094

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