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One Health, Planetary Health & Global Health – integrated health approaches for the complex health challenges of the 21st Century

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5. **Falkenberg, T.**, Saxena, D. and Kistemann, T. (2018). Impact of wastewater-irrigation on in-household water contamination. A cohort study among urban farmers in Ahmedabad, India. Science of the Total Environment *639*, 988-996. https://doi.org/10.1016/j.scitotenv.2018.05.117 (JIF: 5.589)

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Abbreviations

ABR	Antibiotic Resistance
AMR	Antimicrobial Resistance
ATE	Average Treatment Effect
FAO	Food and Agricultural Organisation of the United Nations
HEPA	High-Efficiency Particulate Air (filter)
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
NCD	Non-Communicable Disease
NTD	Neglected Tropical Disease
OHHLEP	One Health High-Level Expert Panel
PICO	Problem, Intervention, Comparison, Outcome
PoS	Point-of-Source
PoU	Point-of-Use
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SARS-CoV	Severe Acute Respiration Syndrome Coronavirus
UHC	Universal Health Coverage
UNEP	United Nations Environment Programme
WBGU	German Advisory Council on Global Change
WHO	World Health Organization
WOAH	World Organisation for Animal Health

1 Introduction

The health challenges of the 21st Century go beyond the bio-medical sector, as merely treating acute illness is insufficient to maintain the health status of the global population. Biodiversity loss, environmental degradation, climate change and the correlated increase in infectious disease emergence are examples for the necessity of integrated health approaches. The increase in global temperatures leads to expansion of vector ranges (Carlson *et al.* 2022) and can influence the spread of antimicrobial resistance (e.g. Rodriguez-Verdugo *et al.* 2020). Changes in land-use due to urbanization, agricultural expansion or deforestation result in habitat encroachment and fragmentation, influencing the risk of zoonotic spillovers and the emergence of novel pathogens (Allen *et al.* 2017). The complexity of such health interactions cannot be addressed by sectoral approaches and classical public health perspectives. Therefore, holistic and integrated health approaches have been gaining increasing attention not just in academia, but among political leaders, international organizations and civil society.

1.1 Concepts and Approaches

Three holistic health concepts are currently dominant in the international arena: One Health, Planetary Health and Global Health. Although these three share several commonalities it is important to understand their subtle difference to apply them most effectively. All three approaches are interdisciplinary, combining expertise from the natural, medical, social and political sciences. They adopt a holistic perspective and follow the principles of systems thinking (Peters, 2014; Lerner and Berg, 2017). Therefore, in all three, interactions between social, cultural, political, economic and ecological systems are considered. Systems thinking highlights that systems interact in complex and non-linear ways; therefore, simple solutions often lead to repercussions along feedback loops resulting in unintended and often unpredictable outcomes.

A key difference between Global Health, One Health and Planetary Health is their disciplinary origin and resulting vantage point. Global Health evolved from ‘colonial medicine’, which evolved to ‘Tropical Medicine’ and later ‘International Health’ (Holst, 2020). These colonial roots of Global Health make it inherently political and concerned with health security (Fofana, 2020). In recent times Global Health has evolved to a broader concept, which will be further explained below.

One Health emerged from veterinary medicine and highlights that the health of humans, animals and their shared environment are intrinsically interlinked (Atlas and Maloy, 2014). Before the term was established, 'One Medicine' emerged as a concept emphasizing the interlinkage between veterinary and human medicine (Evans and Leighton, 2014). Due to the origin of the approach, the traditional focus of One Health lies on zoonotic diseases with the environment merely serving as the arena for human-animal interaction and transmission (Destoumieux-Garzón *et al.*, 2018). More recently, the disciplines involved in One Health have expanded, leading to the advancement of One Health into topics of antimicrobial resistance (AMR), food safety and environmental pollution. Nonetheless, interaction and codependence between human and animal health remains the primary concern of One Health.

Planetary Health emerged from the environmental movement of the 1970's and is concerned with the impact of anthropogenic environmental changes on human health (Tong and Bambrick, 2022). As such the disciplinary origin lies with ecology and conservation science and consequently focusses on climate change, biodiversity loss and ecosystem degradation. Planetary Health can be understood as both a scientific approach and as an activist social movement (de Castañeda *et al.*, 2023). The stronger ecocentric perspective views human health as a positive externality to environmental protection and conservation, rather than the object of intervention. In Planetary Health the underlying drivers of human health risks are in focus and in consequence the Planetary Health social movement is calling for fundamental transformations of human collective action, including resource extraction, consumption patterns and inter- and intragenerational justice. The planetary boundaries, first assessed by Röckstrom *et al.* (2005), form an important framework within Planetary Health.

1.1.1 Global Health

Global Health, unlike the other two approaches, can be considered a discipline. In its evolution from colonial medicine, via Tropical Medicine and International Health to Global Health the thematic focus shifted from a health security, in the sense of protecting the health of Northern populations from the threats in the Global South, towards health equity and global health governance. The most frequently cited definition of Koplan *et al.* states:

“Global health is an area for study, research, and practice that places a priority on improving health and achieving equity in health for all people worldwide. Global health emphasises transnational health issues, determinants, and solutions; involves many disciplines within and beyond the health sciences and promotes interdisciplinary collaboration; and is a synthesis of population-based prevention with individual-level clinical care” (Koplan *et al.*, 2009:1995).
Accordingly, Global Health involves measures of prevention, including strengthening Public Health systems and building structures for pandemic preparedness and response, as well as clinical care, involving establishment of universal health coverage (UHC), development of health care infrastructure, and training and education of health professionals. Additionally, Global Health is concerned with health issues that transcend national boundaries and cannot be dealt with by individual countries in isolation (Kickbusch and Szabo, 2014). Development cooperation and global governance structures are therefore key for Global Health. Global Health increasingly acknowledges that it is more than “public health somewhere else” (Turcotte-Tremblay *et al.*, 2020), but requires actions in high-income and low- and middle-income countries alike.

1.1.2 One Health

One Health has been endorsed by the Tripartite (World Health Organization (WHO), World Organisation for Animal Health (WOAH, previously OIE) and the Food and Agricultural Organisation of the United Nations (FAO)) since 2010. This high-level support for the approach has placed One Health high on the international policy agenda. In 2022 the United Nations Environment Programme (UNEP) has joined the alliance to form the new Quadripartite Collaboration for One Health. The addition of UNEP reflects the evolution of One Health, which has long been criticized for not adequately representing the environmental sphere (e.g. Essack, 2018). At the same time, the COVID-19 pandemic has cemented One Health as the recommended approach for the prevention and control of emerging and re-emerging infectious diseases and as a cornerstone of pandemic preparedness strategies.
The most recent definition of One Health, which has been endorsed by the Quadripartite, was formulated by the One Health High-Level Expert Panel (OHHLEP) and states:
“One Health is an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals and ecosystems.

It recognizes the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are closely linked and interdependent.
The approach mobilizes multiple sectors, disciplines and communities at varying levels of society to work together to foster well-being and tackle threats to health and ecosystems, while addressing the collective need for clean water, energy and air, safe and nutritious food, taking action on climate change, and contributing to sustainable development" (OHHLEP, 2022:13).
This definition highlights the evolution and thematic expansion of the One Health approach. It clearly emphasizes the environment and ecosystems as intervention sites, as well as highlighting the need for collective action towards sustainable development and tackling climate change. However, despite this more holistic definition of the One Health approach, its application to zoonotic diseases, pandemic preparedness and AMR remains dominant. Nonetheless, the OHHLEP definition marks a degree of convergence of One Health with Planetary Health, as the definition integrates classical elements of Planetary Health and thus further blurring the dividing lines between these two approaches.

1.1.3 Planetary Health

Planetary Health was popularized by the launch of the Rockefeller-Lancet Commission on Planetary Health in 2015. It draws attention to the impact humanity is having on the planet and how the consequent changes in Earth systems are affecting human health (Koplan *et al.*, 2009). The landmark report of the Rockefeller-Lancet Commission defines Planetary Health as:
"the achievement of the highest attainable standard of health, wellbeing, and equity worldwide through judicious attention to the human systems—political, economic, and social—that shape the future of humanity and the Earth's natural systems that define the safe environmental limits within which humanity can flourish. Put simply, planetary health is the health of human civilisation and the state of the natural systems on which it depends" (Whitmee *et al.*, 2015: 1978).
The definition points to the underlying causes of environmental change that are found in humanity's political, economic and social systems. Therefore, Planetary Health is more than a scientific approach to assess the interactions between human behavior, environmental health and human health, as it is fueling a social movement calling for a great transformation

of human systems. Scientifically, the concept relates to the socio-ecological determinates of health that emphasize how human health is determined by the complex interaction between social, biological, material and cultural variables (Lang and Rayner, 2012). Planetary Health, however, goes beyond the traditional notion of health that are applied to individuals (human medicine) or populations (public health), but considers the health of ecosystems and the planet as a whole, as essential foundation for human health. The Planetary Boundaries presented by Röckstrom *et al.* in 2009 and updated by Steffen *et al.* (2015a) and most recently by Richardson *et al.* (2023) highlight that humanity has been overexploiting the planet's natural resources, six of the nine planetary boundaries have been breached (climate change, biosphere integrity, biogeochemical flows and land-system change, freshwater change, novel entities), leading to disruptions of global cycles and threatening the stability of the environmental conditions on which humanity depends. Planetary Health does not only draw attention to the unsustainability of human collective action but also to the inter- and intragenerational injustice. The improvements to human health deriving from unsustainable natural resource exploitation come at "the expense of other populations – now or in the future, or both" (Whitmee *et al.*, 2015:1978). Thus, Planetary Health also involves inquiries into equity, in terms of health, resource use, and economic opportunity.

Whilst the three integrated health approaches, Global Health, One Health and Planetary Health, show significant overlap and similarities, these do present different vantage points. This difference in perspective influences the type of topics studied under the respective approaches and their aims and outcomes. Although all three highlight the importance of interdisciplinary and transdisciplinary collaboration, the disciplinary origin of each approach influences the primary focus of the approaches. Whilst One Health places the primary emphasis on human-animal interactions, Planetary Health places the environment at the center of inquiry. Therefore, taking the example of a neglected tropical disease (NTD), schistosomiasis, a One Health perspective draws attention to the interactions between humans, livestock and the snail vector, whilst from a Planetary Health perspective the focus lies on the water system, its pollution by humans and the consequently arising health risks. Global Health has a much stronger clinical and public health perspective and would emphasize awareness raising and availability and access to treatment. While all perspectives are essentially important to develop effective interventions and policies, the starting point of investigation will differ. Such differentiations will be further elucidated in the following section, where the selected health challenges of the 21st Century will be introduced and placed into the context of the three integrated health approaches.

1.2 Fundamental interconnected Health Challenges

Humanity has fundamentally impacted local and global ecosystems and natural cycles so that the current epoch in Earth history has been dubbed the Anthropocene (Crutzen, 2002). This new epoch in Earth history is marked by the "Great Acceleration", which highlights a steep increase in changes of Earth System structure and functioning induced by modern society (Steffen *et al.*, 2015b). Industrialization, agricultural expansion and urbanizations have contributed to extensive land-use changes, massive natural resource extraction and as a consequence unprecedented loss of biodiversity. Globalization, free trade, and widespread migration has led to an interconnected world where not only goods and services rapidly move across the globe, but also humans, animals and microbes. Due to these developments, humanity has experienced great improvements in life expectancy, reductions in infant and maternal mortality, as well as overall improvements in living standards. However, at the same time water, air, and soil are increasingly polluted, contributing not only to the increasing burden of non-communicable diseases (NCDs) but also to water and food insecurity. Also, when looking at our focus, communicable diseases, findings are alarming: The emergence and re-emergence of infectious diseases are accelerating, NTDs are affecting increasing populations, vectors are expanding their geographic range, and antimicrobial resistance is threatening medical advance. In light of these developments, Kistemann and Exner (2000) highlight the need to reestablish the principles of infectious disease prevention and control. Further, the German Advisory Council on Global Change (WBGU) indicate the need of a "Great Transformation", involving fundamental changes to political, economic and societal systems with substantial alterations of production and consumption patterns across the globe (WBGU, 2011). Therefore, to meet the (health) challenges of the Anthropocene integrated and interdisciplinary approaches are required to understand system dynamics, identify root causes and develop sustainable solutions.

1.2.1 Emerging Diseases and Pandemics

The emergence and re-emergence of pathogens are frequently linked to spillovers from animal reservoirs. The majority of current infectious diseases are of zoonotic origin and it is estimated that 75% of emerging diseases are zoonotic (Taylor *et al.*, 2001). Avian influenza, Ebola, Zika, and most recently COVID-19, are examples of emerging diseases that led to widespread epidemics or even pandemics (Morens and Fauci, 2020). Emerging diseases are defined as "those whose incidence in humans has increased within the past two decades or threatens to increase in the near future" (van Doorn, 2021:659). Emerging diseases do not necessarily originate from novel pathogens but may also come from known pathogens that acquire new resistance mechanisms or mutations. Due to globalization and rapid air travel the risk of a local outbreak turning into a pandemic has been increasing. Key factors influencing the pandemic potential of a pathogen is its ability to spread from human to human and that pathogen shedding is high in pre-symptomatic and asymptomatic persons.

Global Health as a discipline is naturally concerned with pandemics and pandemic preparedness, as the management of these require international cooperation and transnational actions. Within the Global Health community, One Health is considered the most suitable approach for pandemic prevention and preparedness (World Bank, 2022). As most emerging diseases are of zoonotic origin, monitoring animal reservoirs is of crucial importance for detecting relevant mutations. At the same time disease surveillance among at-risk human populations are required for early-detection and corresponding rapid response for containment. A One Health approach will integrate monitoring and surveillance of animal and human populations, while considering environmental indicators to identify hotspots of spillover risk. From a Global Health perspective, such systems cannot be reliant on individual countries, but need to be operated and financed transnationally. Developing policies, infrastructure and mechanisms to operationalize and sustain such One Health systems would fall into the purview of Global Health, as part of development cooperation.

Approaching the issue of emerging diseases from a Planetary Health perspective shifts the focus from early-detection and preparedness towards identification of root-causes and prevention. Taking a Planetary Health perspective, disease emergence can be considered a symptom of human encroachment into nature. Habitat destruction, agricultural expansion and land-use change are forcing wild animals closer to agricultural lands and human settlements, consequently increasing the interaction between wild animals, livestock and humans. Furthermore, biodiversity loss, coupled with increasing livestock populations is considered a risks factor for disease transmission (Morand, 2020). The "dilution-effect" initially hypothesized by Ostfeld and Keesing (2000) for vector-borne diseases highlights that high biodiversity leads to a higher abundance of non-competent hosts, which leads to a dilution of pathogens and consequent lower transmission risk. Consequently, a Planetary Health approach to tackle emerging infectious diseases will focus on ecosystem and biodiversity conservation.

Drawing on all three integrated health approaches it becomes apparent that improving health and preventing disease will require transformation across multiple domains. It is imperative to tackle the root-causes by following Planetary Health principles, i.e. taking a "general proactive approach" (Rohr *et al.*, 2020). At the same time, it must be understood that it will not be possible to prevent all spillover events and contain all outbreaks. Thus, adopting One Health approaches to develop surveillance and response systems is essential to protect global health, following "targeted reactive approaches" (Rohr *et al.*, 2020). Developing health infrastructure, including diagnostic, monitoring and treatment capacities, across the globe and ensuring equitable access to healthcare is a central task for Global Health. In a globalized world it is necessary that capacities are available globally, as an outbreak occurring in remote areas can quickly transform into a pandemic with severe impacts across economic and social systems.

1.2.2 Antibiotic Resistance

The World Health Organization (WHO) has declared Antimicrobial Resistance (AMR) as one of the top ten global public health threats (WHO, 2020). The increasing development of resistances are threatening the advances of modern medicine, as infectious diseases become more difficult and more expensive to treat (Dadgostar, 2019). Whilst AMR encompasses a wide spectrum of resistances, viral, parasitic, fungal and bacterial, the focus here lies on antibiotic resistance (ABR). Whenever bacteria are exposed to antibacterials the selective pressure drives resistance development. Already in 1940, only 12 years after Sir Alexander Fleming discovered penicillin, the first resistances to penicillin were observed. The natural process of resistance development occurs through intrinsic mechanisms, i.e. a genetic trait that is chromosomally encoded, or by extrinsic mechanisms via horizontal gene transfer.

Therefore, as antibiotics are used resistance rates naturally increase. In consequence, the issue of ABR is largely a problem of use, overuse and misuse.

The complexity of ABR arises as antibiotics are not only used in human medicine, but also in veterinary medicine, agriculture and aquaculture. The same classes of antibiotics and in some cases even the same substances are used in both human and veterinary medicine (Kempf *et al.*, 2013). Thus, reductions of usage behavior in one sector is insufficient to slow resistance development. For this reason, ABR is considered a central One Health issue. In animal husbandry, the application of subclinical doses of antibiotics was commonly used as growth promoters and for disease prevention (Butaye *et al.*, 2003), leading to high selective pressure and consequent resistance development. While most countries have now banned the use of growth promoters, intensive livestock production still require large quantities of antibiotics for clinical treatment. Also, in human medicine antibiotic use continues to increase on the global level (Klein *et al.*, 2018).

In both humans and animals, antibiotics are not fully metabolized, therefore, antibiotic residues and resistant bacteria are excreted via urine and feces. This adds the third One Health dimension, the environment, as recipient and transmission pathway of resistant bacteria, antibiotic residues and resistance genes, to the complexity of the issue. Animal excreta is frequently applied to agricultural fields as manure, providing a potential entry pathway into the food chain. Additionally, animal products, meat, eggs and milk may also contain antibiotic residues if antibiotic use is not discontinued in time (Ghimpeteanu *et al.*, 2022). Consequently, ABR is also an issue of food safety. On the human side, excretions are ideally treated in wastewater treatment plants before release into surface waters. In many countries of the Global South, however, sewage treatment capacities are inadequate leading to high volumes of untreated release. As surface water forms a primary irrigation water source, a pathway into the food chain is evident. Even the most modern wastewater treatment plants cannot not fully remove resistant bacteria or antibiotic residues, in consequence various studies have detected resistant bacteria, residues and resistance genes in surface waters (e.g. Bengtsson-Palme and Larsson, 2016). Consequently, additional risks are induced through influx into the food chain and potentially in drinking water systems. From a Planetary Health perspective, the impact on aquatic and soil ecosystems highlights additional indirect human health impacts.

1.2.3. Neglected Tropical Diseases

Neglected Tropical Diseases (NTDs) induce significant economic, social and disease burdens on the populations of tropical and subtropical countries (Ochola *et al.*, 2021). The WHO defined 20 NTDs, all representing complex epidemiology involving environmental interactions, vectors and animal reservoirs. From a Global Health perspective developing financing mechanism for research, drug and vaccine development are essential, as well as awareness raising campaigns, monitoring and surveillance systems, access to treatment and vaccinations, and expanding diagnostic capacities. Additionally, low income populations, women and children are disproportionally affected by NTDs. Health disparities and health equity are also central in a Global Health perspective. From a One Health perspective the often complex transmission pathways involving animal reservoirs and vectors are of primary interest, while a Planetary Health perspective draws attention to environmental pollution as a driver of disease spread. In the following the focus lies on One Health and Planetary Health perspective of schistosomiasis.

Schistosomiasis is caused by a flatworm of the genus Schistosoma and is considered a water-based parasitic disease (Gower *et al.*, 2017). The flatworms require *Bulinus* fresh water snails as intermediate hosts for their development, while humans and animals are definitive hosts (French *et al.*, 2018). The parasite matures in the definite host, the produced eggs are then released via the hosts excreta. Therefore, a number of ecological and human factors influence the epidemiology of the disease (Hunter, 2003). On the one side, abundance of the intermediate snail hosts is an important factor for transmission (Hunter, 1981), on the other side, the influx of Schistosoma eggs determines the infection rate of the intermediate hosts (Kulinkina *et al.*, 2019). Lastly, human water interactions determine exposure and consequently influence disease risks (Angelo *et al.*, 2018).

Human alterations of aquatic ecosystems through the construction of dams or irrigation canals, can create favorable living conditions for the snails, as these can strive in small water bodies, along lake shores and in humid areas along aquatic vegetation (Manyangadze *et al.*, 2016). Particularly in rural and peri-urban areas, where waterbodies are shared between humans and their livestock, transmission risk is high, as human water contact is intense and animals contribute to Schistosoma egg shedding. Lacking sanitation and particularly the practice of open defecation leads to additional surface water pollution from human excreta.

This complex disease ecology makes schistosomiasis interesting from both a One Health and a Planetary Health perspective.

From a One Health perspective a key intervention strategy relies on controlling the snail vector. Strategies including the introduction of predators or competitors, applications of molluscicides, or alterations of the snail habitat have been effective but come with limitations and sustainability issues (Bu *et al.*, 2022). Separating water sources for livestock from those for human use has only limited effect, as controlling wildlife interaction with surface water ways is difficult to manage. Additionally, limited availability of water sources may make such separations unfeasible in many water scarce regions. When adopting a Planetary Health perspective, the human impact on the environment is in focus, therefore, the wider consequences of introducing predators, applying poison or further altering the aquatic environment would render such interventions unfeasible. Rather the underlying drivers of lacking sanitation and clean water sources need to be addressed. Open defecation and the resulting surface water contamination is a key driver of transmission in most endemic regions. Therefore, by halting this adverse impact of humans on water systems, the disease risk could be reduced.

1.3 Water as Integration Medium

Water is a crucial link between people and the environment, it is essential for sustainable development and human survival, and an important indicator for ecosystem health (Anthonj and Falkenberg, 2019). Sufficient and safe water is essential to meet hydration requirements and hygiene needs, as well as for food production. Despite the essential role of water for human survival and development, water pollution is common across the globe. Surface waterways are recipients of agricultural, municipal, industrial and clinical wastewater, leading to a multitude of health risks and environmental challenges.

The Bradley Classification specifies categories of water-related infectious diseases: waterborne, water-washed, water-based, and vector-related (White *et al.*, 1972). These are based on the transmission pathway of the respective diseases and thus indicate interventions for disease prevention. Waterborne diseases are usually caused by fecal-oral pathogens and are thus determined by microbial water quality. The influx of untreated wastewater into surface waterways due to inadequate sanitation, insufficient sewage treatment capacities, and poor drainage are important drivers. Water-washed diseases are linked to insufficient access to water for hygiene and thus emphasize the preventive factor of water for person-to-person transmission. The water-based category refers to pathogens that require water to complete their lifecycle (Bartram and Hunter, 2015), schistosomiasis forms the textbook example. Lastly, the vector-related category includes pathogens that are transmitted by insects that breed or bite near water. Here *Anopheles* and *Aedes* mosquito vectors, responsible for Malaria and Dengue transmission, respectively, are most prominent.

In each of these four categories One Health and Planetary Health interactions can be identified. The complex interactions of water-based diseases have already been outlined above. For vector-borne diseases the vector habitat and the availability of incompetent hosts are central from One Health and Planetary Health perspectives. Although not directly related to water, here the biodiversity hypothesis and the corresponding dilution effect is important. Waterborne diseases are best suited to demonstrate the integrating quality of water.

Most waterborne diseases are fecal-oral diseases, their transmission pathways and barriers are illustrated in the F-diagram, which depicts that fecal pathogens are transferred via fluids (i.e. water), fingers, fields, flies and food to be ingested by a susceptible host (Kawata, 1978). The direct ingestion of unsafe drinking water represents a major transmission pathway. Particularly in regions were drinking water sources are not safely managed, for example unprotected wells or surface water, drinking water contamination is frequent. Although water is only depicted as one possible transmission pathway in the diagram, it is also connected to the other elements. The transfer via fingers is related to personal hygiene, which can only be adequately practiced when sufficient clean water is available at the household-level. While the transfer to agricultural fields can occur due to open defecation practices or the direct application of animal or human manure, transfer via contaminated irrigation water is also common. Irrigation water is essential for the production of food and contaminated irrigation water can transfer pathogens and contaminants to crops and thus into the food chain. Clean water is also required for adequate food hygiene, which represents a final secondary barrier in the diagram.

Surface water is the recipient of all kind of discharge, including point-sources, such as wastewater treatment plants, industry and municipal drainage, as well as non-point sources, including agricultural runoff, storm water runoff and indiscriminate influxes. In consequence not only fecal pathogens are transferred via water, but a broad range of substances and organisms intermix in the aquatic environment. Chemicals, active therapeutics, antibiotic residues, along with pathogenic and non-pathogenic microbes are all commonly found in surface water across the globe. Water, therefore, forms a point of convergence of diverse influxes, whilst simultaneously serving human and animals needs for hydration, hygiene, food production/acquisition, and recreation. The resulting water interactions always represent a certain disease risk depending on the degree and type of contamination. Additionally, interactions between different bacterial species, antibiotic residues and resistance genes can create environments favoring resistance development and horizontal gene transfer. As water is a point of convergence, it is of importance to any integrated health approach. Water can serve as a medium for monitoring and surveillance, it can act as a media for horizontal gene transfer, as transmission medium, and it also acts as a direct link into the food chain via fisheries and irrigation.

From a Global Health perspective, the right to water is a critical framework that links to the requirements of developing WASH infrastructure, promoting hygiene behavior, and wastewater management. Also, the specific requirements of healthcare facilities, pharmaceutical production and schools for water supply and wastewater management fall within the scope of Global Health.

The One Health perspective highlights sharing of water sources between humans, animals and livestock as a point of contact and consequently as a place of pathogen exchange. Food safety and the transfer of pathogens into the food chain are also central from this perspective. Additionally, water monitoring and surveillance, of both wastewater and surface water, can form components of One Health surveillance systems. As water is the recipient of the human waste stream and in turn presents human health risks, Planetary Health interventions target the influx of contaminants into the environment. Further, Planetary Health places emphasis on the impact on aquatic ecosystems and the consequent direct and indirect human health repercussions.

Whilst Global Health seeks equitable access to water for disease prevention and health promotion, One Health can utilize its integrating qualities as part of surveillance systems, and Planetary Health demands halting water pollution to protect aquatic environments and simultaneously protect human health.

1.4 Research Aims and Objectives

In the following sections the results of five research publications are presented. These illustrate the broad thematic range assessed under One Health and Planetary Health approaches. Each represents a distinct Global Health challenge and the role of the environment is inherent in each publication. The aim of this synthesis is to highlight the importance of adopting integrated health approaches to capture the complexity of current health challenges, and to indicate the distinct advantages of the differing perspectives. Solutions to the complex health challenges cannot be found in the health sector alone, but require intersectoral collaborations and interventions.

First, the recent coronavirus outbreak, representing the challenge of emerging and re-emerging diseases, is used to illustrate the evolution of the **One Health** approach. Here the transition from classical One Health, relying primarily on collaboration between human and veterinary medicine, to "extended" One Health, which emphasizes the importance of the environment (both natural and social) was identified. While this expansion of One Health can also be viewed as convergence towards Planetary Health, the classical One Health understanding remains dominant.

Second, a **Public Health** intervention to the COVID-19 pandemic is assessed. The utilization of HEPA filters to reduce contagion was demonstrated in various experimental studies, leading various schools, kindergartens and offices to install such filters. However, in our real-life assessment in kindergartens no preventive effect of HEPA filters could be demonstrated. The particularities of the kindergarten environment, involving multiple potential viral emitters moving and closely interacting with each other, were not adequately reflected before installing HEPA filters. The paper demonstrates the importance of considering the social and human-made environment when developing interventions.

Third, the key **Global Health** challenge of antimicrobial resistance is assessed by focusing on its fundamental driver: antibiotic use. Stark differences in antibiotic use are evident across spatial scales, not only between country groups and countries, but also within countries and regions. Considering the social, economic and build environment, inherent in the compositional, contextual and collective categories of the publication, reveal interesting opposing trends between high-income and low- and middle-income countries. Understanding the determinants of antibiotic use, many of which fall outside the sphere of the bio-medical sector, can help in developing targeted interventions and Global Health policies.

Fourth, the role of human-surface water interactions for the transmission of a Neglected Tropical Disease, schistosomiasis, are reported. The paper represents the **Planetary Health** perspective, demonstrating that human water pollution, primarily via open defecation, coupled with a strong reliance on surface water for domestic and agricultural needs, is a key driver of schistosomiasis infection in children. The classical public health measures of mass drug administration and awareness raising do not lead to sustainable reductions in disease occurrence, instead intersectoral interventions are required that tackle the underlying drivers of the transmission cycle.

Fifth, the impact of wastewater use for irrigation is used to illustrate how fecal pathogens released into the environment can re-enter the household environment and induce disease risk. Following the logic of **Planetary Health,** the paper demonstrates that human contamination of surface water has unexpected impacts on human disease risks. While it is expected that wastewater-irrigation induces health risks for the farmers and the consumers of produce, it is less obvious that water stored in the household is adversely affected by irrigation water quality. The holistic view enables transmission pathways to be identified based on understanding the social and cultural environment as well as the natural and built environment.

Overall, the five publications show the importance of considering social, cultural and environmental factors when assessing the complex health challenges of the 21st Century and developing interventions. The integrated health approaches One Health and Planetary Health provide a framework to consider wider interactions beyond the classical public health domain. Despite important differences between the approaches, their holistic perspectives are essential for the development of effective and sustainable interventions.

2 Research Contributions

2.1 One Health in the context of coronavirus outbreaks

Schmiege, D., Arredondo, A.M.P, Ntajal, J., Paris, J.M.G, Savi, M.K., Patel, K., Yasobant, S., and **Falkenberg, T.** (2020). One Health in the context of coronavirus outbreaks: a systematic literature review. One Health *10*, 100170. https://doi.org/10.1016/j.onehlt.2020.100170

Background & Aim:

The recent coronavirus outbreak sparked loud calls for implementation of One Health approaches to manage and prevent zoonotic disease outbreaks. A wide consensus across academia, practice and policy emerged that One Health is an integral part of pandemic preparedness and prevention. However, the COVID-19 pandemic is not the first time that coronaviruses have led to outbreaks of pandemic proportions. The first outbreak of Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) occurred in 2002/2003, leading to an estimated 8,000 cases across the globe and a case fatality rate of 10%. The second outbreak started in mid-2012, the Middle East Respiratory Syndrome coronavirus (MERS-CoV) spread from dromedary camels to humans in Saudi Arabia and led to human-to-human transmission in 26 countries. The most recent outbreak occurred in late 2019 in China, leading to several million confirmed cases in 188 countries within the first year. In all three outbreaks the human-animal interface has a distinct role in the outbreak epidemiology. Coronavirus outbreaks provide an ideal case to review the evolution of One Health approaches in outbreak management, prevention and control, by highlighting One Health actions.

Methods & Results:

The systematic review followed the PRISMA[1] methodology to analyze how One Health was framed in the context of coronavirus outbreaks. Eight scientific databases were continuously screened between April and September 2020 using a set of standardized search terms adapted from Elsevier's "Novel Coronavirus Information Center". 478 studies were identified after duplicates were removed, screening of title and abstracts led to 86 articles for full-text assessment. Finally, 53 articles met the inclusion criteria and were included in the analysis and synthesis. The type of One Health approach was classified into two categories: "classical

[1] Preferred Reporting Items for Systematic Reviews and Meta-Analyses;
see http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1

One Health" and "extended One Health". Where the "classical One Health" approach entails disease management of humans and animals, and the "extended One Health" approach is focusing on human-animal interrelationships with the environment and/or considering broader social, cultural and economic factors. For all included studies, study type, spatial scale, methodological approach, OH domains (animal, human, and environment), OH actions, and OH understanding were extracted. The dominant One Health understanding across all studies is One Health as "institutional coordination and collaboration", followed by specific actions and implementation measures. The extended One Health approach, i.e. involving the environment component, has been increasing, but remains the least common One Health understanding. The identified One Health actions are numerous, ranging from very classical One Health actions to reduce viral shedding in humans and animals, identification and monitoring of pathogen reservoirs, and food safety (i.e. milk and meat products), to actions considering environmental outcomes, including: limiting animal mobility and trade, bio-surveillance of wet markets and occupational hygiene interventions. Lastly some actions at the animal-human-environment interface were identified: monitoring of waste disposal from abattoirs, assessing viral concentration in air and water, and actions in urban land-use planning and identification of spatial hotspots and high-risk areas.

Conclusion:

The role of the environment as well as the role of social, cultural and political systems has been expanded in the One Health approach. Nonetheless, the narrower "classical" One Health understanding remains dominant, placing the emphasis on human-animal interactions. Intuitional coordination and collaboration is the most dominant understanding of One Health, ideally involving joint actions. However, knowledge gaps remain, particularly in the operationalization of One Health (including understandings about required material, human, and financial resources, as well as the added benefit), and the integration of the environment. The COVID-19 pandemic has highlighted the importance of One Health for outbreak management and control, but it has also become evident that effective prevention and preparedness requires further intersectoral action including active surveillance of natural reservoirs and environmental compartments.

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One Health in the context of coronavirus outbreaks: A systematic literature review

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ABSTRACT

The ongoing coronavirus disease 2019 (COVID-19) pandemic threatens global health thereby causing unprecedented social, economic, and political disruptions. One way to prevent such a pandemic is through interventions at the human-animal-environment interface by using an integrated One Health (OH) approach. This systematic literature review documented the three coronavirus outbreaks, i.e. SARS, MERS, COVID-19, to evaluate the evolution of the OH approach, including the identification of key OH actions taken for prevention, response, and control.

The OH understandings identified were categorized into three distinct patterns: institutional coordination and collaboration, OH in action/implementation, and extended OH (i.e. a clear involvement of the environmental domain). Across all studies, OH was most often framed as OH in action/implementation and least often in its extended meaning. Utilizing OH as institutional coordination and collaboration and the extended OH both increased over time. OH actions were classified into twelve sub-groups and further categorized as classical OH actions (i.e. at the human-animal interface), classical OH actions with outcomes to the environment, and extended OH actions.

The majority of studies focused on human-animal interaction, giving less attention to the natural and built environment. Different understandings of the OH approach in practice and several practical limitations might hinder current efforts to achieve the operationalization of OH by combining institutional coordination and collaboration with specific OH actions. The actions identified here are a valuable starting point for evaluating the stage of OH development in different settings. This study showed that by moving beyond the classical OH approach and its actions towards a more extended understanding, OH can unfold its entire capacity thereby improving preparedness and mitigating the impacts of the next outbreak.

1. Introduction

At the end of 2019, the novel *Betacoronavirus*, Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), crossed the animal-human barrier resulting in a public health emergency of international concern and a global pandemic [1]. With the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) in 2002/2003 and the Middle East Respiratory Syndrome coronavirus (MERS-CoV) in 2012, this is the third time within the last 20 years that *Betacoronaviruses* have crossed the animal-human species barrier resulting in major zoonotic outbreaks

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[2].

The first SARS outbreak began in the Guangdong Province, China, in late 2002 with 300 cases of atypical pneumonia [3,4]. Despite the measures issued by the Chinese Government and the World Health Organization (WHO) to stop the transmission, SARS spread to *"5 countries within 24 hours and to more than 30 countries on 6 continents within 6 months"* ([5], p. 3), with over 8000 cases worldwide and a 10% fatality rate between 2002 and 2003 [6]. The primary source of infection was attributed to wild mammals traded in local markets for human consumption [5,7]. The epidemic was brought under control by a remarkable coordinated response [4], albeit impacting significantly 36 countries socially, politically, and economically [8].

In mid-2012, MERS emerged in Saudi Arabia due to human exposure to MERS-CoV-infected dromedary camels [9]. Further human-to-human transmission spread it to 27 countries across the globe [10–16] with a total of 2519 laboratory-confirmed cases globally and a case-fatality rate of 34.3% until January 2020 [17]. Measures to control and prevent MERS involved aggressive contact tracing, quarantine, and isolation of the cases [18,19].

On December 8, 2019, the first case of a new atypical pneumonia was confirmed in Wuhan City, China, and since then spread throughout the world [20]. Several million cases have been confirmed in approximately 188 countries as of September 2020 [21]. Based on countries' situations and capacities, various strategies have been implemented to control the pandemic. Those strategies include case detection followed by contact tracking and isolation, avoidance of close contacts between humans (e.g. physical distancing) through lockdown procedures [22], Water, Sanitation and Hygiene (WASH) interventions (particularly hand-hygiene) [23], and the use of personal protective equipment, in addition to increasing available capacities in the health care system.

Increasing human-animal interactions have amplified the likelihood of cross-species infections and spill-over events [24]. Epidemiological links of the three coronavirus outbreaks point to the human-animal interface, highlighting the importance of considering prevention strategies with an integrated approach such as "One Health" [25]. The One Health (OH) approach considers the human-animal-environmental interdependence through multi-sectoral collaborations [26] and recognizes that prevention and "*zoonotic disease control programs are most effective when the broader socioeconomic and ecological determinants of health are included*" ([27], p. 66).

The outbreaks of SARS, MERS, and COVID-19 represent ideal cases for analyzing how the OH approach has been used concerning those zoonotic diseases. Reviewing the experiences and lessons learned from the epidemics allows envisaging the future of public health and OH. Through a systematic literature review, this work contributes to the further development of the OH approach moving from surveillance to the prevention of public health emergencies. The study aims to understand the evolution of the OH approach in relation to SARS, MERS, and COVID-19, and to identify the key OH actions taken for prevention, response, and control of those.

2. Methods

2.1. Study selection

This study used a systematic literature review to analyse how the OH approach was framed in the context of several coronavirus outbreaks, thereby following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) selection method to identify relevant studies [28]. Eight databases were systematically searched (i.e. Google Scholar, JStor, PubMed, Science Direct, Springer Link, Taylor and Francis Online, Web of Science, and Wiley Online Library). The search terms were inspired by Elsevier's "Novel Coronavirus Information Center" [29], and further organized into coronaviruses and combined with OH: (i) coronavirus or "corona virus", (ii) "COVID-19" or "2019-nCov" or "SARS-CoV-2", (iii) "Severe Acute Respiratory Syndrome" or "SARS-CoV" or "SARS", (iv) "Middle East Respiratory Syndrome" or "MERS-CoV" or "MERS", and "One Health". The literature search was repeated several times between April and September 2020 to identify newly published studies constantly.

Studies were considered suitable for inclusion if they specifically mentioned OH in their title or abstract in combination with either SARS, MERS, or COVID-19. Scientific publications in the form of case reports, correspondences, data articles, discussions, editorials, research and review articles, or short communications were included. However, books or book reviews, conference proceedings, and meeting abstracts, front matters, news, posters, practice guidelines, presentations, replication studies, or software and video publications were not considered. The year of the SARS outbreak (2002) was set as the starting point and only studies published in English were included. The full-texts of the studies that met the inclusion criteria were assessed for eligibility subsequently. Only studies that demonstrated an explicit and clear link between OH and coronaviruses were included in the final synthesis.

2.2. Synthesis of results

The studies were divided into two OH approaches observed in the general literature. The first denoted as "classical OH approach" addressed the *"management of the disease threats to humans and animals"* ([30], p. 372); the second, referred to as "extended OH approach" looked into the close interrelationship between humans and animals with ecosystems, environmental health, pathogens, and the broader social, cultural, and economic factors [31–33].

For classifying the studies, data were extracted into a purpose-built data extraction form in a Google Spreadsheet including details on study type, spatial scale, methodological approach, OH domains (animal, human, and environment), OH actions, and OH understanding. The varying nature of the studies did not allow for any internally consistent and comparable quality assessment.

The OH understandings were categorized into groups derived inductively from the wording used by the authors in their texts. Other classifications of OH proposed in the literature [e.g. 34,35] provided a basis for defining the groups. It was thereby possible for a study to be associated with more than one group. Three groups were identified following the patterns of how OH was utilized:

- Institutional coordination and collaboration: OH was framed as a way to communicate, coordinate, and collaborate among stakeholders across sectors in a multi − /inter − / and/or transdisciplinary manner to solve complex health challenges.
- One Health in action/implementation: OH was used in a way to provide a frame for the actions introduced or proposed to prevent and control the respective disease outbreak, e.g. through surveillance and monitoring.
- Extended One Health: OH was framed as a more comprehensive and extended understanding, thereby emphasising the role of the environment (either built or natural) and highlighting the complex interactions at the human-animal-environment interface as well as social, structural and ecological changes.

The documents were also scanned for specific actions that were used or proposed within the OH framework for prevention, control, or response, targeting either SARS, MERS, or COVID-19. The OH actions were classified into twelve sub-groups using terminology observed in the publications to determine the levels of application: (1) Animal movement and interaction between animals and with humans; (2) Awareness creation, operating protocols, and policies; (3) Control and understanding of pathogens; (4) Diagnosis, detection, and treatment capacities; (5) Environmental management and pollution control; (6) Food safety; (7) Human travel control and community control strategies; (8) Immunization; (9) Information management; (10) OH capacity development and research; (11) Preparedness and response plans; and (12) Surveillance and monitoring. The OH classical and extended approaches were used to segregate the OH actions further.

The results are presented quantitatively and are complemented by a qualitative synthesis in the discussion.

2.3. Limitations

Publication bias also applies to this review. However, the influence can be considered low because this study focused on how the respective authors framed OH in the context of coronaviruses, instead of specific (positive) outcomes. Moreover, selection bias can influence this study because this analysis only considered studies published in English. Due to the inclusion of reviews and editorials, it may be possible that some OH understandings and actions were counted more than once. This potential bias was addressed by grouping OH understandings and actions and not relying on individual studies for the analysis. Further consideration has to be given to the fact that the OH approach emerged in the early 2000s, was included in the global health discourse in 2004, and its adoption by international organizations occurred only in 2008 [36]. This may explain why the SARS outbreak in 2002/2003 is covered by far the least in the studies included.

The classification of OH understandings and actions was made based on the words used in the studies, which does not necessarily reflect on the general opinions of the authors concerning OH.

3. Results

3.1. Study selection

The initial online database search, after duplicates were removed, yielded 478 studies. The study selection process for final analysis is illustrated in the PRISMA flow chart (Fig. 1) [28]. Titles and abstracts of all studies were screened of which 86 were included for full-text assessment for eligibility. Out of those, 53 studies met the inclusion criteria and were included in the final synthesis (a list of all included studies can be found in supplementary material A).

Table 1
Characteristics of all 53 studies included for the final synthesis.

Group	Characteristic	No.	%
Spatial scale	Global	34	64%
	Regional	10	19%
	National	9	17%
Study type	Editorial	13	25%
	Opinion and perspectives	12	23%
	Original article	10	19%
	Review	18	34%
Year	2013	1	2%
	2015	2	4%
	2016	2	4%
	2017	2	4%
	2019	7	13%
	2020	39	74%
Disease focus	SARS	4	7%
	MERS	20	37%
	COVID19	37	69%

Note: The sum of the disease focus sub-groups adds up to more than the total of studies because some focused equally on both SARS and MERS; the sum of percentage might not add up to 100% due to rounding.

3.2. Study characteristics

Table 1 displays the characteristics of the included studies. The majority of studies were conducted on a global scale, followed by studies at the national and regional scale, with the majority of countries in the Middle East and North Africa (MENA) that reported MERS outbreaks. Literature reviews and mini-reviews were the most numerous group. Opinions and perspectives, position statements, and commentaries, as well as editorials, guest editorials, and letters to the editor followed. Original research articles had the lowest count. There was a steep increase in publications in 2019 and 2020 explained by the outbreaks of MERS and COVID-19, after a period of relatively few studies between 2013 and 2017. Most studies focused on COVID-19, followed MERS and SARS.

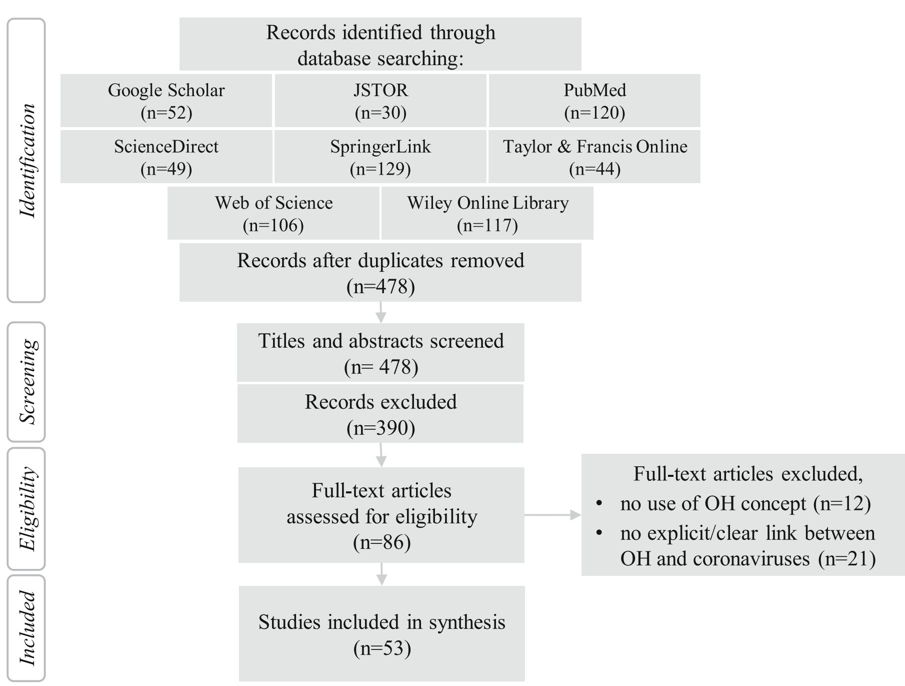

Fig. 1. PRISMA flow chart diagram of the systematic review showing the selection process of relevant studies [28].

Table 2a
One Health understandings identified in studies dealing with SARS or MERS (2013–2020).

	Study	Study type	One Health understanding		
			Institutional coordination & collaboration	OH in action / implementation	Extended OH
SARS or MERS (2013–2020)	Heymann & Dixon (2013)	O	x	–	x
	Crameri et al. (2015)	O	–	x	x
	Edelstein & Heymann (2015)	O&P	x	x	–
	Widagdo et al. (2016)	R	–	x	–
	Zumla et al. (2016)	E	x	x	x
	Alharbi (2017)	R	–	x	–
	Daly (2017)	E	x	x	–
	Dawson et al. (2019)	R	x	x	x
	Farag et al. (2019a)	O	x	x	–
	Farag et al. (2019b)	R	x	x	–
	Hemida (2019)	R	–	x	x
	Park et al. (2019)	O&P	x	x	–
	Ramadan & Shahib (2019)	R	x	x	x
	Werney et al. (2019)	R	x	x	–
	Al Awaidy et al. (2020)	R	x	x	–
	Hemida & Alnaeem (2020)	R	–	x	x

Note: E = Editorials; O&P = Opinion and perspective; O = Original research; R = Review.

3.3. Results of the studies: OH understandings

Three types of OH understandings were identified inductively, Tables 2a and 2b display each study sorted by publication year with their respective study type, and OH understanding grouped into studies dealing with SARS or MERS (2013 – 2020) and COVID-19 (2020).

Across all studies, OH was most often framed as OH for institutional coordination and collaboration (81%), followed by OH in action/implementation, i.e. means for prevention and control (70%), and lastly in its extended meaning concerned with the (natural) environment and

Table 2b
One Health understandings identified in studies dealing with COVID-19 (2020).

	Study	Study type	One Health understanding		
			Institutional coordination & collaboration	OH in action / implementation	Extended OH
COVID-19 (2020)	Ahmad & Hui (2020)	E	x	x	x
	Ahmad et al. (2020)	R	x	x	–
	Ayaji (2020)	E	x	x	x
	Amuasi et al. (2020)	O&P	x	–	x
	Bhatia (2020)	O&P	x	x	–
	Bonilla-Aldana et al. (2020a)	E	x	–	–
	Bonilla-Aldana et al. (2020b)	E	x	x	x
	Chauhan et al. (2020)	R	x	x	–
	Colunga-Salas & Hernandez-Canchola (2020)	O&P	–	x	x
	Decaro et al. (2020)	O&P	x	x	x
	Dhama et al. (2020)	R	x	–	x
	Di Guardo & Vignoli (2020)	O&P	x	–	–
	Egeru et al. (2020)	O&P	x	–	x
	El Zowalaty & Järhult (2020)	O&P	x	x	x
	Enticott & Maye (2020)	O	x	–	–
	Espejo et al. (2020)	O	x	–	x
	Gollakner & Capua (2020)	O&P	x	x	–
	Helmy et al. (2020)	R	x	–	–
	Hemida & Abduallah (2020)	R	–	x	x
	Henley (2020)	E	x	–	x
	Kaphle (2020)	O	x	–	–
	Kasozi et al. (2020)	E	x	–	x
	KC et al. (2020)	R	x	–	–
	Konda et al. (2020)	R	x	–	–
	Lorusso et al. (2020)	O	x	x	–
	Majid et al. (2020)	O	–	x	–
	Marty & Jones (2020)	E	x	x	–
	Mobasheri (2020)	O&P	x	x	–
	Muraina (2020)	O&P	x	x	–
	Mushi (2020)	E	–	x	–
	Parry (2020)	E	x	–	–
	Pokharel et al. (2020)	E	x	–	–
	Poudel et al. (2020)	R	x	x	–
	Sun et al. (2020)	O	x	x	–
	Wang et al. (2020)	O	x	x	–
	Ward (2020)	E	x	x	–
	Yasobant et al. (2020)	R	–	x	–

Note: E = Editorials; O&P = Opinion and perspective; O = Original research; R = Review.

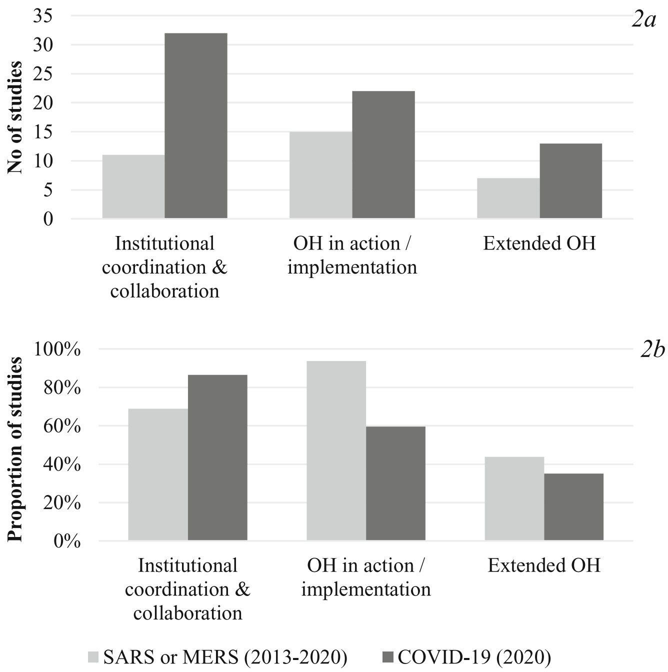

Fig. 2. a/b. Number (2a, top) and proportion (2b, bottom) of studies grouped by disease focus for each OH understanding.

interactions at the human-animal-environment interface (38%).

Segregating the studies according to their study types revealed that OH was framed as institutional coordination and collaboration in most editorials (92%) and opinion and perspective studies (92%), while 80% of the original articles and only 67% of the reviews used it as such. Understanding OH as action/implementation was found in three-quarter of both opinion and perspective as well as reviews and in less than two-thirds of editorials and original articles. The extended understanding of the OH approach was mentioned more often in editorials (46%), followed by opinion and perspective (42%), reviews (33%), and original articles (30%).

For further analysis, the studies were categorized by disease focus in two groups (i.e. SARS or MERS and COVID-19) (see Fig. 2). The number of studies on COVID-19 pursuing OH as institutional coordination and collaboration was much higher than for the SARS/MERS groups. The application of the extended OH approach has increased, however, it remains the least common understanding of OH. Examining the relative distribution of OH understandings by disease group (Fig. 2b) highlights that the dominant understanding of OH changed from OH in action/implementation, which decreased from 94% to 59%, to institutional coordination and collaboration. The application of an extended OH understanding decreased slightly from the SARS/MERS (2013–2020; 44%) group to the more recent studies on COVID-19 (2020; 35%).

3.4. Result of the individual studies: OH actions

The OH action types were split into actions under the classical and extended OH approaches, and grouped to determine the levels of application.

The actions at the human-animal interface displayed in Table 3 included measures to decrease the risk of viral shedding from human to human [37,38], from animal to animal [38,39], and from animal to human [40]. Further actions targeted the identification and understanding of pathogen reservoirs [38,41–48], and awareness-raising on the diseases [45,49–52]. The identified actions operated on various spatial levels: household level, i.e. to make dairy and meat safe for consumption [10,38] and the pasteurization of camel milk [40]; farm level, i.e. rapid identification of sick camels and their isolation [38,47]; abattoirs level, i.e. standardized protocols for the operation [38]; country and regional level, i.e. limitation of livestock mobility between neighbouring countries [38], improvement in the laboratories´ capacities [41,42,53–55], the collaboration between institutions for a coordinated response to outbreaks [56], and the improvement of surveillance and monitoring [57–62].

A smaller set of control and response actions at the human-animal interface considered the environmental outcomes (see Table 4; a more detailed version of Table 3 and Table 4 can be found in supplementary material B). These include the banning and monitoring of animal transport and trade to avoid the zoonotic bridging in a food system related-environment [45,57,63], increased awareness of personal hygienic measures in occupational settings [50,52], vaccination and monitoring of domestic animals to reduce shedding the viruses to the environment [38,47,51,64–66], bio-surveillance in wet markets [37,61], and public education on zoonosis [37,46,54].

The actions considered at the animal-human-environment interface addressed the environment as transmission and virus shedding route. These actions differentiated between measures applied in built environments such as environmental hygiene and cleanliness [50,57,63], biological waste disposal from abattoirs [38,52], measures applied in natural environments such as monitoring the concentration of the viruses in the air [57], urban land-use planning [67], chemical and pollutants management [38,52,67], and wastewater treatment plants for dealing with drugs and pathogens [54,67]. Further actions at the human-animal-environment interface were concern with the spatial identification of high-risk areas by utilizing Geographic Information Systems [40], and capacity development in a broad range of sectors and disciplines [37,46,49,50,61,68,69].

4. Discussion

4.1. Moving towards an extended OH approach that includes the environmental domain

The studies included in this systematic literature review have a strong focus on addressing zoonotic diseases at the animal-human interface. In contrast, only a few studies referred explicitly to interactions at the human-animal-environment interface [37,39,50,54,67,70], which may be explained by the apparent lack of a clear definition of "the environment". More specifically, general references were made on disease transmission in healthcare settings [52,57], rather than the influence of the natural environment on disease emergence.

Crameri et al. [58] argued, *"that when dealing with an emerging infectious disease with a complex epidemiology, conventional outbreak investigations may not resolve key questions, and thus there is a need for studies which might appear tangential"* (p. 81). In line with this vision, other studies have indicated that environmental factors, e.g. temperature, rainfall, humidity, or vegetation, could play a role in the emergence of coronavirus diseases [39,52,54,57,70,71], calling for the equal inclusion of the environmental domain in the prevention of zoonosis.

Zoonotic disease emergence has been mostly mediated by the mobility of pathogens across species and ecological boundaries [72,73]. Human population growth has increased the demand for housing, food, trade, and tourism thereby directly or indirectly increasing human exposure to viral zoonoses through the expansion and modification of the built environment into natural habitats [74–78]. In addition, as a result of globalization and increased urbanization patterns, the demand for animal protein also increases, driving agricultural expansion and intensification, along with deforestation, as well as animal trade. This increases animal density and contact between animals and humans, leading to an increased risk of pathogen transfers [78]. This is evident in the emergence and re-emergence of viral zoonosis (e.g. Ebola or MERS-CoV) in Sub-Saharan Africa, the Middle East, and Asia [56,74,78]. Moreover, poor waste management leads to environmental degradation and increased exposure and susceptibility of humans to

Table 3
One Health actions at the human-animal interface (i.e. "classical OH") identified in each study.

	Group	References
Classical	Animal movement and interaction between animals and with humans	Hemida & Alnaeem (2019); Hemida (2019); Konda et al. (2020); Zumla et al. (2016a); El Zowalaty & Järhult (2020); Colunga-Salas & Hernandez-Canchola (2020); Dhama et al. (2020); Ahmad et al. (2020)
	Awareness creation, operating protocols, and policies	Farag et al. (2019a); Ajayi (2020); Helmy et al. (2020); Hemida & Alnaeem (2019); Ahmad et al. (2020); Dhama et al. (2020); Gollakner & Capua (2020); Ramadan & Shaib (2019); Hemida (2019); Konda et al. (2020); Lorusso et al. (2020); Mushi (2020)
	Control and understanding of pathogens	Al Awaidy et al. (2020); Di Guardo & Vignoli (2020); KC et al. (2020); Lorusso et al. (2020); Ahmad et al. (2020); Widagdo et al. (2016); Hemida & Alnaeem (2019); Konda et al. (2020); Gollakner & Capua (2020)
	Diagnosis, detection, and treatment capacities	Al Awaidy et al. (2020); Farag et al. (2019a); Sun et al. (2020); Ahmad et al. (2020); Bonilla-Aldana, D, Dhama, K, Rodriguez-Morales, A J (2020); Mushi (2020); Ahmad et al. (2020); Helmy et al. (2020); Lorusso et al. (2020); Bonilla-Aldana et al. (2020); Mobasheri (2020); Muraina (2020)
	Food safety	Hemida (2019); Hemida & Alnaeem (2019); Zumla et al. (2016a); Konda et al. (2020); Poudel et al. (2020); Ahmad et al. (2020)
	Human travel control and community control strategies	Ahmad et al. (2020), Mushi (2020); Ramadan & Shaib (2019); Zumla et al. (2016a)
	Immunization	Ramadan & Shaib (2019); Widagdo et al. (2016); Helmy et al. (2020); Bonilla-Aldana et al. (2020); Ahmad et al. (2020); Decaro et al. (2020); Lorusso et al. (2020)
	Information management	Farag et al. (2019a)
	OH capacity development and research	Bonilla-Aldana, D, Dhama, K, Rodriguez-Morales, A J (2020); Dhama et al. (2020); Mobasheri (2020); Konda et al. (2020); Helmy et al. (2020)
	Preparedness and response plans	Farag et al. (2019a); Hemida & Alnaeem (2019); Hemida & Abdullah (2020); Ramadan & Shaib (2019); Dhama et al. (2020)
	Surveillance, monitoring	Crameri et al. (2015); Hemida & Alnaeem (2019); Muraina (2020); Hemida & Abdullah (2020); Mobasheri (2020); Ahmad et al. (2020); Yasobant et al. (2020); Bhatia, R. (2020)

Note: An extended version of this table with concrete actions can be found in Annex B.

Table 4
OH Actions with outcomes for the environment identified in each study.

	Group	References
Classical towards care of environment	Animal movement and interaction between animals and with humans	Hemida & Abdullah (2020); Konda et al. (2020); Ahmad et al. (2020); Dhama et al. (2020)
	Awareness, operating protocols, and policies	El Zowalaty & Järhult (2020); Bonilla-Aldana, D, Dhama, K, Rodriguez-Morales, A J (2020); Poudel et al. (2020); Hemida (2019); Helmy et al. (2020); Egeru et al. (2020)
	Control and understanding of pathogens	Poudel et al. (2020); Konda et al. (2020); Bonilla-Aldana, D, Dhama, K, Rodriguez-Morales, A J (2020); Ramadan & Shaib (2019); Al Awaidy et al. (2020); Di Guardo & Vignoli (2020); Parry (2020)
	Food safety	Henley (2020); Pokharel et al. (2020)
	Human travel control and community control strategies	Wang et al. (2020)
	Immunization	Alharbi (2017); Hemida & Alnaeem (2019); Daly (2017); Ramadan & Shaib (2019); Widagdo et al. (2016); Hemida (2019); Bonilla-Aldana et al. (2020)
	Information management	Al Awaidy et al. (2020); Ahmad et al. (2020); Yasobant et al. (2020)
	OH capacity development and research	Al Awaidy et al. (2020); Farag et al. (2019a); Edelstein and Heymann (2015); Ahmad et al. (2020); Henley (2020); KC et al. (2020); Muraina (2020); Park et al. (2019); Yasobant et al. (2020); Mobasheri (2020); Helmy et al. (2020); Egeru et al. (2020); Mushi (2020)
	Surveillance, monitoring	Dawson et al. (2019); Farag et al. (2019a); Hemida & Alnaeem (2019); Ramadan & Shaib (2019); Ahmad et al. (2020); Chauhan et al. (2020); Mushi (2020); Yasobant et al. (2020); Bonilla-Aldana et al. (2020), Hemida (2019); Heymann & Dixon (2013); Majid et al. (2020); Lorusso et al. (2020); Pokharel et al. (2020); El Zowalaty & Järhult (2020); Ajayi (2020)
Extended	Awareness, operating protocols, and policies	Espejo et al. (2020)
	Control and understanding of pathogens	Egeru et al. (2020); Hemida & Abdullah (2020)
	Environmental management and pollution control	Hemida & Abdullah (2020); Helmy et al. (2020); Dhama et al. (2020); Espejo et al. (2020); Bonilla-Aldana, D, Dhama, K, Rodriguez-Morales, A J (2020); Poudel et al. (2020); Hemida (2019); Hemida & Alnaeem (2019)
	Information management	Ramadan & Shaib (2019)
	OH capacity development and research	Kasozi et al. (2020); Helmy et al. (2020); Ramadan & Shaib (2019); Amuasi et al. (2020); Espejo et al. (2020); Ward (2020); Ajayi (2020); Enticott & Maye (2020); El Zowalaty & Järhult (2020)
	Surveillance, monitoring	Poudel et al. (2020); Helmy et al. (2020); Yasobant et al. (2020)

Note: An extended version of this table with concrete actions can be found in Annex B.

viral infections [79].

Fewer of the reviewed studies mentioned a broader socio-ecological perspective, by considering underlying drivers such as environmental and climate change, as well as anthropological and demographic changes [39,50,80]. In this context, some studies called for the inclusion of other specialists aside from the human and veterinary health disciplines, namely, ecologists, economists, and other natural and social scientists, to be involved in the effort to prevent and control disease outbreaks caused by coronaviruses [39,40,50,81–83].

The importance of the natural and built environments can be easily identified in the context of the COVID-19 outbreak. Recent studies on SARS-CoV-2 reported that the virus was isolated from toilet bowls, sinks [84,85], different kind of materialistic environmental surfaces, including plastic, stainless steel, paper [86], surgical masks, and personal protective equipment [87], indicating the role of the built environment. As for conditions of the natural environment, morbidity levels of COVID-19 have been related to temperature and humidity [87,88], and atmospheric pollution [89]. These findings suggest the potential importance of measures such as sewage surveillance, strict adherence to hygiene and sanitization measures [84,90], further research on airborne transmission through aerosols [85], and on the effects of weather parameters (e.g. solar radiation, temperature, and humidity) in different climatic zones [91].

4.2. Operationalization of OH through institutional collaboration and action

The different OH understandings make it challenging to operationalize OH, and thereby, highlighting the importance of institutional coordination and collaboration to create a common understanding of OH.

The majority of the studies highlighted the detection, prevention, and control of emerging zoonotic infections as the main motivation for institutional coordination and collaboration [10,37,44,54,62,92]. Those collaborations were implemented at various scales, such as international and national levels. Examples found in the review are the national OH strategies implemented in the countries of the Gulf Cooperation [56], and in Oman [41], based on human-animal health committees, enhancement of capacities to provide diagnostic for humans and animals, collaboration for epidemiological surveillance, joint research projects, multidisciplinary action, and inter-sectoral collaboration between ministries.

Along with the collaboration strategies, OH actions that are specific (e.g. spatial levels, i.e. household, food production units, food processing units, markets of live animals, transportation) and target-oriented (e.g. animal-human and animal-human-environment interfaces) are needed for the operationalization of OH [93]. At the animal-human interface, the understanding of zoonotic pathogen fatality and the spillover from wildlife to humans was the best action for effective prevention and control of zoonotic outbreaks [94]. Considering the environment, another group of actions proposed for the control and response to MERS and COVID-19 can be differentiated between those applied to the built environments and those applied in natural environments.

Combining institutional coordination with specific OH actions can drive the operationalization of OH, however, the initiatives taken until now have different understandings of the OH approach that might hinder effective coordination, collaboration, and action.

Challenges identified were related to different understandings of OH, sectoral power relations and priorities, and funding:

- sectoral actions to reduce the risk of viral shedding, as well as therapeutic interventions, were framed within OH, causing potential biases on the understandings of OH;
- the actions applied at the human-animal-environment interface reflected directly on the mortality and morbidity indicators of humans and animals, but not so on the improved environmental quality;
- the distribution of financial funds was made in a sectoral manner, challenging the contribution of the parts involved in the funding of specific OH actions.

The classical OH approach is the natural choice to guide coordination between sectors at the early stages, moreover, to expand the OH scope to understand the mediating conditions that facilitate infection rates such as social, cultural, economic, or climatic, is a complex task that needs time to be addressed. Notwithstanding this, a more comprehensive understanding of infectious diseases is needed to address unanswered questions related to the complexity of diseases.

5. Conclusion

The evolution of the OH approach has created the opportunity to develop actions at the human-animal-environment interface more equitably. This has become apparent in the latest efforts to address MERS and COVID-19 epidemics, which focused not only on the human-animal interfaces but also started to include the environment. This extended OH approach provides an inclusive and comprehensive outlook on health issues, including the emergence of zoonotic diseases. However, there is still a long way to go for achieving institutional coordination and collaboration across disciplines and sectors, with the inclusion of social, cultural, and economic components.

The actions identified in this literature review are a good starting point for evaluating the stage of OH development in different settings, such as research or policy development. Moreover, the knowledge gaps identified were (1) for the general operationalization of OH: comparing the number of resources needed for OH coordination and actions, with the benefit obtained from those; and (2) for the inclusion of the environment in OH actions: the understanding of disease ecologies within the context of environmental factors (e.g. weather parameters, sewage surveillance, pathogens transmission through aerosols, environmental hygiene and sanitization measures).

The OH contribution to the current COVID-19 control can only be envisioned through therapeutic and preventive options. However, there is a great potential for promoting intersectoral action and active surveillance in natural reservoirs to be prepared and to mitigate the impacts of the next epidemics. Therefore, it is the right time to understand and extend the scope of OH, and appropriate actions need to be taken at the local, national, and global levels.

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Availability of data and materials

All relevant data that supports the findings of this study are within the manuscript.

Authors' contributions

All authors contributed equally to the development of this study. As for the CRediT guidelines,

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Declaration of Competing Interest

None.

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2.2. Effect of HEPA filters on COVID-19 in Kindergartens

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Background & Aim:

The COVID-19 pandemic resulted in severe social, economic and political disruptions worldwide. The closure of schools, kindergartens and daycare facilities placed a significant burden on parents and caregivers, while also depriving children of social contact and education. Reopening of schools and kindergartens was only possible under strict rules, including social distancing, personal protective equipment, mass testing and regular ventilation. As SARS-CoV-2 is an airborne pathogen the utilization of high-efficiency particulate air (HEPA) filters for infection control was widely discussed in academia, politics and the wider society. A number of experimental studies indicated that HEPA filters are effective in reducing SARS-CoV-2 concentration in the air. However, authors also noted that the positioning of the filters is critical for their effectiveness. While the experimental studies are promising, no studies assessed the actual impact on COVID-19 incidence. Our study aims to fill this knowledge gap by assessing the effectiveness of portable HEPA filters in a real-life setting, i.e. kindergartens. As children in kindergartens are highly mobile throughout the day and engage in close person-to-person interactions, this setting does not comply with the experimental assumptions of previous studies.

Methods & Results:

The study applied an interventional design, where the intervention group consisted of kindergartens with portable HEPA filters and the control group of those not using any air filters. All intervention kindergartens were equipped with HEPA filters from the same company, the size of the rooms determined the specific unit to be used. The positioning and size of the filters was determined by the manufacturer in discussion with the head of the kindergarten. Ten kindergartens were enrolled into the intervention group consisting of 663 children and 147 childcare workers. 22 control kindergartens were recruited from neighboring villages and districts, consisting of 1,697 children and 374 caretakers. Data was collected anonymously on the institutional level with the head of the kindergarten providing the data. Two instruments were used, a baseline survey to gain insight into the number children and caretakers, preventive measures and previous COVID-19 cases. The retrospective reporting of COVID-19 cases was clustered according to the pandemic waves. As all cases had to be reported to the local health authorities, the data accuracy of the retrospective reporting is considered high. The second instrument is the continuous case documentation in which cases were reported in a 14-day interval over the period from April 2022 to March 2023. Due to the low number of cases in the first pandemic waves and the HEPA filters only being operational from September 2021, the analysis focused on the Omicron wave. The period prevalence was calculated from November 2021 to May 2022 for each group and was compared using a one-sided Wilcoxon rank-sum test with continuity correction. Additionally, differences in preventive behavior were assessed with Fisher's exact test or chi square test. The period prevalence of the entire sample population was 236 per 1,000 children. In the control group 186 cases per 1,000 children were observed during the Omicron wave, whilst 372 cases per 1,000 children were reported in the intervention group. Consequently, the one-sided Wilcoxon rank-sum test was not significant, indicating no significant preventive effect of the HEPA filters. A significant difference in ventilation frequency was noted, with the control group engaging in more frequent ventilation. Similarly, surface decontamination was practiced more commonly in the control group.

Conclusion:

In the kindergarten setting no preventive effect of HEPA filters on COVID-19 period prevalence was observed. It is hypothesized that the particularities of the kindergarten setting are responsible for these results. Children are not stationary throughout the day and are frequently in close direct contact with each other. Therefore, direct air exchange is expected to occur frequently between the children. The results indicate that the presence of HEPA filters induce reduced adherence to traditional preventive measures. In conclusion, HEPA filters cannot replace traditional preventive measures, including face-masks, frequent ventilation and surface decontamination to control COVID-19 contagion in kindergartens.

BMJ Open

Effect of portable HEPA filters on COVID-19 period prevalence: an observational quasi-interventional study in German kindergartens

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ABSTRACT

Objectives The aim of the study was to evaluate the effect of high-efficiency particulate air (HEPA) filters on COVID-19 period prevalence in kindergartens.

Design The observational study follows an intervention design with the intervention group using HEPA filters and the control group not.

Setting The study was conducted in 32 (10 intervention, 22 control) kindergartens (daycare centres) in Rhineland Palatinate (Germany).

Participants Data of 2360 children (663 intervention, 1697 control) were reported by the kindergarten heads. Data were collected on institutional level without any identifying information on individuals. Thus, all children of all facilities were included; however, no demographic data were recorded.

Interventions The study followed a quasi-interventional design, as no formal intervention was conducted. A charity foundation equipped kindergartens with HEPA filters. These kindergartens were enrolled as intervention group. The control group was recruited from the neighbouring communities and districts.

Outcome measures The primary outcome measure was the number of COVID-19 cases reported by the kindergarten heads, converted into period prevalence rates per 1000 population.

Results The mean COVID-19 period prevalence rates of the control and intervention groups were 186 (95% CI: 137.8 to 238.9) and 372 (95% CI: 226.6 to 517.6) per 1000 children, respectively. The one-sided Wilcoxon rank-sum test indicates a p value of 0.989; thus, the hypothesised preventive effect of HEPA filters could not be confirmed in the kindergarten setting.

Conclusions While HEPA filters can significantly reduce the viral load in room air, this does not lead to reduced COVID-19 prevalence in the selected kindergartens in Germany. It is known that contagion mainly occurs via direct face-to-face air exchange during play and that the contaminated air does not necessarily pass through the filter prior to air exchange between children. The use of HEPA filters may also lead to a sense of security, leading to reduced preventive behaviour.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Evaluation of high-efficiency particulate air filter's effect on actual COVID-19 period prevalence.
- ⇒ Inclusion of all children of the studied kindergartens.
- ⇒ Data are on the institutional level without further information on the cases.
- ⇒ The intervention group was preselected (no random group allocation).

BACKGROUND

The COVID-19 pandemic has caused severe disruptions of everyday public activities across the globe. Different degrees and duration of lockdowns and restrictions on public life have resulted in immense social and economic problems. A particular challenge was the closure of schools, kindergartens and daycare centres, as these not only deprived the children of education and essential social contact, but also placed a high burden on parents and other caregivers. In Germany, reopening schools and kindergartens had a high political, social and economic priority, while also trying to avoid children becoming spreaders of the disease. SARS-CoV-2 is an airborne pathogen that can spread via three relevant routes: directly via droplets, indirectly via fomites and via airborne transmission, that is, aerosols that remain in the ambient air for prolonged periods.[1] In enclosed indoor environments, where close interaction occurs over longer periods, the highest risk of contagion is evident.[2] Reopening of schools and kindergartens was therefore only possible under strict hygiene and prevention measures, including wearing of personal protective equipment (PPE) (particularly facemasks), regular ventilation (every 30 min), mass testing and social distancing through reductions in group size. While these measures could be enforced quite well in schools with older children, for kindergarten children (aged 1–6 years), particularly wearing masks all day, was difficult to enforce. Kindergarten in Germany is defined as a facility for the care and promotion of the development of children of preschool age, that is, daycare centre. Whereas regular or even constant ventilation is easily realised during the warmer month; however, once temperatures drop into the single digits, frequent ventilation is unlikely. Therefore, spending prolonged time periods in confined indoor spaces with a large number of people will place them at risk of infection. A potential solution that has been widely discussed both politically and academically is the use of high-efficiency particulate air (HEPA) filters.

A wide range of HEPA filters and configurations exists with differing removal efficiencies (see 3–5). Such filters can be installed in existing air conditioning systems and are also available as portable air filters. Generally, the efficiency of the filter is the same in centrally installed and portable devices; however, with portable filters, the positioning of the filter in the room as well as the correct use are stated as critical factors and need to be considered.[6 7] HEPA filters in compliance with ISO 29463-1[8] guarantee the removal of at least 99.95% of particles between 0.1 and 0.3 µm.[9] The size and power of the HEPA filter will determine the removal rate, with larger systems filtering larger volumes of air.[10] Manufacturers specify the clean air delivery rate, which is the volume of air passing through the system per minute multiplied with the removal rate. This needs to be considered in regard to the room size in which the device shall be used.[10]

Different experimental studies have been performed to test the potential of HEPA filters to reduce or even eliminate the propagation of SARS-CoV-2. The majority of studies did not use the actual SARS-CoV-2 in their experiment but used aerosols, bacteria or viruses of similar size as surrogate particles (eg, 6–11). A more recent experiment confirmed that the infectious SARS-CoV-2 is effectively removed by HEPA filters; however, the authors note airflow is important to consider as air does not pass through the filter evenly.[12] A systematic review[13] explored the efficiency of portable HEPA filters, highlighting that all reviewed studies indicated a significant reduction in airborne particles. An experiment by Curtius *et al*[7] conducted in classroom settings using four HEPA filters highlighted that the filters significantly reduce concentrations in between ventilation periods, however, should be used in addition to ventilation, rather than replacing other preventive measures. Kähler *et al*[14] stated that the position of the air purifier in the room is a critical factor. It is unquestionable that HEPA filters effectively remove particles from the air, as these filters are tested according to ISO standards, and various experiments demonstrated the effective removal of aerosols. However, no study to date has assessed the impact of HEPA filters on the actual COVID-19 incidence.

In our study, we assess the epidemiological effectiveness of portable HEPA filters in a real-life setting, investigating the COVID-19 period prevalence in kindergartens with portable air filters as compared with kindergartens that do not use them. Assuming that the HEPA filters are operated correctly, it is hypothesised that kindergartens which use portable HEPA filters should show lower COVID-19 incidences compared with those not having such filters. This study aims to fill an important knowledge gap between the theoretical and experimental value of using HEPA filters in kindergartens and schools and their actual epidemiological effect. Providing such filters in public facilities prompts a significant financial investment, thus requiring clear evidence. Particularly in kindergarten settings, high mobility of children throughout the day, various close interactions and suboptimal compliance with hygiene measures create a unique situation that does not adhere to the experimental assumptions of previous studies.

METHODOLOGY

Our study used an interventional design with the intervention group consisting of kindergartens equipped with portable HEPA filters and the control group not using any air filters. The intervention group was equipped with DEMA-airtech air purifiers.[15] The specific units were either AP-160, AP-120, AP-90 or AP-40, adapted to the room size. The DEMA-airtech system uses a coarse prefilter, HEPA H13 filter, activated carbon filter, plasma, titanium dioxide photocatalyst filter and ultraviolet-C light, in this order of configuration. The devices are certified and tested with a removal efficiency of 99.99%. The optimal positioning and required size were decided in discussion with the manufacturer and the head of the kindergartens. An independent research institute (SGS Institut Fresenius) conducted experimental tests in selected kindergartens, which simulated an infected person dispersing aerosols into the room air and found that after 4–9 min, the aerosol concentration was halved, while after 15–30 min, reductions of 90% were achieved. All group rooms, common areas, staff rooms and entrance areas were equipped, if existing also activity rooms (gymnasium) and sleeping rooms were equipped. Consequently, all rooms and areas where multiple people interact with each other were equipped with appropriately sized devices. The air filters were installed between July and September 2021 and were thus fully operational during the Omicron pandemic wave.

Sample sizes

Ten kindergartens in the German Federal State Rhineland Palatinate were equipped with the above-mentioned HEPA filters forming the intervention group. In these 10 kindergartens, 663 children were cared for by 147 childcare workers in 35 groups. The intervention group was selected purposively, as these were equipped with air filters by a local charity foundation (Else-Schütz Stiftung). The control group kindergartens (n=22) were recruited from neighbouring villages and districts. Next to active recruitment, the study was also announced in the local newspaper, calling on kindergartens to participate in the study. The 22 kindergartens of the control group consist of 1697 children and 374 caretakers, organised into 65

Table 1 Sample population

Group	Institutions	Groups	Children	Caretakers
Intervention	10	35	663	147
Control	22	65	1697	374

groups (see table 1). Therefore, the total sample size of the study was 32 kindergartens with 2360 children and 521 childcare workers. This sample size is far beyond the calculated minimum required of 396 children, assuming a 15% difference of population proportions, a 99% confidence level and a 5% margin of error. In total, kindergartens of three districts were enrolled into the study; the three districts did not exhibit significantly different COVID-19 incidences at the population level and are also similar in demographic and social structure.

Methods

The study collected data on the institutional level with the head of the kindergartens serving as respondent. Due to the mandatory reporting requirement to the health authority, data accuracy can be assumed. The data collection involved two instruments: a baseline survey and continuous case documentation. Both instruments were self-administered and conducted online. The data entry mask was hosted on university servers, and each institution received a username and password for data entry. The baseline survey focused on establishing the number of children and childcare workers, prevention measures and previous COVID-19 cases in the kindergarten. Among the prevention measures, facemask wearing, ventilation frequency, surface decontamination frequency and group intermixing were included. Additionally, it was established when the HEPA filters were installed and in which rooms of the individual kindergarten. The retrospective COVID-19 cases were reported according to the waves of the pandemic: wave I (March–April 2020), summer plateau 2020 (May–September 2020), wave II (October 2020–February 2021), wave III (March–May 2021), summer plateau 2021 (June–October 2021) and wave IV (November 2021–March 2022). The baseline survey was conducted between 24 March and 11 April 2022. Starting from 8 April 2022, the continuous case documentation was initiated, which was continued until March 2023. This instrument involved the documentation of all COVID-19 cases occurring in the individual kindergarten. The documentation has been conducted in 14-day intervals, with automated reminders sent to the kindergarten heads on Friday mornings. In the documentation, the numbers of newly infected children and childcare workers during the respective 14-day period were reported. Additionally, closure of the facility, due to quarantines, holidays or similar reasons were noted.

Analysis

As the HEPA filters were only operational starting from September 2021, this paper only reports on the Omicron wave, that is, November 2021 until end of May 2022. For each group, period prevalence rates were calculated by dividing the number of cases by the total number of children and multiplying the result by 1000 to produce the prevalence rate: cases per 1000 children. Here it should be noted that all cases were summed over the time period; therefore, a period prevalence is reported. These period prevalence rates were then compared between the intervention and control groups using a one-sided Wilcoxon rank-sum test with continuity correction. This test was performed to test the hypothesis that the intervention group, that is, kindergartens with portable HEPA filters, have lower period prevalence than the control group. Essentially, testing if a preventive effect of the HEPA filters is observed. A non-parametric test was chosen, as the data were not normally distributed (Shapiro-Wilk test was significant). Additionally, differences between the two groups in preventive measures were tested using Fisher's exact test for binary variables or X^2 test for categorical variables. Statistical significance was considered at $p<0.05$.

Patient and public involvement

Patients or the public were not involved in the design, reporting or dissemination of the research.

RESULTS

The sample population included children of 32 kindergartens. The 2360 children were divided into 663 children in the intervention group, that is, with HEPA filters, and 1697 children in the control group, that is, without HEPA filters (see table 1). Throughout the reporting period, the number of children remained constant.

In the majority of kindergartens (94%), facemasks were worn outside of the group setting, that is, in the hallways and common areas. During the actual childcare activities, which are occurring in the group setting, only 25% of kindergartens indicated childcare workers wearing facemasks. Consequently, in the remaining 75% of kindergartens during the majority of time spent in the kindergarten, no facemasks were worn. No difference between control and intervention kindergartens is evident (see table 2).

In 72% of kindergartens, group allocation was fixed, that is, children were always in the same group and groups were not intermixed. However, only in 6% of kindergartens group intermixing was also prohibited outside, that is, during break time occurring outdoors. In these 6% of kindergartens, outdoor playtime was staggered, so that individual groups did not mix at all. Contact between childcare workers responsible for different groups was restricted in 65% of kindergartens. No significant difference was observed between the control and intervention groups (see table 2).

Ventilation forms a key preventive measure against contagion; 81% of kindergartens ventilated the group rooms once per hour. About 18% of the control group ventilated the group rooms more frequently, that is, once every 30 min, while 20% of the intervention group

Table 2 Facemask wearing and group intermixing

Variable	Group	Yes	No	Fisher's exact test
Wearing facemask outside of group	Intervention	8	2	p=0.091 CI: 0.00; 2.32
	Control	22	0	
Wearing facemask during childcare in group	Intervention	2	8	p=1.000 CI: 0.05; 5.03
	Control	6	16	
Fixed group allocation	Intervention	5	5	p=0.096 CI: 0.03; 1.54
	Control	18	4	
Outdoor intermixing of groups	Intervention	1	9	p=0.534 CI: 0.03; 191.39
	Control	1	21	
Contact between childcare workers	Intervention	5	5	p=0.252 CI: 0.43; 16.40
	Control	6	16	

ventilated their group rooms less frequently, that is, every 2–3 hours. The X^2 test indicates a significant difference in the pattern of ventilation between the intervention and control groups with more frequent ventilation in the control group (see table 3).

Surface decontamination was practised in 84% of the kindergartens; however, the frequency of decontamination differs. On average, the surface decontamination frequency is higher among the control group. The X^2 test revealed a significant difference in the pattern of surface decontamination between the intervention and control groups, with a larger proportion of the control group having practised more frequent surface decontamination (see table 4).

Figures 1 and 2 depict the period prevalence for the different COVID-19 waves for children and childcare workers, respectively. It is important to note that although the control and intervention groups are segregated throughout the time period, the HEPA filters were only installed during summer 2021. Therefore, only wave 4 (ie, the Omicron wave) can be used to assess the effect of the HEPA filters. Yet, the figures clearly show that for both children and childcare workers, minor elevations were noted in waves 2 and 3 without significant differences between the control and intervention groups. Only during the Omicron wave a large increase in prevalence was noted in both groups. The COVID-19 period prevalence per 1000 children for the Omicron wave is presented in table 5. The period prevalence of the entire sample population was 236 per 1000 children for the time period (November 2021–May 2022). In the control group, the period prevalence ranged from 0 to 540 per 1000 children, while the period prevalence ranged from 120 to 869 per 1000 children in the intervention group. The mean COVID-19 period prevalence rate was 372 and 186 per 1000 children in the intervention and control groups, respectively. The one-sided Wilcoxon rank-sum test indicates a p value of 0.989 and a CI from $-\infty$ to 299.7. The period prevalence per 1000 childcare workers (table 6) presents similar results. In the control group, the mean prevalence for the period from November 2021 to May 2022 was 529 per 1000 childcare workers, while it reached 1193 per 1000 childcare workers in the intervention group. The one-sided Wilcoxon rank-sum test failed to reach significance. Therefore, no significant preventive effect of the HEPA filters could be found.

Table 3 Ventilation frequency

Group	Every 30 min	Every hour	Every 2–3 hours	X^2
Intervention	0	8	2	p=0.045
Control	4	18	0	

DISCUSSION

Our study showed no significant preventive effect on COVID-19 period prevalence in the kindergarten setting. This finding may be rather surprising, as various experimental studies have demonstrated the effectiveness of HEPA filters in reducing aerosol concentrations in enclosed rooms. It is, however, important to note that the experimental setting is limited in imitation transmission processes.[11] The effectiveness of HEPA filters to remove bacteria, viruses, allergens and other aerosols from the air is, however, not placed in question here. Nevertheless, such removal does not necessary reduce contagion between individuals situated in an enclosed room over prolonged periods of time, in particular if other measures such as mask wearing is not possible. Furthermore, while HEPA filtering systems certainly can decrease aerosol concentrations, direct transmission via larger droplets still occurs. Hence, air circulation, person density, mask wearing and activity type conducted in the room are very likely to affect the risk of infection and consequently the epidemiological effectiveness of HEPA filters.

In the kindergarten, the children, aged 1–6 years, are not stationary, but continuously move through the rooms. Therefore, multiple potential sources of viral emitters are moving through the rooms throughout the day. The children play with each other in close contact while not wearing PPE. Small children as investigated here have no concept of general hygiene measures for preventing transmission in general. Consequently, it is highly likely that direct air exchange and therefore potential contact and droplet transmission occur frequently between multiple children throughout the day. Our data demonstrate that in the majority of kindergartens, facemasks are not worn inside the group setting, thus also childcare workers are exposed to direct contagion throughout the day. Although it has been demonstrated in literature that the viral load in the room air is lower with HEPA filters compared with a situation without HEPA filters,

Table 4 Surface decontamination frequency

Group	Multiple times per day	Daily	Multiple times per week	Weekly	No	X^2
Intervention	2	2	0	3	3	p=0.001
Control	0	18	2	0	2	

an air filter that is not in direct physical proximity of the infected person cannot reduce the risk of transmission by direct exposition.[11] Air filters may reduce the risk of transmission by reducing the virus burden in the air,[6 7 14 16] but are not able to stop the direct transmission if the infected child stays in direct contact to a susceptible child or childcare worker as indicated by our results. For this reason, it appears that the use of preventive measures, such as facemasks, frequent ventilation and surface decontamination, remain important regardless of HEPA filters being used. Other studies have also highlighted the importance of combining multiple prevention measures to induce effective protection.[7 17] The data obtained in our study provide some indication that the use of HEPA filters leads to a reduction in preventive behaviour. Lower ventilation and surface decontamination frequencies were especially noted in the intervention group. It is suspected that the use of HEPA filters induces a sense of security among the childcare workers, which might lead to a reduced adherence to preventive measures. Hammond *et al*[4] state in their review on portable air filters in homes and workplaces that the existing research lacks important evidence regarding the effectiveness of reducing indoor transmission of respiratory infections, including SARS-CoV-2.

Consequently, there are two suspected reasons why the expected preventative effect of HEPA filters on the period prevalence of COVID-19 could not be confirmed in the kindergarten setting: (1) the close interaction between children during play leads to direct face-to-face air exchange and direct contact, which leads to the exchange of aerosols/droplets that were not previously filtered through the HEPA filter; (2) the presence of the HEPA filters might induce a sense of security that leads to reduced adherence to other preventive measures, such as frequent ventilation, surface decontamination and wearing of facemasks. The background COVID-19 incidence was considered as a confounding factor; however, no significant differences were observed between the

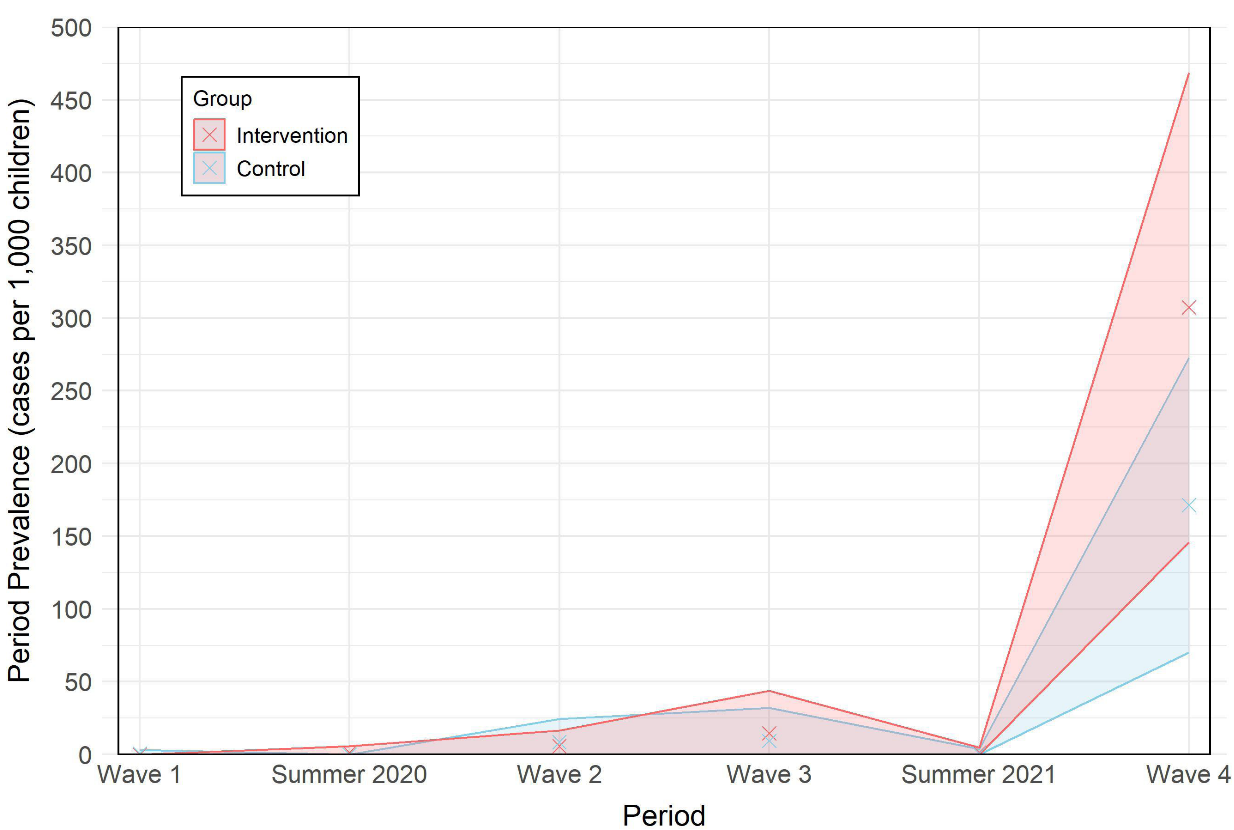

Figure 1 Period prevalence of children by pandemic waves segregated by control and intervention groups. 'X' represents the mean, the upper and lower lines are ±1 SD (values below 0 were omitted).

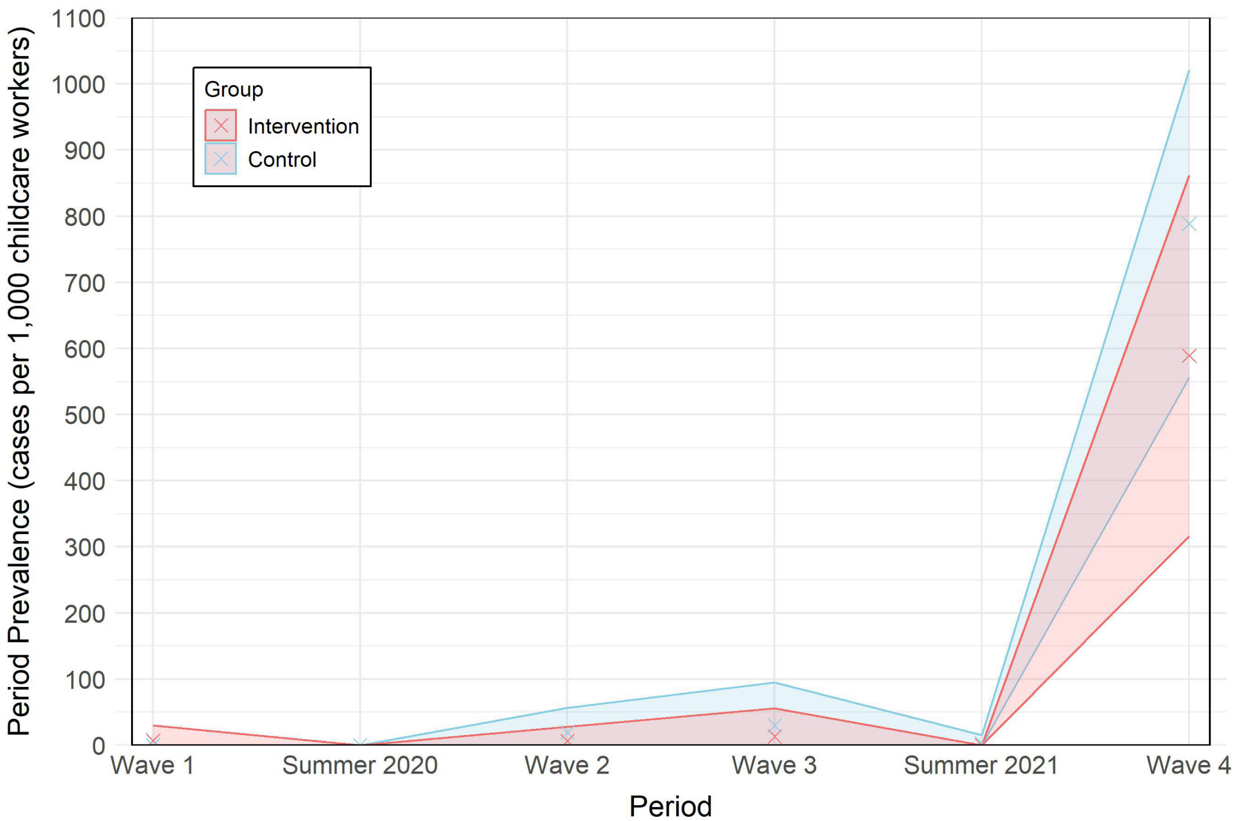

Figure 2 Period prevalence of childcare workers by pandemic waves segregated by control and intervention groups. 'X' represents the mean, the upper and lower lines are ±1 SD (values below 0 were omitted).

districts. The mean 7-day incidence in the three districts was 668, 726 and 801 per 100000 population over the reporting period. Due to the mandatory reporting of COVID-19 cases of the kindergarten heads to local health authority, data accuracy can be assumed, and reporting intensity between the intervention and control groups is comparable. Further research is required to explore behavioural changes associated with the use of HEPA filters, that is, qualitative interviews with childcare workers. Furthermore, the real-world effectiveness of HEPA filters in school settings should be explored, as schools do provide a setting in which the children are more stationary and may use PPE while in the classroom setting.

Limitations

The study relies on the kindergarten heads as information providers; therefore, the preventive measures may occasionally be rather institutional policy than actual practice. Additionally, preventive measures have changed throughout the pandemic; the provided information only forms a snapshot of the measures in place in March/April 2022. The study relies on few central assumptions, which need to be verified: (1) the HEPA filters are operated adequately, (2) the position of the HEPA filters was not altered from the optimal position determined during installation, (3) all COVID-19 cases were reported to the kindergarten head. Despite the mandatory reporting requirement, it may be possible that some parents did not inform the kindergarten of their child having contracted COVID-19. Even if the above-mentioned requirements for the operation of the air filters were not met at all times, they correspond to reality and allow an evaluation of the air filters in terms of their effectiveness in practice.

Table 5 COVID-19 period prevalence rate per 1000 children from November 2021 to May 2022

Group	Mean	95% CI	Min/max	N
Intervention	372.1	226.6 to 517.6	120.5/869.0	663
Control	186.5	137.8 to 238.9	0/540.0	1967

Table 6 COVID-19 period prevalence rate per 1000 childcare workers from November 2021 to May 2022

Group	Mean	95% CI	Min/max	N
Intervention	1193.2	584.8 to 1801.6	312.5/3555.6	147
Control	529.7	368.9 to 690.5	0/1500	374

Conclusion

In this study, the COVID-19 period prevalence of children in German kindergartens was compared between kindergartens with portable HEPA filters and those without HEPA filters during the Omicron wave. It was hypothesised that the HEPA filters will have a preventive effect, thus leading to lower COVID-19 period prevalence among the intervention group. This hypothesis was rejected as the one-sided Wilcoxon rank-sum test with continuity correction did not produce significant results. In fact, the mean period prevalence of the control group was 186 per 1000 children, whereas a mean COVID-19 period prevalence of 372 per 1000 children was observed in the intervention group. Therefore, a preventive effect of HEPA filters against COVID-19 in kindergarten settings was not confirmed. Classic preventive measures, such as wearing of facemasks and frequent ventilation, remain of utmost importance in kindergartens to curb COVID-19 contagion.

Contributors TF designed the study, conducted data collection and analysis, wrote the main manuscript text and acts as guarantor. FW conducted data collection, managed the database, conducted statistical analysis and prepared the figures. NZ contributed to the study design, development and testing of the data collection instruments and drafting of the manuscript. NM and TK contributed to the design of the study, data collection instruments and data analysis. All authors critically revised the manuscript and provided final approval of the version to be published. NM and TK share the last authorship of the paper.

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Disclaimer The funder had no influence on data collection, study design or analysis, and on the reported results.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval Ethical approval was obtained from the ethics commission of the Medical Faculty of the University of Bonn (Lfd. no. 092/22). No ethical or data protection concerns are evident. Accordingly, informed consent was obtained by the information givers, that is, head of institution. All methods were carried out in accordance with relevant guidelines and regulations.

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Data availability statement Data are available upon reasonable request. Please contact the corresponding author for a request for data sharing.

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2.3 Antibiotic Use at the Community Level

Schmiege, D., Evers, M., Kistemann, T., **Falkenberg, T.** (2020). What drives antibiotic use in the community? A systematic review of determinants in the human outpatient sector. International Journal of Hygiene and Environmental Health *226*, 113497. https://doi.org/10.1016/j.ijheh.2020.113497

Background & Aim:

The overuse and misuse of antibiotics are the key driving factors for rapid development of antibiotic resistance. Antibiotic use in humans, animals and in agriculture all contribute to this development and in combination threaten the effectiveness of fundamental treatment options. A large proportion of the total antibiotic use occurs in the human outpatient sector, while immense regional differences in antibiotic consumption are evident across various geographic scales. Differences are not only found between country groupings or between countries, but also within countries and even within sub-regions. The distribution of infectious diseases cannot explain the difference in antibiotic consumption observed across the spatial scales. Therefore, it is necessary to expand the scope and explore the factors determining antibiotic use. The aim of this review is to synthesize the evidence on the determinants of antibiotic use considering compositional, contextual and collective factors and different geographic scales.

Methods & Results:

A systematic literature review was conducted in three scientific databases during November 2018. Due to the explorative nature of the review, broad search terms were used consisting of three concepts: synonyms for antibiotics, synonyms for antibiotic use, and a range of terms for potential determinants. The study selection followed the PICO[2] format. In total 3,541 articles were identified after duplicates were removed. After title and abstract screening, 118 articles remained for full-text screening, additionally 29 articles were added through a hand-search of the reference lists. After full-text eligibility screening of 147 articles, 73 studies remained and were included in the assessment. The results highlight an uneven distribution of studies with the majority being conducted in high-income countries and at sub-national level. In the 73 studies, 592 variables were identified and sorted into 102 variable and 46

[2] PICO = Problem, Intervention, Comparison, Outcome;
see https://beckerguides.wustl.edu/SystematicReviews/pico

determinant groups. For each determinant group the direction of the main trend was determined, as positive, negative or bidirectional differences. Compositional factors, i.e. characteristics of individuals located in a particular region, are most frequently studied (e.g. demographics), followed by contextual factors, i.e. opportunity structures (e.g. housing quality or access to healthcare) and collective factors, i.e. socio-cultural features (e.g. norms and values). This does not reflect the importance of these variables in determining antibiotic use, but rather reflects data availability. Despite the underrepresentation of low- and middle-income countries interesting differences between high- and low-income situations were observed. Whilst socio-economic status is negatively correlated with antibiotic use in high-income countries, a positive correlation is found in low-income countries, pointing to access as a determinant. Over-the-counter sales were strongly related to high antibiotic use, while price exhibits a negative correlation. The role of the prescriber is highly variable without clear patterns, for example both low and high experience were associated with lower antibiotic prescriptions. Also, utilizing training opportunities results in low prescription behavior. The availability of health care facilities and pharmacies produced largely insignificant results, indicating that it is not the availability of the facility but rather the personnel that determinants usage behavior. Assessment of Hofstede's dimensions of national culture (Hofstede *et al.*, 2010) revealed that masculinity, power distance, and uncertainty avoidance are positively related to antibiotic use.

Conclusion:

Determinants of antibiotic use are numerous and not necessarily consistent across spatial scales. Reliance on available secondary data in the majority of included studies results in compositional factors being assessed most frequently. Age, gender, education, socio-economic status, morbidity all influence antibiotic use but cannot fully explain the variations observed across spatial scales. Contextual and collective factors provide some insight into potential reasons for variability in antibiotic use. However, the available data for these determinant groups are often insufficient to determine clear trends and associations. It is clear that regulations and access options have an influence, but further information are required to disentangle the effects of multiple determinants acting simultaneously. It is, therefore, necessary to conduct more primary research that collects more specific variables. Additionally, more evidence is required from low- and middle-income countries, as these regions are currently underrepresented in the research body, while exhibiting high growth in

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What drives antibiotic use in the community? A systematic review of determinants in the human outpatient sector

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ABSTRACT

Inadequate and excessive use of antibiotics in humans, animals, and plants has been identified among the key drivers of antibiotic resistance (ABR). In human medicine, the great majority of antibiotics are prescribed in the outpatient sector with profound differences in antibiotic consumption across various geographical scales and between health care sectors; raising questions around the underlying drivers.

Moving beyond individual patient-related determinants, determinants of antibiotic use in the outpatient sector were categorized as compositional, contextual and collective, enabling an analysis of potential area effects on antibiotic use. 592 variables identified in 73 studies were sorted into 46 determinant groups. Compositional determinants provided the strongest evidence with age, education, employment, income, and morbidity exhibiting a clear influence on antibiotic use. Regarding contextual and collective determinants, deprivation, variables around health care services, Hofstede's dimensions of national culture and regulation affect antibiotic use.

The results are biased towards high-income and western countries, often relying on secondary data. However, the findings can be used as signposts for associations of certain variables with antibiotic use, thereby enabling further research and guiding interventions.

1. Introduction

In terms of attributable deaths, the currently unfolding global public health crisis of antimicrobial resistance (AMR) bears the risk of potentially surpassing many communicable and non-communicable diseases by 2050 (O'Neill, 2016). AMR is also linked to impediments of medical routine procedures as well as significant additional health care costs (Laxminarayan et al. 2013). Within AMR, particularly antibiotic resistance (ABR) receives a lot of research attention. Inadequate and excessive use of antibiotics in humans, animals, and plants has been identified among the key drivers for accelerating this otherwise natural process (Chatterjee et al., 2018; Davies and Davies, 2010). Globally, antibiotic consumption rates increased between 2000 and 2015 with varying magnitudes in higher- (HIC) as well as lower- and middle-income countries (LMIC), and this growth is projected to continue even further (Klein et al., 2018).

Differences in antibiotic consumption are observed not just between country groupings but also between (e.g. Blommaert et al., 2014; Deschepper et al., 2008) and within individual countries (Kliemann et al., 2016; de Jong et al., 2014). Such differences are evident on all spatial scales, from the macro down to the local level (Jensen et al., 2016; Franchi et al., 2011), from cross-country to intra-city variations (Togoobaatar et al., 2010; Henricson et al., 1998).

Besides geographical differences, there are also variations in antibiotic use in different health care sectors. In Europe, for instance, antibiotic consumption is ten-fold higher in the human outpatient sector as opposed to the hospital sector (European Centre for Disease Prevention and Control, 2018). In Germany, 85% of all antibiotic prescriptions to humans occur in the ambulatory care sector (BVL & PEG 2017), underlining the role of the outpatient sector as an important contributor and driver of ABR.

The occurrence and distribution of bacterial infectious diseases alone are not able to explain exhaustively those variations in antibiotic consumption between and within countries and health care sectors. Hence, it is necessary to broaden the focus and examine additional determinants of antibiotic use. In a recent review, Zanichelli et al.

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(2019) focused on patient-related determinants of responsible antibiotic use, highlighting several crucial factors on the individual level (e.g. demographic and socio-economic characteristics, patient-doctor interactions, and treatment characteristics). However, antibiotic use is not only determined by individual factors, but potential area effects need to be considered, placing the focus on both people and places.

To differentiate the determinants of spatial variation in health and health behaviour, the classification by Macintyre (1997) (compositional, contextual and collective) will be applied. This concept helps to frame and understand the geographical patterning of health and has already been applied to different health outcomes, including mental health and well-being, and neglected tropical diseases (Collins et al. 2017; Armah et al. 2015).

The compositional category entails “the characteristics of individuals concentrated in particular places” (Macintyre et al. 2002, p. 130), such as demographics, while the “opportunity structures in the local physical and social environment” (Macintyre et al. 2002:130), e.g. housing or access to health services, fall into the contextual category. “Lastly, “socio-cultural and historical features of [the] communities” (Macintyre et al. 2002:130) like norms and values are captured in the collective category. Revising their classification, Macintyre et al. (2002) argued that collective effects should not be separated from contextual mechanisms anymore, as the distinction between those two appeared to exist rather in theory than in reality. However, for a clearer overview, collective determinants are presented separately in this systematic review. Those categories should, however, not be treated as mutually exclusive but the interactions between conditions of the individual(s) and different features of the neighbourhood should be considered (Macintyre et al. 2002).

The objective of this systematic review is to identify existing evidence on the determinants of antibiotic use in the outpatient sector, across various scales and geographic settings; categorizing their respective effects into compositional, contextual and collective. This overview can guide further research and enables a more layered approach to determinants of antibiotic use in the community, thereby providing a starting point for more targeted interventions (e.g. awareness raising campaigns).

2. Materials and methods

2.1. Search strategy

A systematic review of peer-reviewed literature was conducted. Three scientific databases, PubMed, ScienceDirect, and Web of Science, were systematically searched during November 2018 using different combinations of indexed and free-text search terms (see supplementary material A). Due to the exploratory and inclusive approach chosen, broad search terms were used, covering three concepts: synonyms for antibiotics, synonyms for antibiotic use, and a broad range of terms for potential determinants. In addition, a search alert was set up in each database in order to receive notifications about the most recent publications. This did not yield any relevant study. Reference lists of studies deemed eligible for the full-text analysis were hand-searched manually. The hand-search also followed a tiered approach. Titles were screened first, followed by abstracts. No date or language restrictions were applied to the literature search. However, in the final data analysis, only publications available in English or German were included.

2.2. Selection criteria

Studies were selected based on the criteria illustrated in Table 1, following the population, intervention, comparator, outcome, and study design (PICOS) format (McKenzie et al. 2019). Peer-reviewed studies assessing determinants of human antibiotic use in the outpatient sector or the community were included in this review not limited to a specific geographic setting.

2.3. Data extraction

Essentially, variables influencing antibiotic use in the outpatient sector or the community are of key interest to this systematic review. Information from the included full texts was extracted in a purpose-built standard data extraction form in Microsoft Excel (see research data).

2.4. Quality assessment

Only peer-reviewed studies in scientific journals were included. These studies were of observational nature, often using an ecological study design, for which there are no agreed quality assessment tools readily available. In addition, the variety and heterogeneity of the studies made it infeasible to conduct an internally consistent and comparable quality assessment across all included studies. Thus, no structured quality assessment was conducted. However, two key quality criteria for eligible studies were applied: 1) whether they have a reliable measure of antibiotic use, and 2) whether they have a clear reporting of the influence of the variable investigated on antibiotic use. All studies included had to match these two quality criteria.

2.5. Data analysis

Due to the heterogeneity of the studies included, a meta-analysis was not feasible; thus, the analysis is based on a quantitative summary and a qualitative narrative synthesis of the findings. The main outcomes of interest are antibiotic use, which here stands as a proxy for acquisition, prescription, sale, reimbursement, and actual consumption data by the respective studies, and its determinants.

After extracting all relevant information into the standard data extraction form, similar variables were grouped into a second purpose-built spreadsheet in Microsoft Excel (see supplementary material B). In order to ensure the transparency and reliability of the grouping, the variables were sorted based on two successive criteria. Fig. 1 illustrates the hierarchy of terminology established as well as an example presented in italics. Variables using the same or similar wording were arranged as one “variable group”, e.g. parental employment. If the first criterion did not apply, thematically closely linked variables were also grouped into “variable groups”, e.g. fever, cough, earache, and throat soreness, among others, form the variable group “Symptoms”. In case multiple variable groups were associated with a certain topic, these were combined into “determinant groups”, e.g. employment. Finally, the determinant groups were assigned to one of the determinant categories: collective, compositional, and contextual. All variables and their respective grouping can be accessed in supplementary table C.

The analysis of determinants was implemented at the variable group level whereby the main trend, opposing trends, and non-significant results were examined. The “main trend” of each variable group indicates the direction of influence on antibiotic use exhibited by the majority of variables within this group, whereas the “opposing trend” shows the inverse direction. “Non-significant” results are also viewed as opposing the main trend but displayed separately from the opposing trend. Generally, the trends are expressed as positive or negative relationships. In only a few cases, it was not possible to distinguish the main trend. Those variable groups are labelled as only “showing differences”, thus not indicating a direction of association.

Table 1
Inclusion and exclusion criteria for study selection following the population, intervention, comparator, outcome, and study design (PICOS) format (McKenzie et al. 2019).

Criteria	Inclusion	Exclusion
Population	● Human medicine – outpatient/community ● All ages ● Both sexes (i.e. male, female) ● All geographic settings ● All spatial scales	● Human medicine – inpatient sector ● Animals ● Plants ● Agriculture
Intervention	● Variables of any kind that explain variations in antibiotic use	● Studies focusing exclusively on knowledge, attitudes, experiences, perception or awareness around antibiotic use ● Compliance with treatment ● Any other intervention (e.g. antibiotic stewardship programs)
Comparator	*Not applicable*	
Outcomes	● Antibiotic use in humans (investigated as consumption (including self-medication or misuse), acquisition, prescription or sales) ● All antibiotics for systemic use (WHO ATC code J01)	● Antivirals, antimycobacterial, antifungals, or anti-parasitic drugs ● Association between antibiotic use and antibiotic resistance ● The occurrence of antibiotics in the environment
Study design	● Peer-reviewed studies ● Ecological analysis ● Cross-sectional, observational, and retrospective studies	● Studies not using data, i.e. editorials, letters, conference abstracts/reports, protocols, and conceptual papers ● Systematic reviews ● Longitudinal, compositional or descriptive analysis of antibiotic use ● Studies with a methodological focus

2.6. Risk of bias

Every systematic literature review encounters publication bias. In order to reduce the influence of this bias, both significant and non-significant results were extracted and used in the analysis. However, this does not eliminate the fact that significant results might be published more often. Additional risks of bias are owed to the observational nature and ecological study designs on which the majority of publications rely: confounding bias and ecological fallacy. Many studies used secondary data for analysis with pre-determined sets of variables available, fundamentally an issue of data availability, disabling the opportunity to test for other confounding factors not included in the initial data set. The ecological fallacy is a specific form of confounding whereby an association that exists at the group level is assumed to be also true on the individual level (Levin, 2006). During the interpretation of the results, these potential biases were taken into consideration.

3. Results

3.1. Study selection

The initial database search yielded 4164 studies that were transferred into the literature management software Mendeley. In order to identify relevant studies for inclusion, the step-wise approach presented in the PRISMA flow chart (Fig. 2) was applied (Moher et al. 2009).

After duplicates were removed, 3541 studies remained. Title and abstract screening reduced the number of studies for potential inclusion to 118. The hand-search of the reference lists added 29 studies. 147 full-text articles were obtained and assessed for eligibility. Applying the

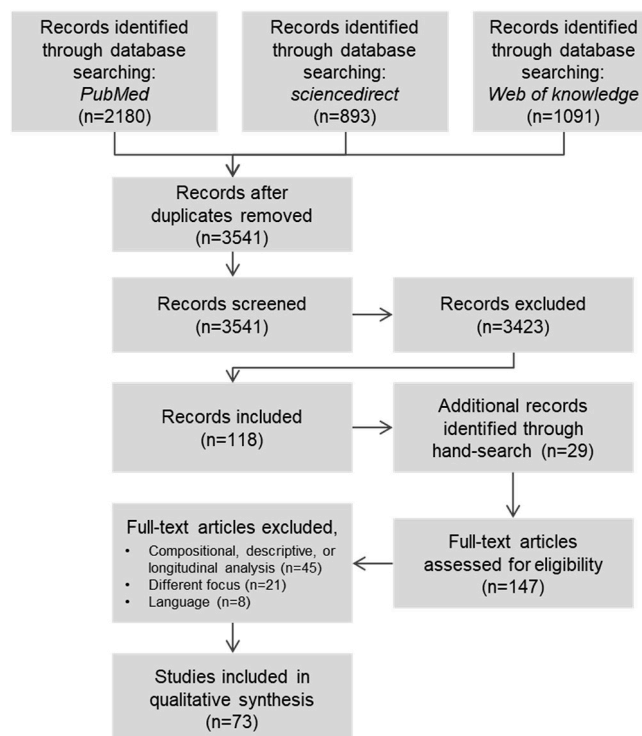

Fig. 2. PRISMA flow chart diagram of the systematic review showing the selection process of relevant studies.

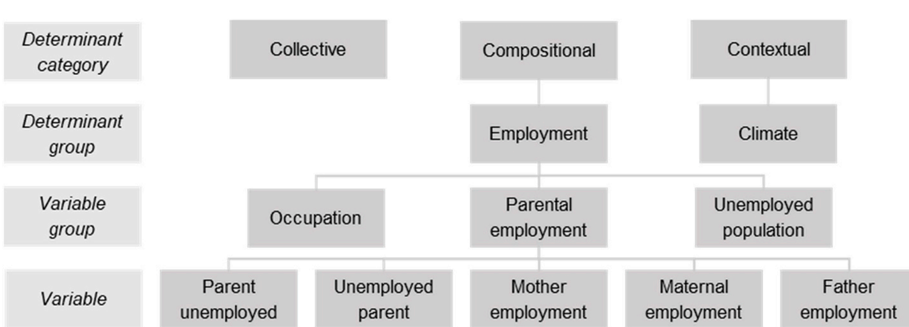

Fig. 1. Hierarchy of terminology and grouping of variables shown by means of an example of the determinant group “Employment” starting from the bottom with the variables, which were grouped into the variable group “Parental employment”, which was subsequently sorted into the determinant group “Employment” jointly with “Occupation” and “Unemployed population”.

Table 2
Studies grouped into the WHO regions with the number of countries.

WHO region	No. studies		No. countries	Countries included[a]
African Region	1	1%	1	GH
Region of the Americas	9	12%	3	BR, CA, US
Eastern Mediterranean	7	10%	7	AE, IR, JO, LB, SA, SD, SY
European Region	49	67%	17	BE, CH, DE, DK, FR, HR, HU, IL, IT, LT, NL, NO, PL, SE, TR, UK
South-East Asia Region	2	3%	1	IN
Western Pacific Region	5	7%	1	MN, NZ
Total	*73*			

[a] ISO codes of countries.

Table 3
Characteristics of all 73 studies included for the final synthesis.

Characteristics	Total (n = 73)
Analytic methodology[a]	
Descriptive statistics	10
Test statistics	12
Correlation	15
Econometrics	4
GEE and MI-GEE	2
Regression[b]	2
Binominal regression	1
Linear regression	12
Logistic regression	23
Ordinary Least Square-regression	2
Poisson-regression	4
Spatial regression	1
Antibiotic use data[c]	
Administered/consumption	4
Claims/reimbursement	6
Dispensing	5
Prescription	34
Sales	9
Self-reported	18
Data type	
Primary data	20
Secondary data	53
Worldbank income group	
High-income countries	61
Lower- and middle-income countries	12
Level of analysis	
Sub-national	63
National	10
Study population	
General population	53
Pediatric population	20
Year range	
1990–1999	2
2000–2009	25
2010–2019	46

[a] The sum of analytic methodologies exceeds the total amount of studies included because some articles used several methods.
[b] In some studies, the method was not further defined than "regression".
[c] The sum of antibiotic use data exceeds the total amount of studies included because two studies used several data types.

inclusion and exclusion criteria (see Table 1), 74 full-text articles were excluded. Eventually, 73 studies were included in the qualitative synthesis (references of all 73 studies can be accessed in supplementary material D).

Table 4
Characteristics of studies for each determinant category including their income grouping, study population, and data type.

Determinant category	No. studies	No. variables	HIC	LMIC	GP	PP	PD	SD
Compositional	69	325	58	11	50	19	19	50
Contextual	55	223	47	8	44	11	12	43
Collective	14	44	12	2	12	2	4	10
Total	73	592	61	12	53	20	20	53

Note: HIC: High-income countries; LMIC: Lower- and middle-income countries; GP: general population; PP: paediatric population; PD: primary data; SD: secondary data. The values of the determinant groups do not add up to "Total" vertically because one study can investigate factors in different determinant groups.

3.2. Study characteristics

The 73 studies included cover 30 different countries across the world as well as the European Union (EU) revealing an uneven global distribution of studies on antibiotic use in the community. Grouping the countries into the World Health Organization (WHO) regions (see Table 2) underlines this uneven distribution, highlighting the dominance of the WHO European Region.

The number of studies per country varies between a single study in the majority of countries and up to seven in Italy and Sweden. Ten studies were conducted on the EU-level. Additional characteristics of the 73 studies included are shown in Table 3.

The majority of studies were implemented at the sub-national level (86%) and in high-income countries (84%). The year of publication ranges between 1998 and 2018 with more than half of the articles published after 2012, clearly showing the increasing research interest. Almost three-quarters of studies were conducted in the general population (73%) relying on secondary data for the analysis (73%). Secondary data, here, refers to data that has not been collected by the authors of the respective paper but by someone else, as opposed to primary data, which is collected directly by the reporting authors, including, for instance, qualitative or quantitative surveys. There is a great variety of analytic methodologies used in the respective studies. Antibiotic use was most often analysed by using prescription data, followed by self-reported use via surveys.

3.3. Results of the individual studies

Overall, 592 variables were identified in the 73 studies (Table 4).

Compositional variables dominate the determinant categories accounting for more than half of all determinants examined. The majority of studies (57/73) investigated at least one variable of at least two determinant categories. Sixteen studies focused their analysis on only one particular category and in the remaining twelve studies, all three determinant categories were covered.

The 592 variables identified were sorted into 102 variable and 46 determinant groups. Fig. 3 displays the determinant groups with the corresponding number of studies sorted alphabetically, starting on top with the compositional variable: "Age (50)", and then moving around clockwise.

In the following sections, the individual results of each determinant category will be presented. Figs. 4–6 illustrate the results for each variable group in alphabetical order. The main trend of each variable

Fig. 3. Determinant groups and their respective number of studies in brackets categorized into collective, compositional, and contextual in descending order starting on top with the collective determinant group "Attitude (5)" and then moving clock-wise.

group is represented as bars to the right in dark grey, whereas opposing trends and non-significant results are indicated by bars to the left in lighter grey colours. The direction of the main trend, i.e. positive ("+"), negative ("-") or differences ("+/-"), is shown on the right.

This way of presenting the data allows for a visual assessment of the influence the respective variable group has on antibiotic use. It provides an impression of the number of variables investigated per variable group as well as whether there is a main trend, which is potentially counterbalanced by opposing trends or non-significant results. In the determinant group "Sex" (compositional), for instance, 12 variables investigated the influence of sex on antibiotic use in the paediatric population, i.e. variable group "Paediatric: boys". Five variables linked higher antibiotic use to boys constituting the main trend. Four variables showed lower antibiotic use in boys therefore being an opposing trend and three variables were not significant. Whereas there appears to be evidence for higher antibiotic use in boys (five variables) overall, it is not possible to draw an overarching conclusion for the variable group because main trend and opposing trends as well as non-significant results level each other out. Using another example, the variable group "Disease diagnosis" offers clear evidence. 22 variables showed higher antibiotic use with certain disease diagnoses with only one variable opposing this. An additional ten variables were not significant. As opposed to "Paediatric: boys" here it appears reasonable to conclude that this variable group has a clear one-directional influence on antibiotic use.

3.4. *Determinant category: compositional*

The majority of studies (69/73) investigated compositional determinants, making it the category with the highest number of variables (325/592). Fig. 4 presents the results of the variable groups, sorted alphabetically by the corresponding determinant groups. In total, 40 variable groups in 22 determinant groups were examined with seven variable groups being investigated by a single study only.

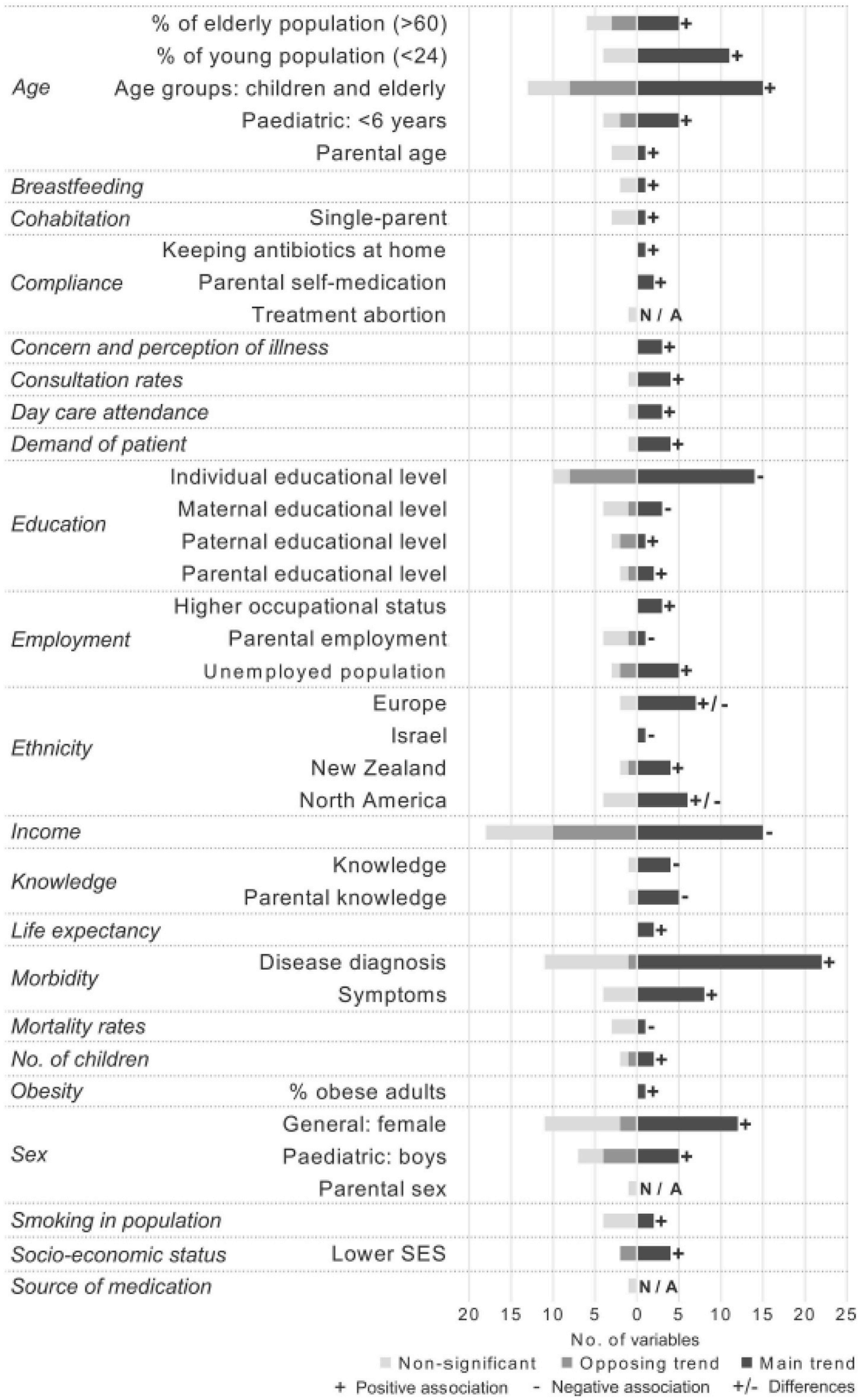

Fig. 4. Influence of compositional variable groups on antibiotic use indicated by the main trend to the right and opposed by number of variables in the opposing trend and non-significant results. The direction is displayed as either positive, negative, differences or "not applicable (N/A)". Determinant groups are displayed in italics.

3.5. Determinant category: contextual

Contextual determinants are the group with the second-most factors investigated (232/592) in the second-most studies (57/73). After extracting the data from the literature, contextual determinants could be grouped into 35 variable groups in 14 determinant groups as displayed in Fig. 5.

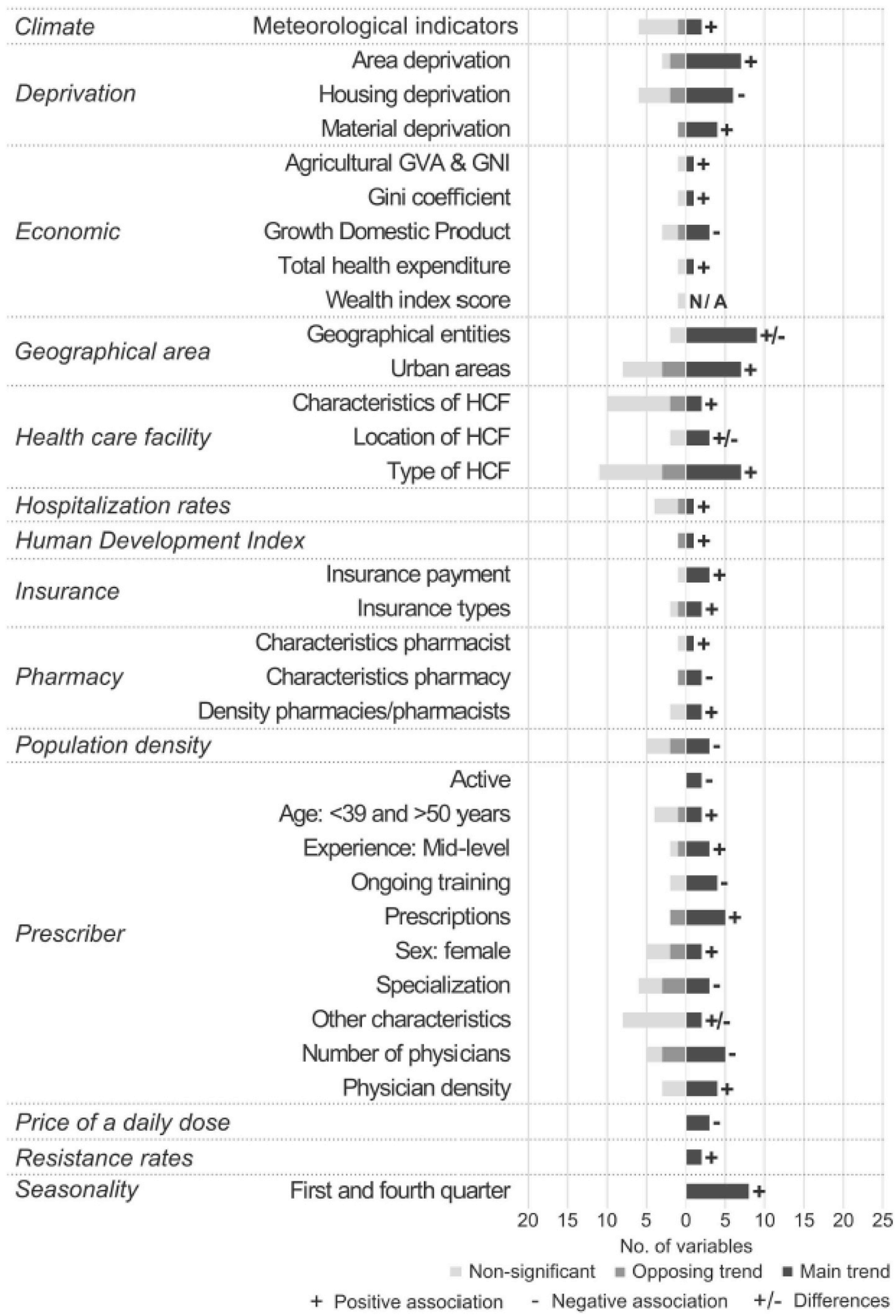

Fig. 5. Influence of contextual variable groups on antibiotic use indicated by the main trend to the right and opposed by number of variables in the opposing trend and non-significant results. The direction is displayed as either positive, negative, differences or "not applicable (N/A)". Determinant groups are displayed in italics.

3.6. Determinant category: collective

Fig. 6 shows all ten determinant groups with their 27 variable groups categorized as collective determinants. In general, collective determinants were the least researched determinant category with only a few variables (44/292). The majority of variable groups (18/27) were examined by one study only, followed by variable groups with three studies (5/27) and two studies (4/27).

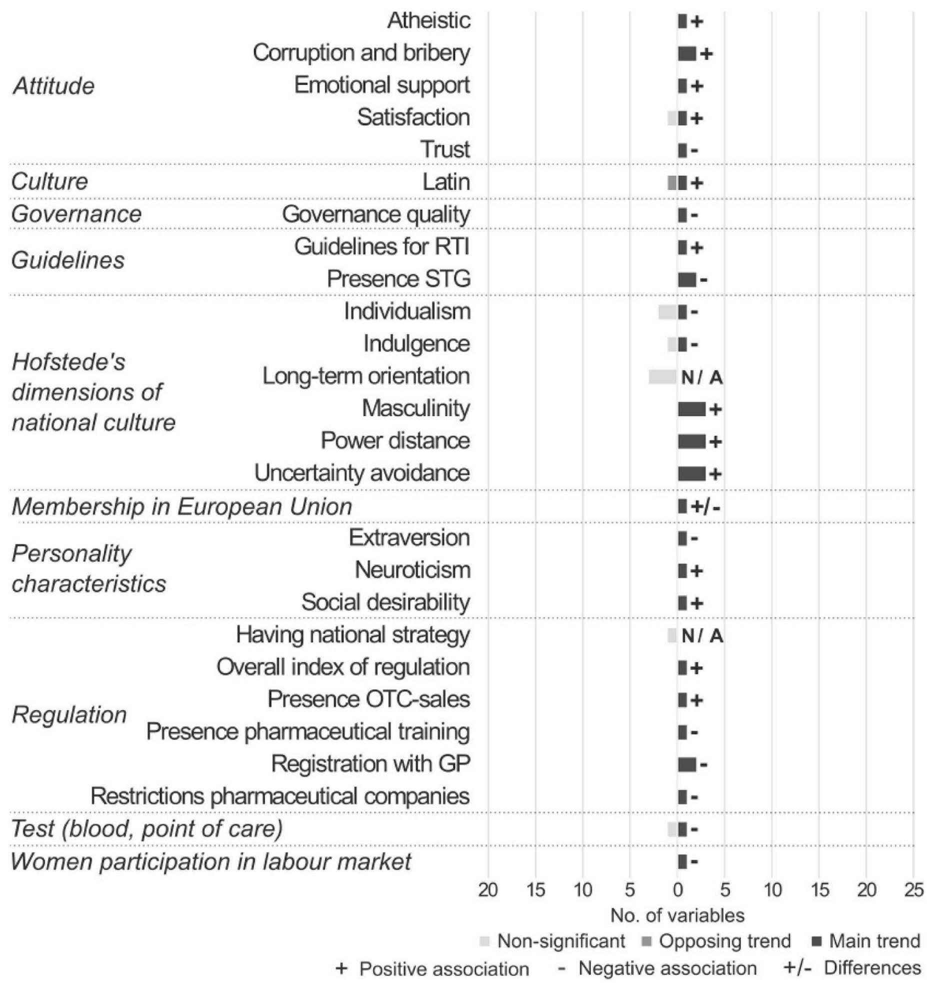

Fig. 6. Influence of collective variable groups on antibiotic use indicated by the main trend to the right and opposed by number of variables in the opposing trend and non-significant results. The direction is displayed as either positive, negative, differences or "not applicable (N/A)". Determinant groups are displayed in italics.

3.7. Risk of bias across studies

Significant results, which were used to create the main and opposing trends, respectively, should be investigated with caution. They can rely on simple test statistics or be the result of a sophisticated regression model. However, they were grouped together to allow for a clearer results presentation.

4. Discussion

4.1. Summary of evidence

Categorizing the variables identified into compositional, contextual, and collective determinants revealed large differences in the amount of available evidence for each determinant category, determinant group, and variable group. Globally, there is an uneven distribution of evidence for determinants of antibiotic use in the community. The great majority of studies focused on WHO European Region, followed by the WHO Region of the Americas in which seven out of nine studies were conducted in either the US or Canada. This shows that the findings are biased towards higher-income countries (HIC) and western countries, highlighting that more evidence is needed from lower- and middle-income countries (LMICs) and other regions.

The varying amount of evidence on the determinant category level needs to be considered against the background of the reliance on secondary data in the majority of studies (53/73). Using secondary data often restricted the diversity of variables examined, creating a context in which the choice of variables seemed to be limited and pre-determined. Moreover, in the majority of studies, the choice of variables was rarely explained, justified or discussed but rather taken for granted. This may distort the evidence base towards variables, which are easier to document, more frequently surveyed, and therefore readily available in different databases, such as the demographic standards. This provides a potential explanation for the dominance of compositional determinants. This generates a situation in which the choice of variables appears to be led by a selection "off-the-shelf" approach rather than theory-guided (Mitchell et al., 2000).

4.2. Determinant category: compositional

Out of the younger (< 24) and elderly (> 60) population groups, particularly the age groups < 15 and > 65 years show positive associations with antibiotic use in the community, supported by studies examining several age groups that show similar trends. Findings in the paediatric population even refine the results for the younger population further by indicating higher antibiotic use in younger children (< 6 years). Higher antibiotic use in the elderly population could be linked to increasing (co-)morbidity or higher susceptibility to infectious diseases. Aside from also higher susceptibility, higher antibiotic use in the younger population can possibly be explained through less treatment hesitance in case of uncertainty of a concrete diagnosis or parents' pressure. Concluding, this points to a U-shaped association between age and antibiotic use whereby antibiotic use is higher in the younger and elderly population.

The determinant group “Education” revealed that education influences antibiotic use differently in HICs and LMICs. Whereas there is a negative association with antibiotic use in HICs (12/14 variables), education exhibits a positive relationship with antibiotic use in LMICs (5/6 variables). This association, based on the individual educational level in the general population, also applies to results in the paediatric population, although less pronounced.

Regarding “Employment”, higher occupational status is linked to higher antibiotic use in three studies of which two were conducted in LMICs. The relationship of the unemployed population and antibiotic use was investigated in HICs by studies (6) on the country level indicating a positive association. Findings from the determinant group “Income” point in a similar direction. The main trend (negative association) consists exclusively of variables examined in HICs, whereby half of the variables making up the opposing trend (positive association) are from studies in LMICS.

Integrating the findings reveals further interesting insights. Education, employment, and income all show contrasting trends in the country groupings. Whereas education and income in HICs exhibit a negative association with antibiotic use, the main trend in LMICs is exactly the opposite. Moreover, the unemployed population in HICs indicates a positive relationship, while higher occupation status was linked to higher antibiotic use in LMICs. In addition, “Socio-economic status” (SES), often an aggregate of such indicators, also indicates higher antibiotic use with a lower SES in studies conducted in HICs. These findings highlight potential collinearity among these determinants.

It can only be speculated as to why and how those determinants work differently in those country groupings. In both HICs and LMICs, the disease burden is often higher with lower socio-economic status (due to various reasons). This trend is observable in the data for HICs where lower education, less employment, and lower income leads to higher antibiotic use. However, the opposite is true for data from LMICs. This contrary effect is possibly caused by the effect of access to health care services. In HICs, universal health coverage enables the whole society to seek medical advice and treatment at low to no cost, whereas in LMICs, private payments are often needed to get access to the health care system (Peters et al., 2008). The latter is reflected in the data where higher education, higher occupational status, and higher income are linked to higher antibiotic use in LMICs. Furthermore, poorer population groups in LMICs are often unable to access health services or utilize informal markets to purchase medication (Bloom et al., 2011), which leads to them not appearing in any statistics, highlighting the issue of data availability and data completeness.

Unsurprisingly certain “Symptoms” or “Disease diagnosis” increase antibiotic use as shown in the determinant group “Morbidity”. The evidence base for “Disease diagnosis” is larger than for “Symptoms”, which were investigated by twelve variables in only three studies. Overall, the influence of the determinant group “Morbidity” on antibiotic use was expected as it can be assumed that with certain disease diagnoses or symptoms, antibiotics are prescribed because curing infectious bacterial diseases is the main purpose of their use.

The main trend in the general population regarding “Sex” and antibiotic use points towards higher antibiotic use in females being opposed by mainly non-significant results. Findings in the paediatric population are less conclusive. Main and opposing trends both consist of variables tested in HICs only offsetting each other.

Age, morbidity, and sex are an example for potential confounding among the determinants of antibiotic use. Antibiotic use appears to be higher in females, different disease diagnoses are a strong predictor for antibiotic use, and antibiotic use was found to be higher in the younger and elderly population groups. Bringing those findings together, females around the world tend to live longer than males, and with increasing age, the likelihood for both sexes of acquiring multiple diseases (multi-morbidity) increases as well. Here again, we find an intertwined web of potential pathways of how those determinant groups possibly influence antibiotic use, which requires further investigation.

Lastly, also those variable groups are noteworthy, in which non-significant results prevail. The variable groups “Parental age”, “Breastfeeding”, “Single-parent”, “Parental employment”, “Mortality rates”, and “Smoking in the population” were all tested in at least two different studies. However, the majority of variables tested showed non-significant results implying that those variables may not influence antibiotic use.

4.3. Determinant category: contextual

In general, variable groups categorized as contextual show a greater within-group variation of variables than compositional determinants.

Main trends in the determinant group “Deprivation” should be treated with caution because of the diversity of variables included. Trends in “Area deprivation” and “Housing deprivation” are limited to HICs. In “Material deprivation” the main trend indicates a positive association with antibiotic use but encompasses seemingly contrary variables, i.e. “Receiving free access to selected medicine” (HIC) and “Having less access to medical care” (LMIC, antibiotic use without a prescription) are both positively associated with antibiotic use. However, this determinant group is a good example of how compositional (people) and contextual and collective (places) determinants may interact in shaping health outcomes. Concluding, aside from the variables in “Material deprivation”, deprivation in general probably does not affect antibiotic use directly but is rather a proxy for other underlying area factors, e.g. drivers of infectious diseases for which antibiotics are administered.

Owing to the variety of “Geographical entities” examined, ranging from local health units and county of residence over latitude to regions in Europe or US census regions, only differences were detectable. The results, therefore, confirm the basic assumption of this systematic review. In addition, antibiotic use appears to be higher in urban areas. This can be explained through the complex matter of availability and access to health care facilities, services, or medical personnel in urban and rural areas. Here again, we find a potential interlinkage with compositional determinants.

Examining variable groups in the determinant group “Health care facility” (HCF) reveals many non-significant results. The location and characteristics of HCF seem to not play any role, whereas the type of HCF, an indicator for the presence of different institutions, shows a positive association. In addition, no reliable trends can be identified for the determinant group “Pharmacy” due to its diversity of variables. These findings have two implications: 1) they hint at the importance of the existence of health care services and HCFs rather than its characteristics and 2) suggest that there may be additional factors that influence antibiotic use, e.g. the medical personnel working in such facilities.

“Prescriber” is the determinant group encompassing the most variable groups for a single determinant group, indicating high diversity. Owing to this variety, the variable group “Other characteristics” was introduced to cover characteristics that are not included in any of the other groups consisting mainly of non-significant results. Summarizing the results, prescribers, which are active, utilize training opportunities, are mid-age, have lower or higher experience than mid-level, are male, and specialized (vs. general practitioners) tend to prescribe fewer antibiotics. However, those findings need to be treated with great caution as the individual variable groups often consist of a few variables only and are sometimes opposed by an equal number of opposing variables and non-significant results. Moreover, the two variable groups “Age” and “Experience” as well as “No. physicians” and “Physician density” even contrast each other.

Higher antibiotic use in the first and/or fourth quarter of the year is an interesting outcome of the determinant group “Seasonality”. Seasonal variation is sometimes treated as an indicator for potential misuse of antibiotics for viral infections. However, secondary bacterial infections could also play a crucial role in explaining the seasonal variation of antibiotic use. This hypothesis could not be tested here. Linking this finding to meteorological indicators, however, does show that the latter does not have a strong influence on antibiotic use. The majority of indicators, i.e. average temperatures or precipitation, did not show any significant results, with only the "Yearly average dew point", "The climatological Dantin-Revenga Index", and "July average temperature" indicating some impact. Integrating those two outcomes hints at other driving factors for seasonality than meteorological variables.

4.4. Determinant category: collective

Collective determinants lag far behind in terms of numbers of variables investigated. In addition, the high volume of variable groups (27) with only 44 variables already shows that this determinant category is very heterogeneous. In this context, it is important to note that antibiotic stewardship programs were not explicitly targeted in this systematic review, which would, however, count as collective determinants already showing promising results. Overall, variable groups arranged as collective determinants are characterized by often consisting of a single variable only.

"Hofstede's dimensions of national culture" were tested in three studies at the EU level in the general population, revealing a positive association between antibiotic use and masculinity, power distance, and uncertainty avoidance as well as a non-significant effect of long-term orientation. Masculinity describes a society that is more competitive thereby preferring work goal items such as earnings, recognition, advancement, and challenge over manager, cooperation, living area, and employment security (Hofstede et al., 2010). Employment and income are determinant groups that could play a role in this context in regard to antibiotic use. Power distance deals with "the way society handles inequality" (Hofstede et al., 2010, p. 54); about a direct connection with antibiotic use can only be speculated but availability and access to health care services could play a role. The association of uncertainty avoidance, i.e. ways to handle uncertainty and ambiguity (Hofstede et al., 2010), and antibiotic use can be established via the doctor-patient relationship. In both cases, patients or doctors, which are more careful and uncomfortable with uncertainty, might use or prescribe more antibiotics, respectively.

The majority of variable groups in the determinant group "Regulation", i.e. registrations with GPs, restrictions on pharmaceutical companies, and continued pharmaceutical training show negative relationships with antibiotic use (Overall index of regulation: low scores approximated an increase in the level of regulation). Only the presence of over-the-counter (OTC) sales increases antibiotic use. In this line, governance quality and Standard Treatment Guidelines (STG) for hospital care and paediatric conditions are also linked to lower antibiotic use. Contextualizing these findings, this evidence is based on three studies conducted exclusively on the EU-level.

There is an interlinkage between regulatory determinants and contextual determinants. "Price" is also negatively associated in three studies with antibiotic use offering an additional potential intervention point for regulators.

4.5. Limitations

Categorizing and grouping the determinants enabled a more detailed analysis providing insightful findings. However, the procedure of creating the categories and groups albeit being based on transparent criteria is ultimately a subjective process. This applies particularly to those variable groups that were formed based on the second criterion, i.e. closely linked variables (that did not use the same wording). In order to minimize introducing potential bias by following this procedure, it was decided to create variable groups on the lowest common denominator before grouping them into determinant groups.

The heterogeneity of studies included in terms of methodologies and settings is simultaneously advantage and limitation of this systematic review. This explorative and inclusive approach allowed for the identification of a variety of variables. However, due to the heterogeneity of methods applied in the included studies, it was not possible to conduct a meta-analysis. The resulting trends of the variables can therefore only be understood as signposts indicating the direction of a potential influence of this variable on antibiotic use. In the same line of argument, the heterogeneity did not allow for a consistent quality assessment of the included studies. However, relying exclusively on peer-reviewed literature may have helped to attenuate the introduction of potential bias.

Lastly, antibiotic use was the outcome measure of interest, which in itself is quite diverse, including administered, claims and reimbursement, dispensing, prescription, sales, and actual self-reported use. Besides the last category, which is also prone to reporting bias, all others are only proxies for a potential consumption of antibiotics. In addition, all of them imply that there is a reporting system in place, in which data can be collected. This might also be the reason, why LMICs are under-represented as they often lack the availability of reliable data.

5. Conclusion

Determinants of antibiotic use in the community are manifold. This systematic review identified 592 variables grouped into 46 determinant groups, subsequently categorized as compositional, contextual and collective. Applying this categorization revealed varying evidence bases with compositional determinants being researched the most, followed by contextual and collective. It, therefore, allowed for an analysis of potential area effects on antibiotic use in the outpatient sector highlighting the importance of both people and places.

For compositional determinants, an integrated analysis of education, employment, and income revealed contrary effects of those determinant groups on antibiotic use in HICs and LMICs, potentially through differences in the availability of and access to health care services. In addition, age, morbidity, and sex also exhibit clear trends. Also noteworthy are determinant groups in which non-significant results prevail. In this context, cohabitation, mortality, and smoking appear to not influence antibiotic use significantly. Contextual determinant groups showed a greater within-group variation and less obvious trends. Determinants that present potential area effects, including deprivation, indicate a clear relationship with antibiotic use. Seasonality also seems to be a strong predictor of antibiotic use. Variables around health care services, i.e. health care facility, pharmacy, and prescriber, produced many non-significant results with weak main trends. Regarding collective determinants, only Hofstede's dimensions of national culture and regulation offer some insights.

As argued by Macintyre et al. (2002), compositional, contextual and collective should not be treated as mutually exclusive categories. Findings from this systematic review support this argument as there are several determinant groups, e.g. deprivation and education, income and employment, or regulation and price that indicate interactions between different determinant categories. Therefore, research emphasis should be placed on both people and places when considering health outcomes.

The findings of this systematic review raise several questions around pathways of how certain variables influence antibiotic use calling for disentangling the complex web of determinants. Due to the reliance on secondary data and the associated selection "off-the-shelf" approach, it was often not possible to test for other (confounding) variables other than those readily available from the respective database. This calls for more primary studies with a greater focus on individual determinants. In addition, the evidence is biased towards HICs and western countries, sometimes not allowing for any conclusions drawn for LMICs or other regions, demanding more research in those countries.

Overall, the results function as signposts of potential relationships between variables and antibiotic use in the community and the outpatient sector thereby pinpointing starting points for further research and interventions.

Declaration of competing interest

No conflict of interest was identified related to this work. This study was financed through the North Rhine-Westphalia (NRW) Forschungskolleg "One Health and urban transformation" by the NRW Ministry of Culture and Science. The founder had no influence on this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2020.113497.

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2.4 Human-surface water interactions and schistosomiasis

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Background & Aim:

Human interactions with (surface) water determine the pollution pattern of the waterway as well as the degree of human exposure to substances and pathogens. Particularly in regions where access to improved water sources and sanitation is limited, intense interaction with surface water and consequently high water-related disease risks are observed. In the peri-urban and rural areas of Ghana such conditions are frequent, leading to high burden of water-related diseases. In 2018, 52% of all water-related disease cases were due to schistosomiasis. The study aims to demonstrate the role of access to water and sanitation infrastructure and the type and pattern of human-water interaction on the transmission of schistosomiasis in schoolchildren of a peri-urban area of Ghana (Greater Accra region).

Methods & Results:

Six communities were purposively selected along the Densu river and its tributaries. In each community its public school served as the sampling frame. From each school 56 children were randomly selected, leading to a total sample size of 336. A cross-sectional survey was conducted to gain insights into: human-water interaction patterns, access to clean water, sanitation and hygiene facilities, self-reported experiences of schistosomiasis (i.e. blood in urine), and risk perceptions. Additionally, longitudinal observations of the primary water-contact points were conducted twice per week over three months. During these observations the type of water-contact and its duration was recorded, as well as information about the people engaging in these water-contact activities (age group and gender). Utilizing descriptive statistics, Spearman rank correlation test and logistic regression analysis, the interactions between the risk factors and the (self-reported) occurrence of schistosomiasis was assessed. The study found that the communities strongly rely on surface water for washing, cooking, personal hygiene and in some cases even for drinking. Although sanitation is generally available, due to poor conditions or access barriers open defecation is common in these communities and is usually performed along the waterways. All children engage in water-contact activities, mostly recreationally but also for domestic and occupational purposes. The frequency and duration of water contacts is related to the water use type. Recreational exposure is usually longer but less frequently, while domestic exposure is shorter but very frequent. More frequent exposure (> twice per week) and longer exposures (> 30 min.) were associated with significantly higher odds of reporting blood in urine. Overall, awareness of the disease was high, with 88% of children knowing risk and exposure factors. Nonetheless, they engage in these risk behaviors. Despite mass drug administration occurring in the communities, high prevalence (about 30% of children reported blood in urine) was observed.

Conclusion:

Relying on classical public health interventions, including risks communication, awareness raising and mass drug administration is insufficient to control schistosomiasis in peri-urban Ghana. Despite knowledge and awareness of the risk factors, reliance on surface water to supplement household water supply make frequent water-contacts unavoidable. Coupled with inadequate access to sanitation, which drives people towards open defecation near waterways, high risk of disease transmission is evident. Establishment of effective primary barriers through ensuring access to clean (and affordable) sanitation facilities is essential to break the transmission cycle. Further, development of adequate water supply infrastructure can contribute to reducing reliance on surface water for domestic needs and in consequence exposure.

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Influence of human–surface water interactions on the transmission of urinary schistosomiasis in the Lower Densu River basin, Ghana

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Credit author statement

J. Ntajal, T. Falkenberg, and M. Evers: Conceptualization and methodology. J. Ntajal: Data curation. J. Ntajal and T. Falkenberg: writing—original draft preparation. T. Falkenberg and M. Evers, and T. Kistemann: writing – review, and editing. T. Falkenberg, M. Evers, and T. Kistemann: Supervision. T. Falkenberg, M. Evers, and T. Kistemann: Funding acquisition.

1. Introduction

Human interactions with surface water systems are reflections of humanities' dependence (directly or indirectly) on water resources for survival (Massuel et al., 2018; Tanaka et al., 2016). These interactions influence surface water systems' pollution pathways and the exposure of humans to water-related infectious diseases (e.g. schistosomiasis) (Ciddio et al., 2017; Kulinkina et al., 2019). Schistosomiasis is one of the Neglected Tropical Diseases (NTDs) that pose a huge economic burden and health challenges in tropical and subtropical regions (Kulinkina et al., 2019; Rostron et al., 2019). Schistosomiasis, a water-based infectious disease, is a parasitic disease of considerable medical and veterinary significance, which is caused by flatworms of the genus *Schistosoma* (Gower et al., 2017; Webster et al., 2013).

Schistosomiasis has a complex lifecycle (see Fig. 1) that requires freshwater snails (*Bulinus*), which serve as the intermediate host in which the parasite undergoes development, and the definitive hosts (humans and animals) in which the parasite matures (French et al., 2018; Tchuem-Tchuenté et al., 2017). Schistosomiasis transmission depends on water-contact patterns as well as the presence and distribution of infected intermediate snail hosts within watercourses (Chadeka et al., 2017; Grosse, 1993; Hunter, 2003). The cercariae, a parasitic fluke released from the snails, penetrate the skin of humans and animals, transform into *schistosomula* and enter the bloodstream or the urinary system, mature, pair up and begin to produce eggs after about two weeks (Ciddio et al., 2017; Grimes et al., 2016; Tchuem-Tchuenté et al., 2017).

Ecological and human factors play major roles in the epidemiology of the disease (Hunter, 2003; Hunter et al., 1983). Ecological changes resulting from the construction of dams, ponds, or irrigation canals, along with the hydrological dynamics of a given environment, influence the survival, dispersal, distribution, and abundance of the cercariae and the snail hosts, due to changes or modifications to the habitat conditions (Ciddio et al., 2017; Hunter, 1981).

Further, the risk of human infection depends on the degree of exposure (water-contacts), host immunity, and hygiene and sanitation conditions, particularly open defecation (Angelo et al., 2018; Schmidlin et al., 2013). The pollution of surface water with human excreta containing schistosoma eggs is the key driver of schistosomiasis transmission in most endemic areas across the world, particularly in Sub-Saharan Africa (Kulinkina et al., 2019; Webster et al., 2016). Given the underlying risk and exposure factors, schistosomiasis infected persons can experience some general symptoms, including blood in urine, pains (in the abdomen and joints), and whole-body sicknesses, such as itching, skin rashes, fatigue, fever, and weight loss. The occurrence and severity of these symptoms depend on the immune systems of the definitive host (Tchuem-Tchuenté et al., 2017).

As of 2018, the number of people suffering from schistosomiasis worldwide was approximately 252 million, and it was estimated that between 4400 and 200,000 people die annually from the disease (Niu et al., 2018). Over the past decades, it has been reported that about 90% of global schistosomiasis cases are reported in Sub-Saharan Africa (Anyan et al., 2019; Hughes and Hunter, 1970; WHO, 2020). Among the numerous species of schistosoma discovered in the tropics and sub-tropical regions, S. *haematobium* and S. *mansoni* are most commonly reported for human infections in Sub-Saharan Africa (Stadley et al., 2012). In many West African countries, including Senegal, Mali, Ghana, Burkina Faso, Niger, and Nigeria, schistosomiasis is considered endemic (Kulinkina et al., 2019; Martel et al., 2019; Walz et al., 2015; Woodall and Kramer, 2018).

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In Ghana, schistosomiasis is not a new disease, instead, it has become a permanent health challenge, since the construction of dams and ponds for hydropower, irrigation, and community water supply in the early 1950s (Grosse, 1993; Hughes and Hunter, 1970; Hunter, 2003). It has been reported as the most neglected among the Neglected Tropical Diseases (NTDs), and is widespread in the peri-urban and rural communities of Ghana, where access to clean water, improved hygiene, and sanitation is limited (Kulinkina et al., 2019; Martel et al., 2019; Nyarko et al., 2018). S. *haematobium* is the most commonly reported schistosome species in Ghana, which causes urinary schistosomiasis (Anyan et al., 2019; Kulinkina et al., 2019; Martel et al., 2019). In 2018, the proportion of schistosomiasis among all reported cases of water-related infectious diseases in Ghana was approximately 52%, while the prevalence rate was 27.5% (Anyan et al., 2019; Martel et al., 2019; Nyarko et al., 2018). The underlying exposure and risk factors associated with such cases were not explicitly highlighted, although control measures such as mass drug (praziquantel) administration (MDA) were implemented (Martel et al., 2019; Nyarko et al., 2018). Praziquantel is described as an anti-worm drug used to prevent the newly hatched schistosoma worms from multiplying in the human body (Vale et al., 2017).

Despite the interventions, including the mass drug administration and schistosomiasis sensitization programs by the Government of Ghana and the World Health Organization (WHO), schistosomiasis continues to be a stern health challenge in the country (Kulinkina et al., 2018, 2019; Tetteh-Quarcoo et al., 2013). Reports of research studies in the southern part of the country revealed that the prevalence and impacts of the disease have often been underestimated (Anyan et al., 2019; Kulinkina et al., 2019; Martel et al., 2019). Research studies on schistosomiasis in the Densu River basin focused mainly on the prevalence, parasitic egg counts, intensity, environmental factors, and control measures (Anyan et al., 2019; Martel et al., 2019; Nyarko et al., 2018). There is a need for comprehensive investigations, from a transdisciplinary perspective, to understand the human-water contact patterns and exposure factors that reinforce the schistosoma lifecycle and its transmission. This study explored and examined the influence of the availability and accessibility to safe drinking water and improved sanitation, the places of open defecation, and the type and pattern of human-water-interactions on the transmission pathways of urinary schistosomiasis in the Lower Densu River catchment in Ghana.

2. Study area

The study was conducted in the Ga South and Ga West Municipal Assemblies in the Lower Densu River catchment in Ghana, a coastal country located in West Africa (Fig. 2). The Densu catchment occupies an area of about 2490 km^2 with a total population of over 600,000 people spread over 200 settlements, equating to a population density of 240 persons per km^2 (Ghana Statistical Service, 2014). The catchment is located in the southeastern part of Ghana, which stretches between longitudes 0°10′ W - 0°40′ W and latitudes 5°30′ N - 6°15′ N (Fig. 1).

This area experiences a bimodal rainfall pattern. The average annual rainfall is about 800 mm, with higher monthly rainfall in June and July (Nkrumah et al., 2014). The annual temperature ranges between 23 °C and 33 °C with the hottest periods between February and April (Codjoe and Larbi, 2016). The source of the river lies in the Atewa mountain ranges and flows for about 116 km southwards into the Weija reservoir before entering the sea at the Gulf of Guinea (Attua et al., 2014). The Densu reservoir serves as a drinking water source for most parts of the city of Accra and its peri-urban areas (Karikari and Ansa-Asare, 2006; Yorke and Margai, 2007).

The communities along the Densu river depend directly on the river and its tributaries as a source of livelihood and domestic water supply, which exposes them to water-related pathogens and parasites (Tetteh-Quarcoo et al., 2013; Nyarko et al., 2018). The major occupation and livelihood activities in the communities are subsistence farming, fishing, and petty trading.

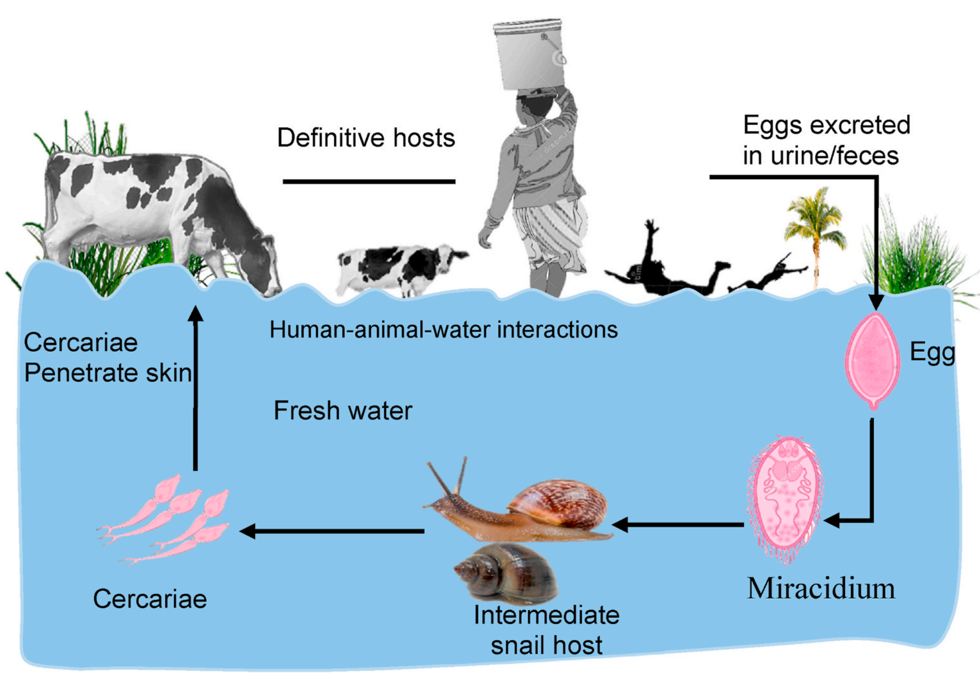

Fig. 1. Schistosoma transmission lifecycle. Source: adapted from Ciddio et al. (2017) and McManus et al. (2010).

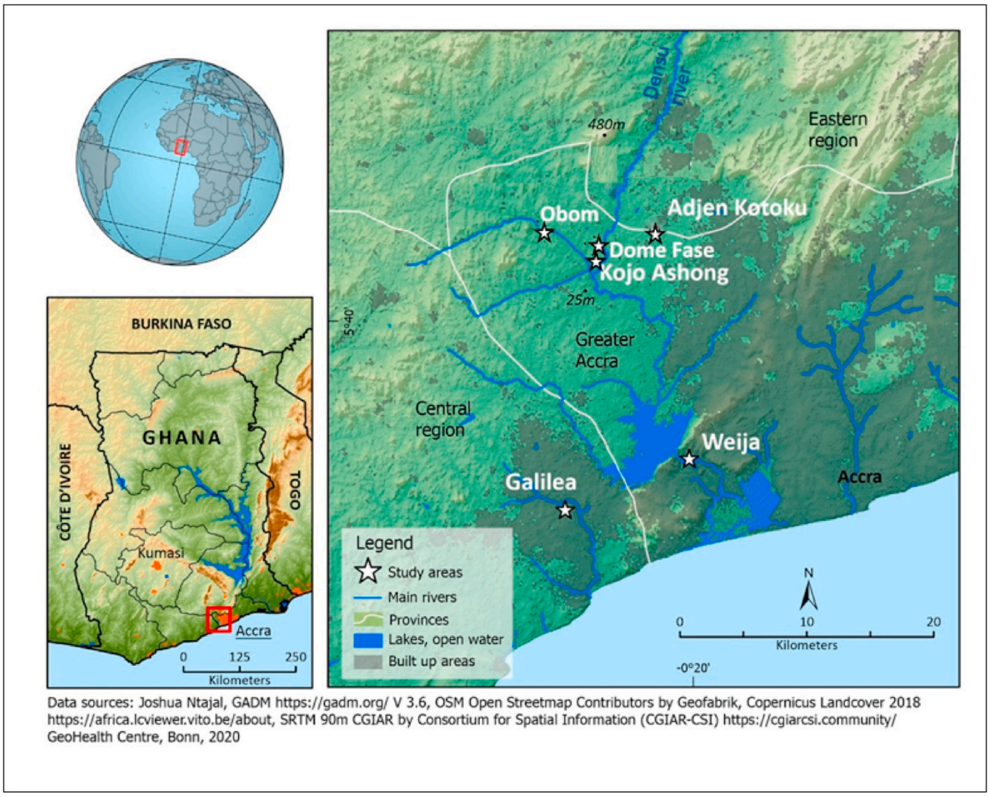

Fig. 2. Map of the study area.

3. Materials and methods

3.1. Sampling and sample size estimation for the survey

The minimum sample size determination approach of Pourhoseingholi et al. (2013) as stated in *Equation* 1 was used to determine the sample size of 306 for the cross-sectional survey (seeAppendix I).

$$n = \frac{Z^2 P(1-p)}{d^2} \tag{1}$$

Applying a buffer of 10% to account for potential non-response, 337 schoolchildren were randomly sampled from six schools. The selection of sampling sites was based on the proximity of the respective communities to surface water bodies (river, streams, and ponds), the communities' interactions with surface water, and the prevalence of schistosomiasis (Attua et al., 2014; Codjoe and Larbi, 2016; Kulinkina et al., 2019; Nyarko et al., 2018). The public schools with the largest number of schoolchildren were selected as they were all part of the "free and compulsory" basic schooling program of Ghana, which gives equal opportunity to all residents to acquire basic education. The six selected schools were found to be homogeneous and the targeted sample frame was made up of children with similar demographic characteristics, including the same age groups; hence, the total sample size of 336 was equally distributed among the selected schools (see Zimmerman, 1996). The names of the schools were coded with letters (i.e. A, B, C, etc.) to protect their privacy.

Through consultation with the Schistosomiasis Control Program at the Center for NTDs in Accra, Ghana, schoolchildren aged between nine and fifteen years, who have spent at least five years within their respective communities, were considered eligible to take part in the survey. These eligibility criteria are based on the experiences of the Center for NTDs, indicating that a minimum of five years of residency is required to ensure that recorded prevalence rates can be attributed to community-level exposure factors. To ensure the data collected in this study is compatible with the existing schistosomiasis database in Ghana, the eligibility criteria of the Center for NTDs were followed. A systematic random sampling approach, using the school attendance record book with the names of the pupils, was used to select the participants. The list of schoolchildren was segregated by gender (to obtain a gender-balanced sample) and the names of the children were numbered from one to the *n*th person. The first participant was randomly selected and subsequently, every fifth student on the list was selected until the required sample size was obtained. The consent to participate in the study was granted by 336 schoolchildren, hence, 56 schoolchildren (28 males and 28 females) were sampled from each of the six basic schools.

3.2. Data collection

Prior to conducting the surveys, gatekeepers (assembly members, school staff, and chiefs of the communities) were consulted to gain full entry and access to the communities and the basic schools. In addition, research practice partners (i.e. key stakeholders and institutions who supported the fieldwork and data collection process) including experts in water and sanitation research, disease control officers of the various health centers in the communities, school staff, and experts of schistosomiasis research were identified and consulted to support the design and data collection activities.

A cross-sectional survey was conducted to obtain primary data on the pattern of human-water interactions, access to clean water, sanitation and hygiene facilities, self-reported experiences of schistosomiasis (blood in urine), and perceptions on exposure and risk factors. An expert interview was conducted to obtain data on disease control and preventive measures. The collection of blood, stool, or urine samples was not included in this study due to logistics and financial constraints. The different types of water-contact activities in the communities were classified according to the reasons for engaging in such activities. Therefore, all water-contact activities were classified into four major categories: domestic, occupational, recreational, and cultural/religious.

3.3. Water-contact observations

In order to complement the self-reported water-contact patterns, on-site observation of water-contact activities was conducted at the major water-contact points in each community twice per week over three months (February to April). The water-contact activities, the people (i.e. age group and gender) involved, and the duration of water-contacts were the key items of the observation.

3.4. Statistical analysis

This study utilized descriptive statistics and bivariate odds ratios for data analysis. In order to identify the predictors of S. *haematobium* infection, an analysis of the Spearman rank correlation test was performed. The output of the test allowed for selection of the most potent factors that can likely explain infection. In addition, a bivariate logistic regression was performed, calculating odds ratios. The results were considered statistically significant at a *P-value* of *0.05* or less.

3.5. Ethical issues

Ethical approval was obtained from the Ethical Committee at the Center for Development Research (ZEF), University of Bonn, Germany. In addition, ethical approval was obtained from the Ethical Clearance Committee at the University of Ghana, and the Ghana Education Service. A letter of approval to conduct the study was obtained from the education offices in the Ga South (Weija) and the Ga West (Amasaman) Municipal Assemblies. The ethical clearance letter, together with a copy of the consent form and a sample of the questionnaire, was presented to the school staff to also seek their approval. One week before the commencement of the survey, copies of the consent forms were given to the participants (schoolchildren) and their parents or guardians to obtain their informed consent. The researcher received the endorsed copies of the consent forms before the commencement of the study. The participants were informed that they are free to withdraw their consent or discontinue their participation in the study at any point and for any reason. An identification number (ID) was assigned to each respondent to ensure their anonymity.

Table 1
Age distribution of the sampled children in the surveyed schools. Source: based on primary data collection in Ghana between February 2019 and April 2019. Availability and accessibility of sanitation facilities.

Age group	A	B	C	D	E	F	Total
09–10 years	10	12	26	13	15	23	99
11–12 years	18	22	22	33	32	17	144
13–14 years	21	18	7	8	9	16	79
15 and above	7	4	1	2	0	0	14
Total	56	56	56	56	56	56	336

Table 2
Access to sanitation facilities in the communities.

Community	Public (VIP)	Private pit latrine	Private flush toilet	Open defecation
Obom	16 (29%)	8 (14%)	1 (2%)	31 (55%)
Kojo Ashong	18 (32%)	4 (7%)	0 (0%)	34 (61%)
Weija	34 (61%)	5 (9%)	3 (5%)	14 (25%)
Adjen Kotoku	46 (82%)	6 (11%)	3 (5%)	1 (2%)
Galilea	41 (73%)	11 (20%)	2 (4%)	2 (4%)
Dome Fase	24 (43%)	4 (7%)	0 (0%)	28 (50%)
Total	179 (53%)	38 (11%)	9 (3%)	110 (33%)

Source: based on primary data collection in Ghana between February 2019 and April 2019.

4. Results

4.1. Demography and WASH characteristics

4.1.1. Gender and age distribution

In each of the six schools, 28 males and 28 females took part in the survey, resulting in a response rate of nearly 100% with a total sample size of 168 males and 168 females. Further, the age of the study participants ranged from 9 to 15. The highest number of children were found within the age group of 11 and 12 years (144), while the lowest number of children were within the age group of 15 years and above (14) (see Table 1).

The availability and accessibility of sanitation facilities were found to be a challenge in the selected schools and their respective communities. In all the selected schools in the Ga West and Ga South municipal assemblies, public toilet facilities, commonly known as “Ventilated Improved Pit latrines” (VIP) were available and accessible to all schoolchildren, however, these facilities were poorly maintained. At home, 53% of the schoolchildren depended on public toilet facilities, which were also found in poor condition. This compelled 33% of the schoolchildren and other members of their households to practice open defecation (see Table 2). One of the reasons for engaging in open defecation was the usage fees of the VIP. In addition, the distance between the home and the nearest toilet facility, on average between a two to 4-min walk, was noted as a common reason for not utilizing these facilities. Lack of improved sanitation facilities compelled 61% of the schoolchildren to practice open defecation at Kojo Ashong. Similarly, limited access to improved sanitation and hygiene was identified as the motivating factor for open defecation among 55% of the schoolchildren in Obom. Communities such as Weija, Adjen Kotoku, and Galilea are peri-urban areas with relatively high access to sanitation facilities compared to the rural communities: Obom, Kojo Ashong, and Dome Fase.

4.1.2. Places of open defecation

Despite global and national efforts to end open defecation (OD), rural communities in Ghana, including those in the lower Densu River catchment, still practice OD. It was found that 33% of the children were compelled to practice OD due to limited access to improved sanitation at home. The crucial aspect of OD in this study was the places it is practiced (see Fig. 3). Importantly, 48% of OD was practiced in and around the Densu River (and its tributaries). The uncleared bushes and grasses around the buildings were the next suitable OD sites for 32% of the children. Other places such as public dumping sites and uncompleted buildings were also identified as places for OD, particularly at night, when the surrounding environment becomes dark.

4.1.3. Sources of drinking water

In schools of the peri-urban communities, the main source of

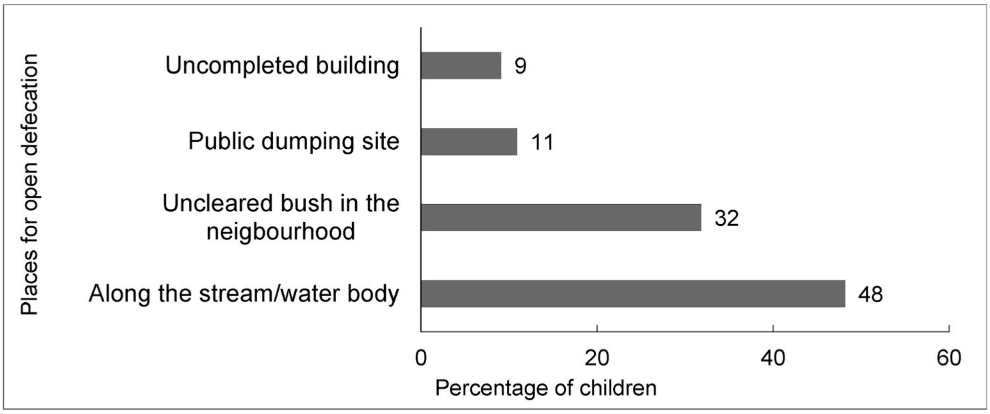

Fig. 3. Places of open defecation in the communities.
Source: based on primary data collection in Ghana between February 2019 and April 2019.

drinking water was bottled (or sachet) water. However, in rural communities, the main source of drinking water at school was piped water, which is tapped from the main Municipal Water Supply System (from the Weija Dam). For example, 43 out of 56 schoolchildren at Weija depended on bottled (or sachet) water. The bottled (or sachet) water is sold on the schools' premises. Hence, the schoolchildren who could not afford it, as was the case at Dome Fase, had to rely on river water at school. At home, the schoolchildren in communities such as Dome Fase, Kojo Ashong, and Obom depended on unimproved water sources (directly from Densu River and its tributaries) as their main source of drinking water (see Fig. 4). Although the municipal water supply (piped water) is available in all selected communities, it is not affordable to all households. In communities such as Obom, where the Densu River is relatively difficult to access, 28 out of 56 of the schoolchildren revealed that their households depended on the *Ponpon* stream, a tributary of the Densu River.

4.2. Water interaction and contact patterns

4.2.1. Self-reported water-contact activities

Human contacts with polluted surface water systems that contain the infected intermediate snail host are crucial in the transmission cycle of *S. haematobium*. Water-contact activities at the community level give a holistic view of human interactions with surface water. For example, the major water-contact activity in all the communities was recreational (53%), primarily swimming (see Table 3). 28% and 18% of the schoolchildren were engaged in domestic and occupational water-contact activities, respectively. Only one percent of the entire sample population had water-contact for cultural/religious reasons, e.g. during the "holy baptism". Water-contact activities, such as assisting parents in fishing, crossing the river to reach school, or irrigating crops, were the common occupational activities among the children. Further, a gender difference was found, with 34% of males engaging in recreational water-contact activities compared to only 19% of females. On the other hand, 20% of females were involved in domestic water activities, whereas only 8%

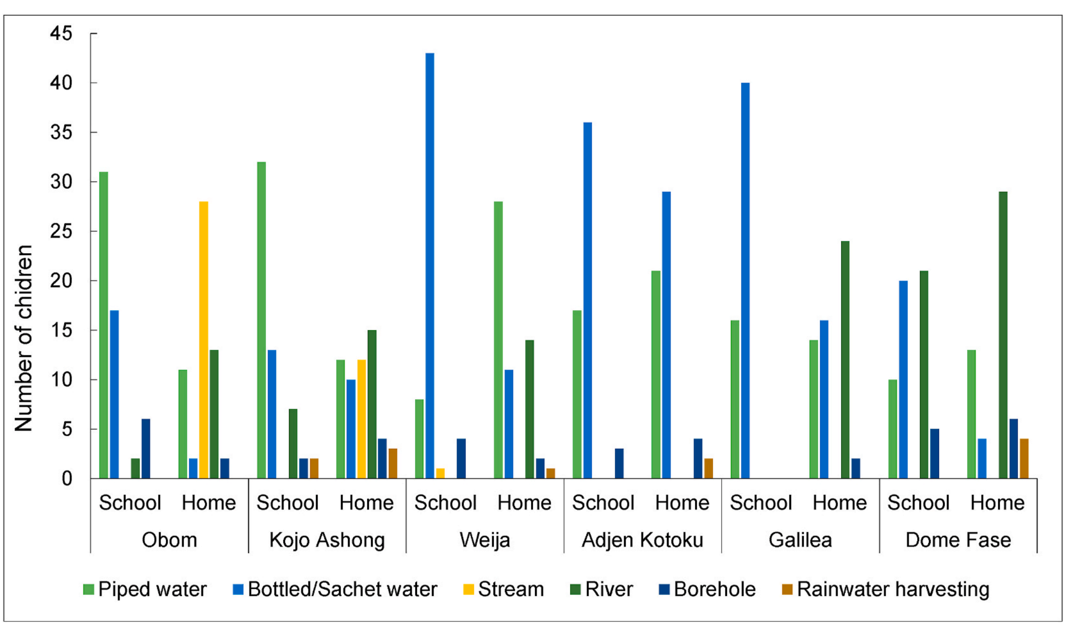

Fig. 4. Sources of drinking water at school, and at home.
Source: based on primary data collection in Ghana between February 2019 and April 2019.

Table 3
The outcome of the self-reported water-contact activities in the communities.

Water-contact activities									
Recreational	Domestic	Occupational	Cultural						
Gender	Male	Female	Male	Female	Male	Female	Male	Female	Water type
Obom	22	10	4	13	2	4	0	1	River & stream
Kojo Ashong	20	15	3	11	5	2	0	0	River
Weija	17	12	4	8	7	6	0	2	River
Adjen Kotoku	16	8	4	11	8	9	0	0	Ponds
Galilea	18	9	7	13	2	6	1	0	River
Dome Fase	21	11	4	12	3	5	0	0	River
Sub total	114 (34%)	65 (19%)	26 (8%)	68 (20%)	27 (8%)	32 (10%)	1 (0.3%)	3 (0.9%)	
Grand total	179 (53%)	94 (28%)	59 (18%)	4 (1%)					

Source: based on primary data collection in Ghana between February 2019 and April 2019

of males indicated such water-contact activities.

4.2.2. Age distribution of water-contact activities

The segregation of water-contact activities by age group (see Table 4) shows that recreational activities are the most common water-contact activity practiced by children of all age groups, with an increasing proportion in older age groups. Whilst 45% of 9-to-10-year-old children engage in recreational water activities, 62% and 71% of children aged 13 to 14 and above 15 years engage in the behavior, respectively. Interestingly, it was found that younger children, i.e. age groups 9–10 years and 11 and 12 years, are more frequently engaged in occupational and domestic water-contact activities compared to the older children. In fact, 23% of the 9-to-10-year-old children indicated being involved in occupational water-contact activities, whilst only 10% of the older children (13 years and above) indicated such behavior. It is thus indicated that with increasing age, children are less engaged in domestic and occupational water-contact activities and more engaged in recreational water activities.

4.2.3. Self-reported versus observed water-contact activities

Comparing the outcomes of self-reported with observed water-contacts at the community level (see Fig. 5A), both methods revealed that children were most commonly engaged in recreational activities in all communities except at Galilea, where observed domestic water-contact activities were similarly common to recreational activities.

Segregating water-contact activities by gender (see Fig. 5B) confirms that males are more frequently engaged in recreational activities compared to females. The observational data further confirm that females are more frequently engaged in domestic water activities compared to males, however, the observations revealed a slightly higher proportion of males than the self-reported results (28% and 34%). The gender distribution of the occupational water contact category differed between the observational and self-reported data. While the self-reported results indicated that more females were engaged in occupational water interactions, observation showed a higher proportion of males engaging in such activities. Similarly, more males were observed engaging in cultural water interactions, whilst the results of the self-reports indicated that more females were engaged in such activity. As the number of both reported and observed cultural water activities was very low, the gender distribution in this category is not robust and should therefore be ignored. Additionally, it should be noted that the surveyed children were asked to indicate their primary water contact activity, which may have led some males to omit their engagement in occupational water contact activities. Further, it cannot be excluded that some reporting bias was evident during the survey.

Table 4
Cross-tabulation of age groups and water-contact activities.

Age group	Water-contact activities			
	Recreational	Domestic	Occupational	Cultural
09–10 (n = 99)	**45**	**30**	**23**	**1**
11–12 (n= 144)	75	41	26	2
13–14 (n=79)	49	20	9	1
15 & above (n=14)	10	3	1	0
Total (n=336)	179	94	59	4

Source: based on primary data collection in Ghana between February 2019 and April 2019

4.2.4. Frequency and duration of water-contacts

Thirty-two percent of the children indicated in the survey to have water-contacts more than twice per week (see Table 5). For example, children who were involved in fetching drinking water to be used at school and/or at home in Dome Fase and Galilea. In addition, it was found that recreational activities occurred once per week (only on weekends) at Adjen Kotoku, Weija, and Obom, and more than twice a week at Kojo Ashong and Galilea.

The water contact duration was categorized as either more than or less than 30 min. Both the self-reported and observational data indicate a higher proportion of children engaging in water contact activities for less than 30 min. The self-reported results showed a higher percentage of children engaging in longer water-contacts (42%) compared to the results of the observed data (31%). This difference may be attributed to the aggregation of water contact durations. While the observation recorded the duration of a single water-contact event (e.g. duration of a single swimming event), the respondents of the survey may have aggregated the total water-contact duration (i.e. duration of multiple swimming events).

4.3. The occurrence of self-reported blood in urine

The results of the self-reported occurrence of blood in urine among the schoolchildren revealed that 98 children (76 males and 22 females) reported blood in their urine, representing 45% and 13% of the total male and female sample populations, respectively. Overall, a strong gender effect is evident, with more males reporting blood in urine compared to females. At the community level, Kojo Ashong recorded the highest case count of 19 male children and 7 female children (see Fig. 6A), followed by Obom with 21 cases. Weija and Dome Fase had relatively moderate case counts among the male children. Adjen Kotoku had the lowest number of cases, which was partly due to the type of water body (pond) in the area and the corresponding water-contact patterns.

Further, when we compute the percentage of children with reported cases of blood in urine for each age group, the results show that 57% of

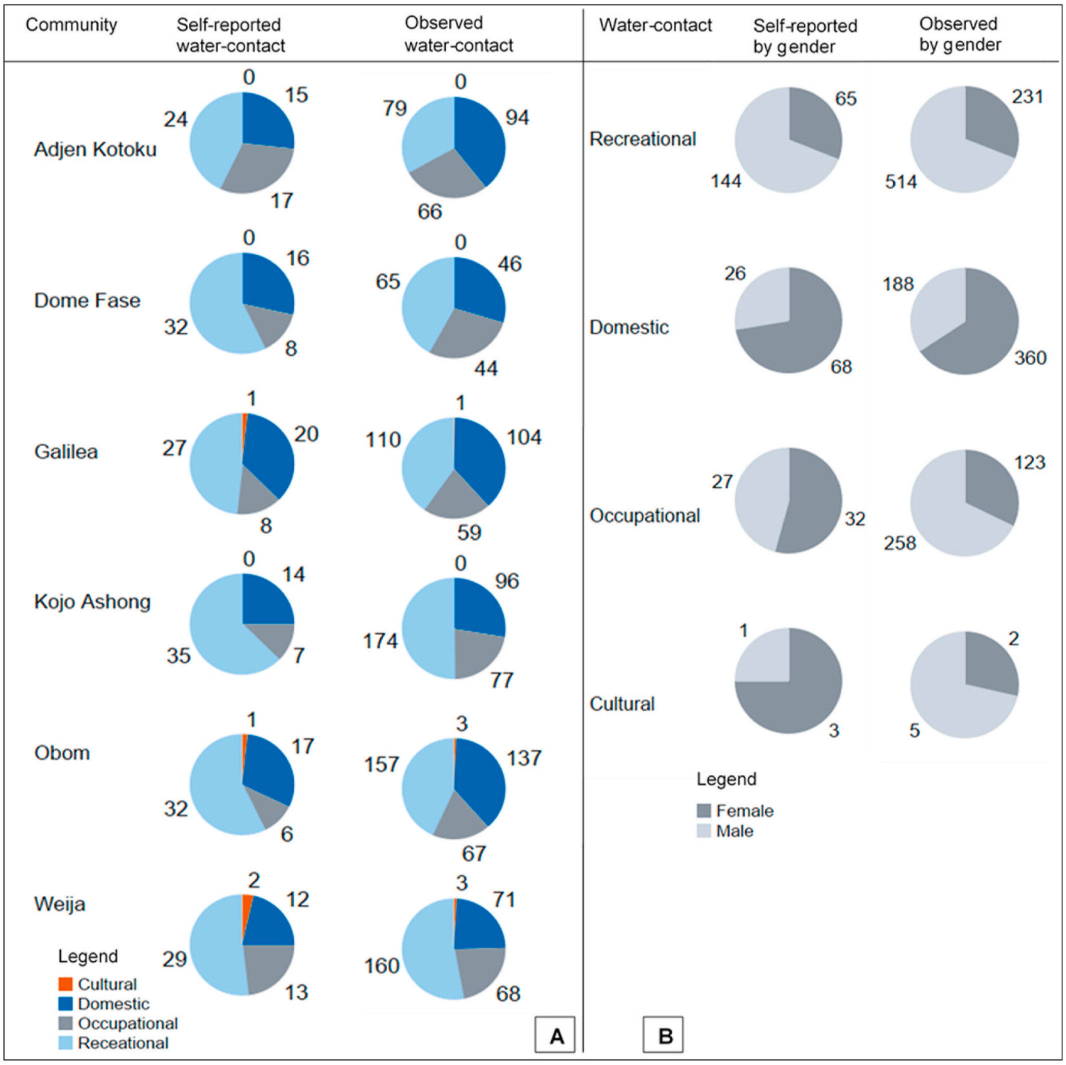

Fig. 5. **A**: self-reported versus observed water-contact activities; **B**: gender distribution of water-contact activities.
Source: based on primary data collection in Ghana between February 2019 and April 2019.

the older children within the age group of 15 years and above reported blood in urine (see Fig. 6B). Similarly, 47% of the children aged 13–14 years reported blood in urine, compared to 23% of the children of 10 years and below. This result shows that older children (13 years and above) experienced more cases of blood in urine.

The blood in urine segregated by age group was calculated using the total number of self-reported cases of blood in urine in each age group divided by the total number of children in that age group.

Source: based on primary data collection in Ghana between February 2019 and April 2019.

Table 5
Frequency and average duration of water-contacts.

	Frequency of water-contacts	Number of children	Percentage
Self-reported	Less than twice in a week	205	61%
	More than twice per week	131	39%
	Total	336	100%
Self-reported	Less than 30 min	194	58%
	More than 30 min	142	42%
	Total	336	100%
Observed	Less than 30 min	1162	69%
	More than 30 min	519	31%
	Total	1681	100%

Source: based on primary data collection in Ghana between February 2019 and April 2019.

4.4. *Perceived exposure factors among schoolchildren*

Knowledge about places of exposure to cercariae is imperative for the control and prevention of schistosomiasis. This study found that 55% of the schoolchildren perceived that frequent swimming in polluted water is the cause of blood in urine, while 10% of the children did not know any exposure factors, and 2% perceived schistosomiasis as a spiritual issue or punishment from the gods (see Fig. 7). It could be observed that the majority of the schoolchildren were aware of some exposure factors, such as fetching water and fishing in the *Bulinus* dominated water.

4.5. *Odds ratios of blood in urine and water-contact activities*

The output of the correlation analysis (see Appendix II) revealed that blood in urine is correlated with recreational, domestic, and occupational water-contact activities, as well as frequency and duration of water-contacts, whilst these also correlate with each other, leading to issues of collinearity. Therefore, a bivariate analysis (calculation of odds

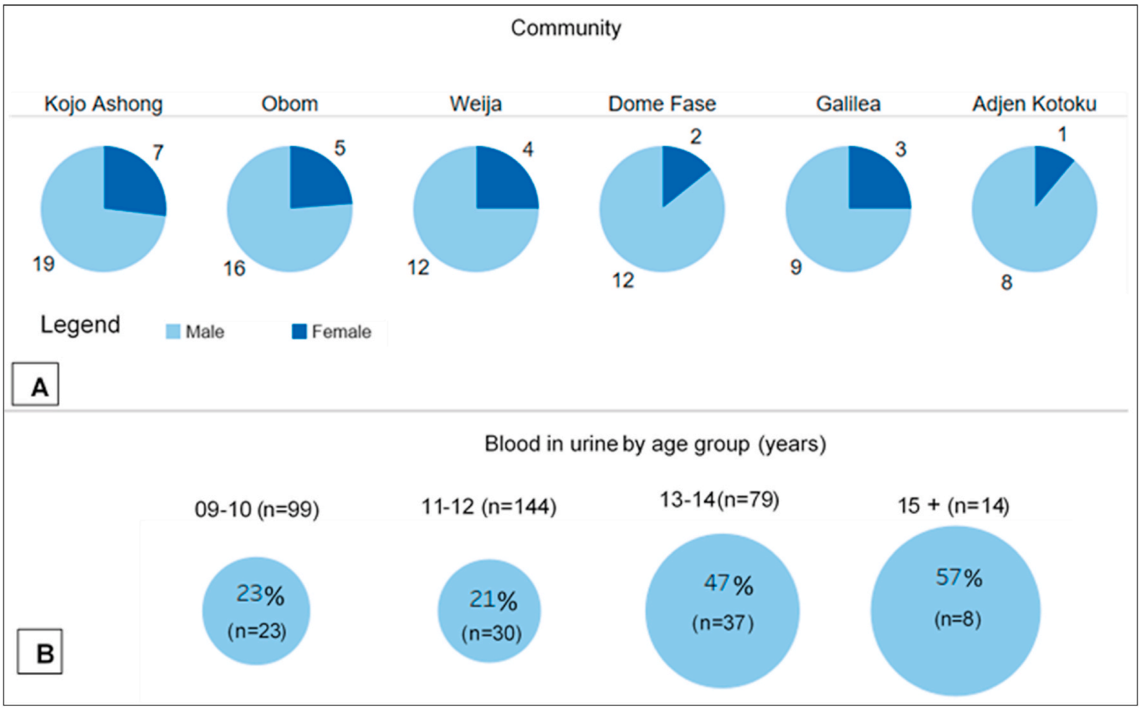

Fig. 6. **A**: self-reported cases of blood in urine in the communities by gender; and **B**: self-reported cases of blood in urine in each age group.

ratios) was performed between blood in urine and each of the exposure variables (see Table 6).

A strong gender effect is evident with males having 5.5 times the odds of blood in urine compared to female children. Additionally, an age effect was found with significantly elevated odds of blood in urine among the 15 years and above (OR = 3.4) and 13–14 years (OR = 1.7) age group. The three dominant water-contact activities, domestic, recreational, and occupational, all show significantly elevated odds of blood in urine. The highest odds ratios were found for recreational water-contact activities followed by occupational and domestic activities. More frequent and longer water-contacts also led to elevated odds of blood in urine. Considering the interactions between these variables, it was found that children involved in domestic activities are more likely to have more frequent water-contacts, i.e. more than twice per week, while recreational and occupational water-contacts are linked to longer water-contact durations, i.e. more than 30 min. Additionally, the results indicate a preventive effect of mass drug administration (MDA), where children receiving the treatment show 0.4 times lower odds of blood in urine compared to children not receiving treatment.

4.6. Control and prevention measures

Key informant interviews with disease control officers in the various health centers of the communities revealed that the common schistosomiasis control measure was MDA with praziquantel. In addition, an interview with the school staff at Obom and Galilea revealed that sensitization programs were organized occasionally for awareness-building, and to discourage swimming in the polluted water; however,

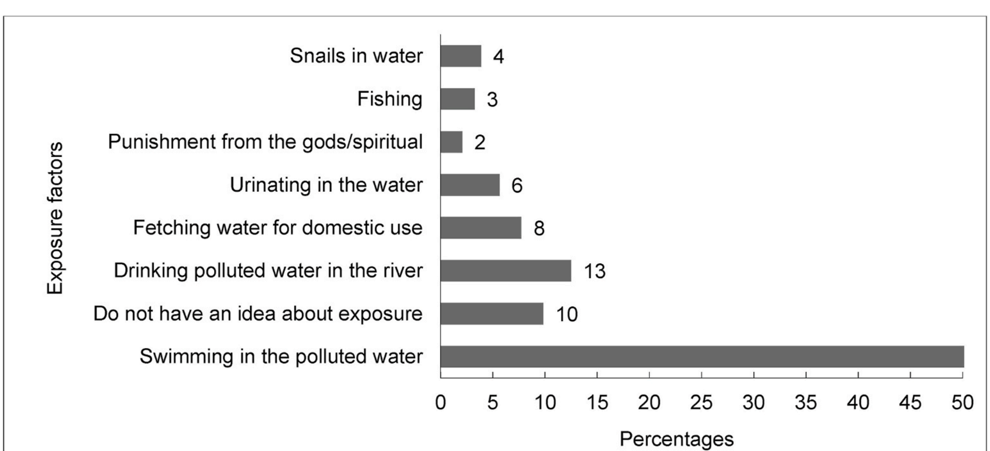

Fig. 7. Perceived exposure factors.
Source: based on primary data collection in Ghana between February 2019 and April 2019.

Table 6
Bivariate regression analysis showing odds ratios of self-reported blood in urine.

Variable	Odd ratio	Significance	95% CI
Gender	5.482	0.000	3.190–9.422
Improved water supply	0.733	0.202	0.455–1.181
Open defecation	1.287	0.317	0.786–2.109
Domestic	2.749	0.001	1.490–5.073
Recreational	4.202	0.000	2.466–7.158
Occupational	3.634	0.002	1.588–8.318
Cultural	1.238	0.854	0.127–12.052
Water-contact more than twice/week	1.857	0.014	1.131–3.051
Water-contact more than 30 min/week	2.898	0.000	1.785–4.705
Mass drug administration	0.439	0.001	0.272–0.710
09–11 years	1.530	0.123	0.891–2.627
11–12 years	1.347	0.226	0.832–2.180
13–14 years	1.702	0.050	0.999–2.897
15 years and above	3.437	0.026	1.160–10.183

The variables were considered statistically significant at a *P-value* of *0.05* or less. Source: all the variables were self-reported in the survey conducted in Ghana between February 2019 and April 2019.

such programs did not yield significant positive results.

5. Discussion

The interactions between humans and surface water systems influence urinary schistosomiasis, particularly regarding the type of water-contact behavior, availability of safe drinking water supply, and sanitation. The direct dependence on unimproved water sources, i.e. surface water, increases the chances of exposure to contaminated water and thus, the risk of S. *haematobium* infection. This study found that peri-urban and rural communities (e.g. Dome Fase and Weija) directly depend on surface water from the Densu River and the Weija Lake to supplement their domestic water supply. Consequently, these surface water sources are extensively used for washing, cooking, personal hygiene, and drinking. This is of particular concern as open defecation (OD) is widespread in these communities. Although sanitation facilities generally exist, the poor conditions of these, required usage fees, and relatively long distances between homes and public sanitation facilities were key factors driving community members to engage in open defecation. In this study, it was identified that OD is commonly practiced along the watercourse, leading to fecal contamination of surface water systems and thus contributing to the transmission of fecal-oral diseases, including schistosomiasis. While OD was not statistically significant in this study, Schmidlin et al. (2013) found it to be a statistically significant risk factor of S. *haematobium* in the Taabo area of south-central Côte d'Ivoire. Poor hygiene and sanitation linked to the practice of OD play crucial roles in the transmission cycle of S. *haematobium*, as the schistosome eggs are released into water systems via feces and urine (Schmidlin et al., 2013). The eggs released from infected humans hatch and infect the snails (intermediate hosts), which in turn release the parasites to infect humans (Kulinkina et al., 2019; Martel et al., 2019). OD forms a precondition for infecting *Bulinus* snails with S. *haematobium*. A related study on schistosomiasis in other peri-urban communities of the Ga West and Ga East Municipal assemblies highlighted that the schistosomiasis risk of children was linked to limited access to safe drinking water, swimming activities, and low investment in improved hygiene and sanitation infrastructure (Nyarko et al., 2018). Therefore, eradicating OD can contribute greatly to breaking the S. *haematobium* transmission cycle.

5.1. Human-water interactions and occurrence of blood in urine

It was found that all children engage in some kind of water-contact activity. The most common were recreational water-contacts (53%), followed by domestic (28%) and occupational water-contacts (18%). Direct water contact exposes the children to the cercariae and thus places them at risk of infection. Ajakaye et al. (2017) reported that individuals who directly depended on freshwater as a source of livelihood had higher exposure to the cercariae in Nigeria. Similarly, Codjoe and Larbi (2016) highlighted that children with relatively high levels of exposure to cercariae in the Densu Basin in Ghana were those engaged in frequent water-contacts, such as fetching water for household use. Occupational water-contacts, such as fishing or crossing water, were reported as exposure factors in the Eastern region of Ghana and the Migori county in Kenya, where schoolchildren cross water bodies with bare feet to and from school (Martel et al., 2019; Ng'ang'a et al., 2016). It is therefore evident that water contact is common and, in many cases, unavoidable. Additionally, it was identified that the type of water-contact activity is related to the frequency and duration of the water-contact, which in turn correlates with the level exposure. Whilst, domestic water-contact activities are linked to more frequent (but rather short) water-contact activities, recreational water-contact activities occur less frequently but usually for longer durations. Similar patterns were observed in a study in the Shinyanga District of Tanzania, where swimming activities were positively correlated with longer water-contact durations, thereby increasing the exposure to schistosomiasis (Angelo et al., 2018). In addition, studies in Senegal revealed that exposure of women and children to cercariae was influenced by the frequency and duration of water-contacts, and the proportion of the human body exposed to the cercariae (Ciddio et al., 2017; Webster et al., 2013). This indicates that the type of water interaction is an important factor mediating exposure to cercariae and the risk of schistosomiasis. As swimming activities usually involve longer water-contact durations as well as full submersion of the body, it is not surprising that our data indicates these recreational water-contact activities as having the highest odds of experiencing blood in urine. Similarly, more frequent water-contacts (more than twice per week) and longer water-contact durations (more than 30 min) also showed significant increases in the odds of blood in urine.

5.2. Control and prevention measures

The identified control measure in the communities was mass drug administration (MDA), which does produce some degree of protection against blood in urine. However, the degree of protection appears to be low. While studies have demonstrated the vital role of praziquantel in the control of human schistosomiasis, other reports have highlighted its weaknesses regarding the development of resistance (Chai, 2013; Vale et al., 2017). For example, studies in Ghana show a wide coverage of MDA in schistosomiasis prone communities, however, health centers in these communities continue to record new and recurrent cases of schistosomiasis (Martel et al., 2019; Nyarko et al., 2018). Additionally, It was discovered that the drug has side effects, including increasing allergic and hypersensitivity reactions (Chai, 2013). This is an illustration that MDA may be insufficient to eliminate the disease. Therefore, measures to tackle the underlying causal factors, including open defecation and limited access to safe drinking water, are required alongside awareness-building campaigns.

5.3. Level of awareness of schistosomiasis risk factors

Our study found that 88% of children were aware of the risk and exposure factors of schistosomiasis. Nonetheless, these children still engage in risky behaviors. Interestingly, reports on schistosomiasis in the northern part of Ghana and southern Burkina Faso from the 1950s and 1960s already indicated that these water-contact behaviors were the drivers of schistosomiasis transmission (Hunter, 1981, 2003; Hunter et al., 1983). The findings of these reports and the results of our study show that there has not been a significant change in the water-contact behavior of children over the past decades, despite successful awareness-raising campaigns (as indicated by the relatively high level of awareness of key risk behaviors among the children). This is an important finding with a significant policy implication, highlighting that awareness-raising is insufficient to sustainably change behavior or reduce schistosomiasis transmission. There is a pressing need for the development and implementation of more efficient and sustainable strategies that target the root causes of schistosomiasis transmission, such as the provision of functioning primary barriers (i.e. sanitation facilities). In the hot Ghanaian summers, it will be unavoidable that children engage in recreational water activities and the occupational utilization of water resources form important components of local livelihood strategies. Avoiding water contacts is therefore not be a solution to schistosomiasis transmission, but what is required is the establishment of effective primary barriers. Additionally, the provision of a safe and sufficient drinking water supply can significantly reduce exposure, particularly among populations that rely on these surface water systems for drinking water or domestic water uses.

5.4. Limitations

The study relies on self-reported cases of blood in urine, hence, some degree of reporting bias must be expected. Particularly, the gender and age effects should be viewed with great caution. Although all children engage in multiple water-contact activities, only the dominant water-contact activity was reported. This may affect the respective effects of the individual water-contact activities. The study design is based on the assumption that all children have some degree of exposure, therefore there was no control group, thus not allowing robust case-control analysis.

6. Conclusion

This study assessed human water interactions and their influences on schistosomiasis prevalence. There is limited access to improved sanitation and safe water supply, which compels the communities to rely on open defecation and untreated river water, reinforcing the schistosomiasis transmission cycle. Particularly, open defecation along the waterways forms a precondition for schistosomiasis transmission. Water-contact activities, including domestic, recreational, and occupational activities, are practiced by all children, therefore creating a widespread exposure pattern. The type of water-contact activity influences the frequency and duration of water-contact, which in turn determines the level of exposure. Higher frequencies and longer durations are linked to a higher prevalence of blood in urine.

The majority of children are aware of the underlying exposure factors, yet still engage in these risk behaviors. It is therefore indicated that awareness-raising campaigns are insufficient to break the schistosomiasis transmission cycle. Next to such campaigns, the common schistosomiasis control measure is mass drug administration. Although significant preventive effects were noted, the effect size was found to be rather low. Current control strategies target the human definitive host by promoting behavior change and preventive treatment. However, these strategies failed to sustainability break the transmission cycle, as these do not tackle the underlying causal factors. Ensuring a sufficient and safe drinking water supply is needed to reduce the requirement to utilize surface water for domestic purposes, which thus reduces the frequency of exposure. Additionally, sensitization campaigns are required for occupational users to ensure that adequate protective gear is being utilized during prolonged water contact, also contributing to exposure reduction. However, the transmission cycle cannot be broken by exposure reduction, but rather, requires the development of effective primary barriers. The provision of improved sanitation facilities can form an effective strategy by halting infection of the intermediate snail host. In order to sustainably tackle schistosomiasis, the transmission cycle must be broken by preventing open defecation through the provision of improved sanitation facilities.

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Declaration of competing interest

The authors declare no conflict of interest.

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Appendix I. Sample size estimation

The sample size was estimated, using the method stated in *Equation* 1.

$$n = \frac{Z^2 P(1-p)}{d^2} \tag{1a}$$

where n is the sample size, $Z$is the statistic corresponding to the level of confidence (1.96), P is the prevalence rate of *S. Haematobium* (27.5%) (Nyarko et al., 2018) and d is precision (95%), which is widely used (Pourhoseingholi et al., 2013).

Therefore.:$n = \frac{(1.96)^2 * 0.275(1-0.275)}{(0.05)^2} = \frac{3.8416 * 0.766}{0.0025} = 306$

As a result, the sample sized (n) is 306. Using a buffer of 10% $(0.1 * 306 = 30.6)$ of the estimated sample size as a non-response rate, the final estimated sample size was. 337.

Appendix II

Table 7
The correlation matrix of S. *haematobium* predictors

	Blood in urine	Gender	Improved water supply	Open defecation	Domestic	Recreational	Occupational	Cultural	Water-contact more than twice	Water contact more than 30 min	Vaccination	10–11 yrs.	11–12 yrs.	13–14 yrs.
Gender	.354**													
Improved water supply	-.070	.067												
Open defecation	.055	-.038	-.162**											
Domestic	.181**	-.265**	.043	-.011										
Recreational	.299**	.280**	-.099	.107	.665**									
Occupational	.176**	-.055	.070	.122*	.288**	.493**								
Cultural	.010	.000	.033	-.018	-.068	-.117*	-.051							
Water-contact more than twice	.134*	-.139*	.035	.079	.209**	.376**	.226**	.073						
Water contact more than 30 min	.239**	.153**	-.014	.119*	-.172**	.259**	.144**	.025	-.334**					
Vaccination	-.185**	.060	.159**	.058	-.108*	.167**	-.095	.009	-.008	.134*				
10–11 yrs.	.084	-.007	.016	-.131*	.034	-.101	.096	-.011	.085	-.062	-.123*			
11–12 yrs.	.066	-.229**	-.012	.011	.010	-.021	.011	.016	-.091	-.002	-.024	-.560**		
13–14 yrs.	.107*	.232**	.047	.107	-.033	.097	-.090	.004	-.031	.046	.110*	-.358**	-.480**	
15 yrs & above	-.128*	.089	-.105	.045	-.030	.076	-.057	-.023	.094	.047	.107*	-.135*	-.181**	-.116*

All variables were self-reported in the survey conducted in Ghana between February 2019 and April 2019.

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2.5 Impact of wastewater use for irrigation

Falkenberg, T., Saxena, D., and Kistemann, T. (2018). Impact of wastewater-irrigation on in-household water contamination. A cohort study among urban farmers in Ahmedabad, India. Science of the Total Environment *639*, 988-996.

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Background & Aim:

Increasingly scarce freshwater resources and growing water demand place high pressure on this essential resource. A key user of freshwater is the agricultural sector, which requires large quantities for irrigation. It is, therefore, unsurprising that wastewater use for irrigation is widespread across the globe. While planned use of wastewater can create environmental and economic advantages, unplanned and often unaware use of wastewater can induce significant health risks for farmers and consumers. As the release of untreated wastewater into surface water is common in many low- and middle-income countries and farmers routinely rely on surface water as irrigation source, use of diluted wastewater frequently occurs unplanned. Wastewater-irrigation, therefore, introduces or re-introduces fecal pathogens into the community. In most low- and middle-income countries, household water supply is intermitted. Thus, even households with a piped water connection are required to store drinking water for prolonged periods in their household. In this study it is hypothesized that exposure to wastewater irrigation increases contamination of hands and clothing and thus also the risk of transferring these contaminants to the drinking water during storage and withdrawal. Thus, the study aims to assess the extent to which wastewater irrigation influences the degree of in-household water contamination.

Methods & Results:

The one-year cohort study followed 204 households (1,286 individuals) in four communities of Ahmedabad, India. The four communities represent different types of irrigation water sources, groundwater (control), surface water (river and canal), and wastewater (exposure). In each community, households were randomly sampled using snowball sampling. Data collection was split into four phases, representing the seasons (winter, summer, monsoon and post-monsoon). During each season water samples were drawn at the irrigation water source, the drinking water source and the household water storage container. The samples were analyzed for the fecal indicator bacterium *Escherichia coli* utilizing the Most Probable

Number (MPN) method. During each visit a spot-check was conducted to assess the hygiene situation of the household. This structured observational approach was conducted with five categories: water, sanitation, food, environment and personal, and was used to calculate a Hygiene Index. Next to these longitudinal data collection methods, three cross-sectional surveys were conducted over the study period: baseline survey, farm survey and hygiene survey. T-tests were utilized to compare the point-of-source (PoS) and the point-of-use (PoU) water quality between the groups. For further analysis, the difference between PoS and PoU water quality was used to represent in-household water contamination. Households with differences > 1 *E. coli* per 100 ml were classified as having in-household water contamination. The study revealed that in-household water contamination is widespread across the sample population. During the peak of contamination during the monsoon period only 6% of households had safe water at the PoU and even during the period of lowest contamination in the winter, only 31% had safe PoU water. The use of wastewater for irrigation has a significant effect on in-household water contamination with an odds ratio of 4.08. The Average Treatment Effect (ATE) indicates that households utilizing wastewater irrigation add on average 18 *E. coli*/100 ml to their drinking water during storage.

Conclusions:

In-household water contamination is widespread throughout all seasons and in all communities. The findings indicate that access to sanitation, adequate personal hygiene and safe water storage behavior (i.e. covered water storage container) form key barriers to in-household water contamination. Water treatment at the point-of-use was identified as an important secondary barrier. The main result, however, indicates that utilization of wastewater for irrigation leads to transfer of pathogens from the farm to the home environment. Therefore, the health risks associated with wastewater irrigation are not restricted to the individuals directly engaged in farming activities but affect the entire household. The high ATE suggests that wastewater irrigation is a more important source of in-household contamination compared to open defecation. It is therefore indicated that effective barriers are required for wastewater irrigation, similar to the necessity of ensuring access to sanitation.

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Impact of wastewater-irrigation on in-household water contamination. A cohort study among urban farmers in Ahmedabad, India

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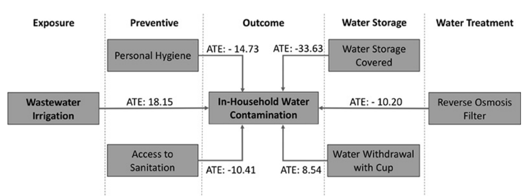
HIGHLIGHTS

- 78% of households drinking water further deteriorated between point-of-source (PoS) and point-of-use (PoU).
- During the monsoon only 6% have access to safe PoU water.
- Wastewater irrigation increases the odds of in-household water contamination 2.5.
- Reverse osmosis filters reduce the odds of in-household water contamination by 94%.
- Access to sanitation and good personal hygiene show preventive effects.

GRAPHICAL ABSTRACT



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ABSTRACT

This cohort study explores the contribution of wastewater irrigation, in the context of WASH (Water, Sanitation, Hygiene), on in-household water contamination among urban farming households in Ahmedabad, India. Drinking water samples of 204 households in four peri-urban farming communities were collected from the point-of-source (PoS) and point-of-use (PoU) of each household four times over the 12-month follow-up period. Next to the quantification of *E. coli*, three household surveys (baseline, hygiene and farm) were conducted. Additionally, an observational spot-check was undertaken in bi-monthly intervals throughout the follow-up period. Significant positive differences in water quality between PoS and PoU samples were identified in 78% of households. During the monsoon, the peak of contamination, only 6% of households had access to safe drinking water at PoU. The Average Treatment Effect (ATE) of wastewater irrigation indicates an adverse effect on in-household water contamination, larger in effect size than the mitigation effect of access to sanitation or personal hygiene. To control transmission of fecal pathogens, effective barriers are required for wastewater irrigation similar to the necessity of ensuring access to sanitation and practicing adequate hygiene behavior.

1. Introduction

Globally, the utilization of wastewater for irrigation is widespread (Molden, 2007; Drechsel & Evans, 2010). Its importance is continuously growing in light of scarce fresh water resources and increasing water demand due to population growth, urbanization and increasing living standards. While the planned reuse of wastewater, as promoted by

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urban agriculture, can induce significant environmental and economic advantages (Bellows et al., 2003; Holt-Giménez & Patel, 2009; Drechsel et al., 2010), the unstructured and often unaware utilization of wastewater for irrigation bears health risks to the farmers and their families, the consumer as well as the wider community (Lee-Smith & Prain, 2006; Hamilton et al., 2007). The release of large volumes of untreated wastewater into surface waterways is common in many emerging economies (UNESCO, 2003), while farmers often rely on these surface waterways for irrigation purposes. Wastewater irrigation therefore forms a pathway of reintroducing fecal pathogens as well as introducing new pathogens into the community and thus forming an integral element of the WASH (Water, Sanitation and Hygiene) nexus (see Fig. 1). Fig. 1 is an expansion of the F-diagram, where wastewater irrigation is conceptualized as an exposure source parallel to lacking sanitation, transferring fecal pathogens via hands, water, farm, environment and food into the community and inducing adverse health impacts.

Water-borne infections remain a key public health challenge on the global level. Diarrheal disease threatens the health and adequate development of young children, with 800,000 premature deaths still attributed to the disease annually (UNICEF, 2012). Diarrheal disease remains the second leading cause of death for young children in developing countries (UNICEF, 2012). In recent years, various global and national efforts to reduce the burden of diarrhea have been initiated, aiming at creating safe and improved drinking water sources through the adequate provision and treatment of drinking water, as well as providing access to improved sanitation (Wolf et al., 2018). Such efforts are often coupled with hygiene interventions, as it has been understood that the disease risk cannot be eliminated in isolation but integrative WASH programs are required to simultaneously educate the community, develop infrastructure and promote behavior change. The key indicators of progress: access to improved water sources and sanitation facilities, often fail to provide the full picture.

In most low- and middle-income countries, even where the government provides piped household drinking water, the supply is intermittent (Brown et al., 2013). Households are thus required to store their drinking water over prolonged periods of time (see Fig. 2). Nonetheless, households with such non-continuous water connections are classified as 'improved water source' under the original JMP definition (Howard & Bartram, 2003; UNICEF & WHO, 2015) and achieve the second highest rung of the JMP service ladder (corresponding with "basic" access) (WHO/UNICEF, 2017). It can therefore be assumed that the water is monitored and treated by the government, ensuring the provision of safe water to the population. Nonetheless, it needs to be noted that while "improved" water sources do exhibit lower odds of contamination compared to "unimproved" sources, it is estimated that a quarter of "improved" sources are fecally contaminated (Bain et al., 2014). Regardless of the source contamination level, higher effectiveness of point-of-use (PoU) water treatment compared to treatment at the point-of-source (PoS) has been observed (Clasen et al., 2007; Waddington et al., 2009); as in-household water contamination may render previously safe PoS water unsafe at the PoU. A meta-analysis of Shields et al. (2015) highlights that noncompliance with the water standard is more common in PoU water than PoS water, a finding confirmed by Alarcon Falconi et al. (2017). In this study PoU is defined as water as it is consumed, thus water drawn from the household water storage container. PoS is defined as the point where households collect their drinking water, this may be a household tap or a bore well. The intermittent water supply forces households to collect and store their drinking water, which form key points of in-household water contamination (Eshcol et al., 2009; Rufener et al., 2010, Adane et al. 2017). It is hypothesized that exposure to wastewater irrigation increases the likelihood of contamination of hands, feet and clothing and thus also the risk of transferring these contaminants to the drinking water during storage and withdrawal. It has been demonstrated that safe water storage and transport does not only lead to improvements in water quality, but also induces health benefits (Günther and Schipper, 2013). Therefore, adequate hygiene behavior, including safe water storage and use, are essential for disease prevention. While the association between WASH and diarrheal disease is well established (Esrey & Habicht, 1986; Clasen et al., 2006; Wolf et al., 2014; Wolf et al. 2018), the role of wastewater irrigation in regard to in-household water contamination and PoU water quality is seldom discussed.

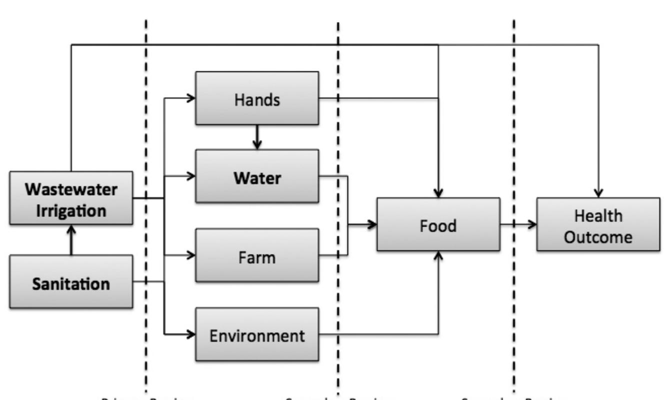

Fig. 1. Fecal-oral transmission pathway. Based on Wagner & Lanoix, 1958. Boxes represent the variable quantified in the study. Arrows represent transmission routes of fecal-oral pathogens. Dashed lines represent primary and secondary barriers.

Fig. 2. Drinking water storage. Drinking water storage in matakas (clay vessels), one wrapped in wet cloth to cool water. Blue plastic drum stores general purpose water. Plastic sieve used for water filtration when filling the matakas.
Foto: Timo Falkenberg.

In this study wastewater irrigation is treated as an integral component of the WASH nexus, essentially forming a potential failure of the primary barrier (sanitation) on the municipal and farm level, leading to the release of fecal pathogens into the environment (Fig. 1). Regardless of the sanitation coverage of a particular community, wastewater irrigation may reintroduce fecal pathogens (as well as potentially harmful chemicals) into the community. This study assesses the extent to which wastewater irrigation influences the degree of in-household water contamination, underlying the assumption that fecal pathogens are transferred from the farm to the household and ultimately into the water storage vessel.

2. Material and methods

2.1. Study area

The study was conducted in Ahmedabad, the most populous city of the state Gujarat, India (census India, 2011). The infrastructure of the city is well developed, with organized water provision dating back to 1891 (AMC, 2006). The city's water supply is reliant on surface water, primarily drawing water from the Sabarmati river (AMC, 2006). The water is treated at two treatment plants and supplied to households via a pipeline network (AMC, 2006). According to the Ahmedabad Municipal Cooperation (AMC), the governing body of the city, 95% of the city is supplied by improved water sources (90% piped connections) and about 90% have access to sanitation infrastructure (AMC, 2006). On the peripheries of the city, however, piped connections have not been developed, and in consequence district-level bore wells are operated by the AMC to supply safe water. The AMC is undertaking continuous large-scale drinking water monitoring to ensure the water supplied is safe for drinking, next to testing for excess amounts of undesirable substances (e.g. aluminum, iron or nitrate), toxic substances (e.g. cadmium, lead or arsenic), radioactive substances (alpha and beta emitters) and pesticide residues (e.g. Atrazine, Chlorpyriphos or Phorate), also bacteriological quality (i.e. *E. coli* not detectable in any 100 ml sample) (BIS, 2012). The AMC tests water samples daily and any deviation from the drinking water standard is intended to be explored and corrected. In case a deviation from the standard is detected, the AMC repeats the sample to confirm the deviation. Confirmed deviations from the norm are communicated with the affected community and actions are taken by the municipal government to correct the situation (e.g. construction of new bore well or increase chlorination). Additionally, all drinking water is chlorinated: the centrally supplied water, which is available in the inner city as well as in upper-class housing complexes, is centrally chlorinated by the AMC. The remaining AMC bore wells, which are utilized in the peri-urban areas, are chlorinated by AMC appointed bore well operators. The operators receive chlorine free of charge from the AMC and add it to the water supply on a daily basis. It can hence be assumed that the drinking water quality in Ahmedabad is generally safe for drinking. However, monitoring is conducted at the bore well only, thus not capturing contamination points along the distribution and storage system.

2.2. Sample selection

The study was designed as a cohort, with a one-year follow-up period. The samples were drawn from four administrative zones located in the urban area of Ahmedabad. These communities were purposively selected according to a set of criteria, including a large farming population, differing irrigation water source and geographic location (Fig. 3). One area (area I) is situated in the north of the city, upstream of the river; farmers in the area primarily utilize groundwater for irrigation and area I, therefore, forms the control group of the study (average irrigation water quality: 411 *E. coli*/100 ml). The other three communities are located in the south of the city and form the exposure groups. Area II and III rely on surface water for irrigation (average irrigation water quality: 9.28×10^5 *E. coli*/100 ml), with area II utilizing a mix of river and canal water and farmers in area III irrigating with canal water only. The primary exposure group, area IV, utilizes wastewater for irrigation (average irrigation water quality: 4.02×10^9 *E. coli*/100 ml).

In each of these areas snowball sampling was used to draw the samples. During the selection process attention was paid to the spread of households, ensuring that the entire spatial dimension of the zones was captured. The sample made up between 10 and 30% of the total district population with the exception of area II, where due to its small size an absolute sample was drawn. The total sample size amounted to 204 households comprised of 1286 individuals (area I: 56; area II: 40; area III: 48; area IV: 60).

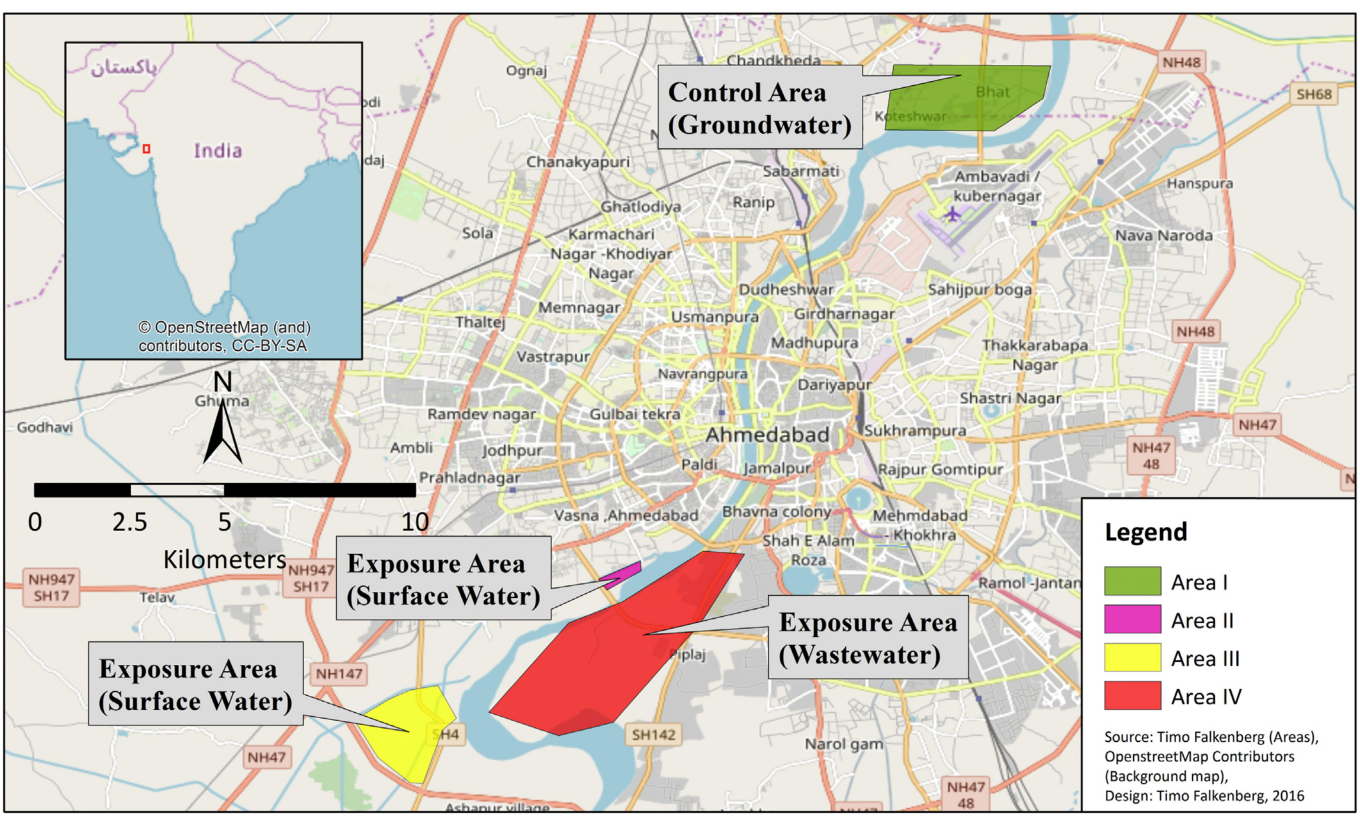

Fig. 3. Overview map of the sample areas. The map was created using ArcGis 10, the basemap was retrieved from OpenStreetMaps. The shaded ares show the geographic location of the four research areas. Area I: control; Area II: river/canal; Area III: canal; Area IV: wastewater. The red box on the inset map shows Ahmedabad.

2.3. Data collection

The data collection process was split into four phases, according to the seasons: winter, summer, monsoon and post-monsoon. During every phase, drinking water samples were collected from each household, once from the PoS and once from the storage container, equivalent to PoU. Water was sampled using a standard protocol; 110 ml sterile water sampling containers were used to collect the water samples, which were then stored on ice and transported to the laboratory within 3 h. For the analysis of the fecal indicator bacterium *Escherichia coli*, the Most Probable Number (MPN) method was used, applying the standard method for drinking water with one-50 ml tube five 10 ml tubes and five 1 ml tubes (EPA, 2002). *E. coli* was chosen as indicator bacterium as it is linked to fresh fecal contamination and the presence of other fecal pathogens (Moe et al., 1991; WHO, 2001; Bitton, 2005). A wide range of fecal pathogens are potentially detectable in the presence of *E. coli*, including bacteria (e.g. *Shigella* spp. or *Vibrio cholera*), viruses (e.g. Hepatitis A/E or Rotavirus) and protozoans (e.g. *Giardia lambia* or *Ascaris lumbricoides*). Consequently, *E. coli* is utilized internationally as indicator for water contamination. The classification of safe drinking water followed the internationally recognized WHO standard of <1 *E. coli*/100 ml or < 10 thermotolerant coliforms/100 ml (WHO, 1997). The samples were analyzed in the state reference laboratory, GMERS Medical College,[1] and the private laboratory, Supratech Micropath.[2] 10% of the samples were analyzed in both laboratories for cross-verification, where the results of GMERS Medical College were viewed as gold standard.

A spot-check was conducted during each visit to quantify the hygienic situation of the households. The spot-check method is a structured observational approach, which has been adapted from Herbst (2006) and Webb et al. (2006). The hygiene index is divided into five categories: water, sanitation, food, environment and personal. For each category, a set of possible observations was determined that reflect good or inadequate hygiene practice (see Table 1). For example, in the environment category observations include: garbage, feces, stagnant water and flies. According to the observations, each category is scored as −1, 0 or +1; with −1 indicating unhygienic conditions, 0 meaning the presence of some unhygienic factors and +1 implying good hygiene. The hygiene index does not capture hygiene behavior directly but rather proxies it through the observation of factors implying inadequate hygiene practice. To ensure a common understanding of the hygiene index components as well as its comparability across time and space, extensive training was provided for the data collection team, included practical in-field exercises.

In addition to the longitudinal data collection, three surveys were also conducted during the 12-month period. These surveys provide important demographic, infrastructure and behavioral information, which is primarily used for stratification and control of confounding factors. The first survey was conducted with the head-of-household during the initiation period and was coined as baseline survey. It consists of seven sections: general information, diet & food, farming practices, drinking water, water & hygiene, sanitation and food expenditure. The second, hygiene survey, was conducted with the female head-of-household, as it is assumed that as primary caregiver she has the most in-depth knowledge of the overall hygiene situation of the household. Some questions were included both in the baseline and the hygiene survey allowing for the triangulation of hygiene practice. The hygiene survey was divided into four sections: food, hygiene, drinking water and sanitation. The third survey conducted was the farm survey, which was undertaken with the household member most frequently engaged in agricultural activities. This survey was conducted on the farm to allow for observations and cross-verification of answers. The farm survey sheds light on land ownership, crop selection, irrigation method, fertilization, water treatment and safety precautions.

Ethical approval was obtained from the University Bonn, Germany and the Indian Institute of Public Health – Gandhinagar, India. Prior to data collection informed consent was obtained from the head-of-household, on behalf of all household members.

2.4. Data analysis

The data was managed with RedCap and was statistically analyzed with STATA 12. The mean *E. coli* concentrations were calculated for PoS and PoU water samples. To determine whether differences in mean concentrations were statistically significant, a series of *t*-tests was performed. The difference between PoS and PoU water quality was then used for further analysis. Households with differences larger than 1 *E. coli* per 100 ml were classified as having in-household water contamination, whilst those exhibiting no or negative differences were classified as 'no in-household water contamination'. In consequence the continuous water quality variable is transformed into a binary variable of in-household water contamination.

In the bivariate analysis Odds Ratios were calculated for factors hypothesized to influence in-household water contamination. To allow for the estimation of the Average Treatment Effect (ATE) all confounders needed to be balanced between the control and exposure group. This balancing was achieved through propensity-score matching, where the propensity score was estimated through multivariate linear regression of the following variables: wastewater use, access to sanitation, hygiene index (environment, water, food, personal), hand washing behavior (after defecation, before eating, before cooking, after work), reverse osmosis filter, outflow valve, using cup for water withdrawal, storage container covered, storage volume, proportion of children living in household, socio-economic-status, education level of the head-of-household. The propensity score was calculated multiple times utilizing the same factors but omitting the variable for which the ATE is to be calculated. In this study "treatment" is understood as exposure to pathogens in wastewater, therefore essentially the average exposure effect was calculated. The "treated" (i.e. exposed to pathogens in wastewater) and control households were matched according to their propensity score. It is assumed that cases with similar propensity scores exhibit similar characteristics across all control variables, thus differences in the outcome variable are induced by the "treatment" variable (=wastewater irrigation). The ATE was calculated through comparing matched "treated" and control households without allowing for replacement.

3. Results and discussion

Water contamination occurring within the households is widespread among the sampled population. During the peak of water contamination, i.e. during the monsoon months, only 6% of households have safe drinking water at the PoU (mean *E. coli*/100 ml: 91 (Std. Dev. = 75.4)), and even during the winter, where contamination is lowest, a mere 31% had safe PoU water (mean *E. coli*/100 ml: 29 (Std. Dev. = 51.9)). Fig. 4 illustrates the *E. coli* concentration of PoS and PoU water across the research groups throughout the sampling period. In all the sampled areas drinking water was stored in the household throughout the day, as water supply is intermittent. A series of *t*-tests revealed that the average quality of PoU water was significantly ($p < 0.05$) lower than that of the PoS water, indicating a significant level of in-household water contamination (Table 2a). A high degree of in-household water contamination was evident among the entire sample population as indicated by the significant positive difference between source and stored drinking water throughout the duration of study. The continual occurrence of in-household water contamination is in consensus with the existing evidence citing the relative importance of

[1] GMERS Medical College & Hospital, Sola (Department of Microbiology) – S.G. Highway, Ahmedabad; www.gmersmchsola.com/home (phone: +91 79 27661527).

[2] Supratech Micropath Laboratory & Research Institute Pvt. LTD. – "Kedar", Opp. Krupa, Nr. Parimal Garden, Ahmedabad – 380 006; www.supratechmicropath.com (phone: +91 79 26408181).

Table 1
Hygiene index components.

Hygiene index				
Environment	Sanitation	Water	Food	Personal
Fecal contamination Waste piles Stagnant water Free roaming animals Significant number of flies	No sanitation/open defecation Unimproved sanitation No water access Fecal contamination	Unimproved water source Storage container dirty Containers not covered Inadequate withdrawal method	Inadequate food storage Significant number of flies Kitchen area contaminated Food stored on the ground Food stored uncovered Dirty dishes	Dirt under finger nails Dirty hands Dirty clothes Not wearing shoes Black or red teeth

The hygiene index consists of five categories each represented by one column. The spot-check items of each category are listed in the column. If any of these items are observed the respective category is scored −1 or 0 depending on the item and the severity contamination. Categories are scored +1 if none of the items were observed.

PoU water quality in regard to drinking water treatment (Clasen et al., 2007; Waddington et al., 2009). Treatment of the source water is hence less effective in the combat against fecal-oral diseases as significant recontamination occurs inside the household during water storage and withdrawal. Bivariate analysis revealed that in-household water contamination was common among the sample population; in 78% of households drinking water quality deteriorated between the PoS and PoU water samples. These results are alarming, as the majority of the sample population did not have access to safe drinking water at the PoU and was consequently exposed to waterborne pathogens.

A statistical significant difference ($p < 0.05$) in in-household water contamination between the control and exposure group (Table 2b), was only reached during the summer sampling period ($t = -3.09$ ($p = 0.0023$). As no significant difference was observed on average, nor in winter, monsoon or post-monsoon, the confounding effects of different WASH variables on in-household water contamination were further analyzed.

Whilst water storage behavior was quite homogenous among the sample population, access to improved sanitation as well as piped water on premises is more prevalent in the control area (Table 3). Drinking water is stored in clay vessels (*mataka*) (95%), while a small proportion of the sample also utilizes plastic storage containers (15%) or resort to jerry cans, buckets or other vessels (11%). 89% of households indicated covering their water storage container, with 84% of households drawing water by hand, with the help of a cup, and 12% utilizing an outflow valve; the remaining 4% use a scoop.

Threefold lower odds of in-household contamination ($p = 0.0058$ [95% CI: 0.11–0.82]) was observed among households utilizing an outflow valve to withdraw water from the storage vessel (Table 4). These results can be explained by direct contact between hands and water, which is highly likely when using a cup or scoop, thus forming a potential contamination path. Consequently, hands are suspected to be a primary vehicle for in-household water contamination; hand hygiene behavior forms an important confounding factor. The critical hand washing times, after defecation (OR = 0.60 [95% CI = 0.30–1.20] $p = 0.1207$) and before cooking (OR = 0.49 [95% CI = 0.24–0.98] $p = 0.0284$), both show the expected mitigation effect in the bivariate analysis, however, only hand washing before cooking reaches statistical significance (see Table 3). As self-reported hand hygiene behavior is prone to reporting bias, the hygiene index was quantified additionally. Each hygiene index category demonstrates a mitigation effect, with the environment (OR = 0.49 [95% CI = 0.24–0.89] $p = 0.0280$), water (OR = 0.34 [95% CI = 0.16–0.71] $p = 0.0015$) and food (OR = 0.50 [95% CI = 0.24–1.00] $p = 0.0346$) categories reaching significance. The most pronounced mitigation effect was found in the water hygiene category, indicating significantly ($p = 0.0015$) lower odds of in-household water contamination among households exhibiting adequate water hygiene behavior. On the other side, 4 times (95% CI = 1.48–13.9) higher odds of in-household contamination ($p = 0.0030$) was observed among the exposed population, indicating a clear negative effect induced by the utilization of wastewater for irrigation.

The existences of primary and secondary barriers are considered essential mechanisms in the control of water borne diseases (Curtis et al., 2000). Primary barriers are those that prevent pathogens from entering the system, thus access to sanitation and adequate disposal of sewage form the key primary barriers. Additionally, hand washing after defecation is classified as primary barrier, as it halts the spread of pathogens from the place of defecation to the wider community environment

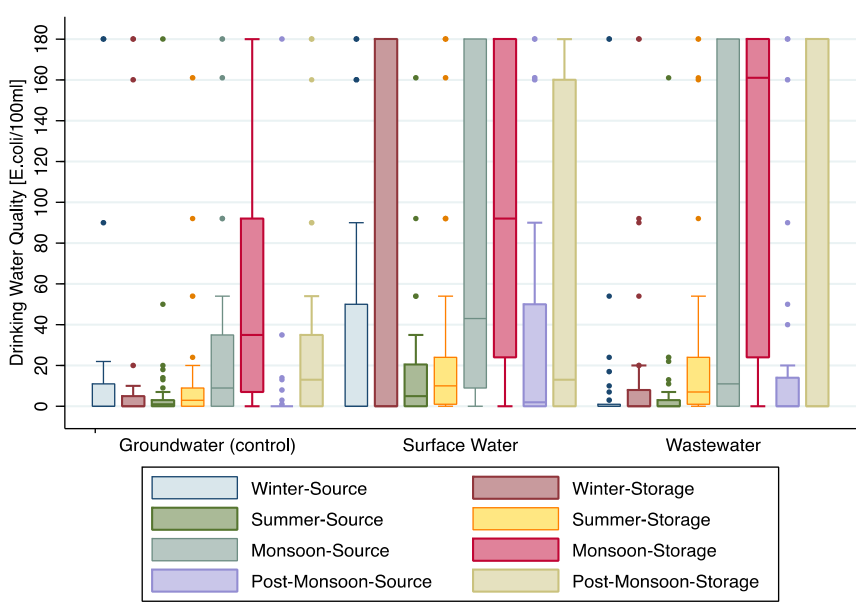

Fig. 4. Drinking water contamination at source and at storage among the research groups.

Table 2a
Difference between point-of-source and point-of-use water quality.

	Winter	Summer	Monsoon	Post-monsoon	Year
Arithmetic means	*E. coli* [/100 ml]	*E. coli* [/100 ml]	*E. coli* [/100 ml]	*E. coli* [/100 ml]	*E. coli* [/100 ml]
Point-of-source	28	12	62	29	33
95% CI	20.2–36.5	7.16–16.1	51.3–73.3	20.6–42.5	27.9–38.4
Point-of-use	37	29	88	53	53
95% CI	26.5–45.8	21.1–36.6	77.5–99.9	42.5–63.9	47.1–59.2
t-Test	−1.27 (p = 0.2046)	**−4.24** (p = 0.0000)	**−3.71** (p = 0.0003)	**−3.86** (p = 0.0001)	**−6.02** (p = 0.0000)
N	195	180	172	191	199

Storage water samples were collected from the household drinking water storage vessel; source water samples were collected from the households' drinking water source (e.g. handpump, borewell, pipe connection).
Bold numbers indicate significance at $p < 0.05$.

(Prüss et al., 2002). Although access to sanitation does demonstrate a mitigation effect (OR = 0.60 [95% CI = 0.32–1.30]), in the bivariate analysis significance was not reached (p = 0.1216). Secondary barriers on the other hand side reduce or eliminate pathogens that have already entered the community system; water treatment forms the most important secondary barrier (Curtis et al., 2000). For the purpose of this paper only PoU water treatment is considered. Utilizing modern reverse osmosis filters (RO) significantly ($p < 0.0000$) reduced the odds of in-household water contamination (see Table 4). In fact, households filtering their water with RO, improved water quality between PoS and PoU. The presence of RO filters was assessed in the baseline and hygiene survey and was confirmed by in-field observations. Households connect the RO system between the inflow tap and their storage container, so that the water is treated before storage. The stored water is not retreated before consumption. The high treatment capacity of RO filters was expected; however, promoting the widespread adoption of the treatment technology is unfeasible due to the high cost of procurement and maintenance.

The bivariate analysis identified one strong mitigation effect (Reverse Osmosis Filter: OR = 0.60 [95% CI = 0.04–0.32] $p < 0.0000$) and one strong adverse effect (wastewater irrigation: OR = 4.08 [95% CI = 1.48–13.9] p = 0.0030) (Table 4). Additionally, personal hygiene (OR = 0.59 [95% CI = 0.29–1.17] p = 0.1036) and access to sanitation (OR = 0.60 [95% CI = 0.32–1.30] p = 0.1216) showed mitigation effects without reaching significance. Furthermore, water withdrawal with help of a cup (OR = 2.11 [95% CI = 0.91–4.74] p = 0.0501) proved to form a key point of in-household water contamination. The ATE of each of these variables was calculated to confirm the direction and strength of the relationships and allow comparisons of their effect sizes.

The estimation of the ATEs confirmed the adverse effect of exposure to wastewater irrigation on the degree of in-household water contamination (Table 5). The ATE indicates that wastewater farmers add on average 18 *E. coli*/100 ml to their drinking water during storage, confirming that pathogens are transferred from the irrigation water to the stored drinking water of the household. The analysis also confirmed that covering the water storage container is a fundamental component of safe water storage behavior, as it showed the largest mitigation ATE. Similarly, the mitigation effect of adequate personal hygiene was confirmed, indicating that the difference between PoS and PoU water quality is on average 14 *E. coli*/100 ml lower among households with good personal hygiene. The individual mitigation effects of personal hygiene and storage behavior (covered storage container) were larger than the ATE of RO filters, highlighting that adequate preventive behavior is essentially important in the combat against in-household water contamination. Nonetheless, the use of RO filters showed a strong mitigation effect, asserting its role in the provision of safe PoU water. Utilization of PoU water treatment should be part of safe water strategies, particularly for populations faced with unsafe PoS water.

Access to sanitation is instinctively associated with hygiene and health advantages, however, the mitigation effect on the degree of in-household water contamination could not be confirmed in the bivariate analysis. The calculation of the ATE revealed the expected mitigation effect of access to sanitation, however, the effect size of exposure to wastewater irrigation was larger (see Table 5). This highlights that in-household water contamination is not solely depended upon access to sanitation, personal hygiene and safe water storage behavior: utilizing wastewater for irrigation forms another significant key exposure source which may not be neglected.

4. Conclusions

Water contamination occurring within the households is widespread among the sampled population throughout all seasons, indicating the continual occurrence of in-household water contamination. Observations from the present study confirm that access to sanitation, adequate personal hygiene and safe water storage behavior (i.e. covered water storage container) form key barriers to in-household water contamination. These findings are consistent with the expected transmission pathway, where access to sanitation and personal hygiene are primary barriers and covering the storage vessel protects its content during storage. Water withdrawal was also identified as a key point of contamination. Using a cup to draw water from the storage vessel leads to potential contact between hands and water and thus water contamination. It is suspected that employing adequate water withdrawal methods that avoid direct contact between hands and water would lead to reductions in in-household water contamination. The effect size of utilizing an outflow valve could not be estimated due to the low number of households employing the technology, but the bivariate analysis indicated a mitigation effect. Water treatment at the PoU was identified as an effective secondary barrier as highlighted by the mitigation effect of the reverse osmosis filters.

The key finding is the significant impact of exposure to wastewater irrigation on the degree of in-household water contamination. This

Table 2b

	Winter	Summer	Monsoon	Post-monsoon	Year
[PoU − PoS] arithmetic means	Δ*E. coli* [/100 ml]	Δ*E. coli* [/100 ml]	Δ*E. coli* [/100 ml]	Δ*E. coli* [/100 ml]	Δ*E. coli* [/100 ml]
exposure group (wastewater & surface water)	12 (n = 128)	26 (n = 119)	24 (n = 108)	21 (n = 123)	20 (n = 131)
95% CI	−3.26–26.3	15.1–36.9	5.96–42.9	5.57–37.1	11.5–29.4
Control group (groundwater)	0.89 (n = 64)	−0.66 (n = 56)	34 (n = 61)	28 (n = 64)	16 (n = 65)
95% CI	−21.5–23.3	−9.76–8.44	11.6–55.5	7.31–48.4	4.91–27.4
t-Test	−0.81 (p = 0.4213)	**−3.09** (p = 0.0023)	0.62 (p = 0.5380)	0.49 (p = 0.6239)	−0.57 (p = 0.5689)
N	192	175	169	187	196

Δ*E. coli* = storage water *E. coli*/100 ml − source water *E. coli*/100 ml; storage water samples were collected from the household drinking water storage vessel; source water samples were collected from the households' drinking water source (e.g. handpump, borewell, pipe connection).
Bold numbers indicate significance at $p < 0.05$.

Table 3
Descriptive table of water storage behavior and WASH factors.

Variable	Groundwater (control)		Surface water		Wastewater		Total population	
	N	Mean (std. dev.)	N	Mean (std. dev.)	N	Mean (std. dev.)	N	Mean (std. dev.)
Household size	54	5.78 (2.53)	86	6.48 (2.80)	59	7.11 (3.57)	199	6.48 (3.01)
Improved sanitation	54	0.67 (0.47)	86	0.51 (0.50)	59	0.37 (0.49)	199	0.51 (0.50)
Piped water on premises	54	0.94 (0.23)	86	0.49 (0.50)	59	0.69 (0.46)	199	0.67 (0.47)
Mataka	54	0.98 (0.14)	86	0.91 (0.29)	59	0.98 (0.13)	199	0.95 (0.22)
Bucket	54	0.33 (0.48)	86	0.35 (0.19)	59	0.02 (0.13)	199	0.11 (0.32)
Plastic storage container	54	0.39 (0.49)	86	0.11 (0.31)	59	0 (0)	199	0.15 (0.36)
Storage container covered	54	0.81 (0.39)	86	0.94 (0.24)	59	0.88 (0.33)	199	0.89 (0.31)
Cup	54	0.81 (0.39)	86	0.77 (0.42)	59	0.95 (0.23)	199	0.84 (0.37)
Scoop	54	0.04 (0.19)	86	0.05 (0.21)	59	0.02 (0.13)	199	0.04 (0.18)
Outflow valve	54	0.13 (0.34)	86	0.19 (0.39)	59	0 (0)	199	0.12 (0.32)
Reverse osmosis	54	0.17 (0.38)	86	0.13 (0.34)	59	0.02 (0.13)	199	0.11 (0.31)
HW- after defectation	54	0.59 (0.50)	86	0.60 (0.49)	59	0.22 (0.42)	199	0.49 (0.50)
HW- before cooking	54	0.44 (0.50)	86	0.65 (0.48)	59	0.25 (0.44)	199	0.48 (0.50)

clearly indicates a transfer of pathogens from the farm to the home environment. The risks of utilizing wastewater for irrigation are not only limited to individuals involved in farming activities, but also extend to the entire household. As in-household water contamination is directly affected by exposure to pathogens in wastewater, it can be deduced that pathogens are also transferred between household members as well as between fomites. The high ATE renders wastewater irrigation even a more important source of in-household contamination than open defecation. It is therefore indicated that effective barriers are required for wastewater irrigation, similar to the necessity of ensuring access to sanitation. Essentially wastewater irrigation needs to be understood as an integral component of the WASH nexus. It is thus suggested to transform WASH into WISH (Water, Irrigation, Sanitation and Hygiene).

4.1. Policy recommendations

As in-household water contamination is widespread, a health education campaign on safe drinking water storage is urgently warranted. Furthermore, drinking water treatment (through boiling, filtering or reverse osmosis) needs to be promoted, especially during the high-risk times (i.e. Monsoon). In the long-term it is essential to ensure continual supply of water through the distribution network, as the intermittent supply necessitates drinking water storage and thus enables in-

Table 4
Odds ratios of factors possibly influencing in-household water contamination.

Category	Variable	Odds ratio	95% CI
Exposure	**Wastewater irrigation y/n**	**4.08** **(p = 0.0030)** (n = 204)	1.48–13.9
Sanitation	Access to sanitation y/n	0.60 (p = 0.1216) (n = 204)	0.30–1.20
Water access	Piped on premises	0.85 (p = 0.6426) (n = 199)	0.39–1.78
Hand washing	After defecation y/n	0.60 (p = 0.1207) (n = 200)	0.30–1.20
	Before cooking y/n	**0.49** **(p = 0.0284)** (n = 204)	0.24–0.98
Hygiene index category	**Environment**	**0.49** **(p = 0.0280)** (n = 204)	0.24–0.98
	Sanitation	0.65 (p = 0.1929) (n = 204)	0.32–1.30
	Water	**0.34** **(p = 0.0015)** (n = 204)	0.16–0.71
	Food	**0.50** **(p = 0.0346)** (n = 204)	0.24–1.00
	Personal	0.59 (p = 0.1036) (n = 204)	0.29–1.17
	Hygiene index	0.59 (p = 0.1036) (n = 204)	0.29–1.17
Withdrawal method	**Outflow valve**	**0.30** **(p = 0.0058)** (n = 199)	0.11–0.82
	Cup	2.11 (p = 0.0501) (n = 204)	0.91–4.74
Treatment method	**Reverse osmosis filter**	**0.11** **(p = 0.0000)** (n = 204)	0.04–0.32
	Any water treatment	**0.50** **(p = 0.0348)** (n = 204)	0.25–1.00
Water storage	Storage container covered	0.84 (p = 0.7429) (n = 204)	0.23–2.53
	Mataka (clay vessel)	1.31 (p = 0.7003) (n = 199)	0.21–6.04
	Bucket	0.87 (p = 0.7824) (n = 199)	0.30–2.89

Bold numbers indicate significance at $p < 0.05$.

Table 5
Average treatment effects (ATE) of key variables on in-household water contamination.

Variable	N	ATE	Mean bias
Wastewater	119	**18.15**	16.2
Personal hygiene	194	**−14.73**	14.1
Access to improved sanitation	163	**−10.41**	19.2
Reverse osmosis filter	98	**−10.20**	18.1
Water storage covered	194	**−33.63**	27.4
Cup (water withdrawal)	153	**8.54**	50.5

ATE = average treatment effect. Calculated after propensity score matching.

household water contamination. Additionally, drinking water monitoring needs to extend beyond the well-level, to also include household connections, to identify contamination points in the pipeline network.

In agricultural areas utilizing surface-, or wastewater additional health education programs are needed to raise awareness and promote preventive behavior (i.e. personal hygiene, protective clothing, etc.). In the long-term the discharge of untreated wastewater into surface waterways needs to be halted, through expansion of the sewerage network and wastewater treatment capacity. Urban agriculture can be an integral component of the municipal wastewater management strategy, through the adaptation of planned usage of the urban wastewater stream. The utilization of small-scale on-farm treatment systems can provide safe irrigation water, while reducing the water volume requiring treatment.

4.2. Limitations

A shortcoming of this study lies in the sampling design. As population registers of the individual research areas were unavailable, a true random sampling technique could not be employed. Nonetheless, the resulting non-random sample provides a representative sample of the research areas, as the entire spatial extent of the village was covered and clustering of households was avoided. As the individual research areas were selected purposively generalizing the results on the metropolitan level should be with caution. Nonetheless it can be assumed that certain characteristics, such as the degree of surface water contamination, are similar in other agricultural communities in Ahmedabad, thus generating similar exposure.

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Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2018.05.117.

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3 Discussion

The five research papers exemplifying important global health challenges of the 21st Century, antibiotic resistance, emerging zoonotic diseases, neglected tropical diseases, and microbial water pollution, highlight the importance of adopting integrated health approaches. Considering interactions with the natural, built, cultural and social environments often reveal further complexity and indicate that required interventions also lie outside the health sector and therefore require intersectoral collaborations and joint action.

The integrated health approaches, One Health and Planetary Health, both emphasize this need for intersectoral collaboration (Whitmee *et al.*, 2015; OHLEEP, 2021). Despite differences between approaches, particularly in their vantage point, calls for convergence are frequent in the literature (e.g. Zinsstag, 2012; Rabinowitz *et al.*, 2018; Correia *et al.*, 2021; de Castañeda *et al.*, 2023). Kahn *et al.* (2014) argue that Planetary Health needs One Health and critique Horton *et al.* (2014) for not including the important animal dimension in their 'manifesto for planetary health'. Many environmental threats emerge at the human-animal interface; therefore, One Health interventions are crucial for Planetary Health. On the other side, One Health has been criticized by Woldehanna and Zimicki (2015) for not including social and ecological factors. They proposed an expanded One Health model, emphasizing that spillover events result from a complex range of socio-ecological factors that cannot be understood without considering social and ecological dynamics. Despite growing acceptance of One Health the lacking incorporation of environmental concepts as well as cultural and social science aspects remain (Correia *et al.*, 2021). The most recent definition of One Health by OHHLEP (2021) embraces the critique and explicitly mention the wider environment and ecosystems, as well as the need to involve multiple disciplines. The explicit mention of sustainable development and action on climate change do indicate a degree of convergence towards Planetary Health, however, it remains questionable if this change in definition will alter the primary focus of One Health on zoonotic and emerging diseases.

Prior to Planetary Health, the EcoHealth approach focused on the ecological context as a health determinant. Due to thematic overlaps and envisioned benefits of integration, EcoHealth and One Health increasingly converged (Harrison *et al.*, 2019). However, this convergence did not lead to a true expansion of the One Health approach, rather the decline of EcoHealth fueled the need for Planetary Health. In his manifesto, Horton *et al.* (2014) emphasize the need to respond to the environmental threats that undermine the foundation of human existence. While the critique that Planetary Health is anthropocentric (e.g. Lerner and Berg, 2017) may be justified, as the protection of the environment is always framed as benefitting human health, the emerging social movement for Planetary Health has a clear ecocentric vision. The principles formulated in the Canmore Declaration (Prescott *et al.*, 2018) and the more recent call for action of the São Paulo Declaration (Myers *et al.*, 2021) highlight the necessity of a societal transformation involving swift changes in the way humanity produce and consume food, energy and manufactured products. Although the end goal of Planetary Health is anthropocentric in the sense that it aims to sustain human life, it requires a structural transformation towards ecocentrism, where the impact of humanity on the natural environment is reduced and the value of ecosystems is fully appreciated.

The significant overlaps between One Health and Planetary Health and the calls to break down silos may warrant the idea of convergence. While it must be avoided that One Health and Planetary Health become new silos, the research contributions provided in this synthesis are meant to highlight the importance of both perspectives. The differing vantage points of One Health and Planetary Health are both valuable for Global Health and Public Health as a whole. Here it is important to highlight that Global Health is considered a sub-discipline of Public Health, while One Health and Planetary Health are approaches utilized within (and beyond) these disciplines. It can be considered that Planetary Health encompasses One Health, as the human-animal relationship is one aspect leading to environmental degradation, while land-use changes and agricultural expansion also influence this relationship and in turn produce health effects. At the same time One Health goes beyond the scope of Planetary Health, as also the influence of the human-animal bond on non-communicable diseases and mental health are considered (Turner and Hediger, 2021). Thus, there is a risk that convergence reduces the approaches to their smallest common denominator. Rather than converging One Health and Planetary Health, collaboration between the two should be sought. For this it is important to understand and appreciate the different vantage points of the approaches and indicate which approach should be used for which purpose.

The selected publications provide some indication for the applicability of the individual approaches to specific global health challenges. COVID-19, as an example for an emerging disease outbreak, illustrates the importance of One Health. Monitoring and surveillance in humans, animals and environmental compartments are essential for early-detection and containment. Collaboration between human and veterinary medicine is important to control zoonotic disease outbreaks and development of One Health structures is, therefore, an integral component of an outbreak response system. However, it appears that One Health is mostly reactive, in the sense that it develops systems and structures to detect spillovers, contain and respond to outbreaks, and prevent pandemics. The approach is less concerned with tackling the underlying driving forces leading to increased risk of spillovers. Here the Planetary Health perspective comes into play. From this perspective spillover events are considered a symptom of humanities adverse impact on the environment. Deforestation, habitat destruction, intensification of livestock production, land-use changes are just a few examples of how humanity has been creating the ecological pressures favoring zoonotic spillovers. In this sense, Planetary Health can be considered proactive, as the root causes are addressed. Both perspectives are valuable and are required in parallel to achieve the most sustainable impact. Whilst for One Health pandemic preparedness is a primary goal, reducing the risk of zoonotic spillovers would be one health effect of the great (societal) transformation demanded by Planetary Health.

Although, One Health and Planetary Health have significant thematic overlap, they provide distinct perspectives that are both required to tackle the complex global health challenges of the 21st Century. The operationalization of One Health develops structures that monitor and respond to disease outbreaks at the human-animal interface, integrating actors from human and veterinary medicine, agriculture, wildlife, environment and society. Research within the sphere of One Health will thus always focus on disease issues at the human-animal interface. Planetary Health, on the other side, is fueling a social movement that is demanding a great transformation in the way humanity lives on Earth. The focus is less on individual diseases, but rather on health impacts of specific environmental issues. Planetary Health interventions tackle the causes of environmental destruction and pollution, while inducing health benefits as a side effect. As the required great transformation demanded by Planetary Health cannot be achieved in the short-term, it is essential to also develop One Health systems that manage and control the adverse health effects. Therefore, both approaches are important and need to be pursued in parallel.

3.1 Conclusion

The Anthropocene is marked by a “Great Acceleration” of human impacts on Earth systems. These are manifesting in a multitude of direct and indirect health risks that require integrated health approaches for their prevention and control. Multiple such approaches have emerged over the past decades, the most prominent being One Health and Planetary Health. Although the two approaches overlap thematically and methodologically, they represent distinct perspectives that are both important to deal with the complex health challenges of the 21st Century. The One Health approach entails collaboration between human and veterinary medicine, as well as the environmental and agricultural sectors for the monitoring and control of zoonotic diseases and other health challenges at the human-animal-environment interface. Planetary Health, on the other hand, views anthropogenic environmental degradation as a fundamental determinant of health. In consequence, the focus of the approach lies on specific environmental challenges or factors and the assessment tries to understand both the impacts of these on health, as well as the underlying societal factors driving environmental degradation. Planetary Health seeks and contributes to the "Great Transformation", while One Health is concerned with controlling and managing imminent health threats. Therefore, both approaches are required to meet the health challenges of the Anthropocene.

4 Summary

The health challenges of the 21st Century are determined by complex interplay between economic, ecological and social systems. Human socio-economic development has not only resulted in immense gains in life expectancy and prosperity, but has come at the expense of unsustainable resource extraction, deforestation, and environmental degradation. As a result, solutions to current health challenges cannot solely be found in the bio-medical sector, but require interdisciplinary and integrated approaches. The most prominent approaches are One Health, Planetary Health and Global Health. Although these show significant overlaps in scope and methodology, distinct differences between them are evident. Initially it is important to highlight that Global Health can be considered a sub-discipline of Public Health, whilst One Health and Planetary Health are approaches applied within and beyond Global Health. A primary difference between One Health and Planetary Health lies in their disciplinary origin, which influences the vantage point from which the issue as assessed. Whilst One Health originated from veterinary medicine, Planetary Health evolved from environmental and conservation science. Resultingly, One Health focuses on the human-animal interface, while Planetary Health assesses the influence of humans on the environment and *vice versa*. Both approaches have been critiqued for neglecting the respective other dimension, i.e. One Health neglecting the environmental dimension and Planetary Health neglecting the animal dimension, leading to expansion of the approaches. In consequence, the dividing lines between the approaches are increasing blurred. Whilst various authors call for convergence of the two approaches, here the distinct importance of each approach is illustrated. Utilizing the examples of emerging diseases, antimicrobial resistance, neglected tropical diseases, and water pollution, the perspective of each integrated health approach is highlighted. As most emerging and re-emerging diseases, including the recent COVID-19 pandemic, are zoonotic, One Health is considered the ideal approach for its management and control. Particularly, the establishment of integrated surveillance systems involving humans, animals and environmental compartments form a primary One Health measure. A Planetary Health approach shifts the focus from early-detection and preparedness towards identification of root-causes and prevention. Human destruction of ecosystems and habitats, as well as encroachment into natural environments and biodiversity loss are considered risk factors for disease emergence and transmission. A Planetary Health intervention to mitigate disease emergence, therefore, involves environmental protection and conservation. Similarly, antimicrobial resistance is best managed by a One Health approach, as it requires collaboration and coordination between human and veterinary medicine as well as the agricultural sector. Planetary Health assesses the environmental fate of antimicrobials, as well as the impact on aquatic and soil ecosystems and the resulting human health impact. The case of schistosomiasis, as an example for a neglected tropical disease, highlights distinct interventions. From a One Health perspective, controlling the intermediate snail vector forms a primary intervention strategy, while from a Planetary Health perspective, the influx of human fecal matter and the resulting water contamination are considered as underlying driving factor. Interventions would thus focus on reducing open defecation by developing sanitation infrastructure. The examples illustrate that One Health is a more reactive approach, concerned with managing and monitoring disease outbreaks and health issues, while Planetary Health is rather proactive, aiming to tackle the causes of environmental destruction and pollution, and creates health benefits as a side effect. As the great transformation demanded by Planetary Health will not be achieved in the short-term, the development of One Health systems to manage and control the adverse health effects is essential.

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