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Title:

Advancing One Human-Environmental-Animal Health for Global Health Security: What does the evidence say?

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The ongoing COVID-19 pandemic vividly illustrates that the emergence of a new lethal pathogen of probable animal origin in one part of the world affects public health everywhere. In this article, we review the contributions of human-animal-environmental (ONE-HEALTH [OH]) approaches to improving global health security (GHS) across a range of health hazards and summarise contemporary evidence of incremental benefits of an OH approach and impact on reporting to FAO, OIE and WHO. Using IHR (2005) Monitoring and Evaluation Framework and OIE Performance of Veterinary Services Pathway (PVS) reports, case studies and a narrative literature review, we assess progress of inter-sectoral OH approaches to build human capacity, bridges between stakeholders and institutional adaptation at national and international levels to contribute to global health security (GHS) across a range of health hazards. Examples from joint health services and infrastructure, surveillance-response, antimicrobial resistance (AMR) surveillance, food safety and food security, environmental hazards, water and sanitation, and zoonoses control clearly show incremental benefits of OH approaches. OH approaches appear to be most effective and sustainable in the prevention, preparedness and early detection of evolving risks/hazards and the evidence base for their application is strongest in the control of endemic and neglected tropical diseases. Significant gaps remain at the OH interface to rapidly detect and reduce the risk of widespread community transmission of new and re-emerging infections. For benefits to be maximised and extended, improved One Health Operationalisation (OHO) is needed with strengthening of multisectoral coordination mechanisms, for example by fostering a closer interaction between the IHR (2005) and OIE PVS Pathways. Case studies show evidence for OHO at the institutional and community level. The FAO, OIE and WHO currently play pivotal roles in stimulating OHO at the national and regional levels but will need increased support and allies to both strengthen current activities as well as address a wider set of health hazards across the Socio Ecological System. Progress in sustained OHO should be urgently prioritised at global, regional and national levels by building on, and inclusively broadening existing institutional collaborations at the wildlife-domestic animal-environmental-human interface to better reflect evolving risks and hazards across the Socio-Ecological System.

Keywords: One Health, Global Health Security, International Health Regulations, Performance of Veterinary Services Pathway

Key messages:

1. **One Health means that cooperation between human, animal, environmental health and related disciplines leads to benefits that could not be achieved if the different sectors work alone. There is clear evidence for benefits in terms of saved lives of humans and animals and financial savings from a closer cooperation between the sectors across a range of hazards and operational functions. Our analysis indicates greater investment**

should be directed towards prevention and preparedness interventions across the SES where the evidence base is most firmly established. This represents a shift of the disease control paradigm upstream, away from an overwhelming focus on surveillance and response in humans which currently predominates, to greater and more pro-active investment in preventive interventions, surveillance in environmental and animal systems and integrated response across all sectors.

2. **OH has a high potential to sustainably improve GHS for all by first prioritising national and local capacity building across One Health sectors and disciplines. This horizontal approach should first focus on endemic One Health issues across the ecosystem including those with implications for food security, local community health needs and hazards where the evidence base is most strongly established before considering emergent risks of more global concern.**
3. **There is still a daunting gap to fully operationalize One Health for optimal GHS. As the evidence for its effectiveness broadens, current and future OH approaches should more fully integrate environmental and wildlife issues across the Socio Ecological System (SES) to better address contemporary challenges like pandemic risks.**
4. **Many national governments have started operationalizing One Health in their governance and programmes, which are increasingly reflected in reporting to the International Health Regulations (IHR 2005). The IHR have been an effective catalyst to embed cross sectoral, whole system approaches to public health emergency prevention, preparedness and response but an evidence-led acceleration of implementation and expansion across a wider spectrum of SES hazards is now needed.**
5. **The international organizations World Health Organization (WHO), World Organization for Animal Health (OIE) and the Food and Agricultural Organization of the United Nations (FAO) spearhead One Health technical cooperation at the global level. The addition of United Nations Environmental Program (UNEP)to that collaboration represents an opportunity to to more holistically provide technical support to national governments in building their One Health related health security capacities.**
6. **Further primary research and systematic reviews are needed to evaluate the effectiveness of One Health approaches for specific hazards categories across the SES. These should include analyses on cost effectiveness, comparisons of uni-sectoral versus multisectoral approaches and include relevant outcome measures relating to animal and environmental health, in addition to the primary concerns around human health security.**

INTRODUCTION

Human development, expansion of domestic animal populations and transformed landscapes engineered for human populations are having profound effects on the evolution and epidemiology of infectious and non-communicable diseases of all species. Intimate and rapid global interconnections mean that uncontrolled infectious diseases in one part of the world threaten plant, animal (wildlife and domestic) and public health everywhere. Whilst technological advances are making public health services better equipped for detecting, preventing and controlling new infectious diseases and other health hazards, as the current COVID-19 pandemic highlights, major gaps exist in conversion of these advances into effective actions and policies at the animal-human-environment interface[1]. National institutions addressing these challenges worldwide are most often not able to adequately address the myriad array of interconnected risks. There have been numerous human-animal-environmental health approaches to improving global health security (GHS) across a range of health hazards. The ongoing COVID-19 pandemic vividly illustrates, that the emergence of a lethal pathogen of probable animal origin in one part of the world affects public health everywhere.

The Food and Agriculture Organization (FAO), World Health Organization (WHO) and the World Organisation for Animal Health (OIE), support countries to implement international standards and frameworks, such as the International Health Regulations (IHR, 2005), the Terrestrial and Aquatic Codes and Manuals[2] and the Codex Alimentarius (food safety law)[3]. The revised IHR came into force in June 2007 and required all countries to develop core capacities for preventing, detecting and responding to public health emergencies including for infectious agents that can impact the public health of people across countries and adversely affect travel and trade. The IHR promoted building robust public health and animal health systems based on good governance and implementation of internationally accepted standards.

In 2010, a Tripartite concept note between WHO, OIE and FAO recognised a shared responsibility in addressing health risks at the human-animal (wildlife and domestic)-environment interface, with avian influenza, rabies and antimicrobial resistance (AMR) as priorities. The shared views of these international organizations contributed strongly to mainstreaming integrative approaches like One Health (OH) (**Box 1**) that contribute towards global health security (GHS), taking advantage of the legal mandate of the IHR (2005) as a driving force[4,5]. To support countries in developing regulations, assessing their capacities to prevent, detect and rapidly respond to public health risks, WHO developed the IHR Monitoring and Evaluation Framework (IHR MEF)[6], which includes inter alia the i) State parties reporting tool for the mandatory annual reporting of level of compliance to the IHR, and ii) the Joint External Evaluation (JEE) for voluntary reviews with peers. The COVID-19 pandemic is an extraordinary reality check for GHS and calls for a review of the effectiveness of these instruments and other tools for assessing national capacities as well as challenging the assumptions around the operational value of integrated approaches like One Health. [7].

In this article, we review the contributions of human-animal-environmental (ONE-HEALTH [OH]) approaches to improving global health security (GHS) across a range of health hazards. We summarise contemporary evidence assessing the incremental benefits of an OH approach and how this evidence is reflected in reporting to FAO, OIE and WHO. We identify gaps which remain at the OH interface to rapidly detect and respond to the risk of widespread community transmission of new and re-emerging infections and other health hazards. Through examples from the field we build the case for One Health Operationalisation (OHO) and strengthened multi-sectoral coordination mechanisms. As the IHR adopts an all-hazards approach to GHS, our paper reviews the literature to determine which of the WHO's priority threats to global health[8] would benefit from an OH approach using the classification of hazards outlined in the WHO Health Emergency and Disaster Risk Management Framework[9]. We performed an analysis of the contributions of OH approaches to GHS using a variety of methods detailed in online supplement 1 (S1).

Historical aspects of OH (723 words)

OH appeared for the first time in the medical literature in 2005 to emphasize its potential to strengthen health systems[10] by demonstrating value added from a closer cooperation between human and animal health that could not be achieved by the disciplinary approaches alone[11]. This point however revealed the fragmentation of the health communities and differing agendas and much of the ensuing years have been fraught with debate and discussion about what exactly OH is about. **Box 1** summarises current OH theoretical foundations and applied methods for demonstrating the incremental benefits of the approach are outlined in **Boxes 2 and 3.** [12] The first paper to use the term OH in 2005 stated, with regard to avian influenza, that: "research for vaccines should urgently be complemented by modifications to smallholder livestock systems and live-animal markets to prevent or reduce interactions between [wildlife] and [livestock], which might be reservoirs for future human pandemics"[10]. "However, these implementations should be handled carefully to avoid impending poverty…". This warning, published 15 years ago in *The Lancet*, sounds like a forecast in the face of the current COVID-19 pandemic, but remained largely unheard with a limited global response to preparedness. This may still be a narrow view on how these emergent pathogens are established. Certainly it is not just the transmission and interface which matters but also the socioecological and economic context in which these occurrences happen, enabling expansion and establishment of pathogens across species, much of which happens in the domestic and peri-domestic landscape[13,14].

Conceptual relationship of OH, EcoHealth and PH

As such there remains an acute need for a proper framing of integrative concepts like OH, EcoHealth or Planetary Health (PH) to promote a better integration across sectors[15] including, importantly, wildlife health which often necessitates being distinguished from animal health where the focus is almost entirely on domestic animals, both legally, economically and practically[12]. OH's conceptual

relationship to related ecosystem approaches to health (EcoHealth) and PH are explained in **Figure 1.** a **Figure 2** shows the "One Health-ness" spider diagram of a semi-quantitative assessment of the level of OH operation and infrastructure in a given hypothetical context adapted from[16.] and relates to earlier graphical depictions[12,15]. In Figure 1, OH is in the first place at the intersection of human (red ellipse) and animal (currently primarily domestic) health (green ellipse), aiming to demonstrate a benefit from a closer cooperation of human and veterinary medicine. Clearly, there are large sections of separated human and animal health not requiring an OH approach. Broader approaches, considering interactions of health and the environment, within social-ecological systems (SES)[17] incorporate OH. OH is thus embedded within ecosystem approaches to health, for which a newer term "Health in Social-Ecological Systems" (HSES) has been coined[18]. SES are most often delimited by a given context of a country or a region (black ellipse). OH, by the definition of this paper, includes social and environmental (ecological) factors, which are depicted by the yellow gradient circle, reaching beyond the limits of public and (domestic) animal health.

A first step in operationalising this element will be the proper incorporation of wildlife health, ecosystem science and its actors into the community. The yellow gradient symbolizes the overlap and expanding transition to the health of the whole SES, identifying appropriate proxy indicators for monitoring SES, growing the evidence base and recognizing its contribution to supporting efforts to achieve the United Nations sustainable development goals (SDG), especially SDG-3[19]. It is also in line with the Berlin principles[20], including mitigation of the causes and adaptation to the impacts of climate change[21]. Planetary Health (PH) sets the ambitious task of understanding the dynamic and systemic relationships between global environmental changes and health including climate change, transboundary fire emissions, persistent organic pollutants and other changes[22] (blue ellipse). PH conceptual thinking aims to identify co-benefits across targets, but remains centred on human health and does not explicitly include animal health[20,22].

PH can be seen as a historical extension from global health and international health. PH attempts to demonstrate linkages of global environmental change and health, which are hard to prove, based on the inherent data variability, confounding factors, and the duration and scale of the phenomena (Equation 5, Box 2). Thus OH should be still in the centre of interest, building inter-sectoral cooperation from the inside and gradually expanding it to more complex issues and health security hazards across the whole of the SES, as the evidence base for its effectiveness matures [16,23].

Evidence for the benefit of OH

While there is consensus that the OH approach is crucial for tackling challenging global health security threats, it is not yet clear that evidence of its effectiveness has been reliably demonstrated. OH characterises the logical view that by coordinating the people and systems working to improve the health of humans, animals and the environment, any associated health threats can be identified as

early as possible. This results in reduction or even prevention of harm to health and fewer resources required to deal with the long-term repercussions. There is evidence of benefits of OH across a range of health hazards[9] for health services, newly emerging and endemic zoonoses control in the domestic animal environment, food safety and food/nutrition security, integrated disease and antimicrobial resistance (AMR) surveillance-response systems, water security and sanitation, infrastructure sharing and communication[21]. For example, joint human and animal routine vaccination services for mobile pastoralists in Chad provide access to health care for populations which would otherwise be excluded and save financial resources by sharing cold chain and transport[24]. Mass vaccination of livestock against brucellosis in Mongolia is not cost effective for public health alone, but when benefits for livestock production and nutrition security are also included it is financially three times more profitable[25] (Formula 3, Box 2). Combining dog vaccination with human post-exposure prophylaxis in an African city is less costly than human post-exposure prophylaxis alone after ten years [26,27] and may lead to the elimination of rabies (Formula 4, Box 2).

The Institute of Medicine (IOM) in 2009[28], and later the World Bank, conceptualized integrated surveillance response in a visionary way, as a time sequence of detection in the environment, wildlife, domestic animals and humans (**Figure 3a**)[29]. The model shows ever increasing costs the later a new emerging pathogen is detected[21,30]. The current COVID-19 pandemic could not be a better example of the urgent need for the kinds of integrated environment-entomological-wildlife-domestic animal-human surveillance and response systems that the World Bank proposes, and the catastrophic socio-economic consequences of failure to implement such systems. There are several examples of the potential benefit of more targeted surveillance of vector borne zoonoses. The integrated surveillance and response of West Nile Virus in mosquitos, wild birds, horses and humans in Emilia Romagna region (Italy), saved more than one million Euros between 2009-2015 compared to separate human and animal surveillance[31]. Wielinga et al. similarly argue that inter-sectoral surveillance has had a significant impact on reducing human salmonellosis through lowering *Salmonella* prevalence in animals[32] citing research which described how disease control was achieved in Denmark through integration of control measures in farms and food processing plants, saving 25.5 million USD [33].

The Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) saves financial and infrastructural resources and reduces time to detection of newly emerging AMR[18,34]. The CIPARS was able to demonstrate the impact of regulating antimicrobial use on the number of resistant salmonella isolates identified in humans and chickens[35]. A decrease in the number of *Salmonella heidelberg* isolates coincided with the introduction of a voluntary ban on the use of ceftiofur in Quebec, with a subsequent increase when the antibiotic was partially returned to use. Without such integrated surveillance systems, it would not have been possible to determine the impact and cost effectiveness of interventions designed to reduce AMR in human and livestock populations.

The World Bank estimates a saving of 26% of the operations cost of the Canadian Science Centre in Winnipeg, which hosts laboratories for human and animal highly contagious diseases under one roof, when compared to running two separate laboratories for human and animal diseases[36]. The outbreak of Q-fever in the Netherlands (2007-2009) with several thousand human cases could probably have been largely avoided if the veterinary and public health authorities had maintained continuous communication[37] (**Figure 3a**), or if joint human and animal studies had been done, as they were in the case of brucellosis in Kyrgyzstan[38] (**Box 2**). These examples demonstrate that where capacity exists in both animal (domestic) and human health to address these issues, progress is made. The under-resourced wildlife environment interface remains a major challenge to applied One Health approaches.

As food safety and nutrition security cuts across human, animal and environmental concerns, OH is similarly considered key to multi-sector coordinated progress[39]. The limited research in this area reinforces the importance of coordinated responses but only seldom supports the benefit of OH with consistent evidence of effectiveness, whether in terms of directly attributable improvement to health outcomes or financial savings. Meanwhile the burden of food borne disease is well established: according to the WHO Foodborne Disease Burden Epidemiology Reference Group (FERG), 31 foodborne hazards were estimated to have caused more than 600 million illnesses and 420,000 deaths globally in 2010.[40,41]. The World Bank describes an example of 'applying One Health' to foodborne disease (FBD) in the European Union's coordination of control programs for salmonellosis. The evidence provided is a reduction in reports of human salmonellosis cases from over 200,000 before 2004 in 14 member states to under 90,000 cases in 2014. Integration is described as the involvement of member states and four major institutions (the European Commission, the European Parliament, the European Food Safety Authority, and the European Centre for Disease Prevention and Control), while methods highlighted as key to success range from target reductions to salmonella in livestock to the imposition of trade restrictions[42].

The direct impact of funding provided to integrated systems was assessed by the World Bank using data from FERG. This compared the 'adequacy' of operational funding for veterinary services, based on OIE PVS reports, and found that the burden of foodborne disease caused by Animal Source Foods (ASF) was lower in sub-Saharan African countries with adequate funding, with 208 disability adjusted life years (DALYs) per 100,000 population vs. 569 DALYs per 100,000 population in countries with inadequate funding[42].

In the same report, the World Bank identified only seven countries from low or lower-middle income countries with adequate operational funding for their veterinary services (based on PVS reports). The burden of FBD in these countries was 192 DALYs per 100,000 people, compared to 407 per 100,000 in the 48 other low and lower-middle income countries observed[42]. These findings were translated into productivity losses of approximately 95 billion USD (based on their assessment of 2016 income data) due to illness, disability, and premature deaths related to unsafe food[42]. Despite these published

examples emphasising improvements to food safety/security as a result of an applied OH approach, the evidence, or lack of evidence, does not allow improvements to be directly attributed to any particular measure. This is unsurprising given the multi-sector, systems-based nature of OH which cannot be studied in isolation and therefore cannot easily adjust for the impact of confounding factors.

Emerging evidence from sewage analysis in the UK and elsewhere suggests that a One Health approach to COVID-19 transmission risk at the human/environmental interface could inform both case detection efforts as well as measures to prevent potential transmission via wastewater[43]. Given suggestions that the COVID-19 pandemic will result in annual UK borrowing this year at five times the amount borrowed in the previous financial year[44], One Health measures which work to identify and control potential sources of infection would prove to be cost-effective.

These examples across the spectrum of disease control from prevention to preparedness, detection and response clearly show the benefits of OH approaches across a range of health hazards. In order for such benefits to be maximised and extended, we need a better and more sustained OHO. The United Nations Environment Program (UNEP) recently joined the Tripartite to address the wildlife environment interface, which is a strong signal for a stronger integration of the environmental dimension of health. This opportunity to integrate the environmental sector more fully opens up an exciting new array of potential partnerships and interventions to improve GHS. For example, the piloting and scaling up of biological control programmes for emerging and endemic infectious diseases has the potential to add new tools to the GHS armoury[45,46]. Already in use widely to support vector borne disease control in malaria programmes, the use of biological controls can be further expanded to help control endemic neglected diseases such as shistosomiasis, through the introduction of cercariae devouring river prawn species[47], to the use of larvivorous fish species and predatory copepods to reduce and prevent dengue transmission as demonstrated successfully in Vietnam[48]. Here in particular, OH approaches across the SES are necessary to test these types of interventions and help describe the complex interplay between host-pathogen -vector-natural predator and their impact on other species within the ecosystem. Environmental science can also help support the control of invasive plant species such as mesquite (*Prosopis juliflora*), which are implicated in maintaining mosquito populations in the dry season[49] and driving malaria, rift valley fever and dengue transmission, while also taking over vast areas of grazing and farmland, outcompeting native vegetation preferred by livestock resulting in large numbers of poisoned cattle and goats, and ultimately depleting water sources[50]. Ironically, the plant was introduced for supporting livestock agriculture by international development agencies, the focus on forage for small ruminants in particular, with sectoral benefits but without consideration of the wider ecological impacts – underscoring the need for wider environmental expertise when testing interventions. With COVID-19 highlighting the intimate links between populations density, urban health and pandemic spread, air quality management for the control of respiratory illness and co-morbid conditions has become a priority for policy makers[51]. Here too, environmental science along with urban planners can play an

important role in advancing a OH approach with the introduction of plant and tree species that specifically reduce air pollution[52]. This way, strategies and plans can be aligned, for example, towards a global solidarity for the control of zoonoses and other diseases across the human-animal-environment interface (**Figure 3b**), analogous to the Global Fund to Fight AIDS, Tuberculosis and Malaria[5].

Relevance of OH for IHR (2005) and OIE PVS

Our analyses of WHO IHR MEF and OIE PVS reports show: 1) further appropriation of the use of the term OH in the global evaluation tools and reporting in relation to IHR and PVS, which can be linked to 2) an increased awareness of the relevance of OH for global health security and the use of this terminology or its essence in the language of national leaders and politicians, 3) that despite the progress made in integrating OH for GHS, the IHR MEF would benefit from a separate category in which the operationalisation of OH is systematically evaluated, 4) a certain vagueness of the commonly used definition that allows for mobilising global and local stakeholders from different sectors, but may render the evaluation of its operationalisation more challenging. This is particularly relevant in the definitions of Animal Health which currently in practice excludes non-domestic animals to a large degree.

In the implementation of the IHR MEF, WHO puts forward their collaboration with FAO and OIE in order to support bridging the human-animal interface for the implementation of the IHR for global health security. Tools such as the IHR-PVS National Bridging Workshop have been developed in order to support this joint review[53].

Many of the WHO members state identified gaps with regard to their OHO, also with reference to the recommendations by the team of experts in the JEE reports. The narratives of some of the countries point to their limitations in their current *ad hoc* collaborations based on emergencies or their focus on multi-sectoral approaches with regard to a particular disease. These are aspects that WHO describes as "vertical" approaches, and the aim would be to achieve more "horizontal" and sustainable solutions[54] for disease surveillance and global health security. In order to make progress within the policy cycle, partnership between public institutions and a myriad of private sector actors is required, to establish robust health systems which meet the needs of society. For example, the integration of emerging infections and health impact assessment into the environmental impact assessment process for large scale industrial and land transformation projects could be one area where public-private sector collaboration could be key in mitigating the risk of emerging infectious diseases while also helping companies manage their business continuity risk. Struggles to provide (human) resources for establishing sustainable mechanisms for multi-sectoral collaboration were mentioned at several stages in the available reports, while external long-term funding enabled particularly successful foundation

for some of the national OH mechanisms mentioned in the reports (see, for example, the case study on Côte d'Ivoire in S2).

While OH in forms of multi-sectoral collaboration or external coordination found its way into the discourse of the policy documents evaluating countries' IHR implementation, our analysis also reveals some vagueness in the definition of the term OH. As mentioned earlier, such a "productive vagueness" is not necessarily considered as a disadvantage as it may facilitate communication among different social worlds. At the same time, however, it may prevent active engagement if global as well as local actors interpret their existing activities as already within the scope of OH. One Health, in this capacity may also be described as a "soft global health governance"[55], dependent on peer influence of global and local actors rather than the pressure of law[56]. Governance issues are discussed in greater detail in paper four of this series.

Multisectoralism is highly promoted and clearly advocated in the JEE tool and the voluntary request by countries may already reveal a certain commitment to OH, transparency, multisectoral engagement and responsibility to take a systems approach to building the core capacities required under IHR (2005). The available data from the JEE reports therefore also have to be read in this light, and it is noticeable that a high proportion of completed JEE missions have been conducted in African countries (total number 44), revealing particular priorities and aspects linked to donor funding of such missions. In addition, it is important to take into account the different methodologies and the variable quality control that is inherent to the different reporting tools.

The JEE could be advantageously complemented with a tool rating the level of a country's OHO, such as network for evaluation of OH (NEOH), keeping in mind that other tools such as the IHR-PVS National Bridging Workshops (NBW) can complement by helping countries developing concrete roadmaps to improve performance at the human-animal interface[4]. An additional category in the SPAR reporting could be advantageous as this compulsory evaluation is performed annually by all member states and could therefore provide a global overview of countries' self-assessments of their OH-ness on a regular basis.

The newest development of the current COVID-19 pandemic shows that a global technical (WHO-FAO-OIE-UNEP) and political coordination (United Nations) of pandemics is crucial, especially when taking into account the current global context with multiple actors and interests involved on different scales (**Box 4**).

Certainly, the JEE and the other elements of the IHR MEF, along with other existing tools such as the Global Health Security Index, require improvements to adequately assess country preparedness and response capacity to all public health hazards – by adoption of a broader vision of OH more in keeping with a holistic HSES framework. As such, the IHR MEF will likely need to be revisited if OH is to be firmly embedded in the future and the gaps in the all-hazard approach can be closed as far as possible.

Considering the above examples of the benefit of OH and the analysis of the relevance of OH for IHR (2005) we can summarize the evidence that OH approaches work for tackling GHS risks and hazards as follows: For emerging infections and novel pathogens there are OH institutional (governance) arrangements and engagements, but only episodic effective integrated wildlife-domestic animal-human surveillance and response programs[31,57]. There is an appalling weakness and much need for improvement of OHO, as shown in the current COVID-19 pandemic. Most of the current research reactively focuses on vaccines and drugs with very little on how to prevent future pandemics. For AMR there are important institutional efforts and engagement and more and more nations implement integrated AMR surveillance programs analogous to the Canadian CIPARS. One Health oriented AMR control programmes have certainly benefitted from greatly increased levels of funding despite the evidence base for these approaches being relatively weak. For endemic infections and Neglected Tropical Diseases (NTD), there is a strong evidence base for OHO, including control programs and proof of economic benefits. Institutions and engagement are well established, but still require a stronger political will for example for rabies[58] or brucellosis elimination[59]. OHO for food safety and nutrition security, institutions and engagement are well established. Surprisingly there is little formal analysis of incremental economic benefits of OHO for food safety and nutrition security, requiring more research. There is a clear shortfall of evidence of OHO for extreme weather, water security and environmental degradation despite the wide array of expertise, experience and insight the environmental sciences have to offer. The recent joining of United Nations Environment Program (UNEP) of the Tripartite FAO/WHO/OIE, becoming a quadripartite engagement is a most welcome extension towards environmental and ecological sectors and actors. The same applies also for the prevention of emerging infections and novel pathogens (see below). Across all the hazard groups, the evidence base was most strongly established for prevention and preparedness interventions using a One Health approach versus those relating specifically to response. **Table 1**, summarises the strength of the current evidence base of applied One Health approaches across a range of health security hazards based on the reviewed literature and JEE/PVS reports analysed in this paper

DISCUSSION

Outlook on future OHO

The conclusions of the current state of OHO are mixed. Although excellent in themselves, institutions, laws and capacities even if intending to do otherwise, globally fail to integrate environmental risk factors of all types and or consider the role of the natural systems (wildlife) in both preventing and promoting microbial evolution and pathogen emergence. There are significant efforts to operationalize OH by many countries, as shown by the case studies (S2) however, there is still a long way to go towards mainstreaming of OHO[60] with sustainable (programmed) budgetary implications to

make it effective in the immediate and long term. This is of concern in the face of the current COVID-19 pandemic, which outweighs by a factor of several tens of thousands the cost of the preventive effect of effective OHO. To demonstrate this conceptually, we use the World Bank [30] framework of **Figure 3a** as a starting point. We modified it to include environmental risk [21] as a vision for OH in Global Health Security (**Figure 3a-c**) and its longer term effects (DALYs) to society and households. In essence, the figure shows how the cumulative societal cost increases from earliest detection of emerging pathogens of zoonotic origin from both wildlife and domestic animals until it reaches human populations. The earlier a novel pathogen, food security risk or other SES-relevant hazard (e.g. impending drought/natural hazard) can be detected (reduced time to detection) and the faster information is communicated between animal and human health sectors, the earlier an effective response, preventing exposure and reducing risk of transmission, can be organized and the lesser are the cumulative societal costs of the outbreak or emergency (**Figure 3b-c**). **Figure 3c** would be the final desirable expected stage of global health security through an OH approach. Despite existing environmental threats and some animal exposure, fewer human cases would be observed and cost could be kept at a minimum[61]. This is in keeping with our analysis of hazards across the GHS spectrum (table 1) which indicate that the evidence base favours shifting the paradigm of disease control upstream from the current focus on detection and response in humans, to prevention and preparedness across the SES. This is the avenue where global OHO can lead in the prevention of future pandemics and other health emergencies[62].

This "early detection-early response (EDER)" framework can be used as a backbone for the OHO within the IHR (2005) and can be evaluated by the four instruments of a revised IHR MEF.

Within GHS, not all global health threats health[8,63] can be analysed by this EDER framework alone when grouped into hazard categories. Some of these hazards and risks are more amenable or relevant to being addressed through an OH approach than others and any linked investment should be based on evidence of effectiveness. Advancing OHO would also require the use of different methodological approaches in specific Animal-Human Interfaces (AHI)[11],[64]. AHI can use linear[38] or non-linear models[26,65] and different types of cross-sector economic analyses[25,66]. Case examples like the above mentioned West Nile Virus Surveillance in Italy, can be generalized, paving the way to OH economics of integrated disease surveillance-response systems[31,57]. Novel evaluation frameworks[23,67] will need to be included and tested for complementary usefulness to the IHR MEF. OH dimension in the core indicators of the IHRMEF, functional regional platforms, multi-hazard national public health preparedness, epidemiology training programs and disease specific targets could be assessed as a proxy for the current status of national OHO coordination.[61] Where proxy indicators are lacking for more holistic OH-based assessments of the health of the whole SES, these should be developed, and agreed to ensure that the IHR and other GHS initiatives are truly all-hazards in their approach. These considerations around improved monitoring and indicators are further explored in paper three of this Lancet series.

Towards policies and implementation of OHO

OHO at the national level requires regulations for the prevention, preparedness and response to epidemics and other health emergencies and hazards that are written into environmental standards and public health, animal (domestic and wild) health law[68]. This includes the preparation for an early response to crises through mechanisms that engage all relevant government institutions (whole-of-government emergency management), as well as private sector and civil society organizations. OH and its operationalisation should be specifically defined and expanded based on available scientific evidence. A clear purpose of OHO should be expressed with regard to its relationship towards ministries and government. The legal basis of OHO tasks should be specified with regard to community participation, technical support, multi-sectoral coordination, communication, and scientific exchange. The composition of organisational structures for OHO surely includes representatives of community organisations, public (IHR National Focal Points) and animal (domestic and wild) health, environment (e.g. UNEP National Focal Points), industry, city and town planning (e.g. UN HABITAT, UNIDO National Focal Points), agriculture, nutrition and defence at national and provincial level. The involvement of non-governmental organisation, educators and academia (which are often drivers of OH approaches) and the private sector should be specified. The organisation and leadership, for example, in rotation between sectors, should be clarified. Schedules of meetings and standing committees and taskforces are needed. Procedures for coordination, joint prioritization and agenda setting, decision making, implementation and evaluation / feedback are required. Communication and information channels should be clarified between sectors.

Most importantly the funding of OHO has to be negotiated between the different government sectors, along with the potential of cost sharing[25]. Both donor and national OHO funding should be focused sustainably on those hazards where clear benefits of OH approaches have been demonstrated, and which are initially framed around local and endemic hazards where the evidence base on effectiveness is most firmly established and where the various sectoral interests are equitably met. This horizontal approach to OHO at the national and sub-national level is essential for implementation of GHS on the ground. This should be reflected by increasingly harmonised and further developed reporting mechanisms within the IHR (2005) and PVS Pathways (**Figure 3c**) and more comprehensive surveillance and monitoring using indicators of relevance across the spectrum of hazards in the SES. The COVID-19 outbreak clearly shows that besides a global technical leadership, political coordination mechanisms are needed to achieve GHS at national and international levels.

CONCLUSIONS

OH approaches show quantitative incremental benefits for health services and infrastructure, surveillance-response systems, AMR, food safety and nutrition security, environmental sanitation and zoonoses control for GHS, but gaps in the realisation of OH to covers all species of interest remain.

The evidence base is generally strongest for those OH interventions focused on prevention and preparedness across the spectrum of GHS hazards. In order for such benefits to be maximised and extended for GHS, a wider, global operationalisation of OH is needed, which must be budgeted in multiannual national plans and include a larger allocation of resource towards prevention and preparedness. The existing tools of IHR and PVS reporting are working in principle, but they remain insufficient, as the current COVID-19 pandemic shows, and should be further developed to be more effective in future GHS incidents. Specific OH categories in the IHR MEF should contribute to increased fostering of OHO. Certain vagueness of commonly used definitions across the spectrum of hazards and risks, such as zoonoses, require further efforts to better frame integrative health concepts and promote understanding across sectors. The Tripartite international organizations FAO, OIE and WHO play a pivotal role for the expansion, implementation and guidance of OHO at the international and regional level and can encourage and support implementation at national and local levels, although this is ultimately the responsibility of national governments. Further research is needed to demonstrate financial savings associated with OHO similar to the examples mentioned in this paper (S2) and systematic evidence reviews are required of the effectiveness of OH approaches within specific GHS hazard groups. The recent inclusion of UNEP to the Tripartite and the establishment of a One Health high level expert panel[69] is most welcome and would further benefit from the contributions of other institutions such as UN HABITAT, UNIDO to broaden the understanding of ecosystem health and ecosystem services, industrial, rural and urban development and their impact on human and animal agriculture, wellbeing, and welfare. OH has a high potential to sustainably improve GHS for all by first prioritising national capacity building and focusing on local community health needs and hazards before considering those risks of more global concern.

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OD, DH, RK and AZ ideated the Lancet Theme Series on ONE-HEALTH and GLOBAL HEALTH SECURITY and developed the outline articles and selected lead authors. JZ developed the first and subsequent drafts and led the writing of this article. AKG, BB, ED, FC, HB, JH, JL, KHT, LC, OD, RS, SdR, SS, VRV contributed to the content and planning. AKG, FC, JZ, KHT, SdR, VRV contributed to the data collection and analysis; AKG, DM, ED, JZ, KHT, OD contributed to the cases studies; All authors contributed to the writing of the manuscript; AKG, FC, HB, JH, JL, JZ, KHT, LC, OD, SdR, VRV, AZ, RK, DH contributed to the article revision and pre-final editing.

Declaration of interests

All authors have an interest in ONE-HEALTH. All authors declare no conflicts of interest. The views and opinions expressed in this article are those of the authors and not of their institutions.

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LEGENDS

Legends to figures:

Figure 1: Venn diagram Boolean conceptual relationships of OH, EcoHealth, Health in Social-Ecological Systems and Planetary health.

Figure 2: "One Health-ness" spider diagram of a semi-quantitative assessment of the level of OH operation and infrastructure in a given hypothetical context

Figure 3: Vision of One Health governance (OHG) in Global Health Security:
3a) Status quo with very limited collaboration between animal and public health and separated surveillance and response systems.
3b) OHG supported closer collaboration between animal and public health; onset of integrated human-animal-environment surveillance and response systems
3c) Full One Health status with closest possible collaboration between animal and public health and integrated human -animal-environment surveillance and response systems.

Legends to boxes

Box 1. OH background and contemporary theory
Box 2: Quantitative OH methods
Box 3: Qualitative OH methods
Box 4: COVID-19 and OHO

Legend to table:

Table 1, Summary of the evidence that One Health approaches work when tackling critical Global Health Security risks and hazards

WEB APPENDIX

S1 Analysis method of One Health governance
S2 Case studies of One Health governance
ST1 Table One Health Governance appearing in JEE reports
ST2 Table One Health Governance appearing in PVS Pathway reports

Figure 1: Venn diagram Boolean conceptual relationships of OH, EcoHealth, Health in Social-Ecological Systems and Planetary health.

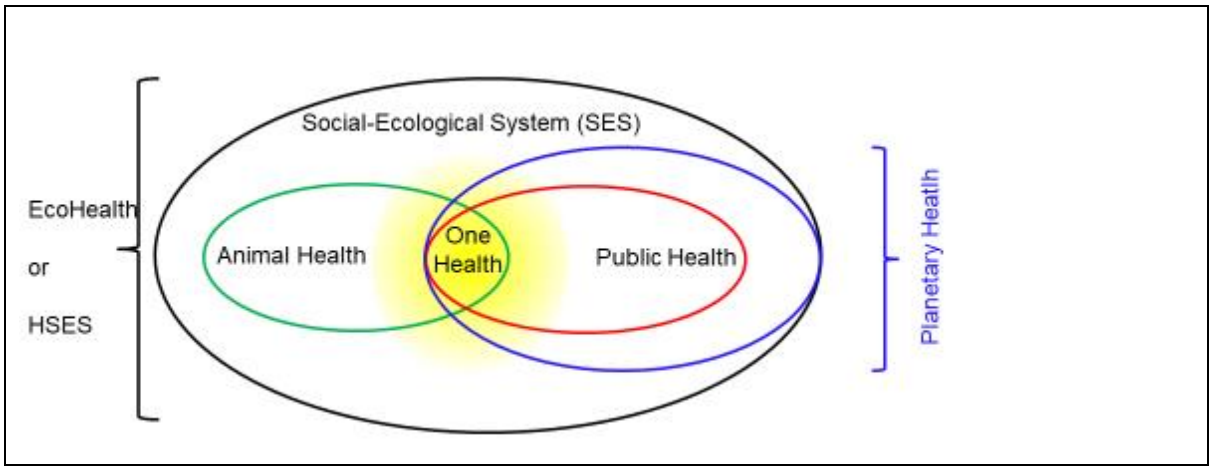

Figure 2: "One Health-ness" spider diagram of a semi-quantitative assessment of the level of OH operation and infrastructure in a given hypothetical context

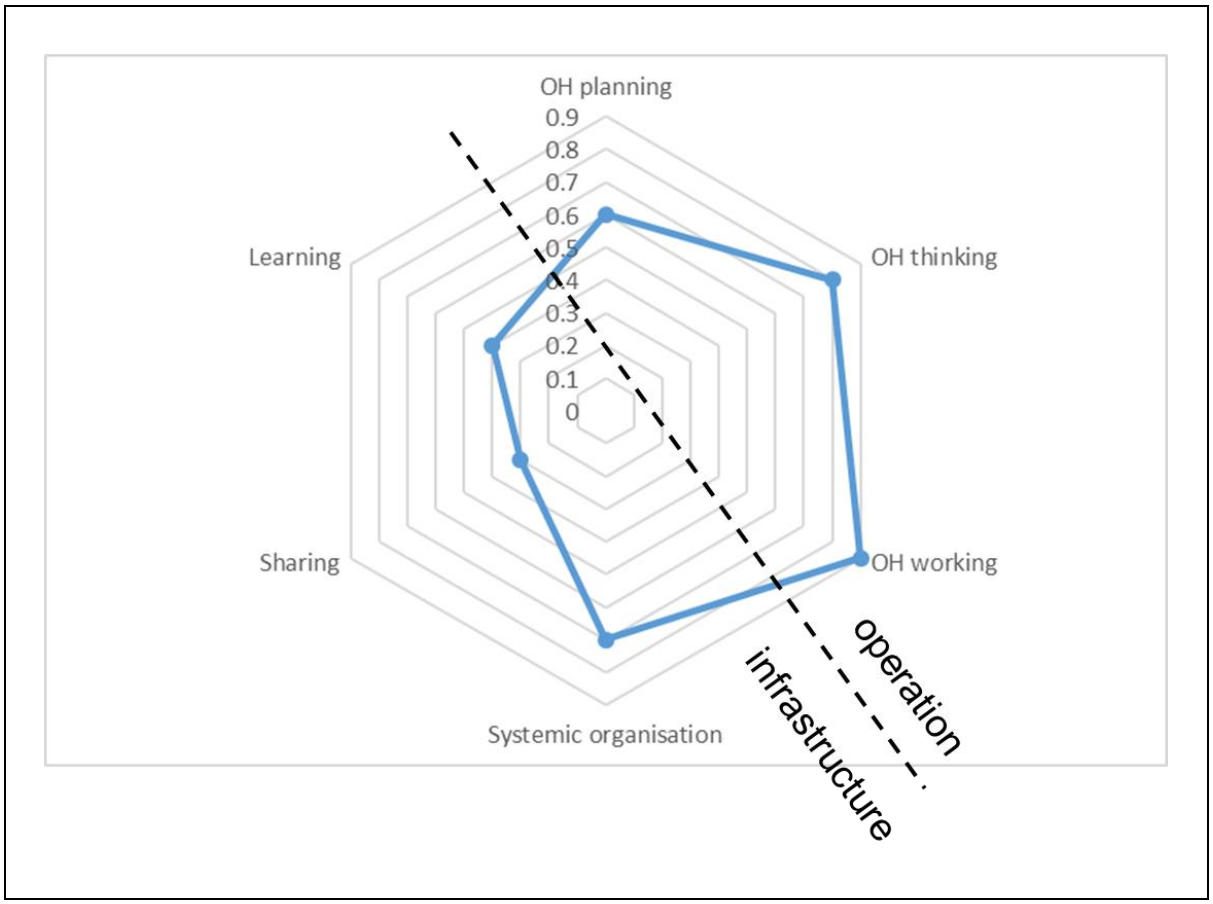

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Figure 3a)

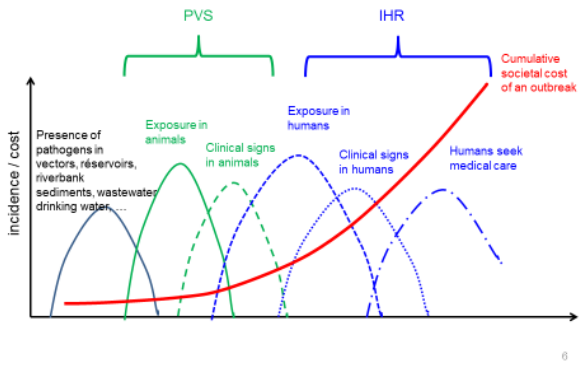


Figure 3b)

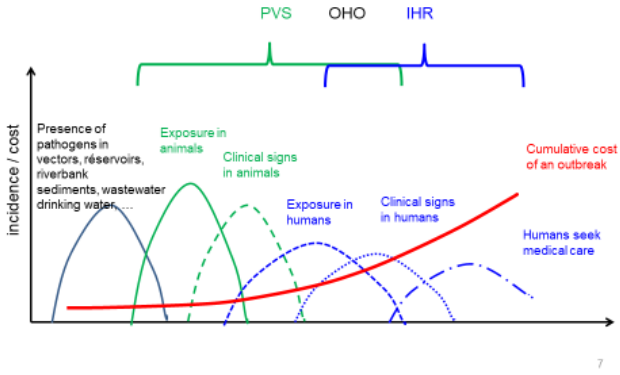
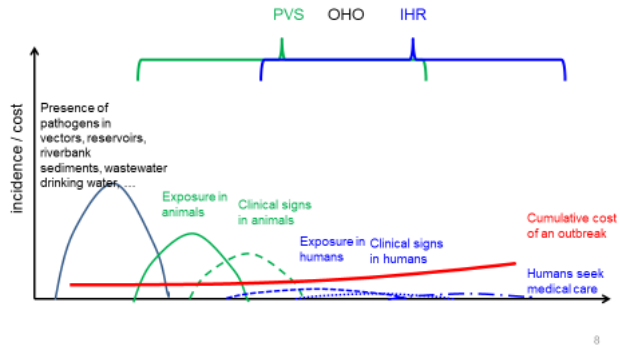


Figure 3c)



Box 1. OH background and contemporary theory

In the 1960s, the veterinary epidemiologist Calvin Schwabe coined the term "One medicine" to focus attention on the commonality of human and animal health interests[70]. Historically, such unifying views are much older[71]. For example, institutional developments such as Veterinary Public Health emerged as a contribution of veterinary medicine to public health in the 1950s[72]. More recently, growing interest in sustainable development has pointed towards the inextricable linkage of human, animal and ecosystem dimensions of health[73-75]. In 2004, the Wildlife Conservation Society (WCS) coined the phrase "One World, One Health™" to underscore the importance of securing human and animal health, ecosystem integrity and the protection of conservation areas under the manifesto of the "Manhattan principles" [76] which were renewed by the "Berlin principles on One Health" in 2019[20].

There has been a range of different adoptions of OH approaches. All of them incorporate human and animal health (although infrequently wildlife), and some also involve contributions from natural and social sciences and the humanities. At its best, OH as a societal problem solving approach, which engages with non-academic actors in the co-production of transformational knowledge for societal problem solving[77,78]. Cooperating partners and stakeholders seek a benefit of working together. A *necessary but not sufficient requirement* for OH is to fully understand systemically, how humans and animals (wildlife and domestic) and their environment are interrelated over all time and space scales. While several definitions of OH have been proposed[12,61], we consider as a *sufficient requirement* for achieving OH to demonstrate benefits resulting from the crosstalk and closer cooperation between human and animal health (domestic and wild) and all related disciplines and stakeholders. This can be expressed as any *added value in terms of health of humans, wildlife, domestic animals and their ecosystems, financial savings, social resilience and environmental sustainability achievable by the cooperation between individuals and institutions working in human and animal health and including other disciplines when compared to the two medicines and other disciplines working separately*[11].

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806 **Box 2: Quantitative OH methods**

Quantitative and qualitative OH methods

Demonstrating incremental benefits of OH requires an understanding of the human / animal health interface. Box 2 describes both linear and dynamic quantitative approaches that have been used to develop the evidence base and demonstrate these incremental benefits in terms of OH (Box 1). Human health H and animal health A can be related as linear regression (Equation 1):

$$H_i = \alpha + \beta_k A_{jk} + e_{jk} \quad (1)$$

Whereby H_i is, for example, the brucellosis seroprevalence status of the i-th human community, related to the brucellosis seroprevalence status A_{jk} of the j-th animal of the k-th species in close spatio-temporal relationship, say a household or a village. The term α is the intercept and e_{jk} the residual in the notation of linear regression. In this way, we could show that human brucellosis seroprevalence in Kyrgyz villages most strongly depended on the brucellosis seroprevalence of sheep and not of goats or cattle in this setting, with behavioural risk factors captured in the residual[38]. The relative importance of sheep for the transmission of brucellosis was confirmed by molecular typing of brucellosis strains[79]. The method is interchangeable in that animal health can also be the dependent on a human health indicator.

For dynamic relationships like the transmission of directly transmitted zoonotic diseases (stage 2[80]), the animal-human interface can be expressed as coupled differential equations in a simplified way, ignoring demographic processes, as Equation 2 for newly infected humans:

$$\frac{dI_h}{dt} = \beta I_a S_h \quad (2)$$

Whereby the instantaneous change of newly infected humans I_h is equal to an animal-human transmission constant β times the number of infectious animals I_a and the number of susceptible humans S_h. Such models allow assessing, for example, the effect of animal mass vaccination on the number of human exposures for brucellosis[81] or rabies[82]. Such models can be expanded to meta-population or contact network models[83,84]. Similarly, such models can also describe the dynamics of human to animal transmission in an interchangeable way.

Cross sector economic analyses show that Benefit-Cost Ratios (BCR) including benefits to humans and animal health are greater than BCR including human health benefits only (Formula 3)[25].

$$\frac{\textbf{Public health and animal benefits}}{\textbf{Intervention cost in livestock}} >> \frac{\textbf{Public health benefits}}{\textbf{Intervention cost in livestock}} \quad (3)$$

Similarly, the Cost-Effectiveness (CE), expressed as cost per disability adjusted life year (DALY) averted, of interventions in animals and humans is higher (i.e. requires less cost per disability

adjusted life year (DALY) averted) than the CE of interventions in humans only, if transmission between animals, and consequently transmission from animals to humans, can be interrupted.[25] In the case of directly transmitted stage 2 zoonoses, it can be shown that the societal cumulative cost of interventions in animals and humans are lower than interventions in humans only (Formula 4).

Cumulative cost$_{(animals\ and\ humans)}$ < Cumulative cost $_{(humans)}$ (4)

This is because, in the case of directly transmitted zoonoses, interventions in animals interrupt transmission between animals and consequently from animals to humans, while interventions in humans alone do not interrupt transmission from the animal reservoir. This has been demonstrated for the example of rabies control by dog rabies mass vaccination in N'Djaména, Chad[27,85]. Such analyses should be context specific to assure local validity. If cross-species transmission is rare, human health benefits may be too low to justify intervention costs in animals[86].

The systemic understanding of human and animal health would benefit from expansions to include parameters of the ecosystems (EcoHealth)[73,74] (**Figure 1**). Dynamic changes of human health, animal health and environmental determinants can again be expressed as coupled differential equations, as in Equation 5.

$$\frac{dI_h}{dt} = \beta I_a S_h + \gamma E S_h + \varepsilon E S_a \quad (5)$$

Newly infected humans I_h depend on the transmission from infected animals I_a and exposure to the environment E (environment-human transmission constant γ) and indirectly from E and susceptible animals S_a (environment – animal transmission constant ε). Equation 5 is applicable for example to the transmission dynamics of human exposure to anthrax *(Bacillus anthracis)* from animals (food), water and other environmental sources. Expansions to ecological determinants are more complex and data variability increases. In a recent study on the dependence of human vitamin A status in pastoralists in Chad, we could demonstrate a link between human serum retinol status and consumed milk, but not between cow milk retinol levels and the level of beta-carotene in the pasture grass[87]. This example shows that eco-systemic studies of human and animal health have the potential for a broader understanding but are more difficult to prove due to the high variability of environmental factors.

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818 **Box 3: Qualitative OH methods**

There are other benefits from OH cooperation that can be difficult to quantify, such as improved insights into complex and context-specific systems, capacity development of institutions and practitioners, or better designed regulatory and non-regulatory interventions generating confidence and resulting social cohesion. By expanding the integration of health towards broad social-ecological issues like antimicrobial resistance or deforestation, complex interactions can become "wicked" and untractable. Rüegg et al. state: "There is a need to provide evidence on the added value of these integrated and transdisciplinary approaches to governments, researchers, funding bodies and stakeholders"[16,23]. The network for evaluation of OH (NEOH) proposes a qualitative and semi-quantitative evaluation and knowledge framework addressing OH operations and infrastructure like Thinking, Planning, Working, Sharing, Learning and Systemic organization within a policy and intervention cycle[16]. This involves a number of components. A OH index is proposed as a spider diagram, whose surface can be calculated and expressed as the so called "One Health-ness" of a program or health system (Figure 2). NEOH has further developed an OH knowledge integration approach to support international health governance[67] (see also below Relevance of OH for IHR). The OH index has been applied to West Nile virus surveillance in Italy[57]. An OH policy cycle analysis allows the assessment of different stages of OH policy development and governance by reviewing systemic thinking and transdisciplinary processes developing target and transformation knowledge for policy development. This is the basis for OH agenda setting, policy formulation and decision making which leads to implementation and evaluation as an iterative process[16,23,67]. It is postulated that a truly One Health integrative approach, not yet achieved in any health sector, will reduce the risk of the global community suffering further pandemics and health crises that cripple the world's economies and cause hardship to rich and poor communities and considerable loss of life.

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833 **Box 4: COVID-19 and OHO**

The COVID-19 pandemic clearly shows that GHS cannot be disconnected from socio-economic wellbeing, whether poor or rich, and consequently public health and economic imperatives have to be balanced against the detrimental socioeconomic impact of pandemic prevention measures at local, national and global levels[78,88]. Vulnerabilities to infectious disease emergence and pandemics like COVID-19 exist at all scales from local to global with implications for all sectors of business and society. There appears to be a paradox between health and wellbeing related development goals and a consumption driven economic model purporting to help achieve these through ever increasing intensification and efficiency of production. Ultimately, more research is needed on how we can adapt the largely consumption driven economy towards a more ecologically and socially sound economy, reducing the risk of new pandemics of zoonotic origin while maintaining essential livelihoods.[78]

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Table 1, Summary of the evidence that One Health approaches work when tackling critical Global Health Security risks and hazards *(based on consensus view of the authors)* .

		Strength of evidence				
		No evidence/little evidence	Limited	Medium	Strong	Very strong
Health security risks/ hazards	Emerging infections and novel pathogens including AMR			XXX		
	Endemic Infections and Neglected Tropical Diseases				XXX	
	Food safety and food/nutrition security			XXX		
	Extreme weather, water security and environmental degradation				XXX	

Colour coding for boxes in table:
blue (prevention/preparedness measures) green (detection/surveillance measures) yellow (response/service delivery)