Editorial commentary

A One Health approach to predict, monitor and prevent arbovirus infections, an extensive case study from the Netherlands - Editorial

1. Introduction

The pandemic of COVID-19 and the expanding outbreak of Mpox have confronted the world with a risk that had already been highlighted in the years before: the increasing likelihood of new, disruptive global infectious disease outbreaks. Climate change is believed to be a general risk factor for the emergence of novel pathogens and increase in human infections [1,2]. Especially arthropod borne (arbo) infections seem to be influenced by changing temperatures and precipitation [3]. An example of an unexpected arbovirus disease outbreak was the Zika outbreak in 2015 [4]. Zika was first discovered in non-human primates in 1947 in Uganda, but the first known human outbreaks were not reported until 2007, in Gabon and the Pacific [5]. However, the later epidemic spread of Zika virus to a much wider geographic region, was unexpected and led to a devastating epidemic of infant disability in the Americas, resulting from infections of mothers during pregnancy. Moreover, genomic epidemiology studies found that the time of introduction of the virus into the Americas was at least one year before the first cases were detected, as the mild clinical presentation in most cases had not raised any flags and Zika virus diagnostics were not routinely available [6]. Despite massive efforts to contain this outbreak, it spread seemingly unabated and highlighted systemic problems in the level of preparedness with insufficient capacity for essential public health work. Other arboviruses, such as West Nile Virus (WNV), dengue virus (DENV), yellow fever virus (YFV) have also increased in prevalence and geographical distribution in recent years [7,8].

While there is a widespread agreement that global change will impact the spread of arboviruses, only few studies address this concern in an integrated manner. Disease emergence is the result of a complex interplay of factors at the interface of humans, animals, ecosystems and, vectors and viruses, and therefore needs to be studied in an integrated "One Health" manner. Such studies are pivotal for the development of strategies to manage and prevent these arboviral diseases. The Netherlands, with its water-dominated ecosystems, dense populations of humans and livestock, abundant wildlife and busy international transport and travel hubs, is increasingly vulnerable to infectious disease outbreaks. These risk factors, combined with arbovirus research expertise in multiple disciplines and the availability of high-resolution data on key drivers of disease introduction and spread, make the Netherlands an ideal country to study the process of arbovirus disease emergence in an integrated way ("One Health"). Recently, in 2020, the Netherlands experienced the first outbreak of West Nile virus [9], and a few years earlier the related Usutu virus (USUV) was detected [10,11] as well as the first cases of tickborne encephalitis (TBEV; [12–14]. As such, the

Netherlands can serve as a model to further understand the complex interplay underlying arbovirus emergence and spread.

Although USUV and WNV are considered endemic in Europe, we are still unable to predict where the next outbreak will take place and what the requirements are for local virus circulation and outbreaks. To a large extent this is due to a lack of understanding of the external factors (*e.g.*, land use, climate conditions and changes therein), host presence, abundance and behaviour (reservoir hosts, mosquitoes, travel behaviour) as well as the intrinsic factors (host and mosquito virome and immune response), all of which can be important determinants of the success of arbovirus outbreaks. However, studies addressing the ecology and natural history of arboviruses often focus only on a particular part of this complex interplay of actors. This led to the launch of a Dutch One Health research programme (OneHealthPACT.org), in which experts from a range of disciplines, spanning the human, animal, ecosystem interface, aim to improve our understanding of arboviral disease emergence and spread and subsequent interventions.

In this special issue we provide initial results from a suite of studies aiming to generate a better understanding of the deeply complex set of factors that revolve around the emergence and spread of a novel arbovirus, as well as the measures that can be taken to monitor and mitigate the virus. All of this will be discussed in three sections: 1) determinants of vector and ecosystem changes; 2) animal reservoirs and how to monitor them; 3) human health impact assessment and interventions. In this special issue we present the results of the first two years, so many questions remain to be answered. However, already we show the complexity of different hosts, ecosystems and climate and interacting risk factors.

2. The vector and ecosystem component: critical factors that determine the success of arbovirus outbreaks

Variability in environmental factors (temperature, landscape) plays an important role in the ecology of mosquitoes and therefore in suitability of an ecosystem and region for arbovirus emergence and spread. Indeed, Krol et al., show that mosquito (*Cx. pipiens*) abundance and diversity consistently differ among land use- and soil types, depending on rainfall, thus pointing at important landscape covariates [15]. These findings underscore the notion that disease risk is not homogeneously distributed across the landscape, and that variation in local land use and climate are important determinants of mosquito abundances and thereby also likely determinants for disease risk. Mosquito abundance and virus presence during winter were further investigated by Blom et al. to assess their possible role in carry-over of a commonly present

arbovirus that mainly affects birds (Usutu virus) [16]. Contrary to expectations, and despite re-emergence in the summers after, they did not detect any infected overwintering mosquitoes [9]. This begs the question whether the mosquito hibernation route is really the only one for maintaining enzootic presence or whether there are other, less well explored routes. Not only external factors influence transmission dynamics, but there are also intrinsic variables that possibly influence virus replication in mosquitoes. Moonen et al. provide an extensive review on the role of the mosquito virome, mostly consisting of unknown viruses, and how this may interact with known pathogens [17]. In addition, understanding immunomodulatory effects of mosquito saliva and the impact of new mosquito-virus combinations on transmission and disease progression is another key gap in knowledge reviewed in Visser et al. [18].

3. Animal reservoirs and how to monitor them

For most arbovirus surveillance systems, including mosquito, bird and human surveillance, obtaining samples is often time consuming, technically challenging and/or expensive, hampering adequate monitoring and outbreak research. Therefore, part of the research is dedicated towards optimization of sampling designs and detection techniques. Atama et al.*,* therefore set out to find sample types for arbovirus detection that can be collected from birds without disturbing animals or that require specialist knowledge, such as feathers [19]. In another paper in this special issue, Streng, de Best et al identified the multiple barriers for both reuse of existing sample collections as well as active sample collection [20]. Both show the possibility to improve arbovirus surveillance designs without disturbing more animals. Agliani et al., discusses that understanding the clinical and pathological characteristics, along with the mechanisms of disease development of USUV and WNV in different bird species is crucial not only for identifying suitable sentinel species for surveillance but also for the identification of potential pathways that can be targeted for therapeutic and preventative strategies [21]. One poorly understood, but potentially important factor in disease development in birds may be co-infections leading to a possible interplay between different pathogens. Hence, Agliani et al. studied how avian malaria infections (*Haemoproteus spp.*, *Plasmodium spp.*) may impact the severity of USUV infection [22]. Due to the very high prevalence of avian malaria in the study population, no correlations were found but results of this study underscore the need to further investigate this pathway.

4. Human health impact assessment and interventions

De Bellegarde et al.*,* set out to understand the risk to humans of USUV and WNV in the Netherlands, by studying the exposure to arboviruses in bird ringers, using serology. They found that bird ringers more often have antibodies to Usutu virus than community controls [23]. They also show that the interpretation of arbovirus serology is not straightforward and that well-designed cohort studies and testing algorithms are important.

Ultimately, the One Health-PACT project aims to develop intervention strategies that can prevent and mitigate the spread of arboviruses and their public health impact. The publications from the first half of the project already helped gain more insight into the vector-virus-host triad as well as the interplay between ecosystems, hosts and viruses. This will aid in predicting the potential transmission risk of emerging vector-borne diseases. Moreover, found patterns of association may open a more tailored approach to disease mitigation, particularly if these patterns also hold for larger areas. In addition, vaccines can be used as intervention measure to reduce human health impact. This may be applied in risk populations [23]. Therefore, van Bree et al. reviewed recent developments in novel vaccine platforms that can be used to rationally design live-attenuated vaccine candidates [24]. Also, they highlighted the importance of different models for pre-clinical evaluation of safety and protective efficacy, especially implementing challenge models that take into account the possible impact of mosquito saliva on virus transmission and disease progression [18,24].

5. Outlook to the future

Together, the studies presented in this special issue paint a picture of the initial work done within this consortium. In the next two years, the focus will be on integration of knowledge from the different studies, to further understand the complex ecology of arboviruses and to translate these findings into recommendations for policy makers in preparing for outbreaks. Part of the One Health approach is the development of sustainable collaborations between disciplines as well as citizen scientists that provide crucial knowledge [9,25]. This is not an easy task and requires a long term investment in such collaborations, which is challenging in a competitive and often monodisciplinary funding environment. The collaboration built over the past years has allowed for the continuous study of migrating, resident and dead birds [10,11,26,27], which proved instrumental to most papers in this special issue. Such collaborations will prove indispensable if we are to provide a true One Health answer to tomorrow's arbovirus challenges.

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