Emerging arboviral diseases

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Summary

Emerging pathogens pose an important threat to human and animal health. A large proportion of emerging diseases are transmitted by vectors. Recent examples such as Schmallenberg disease, tick-borne encephalitis, Usutu, and West Nile Fever have shown that Dutch livestock, wildlife, and human populations are at risk of outbreaks of emerging vector-borne diseases. Pathogen spillover to new host populations can be the starting point of emergence, but for this to occur, favourable conditions for host, vector, and virus need to align in space and time. The circumstances enabling disease emergence are constantly shifting due to global and local changes for example in human demographics, land use, international travel, and climate.

Given the clear interplay between human, animal, and environmental health, it is crucial to approach the challenge of emerging vector-borne diseases with a One Health perspective. Within the One Health PACT (Predicting Arbovirus Climate Tipping points) research consortium we follow an integrated approach measuring and modelling how projected changes will impact the risk of emergence of arboviruses in the Netherlands, and translating this understanding into effective, integrated outbreak preparedness and response actions.

Samenvatting

Opkomende pathogenen vormen een belangrijke bedreiging voor gezondheid van mens en dier. Een groot deel van de opkomende ziektes wordt overgedragen door vectoren. Recente voorbeelden van introducties in Nederland zoals tekenencefalitis-, Schmallenberg-, Usutu- en westnijlvirus, tonen aan dat ook in Nederland mens en dier risico lopen op uitbraken met opkomende vectoroverdraagbare pathogenen. Het overspringen van pathogenen naar nieuwe gastheerpopulaties kan het begin zijn van verdere transmissie, maar hiervoor moeten gunstige omstandigheden voor zowel gastheer, virus als vector samenkomen qua plaats en tijd. Huidige globale en lokale veranderingen in bijvoorbeeld demografie, landgebruik, internationaal reizen en het klimaat zijn hierop van invloed.

Gezien de sterke samenhang tussen gezondheid van mens, dier en milieu, is het van belang om het probleem van opkomende vectoroverdraagbare ziektes te bekijken vanuit een 'One Health'-perspectief. Binnen het One Health PACT (Predicting Arbovirus Climate Tipping points) onderzoeksconsortium gebruiken we deze geïntegreerde benadering om te meten en modelleren wat het effect is van de verwachte veranderingen op het risico van opkomende arbovirussen in Nederland. Deze kennis wordt gebruikt om voorbereiding en respons op een arbovirusuitbraak te verbeteren.

Background

An emerging infectious disease (EID) can be defined as a disease whose incidence increased over the past decades or is predicted to increase in the foreseeable future. This includes diseases caused by known pathogens, which appear in new host populations or in

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new geographical areas, as well as newly identified pathogens, of which a large proportion spill over from an animal reservoir to the human population[1]. Recently (re-)emerged diseases such as Ebola, avian influenza and COVID-19 have illustrated the significant impact they can have on global human health, animal health, and economies.

A large proportion of EIDs are vector-borne diseases [2]. These diseases are caused by either bacterial, parasitic, or viral pathogens [3]. Examples of bacterial and parasitic vector-borne diseases are Lyme disease (caused by Borrelia) and leishmaniasis. Viral vector-borne diseases transmitted by arthropod vectors, such as mosquitoes, midges, sand flies, and ticks, are called arboviruses. Throughout the rest of this article, the focus will be on arboviruses. Viruses within the Togaviridae, Flaviviridae, and Bunyaviridae families are the main arboviruses causing human disease today [4]. Recent examples of emerging vector-borne diseases such as tick-borne encephalitis, Schmallenberg disease, Usutu and West Nile Fever have shown that also Dutch livestock, wildlife, and human populations are at risk of outbreaks of emerging arboviruses. Recurring outbreaks of Schmallenberg disease caused major issues in sheep, goat, and cattle industries from 2011 onwards [5]. Emergence of Usutu virus resulted in large bird die-offs, mainly in blackbirds, during an outbreak in 2016 and has been circulating in the Netherlands ever since [6]. In August 2020, West Nile virus (WNV) was detected in wild birds and mosquitoes for the first time in the Netherlands [7]. Later that year, the first seven autochthonous human cases were identified [8]. The One Health PACT (Predicting Arbovirus Climate Tipping points) research consortium, which was initiated in 2020, studies factors that lead to vector-borne disease outbreaks in our changing environment, in order to improve our ability to predict, detect and respond to emerging mosquito-borne arboviruses such as WNV and Usutu virus (see Box 1, see page 124).

The increasing risk of arboviruses

Some of the most notorious arboviruses such as Zika, dengue and chikungunya have become increasingly present across the globe in the past decades [9]. While Zika and chikungunya have caused multiple outbreaks mostly in the Americas, Asia, and the Caribbean, dengue is endemic across the globe [9]. The global spread of dengue has increased dramatically since the early 1970s [10]. Urbanisation and global travel are seen as the most important causes for this spread [10]. The abovementioned viruses are mainly transmitted by the mosquito species Aedes albopictus and Aedes aegypti. While these vectors were previously absent in Europe, habitat conditions are increasingly suitable for establishment and expansion throughout the continent [11,12]. Furthermore, local vector species such as Culex pipiens are competent in transmitting multiple arboviruses [13]. The presence of competent vectors, together with the introduction of exotic viruses, has already led to autochthonous clusters of dengue, outbreaks of chikungunya, and endemic circulation of WNV in Southern Europe, as well as WNV outbreaks in the Netherlands and Germany [8,14-18].

To prevent future emergence and spread of arboviruses, research into arboviruses, vectors, potential host reservoirs, and hotspots for virus introduction is essential. The One Health PACT consortium sets out to study the interplay of factors that may lead to arbovirus emergence in changing environments, and aims to translate findings in these research fields into improved outbreak preparedness and response actions (see Box 1).

Transmission and spillover

Arboviruses can be transmitted between different vector and host species. Depending on the role of the host, arboviruses may circulate in wildlife, domestic animals, human populations, or a combination of these [19]. Host species can play various roles in transmission; they can act as a reservoir for the virus; they can amplify an infection if the virus replicates to high levels; or they can be dead-end hosts, meaning they may experience symptoms but do not contribute to onwards transmission. Pathogens can also move from one host population to another, leading to spillover infections. Examples of these are human infections with Rift Valley Fever virus, and equine and human infections with WNV [20].

Spillover arbovirus infections are the first step towards disease emergence. These infections rarely lead to sustained transmission but sometimes they can be the start of a new outbreak if the new host can efficiently transmit the virus onwards to other individuals. Many interacting risk factors for spillover and emergence have been identified on virus, vector, host, and environmental levels, making prediction of emergence challenging [21]. Spillover only occurs when gaps in

Box 1. *One Health PACT*

The One Health Predicting Arbovirus Climate Tipping points (One Health PACT) consortium is a research collaboration of experts in a wide variety of fields relevant for infectious disease outbreaks, ranging from ecological and climate modelling to medical entomology, virology and public health.

The current emerging disease surveillance and preparedness follows an ad-hoc, reactive and fragmented approach, which is ineffective and inefficient. Following from the One Health philosophy, collaborating partners in One Health PACT adopt a pro-active, integrated, multisectoral, One Health approach in studying emerging infectious disease outbreaks. We work on measuring and modelling how projected demographic, climatological, ecological, and landscape changes will impact the risk of emergence of arboviruses in the Netherlands, as a basis to improved outbreak preparedness and response actions.

The One Health PACT consortium includes 26 PhD projects and one post-doctoral research project. These research projects are divided into four pillars, each focusing on a specific part of the overall aim.
Pillar A: Ecosystem mapping
This pillar focuses on the collection and generation of (field) data on different animal species, including mosquitoes and humans. Surveillance of these animals and vectors, performed by researchers or via citizen science will provide critical data for Pillar B.
Pillar B: Forecasting and early detection
Pillar B focuses on the development of multiple models that aim to unravel the complex interplay between different factors in the human-animal-environmental ecosystem. With these models, future changes in 1) climate, 2) water management, 3) farming practices and 4) importation risk of vectors and viruses, will be analysed.
Pillar C: Impact and severity assessment
This pillar will assess the impact and severity of several different arboviruses by using in vitro and in vivo studies in mosquitoes, hosts and other animal models. Vectorcompetence, host range, reservoir potential and transmission dynamics will be studied within this pillar.

Pillar D: Interventions
Using the outcomes of pillars, A, B and C, early warning systems and intervention strategies will be developed. These consist of fieldable diagnostics, intervention strategies focused on vector control and vaccine development. Additionally, protocols and guidelines will be developed to serve as tools for arbovirus preparedness and response at the governmental level.

Partners
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Utrecht University – Faculty of Veterinary Medicine
University Medical Center Utrecht
Wageningen University & Research
Leiden University
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Avans Hogescholen
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Koninklijk Nederlands Meteorologisch Instituut (KNMI)
Red Cross Blood bank Foundation, Curacao
Sanquin – Department of Blood-borne infections
Technasium Foundation
Netherlands Centre for Monitoring of Vectors (CMV)
Deltares
SOVON Dutch Centre for Field Ecology
Municipal Health Service Rotterdam
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all barriers align in space and time (figure 1). Movement, density, and behaviour of vector and hosts determine the probability of contact and exposure [22]. This highlights the importance of a thorough understanding of host and vector ecology, including interaction and competition within and between species. Examples of bottlenecks that prevent spillover from occurring include a lack of temporal overlap in the presence of vectors and hosts, and a limited biting preference of vectors.
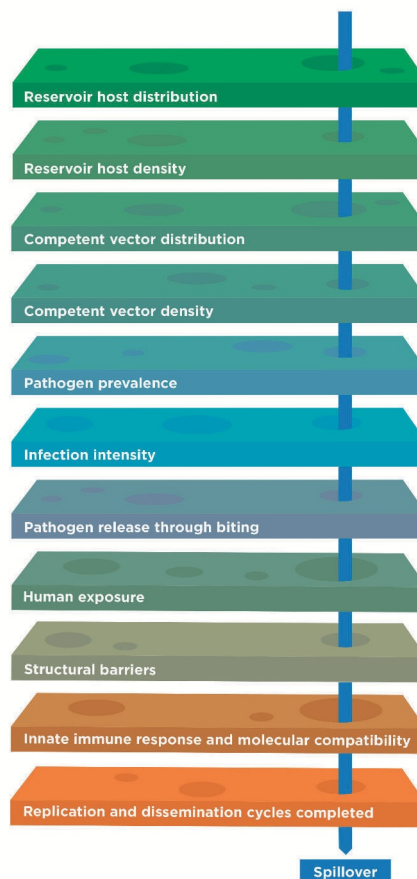
Pathogen characteristics and within-host processes affect the probability that the infection will be transmitted to and replicate in the new host [21,22]. Barriers to infection and dissemination include physical barriers such as skin, absence of receptors that enable pathogen cell entry, and immune responses. These barriers are not only relevant in host species, but physical barriers and immune responses in mosquitoes also play a role. The strength of these barriers may vary between individuals for example due to immunodeficiency or genetic variation [22]. Also interventions, such as vaccination, can affect a host's ability to transmit the pathogen.

The presence and strength of many of these barriers are shaped by the environment in which they occur. However, this environment is constantly changing, making spillover and emergence events difficult to predict. To understand how outbreak risk changes over time, we have to know how the environment has changed in the past and how it might evolve in the future.

A changing environment

Climate change brings warmer temperatures, increasing mosquito metabolic rates and causing them to develop faster [23]. This, combined with a shorter generation internal, faster bloodmeal digestion and a longer mosquito season can lead to higher abundances [24]. Higher temperatures also lead to the establishment of new mosquito species (and consequently new viruses) not previously found in the Netherlands, as the climate becomes more favourable to them [25]. In addition, the infection and transmission rates for some (strains of) viruses increase with temperature [26]; a shorter incubation period means that more mosquitoes will survive long enough to become infectious. Climate change also brings changes in rainfall patterns, which can affect the avail-ability of breeding sites [24].

Urban and natural areas are growing while rural areas are shrinking [27]. This affects all sorts of wildlife, potentially leading them to new habitats and increasing host-vector interactions. In addition, urban habitats contain both a wide range of breeding habitats and plenty of mammal/human hosts, making them particularly favourable to certain Culex spp. mosquitoes (known carriers of WNV, Usutu virus and Sindbis virus) [28].

Changes in other areas, such as agricultural practices, water management, and tourism can all affect vector and host populations. This may be through habitat creation or destruction, changing water quality, transfer of species or viruses to new areas, or a whole range of other factors.

Figure 2. *Multiple global changes in the human-animal-environment ecosystem, creating favourable conditions for arbovirus spillover events and consequently emergence of arboviruses (adapted from Sikkema and Koopmans, 2021 [29]).*

Many drivers of spillover and EID outbreaks have been identified and described in literature (see figure 2). These can be summarised as changes in (1) human demographics, including urbanisation and a growing demand for food production, (2) land use, including farming practices (3) international travel and trade, (4) climate and weather [29]. Understanding these changes is crucial for predicting the future risk of arboviral outbreaks and for planning how to deal with them.

Integrated One Health approach

With these drivers interacting at multiple levels across human, animal and ecosystem health, researchers and policy makers working on EID should embrace an interdisciplinary approach. This One Health approach is essential in preventing, detecting, and controlling spread at the human-animal interface. This need has been recognized by WHO chief Tedros Adhanom Ghebreyesus: "We can only prevent future pandemics with an integrated One Health approach to public

animal health and the environment we share" [30]. In the Netherlands, the One Health PACT consortium is applying this principle in their research into arboviruses, to contribute to a proactive approach to emerging arboviral diseases (see Box 1)

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