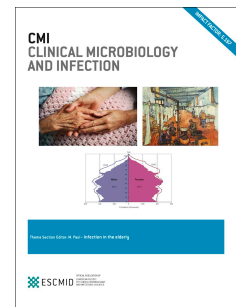


Accepted Manuscript

Laboratory Preparedness and Response with a focus on Arboviruses in Europe

Chantal B. Reusken, Margareta Ieven, Louise Sigfrid, Isabella Eckerle, Marion Koopmans



PII: S1198-743X(17)30683-3

DOI: [10.1016/j.cmi.2017.12.010](https://doi.org/10.1016/j.cmi.2017.12.010)

Reference: CMI 1152

To appear in: *Clinical Microbiology and Infection*

Received Date: 21 October 2017

Revised Date: 8 December 2017

Accepted Date: 12 December 2017

Please cite this article as: Reusken CB, Ieven M, Sigfrid L, Eckerle I, Koopmans M, Laboratory Preparedness and Response with a focus on Arboviruses in Europe, *Clinical Microbiology and Infection* (2018), doi: 10.1016/j.cmi.2017.12.010.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Laboratory Preparedness and Response with a focus on Arboviruses in Europe.

Chantal B. Reusken^{1*}, Margareta Ieven², Louise Sigfrid³, Isabella Eckerle⁴, Marion Koopmans¹

¹Department of Viroscience, WHO Collaborating Center for Arboviruses and Viral Haemorrhagic fever Reference and Research, Erasmus University Medical Centre, Rotterdam, the Netherlands

² Department of Medical Microbiology, Antwerp University Hospital, Antwerp, Belgium, Vaccine & Infectious Disease Institute (VAXINFECTIO), University of Antwerp, Antwerp, Belgium

³Centre for Tropical Medicine and Global Health, Nuffield Dept. of Medicine, University of Oxford, Oxford, UK

⁴Department of Virology, Universitäts Klinikum Bonn, Bonn, Germany

*Corresponding author. Chantal Reusken, Department of Viroscience, Erasmus MC, Wytemaweg 80, Rotterdam. e-mail: C.Reusken@erasmusmc.nl.

Abstract

Background. The global health burden of arboviruses is continuously rising which results in increasing pressure on local and (inter)national laboratory infrastructures. Timely and accurate diagnosis of cases is one of the main pillars for public health and clinical responses to an arbovirus emergence.

Aims and Sources. This narrative review aims to summarize recent advances and to identify needs in laboratory preparedness and response activities, with a focus on viruses transmitted by arthropods in Europe. The review is based on evidence extracted from PubMed searches, Public Health and clinical laboratory experiences from the authors and the authors' opinions substantiated by peer-reviewed scientific literature.

Content. We illustrate the importance of inter-epidemic laboratory preparedness activities to ensure adequate Public Health and clinical responses. We describe the status of arbovirus endemicity and emergence in Europe thereby highlighting the need for preparedness for these viruses. We discuss the components and pitfalls of an adequate laboratory preparedness and response and the broader context of the current landscape of international research, clinical and laboratory preparedness networks. The complexity of arbovirus laboratory preparedness and response is described.

Implications. Outbreak preparedness plans need to look beyond national reference laboratories, to include first-line responding onsite hospital laboratories and plans for strengthening of such local capacity and capability as required depending on the nature of the outbreak. In particular, the diagnosis of arbovirus infections is complicated by the existence of geographic overlap of circulation of numerous arboviruses, the overlap in clinical manifestation between many arboviruses and other etiologies and the existence of cross-reactivity between related arboviruses in serology testing. Inter-epidemic preparedness activities need strong national and international networks addressing these issues.

However, the current mushrooming of European preparedness networks requires governance to bring the European preparedness and response to a next level.

Background.

In the past decade arthropod-borne viral diseases have continued their world-wide geographic expansion and thereby exert an increasing pressure on global health [1]. Arthropod-borne viruses (in short arboviruses) are viruses that replicate in and are transmitted by arthropods, such as mosquitoes, ticks and sandflies, between vertebrate hosts. Arboviruses can cause severe disease in humans and/or animals and are maintained in complex multi-component life-cycles. Through globalization of travel and trade, increasing population density, and possibly under influence of climate change (novel) arbovirus diseases have expanded considerably over the past years [2, 3]. Recent examples of large outbreaks in humans resulting from a fast geographic expansion of arboviruses upon introduction in naïve areas with suitable vectors are the emergence of chikungunya virus (CHIKV) and Zika virus (ZIKV) in the New World in 2013 and 2015 respectively [4, 5], the latter leading to the declaration of a Public Health Emergency of International Concern (PHEIC) by WHO in the period 1 February – 18 November 2016 [6, 7].

During the past decade, arboviruses have been expanding to and within Europe, with autochthonous transmission of dengue virus (DENV) in Croatia, France and Madeira (Portugal), CHIKV in France and Italy, West Nile virus (WNV) in Central and Southern Europe, and the first human cases with Crimean-Congo hemorrhagic fever (CCHF) in Spain [8-17]. In addition in 2016, Usutu virus (USUV), a mosquito-borne bird flavivirus with proven zoonotic potential, has rapidly expanded its geographic coverage in Europe in a multi-country outbreak of multiple virus lineages in birds [18-20]. A recent study in Italy indicated that human USUV infection may not be a sporadic event. USUV infections in patients with or without neurological impairments occurred more frequently than West Nile virus (WNV) infections in a four-year period in Italy [21]. Acute USUV infections have been detected in blood donations in Germany and Austria, raising blood safety concerns [22, 23].

A risk-assessment by WHO-Europe indicated that the risk for an outbreak with ZIKV in Europe should not be underestimated, in particular in countries with established presence of the vectors *Ae. aegypti* and *Ae. albopictus*, [24, 25] although, in contrast to *Ae. aegypti*, field and laboratory evidence do not point to a significant role of *Ae. albopictus* in the transmission of ZIKV [26-31]. While both *Aedes* vectors are established in some parts of South and South-East Europe, other parts of Europe have the established presence of other exotic mosquito vectors [24] in addition to autochthonous vector species e.g. various *Culex* species that vector WNV, USUV and Japanese encephalitis virus (JEV) [32-34]. The 2016 USUV outbreak in North-West Europe showed similarity to the explosive outbreak with the closely related WNV lineage 2, in Central Europe in 2008-2009 and in Greece in 2010 after a few years of limited local circulation [35]. It has been speculated that the expanding emergence of USUV might be a prelude to the emergence of WNV, both with a similar avian-mosquito lifecycle and both being introduced to naïve regions via viremic migratory birds (humans are dead-end hosts for WNV and USUV)[36].

Viremic travelers returning from endemic regions to naïve regions with competent local vectors are thought to have initiated the outbreaks with CHIKV and ZIKV in the America's and the local transmission events with DENV and CHIKV in Europe [9, 16, 17, 37, 38]. Globally the number of yearly travelers has risen from 450 million in 1990 to nearly 950 million in 2010. European Union (EU) Tourism Statistics indicate that in 2014 EU residents above 15 years of age made an estimated 1.2 billion trips (accounting for 2.6 billion nights), of which 6.2% were to destinations outside the EU. Destinations outside Europe made up 14.6 % of all EU outbound trips: 1.8% to Latin America, 3.6% to North America, 4.7 % to Asia, 0.5% to Oceania and 4.0 % to Africa, although the distributions of travel destinations may differ significantly for travelers from different countries [39]. Outbreaks and/or geographic expansion of arboviruses globally are reflected in (periodic) increases in arbovirus diagnosis in returning travelers. An illustrative example is the increase in reported yellow fever cases (n=4) in European Union travelers in the period August 2016 –March 2017 which reflected the increased activity of YFV in South America

[40]. Some virus infections in returning travelers (e.g. CHIKV, ZIKV, DENV) constitute a risk for further spread if competent vectors are present [2, 16, 17, 41]. The majority of ZIKV cases imported into the EU/EEA (n=2130 since June 2015) were found in France (54%) and Spain(14%) where *Ae. albopictus* has an endemic presence [41, 42], indicated by WHO-Europe as risk factor for autochthonous transmission [25]. One of the other identified factors in an European country's risks for a ZIKV outbreak was the ability of a country to robustly detect ZIKV introduction and local transmission [25].

In addition to the above examples of emergence of arboviruses, several other human pathogenic arboviruses are endemic to Europe, such as the tick-transmitted viruses tick-borne encephalitis (TBEV) and Crimean-Congo hemorrhagic fever virus (CCHFV) and mosquito-borne viruses like Sindbis virus in Northern Europe and WNV in the Balkan and Northern Italy. These show occasional peaks in incidences due to variable local biotic and abiotic drivers of emergence [43-50]. Awareness among clinicians and targeted multi-component surveillance is needed to monitor the epidemiology of these viral infections [51].

The emergence of arbovirus disease in the human population is the result of complex processes usually involving animal reservoirs, arthropods and humans, while in a few cases the pathogen has completely adapted to an urban human-mosquito-human cycle (i.e. CHIKV, DENV, urban YFV and ZIKV)[2]. Although the timing is, the nature and geography of emerging disease events is often not completely unexpected [3, 52, 53], e.g. the emergence of CHIKV and ZIKV in the America's and the geographic expansion of WNV, USUV and TBEV in Europe. In this light the world might be facing the emergence of YFV in Asia and of JEV in Africa. Indeed, in April 2017 the first case of autochthonous JEV infection was reported from Angola [54]. These continuously changing dynamics of arbovirus emergence and the rise in its global health burden will increasingly exert pressure on local and (inter)national laboratory infrastructures. As

diagnostics are the pillars of surveillance, individual patient care and (clinical) outbreak response, this asks for inter-epidemic laboratory preparedness.

Laboratory response: disease detection

As human arbovirus disease is an endpoint of a complex infection cycle involving vectors and reservoir hosts, timely detection of arbovirus infections requires multidisciplinary collaboration, including ecologists, entomologists, veterinarians, and wildlife disease experts. Laboratory preparedness and response therefore can be seen as a continuum of activities, one of which is the routine diagnostic capacity for evaluation of illness in humans (Figure 1). For common diseases known to be endemic in a region, diagnostic capacity needs to be available in- or rapidly accessible for- routine clinical laboratories. For rare, exotic diseases diagnostics is generally referred to specialized (inter)national reference laboratories. These reference centers have the expertise to support preparedness and response in its broadest sense, including access to diagnostics for rare viruses and laboratories for Risk Group 3 and 4 pathogens, and research-based monitoring of the evolution of viruses to ensure diagnostic accuracy and development of improved diagnostic platforms. For emerging disease threats with epidemic potential, diagnostic capacity available at reference centers ideally would need to be deployable to clinical laboratories to scale up local laboratory capacity.

The laboratory response to an emerging event needs to be timely, i.e. as early as possible, and accurate, i.e. with high sensitivity and specificity [55-58]. *Timeliness* can be assured by thorough preparedness. Laboratory preparedness should comprise a range of inter-epidemic activities in which barriers and challenges for reference laboratories to rapidly implement diagnostics to emerging pathogens could be addressed. For an *accurate* response, the essential basic questions for diagnostic triage (Table 1) need to be known and if (partially) unknown, these knowledge gaps would need to be systematically identified. Awareness of the existing diagnostic knowledge gaps is important to define a proper

sampling strategy, for an adequate choice of type of test to use and for a correct interpretation of laboratory results and thus correct confirmation or ruling out of an infection [55-58]. Furthermore it can provide guidance to the clinical and public health response where the identified critical knowledge gaps can be addressed [51]. This requires intensive integration and collaboration between these, traditionally often autonomously operating, disciplines. For example during the first phase of the emergence of ZIKV in the Americas, the lack of knowledge on the infection kinetics of ZIKV in various population groups (i.e. pregnant women) was identified by reference laboratories as a crucial gap to be addressed [57] and this issue was a topic of research in numerous clinical studies during the course of the outbreak [59-63].

Laboratory preparedness.

While in theory there is good coverage of clinical diagnostic laboratories and reference centers across Europe [64, 65], a challenge is how to focus the preparedness activities, in view of the expanding list of arboviruses of relevance for Europe and the threat of local outbreaks. Optimal laboratory preparedness constitutes a multi-component approach:

Foresight and the establishment of generic approaches to diagnostic preparedness. A challenging question is how to prioritize the choice of pathogens to develop toolboxes for. Prioritization exercises like the WHO R&D blueprint that prioritizes diseases likely to cause epidemics in the future could provide guidance to these inter-epidemic activities. The January 2017 blueprint included four arboviruses, i.e. ZIKV, CCHFV, RVFV and Severe Fever with Thrombocytopenia Syndrome virus (SFTS) [66]. Another tool that has been developed to inform preparedness activities is the ECDC on-line tool for the prioritization of infectious disease threats [67]. Furthermore numerous short-lists identifying and classifying emerging virus threats have been published in the past two decades [68-73]. The availability of toolboxes for high risk virus groups would facility the laboratory response to novel emerging viruses

as well, e.g. the genus orthobunyavirus, family *Peribunyaviridae* is known to be prone to yielding novel (re-assorted) arboviruses of importance to veterinary and public health [74-76] while a wide range of studies in bats and rodents has taught us that there is still a lot “out there” to surprise the world [71, 77, 78].

Mapping and overcoming logistic and sharing barriers. While there is widespread capacity to develop primer/probe combinations for (RT-)PCR detection, an obstacle for rapid deployment and implementation of laboratory response to an emerging event are the dissemination logistics for international sharing of materials critical for diagnostic set-up and validation, due to accumulating restrictive regulations fueled by biosecurity concerns (“dual-use”) [79] and the Nagoya Protocol on Access and Benefit-sharing [80]. Inter-epidemic preparation of and negotiation on so-called umbrella permits and Memorandums of Understanding together with internationally generally accepted Standard Operating Procedures (SOP) for shipment should facilitate these issues in outbreak situations.

The establishment of sequence data-sharing platforms. With the rapid development of (next generation) sequencing (NGS) approaches, NGS as generic tool for agnostic detection of pathogens has great potential for the emerging infectious diseases field. In this field, sharing of data seems suboptimal, for a range of reasons, including practical, legal, ethical, political barriers [81]. The development and use of data sharing platforms where sequences, preferably linked to essential background information (e.g. date, location, host species, sample type, travel information, clinical manifestation) and bioinformatics workflows are deposited and shared will contribute to an effective laboratory response and overall response to emerging disease events. The sharing of data regarding emerging infectious diseases is not without problems, as it involves multiple stakeholders with different incentives [82,83]. The mapping of barriers to data sharing in order to identify possible solutions is widely debated, with the overall agreement that better systems need to be developed [81-84]. Examples of such data sharing

platforms/networks are the WHO managed DengueNet, the Germany hosted Global initiative for sharing all influenza data (GISAID, [85, 86]), networks managed by national and supranational organizations, and investigator driven platforms for sharing of sequence data and analyses like Genometrack and virological.org [84, 87, 88]. These activities and platforms all share pathogen data and metadata, but the approaches to do so differ greatly.

Quality assurance. Diagnostic laboratories need to comply to accreditation schemes (e.g. ISO15189), which requires extensive validation of assays used, although accreditation requirements differ per country. A specific hurdle to implementation of diagnostics for emerging or newly established infections is that accreditation schemes often do not accept validations done by other laboratories. Clinical samples needed for validation may be difficult to come by when dealing with an emerging disease. In an assessment of the ZIKV laboratory response in European reference laboratories it became clear that although a majority (84%) of laboratories were willing to share their validation data with other laboratories, external validation was only acceptable for 34% of the laboratories [58]. The availability of validation panels and positive controls to assure diagnostic accuracy is generally a major obstacle for a rapid response. Forty-seven percent of the EU/EEA reference laboratories for ZIKV diagnostics indicated that the availability of well-defined serology validation panels was their biggest challenge for implementation of diagnostics closely followed by the lack of positive reference materials (43%) [58]. Of 39 European laboratories responding to an Ebola virus (EBOV) laboratory response questionnaire, 12% indicated the availability of positive reference material as a major obstacle for an adequate response to the EBOV outbreak in West Africa in 2014-2015 (Reusken et al., *in press*). These issues could be addressed during inter-epidemic activities involving general bio-banking of a wide range of well-defined validation cohorts and the establishment of validation data sharing platforms. Bio-banking is addressed for instance by the EU H2020 program EVAg [89]. However, established platforms for timely sharing of validation data are currently lacking. Sharing of such data is mostly done bilaterally between

collaborating laboratories or only too late in the response process through peer reviewed publication, while specialized networks like the ECDC Emerging viral disease expert laboratory network EVD-LabNet [94] and the EU Joint Action EMERGE [95] might facilitate. ZIKV emerged in the America's in May 2015 and the first publications putting serology test validation data in the public domain appeared > 1 year later, with substantial test comparisons even > 2 years later [90-93].

Capability building. A laboratory's capability for accurate diagnosis of endemic and emerging infectious diseases will benefit from training and External Quality Assessments (EQA, proficiency testing). Both EVD-LabNet and EMERGE provide training courses and twinning partnerships, and run EQAs based on needs indicated by their members [96-107]. The role of the diagnostic laboratory in research, Public Health and clinical response to emerging infectious disease events can be trained, optimized (identification of knowledge/response gaps) and secured in multi-disciplinary outbreak simulation exercises [108-110].

Establishment of preparedness networks. All of the above mentioned inter-epidemic preparedness activities need strong national and international networks addressing these issues. In recent years the European scientific, public health and clinical communities have made substantial progress by establishing a number of international networks like the EU H2020 research networks PANDEM [111], COMPARE [112], ERINHA [113] and EVAg [89], and the Public Health oriented ECDC respectively EC DG Santé-endorsed laboratory response networks EVD-LabNet [94] and EMERGE JA [95]. Clinical research response is addressed in the EU research network PREPARE [114] while the public-private partnership in the Zoonoses Anticipation and Preparedness Initiative (ZAPI,[115]) focuses on the design of new, high throughput manufacturing processes for delivering effective infectious disease control tools. A putative pitfall of this increasing number of preparedness and response networks is the lack of interoperability

between these entities. Establishment of collaboration across the disciplines covered by each of these networks would bring the European preparedness and response to a next level.

Laboratory preparedness for arboviruses.

Preparedness and response for arbovirus emergence is quite challenging mainly for three reasons. First, the clinical manifestations of arbovirus infections overlap and are non-specific in the first phase of disease. In general, the broad pallet of arbovirus syndromes are classified in four main syndrome groups: febrile disease, arthralgia and/or rash, hemorrhagic syndrome and neurological syndrome [2, 51, 116]. Second, arbovirus circulation overlaps geographically which complicates narrowing down the necessary diagnostic panel. Diagnosis of arbovirus infections is often mainly based on serological testing as viremia is typically short-lived [2, 117-120]. Diagnosis based on serology however has severe drawbacks due to frequent cross-reactivity between antibodies triggered by closely related viruses or their vaccines while secondary infections might boost levels of cross-reactive antibodies due to previous infections/vaccinations which complicates a proper interpretation of test results (76-78). Illustrative is the current co-circulation of DENV and ZIKV in the America's. Overlap in disease spectrum, geographic presence, and widespread yellow fever virus vaccination make interpretation of diagnostic serology very challenging. In Europe co-circulation of multiple neurotropic flaviviruses, like TBEV, WNV and USUV, and sometimes locally high vaccination grades for TBEV, represent similar issues [57, 117, 121, 122].

Multiple studies have shown that arbovirus illness is underdiagnosed in returning travelers and in endemic areas [123-127]. A syndromic study among > 2000 Dutch travelers with known clinical and travel history demonstrated that clinicians, irrespective of the likelihood of such an infection, rarely requested arbovirus diagnostics for travelers within Europe and overemphasized arbovirus requests for patients with very severe or very specific presentations while the majority of arbovirus infections present in non-specific syndromes [116]. Although commercially available tools exist to provide clinical

laboratories and clinicians with decision support regarding the necessary differential diagnostics [128], the complexities of arbovirus response cannot be reflected in these ranking tools. Therefore an overall underdiagnosis of arbovirus infections is expected while it is simply not feasible (=cost effective) to determine the cause of a disease beyond the most common and treatable etiology.

While expert laboratories for BSL3 and BSL4 arboviruses in the two European laboratory preparedness networks EVD-LabNet and EMERGE aim to provide expertise and reference [58, 101, 129, 130], first line arbovirus diagnostics will also be performed in routine, primary, secondary and tertiary health care-associated laboratories especially in case of an epidemic when scale up of testing is needed. Although there is a broad European coverage at the country level for priority arboviruses in reference laboratories and the capability for their diagnostics in European reference laboratories has been assessed in the past [96, 105, 129, 132, 133], the coverage of and capability for such assays in routine, health-care associated laboratories and the existence of pre-arrangements for scale-up need to be assessed as well to address the level of preparedness for larger outbreaks/epidemics. This will affect outbreak response and individual patient care as in large outbreaks (national) reference laboratories will lack capacity to handle diagnostic requests while timeliness is often only assured with onsite testing in absence of a pre-arranged efficient sample transport infrastructure. At the beginning of 2016, the Brazilian government distributed 500.000 PCR kits for molecular testing for ZIKV to 27 laboratories in the country, and in October 2016 3.5 million rapid serology tests were distributed [134]. However, proficiency testing in parallel to the upscaling of diagnostic capacity is crucial, as major differences in assay performance in EQA assessments of emerging infections have been observed [97-99, 133, 135-137]. For instance, although ZIKV diagnostics were widely covered in Europe in the first phase of the outbreak, an EQA showed that the capability for molecular diagnosis of a ZIKV infection lacked in sensitivity [58, 107].

Conclusion

The overall global and European health burden of arboviruses results in increasing pressure on laboratory preparedness and response infrastructures. As timely and accurate diagnosis of cases is one of the main pillars for public health and clinical responses to an infectious disease emergence, inter-epidemic activities could ensure such adequate response. (Re)emerging infectious disease outbreak preparedness plans should consider the laboratory pillar and be developed in a collaboration between reference laboratories and hospital laboratories, and include planning of the strengthening of such local capacity and capability when needed e.g. in case of an outbreak overloading the national reference system. The current mushrooming of European preparedness networks requires governance; the establishment of collaboration and alignment across the disciplines covered by each of these networks in order to bring the European preparedness and response to a next level.

Acknowledgements.

This work was funded by the European Commission under H2020 grant number 602525 (PREPARE).

Dr. Reusken reports grants from EU H2020, during the conduct of the study.

References.

- 1 Wilder-Smith A, Gubler DJ, Weaver SC, Monath TP, Heymann DL, Scott TW. Epidemic arboviral diseases: Priorities for research and public health. *Lancet Infect Dis*. 2016.

- 2 Cleton N, Koopmans M, Reimerink J, Godeke GJ, Reusken C. Come fly with me: Review of clinically important arboviruses for global travelers. *J Clin Virol.* 2012; **55**: 191-203.
- 3 Liang G, Gao X, Gould EA. Factors responsible for the emergence of arboviruses; strategies, challenges and limitations for their control. *Emerg Microbes Infect.* 2015; **4**: e18.
- 4 Mayer SV, Tesh RB, Vasilakis N. The emergence of arthropod-borne viral diseases: A global prospective on dengue, chikungunya and zika fevers. *Acta Trop.* 2017; **166**: 155-163.
- 5 Leparc-Goffart I, Nougairede A, Cassadou S, Prat C, de Lamballerie X. Chikungunya in the americas. *Lancet.* 2014; **383**: 514.
- 6 WHO. *Who statement on the first meeting of the international health regulations (2005) (ihr 2005) emergency committee on zika virus and observed increase in neurological disorders and neonatal malformations.* WHO. 2016.
<http://www.who.int/mediacentre/news/statements/2016/1st-emergency-committee-zika/en/>
- 7 WHO. *Fifth meeting of the emergency committee under the international health regulations (2005) regarding microcephaly, other neurological disorders and zika virus* WHO. 2016.
<http://www.who.int/mediacentre/news/statements/2016/zika-fifth-ec/en/>
- 8 Vilibic-Cavlek T, Kaic B, Barbic L, et al. First evidence of simultaneous occurrence of west nile virus and usutu virus neuroinvasive disease in humans in croatia during the 2013 outbreak. *Infection.* 2014; **42**: 689-695.
- 9 Tomasello D, Schlagenhauf P. Chikungunya and dengue autochthonous cases in europe, 2007-2012. *Travel Med Infect Dis.* 2013; **11**: 274-284.
- 10 Schaffner F, Mathis A. Dengue and dengue vectors in the who european region: Past, present, and scenarios for the future. *Lancet Infect Dis.* 2014.
- 11 Estrada-Pena A, Palomar AM, Santibanez P, et al. Crimean-congo hemorrhagic fever virus in ticks, southwestern europe, 2010. *Emerg Infect Dis.* 2012; **18**: 179-180.

- 12 ECDC. *Rapid riskassessment: Crimean–congo haemorrhagic fever in spain*. 2016.
<http://ecdc.europa.eu/en/publications/Publications/crimean-congo-haemorrhagic-fever-spain-risk-assessment.pdf>
- 13 Rizzoli A, Jimenez-Clavero MA, Barzon L, et al. The challenge of west nile virus in europe: Knowledge gaps and research priorities. *Euro Surveill*. 2015; **20**.
- 14 Rezza G, Nicoletti L, Angelini R, et al. Infection with chikungunya virus in italy: An outbreak in a temperate region. *Lancet*. 2007; **370**: 1840-1846.
- 15 Gould EA, Gallian P, De Lamballerie X, Charrel RN. First cases of autochthonous dengue fever and chikungunya fever in france: From bad dream to reality! *Clin Microbiol Infect*. 2010; **16**: 1702-1704.
- 16 ECDC. *Ecdc rapid risk assessment; clusters of autochthonous chikungunya cases in italy, 14 september 2017*. ECDC. 2017. https://ecdc.europa.eu/sites/portal/files/documents/14-Sep-2017-RRA-Chikungunya-Italy_0.pdf
- 17 ECDC. *Rapid risk assessment: Cluster of autochthonous chikungunya cases in france 23 august 2017*. ECDC. 2017. <https://ecdc.europa.eu/sites/portal/files/documents/RRA-Chikungunya-France-revised-Aug-2017.pdf>
- 18 Rijks JM, Kik ML, Slaterus R, et al. Widespread usutu virus outbreak in birds in the netherlands, 2016. *Euro Surveill*. 2016; **21**.
- 19 Garigliany M, Linden A, Gilliau G, et al. Usutu virus, belgium, 2016. *Infect Genet Evol*. 2016; **48**: 116-119.
- 20 Cadar D, Luhken R, van der Jeugd H, et al. Widespread activity of multiple lineages of usutu virus, western europe, 2016. *Euro Surveill*. 2017; **22**.
- 21 Grottola A, Marcacci M, Tagliazucchi S, et al. Usutu virus infections in humans: A retrospective analysis in the municipality of modena, italy. *Clin Microbiol Infect*. 2016.

- 22 Allering L, Jost H, Emmerich P, et al. Detection of usutu virus infection in a healthy blood donor from south-west germany, 2012. *Euro Surveill.* 2012; **17**.
- 23 Bakonyi T, Jungbauer C, Aberle SW, et al. Usutu virus infections among blood donors, austria, july and august 2017 – raising awareness for diagnostic challenges. *Eurosurveillance.* 2017; **22**.
- 24 ECDC. *Exotic vectors: Mosquito maps*. ECDC. 2016.
http://ecdc.europa.eu/en/healthtopics/vectors/vector-maps/Pages/VBORNET_maps.aspx
- 25 WHO. *Zika virus, technical report*. WHO Europe. 2016.
http://www.euro.who.int/__data/assets/pdf_file/0003/309981/Zika-Virus-Technical-report.pdf
- 26 Jupille H, Seixas G, Mousson L, Sousa CA, Failloux AB. Zika virus, a new threat for europe? *PLoS Negl Trop Dis.* 2016; **10**: e0004901.
- 27 Di Luca M, Severini F, Toma L, et al. Experimental studies of susceptibility of italian aedes albopictus to zika virus. *Euro Surveill.* 2016; **21**.
- 28 Chouin-Carneiro T, Vega-Rua A, Vazeille M, et al. Differential susceptibilities of aedes aegypti and aedes albopictus from the americas to zika virus. *PLoS Negl Trop Dis.* 2016; **10**: e0004543.
- 29 Hayes EB. Zika virus outside africa. *Emerg Infect Dis.* 2009; **15**: 1347-1350.
- 30 Weger-Lucarelli J, Ruckert C, Chotiwan N, et al. Vector competence of american mosquitoes for three strains of zika virus. *PLoS Negl Trop Dis.* 2016; **10**: e0005101.
- 31 Guerbois M, Fernandez-Salas I, Azar SR, et al. Outbreak of zika virus infection, chiapas state, mexico, 2015, and first confirmed transmission by aedes aegypti mosquitoes in the americas. *J Infect Dis.* 2016; **214**: 1349-1356.
- 32 Engler O, Savini G, Papa A, et al. European surveillance for west nile virus in mosquito populations. *Int J Environ Res Public Health.* 2013; **10**: 4869-4895.

- 33 Platonov A, Rossi G, Karan L, Mironov K, Busani L, Rezza G. Does the japanese encephalitis virus (jev) represent a threat for human health in europe? Detection of jev rna sequences in birds collected in italy. *Euro Surveill.* 2012; **17**.
- 34 Huber K, Jansen S, Leggewie M, et al. *Aedes japonicus japonicus* (diptera: Culicidae) from germany have vector competence for japan encephalitis virus but are refractory to infection with west nile virus. *Parasitol Res.* 2014; **113**: 3195-3199.
- 35 Bakonyi T, Ferenczi E, Erdelyi K, et al. Explosive spread of a neuroinvasive lineage 2 west nile virus in central europe, 2008/2009. *Vet Microbiol.* 2013; **165**: 61-70.
- 36 Nikolay B. A review of west nile and usutu virus co-circulation in europe: How much do transmission cycles overlap? *Trans R Soc Trop Med Hyg.* 2015; **109**: 609-618.
- 37 Faria NR, Azevedo Rdo S, Kraemer MU, et al. Zika virus in the americas: Early epidemiological and genetic findings. *Science.* 2016; **352**: 345-349.
- 38 Cassadou S, Boucau S, Petit-Sinturel M, Huc P, Leparc-Goffart I, Ledrans M. Emergence of chikungunya fever on the french side of saint martin island, october to december 2013. *Euro Surveill.* 2014; **19**.
- 39 EuroStat. *Tourism statisticss-top destinations*. EC. 2015. http://ec.europa.eu/eurostat/statistics-explained/index.php/Tourism_statistics_-_top_destinations
- 40 ECDC. *Rapid risk assessment: Yellow fever among travelers returing from south america.*: ECDC. 2017. <http://ecdc.europa.eu/en/publications/Publications/14-03-2017-RRA-Yellow%20fever,%20Flaviviridae-Suriname,%20Southern%20America.pdf>
- 41 ECDC. *Rapid risk assessment: Zika virus disease epidemic; tenth update, 4 april 2017*. ECDC. 2017. <http://ecdc.europa.eu/en/publications/Publications/21-03-2017-RRA%20UPDATE%209-Zika%20virus-Americas,%20Caribbean,%20Oceania,%20Asia.pdf>

- 42 ECDC. *Zika virus and safety of substances of human origin; a guide for preparedness activities in europe; first update, august 2017*. ECDC. 2017.
<https://ecdc.europa.eu/sites/portal/files/documents/Zika-virus-safety-of-substances-of-human-origin-update-2017-web.pdf>
- 43 Chaskopoulou A, L'Ambert G, Petric D, et al. Ecology of west nile virus across four european countries: Review of weather profiles, vector population dynamics and vector control response. *Parasit Vectors*. 2016; **9**: 482.
- 44 Chancey C, Grinev A, Volkova E, Rios M. The global ecology and epidemiology of west nile virus. *Biomed Res Int*. 2015; **2015**: 376230.
- 45 Brown L, Medlock J, Murray V. Impact of drought on vector-borne diseases--how does one manage the risk? *Public Health*. 2014; **128**: 29-37.
- 46 Hoch T, Breton E, Josse M, Deniz A, Guven E, Vatansever Z. Identifying main drivers and testing control strategies for cchfv spread. *Exp Appl Acarol*. 2016; **68**: 347-359.
- 47 Estrada-Pena A, Ayllon N, de la Fuente J. Impact of climate trends on tick-borne pathogen transmission. *Front Physiol*. 2012; **3**: 64.
- 48 Estrada-Pena A, Jameson L, Medlock J, Vatansever Z, Tishkova F. Unraveling the ecological complexities of tick-associated crimean-congo hemorrhagic fever virus transmission: A gap analysis for the western palearctic. *Vector Borne Zoonotic Dis*. 2012; **12**: 743-752.
- 49 Randolph SE. To what extent has climate change contributed to the recent epidemiology of tick-borne diseases? *Vet Parasitol*. 2010; **167**: 92-94.
- 50 Adouchief S, Smura T, Sane J, Vapalahti O, Kurkela S. Sindbis virus as a human pathogen-epidemiology, clinical picture and pathogenesis. *Rev Med Virol*. 2016; **26**: 221-241.
- 51 Sigfrid L, Reusken C, Eckerle I, et al. Preparing clinicians for (re-)emerging arbovirus infectious diseases in europe. *Clin Microbiol Infect*. 2017.

- Gould E, Pettersson J, Higgs S, Charrel R, de Lamballerie X. Emerging arboviruses: Why today? *One Health*. 2017; **4**: 1-13.
- Kilpatrick AM, Randolph SE. Drivers, dynamics, and control of emerging vector-borne zoonotic diseases. *Lancet*. 2012; **380**: 1946-1955.
- Simon-Loriere E, Faye O, Prot M, et al. Autochthonous japanese encephalitis with yellow fever coinfection in africa. *N Engl J Med*. 2017; **376**: 1483-1485.
- de Sousa R, Reusken C, Koopmans M. Mers coronavirus: Data gaps for laboratory preparedness. *J Clin Virol*. 2014; **59**: 4-11.
- Reusken C, Niedrig M, Pas S, et al. Identification of essential outstanding questions for an adequate european laboratory response to ebolavirus zaire west africa 2014. *Journal of Clinical Virology*. 2015.
- Charrel R, Leparac Goffart I, Pas S, de Lamballerie X, Koopmans M, Reusken C. State of knowledge on zika virus for an adequate laboratory response. *Bull World Health Organ*. 2016; **E-pub: 10 Feb 2016**. doi: <http://dx.doi.org/10.2471/BLT.16.171207>.
- Mögling R, Zeller H, Revez J, Koopmans M, group Zrl, Reusken CBEM. Status, quality and specific needs of zika virus diagnostic capacity and capability in national reference laboratories for arboviruses in 30 eu/eea countries. *Eurosurveillance*. 2017; **In press**.
- de Laval F, Matheus S, Labrousse T, Enfissi A, Rousset D, Briolant S. Kinetics of zika viral load in semen. *N Engl J Med*. 2017; **377**: 697-699.
- Jeong YE, Cha GW, Cho JE, Lee EJ, Jee Y, Lee WJ. Viral and serological kinetics in zika virus-infected patients in south korea. *Virol J*. 2017; **14**: 70.
- Joguet G, Mansuy JM, Matusali G, et al. Effect of acute zika virus infection on sperm and virus clearance in body fluids: A prospective observational study. *Lancet Infect Dis*. 2017.

- 62 Rossini G, Gaibani P, Vocale C, Cagarelli R, Landini MP. Comparison of zika virus (zikv) rna
 63 detection in plasma, whole blood and urine - case series of travel-associated zikv infection
 64 imported to italy, 2016. *J Infect.* 2017.
- 65 Paz-Bailey G, Rosenberg ES, Doyle K, et al. Persistence of zika virus in body fluids - preliminary
 66 report. *N Engl J Med.* 2017.
- 67 ECDC. *Technical report: Core functions of microbiology reference laboratories for communicable
 68 diseases.* ECDC. 2010.
 69 [https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/1006_TER_Core_f
 70 unctions_of_reference_labs.pdf](https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/1006_TER_Core_functions_of_reference_labs.pdf)
- 71 ECDC. *Disease and laboratory networks.* ECDC. 2017. [https://ecdc.europa.eu/en/about-
 72 us/partnerships-and-networks/disease-and-laboratory-networks](https://ecdc.europa.eu/en/about-us/partnerships-and-networks/disease-and-laboratory-networks)
- 73 WHO. *R&d blueprint; list of priority diseases.* WHO. 2017.
 74 <http://www.who.int/blueprint/priority-diseases/en/>
- 75 ECDC. *Ecdc tool for the prioritisation of infectious disease threats.* ECDC. 2017.
 76 [https://ecdc.europa.eu/sites/portal/files/documents/Tool-for-disease-priority-
 77 ranking_handbook_0_0.pdf](https://ecdc.europa.eu/sites/portal/files/documents/Tool-for-disease-priority-ranking_handbook_0_0.pdf)
- 78 Havelaar AH, van Rosse F, Bucura C, et al. Prioritizing emerging zoonoses in the netherlands.
 79 *PLoS One.* 2010; **5**: e13965.
- 80 Taylor LH, Latham SM, Woolhouse ME. Risk factors for human disease emergence. *Philos Trans
 81 R Soc Lond B Biol Sci.* 2001; **356**: 983-989.
- 82 Olival KJ, Willoughby AR. Prioritizing the 'dormant' flaviviruses. *Ecohealth.* 2017; **14**: 1-2.
- 83 Olival KJ, Hosseini PR, Zambrana-Torrel C, Ross N, Bogich TL, Daszak P. Host and viral traits
 84 predict zoonotic spillover from mammals. *Nature.* 2017; **546**: 646-650.

- Palmer S, Brown D, Morgan D. Early qualitative risk assessment of the emerging zoonotic potential of animal diseases. *BMJ*. 2005; **331**: 1256-1260.
- Krause G, Working Group on Prioritisation at the Robert Koch I. Prioritisation of infectious diseases in public health--call for comments. *Euro Surveill*. 2008; **13**.
- Tilston-Lunel NL, Shi X, Elliott RM, Acrani GO. The potential for reassortment between oropouche and schmallenberg orthobunyaviruses. *Viruses*. 2017; **9**.
- Beer M, Conraths FJ, van der Poel WH. 'Schmallenberg virus'--a novel orthobunyavirus emerging in europe. *Epidemiol Infect*. 2013; **141**: 1-8.
- Aguilar PV, Barrett AD, Saeed MF, et al. Iquitos virus: A novel reassortant orthobunyavirus associated with human illness in peru. *PLoS Negl Trop Dis*. 2011; **5**: e1315.
- Luis AD, Hayman DT, O'Shea TJ, et al. A comparison of bats and rodents as reservoirs of zoonotic viruses: Are bats special? *Proc Biol Sci*. 2013; **280**: 20122753.
- Moratelli R, Calisher CH. Bats and zoonotic viruses: Can we confidently link bats with emerging deadly viruses? *Mem Inst Oswaldo Cruz*. 2015; **110**: 1-22.
- Drew TW, Mueller-Doblies UU. Dual use issues in research - a subject of increasing concern? *Vaccine*. 2017.
- CBD. *The nagoya protocol on access and benefit-sharing*. CBD. 2014. <https://www.cbd.int/abs/>
- Aarestrup FM, Koopmans MG. Sharing data for global infectious disease surveillance and outbreak detection. *Trends Microbiol*. 2016; **24**: 241-245.
- WHO. *Developing global norms for sharing data and results during public health emergencies*. WHO. 2015. http://www.who.int/medicines/ebola-treatment/data-sharing_phe/en
- WHO. *Policy statement on data sharing by the world health organization in the context of public health emergencies*. WHO 2016. http://www.who.int/ihr/procedures/SPG_data_sharing.pdf

- 84 GLOPID-R. *Glopid-r makes data sharing a top priority*. GLOPID-R. 2017. [https://www.glopid-](https://www.glopid-r.org/find-out-about-our-work/data-sharing-working-group/)
- 85 r.org/find-out-about-our-work/data-sharing-working-group/;
- 86 GISAID. *Gisaid*. GISAID. 2017. <https://www.gisaid.org/>
- 87 Shu Y, McCauley J. Gisaid: Global initiative on sharing all influenza data - from vision to reality. *Euro Surveill*. 2017; **22**.
- 88 WHO. *Denguenet*. WHO20017. 2017. <http://www.who.int/csr/disease/dengue/DengueNetFlyer2006.pdf>
- 89 Allard MW, Strain E, Melka D, et al. Practical value of food pathogen traceability through building a whole-genome sequencing network and database. *J Clin Microbiol*. 2016; **54**: 1975-1983.
- 90 EVAg. *European virus archive goes global*. EVAg. 2015. [https://www.european-virus-](https://www.european-virus-archive.com/)
- 91 archive.com/)
- 92 Huzly D, Hanselmann I, Schmidt-Chanasit J, Panning M. High specificity of a novel zika virus elisa in european patients after exposure to different flaviviruses. *Euro Surveill*. 2016; **21**.
- 93 Steinhagen K, Probst C, Radzimski C, et al. Serodiagnosis of zika virus (zikv) infections by a novel ns1-based elisa devoid of cross-reactivity with dengue virus antibodies: A multicohort study of assay performance, 2015 to 2016. *Euro Surveill*. 2016; **21**.
- 94 Granger D, Hilgart H, Misner L, et al. Serologic testing for zika virus: Comparison of three zika virus igm-screening enzyme-linked immunosorbent assays and initial laboratory experiences. *J Clin Microbiol*. 2017; **55**: 2127-2136.
- 95 L'Huillier AG, Hamid-Allie A, Kristjanson E, et al. Evaluation of euroimmun anti-zika virus igm and igg enzyme-linked immunosorbent assays for zika virus serologic testing. *J Clin Microbiol*. 2017; **55**: 2462-2471.

- 94 EVD-LabNet. *European expert laboratory network for emerging viral diseases*. . EVD-LabNet.
2016. <https://www.evd-labnet.eu/>
- 95 EMERGE. *Emerge ja: Efficient response to highly dangerous and emerging pathogens at eu level*.
EMERGE JA. 2016. <http://www.emerge.rki.eu>
- 96 Grunow R, Ippolito G, Jacob D, et al. Benefits of a european project on diagnostics of highly
pathogenic agents and assessment of potential "dual use" issues. *Front Public Health*. 2014; **2**:
199.
- 97 Domingo C, Escadafal C, Rumer L, et al. First international external quality assessment study on
molecular and serological methods for yellow fever diagnosis. *PLoS One*. 2012; **7**: e36291.
- 98 Domingo C, Niedrig M, Teichmann A, et al. 2nd international external quality control assessment
for the molecular diagnosis of dengue infections. *PLoS Negl Trop Dis*. 2010; **4**.
- 99 Donoso Mantke O, Aberle SW, Avsic-Zupanc T, Labuda M, Niedrig M. Quality control assessment
for the pcr diagnosis of tick-borne encephalitis virus infections. *J Clin Virol*. 2007; **38**: 73-77.
- 100 Donoso Mantke O, Lemmer K, Biel SS, et al. Quality control assessment for the serological
diagnosis of dengue virus infections. *J Clin Virol*. 2004; **29**: 105-112.
- 101 Donoso Mantke O, Schmitz H, Zeller H, et al. Quality assurance for the diagnostics of viral
diseases to enhance the emergency preparedness in europe. *Euro Surveill*. 2005; **10**: 102-106.
- 102 Ellerbrok H, Jacobsen S, Patel P, et al. External quality assessment study for ebolavirus pcr-
diagnostic promotes international preparedness during the 2014 - 2016 ebola outbreak in west
africa. *PLoS Negl Trop Dis*. 2017; **11**: e0005570.
- 103 Pas SD, Patel P, Reusken C, et al. First international external quality assessment of molecular
diagnostics for mers-cov. *J Clin Virol*. 2015; **69**: 81-85.
- 104 Escadafal C, Avsic-Zupanc T, Vapalahti O, et al. Second external quality assurance study for the
serological diagnosis of hantaviruses in europe. *PLoS Negl Trop Dis*. 2012; **6**: e1607.

- 105 Escadafal C, Olschlager S, Avsic-Zupanc T, et al. First international external quality assessment of
106 molecular detection of crimean-congo hemorrhagic fever virus. *PLoS Negl Trop Dis*. 2012; **6**:
107 e1706.
- 108 Escadafal C, Paweska JT, Grobbelaar A, et al. International external quality assessment of
109 molecular detection of rift valley fever virus. *PLoS Negl Trop Dis*. 2013; **7**: e2244.
- 110 Charrel R, Mogling R, Pas S, et al. Variable sensitivity in molecular detection of zika virus in
111 european expert laboratories; external quality assessment, november 2016. *J Clin Microbiol*.
112 2017.
- 113 WHO. *Polio outbreak simulation exercise*. WHO. 2015.
http://www.euro.who.int/__data/assets/pdf_file/0004/290407/Polio-Outbreak-Simulation-Exercise.pdf
- Geering W, Glyn Davies F, Martin V. Traing, and testing and revision of contingency plans. In:
Geering W, Glyn Davies F, Martin VJ, eds. *Fao animal health manual: Preparation of rift valley fever contingency plans*. Rome: FAO 2002; 61-63.
- 110 ECDC. *Ecdc public health training section ;catalogue 2017-2018 ecdc continuous professional development programme*. ECDC. 2017.
https://ecdc.europa.eu/sites/portal/files/documents/ECDC%20Training%20Catalogue%20_2017_2018_outline.pdf
- 111 PANDEM. *Pandem; pandemic risk and emergency management*. PANDEM. 2017.
<http://www.pandem.eu.com/>
- 112 COMPARE. *Collaborative management platform for detection and analyses of (re-) emerging and foodborne outbreaks in europe*. COMPARE. 2016. <http://www.compare-europe.eu/>
- 113 ERINHA. *Erinha; european research infrastructure on highly pathogenic agents*. ERINHA. 2017.
<http://www.erinha.eu/>

- 114 PREPARE. *Platform for european preparedness against (re-)emerging epidemics*. 2015.
http://www.prepare-europe.eu/
- 115 ZAPI. *Zoonoses anticipation and preparedness initiative*. IMI. 2017. <http://zapi-imi.eu/>
- 116 Cleton NB, Reusken CB, Wagenaar JF, et al. Syndromic approach to arboviral diagnostics for
global travelers as a basis for infectious disease surveillance. *PLoS Negl Trop Dis*. 2015; **9**:
e0004073.
- 117 Waggoner JJ, Gresh L, Vargas MJ, et al. Viremia and clinical presentation in nicaraguan patients
infected with zika virus, chikungunya virus, and dengue virus. *Clin Infect Dis*. 2016; **63**: 1584-
1590.
- 118 Buchy P, Peeling R. Laboratory diagnosis and diagnostic tests. . In: WHO, ed. *Dengue: Guidelines
for diagnosis, treatment, prevention and control: New edition* Geneva: WHO press 2009; 91-109.
- 119 Mardekian SK, Roberts AL. Diagnostic options and challenges for dengue and chikungunya
viruses. *Biomed Res Int*. 2015; **2015**: 834371.
- 120 Cusi MG, Savellini GG. Diagnostic tools for toscana virus infection. *Expert Rev Anti Infect Ther*.
2011; **9**: 799-805.
- 121 Waggoner JJ, Pinsky BA. Zika virus: Diagnostics for an emerging pandemic threat. *J Clin
Microbiol*. 2016; **54**: 860-867.
- 122 van Meer MPA, Mogling R, Klaasse J, et al. Re-evaluation of routine dengue virus serology in
travelers in the era of zika virus emergence. *J Clin Virol*. 2017; **92**: 25-31.
- 123 Lindsey NP, Fischer M, Neitzel D, et al. Hospital-based enhanced surveillance for west nile virus
neuroinvasive disease. *Epidemiol Infect*. 2016; **144**: 3170-3175.
- 124 Yactayo S, Staples JE, Millot V, Cibrelus L, Ramon-Pardo P. Epidemiology of chikungunya in the
americas. *J Infect Dis*. 2016; **214**: S441-S445.

- 125 Reusken CB, Bakker J, Reimerink JH, Zelena H, Koopmans MG. Underdiagnosis of chikungunya
virus infections in symptomatic dutch travelers returning from the indian ocean area. *J Travel*
Med. 2013; **20**: 44-46.
- 126 Tonteri E, Kurkela S, Timonen S, et al. Surveillance of endemic foci of tick-borne encephalitis in
finland 1995-2013: Evidence of emergence of new foci. *Euro Surveill.* 2015; **20**.
- 127 Calzolari M, Bonilauri P, Bellini R, et al. Usutu virus persistence and west nile virus inactivity in
the emilia-romagna region (italy) in 2011. *PLoS One.* 2013; **8**: e63978.
- 128 GIDEON. *Gideon, the world's premier global infectious diseases database.* . GIDEON. 2017.
<https://www.gideononline.com/>
- 129 Fernandez-Garcia MD, Negredo A, Papa A, et al. European survey on laboratory preparedness,
response and diagnostic capacity for crimean-congo haemorrhagic fever, 2012. *Euro Surveill.*
2014; **19**.
- 130 Sambri V, Capobianchi MR, Cavrini F, et al. Diagnosis of west nile virus human infections:
Overview and proposal of diagnostic protocols considering the results of external quality
assessment studies. *Viruses.* 2013; **5**: 2329-2348.
- 131 Papa A, Kotrotsiou T, Papadopoulou E, Reusken C, GeurtsvanKessel C, Koopmans M. Challenges
in laboratory diagnosis of acute viral central nervous system infections in the era of emerging
infectious diseases: The syndromic approach. *Expert Rev Anti Infect Ther.* 2016; **14**: 829-836.
- 132 EVD-LabNet. *Evd-labnet diagnostic directory.* EVD-LabNet. 2017. <https://evd-labnet.eu/evd-labnet-directory-search>
- 133 Niedrig M, Avsic T, Aberle SW, et al. Quality control assessment for the serological diagnosis of
tick borne encephalitis virus infections. *J Clin Virol.* 2007; **38**: 260-264.

- 134 Anonymous. *Government will distribute 3.5 million zika virus tests*. Government of Brazil. 2016.
135 [http://www.brazilgovnews.gov.br/news/2016/10/government-will-distribute-3-5-million-zika-](http://www.brazilgovnews.gov.br/news/2016/10/government-will-distribute-3-5-million-zika-virus-tests)
136 virus-tests
- 135 Jacobsen S, Patel P, Schmidt-Chanasit J, et al. External quality assessment studies for laboratory
136 performance of molecular and serological diagnosis of chikungunya virus infection. *J Clin Virol*.
137 2016; **76**: 55-65.
- 136 Niedrig M, Zeller H, Schuffenecker I, et al. International diagnostic accuracy study for the
137 serological detection of chikungunya virus infection. *Clin Microbiol Infect*. 2009; **15**: 880-884.
- 137 Lemmer K, Donoso Mantke O, Bae HG, Groen J, Drosten C, Niedrig M. External quality control
138 assessment in pcr diagnostics of dengue virus infections. *J Clin Virol*. 2004; **30**: 291-296.
- 138 The World Bank. *People, pathogens and our planet: The economics of one health*. World Bank.
139 2012.
140 [https://openknowledge.worldbank.org/bitstream/handle/10986/11892/691450ESW0whit0D0E](https://openknowledge.worldbank.org/bitstream/handle/10986/11892/691450ESW0whit0D0ESW120PPPvol120web.pdf)
141 SW120PPPvol120web.pdf
- 139 Braks M, Medlock JM, Hubalek Z, et al. Vector-borne disease intelligence: Strategies to deal with
140 disease burden and threats. *Front Public Health*. 2014; **2**: 280.

Figure legends.**Figure 1.**

An effective laboratory preparedness and response at reference and clinical laboratory level is the basis for the success of a wide spectrum of disease control measures targeting different phases in the development of an arbovirus disease outbreak. Panel A: Development in time of an arthropod-borne virus enzootic with human spill-over (adapted from [138]). In case of arbovirus infections that transmit from human-to-human there is no involvement of an animal reservoir (green lines). Panel B: the three surveillance pyramids involved in monitoring of arthropod-borne zoonoses (adapted from [139]). In case of a human-mosquito/tick-human transmission there is no involvement of surveillance in animal reservoirs (green pyramid). Early response needs sampling and diagnosis towards the base of the pyramids. Panel C: Two levels, reference and clinical, of laboratory involvement in three scenarios of disease presence: endemic disease, returning travellers and an emerging infectious disease threat. "x" indicates involvement of each of the two levels of laboratory response in the three scenarios. "X*" indicates optional role clinical laboratories in case of common travel-related diseases. Arrows indicate direction of interaction/upscaling of capacity.

