Critical Reviews in Microbiology

ISSN: 1040-841X (Print) 1549-7828 (Online) Journal homepage: http://www.tandfonline.com/loi/imby20

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To cite this article: Wesley de Jong, Musofa Rusli, Soerajja Bhoelan, Sofie Rohde, Fedik A. Rantam, Purwati A. Noeryoto, Usman Hadi, Eric C. M. van Gorp & Marco Goeijenbier (2018) Endemic and emerging acute virus infections in Indonesia: an overview of the past decade and implications for the future, Critical Reviews in Microbiology, 44:4, 487-503, DOI: 10.1080/1040841X.2018.1438986

To link to this article: https://doi.org/10.1080/1040841X.2018.1438986

CRITICAL REVIEWS IN MICROBIOLOGY
2018, VOL. 44, NO. 4, 487–503
https://doi.org/10.1080/1040841X.2018.1438986

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REVIEW ARTICLE

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Endemic and emerging acute virus infections in Indonesia: an overview of the past decade and implications for the future

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ABSTRACT

Being the largest archipelago country in the world, with a tropical climate and a unique flora and fauna, Indonesia habitats one of the most diverse biome in the world. These characteristics make Indonesia a popular travel destination, with tourism numbers increasing yearly. These characteristics also facilitate the transmission of zoonosis and provide ideal living and breading circumstances for arthropods, known vectors for viral diseases. A review of the past 10 years of literature, reports of the Ministry of Health, Republic of Indonesia and ProMED-mail shows a significant increase in dengue infection incidence. Furthermore, chikungunya, Japanese encephalitis and rabies are proven to be endemic in Indonesia. The combination of cohort studies, governmental data and ProMED-mail reveals an integrated overview for those working in travel medicine and public health, focusing on both endemic and emerging acute virus infections. This review summarizes the epidemiology of acute virus infections in Indonesia, including outbreak reports, as well as public health response measurements and their potential or efficacy. Knowledge about human behaviour, animal reservoirs, climate factors, environment and their role in emerging virus infection are discussed. We aim to support public health authorities and health care policy makers in a One Health approach.

ARTICLE HISTORY
Received 19 May 2017
Revised 11 December 2017
Accepted 6 February 2018
Published online 15 February 2018

KEYWORDS
Indonesia; dengue; chikungunya; rabies; viral hepatitis

Introduction

Comprising thousands of islands spread across the equator, Indonesia is the largest archipelago country in the world with 257.5 million inhabitants (Worldbank Indonesia Data 2016). With a broad offer of both culture and nature, Indonesia is a popular travel destination for travellers all over the world, with the number of travellers going to Indonesia increasing yearly (World Economic Forum 2015). Traditionally, tourists visit both Java and Bali Island, but other islands, such as Flores, Lombok, Sumatra, and Sulawesi gain popularity, most likely due to effective advertisement of the islands. However, its tropical climate and subsequent relative high humidity are both favourable conditions for vector-borne disease transmission. In addition, Indonesia yields a large and growing population of notorious reservoirs of zoonotic infections like poultry, rodents, wild birds, dogs, pigs, and monkeys (Konishi et al. 2009; Yamanaka et al. 2010; Dash et al. 2013; Townsend et al. 2013; Lane-DeGraaf et al. 2014).

This constant tread of infection and potential local outbreaks or even pandemics compromise both the people living in Indonesia as well as travellers visiting the archipelago. Infectious diseases remain one of the leading causes of morbidity and mortality worldwide, especially in countries with a (sub)tropical climate (WHO 2014b). Its burden is a result of a constant ground of established infections in the past period, combined with epidemics of emerging infectious diseases (EID) (Morens et al. 2004). An EID is characterized as an infectious disease that appeared and affected a population for the first time or existed before but increased rapidly in case numbers, or geographical spread. They often have the characteristic to easily spread over large areas, infecting people and/or animals with potential significant morbidity, and mortality (WHO-SEARO 2005).

In the past decade, outbreaks of multiple emerging infectious virus diseases (EIVD) have been reported in Indonesia. Especially of note were those of avian

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Supplemental data for this article can be accessed here.

Table 1. Vaccine-preventable diseases as recommendation from the Ministry of Health Republic of Indonesia, Centers for Disease Control and Prevention, Dutch, Swiss, Singapore's and Australian perspective.

Retrieval:	October 24 2016					
Virus/authority	MoH-RI (1)	CDC (2)	LCR (3)	Swiss TPH (4)	MoH-SG (5)	Australian government (6)
Hepatitis A	No	All travellers	All travellers	All travellers	All travellers	All travellers
Hepatitis B	Yes	Tailored	Tailored[a,b]	Tailored[a,c]	Tailored	Tailored (not specified)
Japanese encephalitis	No	Tailored[d]	Tailored[e]	Tailored[e,f]	Tailored[d]	Tailored (not specified)
Measles	Yes	All travellers	All travellers	All travellers	All travellers	All travellers
Rabies	Tailored[h]	Tailored[g]	Tailored[h]	Tailored[i]	Tailored[g]	Tailored[g]

1) Ministry of Health, Republic of Indonesia, retrieved from: http://www.depkes.go.id.
2) Center for Diseases Control and Prevention, Department of Health and Human Service, United States of America, retrieved from http://wwwnc.cdc.gov/travel/destinations/traveler/none/indonesia.
3) Landelijk Coördinatiecentrum Reizigersadvisering (National Coordination Centre for Traveladvise), the Netherlands, retrieved from https://www.mijnlcr.nl (professionals), http://www.lcr.nl (layman).
4) Swiss Tropical and Public Health Institute, Switzerland, retrieved from http://www.safetravel.ch (available in French and German only). Supplemented with data from Bundesamt für Gesundheit BAG, retrieved from http://www.bag.admin.ch/ekif/04423/04428/ (available in German only).
5) Ministry of Health, Republic of Singapore, retrieved from https://www.moh.gov.sg/ and https://www.healthhub.sg/. The latter refers to CDC (2) for vaccine advice.
6) Australian Government, Department of Foreign Affairs and Trade, retrieved from http://smartraveller.gov.au/ No comprehensive travel immunization scheme could be found.
[a]For those having close contact with inhabitants, long-term stay or recreational activities with risk of injury (contaminated blood, non-sterile medical material).
[b]Implemented in national vaccination programme since 2011 for all babies (ever since 1989 for specific populations, such as newborns with a hepatitis B carrier mother).
[c]Implemented in national vaccination programme for all adolescents 11–15 years of age (vaccine status is checked at 25–29 years of age).
[d]For those spending $\geq$1 month in endemic areas during transmission season (including 1) long-term travellers, recurrent travellers, expatriates likely to visit rural/agriculture areas, 2) extensive outdoor (e.g. camping and farming), 3) staying in accommodation without air conditioning, screens, or bed nets.
[e]For those spending $\geq$1 month on rural endemic area in close contact with rice fields and pig population.
[f]During rainy season only.
[g]For those involved in outdoor activities, working with or around animals, taking long trips/moving into Indonesia, children.
[h]For those with frequent and/or possible unnoticed exposure to domestic or wild mammals.
[i]For those with risk of high exposure (hikers, cyclists, cave explorers and zoologists) and those spending more than 3 months in country.

influenza, dengue, chikungunya, and rabies (Soepandi et al. 2010; Kosasih et al. 2013; Townsend et al. 2013; Karyanti et al. 2014). As a result, the Indonesian government has put much effort in trying to control many of these diseases, for instance by implementing surveillance and vector control programmes, or in the case of rabies culling campaigns. This resulted in data of specific interest for those working with infectious disease patients in Indonesia, public health or those working in travel medicine outside of Indonesia. Data from local outbreak reports and from published epidemiological studies give a unique insight in how to optimize EIVD prevention in Indonesia. This data potentially can be used to support public health authorities and health care policy makers.

EI(V)D outbreaks are hard to predict since they are the result of a complex interaction between host, vector, pathogen, and environment. Furthermore, infections in humans often happen unnoticed, such as via contaminated foods, mosquito bites, or inhalation of virus-containing aerosols. From the One Health concept, we know that six out of every 10 infectious diseases in humans are spread from animals (CDC 2016). An optimal insight in this interaction is crucial for executing adequate preventive methods, moreover since no treatment is available for the majority of acute EIVDs. A current overview of EIVDS in Indonesia for (international) clinicians and healthcare authorities does not seem to be available. Furthermore, we observed that authorities from other countries advising their inhabitants for pre-travel vaccinations and precautions could not adequately assess their advices since insight in local literature and governmental data for this region is lacking (Table 1).

We, therefore, have reviewed acute (E)IVD outbreaks in Indonesia in the past decade, using published cohort data, ministry of health reports and reports from the online Programme for Monitoring Emerging Diseases (ProMED-mail). ProMED-mail is open to all sources; it includes a variety of reports ranging from local media to science. Data should be interpreted with care, as reports are susceptible for information bias. Viral diseases able to unnoticeably transmit from vector to human or inter human are discussed as well. Table 2 summarizes the discussed viruses, incidence, transmission route, incubation period, symptomatology, protective actions, and diagnostic methods.

Methods

Based on manuscripts studying the epidemiology of virus infections in South East Asia and ProMED-mail reports, hepatitis A, West Nile virus, Japanese encephalitis, dengue, chikungunya, measles, rabies, hantavirus, avian influenza, and seasonal influenza were considered to be predominantly associated with acute human viral

Table 2. Overview of the major discussed viruses including epidemiology, symptomatology, protective actions, and diagnostics.

Virus	Incidence[a]	Transmission via[a]	Incubation[a]	Symptomatology[a]	Protective actions[a]	Diagnostics
DENV	40:100 000 (MoH-RI, 2014)	Mosquito (*Aedes spp.*)	5–8 d	High fever accompanied with headache, retro-orbital, joint and/or muscle pain, rash, bleeding tendency.	Avoid mosquito bites[b]	Acute phase: RT-PCR on plasma, antigen (NS1) based ELISA or rapid test. Convalescent: IgM/IgG antibodies[c].
WNV	No data available	Birds (reservoir), mosquito (*Culex spp.*)	2–14 d	In 20% of cases a mild course: fever, headache, myalgia, rash, and lymphadenopathy <1% develops neurological symptoms.	Avoid mosquito bites[b]	Acute phase: RT-PCR on plasma or liquor, virus culture, immunohistochemistry on tissue. Convalescent: IgM/IgG antibodies on serum or liquor[c].
JEV	7.1:100 000 (children <10 years, Bali) (Kari et al. 2006)	Mosquito (*Culex spp.*)	6–16 d	In 1% fever, headache, altered mental state, convulsions (suspected meningitis, encephalitis or acute flaccid paralysis).	Vaccination, avoid mosquito bites[b].	Acute phase: IgM antibodies on serum or liquor. Repeat on convalescent samples when high suspicion. Confirm with virus neutralization test. Convalescent: IgM/IgG antibodies[c].
CHIKV	0.002 (MoH-RI, 2014)–22 (MoH-RI, 2009) per 100 000	Mosquito (*Aedes spp.*)	2–4 d	Acute febrile illness, maculopapular rash and joint pain as key symptom.	Avoid mosquito bites[b]	Acute phase: RT-PCR on plasma, virus culture. Convalescent: IgM/IgG antibodies.
MV	5:100 000 (MoH-RI, 2014)	Human-human (aerosols)	7–14 d	Fever, cough, coryza, conjunctivitis, Koplik's spots. Characteristic erythematous and maculopapular rash.	Vaccination	Acute phase: RT-PCR on plasma and/or throat swab, urine. Convalescent: IgM/IgG antibodies (note: possible positive due to previous vaccination).
RABV	17:100 000 (MoH-RI, 2014)	Dogs, monkeys, bats bite/scratch or licking damaged skin.	As less as a few days	Flu-like symptoms, progressive to cerebral dysfunction, agitation, and eventual death when untreated.	Vaccination (no need of immunoglobulins after bite/scratch), avoid contact with animals. When indicated: adequate treatment with immunoglobulins (passive antibodies).	Test euthanized animal that possibly transmitted RABV (brain sample); concurrently test saliva (RT-PCR or virus isolation), serum, spinal fluid (antibodies), and skin biopsies in nape of the neck (antigen).
HANV	No data available	Rodents (rats and mouse)	2–4 weeks (7 d was reported)	Flu-like symptoms, high fever, bleeding tendency, kidney injury.	Pest control, avoid contact with faeces/urine of rodents (via food or by breathing in virus-containing particles).	Acute phase: RT-PCR. Convalescent: IgM/IgG and confirm with virus neutralization.
AI	No data available	Poultry	2–5 d	Conjunctivitis, influenza-like illness sometimes accompanied by gastro-intestinal symptoms and respiratory illness.	Avoid contact with possible infected poultry. Preventively administer influenza antivirals.	RT-PCR on swab of upper respiratory tract (nose or throat).
HAV	No data available. Note: high seroprevalence (up to 100% in elderly).	With faeces contaminated food, water, surfaces, etc. (faecal-oral).	15–50 d	Fever, fatigue, loss of appetite, gastro-intestinal symptoms, jaundice, dark urine. Below 6 years of age: 70% asymptomatic.	Vaccination	Acute: IgM on blood. Occasionally RT-PCR on blood or faeces. Convalescent: IgM/IgG on blood.
Influenza	No data available	Human-human via droplets	1–4 d	Abrupt onset of respiratory signs and symptoms, such as fever, myalgia, headache, and malaise).	Yearly flu vaccine	When indicated: RT-PCR on swab of upper respiratory tract (nose or throat).

[a](*n*) refers to publication. Where MoH-RI is stated, information from Ministry of Health, Republic of Indonesia was used. Assumed population of 250×10^6.
[b]To avoid mosquito bites: use insect repellent (such as DEET), wear proper clothing (long sleeves, pants, etc.) and reduce exposure to mosquitos during peak biting hours (i.e. for Aedes mosquito: early in morning and before dusk).
[c]Known cross-reactivity in flavivirus essays, interpret with care.

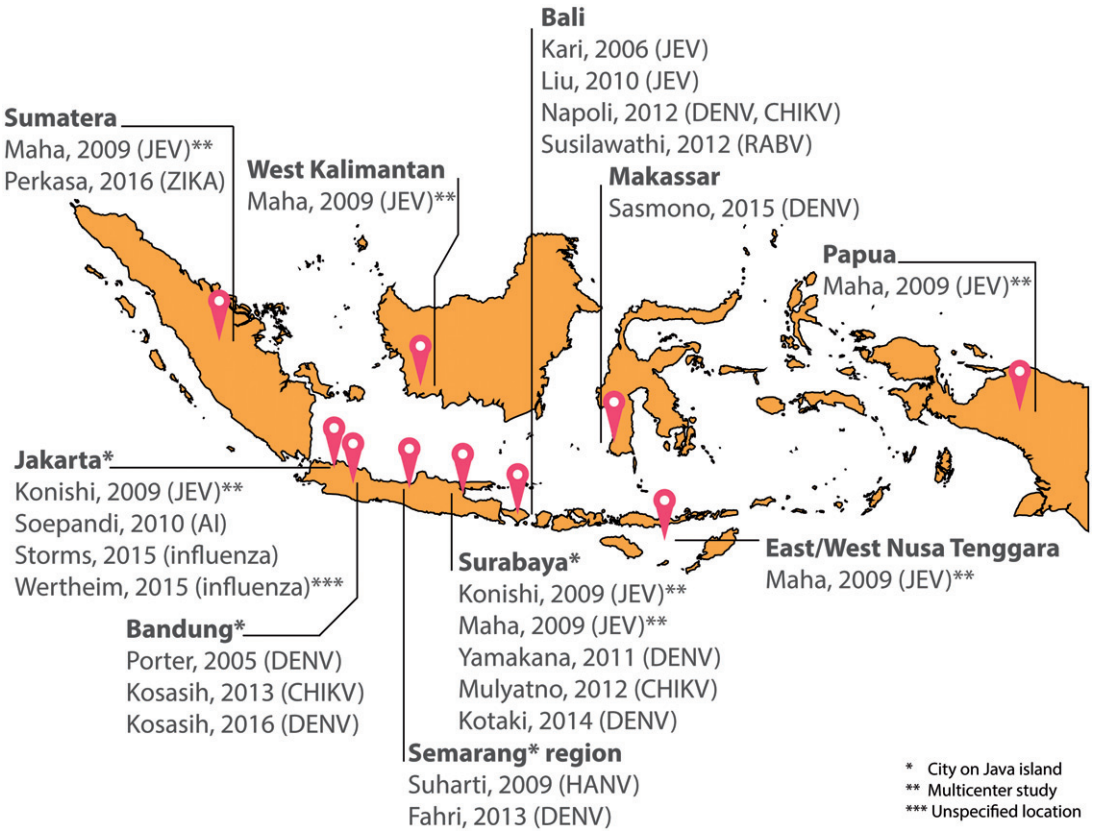

Figure 1. Map of Indonesia with location overview of the discussed cohort studies conducted or reported from 2006 until May 2016 - not including case reports and/or export cases.

disease in SEA region (Cleton et al. 2012; WHO 2014a). Since more recently diseases, such as Zika, hepatitis E, and MERS-CoV (re-)emerged in the South-East Asia region; these were taken into consideration as well. We conducted a search of the literature for research performed in Indonesia and to human cases with a history of recent travel to Indonesia using the PubMed (including MesH) and Embase databases from May 12 to 19 2016. Search strategy is available as supplemental data (Supplemental data 1). Two authors independently selected articles written in English and Bahasa Indonesia by first reading title/abstract from human and animal/vector studies published from May 2006 to 2016. We checked reference lists for references to relevant first published data (i.e. first virus detection or clusters of cases) and we extracted data when available. Scientific literature about selected human research is available as supplementary data (Supplemental data 2). Figure 1 represents a map of Indonesia with a visual overview of the locations where the discussed cohort studies were conducted. We accessed Ministry of Health, Republic of Indonesia (MoH-RI) and World Health Organization (WHO) information at May 12 2016. MoH-RI reports for 2006–2015 were available for retrieval. Where applicable, WHO reports are referred to in text. Furthermore, ProMED-mail was searched for reports from Indonesia at Oct 21 2016. ProMED-mail together with MoH-RI data is visually presented in Figure 2 to give insight in the trends in reporting for some EIVDs of interest and is also available as supplemental data (Supplemental data 2).

Dengue virus (DENV)

Dengue virus (DENV) is a *Flavivirus* (genus including yellow fever and Zika virus) belonging to the family of *Flaviviridae*. DENV infection is a mosquito-borne infection caused by one of the four DENV serotypes (DENV 1–4) and is primarily transmitted to humans by the *Aedes* mosquito. DENV has a worldwide distribution, is geographically concentrated around the equator and is endemic in Southeast Asia. The estimated number of infections worldwide is 50–100 million, with estimated 500 000 people requiring hospitalization each year. The incubation period is 5–8 d. Severe DENV could potentially lead to haemorrhagic shock and organ failure. Most of the symptoms become manifest around the time of defervescence. Treatment is supportive and mainly directed to maintenance of the body fluid volume. Safe and effective DENV vaccines are under

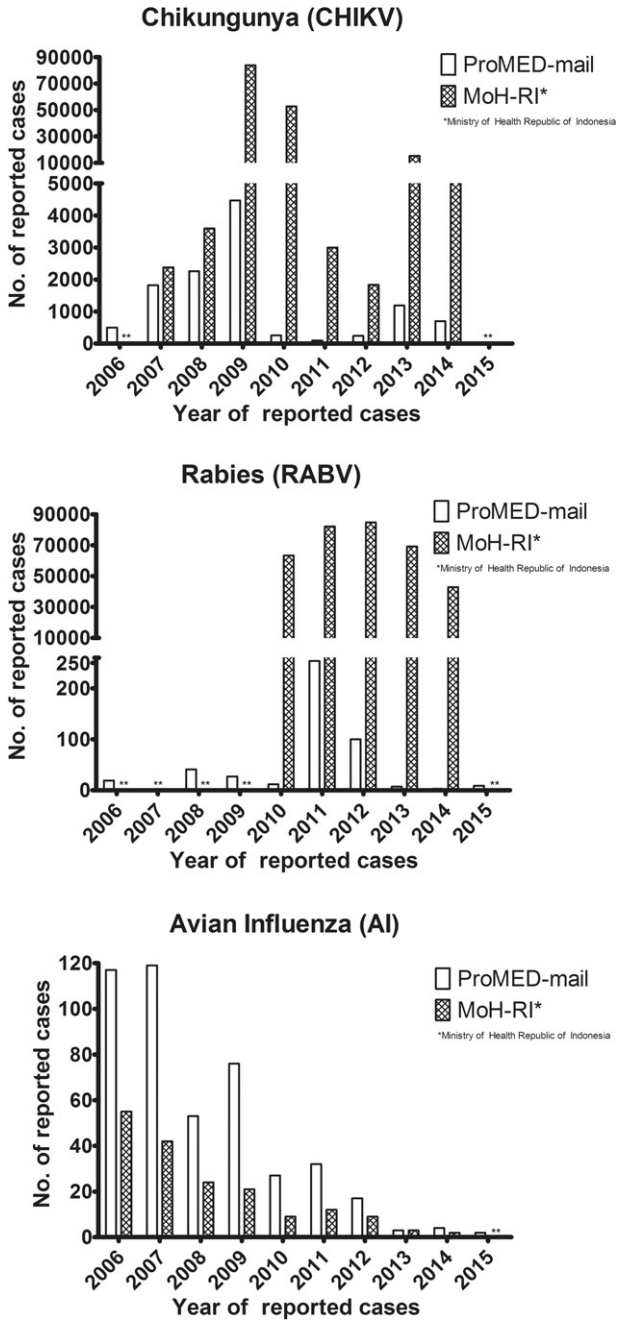

Figure 2. Trends in ProMED-mail and Ministry of Health Republic of Indonesia for the reporting of chikungunya, rabies and avian influenzain Indonesia Reporting up till 21st October 2016. Source data ProMED-mail available as supplementary data 2. Restricted to human cases (both laboratory confirmed and unconfirmed), not including summarizing outbreak reports. **indicates no data available.

development in several stages of research (Martina et al. 2009; Meltzer and Schwartz 2009; Ooi and Gubler 2009; Chen and Wilson 2010; Mangold and Reynolds 2013; Vannice et al. 2016). Currently, Dengvaxia® (a tetravalent, live attenuated, chimeric dengue vaccine in a yellow fever 17D backbone developed by Sanofi Pasteur, Swiftwater, PA) is registered for use in individuals 9–45 years of age living in endemic areas (WHO 2016b). However, current data does not support implementation in the Indonesian vaccination programme.

The nationwide DENV surveillance programme started in 1968. Besides increasing DENV incidence numbers, surveillance showed an annual increase of dengue haemorrhagic fever (DHF), classified as DHF according to former classifications with at least two of four clinical manifestations (fever, haemorrhagic manifestations/positive tourniquet test, hepatomegaly, and circulatory failure combined with thrombocytopenia) from 0.05/100 000 to 35–40/100 000 in 2013. DHF incidence increased significantly in people aged 15 or above (Karyanti et al. 2014).

DENV import cases from Indonesia were reported in literature (Napoli et al. 2012). For instance, in Norway 2 DENV infections were reported from 2008 to 2010 (Vainio et al. 2010). Furthermore, in Italy (2010) an imported case was reported with viremia lasting for several days. The authors stress out the importance of performing diagnostics and the potential for a local outbreak since *Aedes* mosquitos are present in Italy (and other parts of Europe) (Rovida et al. 2011).

There is data available suggesting a succeeding episode of DENV infection may lead to detrimental clinical disease, the so-called antibody depended enhancement theory. However, virulence seems mainly determined by difference in genotypes and increased virulence (Martina et al. 2009). Multiple studies report the continuous change of DENV serotypes and their lineages. Both clustering of lineages and subtypes during outbreaks (e.g. lineage 4 of DENV-2 between December 2011 and March 2012 (Yamanaka et al. 2011; Kotaki et al. 2014b; Ernst et al. 2015)) as well as the concurrent presence of all four DENV genotypes is reported in Indonesia (Kotaki 2014a; Kotaki et al. 2014b).

Clinical studies on the epidemiology of febrile illness in Indonesian cohorts report various rates of molecular, antigenic or serological evidence for DENV. Overall, for both urban and rural areas, DENV is detected in 12–55% of all tested febrile cases; this includes all four DENV genotypes. With a follow-up period up to seven years in specific reports (Porter et al. 2005; Fahri et al. 2013; Sasmono et al. 2015; Kosasih et al. 2016).

The MoH-RI national control programme in the DENV epidemic includes surveillance of mosquito larvae in households and eradication of mosquito breeding spots, as a community-based programme (MoH-RI 2009). The importance of such interventions is emphasized by several studies: Stahl et al. showed that indirect costs take up to 44% of the total costs (est. 2 979 902 US$) per DENV outbreak (Stahl et al. 2013). Tourism and labour flow contribute to DENV incidence, as is

shown in field research studies in Bali – one of the most popular islands as tourism destination. It is suggested to reduce vector populations and spread knowledge of vector transmittable diseases, though in this study no effect measurements are done (Yoshikawa and Kusriastuti 2013).

To add up, multiple manuscripts suggest adjusting for underreporting DENV cases during an epidemic and to analyse currently available data from cohort studies or MoH-RI with expansion factors (Shepard et al. 2013; Undurraga et al. 2013). Possible resistance to larvicides, such as temephos (Mulyanto et al. 2012), understanding the mosquito population (Rasic et al. 2015), and the ability to predict the number of DENV cases in advance (Halide and Ridd 2008; Wijayanti et al. 2016) all could play an important role in further understanding of DENV outbreaks.

West Nile virus (WNV)

West Nile virus (WNV), an arthropod-borne *Flavivirus*, is a zoonotic infection mainly of birds and horses. Birds serve as reservoir and transmission occur via mosquitoes. WNV is found in West Asia, as well as Africa, Europe, Middle East, and North America (Chancey et al. 2015). Mammals are considered dead-end hosts that do not contribute to the epidemic spread of the pathogen (van der Meulen et al. 2005). The average incubation period lasts 2–14 d. Of humans infected, 20% will experience a mild, non-specific disease presentation including high fever, headache, myalgia, sometimes with rash, and lymphadenopathy; $<$1% will develop severe neurological symptoms (Watson et al. 2004).

In Indonesia, the data regarding WNV epidemiology is scarce. WNV was isolated from a 15-year-old patient with fever in 2004. Phylogenetic analysis showed a relation with WNV strains isolated in Africa (Myint et al. 2014). Only limited reports of WNV in humans in Indonesia are available. For instance, based on the work of Nasronudin et al. (2014) and Wicaksono et al. (2014) there is a suggestion of WNV infection in human in Indonesia. However, these studies offer a low level of evidence since they used a sub-optimal methodology and confirmation by a third party lab was not performed. No surveillance programme exists for WNV and no entries exist on ProMED-mail, thus only current case studies suggest potential circulation of WNV in Indonesia.

Japanese encephalitis (JEV)

Japanese encephalitis virus (JEV) is an arthropod-borne *Flavivirus*. It is the leading cause of encephalitis in most of South-East Asia and Western Pacific regions, where 24 countries are known to have endemic JEV transmission (WHO 2015b). The incubation period of JEV is 6–16 d. The majority of cases are non-specific or asymptomatic; only less than 1% of the individuals develop clinical symptoms, such as fever, headache, altered mental state, and convulsions. When encephalitis occurs, mortality rises from 30 to 40–50% in comatose patients. JEV is known for long-term neuropsychological sequelae in 30–50% of those who recover from intensive care support. Vaccination is considered the single and most important control measure for JEV (Unni et al. 2011; Tiwari et al. 2012).

The first manuscript describing JEV in humans in Indonesia dates from 1974 (Van Peenen et al. 1974). From then, a number of cases were reported in the 80–90s in both returning travellers (Macdonald et al. 1989; Wittesjo et al. 1995; Buhl et al. 1996) as well in Indonesian inhabitants (Yoshida et al. 1999). Early research to JEV was done on the reservoir (pigs) (Van Peenen et al. 1975), vector (detected in both *Culex* and *Anopheles* species) (Van Peenen et al. 1975; Olson et al. 1985a; Olson et al. 1985b), and humans (Van Peenen et al. 1974). Studies of Yamanaka et al. investigated JEV viremia and antibodies in 219 pigs from Bali and East Java in 2008. Of these pigs 49% in Bali and 6% in Java had viremia and 24% of 123 pig samples tested in Bali showed positive JEV IgM antibodies (none in the Java population) (Yamanaka et al. 2010). In contrast to the above-mentioned, only two human cases exist in ProMED-mail in 2011 and 2015, whereas sero-surveillance studies from 1999 to 2001 on Java Island detected 2.2% JEV antibodies (titres $\geq$1:160) involving over 2000 samples (Konishi et al. 2009).

A number of clinical studies report a noteworthy incidence of JEV cases in children, of which a significant number report subsequent neurological sequelae. A study performed between 2001 and 2003, involving all healthcare facilities on Bali island, reported an average incidence rate of 7.1 per 100 000 children aged 10 or below (Kari et al. 2006). Another study followed up 65 out of 72 cases of laboratory-confirmed JEV in children between 2001 and 2004. In this study, a total of 16 children were deceased at the follow-up assessment (average 13 months after discharge, range 4–24 months). No less than 25% of the children had sequelae in such way, that they were dependent on their daily functioning and only 25% of the children were considered to be fully recovered (Maha et al. 2009). A case-control study of Liu et al. confirmed JEV in about one-third of the clinically identified viral encephalitis or aseptic meningitis in children aged 0–11 years. Multivariate analysis revealed that pig ownership by

their family, close proximity to the rice fields and older age was significantly associated with the incidence risk of JEV in children (Liu et al. 2010). No such studies seem to have been carried out in adults in the past decade.

Despite being discussed at World Health Organization's meetings (Tsai 2000) and its relevance as pointed out above, currently, no surveillance programme nor a vaccination programme exist in Indonesia, even while the latter was reported as cost-effective for a two-dose regime on Bali island (Liu et al. 2008). To our knowledge, the MoH-RI is advancing towards implementation of a childhood vaccine for JEV; it is, however, unclear what a surveillance programme will look like.

Chikungunya (CHIKV)

Chikungunya virus (CHIKV) is an Alphavirus belonging to the *Togaviridae* family, transmitted in Asia by mosquitos of the *Aedes* family (Caglioti et al. 2013). After an incubation period of 2–4 d (range 1–12 d) (Caglioti et al. 2013; Thiberville et al. 2013), the majority of the infected patients become symptomatic. CHIKV is characterized by an onset of acute febrile illness and maculopapular rash. Severe joint pain is described as main symptom and is present in almost all cases; arthralgia in specific cases can last up to 24 months (Kucharz and Cebula-Byrska 2012; Thiberville et al. 2013). Treatment is symptomatic. The re-emergence of CHIKV was reported in Indonesia in serological studies in 1999 (Porter et al. 2004) and in outbreak reports from 2001 to 2003 (Laras et al. 2005). Furthermore, CHIKV was isolated from patient sera in febrile illness cases from prospective cohorts from 2000 to 2008 – with incidence rates of 10.1/1000 CHIKV infections per person-years (Mulyatno et al. 2012; Kosasih et al. 2013). When comparing MoH-RI reported incidence numbers of CHIKV in 2014 (MoH-RI 2015) to confirmed cases in a cohort study of 2010–2011, there is reason to believe that there is underreporting of CHIKV in Indonesia. This is likely the result due to the similarities in clinical presentation for both DENV and CHIKV (Mulyatno et al. 2012), the sparse availability of routine diagnostics and not the trends in the CHIKV outbreak Figure 2 highlights these trends for CHIKV, avian influenza, and rabies. Both MoH-RI and ProMED-mail data are prone to reporting bias; the figure shows clear trends and discrepancies in reporting between MoH-RI and ProMED-mail. For CHIKV, there seems a fixed ratio of ProMED-mail reports versus MoH-RI data in 2007 and 2008, whereas in later years, it is definitely questionable how to adequately assess the real incidence numbers, since ProMED-mail numbers decline and MoH-RI numbers both drop and raise.

Measles (MV)

Measles virus (MV), a *Morbillivirus* belonging to the *Paramyxoviridae*, is a highly contagious virus, with the number of new infections that can result from one infected person ranging from 12 to 16 (also referred to in literature as the R_0). It spreads directly from human to human by virus-containing aerosols. Especially at risk are people naïve to the virus, being those not vaccinated and children losing passive antibodies after birth. The infection is characterized by illness with fever, cough, coryza, conjunctivitis, and Koplik's spots. A characteristic erythematous and maculopapular rash appears which lasts for 3–5 d (Moss and Griffin 2012). In 40% of the cases, measles infection is complicated, for instance by pneumonia, due to a relative immunosuppression after measles virus infection (de Vries et al. 2012; Mina et al. 2015). The incidence number of MV is successfully being reduced by vaccination, although outbreaks do occur, both in countries with and without vaccination programme due to vaccine effectiveness and vaccine coverage (WHO 2012; Durrheim et al. 2014). The implementation of a regular immunization programme for MV led to vaccination coverages above 90% in most of Indonesia, a target as set by WHO, with a declining number of provinces not meeting this target over the past years (Dalimunthe et al. 1990; Serquina-Ramiro et al. 2001; MoH-RI 2014). When comparing these data to WHO reports, it can be depicted that the overall 1st dose coverage among one-year-olds is still below the 90% target (WHO 2016a). Also, ProMED-mail reports show no evidence of MV outbreaks, while MoH-RI still reports a number of cases totalling to an incidence rate of about 5–6 per 100 000 inhabitants (MoH-RI 2014, 2015).

Rabies (RABV)

Rabies (RABV) is caused by a number of *Lyssaviruses* including the rabies virus and bat *Lyssaviruses*. Saliva from infected animals can transmit the virus to humans and eventually cause a lethal infection of the brains. In the majority of cases, dogs transmit the virus; however, transmission of rabies via other wildlife should be taken into consideration (Wang et al. 2014). RABV causes an estimated number of deaths between fifty and a hundred thousand per year. The Asian and African continent account for 95% of the worldwide deaths of the total reported infections (Leung AK et al. 2007).

RABV is endemic in Indonesia, especially in Bali and East Nusa Tenggara and is likely present since the 1880s, based on multiple manuscripts describing clinical cases following bites from "mad dogs" (Ward 2014).

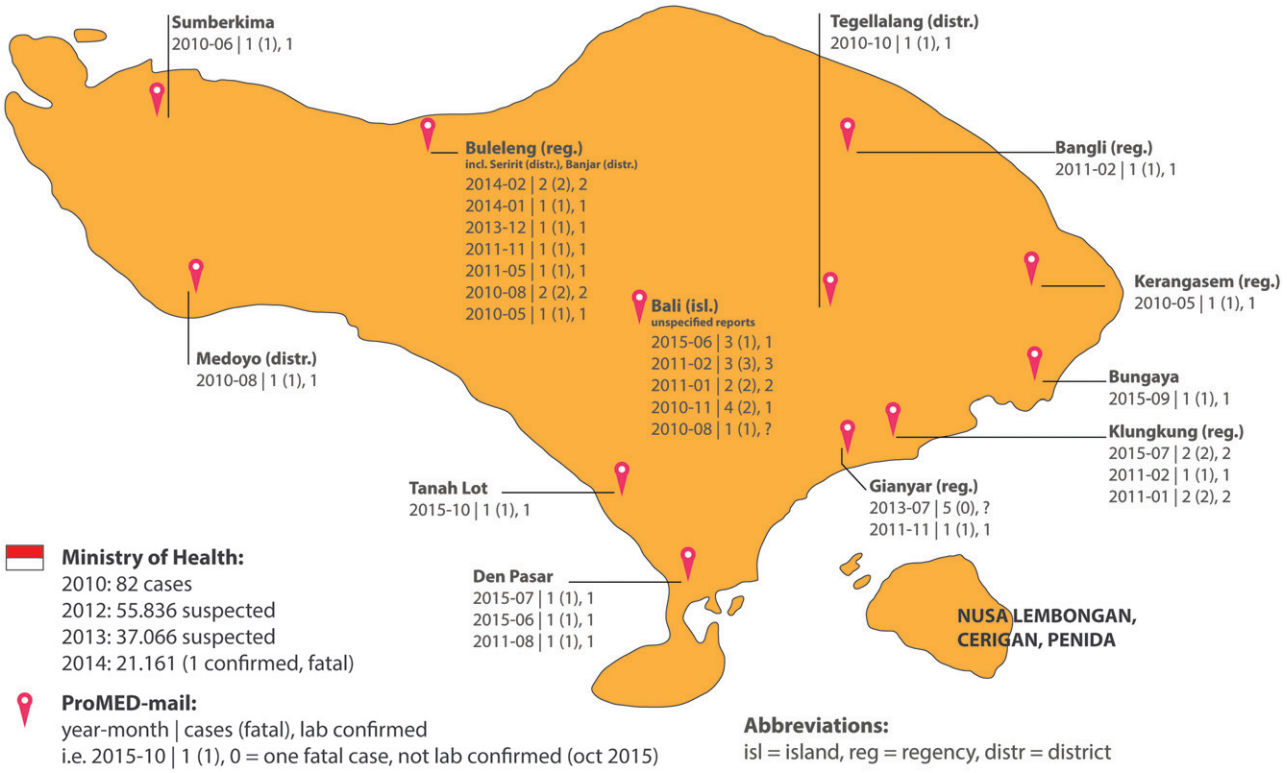

Figure 3. Rabies outbreak heat map to demonstrate the benefit of combining Ministry of Health and ProMED-mail data.

After being last described in late 1980s (Waltner-Toews et al. 1990) an outbreak in Bali and surrounding islands commenced in 2008 (MoH-RI 2009). Up to hundred human cases and a case fatality rate of 100% in laboratory confirmed human cases were reported during the outbreak until 2010 (Susilawathi et al. 2012). Of interest is the data from GeoSentinel and EuroTravNet sites; 12.1% of all post-exposure prophylactic vaccination for RABV was requested by travellers returning from Bali. However, their data shows that the majority of animal-related injuries in travellers returning from Bali are associated with exposure to monkeys, and not dog bites/scratches (Gautret et al. 2011). Figure 2 shows trends in RABV reporting to MoH-RI and ProMED-mail. The trends in reporting to both entities are less well correlated as compared to those in CHIKV. Figure 3 shows outbreak locations in Bali as reported in ProMED-mail and compared to MoH-RI incidence numbers. It could be beneficial to combine Ministry of Health, ProMED-mail and possibly WHO data to get a thorough overview of areas at risk in case of outbreaks since locational data could be of relevance for governmental interventions or travel-related risks.

To further understand the endemic, a number of animal studies were carried out. During the 2008–2010 outbreak, *Dibia* and colleagues showed that Indonesian RABV originated from Java Island and were (re-)introduced in several other islands including Bali (Dibia et al. 2015). Also, a study has been conducted to estimate the owned and unowned dog populations and dog bite cases in (RABV free) Lombok island (Mustiana et al. 2015) in order to get insight in the (potential) spread. From 2008, early preventive measurements to stop the outbreak were implemented. Despite control – including mass vaccinations and culling for dogs – the outbreak continued for four years. This largely had to do with the fact that the dog population in Bali is rather large and the human-dog relationship in Bali is believed to be multifaceted (i.e. for cultural reasons, as guard, but also different point-of-views in dog care and best practices after a bite wound) (Widyastuti et al. 2015). Also culling of dogs seemed to be ineffective. The island-wide vaccination, aiming for a vaccine coverage rate of 70% in dogs, did, however, reduce the incidence and spread of rabies (Putra et al. 2013). Still, a number of RABV cases are reported over the last years, as is summarized in Figures 2 and 3.

Hantavirus (HV)

Hantaviruses (HV) belong to the family of the *Bunyaviridae*. In humans, the rodent-borne HVs cause two different diseases. In North and South America inhalation of virus-containing aerosols with new world hantaviruses could lead to the hantavirus cardio pulmonary syndrome, a syndrome characterized by fever

and acute respiratory distress associated with high case fatality rates (Bi et al. 2008). Of importance for Indonesia, seem to be the so-called Old-World HVs which can cause haemorrhagic fever with renal syndrome (HFRS) (Watson et al. 2014). A triad of fever, haemorrhage and acute kidney injury classically characterizes this syndrome. It is crucial to initiate prompt and proper symptomatic and supportive treatment for HFRS. This includes monitoring of fluid balance, diuresis, kidney function, and the use of fresh frozen plasma/transfusions in case of haemorrhagic complications (Goeijenbier et al. 2013). Small trials and case reports have shown that ribavirin treatment may be useful in the very early phase of HFRS by reducing the risk of haemorrhagic events and the severity of renal insufficiency. Larger trials are needed to corroborate these findings (Moreli et al. 2014). In routine diagnostics, Old World HV infections are diagnosed by both serological detection of IgM and/or IgG antibodies and molecular detection of the virus. However, the extent of viremia varies per HV species and in some cases might be limited to a short period after onset of illness (Bi et al. 2008). Currently, (comparative) virus neutralization tests remain the gold standard in HV serology to confirm an infection with a specific HV species. Neutralization tests remain an absolute necessity since current available serological HV diagnostics suffer from a high percentage of false-positive results, and, therefore, reports solely relying on ELISA or IFA results should be interpreted with care (Goeijenbier et al. 2014). Earlier studies suggested HV infection in humans and rodents in Indonesia (Ibrahim et al. 1996; Plyusnina et al. 2004; Plyusnina et al. 2009; Kosasih et al. 2011; Ibrahim et al. 2013) and a number of cases were found in hospital-based cohort studies conducted between 1995 and 2005 (Groen et al. 2002; Suharti et al. 2009; Kosasih et al. 2011). However, this evidence of human HV infection in Indonesia is based on only IgM ELISA proven cases. For instance, Suharti et al. report ELISA response of a recent infection in 4.2% of DENV suspected patients (Suharti et al. 2009). Although not conclusive, this data does suggest symptomatic human HV infection in Indonesia, which is also supported by the results of Groen et al. who reported serological evidence, based on EIA, ELISA, and IFA results in 11% in a DENV suspected cohort (Groen et al. 2002). Furthermore, serological evidence of HV infection was reported in a clustered case of 2005 in Western Java (Kosasih et al. 2011). In this case, *Rattus sp.* trapped around the living area of the patient showed the molecular presence of Seoul HV, known to cause HFRS in Europe. Seoul virus has been detected by PCR in *Rattus norvegicus*, the known reservoir of the pathogenic Seoul virus (Plyusnina et al. 2004).

Furthermore, a newly discovered HV in the Thousand Island region in Indonesia might be pathogenic to humans (Ibrahim et al. 2013). Urgent studies are needed to estimate the burden of HV disease in humans in Indonesia and for adequate prevention methods (i.e. rodent trapping and human behaviour changes).

Avian influenza (AI)

Avian influenza (AI) infection in human, caused by non-seasonal influenza A viruses of the subtypes H5N1 and H7N9 belonging to the *Orthomyxoviridae* family, is clinically characterized by respiratory disease. The first AI H5N1 reported cases date from 1997 influenza in Hong Kong. Since then, the virus has spread throughout the South East of Asia with Indonesia being hit the hardest (WHO 2015a). In Indonesia, the epidemic in poultry started in December 2003 on Java Island, with now 31 out the 33 provinces being considered endemic. AI in humans was first detected in July 2005. Despite control measures to prevent further transmission among poultry, the infection rate among humans declined from 5 to 3 cases per month in the reports of 2008.

Up to 2015, a total of 195 cases have been WHO confirmed in Indonesia, of which 165 were fatal – mainly in the period of 2005–2009 (Sedyaningsih et al. 2008; WHO 2015a). Reports over 2014 show a continuation of the decline and only 2 cases are reported in the archipelago (MoH-RI 2015). Refer to Figure 2 for an overview of MoH-RI reports and trends in ProMED-mail reporting of AI. The importance of early ProMED-mail reports is clearly shown here, as the number of reports constantly seems to exceed MoH-RI data, which could indicate impaired implementation of a governmental programme (underreporting to the government). Unfortunately, one cannot rule out (unverifiable) over reporting in ProMED-mail.

Transmission of the disease is considered to be caused by direct exposure to infected poultry. Several family case clusters (Kandun et al. 2008) have been reported suggesting the possibility of human-to-human transmission in a study of Yang et al. (2007). However, transmission estimates were only based on one cluster. In addition, blood relatives were shown to be at risk of infection in household outbreaks, supporting the hypothesis for genetic host susceptibility (Aditama et al. 2011; Aditama et al. 2012). Recent data showed that only a couple mutations in current circulating highly pathogenic AI H5N1 viruses, would be enough to enhance human-to-human airborne transmission (Herfst

et al. 2012). This illustrates the pandemic potential and possible concerns for international public health.

Several measures have been taken to control disease, comprising vaccination of poultry, and implementation of a participatory disease surveillance (PDS) programme, a community-based reporting system (Azhar et al. 2010; Mariner et al. 2014). At the beginning of the outbreaks, control of disease has been problematic due to poor gathering of epidemiological information. Since the start of PDS, registration of new cases has been greatly enhanced. Taking social and cultural context of dynamics and distribution of disease into account have been valuable in this process (Mariner et al. 2014).

Hepatitis A (HAV)

Indonesia was generally considered to be part of the Hepatitis A (HAV) endemic regions of the world. This food-borne infection with HAV, related to decreased sanitation conditions, infects over 90% of children under the age of 10 years in endemic regions (Barzaga 2000). Since the infection before the age of five is rather asymptomatic, the burden of disease for inhabitants in endemic regions is rather low, resulting in a high level of community-based immunity for acute HAV infections. Therefore, hardly any outbreaks occur within the community. In upcoming economies like Indonesia, however, the number of infected children drops with a subsequent increase in symptomatic infections on an older age as a results of a clear increase in level of sanitation (Vranckx et al. 1997). This decline in seroprevalence amongst children and adolescents has been reported in Indonesia and other countries on the continent (Kunasol et al. 1998). This change in epidemiologic pattern has clinical and public health implications, where at some point the introduction of nation-wide HAV vaccination might be cost-effective compared to treatment of acute HAV infection (Suwantika et al. 2014), which is symptom driven. For persons traveling to Indonesia, HAV vaccination is generally recommended by travel medicine guidelines (refer to Table 1) – especially for adults, and imported cases of HAV from travellers to and from Indonesia have been broadly reported in literature (Boggild et al. 2010; Utsumi et al. 2014).

Seasonal influenza and influenza-like illnesses

Influenza viruses, the most well-known members of *Orthomyxoviridae* family, cause respiratory disease in humans predominantly. Those mimicking the symptoms of Influenza are known as non-influenza viruses, causing influenza-like illnesses. Of the three influenza virus types (A, B, and C), influenza A is the best known for its ability to drift, re-assort, and the cause of seasonal human flu on a yearly base. Influenza A affects 5–15% of the human population every year. In the tropical Indonesia climate, no true seasonality of influenza is present (Nicholson et al. 2003). The virus seems to be constantly present and cause respiratory disease throughout the whole year. However, Storms et al. studied the prevalence of influenza virus in patients seeking care for respiratory disease in Jakarta, Java over a one-year period starting in 2011 and reported the highest incidence during December–May with the proportion of positive PCR being 76% for patients presenting with classic influenza-like illness. Of those, 36% had more severe disease during the weeks with highest influenza activity (Storms et al. 2015). Most likely, seasonality exists in line with rainy season. Currently, no country -based policies regarding influenza vaccination (such as for risk groups, healthcare professionals, etc.) are implemented in Indonesia.

MoH-RI discusses the recommendation of antivirals like oseltamivir or vaccination policies in Indonesia, since several studies report this high percentage of complicated influenza cases in Indonesia (up to 15%) (Kosasih et al. 2014; Ampofo et al. 2015; Storms et al. 2015). Of interest for clinicians dealing with travellers with travel plans to Indonesia, comes from data of the Geosentinel network. It shows that travellers travelling to South East Asia have a sevenfold higher change of being infected with seasonal influenza compared to those staying at home (Boggild et al. 2012). It, therefore, seems reasonable to vaccinate travellers and inhabitants; however, a yearly seasonal influenza vaccine is currently not implemented in any Indonesian immunization schedule (Table 1) (Goeijenbier et al. 2017).

During a one-year study from 2008, just above 200 respiratory specimens from patients hospitalized in Indonesia (total 1222 patients including hospitals in Thailand and Vietnam) with suspected influenza or influenza-like illness were collected and analysed. In the cohort, 18.7% of the samples tested positive for Rhinovirus, in particular in March. Furthermore, respiratory syncytial virus (RSV, 11.8%) was found from July to November. Other detected viruses included bocavirus (16.4%), parainfluenza (11.5%), adenovirus (8.4%), influenza A and B (7.6%), and coronaviruses (1.8%) (Wertheim et al. 2015).

Zika virus infection, hepatitis E, MERS corona

Three cases of Zika virus infection, caused by a *Flavivirus* transmitted by *Aedes aegypti* mosquitoes, in Indonesia are reported in literature. These infections, clinically characterized by fever, headache, malaise,

arthralgia, myalgia, and rash, were all documented in returning travellers from Jakarta (2012, after 9-d holiday) (Kwong et al. 2013), Bali (2013, after monkey bite in Ubud Monkey Forest) (Leung GH et al. 2015), and Malaysian Borneo (2014, after a 3-week holiday) (Tappe et al. 2015).

Also, seven cases of probable Zika virus infection in inpatient inhabitants of Central Java were reported based on antibody diagnostics (Olson et al. 1981). In samples collected in 2014–2015, during a DENV outbreak in Jambi ($n = 103$), one DENV negative sample was tested positive for Zika (Perkasa et al. 2016). Once, a monkey bite was proposed as a route of transmission, while Zika is generally considered to be a mosquito-borne disease (Leung GH et al. 2015). Since both DENV and Zika manifest clinically similar, it remains unclear whether Zika virus infection is rare in Indonesia or is often mistaken for DENV. Only limited, if none, diagnostics are carried out to Zika and no regular surveillance programmes exist (MoH-RI 2015).

Three outbreaks of hepatitis E infections, transmitted faecal-orally and associated with low standards of sanitation, have been described in West-Kalimantan and Java (Corwin et al. 1995; Corwin et al. 1997; Sedyaningsih-Mamahit et al. 2002). All three outbreaks were related to dependence to polluted river water. Anti-hepatitis E virus seropositivity is shown to be more prevalent in regions where pigs and swines are more incorporated in daily life, as is the case in Bali Island, compared to Java. Samples were taken from farms in Yogyakarta (Central Java), Tulungagung (East Java) and Mengwi (Bali) (Utsumi et al. 2011; Widasari et al. 2013). Also, hepatitis E virus has been detected in wild rats, however, whether their role in human infection is significant or not remains unclear (Mulyanto et al. 2013).

Middle East respiratory syndrome corona virus (MERS-CoV) causes upper respiratory infections in humans with case fatality rates up to 35%. MERS-CoV is prevalent in Arabian countries, including Saudi-Arabia, which is visited by Indonesian inhabitants for hajj (pilgrimage) (Widagdo et al. 2017). So far, no cases of MERS corona virus infections in Indonesia are reported in literature.

Implications and future actions

Summarized data from scientific literature, WHO reports, reports from the Ministry of Health of the Republic of Indonesia and ProMED-mail, presented in this review, provide a unique insight in the past, current and potential of relevant viral pathogens for the Indonesian archipelago. Indonesia seems to be prone to vector-borne and zoonotic diseases, due to environmental conditions suited for arthropod vectors and the presence of reservoirs for zoonotic viruses. Viruses like DENV have been endemic for many years while re-emergence of AI and RABV have drawn attention from governmental institutes and scientists. Relevant for this region, but underreported in MoH reports and literature are HV, HAV, and JEV. Furthermore, only limited data is available about the incidence of influenza and influenza-like illnesses – while these viruses are known to have a significant burden on society in due to economical losses. Furthermore, these viruses most likely account for a substantial number of hospital admissions for the very young or elderly, as they do in Europe and USA.

The description of a (re-)emerging virus is expected to happen in the order of ProMED-mail reports, scientific studies and governmental data (MoH-RI and CDC or WHO). Only parts of the ProMED-mail data regarding outbreak reports were confirmed or became of scientific interest in cohort studies (i.e. this holds especially true for avian influenza). Ministry of Health (MoH-RI) data seems to be partially in line with these findings. ProMED-mail has proven to be a valuable tool in the (early) detection of outbreaks all over the world. For Indonesia, this is very well illustrated with AI reports, for which, in many cases, the ProMED-mail reports are ahead of official statements and literature. Interestingly, ProMED-mail reporting for the rabies outbreak in Bali started in 2010 (Figure 2), while most likely the outbreak started in 2008. Given the goal of ProMED-mail to report emerging diseases on a low-threshold base, it relies heavily on the awareness and possibilities to report (unknown) cases by local healthcare workers. This shows the importance for adequate on-site diagnostics and surveillance programmes. To our experience, the rabies under reporting seems to be an exception in ProMED-mail.

We noticed some discrepancies in MoH-RI data as compared to WHO and CDC data. In MoH-RI data it is not always clear whether data was not available (i.e. not reported to the government) or no cases occurred at all. Furthermore, limited insight is given in number of suspected cases versus laboratory-confirmed cases. In case of RABV, the number of suspected cases (as measured by the number of animal bites) versus administration of RABV vaccine and number of *confirmed* and fatal cases is reported. Information about the used diagnostic methods lacks, as well as the number of tested samples versus laboratory confirmed samples. Since data is not available for local persons exposed to RABV, it is impossible to draw conclusions based on these observations. However, we do know, with special focus on Bali Island, that RABV post exposure is the number two most

prevalent post-travel health care problem in travellers as per Geosentinel data – just above influenza and below travellers' diarrhoea. The number of actual RABV cases, luckily, is actually one of the more rare problems. We also observed over reporting in ProMED-mail, as only few reports of DENV in ProMED-mail exist but dozens of reports for CHIKV and AI were added; we were unable to settle this discrepancy, moreover, both are reported to the government and taken to MoH-RI reports over the past years. ProMED-mail entries should be interpreted with care, as its form is prone to reporting bias and no peer-review system exists.

There is a clear unmet need for cohort studies in a number of primary, secondary, and tertiary care centres evenly spread over the archipelago. In particular, some well-studied acute viral diseases, such as influenza and influenza-like illnesses are only limitedly researched in Indonesia. Furthermore, up-to-date scientific information regarding for instance HAV and MV antibody prevalence – and hence – the risk for those unvaccinated seems to lack for this region.

Incidence numbers as reported in scientific studies serve a different purpose than those reported in MoH-RI (or CDC, WHO) data, due to the selection of a specific population (i.e. a poultry market, hospital-based, or clinical symptoms). These data should guide healthcare workers in their decisions when assessing patients in the general practice or emergency department. Healthcare workers should, therefore, be able to rely on solid surveillance data from the MoH-RI as well as scientific literature.

In recent years, CHIKV (2013, Caribbean islands), Ebola (2014, West Africa), and Zika (2015, South America and 2016, Asia), have proved to be of relevance for both developed and developing countries. No exception exists for Indonesia, especially since Indonesia is an upcoming economy and a popular travel destination. Vector control is relevant in order to control outbreaks. The MoH-RI sets targets to lower the number of larvae around houses as well as targets for lowering the incidence rate for new cases (e.g. DENV) on a yearly base. Next, to this challenging task, there is need for a functional and validated surveillance programme. Government reference laboratories are only available in limited numbers and the geographic layout in terms of the archipelago, including distant areas, and a variety in both economic strength and availability of health care facilities, poses another challenge to get an accurate oversight EIVD epidemiology.

Changes to the Indonesian vaccination programme will be needed to be made in the future, as new vaccines and epidemiological data become available. This especially holds true for new DENV vaccines and existing JEV (refer to Table 1, comparing the MoH-RI immunization scheme to travel immunization advice). Preparedness for EI(V)Ds can only be achieved with an adequate insight and control of current pathogens, a solid surveillance system including reference laboratories and the ability to scale up the resources needed to adequately diagnose, treat, and follow-up patients.

To our findings, resources should be directed to the One Health concept as it is of utmost importance to achieve the correct balance for people, animals, and the environment. Given recent outbreaks in the world, the existence of vectors in Indonesia and the ability to spread diseases in humans, poultry, or goods, it might just be a matter of time before other well-known viral diseases, such as yellow fever or other emerging diseases will be engrafted in Indonesia.

Disclosure statement

The authors report no conflicts of interest.

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