General introduction and outline

Emerging infectious diseases

In medicine, the discipline of infectious diseases is characterized by several unique features amongst which are a constantly changing and sometimes unpredictable need to address new threads. Such threads are relevant for a group of patients or a whole population (1). Emerging infectious diseases are infections that either recently appeared in a given population or those whose incidence or geographic spread is rapidly increasing in the future. Past experience has shown that emerging virus infections and outbreaks could cause a large number of human deaths and potentially have a huge impact on society. The HIV pandemic that started almost 40 years ago, is still going on, and societal impact is huge. With the 2020 UNAIDS 90-90-90 treatment goals and the additional commitments to end AIDS in 2030 there is hope the pandemic can finally be controlled and stopped. Lessons learned from the HIV pandemic are helpful in strategy planning to control other outbreaks. This is for instance demonstrated by the Ebola virus disease outbreak in West Africa in 2014, which has renewed the attention to global health security, for instance due to its unprecedented scale and impact (2). Just months later, Zika virus (re-)emerged, and became an important public health treat in several countries situated around the equator. The virus was difficult to contain as it is transmitted to humans by *Aedes* spp. mosquitos, which are abundantly available in the region (3). Emerging infectious diseases become of more relevance for reasons of increasing travel and mobility, increased crowding and welfare worldwide. Preventing emerging infectious diseases involves several aspects, amongst which are understanding of pathophysiology and epidemiology in conjunction with a framework of a local, regional and worldwide public health system that involves steps of surveillance, emergency preparedness and prevention. In this regard, joined efforts and knowledge from Western countries and local countries are needed to study and act upon diseases as a joint responsibility to combat infectious diseases (2). A significant number of emerging infectious diseases are zoonotic in origin, that is, the disease has crossed the species barrier and is able to cause human diseases. A number of countries around the equator display conditions that favor such conditions, for instance by habiting mammals (e.g. monkeys as natural host) and arthropods (e.g. mosquitos as vector). This includes Indonesia, an emerging low to middle- income country, that is strongly connected with the world for its history in the Colonial Era, emergence as independent country and tourism destination. Unique characteristics such as a variety of cultural habits, religious beliefs within the country and an diverse ecosystem put Indonesia apart from other countries (4). For such reasons, the study of infectious diseases needs to translate international practices to local needs and opportunities.

The archipelago Indonesia

The archipelago Indonesia compromises thousands of islands spread across the equator. It is considered the largest economy in Southeast Asia and is home to 300 ethnic groups, impressive flora, fauna and several touristic highlights. According to data from the World Bank (5), Indonesia is displaying continuous economic growth and is considered an emerging low to middle-income country (6). Poverty rates were cut in half, to 9.8%, in a time span from 1999 to 2018 (5). Still, the

population is vulnerable to economic misbalance, as close to a quarter of the populations income is just above the national poverty line. Great efforts have been made in improving public services (7), but the quality of health clinics is considered uneven to middle income standards. It is one of the reasons why governmental five year medium-term plans, PJMN (*Rencana Pembangunan Jangka Menengah Nasional*), focus on health-care development. More specifically, accessibility of basic health-care facilities for the less privileged people is to be improved (8, 9).

Accessibility of health care

The accessibility of healthcare facilities in Indonesia is different from Western countries. In Western countries healthcare is generally characterized by good accessibility and a healthcare insurance coverage taking care of expenses (10). Those living in Indonesia face the following difficulties: first, a basic health insurance for all inhabitants was only introduced in 2014 and is currently mandated for all inhabitants. Next, some may find themselves distant from health care facilities. Especially those in urgent need of medical care might not reach the hospital in time due to their physical distance or limited self-reliance to facilitate transportation. Last, the understanding and management of both non-communicable (NCD) and communicable (CD) diseases needs a more consolidative approach and a decentralized implementation (9). The group of NCD's includes cardiovascular diseases, chronic respiratory diseases, cancer, diabetes and mental health conditions, which alone are responsible for 71% of all deaths worldwide. It is known that the poorer the people, the more disproportionately they are affected by NCDs (11). Financial self-support of some inhabitants is limited and so is the ability to pay for several medications. In contrast, up to 70% of males cannot refrain from smoking (12).

Communicable diseases (CD)

Communicable diseases (CD) include all human infectious diseases - caused by micro-organisms (e.g. bacteria, parasites) and viruses (13). These pathogens are transmitted directly from one human to another (person to person) or indirectly, via insects, other animals or by consuming contaminated food and water. Seventeen percent of infectious pathogens is spread via arthropods (e.g. mosquitos), which can act directly as intermediate hosts for human infections or via other mammalian hosts. Over recent decades, two views have emerged in this regard. First, climate changes and global warming influence the behavior of vectors (14). This is clearly seen in expanding areas with suited breeding circumstances for *Aedes* spp. mosquitos (15-17). Second, increased understanding of the interplay of mammalian species has resulted in the one-health concept, which delineates collaborative efforts from several fields of work (18). The number of relevant micro-organisms and viruses is extensive and for instance includes dengue and Human Immunodeficiency Virus (HIV). They can result in a heterogeneous spectrum of clinical signs ranging from mild and self-limiting to severe conditions, including chronic/persistent infections, long-term disability/morbidity and even can cause mortality. In this work we focus mostly on for human relevant viral infectious diseases.

Diagnostics

When a patient comes to a hospital with a fever, the treating physician will assess several clinical parameters and obtain specimens from the patient to perform routine laboratory tests. Based on clinical experience and epidemiology he/she might consider an infection with (myco)bacteria or viruses. Initiation of empirical treatment might be indicated and could improve patient outcomes if started promptly. An increasing number of hospitals use molecular assays to detect genetic material of pathogens or viruses in a sample taken from the patient. The data acquired is also relevant for compiling epidemiological reports. While these assays are characterized by their high specificity (19), high costs are a major hurdle to the implementation of such techniques in low-middle income countries. Also, most molecular assays are known to have a turn-around time of at least a few hours from sampling to final reporting and thus cannot be used in the initial clinical assessment. Alternative methods include antigen detection, cell culture (commonly used for bacteria, and if handled correctly for viruses as well) or serological assays. Antigen detection and serological assays are possible through a number of commercially available tests. Culture is considered gold standard for pathogen detection and is often combined with the aforementioned techniques to improve diagnostic accuracy. Serology is based on the response of the human immune system to pathogens and is particularly useful to follow-up an acute infection or to perform serological surveillance in a group of individuals (20).

The burden of flavivirus infections

Flavivirus infections, a genus in the family of *Flaviviridae*, are amongst the most prevalent acute viral infections in human in Indonesia. Dengue virus, a virus in the flavivirus genus, was detected in Indonesia already half a century ago, and while once confined to Asia it now even poses a threat to Europe (21, 22). Dengue is mainly vectored by mosquitos of the *Aedes* spp. and the infection is increasingly stressing the admission capacity of hospitals. *Aedes* spp. mosquitos also facilitates the spread of several other flaviviruses, including Japanese encephalitis – known to cause long term neurological sequelae (discussed in detail in **Chapter 2**) and yellow fever. Yellow fever virus is a vaccine preventable disease (23). It infects all species of monkeys and certain other small mammals. Even though Indonesia habits monkeys in its rain forests, yellow fever has not yet established itself in Indonesia as no current evidence about yellow fever presence in Indonesia is available. Modeling studies however, show that the circumstances in Indonesia would suit yellow fever receptivity, which thus could contribute to local transmission (17).

Human Immunodeficiency Virus

Human immunodeficiency virus - 1 (HIV-1) is a lentivirus from the family of *Retroviridae*. For most human cases, the virus is sexually transmitted. Non-sexual transmission occurs predominantly from mother to child during pregnancy or during birth (vertical transmission). If the virus is left undiagnosed and untreated, virtually all people infected with HIV-1 will progress to acquired immunodeficiency syndrome (AIDS) and eventually will die. AIDS is characterized by depletion

of CD4+ T-cells in the peripheral blood, which in turn results in impaired function of the immune system and hence opportunistic infections arise. Many HIV-infected people are unaware of their status and therefore may contribute to the spread of the virus (24). For this reason, worldwide efforts direct to "test and treat" strategies for HIV (25, 26). Current HIV-1 testing is characterized by high sensitivity and specificity and is based on the development and detection of HIV-1 antibodies and p24 antigen. A positive result should be complemented with tests to differentiate between the HIV antibodies and detection of plasma viral RNA and/or antigen (27). The introduction of antiretroviral treatment (ART) transformed HIV into a chronic condition. Although the virus is not cleared from the body, plasma viral load becomes undetectable, preventing viral transmission and greatly reducing progression to AIDS. During ART, HIV stays latently present in cells, with limited impact on general health. Quality of life over the past years and life-expectancy in people living with HIV improved, as treatment regimens are increasingly simplified and side-effects reduced (28). First call on HIV surveillance in Indonesia is made in a letter of Vranckx and colleagues. Already in 1986, just three years after the first research groups described their findings on a "novel retrovirus" (29, 30), Indonesian researchers stress the need to immediately implement surveillance and control measures (31). Recent data from the Asian-Pacific region shows that Indonesia contributes to 18% of the new HIV infections and to 23% of AIDS-related deaths in that region. Stigma and misconceptions about HIV are abundant in daily life in Indonesia. For instance, more than half of the adults would not buy vegetables from a vendor living with HIV. While the HIV incidence rate decreased from 0.28 (per 1000 - 95% CI: 0.24-0.31) in 2005 to 0.19 (95% CI: 0.16-0.22) in 2017 – AIDS-related deaths are high and are estimated to 39.000 cases in 2017. The number of people living with HIV in Indonesia is estimated at 630.000, 42% (95% CI: 36-49) is aware of their HIV status and only 14% (95% CI: 12-17) is on treatment (data from 2017) (32). Since the discovery of HIV, people are on the search for HIV cure – current efforts look either to functional cure – a situation in which a person living with HIV would be able to suppress HIV without ART; and to viral eradication – a situation in which the body would be free from HIV (33).

Rationale and Outline

The studies in **parts I**, **II**, and **III** aim to address the current situation, explore possible interventions and look into future opportunities for human Emerging infectious diseases in Indonesia. As introduced above, joined efforts and knowledge from Western countries and Indonesia are important in the study and the acting upon infectious diseases in Indonesia. This is reflected in the following chapters, which later integrate to a summarizing discussion, included in part **IV** of this thesis.

The current situation is studied in **Part I**, comprising **Chapters 2-4**. With a main focus on clinical data, we "set the problem". **Chapter 2** is a clinical overview of the available data on acute virus infections in the Indonesian archipelago. Acute virus infections increasingly stress the admission capacity of hospitals. Scientific data is presented jointly with surveillance data from the Indonesian government and also includes data from ProMED mail, an email service to provide informa-

tion about emerging diseases. **Chapter 3** describes the clinical data from a two year prospective cohort study conducted in patients admitted with fever and signs/symptoms of central nervous system (CNS) infections. CNS infections are relevant for their association with high mortality and morbidity and thus have a high impact on a (local) society. In **Chapter 4**, we describe a case from a local outbreak of a vaccine preventable disease that has a potential to emerge in other countries.
In **Part II**, comprising **Chapters 5-7**, we elaborate on challenges that clinicians and healthcare policy makers face. The first challenge is the abundance of outbreaks of flavivirus infections that stress the capacity of healthcare systems. In **Chapter 5**, we studied thrombocyte function in dengue virus infection using a point-of-care test as there is a clinical need to be better able to judge the need for hospital admission in a patient infected with dengue. Another challenge are the increasing number of immunocompromised patients, that are treated for a NCD (e.g. renal transplantation in case of end-stage renal disease). This group of patients needs measures to them from future infections. Last, the abundance of *Aedes* mosquito spp. in Indonesia would potentially facilitate a local outbreak of yellow fever. The challenges to protect the immune compromised patient to infections while home and on travel are discussed in **Chapter 6** and **7**. In **Chapter 6** the challenges to adequately protect immunocompromised patients to infections are studied from the perspective of a Western country. Next, **Chapter 7** explores possible changes in yellow fever vaccination strategies in immune compromised patients, bridging the emergence of immunocompromised patients and the potentially emerging yellow fever virus in Indonesia.
Part III, comprising **Chapters 8-10**, focuses on studies in HIV infected individuals. Amongst the future challenges, the search for a durable control of HIV infection is needed. In **Chapter 8** we explore the current scientific knowledge on HIV from the Indonesian perspective, as there is no current overview on research and knowledge gaps. In **Chapter 9** and **10** we present data of the phase II HTI-TriMix mRNA vaccine clinical trial in HIV infected individuals on stable treatment – as example of studies in the search for a durable control of HIV.
Key findings are summarized and future implications are discussed in the context of current literature in **Chapter 11**.

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Part 1

Setting the problem