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Summarizing discussion and directions for future studies

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"Wonderful Indonesia" - the tagline of the campaign of the Ministry of Tourism, Republic of Indonesia (1) – is imaginative to the enormous diversity in terms of nature, landscapes, arts and culture that the Indonesian archipelago has to offer. Competitive pricing of flights and the strong contributions of the Ministry of Tourism have increased the accessibility of the country. Its continuous economic growth is also reflected in the numbers of air transport, as the Soekarno-Hatta international airport of Jakarta finds itself in the top three busiest international and top ten busiest domestic airports of the world (2, 3). In contrast to the suggestion of fairly welfare as described above, the archipelago struggles with reformations of the healthcare system (4). For this reason, middle to long term plans of the government focus on health-care development. This, amongst other measures that are not within the scope of this work, will without doubt result in improved understanding and control of infectious diseases in Indonesia. As infectious diseases do not restrict to international borders, our findings might be relevant for all working in the field of public health, infectious diseases and government / policy. The views presented in this summarizing discussion are either based on our research findings, available data and personal views / interest – which were gratefully acquired during a number of visits to Surabaya, Indonesia.

OVERVIEW

After the introduction, we "set the problem" in **Part I**. We delineate relevant virus infections for the country (**Chapter I.2**). We then discuss findings from a two year cohort of central nervous system (CNS) infections cases (**Chapter I.3**). We included a chapter (**Chapter I.4**) on a diphtheria case, as upcoming vaccine preventable disease, that might become of international relevance. In **Part II** we explore clinical challenges by bridging international knowledge. Our study on point-of-care testing in dengue infected patients (**Chapter II.5**) aims to better understand the role of thrombocytes in dengue in those in seek of hospital care. Next, over recent years, the number of non-communicable diseases (NCD) in Indonesia has increased drastically, and thus the number of patients in seek of care is rising. Examples for treatment include immune suppressive therapy to prevent organ rejection in case of a renal transplantation or cytostatic drugs that induce immune suppression in cancer. In this regard, **Chapter III.6** studies the impaired awareness and challenges in infection prevention in the immune compromised patient from the perspective of a Western country. The findings are further explored for yellow fever, which has a potential to emerge in Indonesia – in **Chapter II.7**. **Part III** of this work focuses on clinical studies in HIV infected individuals. First, **in Chapter III.8** we summarize studies on HIV in Indonesia, identify gaps in knowledge and we explore potential goals in research. **Chapters III.9** and **III.10** are the results of our collaborative efforts to study alternative approaches that aim for durable HIV control in human. We present the results of the studies of the iHIVARNA consortium, which studied a therapeutic mRNA HTI-TriMix vaccine.

SETTING THE PROBLEM

An adequate overview of endemic and emerging viruses is needed

A thorough review of available literature, a summary of ProMED-mail data and a review of governmental reports on acute virus infections available until May 2016 is presented in **Chapter I.2**. Numerous viruses are either endemic, emerging or have a potential to emerge in Indonesia. The trends observed in availability of literature and ProMED-mail data, are a representation of overall governmental and research resources to study virus infections. Clear peaks were observed in ProMED-mail reports, for instance for chikungunya in 2010, rabies in 2011-2012 and avian influenza in 2006-2009. For a number of viruses, such as dengue, governmental surveillance was already implemented following the first case description. The peaks observed, however, were possibly subjected to re-active surveillance of infectious diseases (e.g. in case of an expected outbreak or following and outbreak), rather than thorough proactive surveillance (i.e. continuous surveillance, that is continuously conducted and is not dependent of any special interest or outbreak). The more recent governmental reports now include background information on the infectious diseases that are discussed and are subjected to routine surveillance, though information on collection and classification of cases is lacking (5). More accurate knowledge on the impact of infectious diseases would be possible if classifications such as “possible, probable or definite” are always included. This would also identify gaps in countrywide availability and accuracy of diagnostic assays, as are introduced in **Chapter 1**. Clinical studies using patient samples are of continued importance, mainly for their identification of new and known viruses (or other infectious pathogens) and second for validation of diagnostic assays. Overall sero-surveillance, which is discussed later, would provide knowledge on the impact of emerging viruses by detecting seroconversion in an otherwise healthy population. This all is relevant for the interpretation of the context from the reports that originate from an extensive diversity of hospitals and healthcare facilities, located in both well and less accessible areas of the country.

Another challenge are the clinical overlapping signs and symptoms for hemorrhagic fevers (i.e. dengue, Ebola, Hantavirus), which are therefore easily misclassified if not adequately studied using additional laboratory assays. For example, this is the case for Hantavirus infections, as clinical signs overlap for instance with leptospirosis, these are not yet routinely reported in governmental reports. Recent data shows that in up to 13% of humans IgG antibodies against Hantavirus was detected for a mixed group of acute cases and sero-surveillance, and sero-prevalence in rodents was up to 34% (6, 7). Import cases to Europe were also described recently (8). For Zika virus – which could clinically present with symptoms similar to dengue, a recent study shows a 9.1% seropositive rate against Zika in 662 human samples taken from 30 urban sites (9). Others however pretend that there would be no Zika around in 2016, though scientific quality seems poor (10), especially given the rapid decline of IgM/IgG antibodies in Zika (11). Apparently, there is other scientific interest in the topic as well, given a numerous number of studies that looked into pregenancy-related issues for Zika or eventual vaccine acceptance (12-14) in the country.

The status of Zika-associated microcephaly, of which scientific evidence became apparent (15), might currently be lacking in Indonesia due to impaired surveillance. In addition, recent disease outbreaks have underlined the necessity to improve surveillance. This may be best illustrated by the outbreaks of chikungunya and avian influenza. Harapan and colleagues have reviewed recent data on chikungunya and found that not only thorough epidemiological data was lacking, but their studies also added to the understanding of re-emergence of chikungunya already in 2001 (16). Adequate policy making is hampered by impaired interpretation and differentiation of overlapping signs, symptoms and diseases.

Diagnostic laboratory assays play a limited role in daily patient care

We have conducted two prospective cohort studies in the RSUD Dr. Soetomo hospital in Surabaya, a teaching hospital in the East-Java region. The results of one study, on CNS infections, conducted on a Neurology ward, are available from **Chapter I.3**. In this study we report the availability of lumbar punctures in 47% of the cases and a mortality of 40%. Based on our data and following guidelines for management of CNS infections (17), the number of lumbar punctures should have targeted 100% in this cohort. From our experience during the collaboration, as is also discussed in **Chapter I.3**, and from a literature review the following factors seem causative to this low number of available data:

- Patient or family refusal of (additional) blood draw or lumbar puncture (unpublished data, (18))
- Physicians knowledge and skills (18)
- Limited interplay between a consulting clinical microbiologist and the treating physician
- Limited availability of diagnostic assays, for multifactorial reasons of limited financial support and strict governance. This includes insurance coverage, the need to prioritize assignment of available budget and logistical challenges to re-stock supplies.

The currently limited diagnostic yield in the study of **Chapter I.3** is worrisome, as current clinical decision making is mainly based on clinical syndromes or scattered epidemiological data. From the previous paragraph (An adequate overview…) it is suggested that such data is "the best there is", which currently seems to hamper sufficient understanding of infectious diseases, with possible preventable Disability Adjusted Life Years (DALYs) as result. A possible approach is in part discussed in **Chapter I.3**. Using a minimal set of routinely available assays, clinicians could differentiate between diseases that benefit from prompt and adequate treatment. Such assays are preferably not subjected to financial barriers such as insurance or reimbursement and should be made available in-hospital. Testing is preferably done using molecular techniques that target a specific pathogen or virus. In this regard, this approach might well be superseded by novel and more integrative approaches, such as syndrome based multiplex (19) or rapid antigen detection techniques. Also, lateral flow based immunoassays might be suited (20), or other near point of care strategies (21) and computer aided machine learning (22). In addition, it seems important

that a random selection of samples may be sent out for reference purposes to a central laboratory. In addition, international collaboration between reference laboratories is necessary to validate samples. This process is possibly hindered by recent anti-bio piracy rules, that might refrain international researchers from investing in future research collaborations in Indonesia (23).

Vaccination hesitancy could be detrimental in infectious disease control

At the time of writing, multiple countries spend a great deal in vaccination hesitancy. High vaccination uptake and coverage are vital in the success of vaccines and vaccine preventable diseases. The importance of such is acknowledged by the WHO, which has established an expert group in the topics of behavioral and social drivers of vaccination uptake (24). Even though the study of (reasons for) vaccination hesitancy in Indonesia is outside the scope of this work, in **Chapter I.4** we present relevant data of the implication of a declining vaccination coverage for the occurrence of diphtheria infections in Indonesia. A declining vaccination coverage for several vaccine preventable diseases, including for instance diphtheria (25) and measles (26), puts those unvaccinated at risk of contracting the disease. This is especially important for vulnerable risk groups, being young children, elderly and immune compromised individuals – the latter of which will be discussed later. In turn, a higher number of people might be in seek of medical care and suffer from complications (27) or can potentially introduce diseases to areas which are currently known disease free – which might include countries overseas. Such challenges in vaccination adherence might be harmful for the availability of resources that are needed in the understanding and management of infectious diseases. For instance, to attain sufficient uptake for vaccines that are currently publicly, freely, available as governmental programs, funding and human resources are needed. Together with the increased impact on medical care, this could negatively impact governance in funding for infectious disease understanding and control.

STUDIES ON CLINICAL CHALLENGES

Alternative strategies in the clinical management of dengue virus infections

As is also discussed in **Chapter I.2**, dengue is endemic in Indonesia. The virus accounts for up to 55% of febrile illness presentations to hospitals. The challenges to deal with dengue virus are multifactorial and include prevention by means of vector control (28), human knowledge and behavior (29), vaccination (30). Clinical management preferably includes timely and adequate detection of dengue cases. In addition, hospital resources are needed in case patients need in hospital follow up. In **Chapter II.5** we evaluated the clinical use of multiple-electrode aggregometry as tool to mark dengue disease severity using bedside thrombocyte testing. Following our study, whole blood aggregation tests using this method could potentially aid clinical management of dengue suspected patients – especially in outbreak situations where there is a need to early differentiate between the patients that are in need of hospital admission or safe recovery at

home (31). A strength of the study is the prospective design, and the results of multiple-electrode aggregometry were not used in clinical judgement or to direct treatment for those admitted to the hospital. The findings however need further validation, as for instance circulating genotypes might have influenced results (32) and each study group included only a limited number of patients. Adequate recognition and detection of dengue was deemed cumbersome, as can also be depicted from a recently published multicenter observational cohort study performed in Indonesia that included close to 1500 cases with suspected dengue infection. The authors suggest that diagnostic accuracy needs optimization for reasons of misdiagnosis of dengue infections and over-estimation of dengue, for instance because just over 10% of cases is misdiagnosed as dengue by clinical sites (33). Even though the number of severe dengue cases is relatively low, which includes low risk of severe dengue for travelers (34) – still the number of patients in seek of hospital care is high. In order to make optimal use of hospital resources – i.e. bed capacity; accurate and rapidly available diagnostics need to be established cost-effective.

Protect vulnerable individuals from future infections

As is introduced in **Chapter 1**, the number of NCDs is increasing drastically in Indonesia. Advances have been made over the past years, for instance in setting up and evaluating of kidney transplants for end-stage renal disease (ESRD) – which disease is closely related to (end-stage) hypertension and diabetes. Kidney transplants are being performed in Indonesia starting late 1970s, but the number of annual transplantations has varied greatly, for instance due to governance issues. Over the past years minimal invasive surgery, extension of age groups and appointment of government hospitals has resulted in a steady increase in transplantations (35, 36). The first heart transplantation will soon be performed in a governmental hospital (no reference available). Such interventions will increase the number of immune compromised patients, as organ rejection needs to be prevented using immune suppressive agents. Similar trends and opportunities are seen in the treatment of auto-immune diseases or cancer – and in this regard, current state of treatment possibilities still has to combat to the services level of Western countries. The immune compromised are more vulnerable for infectious diseases, due to a diminished functionality of the immune system. This includes several viral infections (37). In **Chapter II.6** we performed an integrative study of the opinion of healthcare provides that are closely involved in the care of this group of patients. Forward-looking to the currently ongoing advances in the Indonesian healthcare system, this study was conducted in the Netherlands, as example of a modern Western hospital with extensive treatment options. Interestingly, here, healthcare professionals self-reported a suboptimal knowledge about prevention of infections in immune compromised patients (score 7 on a 1-10 scale). The majority however agreed that they themselves are responsible for adequate measures to prevent their patients from infections that potentially could be avoided. It is suggested to integrate a method of education for immune compromised patients, in order to reduce the number and severity of infections. In addition, investments in increasing vaccine uptake and alleviating barriers to vaccinate was deemed important. Such knowledge can be used to the

advantage for the Indonesia healthcare providers and optimize preventive care. In this regard, we are in the process of setting up a similar study in hospitals in Jakarta and Surabaya – to study the current status quo.

Yellow fever is a flavivirus with a potential to emerge

As discussed previously, the abundance of flaviviruses around in the Indonesian archipelago – in part due to the suitable breeding circumstances for *Aedes* spp. mosquitos that vector a number of flavivirus infections to human, poses challenges due to clinically overlapping symptoms, detection an clinical management. In this regard, yellow fever virus was never described before in Indonesia, while this virus is commonly seen and vaccinated for in other countries situated around the equator. Recent studies have provided evidence that Indonesia might become a possible new infection risk zone for yellow fever, and is primarily at risk for a small urban outbreak caused by an imported case (38). In this line, prominent authors, working in the field of arbovirus research have recently expressed their concerns with regards to the continuous expansion of arbovirus infections, which they illustrate by the recent Zika outbreak. It is suggested for instance to target vaccine development for arboviruses, following the successes of the yellow fever vaccine (39). A rising number of travel movements and increasing number of immune compromised patients becomes even more important in this case than ever before. In **Chapter II.7** we piloted the effectiveness of the live attenuated yellow fever vaccine in immune compromised patients. The study is based on the discrepancy of immune compromised patients that cannot be safely vaccinated against yellow fever whilst they might be traveling to yellow fever endemic areas. They are at risk to contract yellow fever, resulting in a viremia and as such could potentially introduce the virus into populated areas with a high mosquito density, and where the majority of inhabitants have little to no immunity against yellow fever (40) - i.e. Indonesia. We were able to show virus neutralizing antibodies in these immune compromised patients, though larger studies would be needed to estimate the correlates of protection – as this data currently only is available from mostly healthy individuals (41), though recent WHO guidelines (40) are based on multiple studies detailing long-time protection even after receiving small doses of yellow fever vaccine. The worldwide availability of a relative safe and effective yellow fever vaccine has probably limited development of approaches that are more suited for immune compromised patients – for instance the study of inactivated (42) or DNA vaccines (43) against yellow fever. As discussed earlier, multiplex approaches might be used to differentially diagnose between the number of flaviviruses around. Future studies should therefore direct to setting up and evaluating diagnostic assays from both a pro-active and reactive sero-surveillance point-of-view. Flaviviruses should be studied and diagnostics should be validated in Indonesia, using samples obtained in Indonesia, as these samples display a pattern of previous flavivirus exposure that is unique for Indonesia. Assays with a high sensitivity and specificity for the detection of acute yellow fever are needed to timely detect an imported case of yellow fever using approaches as described earlier in this discussion. In addition, as current sero-surveillance for yellow fever is lacking in Indonesia,

the validation and implementation of serological assays able to detect multiple (cross-reactive) flaviviruses could alleviate uncertainties in current public health surveillance (44, 45).

Knowledge and behavior of the general public

Part of the visits to conduct the studies described in this work were combined with the senior high school project Viruskenner (46). In the multinational Viruskenner project, students gained knowledge on several viruses. The aim is to study viruses and come up with innovative ideas to spread knowledge in order to prevent future infections. The Viruskenner project is an example of community engagement in changing human knowledge and behavior to prevent virus infections. Such projects and tailored approaches for individuals are of increasing importance in the prevention of infections – especially in the light of a sharp increase in incidence of arbovirus infections (39) and HIV (47). Even though such studies are beyond the scope of this work, the history of Indonesia being a postcolonial country and a varying citizenship around the country (48, 49), make that such approaches should be carefully governed to sufficiently empower local citizens. In this regard, a framework to conduct citizen science – that is conduct science with help of the general public - could find its way to (areas of) Indonesia in the coming years (50). The strength of this approach for Indonesia was for instance recently demonstrated in studies on long-term ecosystem changes (51).

STUDIES ON CHRONICALLY HIV-INFECTED INDIVIDUALS

The current landscape of HIV research in Indonesia

In **Chapter III.8** we studied the current status and opportunities in HIV research in Indonesia. HIV was studied from the perspective of several scientific disciplines and interest, from its first appearance in Indonesia. The studies conducted have mainly targeted several risk groups of HIV (i.e. men having sex with men, prisoners, i.v. drug users, sex workers) and have primarily focused on attitude, knowledge and behavior. Interestingly, only sparse studies have covered knowledge and behavior of the general public. In addition, testing strategies and willingness to test for HIV (or other sexually transmitted diseases) were studied in risk groups alone. Some of these risk groups play a major in the contributing role in the spread of HIV to the “general” public. For instance, married men may engage in unprotected sex cross the borders of their marriage, and as such become infected with HIV. In doing so, they then can infect their partner within marriage (52). This chapter serves as introduction to the studies from **Chapter III.9** and **III.10**. We have identified that it is mainly prospective studies that seem to be lacking in research in the Indonesian HIV research. In this regard, studies that focus on test- and treatment opportunities (53) seem most in place, as stocking and distributing ART are a daily need and not all HIV infected individuals adequately control their HIV infection – either due to unawareness of their HIV status or for

troubles to maintain therapy adherence. The latter for which the reasons are extremely diverse and will not be discussed here.

iHIVARNA clinical studies using a mRNA vaccine as a promising strategy

In both **Chapter III.9** and **III.10**, the burden of ART and its associated costs were introduced. This drives the search for alternative and more durable strategies, with a same outcome – that is, effective HIV control in infected individuals and prevention of new HIV infections. Within the iHIVARNA consortium, we studied the HIVACAT T cell Immunogen (HTI), a rationally designed mRNA sequence of HIV epitopes that are conserved and predominantly recognized in those with spontaneous low HIV viral loads and were selected for high cytotoxic T cell functional avidity and cross-reactivity (54). TriMix served as adjuvant to further enhance and mount a more durable antigen presenting cells function (i.e. using a constitutively active form of Toll-like receptor 4 (caTLR4), ligand for CD40 (CD40L) and CD70). The HTI-TriMix vaccine was administered to HIV-1 infected individuals using ART. These studies would not have been possible without funding from the European Union and with the expertise of the consortium members. A well designed collaborative study protocol (explained in more detail in **Chapter III.9**) made it possible to not only perform an integrative study around this study product, but also include intranodal vaccination – as relatively new approach to more directly target cells of the immune system and to circumvent a laborious ex-vivo approach. Overall experience with such procedure was good, as it is a relative easy procedure to be performed by a trained radiologist. We observed no major or unexpected adverse events around the procedure – other than those already known for intramuscular or subcutaneous vaccination. Our experience might also add to understanding the safety around lymph node biopsies in HIV infected individuals, as this becomes increasingly relevant in HIV research (55). As discussed in **Chapter III.10**, the study product contained an unexpected error, in that an unintended extra start codon was introduced in the HTI immunogen coding sequence. While further investigations were not done on this study product, mRNA vaccines still represent a promising alternative to conventional approaches – in particular for infectious diseases and oncology. mRNA vaccines were first studied in-vivo already two decades ago. Research was then diverted to other approaches, mainly for reasons of mRNA instability and inefficient in-vivo delivery. Recent “tweaks” to mRNA and establishment of a variety of mRNA vaccine platforms have however rendered synthetic (m)RNA more “stable, deliverable and immunogenic” than before, but there are still challenges to overcome for bridging basic research (i.e. understanding biochemistry and cellular processes) to preclinical (i.e. mouse-experiments) and human work (i.e. daily use of mRNA vaccines) (56). Currently, only limited human studies have entered phase 3 stage research (57). As is discussed in **Chapter III.10**, we have observed a more rapid off-set and higher increases of HIV-specific cellular immune responses in the TriMix-containing arms – although these responses were limited, they most likely represent an effect of the TriMix adjuvant on immune activation, as this was not observed in the water for injection (placebo) arms alone.

Translate experience of iHIVARNA studies to Indonesia

From the iHIVARNA consortium it has become apparent that, even though well and rationally designed, a minor error could have a serious impact on the available resources within a team of researchers. Trial registration, reporting, data sharing and auditing has become more important than it was before. Similarly, good clinical and laboratory practice guidelines and a European Union general data protection act do further secure and tighten up the research opportunities. In addition, scientific journals favor open access publishing and data sharing, sometimes even prior to a completed peer-review process. In contrast, Dutch universities seem to have set low priorities in reporting clinical trials to the authorities, i.e. European Union (EudraCT), as currently only a few studies are reported after completion (58). So, it seems that there is either less urgency or availability of funding to invest in support staff, legal department and a contract research organization. As has become clear from **Chapter III.8**, Indonesia has clear research opportunities for HIV research, that are mainly focused to test and treat of HIV. In addition, more durable HIV control would for instance put less stress on the physical barriers to reach patients from HIV treating facilities. There is however a big financial gap to bridge between funding, identification and exploiting research opportunities, as was partially discussed before. Despite the former, citizen science and relative low labor costs, compared to Western countries, might put Indonesia in a position easily ahead in advanced medical research – for instance with phase 3 clinical trials that need extensive follow-ups and safety reporting.

CONCLUDING REMARKS

In this work, "Endemic and Emerging Infections – clinical challenges and opportunities in Indonesia", we have studied parts of the current situation, clinical challenges and opportunities for human (virus) infections in Indonesia. This work is based on literature review and governmental reports for virus infections, original work and case series from healthcare settings in Indonesia and Europe. In the summarizing discussion we have bridged the research perspectives and opportunities to the Indonesian situation. By no means is this work suggested to be exhaustive, it merely is a reflection of a possible approach integrating trends, scientific data and a personal experience. Opportunities for scientific research to human infectious diseases seem very well present in Indonesia. The recently introduced and ongoing reformation of the healthcare system will for sure need to compel adequate governance to assign available budgets and resources in healthcare, research and education. Overall, there is a need to acquire an optimized oversight of endemic and emerging infections in the country, for instance by optimizing sero-surveillance and setting-up a more comprehensive notification of diseases. Hospitals need far-reaching support in setting up and validating diagnostic assays for infectious diseases in way that such tools are accepted for all participating parties – including government, infectious diseases specialist and medical microbiologists. Prevention, identification and optimizing treatment is in place for a

number of risk groups. These risk groups include, but are not limited to those that are at risk for a dengue infection, become immune compromised or become HIV-infected. Each of these aspects represent extremely interesting future research possibilities that, if fully utilized, will certainly direct Indonesia forward to become a major party in quality of healthcare and medical research.

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