Evaluate the cost-effectiveness of a potential Zika vaccine candidate

A Hypothetical Implementation in Colombia

European Master in Health Economics and Management

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Abstract

Background: Zika virus (ZKV) is the fourth major infectious disease announced as Public Health Emergency of International Concern (PHEIC) by WHO in the beginning of 2016. Until today, there is still no approved vaccine after seventy years since ZKV was discovered. Mobilization of international resources has led to a number of vaccine candidates currently under preclinical or clinical testing. Given the early stage of development, the potential cost-effectiveness of a vaccination campaign is unknown.

Objective: To evaluate the cost-effectiveness of a hypothetical Zika vaccine candidate for potential implementation in Colombia

Materials and method: Compartmental deterministic model is used to describe the dynamic of ZVI, Markov Chain Monte Carlo (MCMC) method is utilized in conjunction with the deterministic result to evaluate the cost-effectiveness of a hypothetical vaccination campaign. Sensitivity, scenario, and value of information (VOI) analysis are used to evaluate uncertainty of the model. Data are derived from literature review (Pubmed search), WHO, CDC and other sources. Data then are synthesized, converted to reflect as close as possible to the local perspective.

Results: Within the model, vaccination campaign is highly cost-effective. From societal perspective, it not only leads to improvement of health outcome but also saves cost. The earlier a potential vaccination program introduced, the more cost-effectiveness it is; introducing vaccination campaign after about one year from the beginning of an outbreak does not lead to health outcome improvement within two and half years horizon. The effect of birth rate drop is significant and there is a need to do further study on this area. Improving yearly delivering capacity could potentially improve the cost-effectiveness exponentially.

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Abbreviations and Acronyms

ADE	Antibody-dependent enhancement of infection
CDC	Centers for Disease Control and Prevention
CEAC	Cost-effective acceptability curve
CZS	Congenital Zika Syndrome
EID	Emerging Infectious Disease
EVPI	Expected Value of Perfect Information
EVPPI	Expected Value of Partial Perfect Information
MCMC	Markov Chain Monte Carlo
MinSalud	Colombian Ministry of Health
NMB	Net monetary benefit
NHB	Net health benefit
OECD	Organisation for Economic Co-operation and Development
GBS	Guillain-Barre Syndrome
PAR	Population at Risk
PPP	Purchase Power Parity
PHEIC	Public Health Emergency of International Concern
QALY	Quality Adjusted Life Year
TPP	Target product profile
ZKV	Zika Virus
ZVI	Zika Virus Infection
WHO	World Health Organization
SEIR	Susceptible-Exposed-Infected-Recovered
UNICEF	United Nations Children's Fund
VOI	Value Of Information

1 Introduction

The recent 2015-2016 Zika outbreak had once again raised an alarming awareness on the threat of Emerging infectious disease (EID) not just for countries within the areas close to the equator (WHO 2017). Zika virus was introduced after two major arboviruses (West Nile and Chikungunya) into Western Hemisphere (Marks and Petersen 2017), and to countries far from the equator by traveling and local transmission (WHO 2017). Zika virus can cause Congenital Zika Syndrome (CZS) (Rasmussen, Jamieson et al. 2016, WHO/Unicef 2017) and Guillain-Barre Syndrome (GBS) (Cao-Lormeau, Blake et al. 2016). There is no approved vaccine for human use (WHO 2017). From a global perspective, a joint effort to counter spreading of EID is inevitably important and there is a need to maintain consistently and persistently to tackle the increasing threat of EID outbreak, lessons learnt from Smallpox, measles, polio and malaria (Fenner, Henderson et al. 1988, Bishai, Johns et al. 2010, Initiative 2015, Shretta, Avanceña et al. 2016). In 2015, WHO issued a list of priority pathogens (WHO 2015), Zika among other pathogens, which are highly infectious and capable of deteriorating human's quality of life, could post other global threats. From local perspective, EIDs are adding burden to the economy. There is a question asked:

How to react to the outbreak of EID in the most effective way?

In an environment where resources are limited and should be allocated wisely across objectives, evaluating the cost effectiveness of joint effort from a local perspective is critical. In each setting, the reaction strategy to the EID should be evaluated in conjunction with preexisting local healthcare infrastructure. There are efforts to do research in multiple areas for better understanding about ZKV e.g. epidemiology, vaccinology, diagnostic, vector control treatment etc. ZKV is no longer under Public Health Emergency of International Concern (PHEIC); however, the status of global thread from this virus is still remained due to devastating consequence of CZS. International movement which focuses on fighting against emerging infectious diseases by vaccines is strongly supported by WHO, Gates Foundation, GAVI and most recently CEPI. Those most recent efforts certainly are a big step forward for the presentation of the new vaccine.

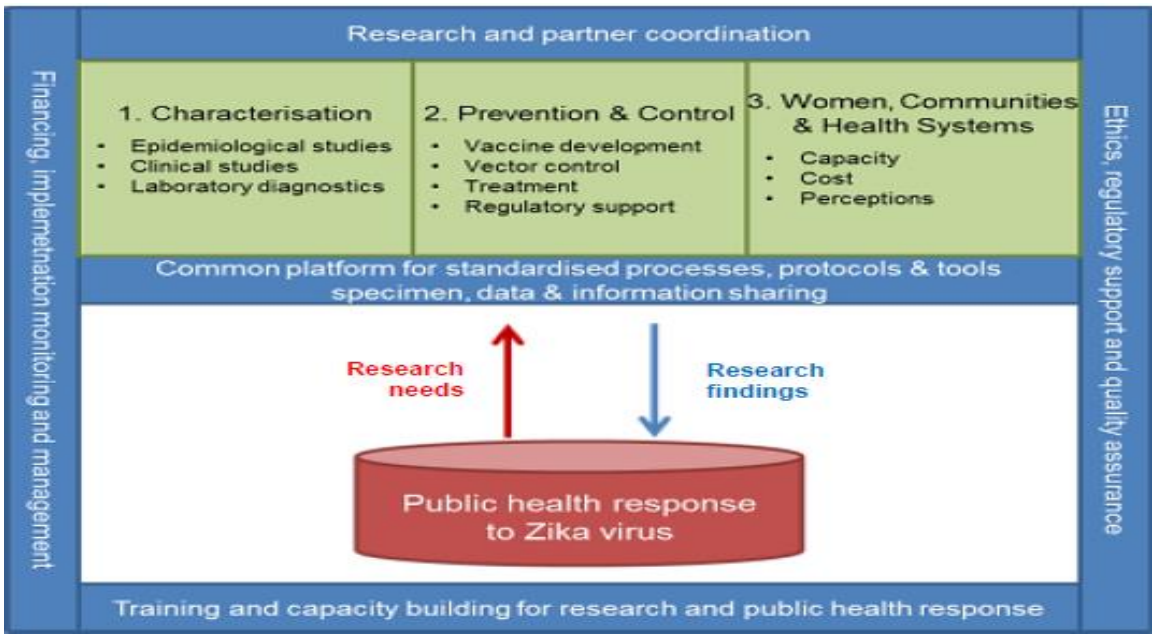

Figure 1: WHO research agendas (WHO 2016)

Vaccine development is considered an important component of potential Prevention & Control measurement from WHO research agendas (*Figure 1*). The impact of vaccine on public health can be substantial, but in the case of Zika, the impact is unknown due to so much uncertainty around understanding the disease and vaccine candidates. In order to further understand how cost-effective a potential vaccination campaign is, this thesis is dedicated to scrutinizing into disease dynamic and vaccination campaign characteristics. By articulating factors from a local perspective which could be determinant in the reality, it might shed the light on further understanding how vaccination research, development and campaign should be conducted.

1.1 Zika Virus

ZKV belongs to genus *Flavivirus*, family *Flaviviridae*, which is closely related to other mosquito-borne Flaviviruses: Dengue, Yellow Fever, Japanese Encephalitis and West Nile Viruses (CDC 2017). According to clinical presentation, infection caused by those viruses can be categorized into two classes: encephalitic (JEV and WNV) and non-encephalitic or viscerotropic *flaviviruses* (Dengue and YFV) (Song, Yun et al.), encephalitic viruses cause invasive neurological diseases and the others cause hemorrhagic fever. In a recent study, thermastability was proved higher on ZKV than on Dengue virus (Kostyuchenko, Lim et al. 2016).

Flaviviruses' major vectors are mosquitos with 27 species, ticks with 12 species and unknown vectors with 14 species (Song, Yun et al.). *Aedes* species mosquitoes, which include *Aedes aegypti* and *Albopictus*, are considered as the primary vector. They are aggressive daytime biters, which also carry the risk of spreading other viruses (Chikungunya, Dengue). After biting an infected object, the mosquito has 50% chance of getting infected (Chiyaka, Tchuenche et al. 2008), after the incubation period, an infected mosquito then could transmit ZKV to susceptible host with the probability of 70% as they feed (CDC 2017). The ability to survive over adverse condition was proved as possible by vertical transmission of ZKV in *Aedes aegypti* mosquitos (Thangamani, Huang et al. 2016). Zika virus infection (ZVI) rarely causes any severe clinical symptoms with 82% of infected patients are asymptomatic (CDC 2017), and very low fatality rate is observed in Colombia (Andraud, Hens et al. 2012, Sarmiento-Ospina, Vasquez-Serna et al. 2016). In addition to mosquito-borne transmission, other modes could be both in practice and theory play important roles: maternal-fetal, sexual, blood transfusion, laboratory exposure and transplantation; mode of transmissions had not been proved include touching, coughing and sneezing; breastfeeding has not been documented as a mode of transmission (CDC 2017). Maternal-fetal and sexual transmission are reported as appearing in both symptomatic and asymptomatic cases (Petersen, Jamieson et al. 2016).

ZKV includes three structural proteins (capsid C, premembrane prM, and envelop E) and seven non-structural proteins (Pierson and Graham 2016). By using high-resolution cryoelectroc microscopy, ZKV is described with high similarity with other *flavivirus* structures, "except for ~10 amino acids that surround an N-linked glycosyplation site in E-DL" (Olagnier, Muscolini et al. 2016). This difference is speculated to create the unique aspects of ZVI dynamics. The cause for CZS is not fully understood, this might also include a number of cofactors (WHO/Unicef 2017), more understanding of virus structure will help to enhance the effectiveness of diagnostic, treatment and prevention.

A phylogenetic study showed that there are two main lineages of ZKV: African and Asian (Faye, Freire et al. 2014). In the outbreak in America, all American strains came from one brand of the Asian lineage (Yun, Song et al. 2016). In the 2015-2016 ZIKA epidemic, a study shows that H/PF/2013, which is isolated from French Polynesia

2013 outbreak, appeared in “all human strain identified” (Olagnier, Muscolini et al. 2016, Wang, Valderramos et al. 2016). The interaction and mechanism of infection between host and ZKV has not been well established yet. Therefore, the causal link between ZVI and CZS, GBS is not completely-understood. There is unproven theory from phylogenetic study discussing the causation effect between some specific amino acid substitutions coincide with the appearance of GBS in French Polynesia (S139N located in M protein) and CZS in Latin America (M/T2634V) (Pettersson, Eldholm et al. 2016). The association is widely accepted and lead to the declaration of PHEIC from WHO. As the discussion is still needed more proof, a teratology study (Rasmussen, Jamieson et al. 2016) concluded the causal relationship between ZVI and CZS is supportable.

1.2 Epidemiology

ZKV was first discovered in Uganda in 1947 (Hayes 2009) on rhesus monkey in Zika forest. One year later, the first human infected case was described (Dick 1952). 60 years after first discovery, ZKV emerged and caused the first large outbreak in 70% of the population of Yap Island 2007. ZKV traveled into French Polynesia (2013), Latin America (2015) and North America (2016), escaping from the equatorial belt from Africa to Asia (Song, Yun et al.). WHO declared PHEIC on 1st February 2016. Even though it is not anymore under PHEIC from November 2016, ZVI still remained as a significant and global long-term threat. Until now, the 2013-2017 outbreak has spread into 84 countries, territories and subnational areas with evidence of vector-borne transmission and 13 countries or territories with human to human transmission (WHO 2017). Among those areas, disease transmission is disrupted in just five countries or territories with the risk of future reintroduction. Beside reported areas, there are high-risk countries or territories not yet affected or detected, high-risk areas here are defined as tropical and sup-tropical with the presentation of *Aedes aegypti* and *Aedes albopictus* as presented in *Figure 2.* South Asia, Southeast Asia, the majority of Africa, Latin America and USA are under risk of vector-borne transmission. Using modeling, a study (Messina, Kraemer et al. 2016) showed the potential cover of ZKV globally. More studies are needed to overcome the lack of local surveillance capacity, transparency and difficulty to differentiate ZVI with other infections caused by other *flaviviruses.* Experience from Dengue and Chikungunya showed that mosquito-borne virus can "exhibit explosive outbreak" (Perkins, Siraj et al. 2016) which might spread into a large proportion of a population. A dengue seroprevalence (prevalence of the pathogen in a population) study in Colombia (Carabali, Lim et al. 2017) indicated an alarming reality in which overall seroconversion rate per month was estimated at 8.7% per 1000 person-month. In a different study from Kenya (Sergon, Njuguna et al. 2008, Perkins, Siraj et al. 2016), Chikungunya was believed to have spread into 75% of the population within one year.

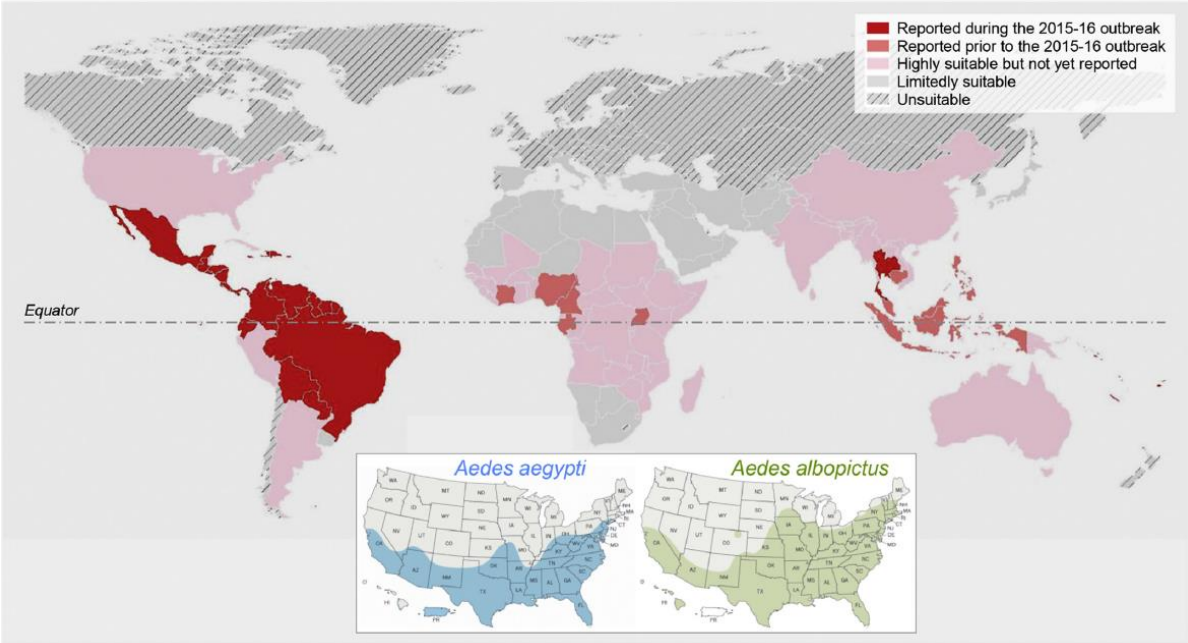

Figure 2: Reported and potential distribution of ZKV (Song, Yun et al.)

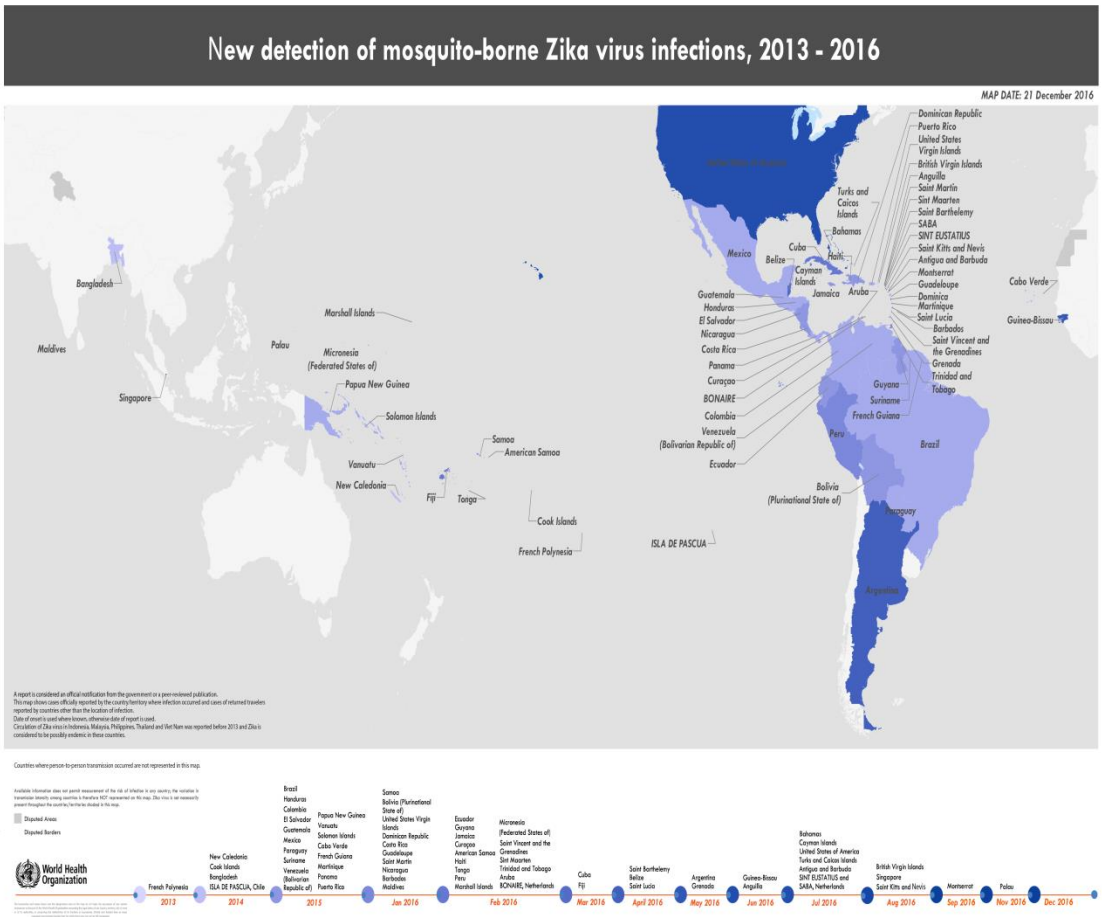

Figure 3: WHO situational report 28 December 2016

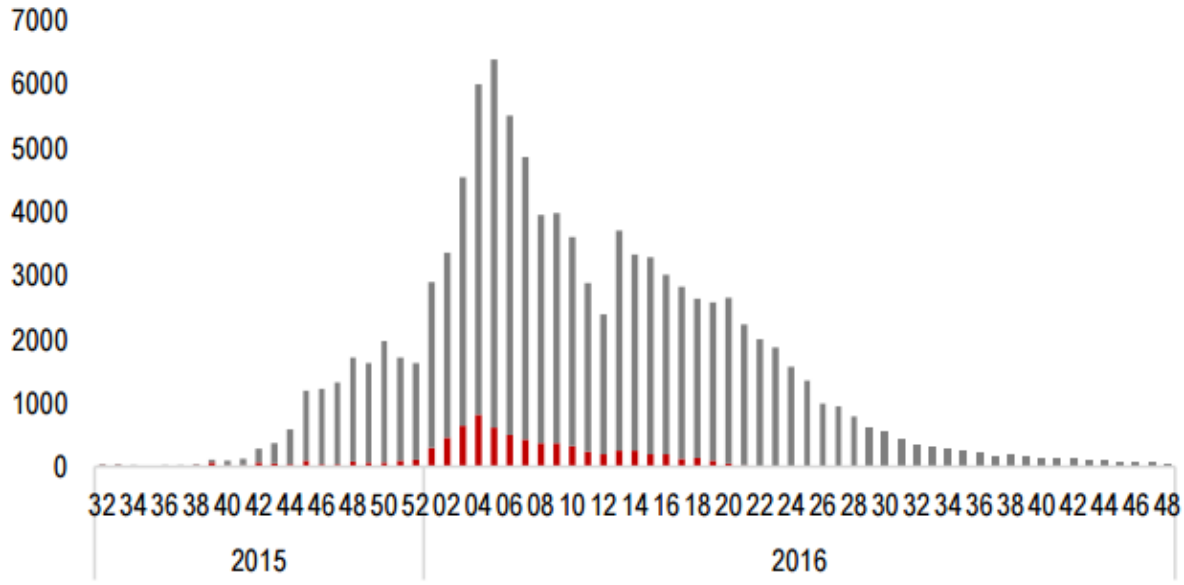

Figure 4: Number of suspected and confirmed ZVI cases in Colombia (INS 2016)

In the beginning of October 2015 (week 40), a Colombian laboratory confirmed the first ZKI case was announced by INS, retrospective serum sample suggested ZKV appear in Colombia from July 2015 (week 27) (Pacheco, Beltrán et al.). A number of new suspected cases peak in the beginning of 2016 (around week 5), coincides with the peak amount of weekly laboratory confirmed cases (week 4).

1.3 Diagnosis

In the regions with preexisting of other infection from Dengue and Chikungunya, a diagnostic method should be conducted first to separate ZVI (Mishra and Behera 2016). ZKV test is recommended for patients with symptoms, pregnant women with or without symptom if they live or traveled to an area with Zika circulating, or have sex with a partner, who live in affected areas, baby born with mother suspected to ZVI. Until the moment of writing this paper, there is no available diagnostic test currently used commercially (CDC 2017). Emergency approval for the use of diagnostic tests is accelerating, there are fifteen diagnostic tests have obtained emergency use status from FDA (FDA 2017).

1.3.1 Clinical symptoms

Features	Zika	Dengue	chikungunya
Fever	++	+++	+++
Rash	+++	+	++
Conjunctivitis	++	-	-
Arthralgia	++	+	+++
Myalgia	+	++	+
Headache	+	++	++
Hemorrhage	-	++	-
Shock	-	+	-

Table 1: Clinical feature comparing with Dengue and Chikungunya (A. Desiree LaBeaud 2017)

From *Table 1*, it is hard to differentiate between ZVI and Dengue, Chikungunya just solely based on clinical symptoms. Among the symptomatic patients, fever, rash, conjunctivitis, and arthralgia are the most common symptoms (CDC 2017). Clinical illness is normally not severe and last for some days to a week. In an investigation in Bolivar (Pacheco, Beltrán et al.), the most common symptoms were rash, fever, and pruritus (*Table 2*) .

Symptoms	Proportion
Rash	93%
Fever	80%
Pruritus	76%
Myalgia	65%
Arthralgia	64%
Headache	62%
Conjunctivitis	55%
Malaise	34%

Table 2: Symptom distribution (Pacheco, Beltrán et al.)

1.3.2 Laboratory tests

After primary diagnosis, which is related to clinical features, travel history and activities, laboratory diagnosis are required to confirm the existence of ZVI. Laboratory tests are conducted based on blood, serum, urine, semen, vaginal fluids, placenta, fetal membranes, umbilical cord, cerebrospinal fluid, amniotic fluid, breast milk. The presenting of ZKV among sample types varies and therefore affects the validity of test result. CDC recommends uses of RNA NAT, Trioplex rRT-PCR, Zika virus-specific IgM, neutralizing antibodies, Zika MAC-ELISA, Plaque reduction neutralization test (PRNT) for detecting ZKV. PRNT is used as the last confirmator. For symptomatic patients with less than 14 days after symptom onset and asymptomatic patients with past possible exposure within two weeks, Trioplex rRT-PCR is recommended; meanwhile IgM test could be used from 2 until 12 weeks after symptom onset/potential exposure to ZKV or all pregnant woman live in the areas where the virus is circulating (CDC 2017).

For pregnant group, CDC issued standard procedure how to use laboratory test as described in *Figure 5*.The whole cycle for testing and final confirming with PRNT could take up to 40 days as described in one case (Malloy 2017). The reliability of the whole test cycle is high, however, the risk of mental suffering due to false positive test from the first round are significant. In countries where the public health system is not comprehensive, formal employed and higher income population are having greater benefit from health care system like Colombia (Tsai 2010), testing capacity is not evenly distributed. The consequences for this might be a discrepancy between the reality and confirmed cases; among confirmed cases, the reliability might potentially a problem.

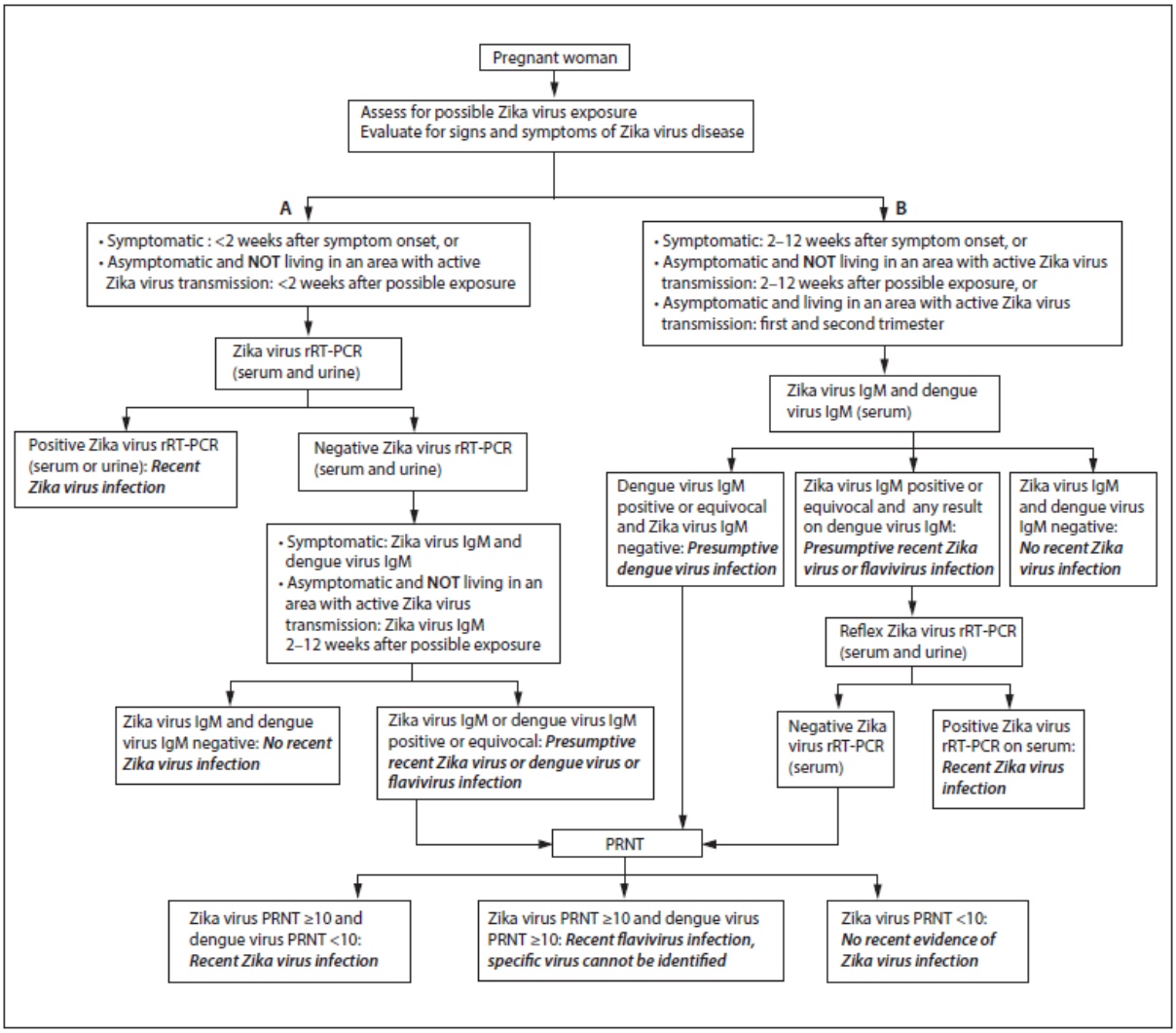

Figure 5: CDC recommended laboratory test procedure.

1.4 Management and prevention

Symptomatic infected patients appeared to have mild symptom as described in the previous section, treatment for those cases are supportive and symptoms based (CDC 2017). In case of fever and pain, medicine with acetaminophen could help. “Aspirin and other non-steroidal anti-inflammatory drugs” should not be used until dengue infection could be excluded (CDC 2017). There is no formal antiviral treatment for *flavivirus* infections (Weaver, Costa et al. 2016), experience from developing Dengue therapeutic could be used to develop drug for ZVI. However, this should be considered prudently since the differences of biology between the two viruses are huge (Weaver, Costa et al. 2016). The requirement for antiviral treatment is ideally on both “brain and systemic sites”.

As we are still waiting for vaccine and treatment, preventive methods are the only options to counter the consequences of ZVI. Preventive measurements include vector control, reducing exposure to mosquito and safe sex education. Vector management includes removal of reproductive sites and using of insecticides (CDC 2017, Sharma and Lal 2017). New vector control tools have been evaluated such as Wolbachia, genetic manipulation mosquito, however, the effectiveness of those methods is unknown and need more evaluation (WHO 2016). Women in the high-risk group (reproductive age) should take extra measurements if she intends or is currently pregnant. Wearing long-sleeved shirt, long pants, using insect repellents, staying away from areas with the presence of vectors are among effective way to avoid infection (CDC 2017). In addition to that, men who live or come back from ZIKA endemic areas should not have sex without safety measurement. 28 days are recommended for traveler coming back from ZIKA spreading areas before having sex with a pregnant partner (Wong, Poon et al. 2016).

1.5 Congenital Zika syndrome:

ZKV is perceived as a neurotropic virus, which is characterized by targeting both neural progenitor and neural cells in all stage of human life (Costello, Dua et al. 2016). Until now, there is no formal treatment for CZS recommended from WHO (WHO 2016). CZS is the general definition for an "unusual cluster of cases of congenital microcephaly and other neurological disorders" first characterized by WHO as a spectrum of abnormalities: neurological, hearing, visual and others (Costello, Dua et al. 2016). Later, CDC has a more detail description on CZS from both structural and functional components (Moore, Staples et al. 2016) (Table 4), CDC issued their five features for CZS (CDC 2017): "Severe microcephaly where skull has partially collapsed, decreased brain tissue with a specific pattern of brain damage, damage to the back of the eye, joints with limited range of motion, such as clubfoot, too much muscle tone restricting body movement soon after birth". With those birth defects, future physical and learning ability would be severely compromised (WHO 2016). A study from Colombia also showed that genitourinary, digestive and cardiac systems could be in the list of manifestation(Costello, Dua et al. 2016). ZVI appeared to be similar with other TORCH agents (Toxoplasma, Rubella virus, Cytomegalovirus, Herpes simplex viruses type 1 and 2, syphilis, parvovirus, coxsackievirus, listeriosis etc.) (Schwartz 2017). From the same study, Schwartz reflected ZKV as most close to rubella virus among TORCH agents.

Pre and post-natal diagnostic could both be used to detect CZS in the fetus and baby, some main diagnostic methods include RT-PCR, MAC-ELISA, ultrasonography, CT, magnetic resonance imaging, microscopic examination. Ultrasound procedure conducted in the late second trimester or third trimester might help to identify a fetus with CZS (Villamil-Gómez, Mendoza-Guete et al. 2016, WHO 2016). Children born with CZS do not necessarily have a smaller skull, a study in Brazil showed that there are 20% with "normal head circumference" among suspected microcephaly cases (Franca, Schuler-Faccini et al. 2016, de Carvalho, de Carvalho et al. 2017).

Scientific evidence with virological and epidemiological data advocate for the association between ZVI and CZS, especially with microcephaly and brain abnormality (Brasil, Pereira Jr et al. 2016, de Araújo, Rodrigues et al. 2016). The causation effect has not been confirmed by any phylogenetic study, the hypothesis is that some substitutions of specific amino acid associated with emerging neurotrophic and epidemiological characteristic from Pacific and Latin American outbreak (Pettersson, Eldholm et al. 2016). However, recently CDC has confirmed formally the causal effect between ZVI and CZS by a teratology study (Rasmussen, Jamieson et al. 2016).

Report from the US indicates 6% of "laboratory evidence of possible recent ZVI" are birth defects (Honein, Dawson et al. 2017). The number appeared to be equal

between 2 groups of symptomatic (10/167) and asymptomatic (16/271) pregnant woman. Meanwhile, infection in the first trimester of a pregnancy coincided with the highest risk of getting CZS. In another paper (Brasil, Pereira Jr et al. 2016), the proportion of babies with abnormal clinical and/or brain imaging is 42% compared with the control group with 3%. Adding the loss of follow-up, this number is 39%, significantly higher than the number reported in the US. 14.4% of follow-up cases with previous ZVI had fetuses died, miscarried and still births, this number is 11.5% in the control group. None of those studies are considered as comprehensively reflecting the incident rate among infected pregnant women because of different methods. For instance, data from CDC faces at least seven drawbacks (Shapiro-Mendoza, Rice et al. 2017), meanwhile, study population from Brazil just included only symptomatic patients (Brasil, Pereira Jr et al. 2016). Social economic, weather, spread of vector and prevalence of other *Flavivirus* disease suggest that data from Brazil is more applicable to Colombian condition.

Categories of Malformations Associated With Congenital Zika Syndrome	
Category	**Examples**
Neurologic	• Microcephaly • Hydrocephalus • Micrencephaly • Lissencephaly • Polymicrogyria • Pachygyria • Agyria • Holoprosencephaly • Ventriculomegaly • Corpus callosum abnormalities • Intracerebral calcifications • Destructive brain lesions
Ocular	• Chorioretinal atrophy • Optic nerve abnormalities • Maculopathies • Vascular abnormalities
Musculoskeletal	• Arthrogryposis • Craniofacial abnormalities (craniosynostosis) • Clubfoot • Acetabular dysplasia
Genitourinary	• Cryptorchidism • Hypospadias
Other	• Intrauterine growth restriction • Anasarca • Pulmonary hypoplasia • Single umbilical artery

Table 3: CZS (Alvarado and Schwartz 2017)

Clinical feature	
Structural	Cranial morphology Brain anomalies Ocular anomalies

	Congenital contractures
Functional	Exclusively related to neurologic impairment

Table 4: Clinical feature of CZS, compiled from CDC data

1.6 Guillain-Barre syndrome

GBS was described 100 years ago by Georges Guillain, Jean-Alexandre Barre and Andre Strohl (Haymaker and Kebnohan 1949). GBS term is used to represent for acute motor axonal neuropathy (AMAN), acute motor sensory neuropathy (AMSAN), acute inflammatory demyelinating polyneuropathy (AIDP), Bickerstaff's brainstem encephalitis (BBE), multiple cranial neuropathy (MCN) and Mille-Fisher syndrome (MFS). MSF's symptoms are ataxia (muscle movement abnormality), ophthalmoplegia (inflexibility of muscle around eyes), and areflexia (lack or absence of reflexes). Different subtype might require specific treatment with various outcome and complication. In Colombia, AIDP and AMAN were among the main subtypes observed (Mahecha, Ojeda et al. 2016). AIDP is the high prevalence sub-phenotype with lower ICU admission in Colombia (Anaya, Rodriguez et al. 2017). Most of GBS cases will fully recover including of severe cases (WHO 2016). However, patients with GBS might suffer some forms of physical and mental health impairment (Darweesh, Polinder et al. 2014). Overall, GBS is considering as a life-threatening disease and requires diagnostic, monitoring and treatment early (van Leeuwen, Lingsma et al. 2016, WHO 2016)

The cause for GBS is considered as the consequence of attack by the immune system, this happens after humoral and cell-mediated reaction to an invasion of a pathogen. Immune cells attack both myelin and axons, causing damage for peripheral neuro system (Jasti, Selmi et al. 2016). Previous vaccination, infection or exposure to toxic substances are proved to associate with GBS (Israeli, Agmon-Levin et al. 2012).

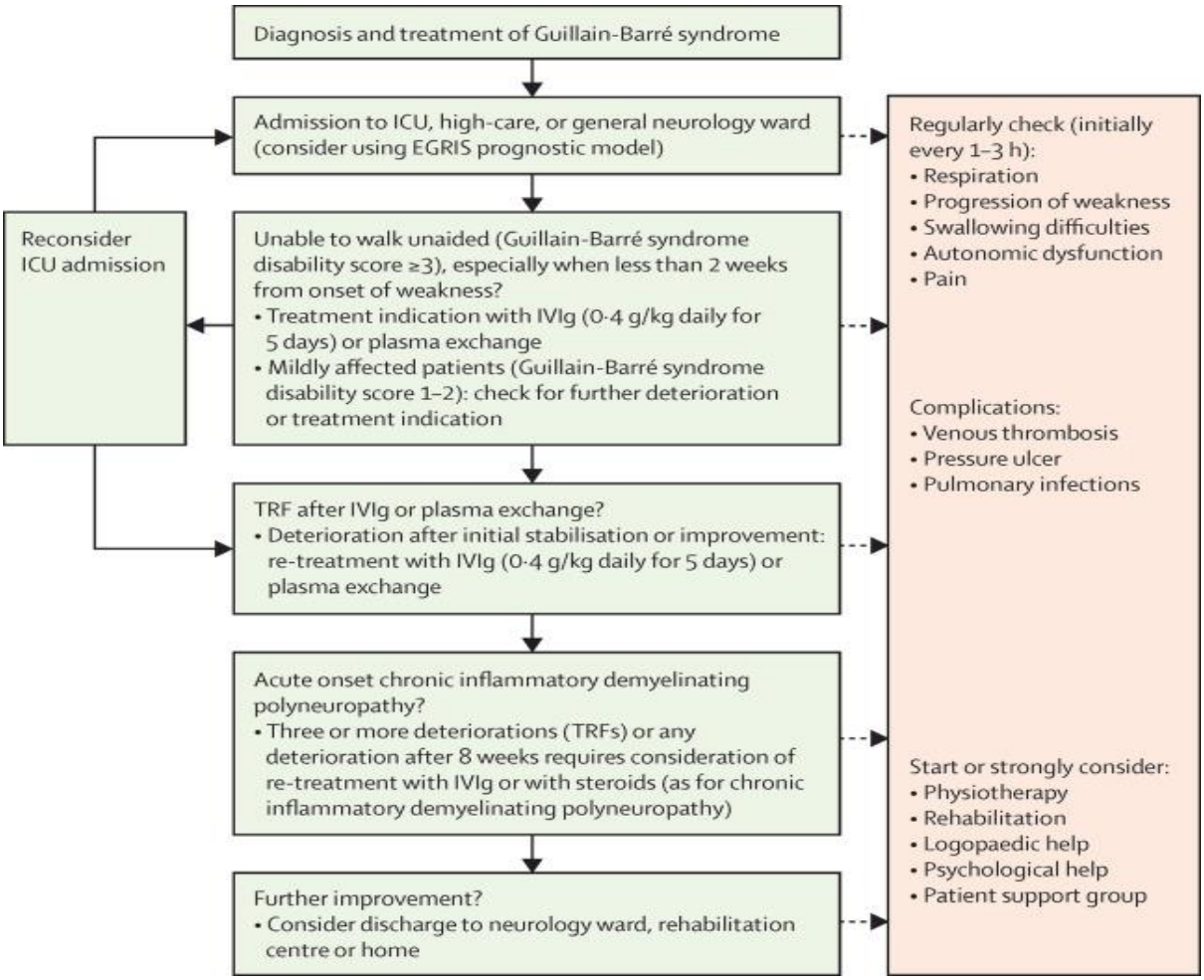

Figure 6: Treatment map for GB (Willison, Jacobs et al.)

From *Figure 6*, proposed treatment map from Willison (Willison, Jacobs et al.) shows that ICU is the necessary measurement after diagnosis, patients could have to readmit to ICU after treatment of Intravenous immunoglobulins (IvIg) and Plasma exchange. Diagnostic for GBS required "careful history, physical examination, CSF analysis, nerve conduction studies, and imaging studies"(Jasti, Selmi et al. 2016). Within four weeks, GBS patients can experience "progressive, symmetrical weakness of limbs" (Hughes and Cornblath 2005, Jasti, Selmi et al. 2016).

Epidemiological data showed that median of GBS incidence is 1.11 per 100,000 persons per year in population without spreading of ZKV at the point of study. Men and older individuals are more likely to suffer from GBS (Jasti, Selmi et al. 2016). In a recently published study from Colombia (Mahecha, Ojeda et al. 2016), the same trend is observed as more men (66.8%) than women (33.2%) have been reported. In contrary to previous studies, the dominant number of cases in the Colombian study is linked to a young population.

Before the introduction of IVIg and plasmapheresis, treatment for GBS is mostly supportive or symptomatic approach with intravenous adrenocorticotropic hormone, corticosteroids. Immunological therapies and supportive care are currently recommended by WHO. Plasmapheresis is the process of removing antibodies from blood before transfusing back into the blood stream, meanwhile IVIg suppress immune-system by infusing human antibodies (Pritchard, Hughes et al. 2016). Almost all of GB patients need admission to hospital, in which 69% admitted to ICU, IVIg is the most popular treatment with more than 72% as cited by Anaya and colleagues (Anaya, Rodriguez et al. 2017). The median duration of ICU stay was 23 days, with an interquartile range varying between 9.5 and 36 days.

In a follow-up study in with the duration between 3 to 5 year (Bersano, Carpo et al. 2006), it showed that time period required for maximum improvement ranged from 15 days to 4 years with the median of 9 months. During the recovery period, approximately 20% of patients are not able to walk up to 6 months (Hughes, Swan et al. 2007). 15% of patients from a systematic review in Colombia died because of GBS (Mahecha, Ojeda et al. 2016). Long term effect as the consequence of GBS is significant with 27% population recorded with minor impaired capacity in daily life and 9% needed constant aid (Bersano, Carpo et al. 2006), meanwhile data from the same study also demonstrated 19 out of 45 patients “make substantial changes in their job, hobbies or social activities”.

2 Objective:

Until official measures are approved to fight against ZKV, we are facing "egg and hen" dilemma since the cost effectiveness of a potential intervention is unknown. This paper will use Colombia as a case study to analyze the cost-effectiveness of potential vaccine candidate from a societal perspective in the fight against spreading of ZKV and its catastrophic consequences. The outcome of this study including of costs, health outcomes, cost-effectiveness and uncertainty analysis would be a tool to inform decision maker in the resource allocation process. The table below is summarization of study objectives and outcomes.

Primary Objective	*To evaluate the cost-effectiveness of a hypothetical Zika vaccine candidate using a potential implementation in Colombia*
Secondary Objectives	1. *To develop a cost effectiveness model integrating epidemiological data, initial data from vaccine candidates and WHO Target Product Profile (TPP)* 2. *To observe sources of uncertainty by Monte Carlo simulation, sensitivity scenario, and value of information analysis* 3. *To compare between model outcomes and actual reported* 4. *To estimate effect of delay introducing vaccination campaign* 5. *To estimate how much should be spent to fight against Zika outbreak*
Primary Endpoint	1. *Net health and monetary benefit* 2. *Incremental cost-effectiveness ratio*
Secondary Endpoints	1. *Total cost from societal perspective* 2. *Number of CZS cases* 3. *Number of GBS cases* 4. *QALY and Life year loss* 5. *Basic reproductive number* 6. *High impact parameters*

Table 5: Study objectives and endpoints

3 Methods

3.1 Model overview

A mathematical deterministic model (Vynnycky and White 2010) is utilized to describe the dynamic of the disease. Development of the model follows steps as mentioned by Emilia Vynnycky and Richard G White:

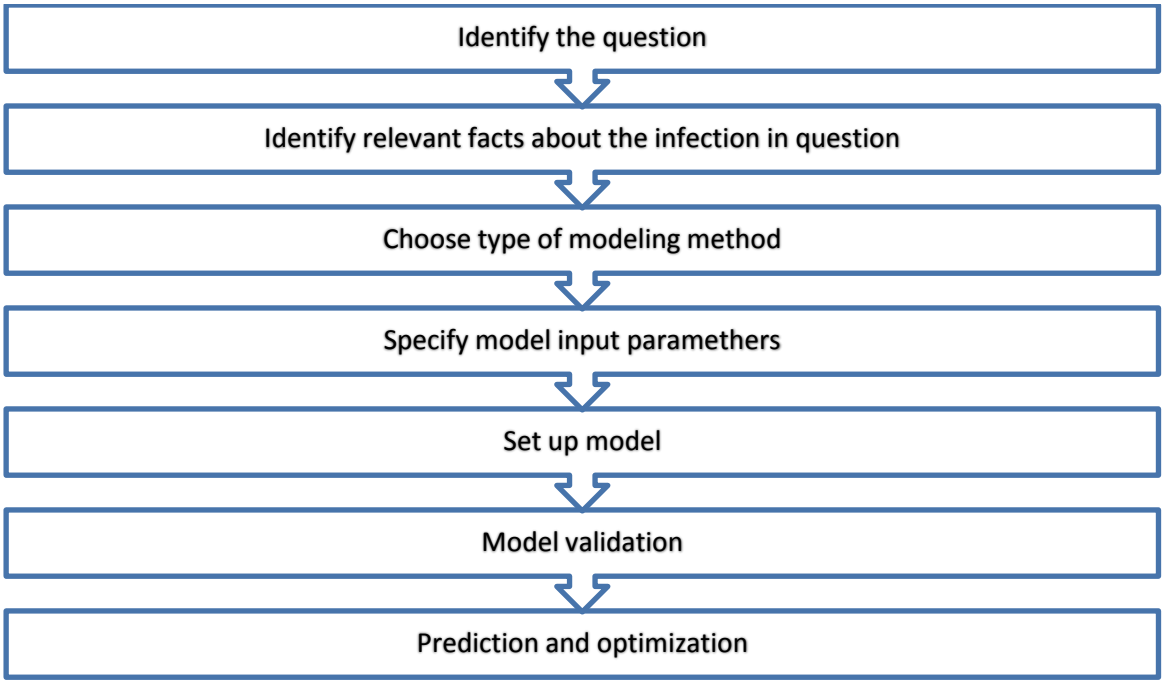

Figure 7: Model's development steps (Vynnycky and White 2010)

A mathematical deterministic model is an average approach, in which all individuals in the same health state are having same fixed predetermined transition probability. This deterministic model is then divided into some sub-group (or health state) e.g. susceptible, exposed, infected, recovered etc. Since input parameters are fixed, the outcome is deterministic and does not reflect the uncertainty. Because of this reason, Monte Carlo simulation (Briggs, Weinstein et al. 2012, Drummond, Sculpher et al. 2015) is used to complement to the deterministic setting. A thousand simulations is conducted and the result is used for Probabilistic Sensitivity Analysis (PSA), which includes: mean result of simulations, cost effective acceptability curve (CEAC) and CE-Plane (Drummond, Sculpher et al. 2015, ISPOR 2016). Each input parameter varies around its expected value following specific distribution, specific way to conduct this is described elsewhere (Hunink, Weinstein et al. 2014)

Mathematic formula (*Appendix 1*) reflects the interaction between human, vector (mosquito) and disease transmission. Host dynamic modeling inspired from (Kucharski, Funk et al. 2016) as SEIR method taken into account asymptomatic patients. A susceptible patient could become exposed as they contact with infected vector or human, after the intrinsic incubation period, exposed individual will become infected. An infected

individual would be fully recovered after the infectiousness period. In addition to this SEIR method, the numbers of GBS and CZS cases are estimated based on infected patients and pregnant women. GBS cases are directly estimated as the proportion of infected cases, and CZS cases are derived from the weekly birth rate and the chance of getting CZS among infected woman.

Meanwhile, vector model, which was reproduced from (Brauer, Castillo-Chavez et al. 2016), is a shorter version of mosquito life cycle. In this way of modeling, the mosquito is modeled from when they are able to spread the disease.

The number of effective contacts calculated using:

$$Beta = c*p$$

c: average contact rate

p: probability for transmission per contact

Effective contact rate is then used to calculate the probability that a susceptible individual moves to exposed compartment.

$$\beta S \frac{I}{N}$$

In this equation, S represents for susceptible population, I is infected and N is the total number of population. This formula is used to express transmission from human to human, human to vector and vector to human. Incubation and infectiousness period is used to calculate transition rate from exposed to infected and infected to recover respectively. Vaccinated population follows the same dynamic as non-vaccinated except they are protected with factor *e* representing for the efficacy of the vaccine. The waning effect is reflected by reducing the number of individual from susceptible and recovered compartment in the vaccinated group.

Basic reproduction number between host and vector (R_{0V}), sexual transmission (R_{0h}) calculated using the method described by Kucharski (Brauer, Castillo-Chavez et al. 2016, Kucharski, Funk et al. 2016):

$$R_{0v} = \frac{\beta_V}{\gamma_H} * \frac{\kappa_V}{\frac{1}{\mu_V} + \kappa_V} * \beta_H \mu_V$$

R_{0v}: Basic reproduction number human-vector

β_V / β_H: Human to vector/vector to human transmission rate

μ_V: Mortality rate vector

$1/\kappa_V$: Extrinsic incubation period

$$R_{0h} = \frac{\beta_{HH}}{\gamma_H}$$

R_{0h}: Basic reproduction number –sexual transmission

β_{HH}: Human to human transmission rate

$1/\gamma_H$: Infectious period in human

Using method from (Brauer, Castillo-Chavez et al. 2016) total basic reproduction number is calculated as:

$$R_0 = R_{0v} + R_{0h}$$

Monte Carlo simulation is then used to capture the uncertainty around this parameter.

Inputs for the model are extracted from literature review, with the objective to mimic not just how ZKV circulates among subjects, but also intend to capture and parameterize local factors in Colombia, which might be key determinants. Most of literatures used in this thesis are the results of Pubmed search with related key words "Colombia" "Zika" "Vaccine" "Cost effectiveness" "Epidemiology" "Mosquito" "Congenital Zika Syndrome" "Guillain Barre Syndrome" and the combination of these. In addition, there are multiple good materials and sources of information are recommended by my supervisor and colleges at Coalition for Epidemic Preparedness Innovation (CEPI). In the absence of mature information from Colombia, data from Brazil was used as a good substitution, taken into account geographic similarity.

For costs which were not available from Colombia, cost parameters were translated from other countries followed the adjusting method:

$$V_{Colombia} = V_{Foreign} \frac{WTP_{Colombia}}{WTP_{Foreign}}$$

Willingness to pay values for Colombia and related foreign countries (Woods, Revill et al. 2016) are based on purchase power parity (PPP), exchange rate is average of 2016 and obtained from OECD.

On the effect side, Quality-adjusted Life-year (QALY) loss for CZS patients is calculated indirectly by Lugner's method combining with using DALY data from Dutch Ministry of health (Lugner, Mollema et al. 2010, Bijkerk 2014). Meanwhile, for GBS, comparison between GBS and reference group is used to measure lifetime QALY loss. In both case, an important assumption applied: life expectancy would not be affected.

Value of Information (VOI) analysis is implemented with the use of Expected Value of Perfect Information (EVPI) and Expected Value of Partial Perfect Information (EVPPI) (Briggs, Claxton et al. 2006, Drummond, Sculpher et al. 2015). VOI is an important piece of uncertainty analysis by measuring "the forgone net benefit of the remaining uncertainty" (Hunink, Weinstein et al. 2014). Additional study could be suggested by

studying EVPI and EVPPI of current evidence used in the model. EVPI and EVPPI also play as an upper bound of additional cost for research (Heath, Manolopoulou et al. 2015). EVPI and EVPPI are calculated from the result of PSA, with one and two level of MC simulation respectively. Detail of the method for calculation could be found elsewhere (Hunink, Weinstein et al. 2014). The threshold used to calculate EVPPI varies from 100 USD to 15 000 USD, about 2.8 times cost-effectiveness threshold used 5464 USD for Colombia (Woods, Revill et al. 2016).

Sensitivity and scenario analysis are used to measure the impact of each/ group of parameter(s) changing. Those two methods used to recognized parameter and structural uncertainty. Parameter uncertainty is related to the estimation of the parameter, and structural uncertainty is defined as the issues with regard to underlying assumption of the model (Briggs, Weinstein et al. 2012). Sensitivity analysis is conducted in order to identify the change of outcomes by changing each input parameter around the mean value and is a method to present the scale of parameter uncertainty (Briggs, Weinstein et al. 2012, Drummond, Sculpher et al. 2015). Ranges of parameters are determined by either confidence interval, standard deviation or realistic value based on specific assumption. Parameters' ranges are determined with supportable values rather than a strict deviation from mean values. The magnitude of relative changes on Net Health Benefit (NHB) will be used to determine the importance of parameter, there are three levels of parameter: mild impact (5% to 10%), moderate (10% to 50%) and significant (more than 50%); NHB could be positive or/and correlated with a parameter. Along with sensitivity analysis, scenarios are constructed to reflect potential realities that might happen but without concrete scientific evidence. In each scenario, a separate model is built and analyzed in the same way as with baseline model. Scenarios relate to changing parameters values and model underlying assumption.

In addition to above analysis to reflect uncertainty, visualized graphs are also used to demonstrate the cost-effectiveness of interventions. There are two main methods used: CEAC and CE-Plane (Drummond, Sculpher et al. 2015). CEAC is the graph show probability that an intervention is cost-effective with multiple threshold values, CE-Plane is a scatter plot used to express the incremental cost and QALY in the same graph.

Excel (with Macro) and Stata /SE 14.2 are used for modeling and analysis.

3.2 Perspective

The societal perspective is utilized to build the foundation for the model. By using this perspective in Colombian context, the model intends to capture the most of the cost as the following consequences of ZKV spread. Societal perspective captures both health care costs needed for diagnostic, treatment and monitoring; and un-related health care cost such as productivity loss. On the other dimension, both direct and indirect impacts would also be reflected. Tourism spending drop represents for indirect and unrelated to health care cost. The choice of perspective is societal, therefore it intends to cover cost more than from the payer or patient perspective (Oderda 2002). The objective of this method is to identify the broadest range of opportunity costs (Drummond, Sculpher et al. 2015) related to ZIKA outbreak. This approach might be considered as irrelevant from Colombian Ministry of Health (MinSalud). In theory, the impacts of productivity loss, tourism drop and direct cost outside of healthcare system e.g. informal caregiver cost, might not be a direct interest of MinSalud. However, by using this broadest perspective there are multiple advantages: first, it covers multiple impacts of the outbreaks in the more comprehensive way; second, cost layers could be removed to cope with the requirement of narrower perspectives. Besides, there are also some drawbacks. Broad nature of this perspective makes it difficult to capture all the opportunities cost, claiming to use this method would be misleading if the study could not quantify cost parameters comprehensively.

3.3 Population

Colombia is located in the northwestern area of South America with the population of more than 47 million, it is the second largest country in South America. There are 85 ethnic groups and Spanish is the official language (Colombia 2017). 90% of Colombians are Christians (Sawe 2017). Colombian climate is regulated by "trade winds, humidity and altitude" with two rainy seasons and two dry seasons (Colombia 2017).

Statutory health law 1751 passed on 16 Feb 2015, in which stated health as a fundamental right and legally guaranteed to all citizens. 89% of the population is covered by the health care system, with increase of almost 7 times coverage from 2003 to 2007 in the rural area (Tsai 2010). Healthcare system has been financed by two sources: direct contribution from payroll tax and subsidies from the government for low-income and informal worker. Since most of the main health care facility distribute mostly in the big city, rural areas appear to suffer the lack of vital infrastructural. The insurance coverage rate therefore is a topic for debate whether or not it reflects accessibility (Abadia and Oviedo 2009).

On 24 Nov 2016, Colombia and FARC signed a new peace deal, ended 50 years of conflict caused the death of estimated 200 000 people (Casey 2016). The peace deal will not immediately improve access to healthcare to the remote areas that had been under control by FARC. This peace deal is the beginning process of healing and harmonizing the whole nation, and the timeline of the process depends on more than just political will but also agreement from all affected. However, related to Zika outbreak, the surveillance system now might reach to the areas controlled by FARC before, those areas had been described as "double vulnerability" with both armed conflict and natural disaster (WHO 2014). From the same report, the need for humanitarian aid coincidently located in the areas where the condition for spreading ZKV more favorable.

The peace deal would improve the quality of reported effect of the outbreak proportionally. Arm conflicts in the past had been contributed half by FARC, the rest has been contributed by PDAG, ELN and other non-identified groups (WHO 2014). Internal displacement by conflict amounted to 224 000 people in 2015 and 6.3 million people at the end of 2015 (Alexandra Bilak and Nadine Walicki 2016). Therefore, the risk of under-reporting due to armed conflict is high, and potentially this would be improved gradually in the foreseeable future.

Indigenous and Afro-Colombian accounting for more than nine million citizens (Mundial 2005) are "structural exclusion, poor legal protection"(WHO 2014). These populations with the lack of basic humanitarian needs are under a wide range of risk from the spread of ZKV.

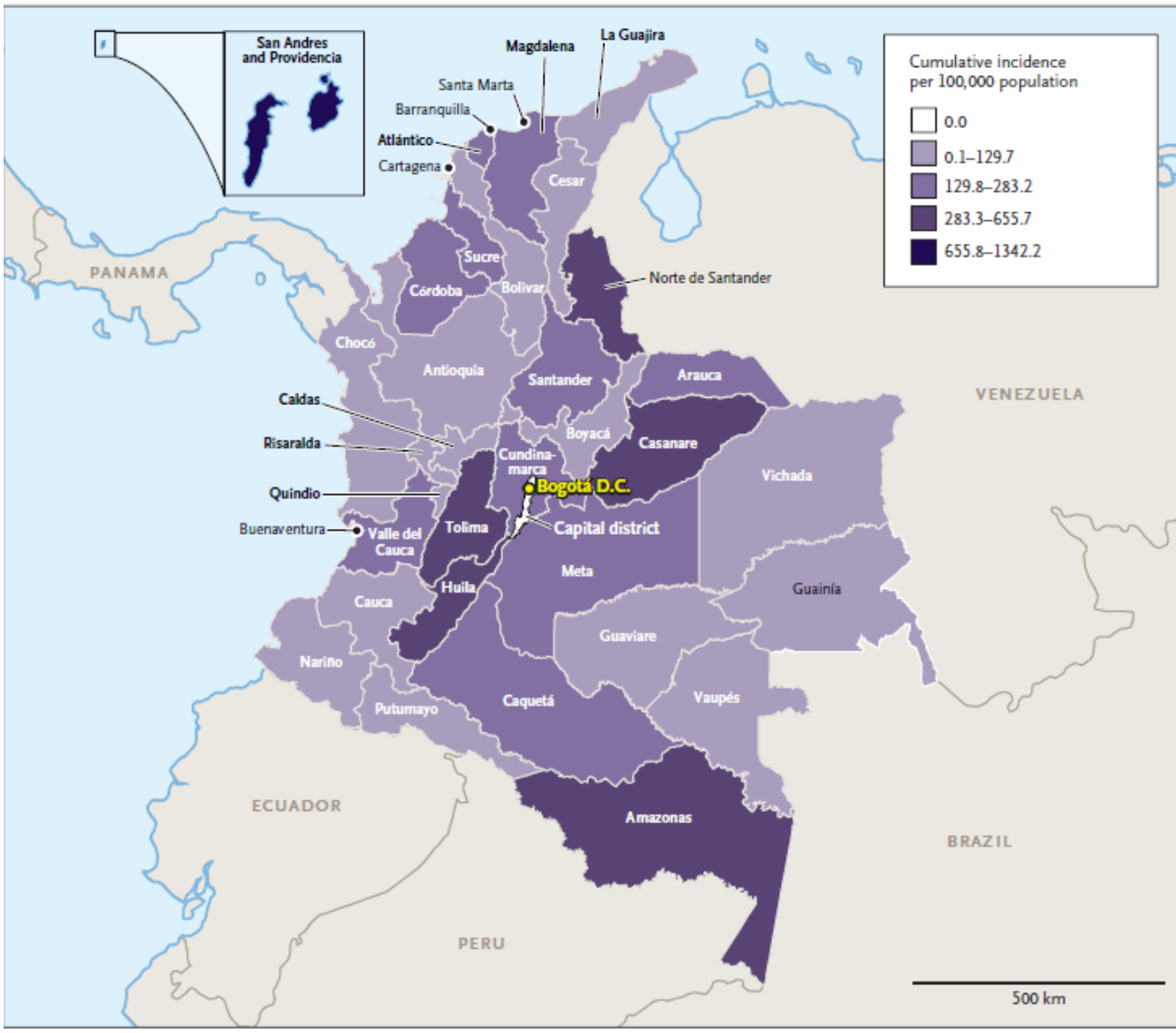

Figure 8: Distribution of ZVI and incidence per 100 000 population (Pacheco, Beltrán et al.)

As recommended, the areas under 2000 meters above sea level are at great risk of ZKV transmission (CDC 2016). From Colombian Ministry of Health, data confirmed that there is an increasing number of GBS cases at the time ZKV spreading (WHO 2017). A preliminary report in Colombia (Pacheco, Beltrán et al.), reported ZVI cases (including of pregnant women) distributed across the countries, under and above 2000 meters, potentially as the consequence of traveling and human to human transmission (Cuevas, Tong et al. 2016).

Abortion has been strictly regulated in Colombia, but Constitutional Court lifted the ban on abortion in 2006 (Prada, Singh et al. 2011). Still, there are just 320 legal abortion cases reported in 2011 compared with estimated 400 400 cases each year (DONALD G. McNEIL Jr. 2016). The incidence rate for unintended pregnancy was

high with 89/1000 woman in the reproductive age group. Two-thirds of unintended pregnancies lead to abortion (Prada, Singh et al. 2011). The practice of abortion therefore might be one of the key factors affecting the number of CZS cases.

3.4 Time horizon

Among South American countries, Brazil is the earliest reported with ZVI with the first case confirmed in May 2015 (Pacheco, Beltrán et al.). A phylogenetic study showed that ZKV circulating in Colombia originated from Brazil (Nextstrain 2017). A retrospective study from Colombian Instituto Nacional de Salud indicated a sample with ZKV from July 2015. In July 2016, Colombian government declared the end of Zika Epidemic, however, ZKV has still been circulating in the country in endemic form (Joseph 2016). Newly infected cases, CZS and GBS are still reported in Colombia until now (PAHO 2017). Considering above analysis, the time horizon for the model would be 2.5 years, taken into account uncertainty that the disease might introduce before first confirmed sample and will last after the point of writing.

3.5 Intervention

WHO and UNICEF with the participation from "epidemiologists, flavivirus vaccine subject matter experts, vaccine developers and global regulators" finalized Target Product Profile (TPP) (WHO/Unicef 2017) for emergency use of Zika vaccine (Vannice, Giersing et al.). This laid a cornerstone on Zika vaccine's development. The new development of Zika vaccine candidate could be observed by using WHO vaccine tracker (WHO 2017). TPP highlights two main scenarios for vaccine intervention: outbreak response and routine/endemic transmission use. This study focuses on the latter strategy.

Platform	Dosage	Candidate	Development phase	Antigen	Adjuvant
Inactivated	2*	8	Non, pre-clinical, phase I	Whole virus	8
Live attenuated		5	Non-clinical	Whole virus, prME	5 none
Recombinant subunit	1, 2, 3***	8	Non, pre-clinical, phase I	E, prME, E and PrME	3, 1 None, N/A
Recombinant viral vector		10	Non-clinical	prME, prME+NS1, surface antigen	7 None, 1 N/A
mRNA	1, 2**	5	Non-clinical, phase I	prME	1 None, 4 N/A
Peptide		1	Non-clinical	Synthetic peptides	1 None
Others		2	Non-clinical	E, preME	1, 1 N/A

Table 6: Zika vaccine candidates and main characteristics. Source: WHO pipeline vaccine tracker

* 2 doses within 28 days with or without prevaccined with Ixiaro and YF-VAX (ZIKV PIV)

** high dose - single shot low and high dose two shot at day 0 and 28 (mRNA-1325)

*** GLS-5700 and VRC ZIKV DNA

From *Table 6*, we might see vaccine candidates spread across seven platform technologies. There are four candidates enter into phase I clinical trial, mRNA-1325, GLS-5700, VRC ZIKV DNA and ZIKV PIV. In this phase, safety is testing on healthy human participants with 1, 2 and 3 doses. The distance between the first and second dose varied from 1 month to 12 months. ZIKV PIV is tested in conjunction to pre-vaccinated with vaccines for Japanese Encephalitis

and Yellow fever virus to test for antibody-dependent enhancement of infection (ADE) (Pierson and Graham 2016). prM and E proteins are main targets of most vaccine candidates. In the most recent study (Pardi, Hogan et al. 2017) testing on animal showed a single dose of mRNA vaccine targeting both prM and E "elicit rapid and durable protective immunity" on the non-human primate. With the existing of current platform technologies, understanding dynamic of ZKV and knowledge about R&D of other flaviviruses (yellow fever, tick-borne encephalitis, Japanese encephalitis and Dengue fever virus), a ZKV vaccine is likely available in the foreseeable future.

National vaccination program in Colombia covers all political area with Polio, DPT, BCG, Hepatitis B, Hib and rotavirus. Every year from 1994 to 2010, data from Colombian Ministry of Health had showed about 800 000 to 1 million individuals had been vaccinated every year (MinSalud 2012). The coverage rate varied across political areas and disease. In 2010, coverage rates are from 74.2% for Rotavirus to 88% for all others campaign. Political areas close to border with Venezuela and Brazil was reported with high incidence rate and low coverage rate of national vaccination program (Pacheco, Beltrán et al.). Therefore, any mass or annual vaccination program for ZKI should reflect this reality, hence a conservative approach with reasonable coverage rate would be applied.

Efficacy of vaccine candidates is not possible to evaluate due to data exclusivity. Experience from most recent Dengue vaccine phase III trial in Latin America (Villar, Dayan et al. 2015) shows that efficacy largely deviates among serotype, ranging from 42.3% for serotype 2 to 77.7% for serotype 4. In the recent update from WHO TPP (WHO/Unicef 2017), expectation for Vaccine Efficacy should vary from 70% to more than 80%. In addition, WHO recommended one dose as the best option, multiple doses if required, should maintain short time interval between doses.

The similarity of Dengue and Zika virus not only results comfortability for cross reference, but also cross-recognition and cross-reactivity. In the areas with the prevalence of ZVI, there is normally existing of Dengue Virus concurrently and previously. Testing *in vitro* showed that pre-infected population with Dengue virus might be affected by antibody-dependent enhancement (ADE) (Dejnirattisai, Supasa et al. 2016, Paul, Carlin et al. 2016), this means Colombia might face a higher risk than reported. Since ADE may happen, vaccination program appears to be riskier, the consequence of the adverse effect might overcome the benefit of a future campaign. Using the experience with Dengvaxia (Flasche, Jit et al. 2016), the model is set based on theoretical inclusion and exclusion criteria:

Inclusion criteria: healthy individual without reporting clinical symptom of ZVI

Exclusion criteria: individual with immunodeficiency or chronic illness, systemic hypersensitivity with trial vaccines' components

Given the fact that the reported prevalence of CZS and GBS in Colombia is low (WHO 2017), the government declared end of Zika outbreak last July (Joseph 2016), the possibility that a mass vaccination campaign would be conducted is low. However, in the peak of the outbreak with spreading of fear and uncertainty, it is reasonable to say that a mass vaccination campaign would be more likely to happen. In fact, WHO with its TPP oriented more on the outbreak response scenario (WHO/Unicef 2017). Experience from 2005-2006 rapid response to Rubella in Colombia showed that it is possible to conducting a mass vaccination campaign in Colombia (Urquijo, Pastor et al. 2011). During a period of 10 months, more than seventeen million individuals were vaccinated, 95% target population were covered. There is no formal estimated cost for the campaign, the whole system was mobilized to achieve this success, and there were much contribution from social partnership, professional advocating and governmental health care system. Mass vaccination is included as a sensitivity analysis rather than baseline.

Based on above analysis, I construct four vaccination scenarios:

S1: Non-discriminate - 1 dose
S2: High-risk population - 1 dose
S3: Non-discriminate - 2 doses
S4: High-risk population - 2 doses

All four scenarios base on set of following assumptions:

- Vaccine effect is life-long, enhance the ability of immune system to fight against ZKI with efficacy less than 100%
- Vaccine delivers to susceptible, exposed, asymptomatic and recovered population; vaccinated population will have same dynamic with un-vaccinated population with extra protection rate.
- In the two-dose scenarios, time duration between the 2 doses is 4 weeks
- Immunised populations obtain long-term effect, a waning rate is used to reflect the fact that protective effect will reduce overtime.
- High-risk population is defined as the population from 15 to 40, which is most of the population at reproductive age. In the model it is assumed all baby are born by individuals in this group.
- Seroprevalence in the beginning of an outbreak is assumed to be zero, there is no cross-recognition or cross-reactivity/ADE among other *flaviviruses'* antibodies.

3.6 Cost-classification

(Shretta, Avanceña et al. 2016) with the systematic review on "The economics of malaria control and elimination" has given a brief introduction on how costs are running in reality. Inspired by this article and in conjunction with Koopmanschap's method of cost classification, a framework was constructed for categorizing cost from a societal perspective in the local level (Table 7):

	Within Healthcare	Outside Healthcare
Direct cost	Personnel, equipment and material cost for vaccination campaign Diagnostic (especially important for pregnant woman) Surveillance and treatment	Informal caregiver (due to CZS)
Indirect cost	Administration cost Future cost	Productivity loss Tourism drop

Table 7: Cost classification

In analyses, vaccine cost, shipping, and administration were at baseline assumed to be $1.143 per dose for the ZKV vaccine (UNICEF 2017). This price is based on that from the Yellow Fever vaccine bought and distributed by Unicef – the biggest vaccine buyer.

Yellow Fever vaccine cost can be decomposed into two components: vaccine ($1.1) and shipping ($0.043) cost. The price charged by the manufacturer is driven by demand, supply, platform technology etc. Therefore, in this case, since all of ZKI vaccine candidates are under development, sensitivity analysis is utilized to reflect the level of price uncertainty. In order to deliver vaccine to a target population, management cost also was taken into account (Ordóñez and Orozco 2014).

In 2016, there was a drop of 8.3% foreign visitors to Colombia (Alsema 2016). The assumption here is tourism drop realized in 2016 as the awareness about the outbreak and its consequences are amplified by WHO declaration of PHEIC, and that the drop will last for one year.

This method of categorizing cost is affected by the availability of data. For instance, long-term loss due to drop of live birth rate or consequences from the false positive test is not mentioned. In addition to that, opportunity costs given up to take care of baby with CZS are not fully reflected (FRANCO 2017)

Discount rate

Both cost and effect are discounted at 3% as for instance recommended by the recent Washington panel on cost-effectiveness (Sanders, Neumann et al. 2016)

3.7 Health related Quality of Life

3.7.1 CZS

Data to reflect the burden of CZS is limited since this is relatively new and need more research. A literature search is conducted with the purpose to collect QALYs data, search strategy focuses primarily on keywords directly related to CZS, the secondary approach is to look for data from other congenital syndromes as discussed above with TORCH agents. ZKV does not lead to "villous necrosis or a maternal or fetal lymphoplasmacellular or acute inflammatory cell reaction", despite this fact differentiates ZKV from TORCH agents, they own the same outcome: similar damage for fetus's CNS (de Carvalho, de Carvalho et al. 2017, Rosenberg, Yu et al. 2017)

A study from the Netherlands (Lugner, Mollema et al. 2010) showed a promising method to overcome the problem lacking of effect data. The method used to extract QALYs is discussed in the previous session.

		Loss of QALY/defect
Central nervous system (CNS)	0.5	39.4
Heart defect	0.87	10.2
Hearing disability	0.93	5.5
Heart defect and hearing disability	0.809	15.0
CNS + hearing disability	0.465	42.1
CNS + heart defect + hearing disability	0.405	46.9
Spontaneous abortion		78.8

Table 8: QALY data extracted from congenital rubella syndrome from the Netherlands population (Lugner, Mollema et al. 2010)

The assumption for this is that the effect is permanent and average number of QALY loss weights by the actual cases, which could be adjusted to reflect Colombian reality.

3.7.2 GBS

In order to capture short and long term effect of GBS by health-related quality of life (HRQOL), groups across countries have been trying to measure those by some methods: SF-12, SF-36, Sickness Impact Profile (SIP), Nottingham Health Profile (NHP)(Darweesh, Polinder et al. 2014), Fatigue Severity Scale (FSS) (Merkies and Kieseier 2016), modified Rankin scale or Rotterdam 9-item scale

(Bersano, Carpo et al. 2006). SF-36 was considered as a comprehensive way to measure health outcome for GBS patients and recommended to use for measuring health outcome for GBS patients (Darweesh, Polinder et al. 2014).

3.8 Model construction

General mathematical SEIR model in form of deterministic model is built to cope with all sets of intervention dynamic of the disease. This is one of three options for studying infectious diseases (Vynnycky and White 2010):

- Individual-based models
- Discrete-time compartmental models
- Continuous time compartmental model

The model used in this thesis can be described by the following equations, more detail for each scenarios and parameters' explanation are described in the *Appendix 1*:

$$\frac{dS^H}{dt} = -\frac{\beta_H S^H I^V}{N^V} - \frac{\beta_{HH} S^H (I^H + I^{Vac})}{N} - \mu_H S^H + b_H N - r_{Vac1} S^H c$$

$$\frac{dE^H}{dt} = \frac{\beta_H S^H I^V}{N^V} + \frac{\beta_{HH} S^H (I^H + I^{Vac})}{N} - \kappa_H E^H - \mu_H E^H - r_{Vac1} E^H c$$

$$\frac{dI^H}{dt} = \alpha \kappa_H E^H - y_H I^H - \mu_H I^H$$

$$\frac{dA^H}{dt} = (1-\alpha)\kappa_H E^H - y_H A^H - \mu_H A^H - r_{Vac1} A^H c$$

$$\frac{dR^H}{dt} = y_H (I^H + A^H) - \mu_H R^H - r_{Vac1} R^H c$$

Those formulas are adapted to one week time circle. β_H and β_{HH} represent for two sources of transmission mode: mosquito to human and human to human. Transitional probability from E to I/A and I/A to R are reverse value of the time duration in that health state. The numbers of weekly new CZS and GBS cases are then determined by

$$\frac{dCZS^H}{dt} = \kappa_H (E^H + E^{Vac}(1 - e_{1d})) b_H p_{CZS}$$

$$\frac{dGBS^H}{dt} = \kappa_H (E^H + E^{Vac}(1 - e_{1d})) \alpha p_{GBS}$$

CZS cases are calculated as the proportion of newly infected pregnant women each week. Meanwhile, the number of GBS cases is the fraction of new symptomatic infected cases. Model dynamic is demonstrated in *Figure 9.*

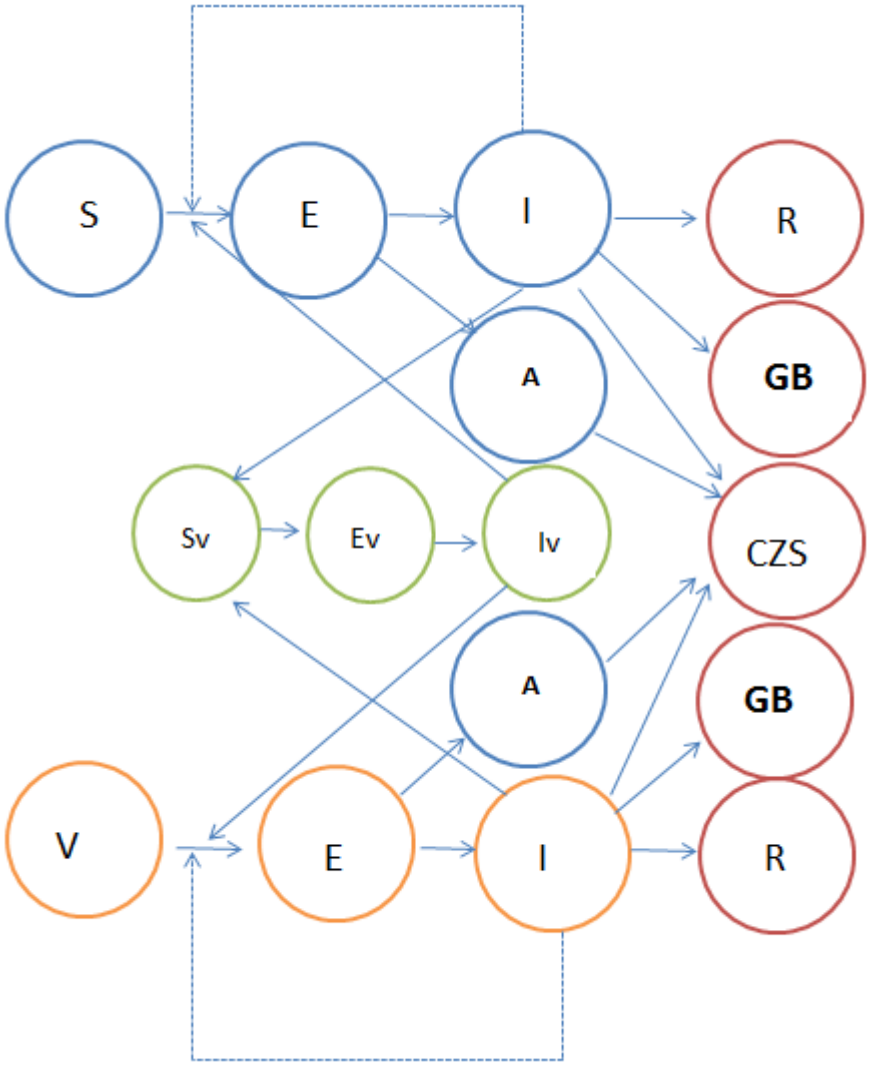

Figure 9: Disease dynamic and modeling approach for spreading of Zika virus
S: susceptible population; V: vaccinated population against Zika virus; E: exposed population after contact with infected mosquitos; I: symptomatic infected population, assumption here is infectious period start after symptom onset; A: asymptomatic infected population; Sv: susceptible mosquito population; Ev: exposed mosquito population; Iv: infected mosquito population; R: recovered population from Zika infectiousness; GB: Guillain-Barre syndrome population that potentially the result of Zika virus infection; CZS: congenital Zika virus syndrome (following WHO description) includes of microcephaly and other malformations of the head, seizures, swallowing problems, hearing and sight abnormalities.

3.8.1 Model structure:

Model is built based on the dynamic of the disease, standard SEIR was developed to reflect the development of Zika virus among human (with and without vaccine) and vector population. Some epidemiological data are derived from Dengue Virus infection. It is

worth noting that Zika and Dengue viruses are from the same genus Flavivirus, have same vector, similar symptom, incubation, and infectiousness period (Shapshak, Sinnott et al. 2015). In addition, a study suggests that "Zika virus could exhibit similar dynamics to dengue virus" (Kucharski, Funk et al. 2016). Therefore, in a case lacking empirical data, uses of alternative sources of Dengue virus are justifiable.

After contact with the infected mosquitos, the susceptible person enters incubation period (Bearcroft 1956, Lessler, Ott et al. 2016), represented by compartment E. Majority of infected patients exhibits mild or no symptom (Duffy, Chen et al. 2009, CDC 2017). The role of asymptomatic patients on transmission nodes is not clearly studied, experience from Dengue showed there is a possibility after having a meal on asymptomatic patients, the mosquitos might be infected; however, this link is not consistent and needs more investigation (Coudeville, Baurin et al. 2016). A scenario analysis would be conducted to reflect this type of uncertainty, in the meanwhile, baseline case would exclude the contribution of asymptomatic patients as a mode of transmission. After symptom onset, patients might start to spread the disease; the assumption is that before symptom onset surrounding susceptible population would not be affected. Infected patients can both transmit ZKV into susceptible human and mosquito population. The route of transmission to human is by sexual intercourse, to mosquito is by biting. After recovering from infection, the model assumes that patient would attain life-long immunity in the non-vaccinated population.

Vaccinated group is a theoretical population since there is no available vaccine for ZKV, majority of vaccine candidate is in the non and pre-clinical phase with very limited information. Even though, there are six clinical trials for phase I candidate conducted by GeneOne Life Science Inc, Inovio Pharmaceuticals, Modena Therapeutics and NIAID, results are still not accessible. Vaccinated population is characterized similar way to unvaccinated population. Infected population from both vaccinated and non-vaccinated group contributes to human-human and human-mosquito transmission. Vaccine protects vaccinated population with certain probability, which is determined by efficacy of vaccine.

Vector (*Ades Aegypty*) dynamic is reproduced from (Kucharski, Funk et al. 2016) and (Gao, Lou et al. 2016). Susceptible vector after biting infected human would enter exposed period, after the period of incubation, infected mosquitos might spread ZKV by biting susceptible human population, infected mosquito group would remain infectious until the end of their lifespan(de Castro Medeiros, Castilho et al. 2011). Transmission of ZKV into the next vector's generation is assumed as not feasible, in contrast with a study stated that this happens with the rate of 1/300 mosquito (Thangamani, Huang et al. 2016).

Herd immunity is modelled by the drop of transmission possibility both human-mosquito and mosquito-mosquito due to decrease of infected cases. Waning effect is modelled after two week of vaccination.

There are two scenarios for vaccination campaign: one and two doses. In the two-dose scenario, vaccinated population is then divided into two sub-groups: one-dose vaccinated group and two-dose vaccinated group, the reason for this is not all of individuals who would take the first dose will follow the procedure and receive the second. This would be

due to number of reason and will be explained further in other section. In other approach, selective strategies were considered and leading to two way of conducting the program: vaccinating for the whole population and vaccinating for high-risk population.

3.8.2 Model input

(1) Human

The population at risk (PAR) is a highly uncertain parameter, as recommended by CDC (CDC 2016) high-risk areas are below 2000 meter. There is not enough data to estimate the total number of population in areas at risk; in addition, states like Valle Del Cauca and Tolima are at the same time under and over that latitude. In the model, we use the whole population as PAR.

Data from the outbreak in Yap Island (2007) is well-accepted by CDC as the indicator for the proportion of symptomatic patients infected by ZKV. It was estimated only 18% (95% CI 10% - 27%) of infected population show symptom from the population size of 7391. We use this percentage in the model.

The incubation period in humans had been estimated from 5 days (Bearcroft 1956) to 7.5 days (Majumder, Cohn et al. 2016) and to 8.5 days from CDC. Newest data (Lessler, Ott et al. 2016) from WHO estimated the average of the incubation period is 5.9 days (95% CI, 4.4 – 7.6), which we used in the model.

Estimation of infectiousness period ranges from 5 days (Kucharski, Funk et al. 2016) to 7 days (Musso, Roche et al. 2015, Gao, Lou et al. 2016, Caminade, Turner et al. 2017) with various degree of uncertainty. Prudent approach is used with a value of 7 days in the model with the standard deviation of 20% following Gao's method (Gao, Lou et al. 2016).

Discussions with regard to the chance of CZS appearing among infected women are continuing. Data from US (Honein, Dawson et al. 2017) showed that among ZKV infected pregnant women, 6% observed with CZS. In the most recent study (Reynolds, Jones et al. 2017), which is considered as the "largest and most comprehensive study" on this issue (Sun 2017), up to 15% among confirmed infected pregnant women have CZS. The numbers are the same for both symptomatic and asymptomatic group. Meanwhile, a study from Brazil (Brasil, Pereira Jr et al. 2016) withdrew result with 39% of the infant from ZKV infected woman related to abnormal outcomes, taken into account for lost due to follow up. There are a number of explanations for this unusual difference. Geographical and demographical factors might play an important role, such as temperature, local lifestyle with regard the risk of transmission and vector dynamics. In addition, pre-infection and co-circulating with other diseases – Dengue and Chikungunya (Cherabuddi, Iovine et al. 2016, Carabali, Lim et al. 2017) in Colombia are similar to Brazil, this is speculating as a key determinant for the high

severity consequences in Brazil. Last but not least, with the presence of co-infection and weak diagnostic capacity, we could also speculate on the possibility that the number of cases had been over reported by including false positives. Nevertheless, using data from Brazil seem to be the best option for the case of Colombia, since the 2 countries share many common geographical and demographical characteristics, standard procedure for detecting and follow up in Brazilian study (Brasil, Pereira Jr et al. 2016) is perceived as better than a primary study from Colombia (Pacheco, Beltrán et al.). With high level of uncertainty, 50% is used as the standard deviation in this case. In addition, all CZS cases are assumed occurring in the middle of pregnancy (4.5 months).

GBS weekly rate is extracted from actual incidence within 58 weeks of the outbreak in Colombia. Both clinical examination and imaging study are needed to correctly diagnose GBS, therefore in this case 50% standard deviation will also be used to reflect the uncertainty of this parameter. Death rate 15% from GBS obtained from a follow-up study among patients in Colombia (Mahecha, Ojeda et al. 2016).

Data from UN (UN 2017) is used to calculate weekly birth and death rate.

(2) Mosquito

The model is a simplified version of mosquito population dynamics, representing the dynamic of the adult mosquito as a node of transmission. Only female mosquito population would be taken into account, other stages: eggs, larvae, and pupae would be ignored (Andraud, Hens et al. 2012). After the infectious blood meal, ZKV follows saliva penetrates into female mosquito body. The level of blood-meal viral titer has a strong negative correlation with the extrinsic incubation period (Chouin-Carneiro, Vega-Rua et al. 2016).

Some epidemiological data is extracted from recent clinical trials conducted in South-East Asia and Latin America, and used in this model (Coudeville, Baurin et al. 2016). In the absence of data from this source, most relevant sources would be used with the priority of most updated data as close as possible to geographic and demographic of Colombia.

Extrinsic incubation period varied from 5 (Majumder, Cohn et al. 2016) to 10 days (Boorman and Porterfield 1956, Andraud, Hens et al. 2012, Chouin-Carneiro, Vega-Rua et al. 2016). Data which Majumder C obtained from an *Aedes Aegypti* population in Singapore would be considered as less relevant than other sources for Colombian population. Mosquito lifespan varied from 4 to 35 days (Gao, Lou et al. 2016) and 4 to 50 (Andraud, Hens et al. 2012), central estimation for this value is well accepted with 14 days (Coudeville, Baurin et al. 2016, Gao, Lou et al. 2016). Conservative approach will be applied to calculate the standard deviation for this value with the range from 4 to 50 days.

	Value	Source
Mosquito lifespan	14	(Coudeville, Baurin et al. 2016, Gao, Lou et al. 2016)
External incubation period	10	(Boorman and Porterfield 1956, Andraud, Hens et al. 2012, Chouin-Carneiro, Vega-Rua et al. 2016)
Mosquito to human ratio	1.5	(Flasche, Jit et al. 2016)

Table 9: Epidemiological data for mosquito

Due to the difficulty of conducting mosquito study, the estimation of mosquito to human ratio depends strongly on the method, geography and temperature (Focks, Alexander et al. 2006). The ratio has tendency to be lower in the dry season than the rainy time of the year. Data used in this model was extracted from team Exeter/Oxford (Flasche, Jit et al. 2016).

(3) Human and mosquito

The interaction between mosquito and human is parameterized with two ways approach: the frequency a human get bit by mosquitos and the frequency the mosquito bites human in a time unit. Mosquito biting rate is considered as affected by seasonality (Caminade, Turner et al. 2017), in addition to that, social economic status and geographic might also adjust the attacking rate (Flasche, Jit et al. 2016). The highest attacking rate among three studies (Andraud, Hens et al. 2012, Flasche, Jit et al. 2016, Caminade, Turner et al. 2017) would be used in this case. Probability to get infected after contact with the infectious vector is linked to data from CDC (Duffy, Chen et al. 2009), meanwhile, the probability of the opposite site got from Exeter/Oxford Dengue modeling team (Flasche, Jit et al. 2016).

(4) Human and human

Until today, there are 13 countries with reported human to human transmission (WHO 2017). Sexual transmission from both symptomatic and asymptomatic patients has been described (D'Ortenzio, Matheron et al. 2016, Frank, Cadar et al. 2016, Freour, Mirallie et al. 2016, Harrower, Kiedrzynski et al. 2016). In the baseline analysis, the study focuses on the symptomatic population, whose sexual activities are not heavily impacted by the disease (Gao, Lou et al. 2016).

In the absence of thorough study of human to human transmission, sexual transmission data is replicated from (Gao, Lou et al. 2016), the population from this study is closely related to Colombia (Brazil, Colombia, and El Salvador). Two important parameters used to calculate human to human transmission rate are: the number of sexual contact carries risk per week and probability get infected after each sexual contact. Those two inputs are extracted from Gao, Lou et al (Gao, Lou et al. 2016).

(5) Vaccine parameters

The capacity is limited for a country like Colombia, data from Ministry of health show that in average there had been around 900,000 people (rounded up to one million in the model) vaccinated in Colombia, therefore the assumption is that this capacity cannot overnight have any significant change.

The vaccination program is hypothesized into four sub-scenarios:

S1: Non-discriminate - 1 dose

S2: High-risk population - 1 dose

S3: Non-discriminate - 2 doses

S4: High-risk population - 2 doses

There are different sets of parameters determined for each scenario: vaccination rate efficacy for each dose. Annual capacity (one million) and coverage rate for vaccination program is determined by a normal capacity for a given disease estimated from Colombian Ministry of Health data (MinSalud 2012). Given the assumption of fixed capacity each year, weekly rates of vaccination for both scenarios were calculated based on annual rate. Coverage rates are not equal among areas, in 2010 only 34% of the target population was vaccinated in Vaupes. Coverage rate 50% (lower than average) with low level of uncertainty (10%) is used to reflect this reality. This parameter will play a role as an upper scale of the vaccination campaign.

Efficacy of the vaccine is assumed based on recently approved dengue vaccine. In the two doses scenario, first dose efficacy is determined by lowest efficacy from Dengue trial 42.3% (rounded to 40%), and efficacy after two doses is 80 extracted from the proportion of immunogenicity group (79.4%) (Villar, Dayan et al. 2015). One dose scenario's efficacy used data from minimal preferred efficacy's value from WHO TPP (WHO/Unicef 2017). 80% of the participants follow the second dose after the first one, this input comes from dropout rate in the same paper. Waning rate 15% is similar with the assumption from Sanofi team (Flasche, Jit et al. 2016).

(6) Cost parameters

As specified in the method part, direct costs in this case include the cost of vaccination and treatment. Vaccination cost data is based on data from other *flavivirus* vaccines (Yellow Fever), the cost for each dose is calculated from average price from 2015, 2016 and projected price for 2017, and four suppliers are taken into account: Bio-Manguinhos, FSUE of Chumakov, Institut Pasteur de Dakar, and Sanofi Pasteur. Price included delivery cost from Unicef. From another paper (Ordóñez and Orozco 2014), the average cost of administration is extracted. Yellow Fever vaccines have been

circulating on the market for a long period, therefore the use of this price for the potential new vaccine is likely too low.

Cost of treatment emerges from three sources: symptomatic patients, CZS and GBS cases.

Mahecha and colleagues reported that most of the patients with GBS require medical attention (Mahecha, Ojeda et al. 2016), in another study in Colombia, there was 69% of patients admitted to ICU with the average duration of 23 days (Anaya, Rodriguez et al. 2017). Cost from GBS could be decomposed into the following main items: the cost of hospitalization, ICU and long-term cost (cost of informal care, opportunity costs lost due to career change etc.); In this study, long-term cost is not included as the consequence of lacking data.

Criteria	Value	SD	Reference
GBS related parameters			
Length of ICU	7	50%	(Anaya, Rodriguez et al. 2017)
ICU admission proportion	69%		(Anaya, Rodriguez et al. 2017)
Cost of ICU/day	$335	50%	(van Leeuwen, Lingsma et al. 2016)
Length of Hospitalization	23	30%	(Anaya, Rodriguez et al. 2017)
Cost of Hospitalization/day	$77	50%	(van Leeuwen, Lingsma et al. 2016)
Cost of IVIG	$1 243	50%	(van Leeuwen, Lingsma et al. 2016)
CZS related parameters			
Lifetime cost per CZS case	$678 821	52%	(Li, Simmons et al. 2017)
Cost of testing and monitoring per infected pregnant woman	$74	50%	(Li, Simmons et al. 2017)
Cost of testing per live-born infant	$36	50%	(Li, Simmons et al. 2017)
Cost of testing per fetus with infected mother	$56	50%	(Li, Simmons et al. 2017)
Symptomatic cases			
Treatment cost	60	30	(Flasche, Jit et al. 2016)
Productivity loss	110.3	55	(Panzer 2016)

Table 10: Parameter inputs used to calculate direct cost

Most of the cost parameters for CZS are translated from a CDC study (Li, Simmons et al. 2017). Direct costs are related to testing and monitoring, including for the mother, fetus and live-born baby. A prudent approach is applied with regards to uncertainty with standard deviation as the higher value from the paper or 50%. Pregnant women are tested with IgM, ultrasound examinations and some of them getting Amiocentesis; fetus test comprises three separate PCRs for placenta, cord and brain tissues; meanwhile testing procedure for live-born infants with infected mother needs IgM, PCR, cranial ultrasound and eye examination (Li, Simmons et al. 2017). Lifetime cost per CZS case is related to both medical cost and supportive care in Li's calculation. Overall, testing and monitoring procedures vary among areas, depending on local capacity and health care structure. Those cost items are from standard procedure in Puerto Rico and recommended by CDC, however, the applicative ability needs further investigation in the context of bigger heterogeneity in Colombia. In addition, there are some other methods of examination used in Brazil (Brasil, Pereira Jr et al. 2016): CT, MRI, TF. It is worth to note that those are expensive procedures and it is uncertain about how much they had been used in Colombia.

Cost inputs for GBS are extracted from (van Leeuwen, Lingsma et al. 2016) following the method describing in the method section (Eur to Usd and then adjusted for the willingness to pay between US and Colombia). The length of stay for ICU, hospital and ICU admission are real data from a cohort study in Cucuta, Colombia (Anaya, Rodriguez et al. 2017). Due to the high uncertainty of translated costs, the model uses 50% standard deviation for each item.

The remaining costs item related to symptomatic patients could be seen as both direct and indirect. The cost of treatment for symptomatic patients is low due to the nature of symptoms. Data is extracted using data from symptomatic Dengue case (Flasche, Jit et al. 2016) from the public payer perspective. Different degree of severity and appearance indicates this value could be overestimated and highly uncertain. From World Bank (Panzer 2016), one-week loss due to the effect of ZKV would be applied on symptomatic patients.

From the local perspective, tourism is considered as an important component of the economy, the total contribution to Colombian GDP in 2014 is 5.9% and created 6.1% of total employment. Those two figures expected to rise 4.1% (contribution to GDP) and 2.4% (contribution to employment) until 2025 (WTTC 2015). Using the data from Colombianreports.com (Alsema 2016) combining with the data from Worldbank, $7.8m is the amount of potential money loss from tourism spending every week. This is purely an assumption based on the idea that all loss of tourism had been contributed by the Zika outbreak only. The starting point of tourism drop used in the model is since WHO declared Zika outbreak as PHEIC, would be nine months after first introduction in the model. This is based on the timeline of the disease, six months are the time-period from first retrospective case confirmed (Pacheco, Beltrán et al.), and three months added to reflect the risk that ZKV might come to Colombia before that.

(7) Effect parameters

As discussed in the previous section, congenital rubella syndrome is used as the primary way to identify health outcome of CZS. Given multiple values of probability baby getting CZS, a study from Brazil (Brasil, Pereira Jr et al. 2016) was used for both purposes of identifying the incident and as intermediate to calculate health outcome (*Table 11*). Recent Colombian Preliminary report (Pacheco, Beltrán et al.) had only result from infected woman in the third trimester, hence would not be used in this study.

	Cases
Microcephaly	4 (8.2%)
Small for gestational age	9 (18.4%)
Cerebral calcification	5 (10.2%)
Cerebral atrophy	2 (4.1%)
Ventricular enlargement	0
Hypoplasia of cerebral	2 (4.1%)
Parenchymal brain hemorrhages	9 (18.4%)
Abnormal result on neurologic examination*	23 (46.9%)
Other result**	22 (44.9%)
Excessive hypersignaling	16 (32.7%)

Table 11: Data compiled from (Brasil, Pereira Jr et al. 2016);

**including of hypertonicity, clonus, hyperreflexia, abnormal movements, spasticity, contractures, seizures; **including of cortical thumb sing, fovea in the knees or elbows, redundant scalp skim, hemiparesis, head lag, branchycephaly.*

Until the time of this writing, there is no available data reflecting the health-related quality of life of CZS. Therefore, QALY data is extracted from congenital rubella syndrome with the data source from Dutch Ministry of Health, Welfare and Sport (Bijkerk 2014). Disability weight ranges from 0.17 for cataract to 0.484 for microcephaly. As described in *Table 11* the clinical examination results from CZS are mostly brain-related, any health outcome measurement should capture this reality, and therefore, purely using data from congenital rubella syndrome is not an optimal way. Multiple complications are also observed from congenital rubella syndrome (Lugner, Mollema et al. 2010). There is high chance that the distribution of CZS's disability weight falls beyond the value of microcephaly case, however, this study will use this as baseline analysis. Using the method from Lugner AK et al., QALY loss is 15.2 for each CZS case.

	Guillain-Barré syndrome Mean (SD)	Poliomyelitis Mean (SD)	Reference group Mean (SD)	p (ANOVA test)
Physical functioning	75.6 (27.1)	69.2 (27.2)	88.4 (15.5)	< 0.0001
Role – physical	57.4 (44.8)	52.8 (46.5)	84.6 (30.3)	< 0.0001
Bodily pain	69.33 (28.6)	63.9 (29.6)	85.9 (21.7)	< 0.0001
General health	60.2 (16.2)	60.1 (15.5)	70.9 (1.8)	< 0.0001
Vitality	55.3 (21.9)	49.3 (24.2)	64.9 (20.5)	< 0.0001
Social functioning	82.0 (21.9)	76.9 (25.0)	92.0 (16.7)	< 0.0001
Role – emotional	75.1 (28.6)	76.9 (36.9)	88.8 (28.0)	0.008
Mental health	78.8 (18.4)	76.6 (17.8)	82.2 (16.0)	0.1

Table 12: Result from follow up study reflecting the long term effect of GBS (Rekand, Gramstad et al. 2009)

QALY loss for GBS case is calculated directly from the patient and reference group (*Table 12*) (Rekand, Gramstad et al. 2009). Long term effect as the consequence of GBS is significant with 27% population recorded with minor impaired capacity in daily life and 9% needed constant aid (Bersano, Carpo et al. 2006), meanwhile data from the same study also demonstrated 19 out of 45 patients "make substantial changes in their job, hobbies or social activities". SF 36 was used to evaluate HRQL, with the assumption that long-term effect is unavoidable, QALY loss was calculated based on the remaining life expectancy among GBS patients in Colombia (4.13 QALY loss).

4 Results

4.1 Epidemical result

Reproduction number was estimated by Kucharski method (Brauer, Castillo-Chavez et al. 2016, Kucharski, Funk et al. 2016) combining with Monte Carlo simulation. By this method, there is one thousand basic reproduction number estimated. Distribution of the result presents in *Figure 10* below.

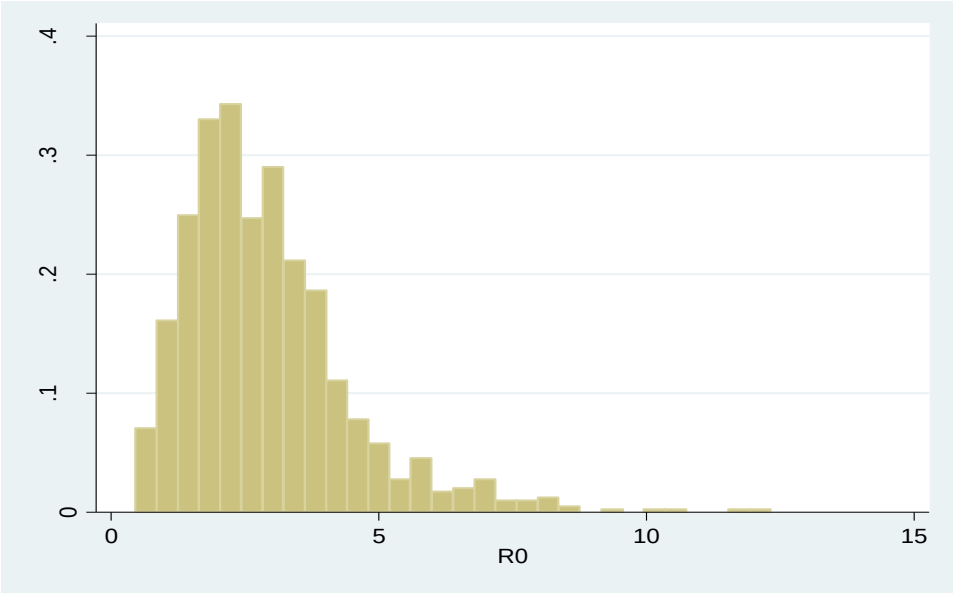

Figure 10: R0 estimated from model.

From *Figure 10*, R0 is relatively skewed to the right, with mean/median value: 2.89/2.61 with 95% CI: 2.798-2.990. Contribution of sexual transmission is 0.603 (95% CI: 0.556 – 0.649)

In the beginning of October 2015 (week 40), Colombia first laboratory confirmed ZKI case was announced by INS, retrospective serum sample suggested ZKV appear in Colombia from July 2015 (week 27) (Pacheco, Beltrán et al.). As described in the epidemiology section, a number of new suspected cases peak in the beginning of 2016 (around week 5), coincides with the peak amount of weekly laboratory confirmed cases (week 4). The discrepancy between modeling and reported number is large, week 61 in the model, which experiences more than one million cases in the non-intervention scenario (*Figure 11*), corresponds to week 5 in 2016, which is approximately 7000 cases.

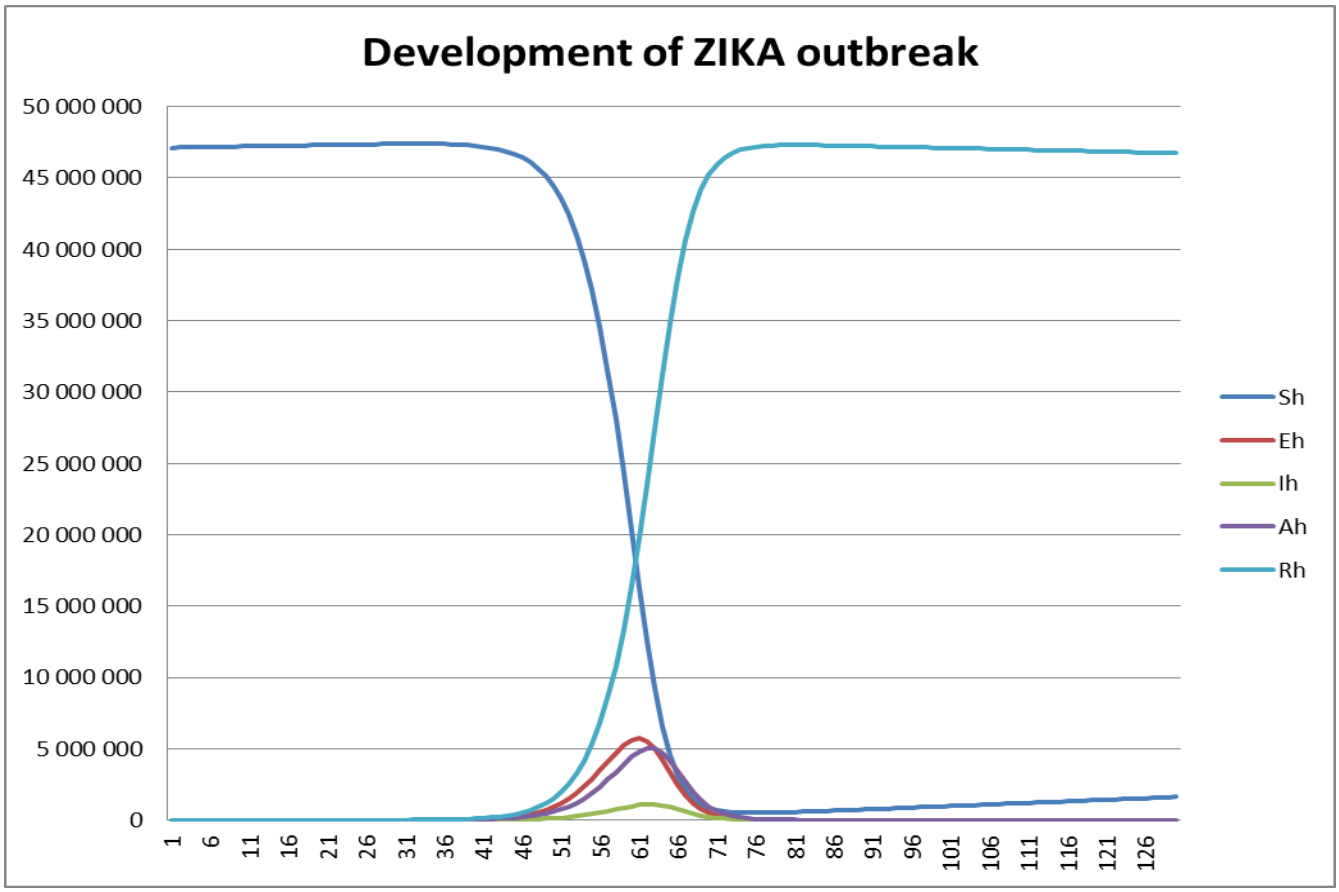

Figure 11: Number of susceptible, exposed, symptomatic and asymptomatic infected, recovered by the time of ZIKA outbreak (without vaccination campaign)

Sh: susceptible population; Eh: exposed population after contact with infected mosquitos; Ih: symptomatic infected population; Ah: asymptomatic infected population; Rh: recovered population

Figure 11 shows the development of ZIKA outbreak without vaccine intervention. At week 40, there are 12 000 symptomatic infected cases and 56 000 asymptomatic cases. Weeks after 40 experience a sharp change in the value of five parameters (SEIAR). The number of symptomatic infected cases peaks at week 61 (1.1 million cases), one week after highest point of exposed cases. Moving forward to the end of time horizon, susceptible population increases, combining with the drop of the immunized population.

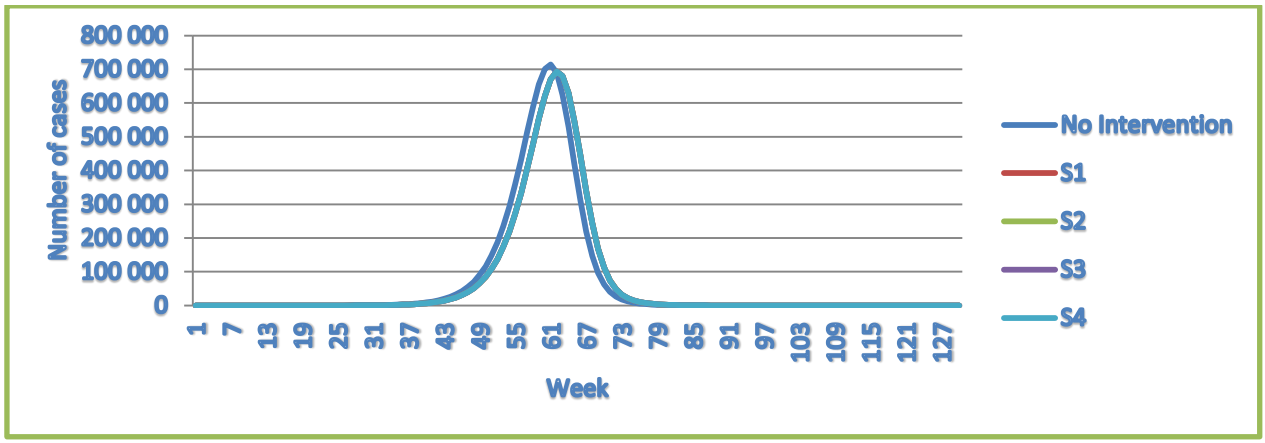

Figure 12: Weekly symptomatic infected cases

S1: Non-discriminate - 1 dose; S2: High-risk population - 1 dose; S3: Non-discriminate - 2 doses; S4: High-risk population - 2 doses

From *Figure 12*, the number of infected cases remained under 100 until week 22 for non-intervention scenario and week 23 for vaccination scenarios. Following that, these numbers increased sharply and peaked at week 60 (714 thousand cases) for non-intervention and week 61 (more than 690 thousand cases) for vaccination scenarios.

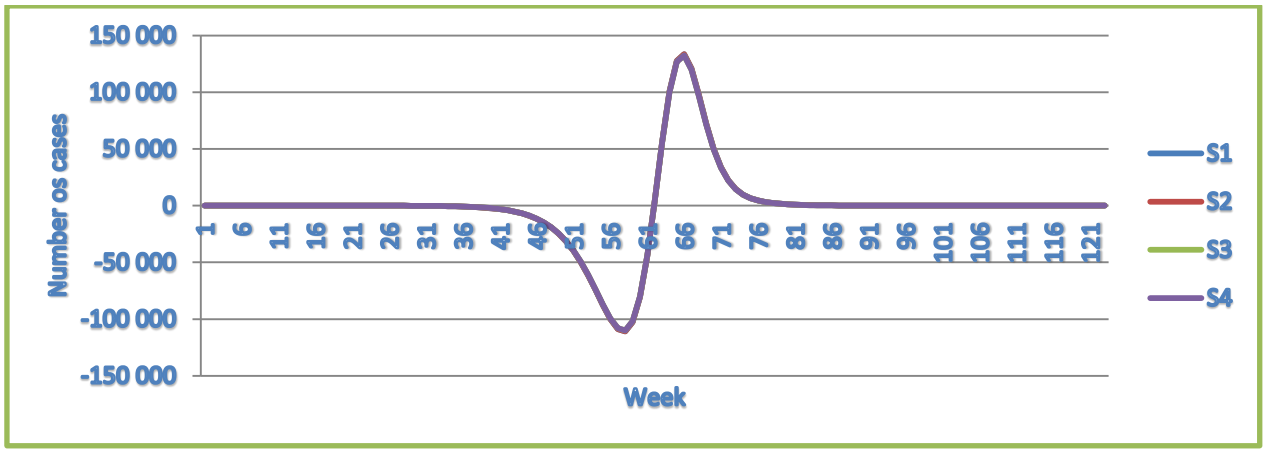

Figure 13: Difference in the number of symptomatic infected cases between vaccination and non-vaccination scenario.

S1: Non-discriminate - 1 dose; S2: High-risk population - 1 dose; S3: Non-discriminate - 2 doses; S4: High-risk population - 2 doses

In the model, vaccination with assumed current capacity would in S1 and S2 reduce the total number of weekly ZVI cases with 135 042 cases and in S3 and S4 with 135 257 cases. In week 58, more than 110 thousands avoided cases are recorded. This effect is offset by surging trend from week 61, as a number of infected cases among four scenarios overcome the nonintervention. In total, the

saving effect before week 61 is larger than surging of the incremental number of infected cases afterward.

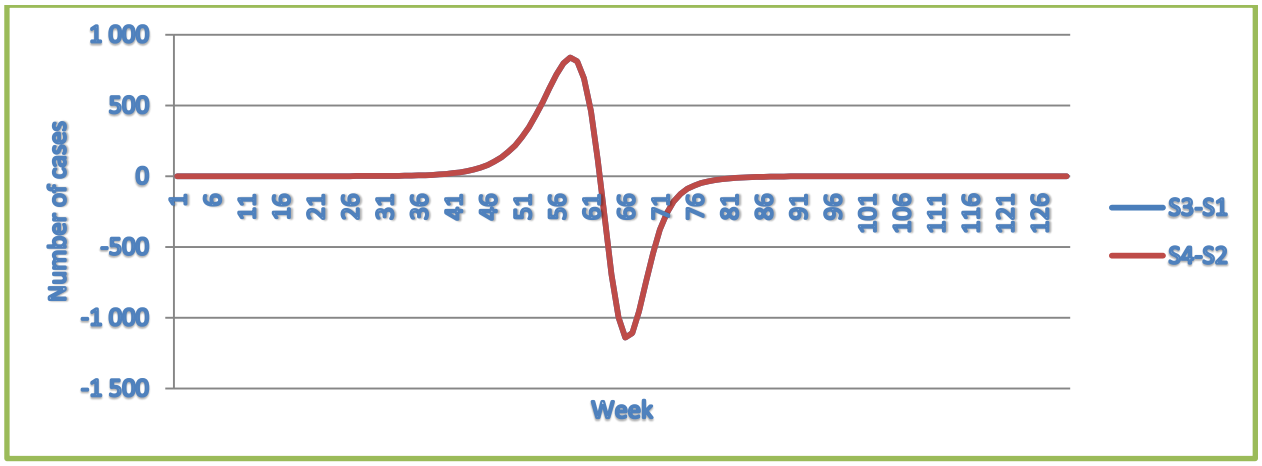

Figure 14: Difference in the number of symptomatic infected cases between one and two-dose vaccination scenarios.

S1: Non-discriminate - 1 dose; S2: High-risk population - 1 dose; S3: Non-discriminate - 2 doses; S4: High-risk population - 2 doses

Comparing one and two-dose scenario, it is observed with opposite pattern, before week 61 two-dose scenarios underperform to one-dose scenario. More than 800 ZVI cases are saved by S1 and S2 compared to S3 and S4 in week 58. In contrary, from week 61 forward, two-dose scenarios prove that they are more effective in countering spreading of ZKV.

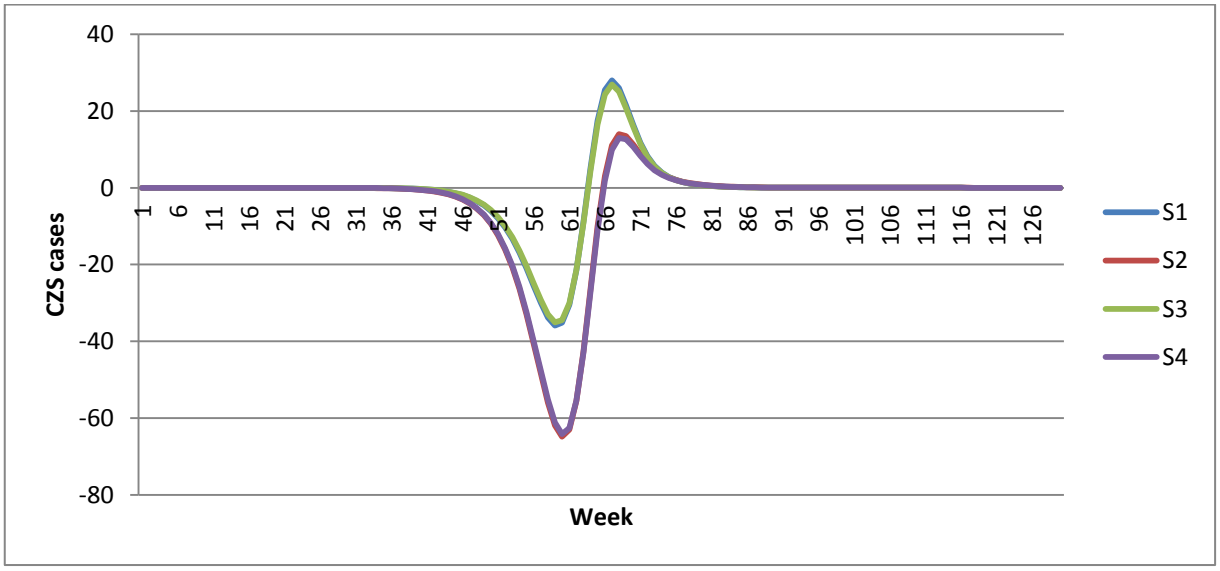

Figure 15: CZS cases different from no intervention scenario

S1: Non-discriminate - 1 dose; S2: High-risk population - 1 dose; S3: Non-discriminate - 2 doses; S4: High-risk population - 2 doses

Among four scenarios, S2 and S4 save most of CZS cases in the peak of the outbreak, approximately 64 cases in week 60, and meanwhile, 35 cases are saved in week 59 by S1 and S3. S1 and S3, S2 and S4 display almost same result. Despite the fact that incremental value of infected cases is similar among four scenarios, total number of CZS cases is significantly different between non-discriminated and high-risk vaccination scenario. Comparing to the number of ZVI cases above, in *Figure 15*, S2 and S4 exhibit different behaviors. As the number of ZVI cases raise again after week 60, the size of CZS saved does not reduce at the same pace. The incremental value of CZS cases for S2 and S4 week 68 compared to no intervention scenario is 20% as of week 60. In terms of absolute value, high-risk focusing vaccination campaigns in total save 527 CZS cases in S2 and 529 CZS cases for S4, at the same time both non-discriminating campaigns (S1 and S3) help to avoid 134 babies from getting CZS.

About the incidence of GBS, routine vaccination campaigns for both non-discriminate and high-risk population strategy in total reduce the approximately same amount (10 cases), which is not a significantly different from non-intervention setting. This implies that routine vaccination campaign might play little role on dropping incident rate of GBS.

4.2 Cost-effectiveness result

Before discussing the cost-effectiveness of all four vaccination strategies, this part will try to articulate from the cost perspective.

	No	S1	S2	S3	S4
Vaccination campaign cost		$ 4 920 367	$ 4 920 367	$ 8 731 482	$ 8 731 482
Productivity cost	$913 219 656	$891 087 163	$891 087 164	$891 139 682	$891 139 681
Tourism drop	$459 138 678				
CZS Lifetime cost	$5 289 716 335	$5 205 396 667	$4 961 138 277	$5 205 297 985	$4 960 427 007
GBS related cost	$3 205 434	$2 727 362	$2 727 362	$2 727 311	$2 727 311
CZS related cost	$3 063 589	$3 014 754	$3 001 152	$3 014 697	$3 001 060
Symptomatic treatment cost	$496 628 659	$484 592 530	$484 592 530	$484 621 091	$484 621 090

Table 13: Vaccination campaign cost

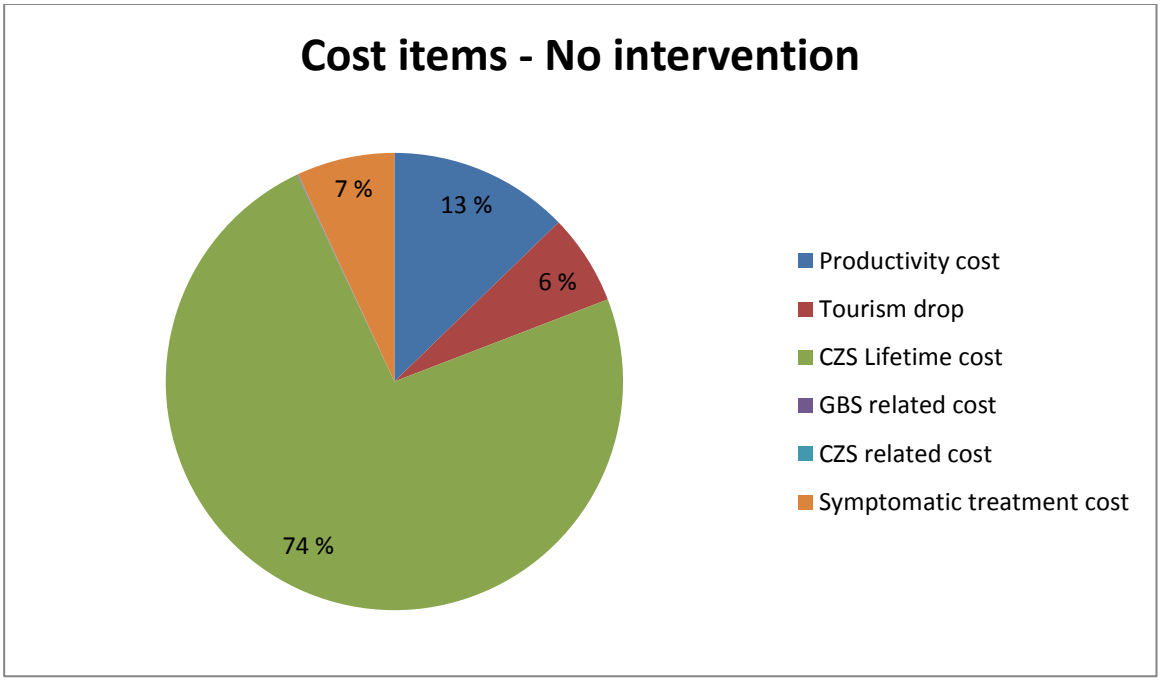

Figure 16: Contribution of cost items into total cost

Table 13 shows total cost for in detail for each scenario. CZS lifetime cost is the most substantial item, it's value exceeds 5.29 billion USD and accounts for 74% of total cost in no intervention scenario. Productivity loss, treatment cost for symptomatic patients and tourism drop is the second, third and fourth important cost item in the list. Productivity loss is two times larger than tourism drop. Weekly loss from tourism was estimated above seven million USD, and the value for the whole period is more than 450 million USD. The cost for the vaccination campaign including of vaccine and

administration cost varies from 4.9 million USD for one dose scenarios to 8.7 million for two dose scenario. The following figure represents the cost-effectiveness of the vaccination campaign.

Results undiscounted

Scenario	Costs	Increment	CZS	CZS save	GBS	GBS save	LY loss	LY gain	QALY loss	QALY gain
No intervention	$7 415 299 471		8514		618		2946		134138	
S1	$6 823 061 868	-$592 237 603	8380	134	608	10	2899	46	132023	2115
S2	$6 570 069 666	-$845 229 805	7987	527	608	10	2899	46	126046	8092
S3	$6 826 959 303	-$588 340 168	8380	134	608	10	2899	47	132020	2118
S4	$6 573 328 923	-$841 970 548	7986	529	608	10	2899	47	126027	8110
Primary result			**Net Health Benefit**		**Net Monetary Benefit**		**incremental costs/ LY gain**		**incremental costs/ QALY gain**	
			61 338		**$613 384 058**		**-$12 753 936**		**-$280 065**	
			92 615		**$926 150 060**		**-$18 202 166**		**-$104 452**	
			60 952		**$609 520 248**		**-$12 649 892**		**-$277 780**	
			92 308		**$923 075 209**		**-$18 103 190**		**-$103 813**	

Results discounted

Scenario	Costs	Increment	CZS	CZS save	GBS	GBS save	LY loss	LY gain	QALY loss	QALY gain
No intervention	$7 164 538 459		8227		597		2846		129613	
S1	$6 591 738 845	-$572 799 614	8096	131	588	10	2801	45	127547	2066
S2	$6 347 338 991	-$817 199 467	7716	511	588	10	2801	45	121773	7840
S3	$6 595 532 247	-$569 006 211	8096	131	588	10	2801	45	127545	2068
S4	$6 350 519 449	-$814 019 009	7715	512	588	10	2801	45	121756	7857
Primary result			**Net Health Benefit**		**Net Monetary Benefit**		**incremental costs/ LY gain**		**incremental costs/ QALY gain**	
			59 346		**$593 460 345**		**-$12 625 334**		**-$277 241**	
			89 560		**$895 603 907**		**-$18 012 261**		**-$104 229**	
			58 969		**$589 691 122**		**-$12 527 063**		**-$275 083**	
			89 259		**$892 592 447**		**-$17 921 185**		**-$103 600**	

Figure 17: Baseline result

Within two and half years, spreading of ZKV without intervention in Colombia could cost the country more than seven billions USD. To put this into perspective, 2015 GDP of Colombia is 292 billion USD (WorldBank 2017). The majority of cost comes from the drop of tourism, lifetime cost from CZS, productivity loss, management cost for GBS and CZS. From a societal perspective, high-risk focus vaccination campaign's saved cost is 1.4 times more than non-discriminate vaccination campaign, with the absolute value of about 250 million USD.

An important assumption for the model is that ZVI with its complications does not affect life expectancy, except for a proportion of GBS patients. The total amount of LYGs gain is almost the same across 4 scenarios with the value range from 45 for discounted and 47 for undiscounted on S3 and S4. In terms of QALYs, the gain ranges from more than 2000 for non-discriminate strategy and more than 7600 for high-risk setting.

In terms of incremental cost-effectiveness ratio, all four scenarios appear to be highly efficient, fall far behind the threshold. Since ICER is negative, leading to some difficulties to interpret, NHB is a good supplement. Total health benefit varies from more than 59 thousand QALY for non-discriminate campaign to more than 89 thousand QALY for high-risk focusing. NMB, which is other form of expressing Net

Benefit, ranges from almost 600 million USD for non-discriminate campaign to almost 900 million USD for high-risk focusing scenarios. Vaccine intervention does not just constrain spreading of ZVI and its catastrophic consequences, but also reduces cost from a societal perspective.

The effect of discounting affects both cost and health outcome. After discounting, cost saved from high-risk scenario reduces with larger magnitude than the non-discriminate strategy. Taking S1 and S2 for example, discount effect reduces cost saving from 592 to 572 million USD for S1 (20 million USD), meanwhile 28 million USD is the decrement value in S2. A similar effect is observed with QALY gain in the appearance of the discount effect. The following table will try to strip layer by layer of cost out of baseline case to see its important on NHB

NHB	S1	S2	S3	S4
Baseline	106 898	157 401	106 206	156 836
Without productivity cost	102 847	153 351	102 165	152 795
Without loss from tourism	18 817	69 321	18 135	68 765
Without CZS lifetime cost	3 385	9 186	2 685	8 500
Without GBS related cost	3 377	9 178	2 677	8 492
Without CZS related cost	3 368	9 143	2 668	8 457
Without symptomatic treatment cost	1 166	6 940	470	6 259

Table 14: ICER from variable cost level

As observed from Table 14, two cost items that have significant effects on the final Net health benefit (NHB): loss from tourism and CZS lifetime cost. It is worth noting that this only related to reducing incremental cost, the number of CZS, GBS and QALY saved stay unchanged. Removing productivity cost has limited effect on the NHBs from all four scenarios. Loss from dropping tourism spending results in large impact with different degree between non-discriminate and high-risk focus scenario. Within non-discriminate strategy, the drop is almost 6 times; meanwhile, with the same procedure, NHB drop 2.2 times in high-risk scenarios. Stripping CZS lifetime cost results another significant decrease on NHB, more than 60 thousand QALY removed from high-risk focusing scenarios and 15 thousand QALY in non-discriminating vaccination campaign. Other costs related to CZS and GBS have limited influence on both strategies.

4.3 Probabilistic

Results discounted										
Scenario	Costs	Increment	CZS	CZS save	GBS	GBS save	LY loss	LY gain	QALY loss	QALY gain
No intervention	$5 969 277 394		6876		508		2416		108125	
S1	$5 531 190 686	-$438 086 708	6696	179	496	12	2358	58	105305	2819
S2	$5 300 280 816	-$668 996 578	6342	534	496	12	2358	58	99919	8206
S3	$5 531 608 434	-$437 668 960	6697	179	496	12	2358	58	105310	2815
S4	$5 299 276 810	-$670 000 584	6342	534	496	12	2358	59	99921	8204
Primary result			Net Health Benefit		Net Monetary Benefit		incremental costs/ LY gain		incremental costs/ QALY gain	
			46 628		$466 280 222		-$7 498 941		-$155 386	
			75 106		$751 057 401		-$11 451 536		-$81 524	
			46 582		$465 815 074		-$7 573 273		-$155 499	
			75 204		$752 041 226		-$11 425 251		-$81 667	

Figure 18: Probabilistic result

From probabilistic analyses, the mean value from a thousand simulations is reported. Cost and health outcomes follow a similar pattern in probabilistic analyses as in deterministic although with somewhat lower estimates. The difference in non-intervention scenario's total cost is more than one billion USD and 1350 CZS cases. Within one-dose scenarios, S1's total incremental cost is 24% lower and S2's total cost is almost 18% lower than the deterministic value. This means less cost is saved as we observe probabilistic value. Incremental health outcomes do not change in the same pattern as with cost. Even with less CZS cases, CZS cases saved by non-discriminate campaigns increase more than 35%, meanwhile, there is a slight increase of 4% in high-risk focusing strategy.

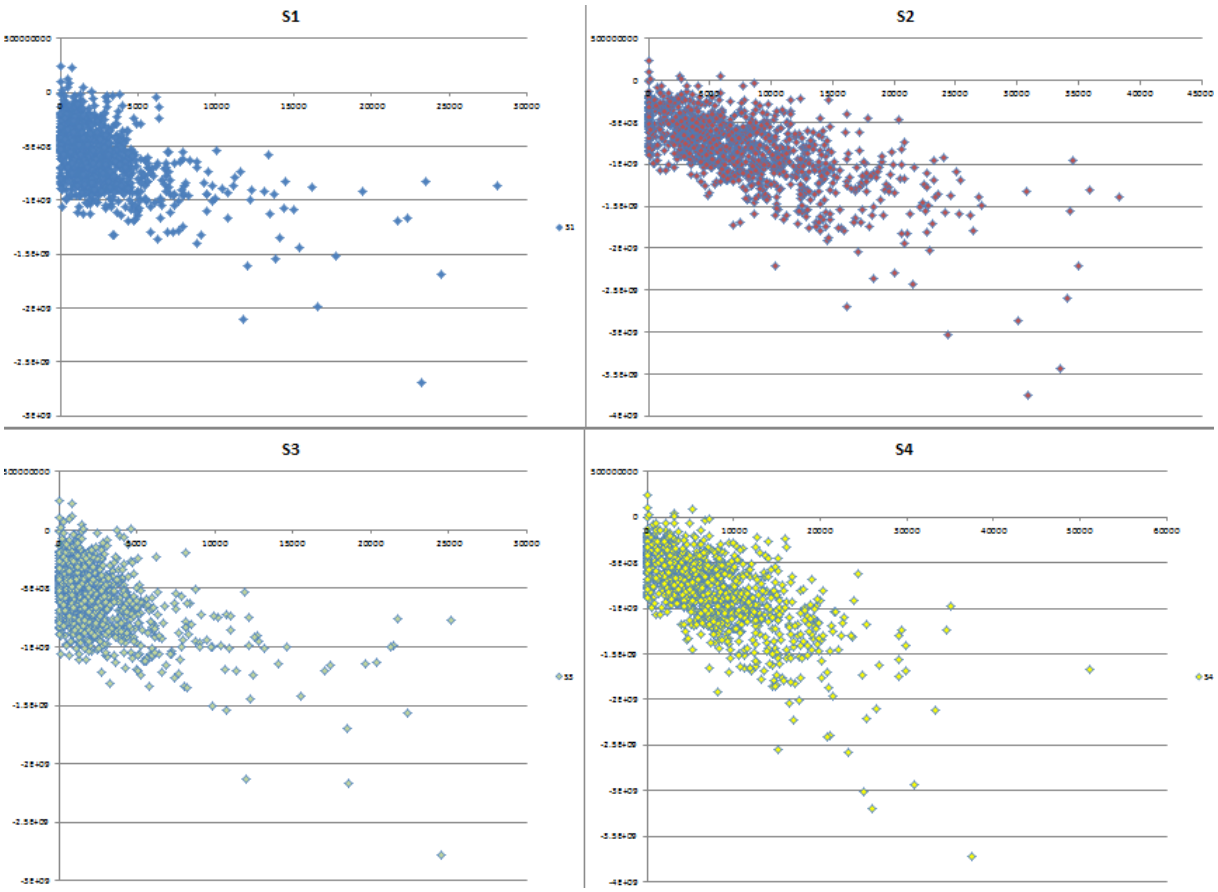

Figure 19: Cost-Effectiveness Plane

S1: Non-discriminate - 1 dose; S2: High-risk population - 1 dose; S3: Non-discriminate - 2 doses; S4: High-risk population - 2 doses

Simulations of all four scenarios' results have mainly located in the southeast quadrant of CE Plane. This means there is a high level of confidence that vaccination campaign with one dose or two doses, non-discriminate or high-risk setting are cost-effective. The distributions of dots in CE Plane are significantly different between non-discriminate (S1 and S3) and high-risk scenarios (S2 and S4). There is more chance that vaccination focusing on reproductive age population will result in higher value of cost-effectiveness with the existences of dots further to the corner.

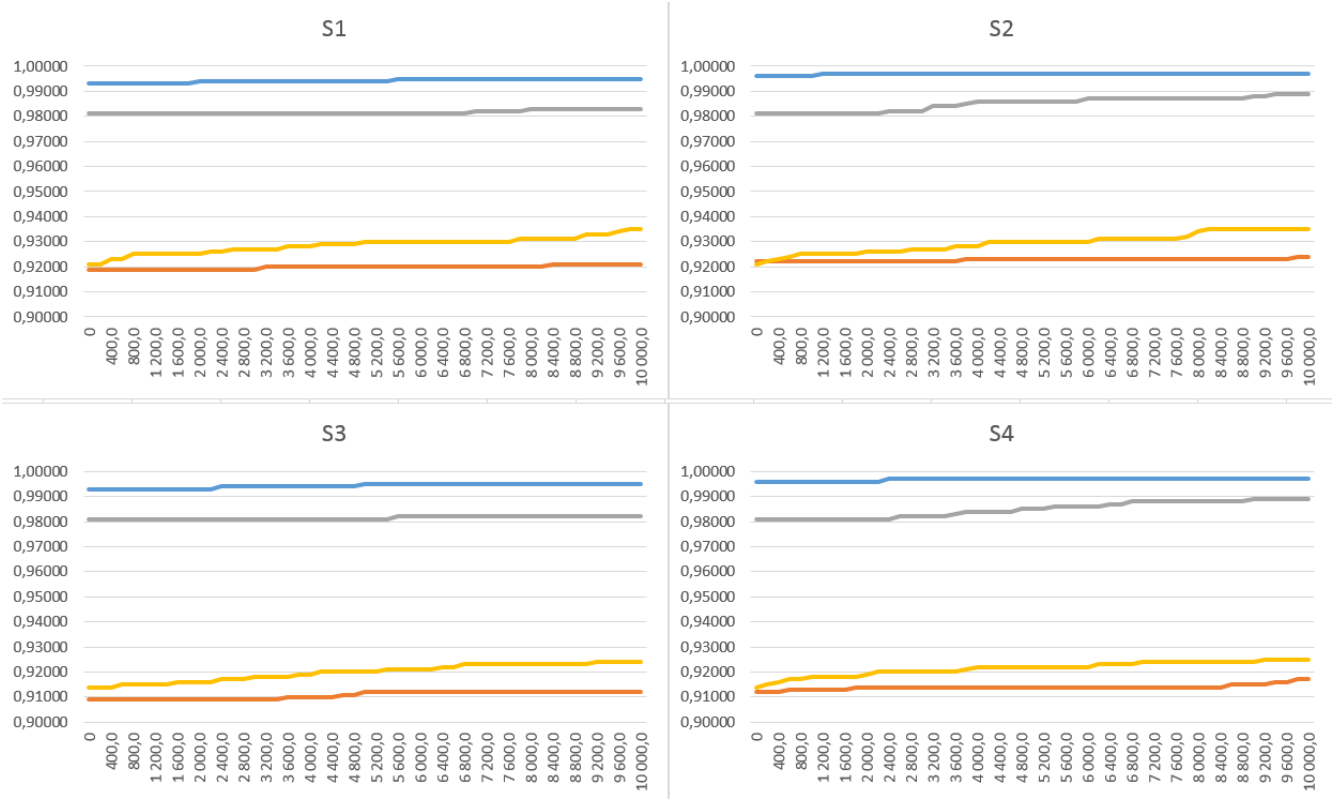

Figure 20: Cost-Effectiveness acceptability curve for multiple layers of cost.

Blue: with all cost included; Gray: exclude tourism drop; Yellow: exclude CZS lifetime cost; Red: exclude both tourism drop and CZS lifetime cost.

S1: Non-discriminate - 1 dose; S2: High-risk population - 1 dose; S3: Non-discriminate - 2 doses; S4: High-risk population - 2 doses

Consistent with above analysis, CEAC presents high cost-effectiveness of all four scenarios. Interestingly, even though QALY gain from S2, S4 is almost four times higher than S1 and S3, at most of the thresholds, the incremental value for extra effort conducting high-risk focusing vaccination campaign is 0.2% to 0.4% on CEAC. This might mean that vaccination program in the lowest setting is already significantly cost-effective, and there is diminishing room for improving. Removing loss from tourism and/or lifetime cost for CZS cases, we see a sharp drop on CEAC from all four scenarios. CZS lifetime cost contributes more than 6% drop of cost-effectiveness level, tourism's contribution meanwhile is around 1% at 5400 USD threshold (Woods, Revill et al. 2016).

4.4 Sensitivity analysis

The primary purpose of doing sensitivity analysis is to identify which factors affect most into outcomes, therefore this step might spot out important factors, and answer the question of how much they affect final primary outcomes including of NHB, NMB, and ICER. The causality explanation is not included in this analysis, instead of answering the question *how does it happen?* it focuses on the correlation between input and outcome. Sensitivity analysis is also an essential way to identify "knowledge gap" that potentially have the big impact on study (Hunink, Weinstein et al. 2014). Based on the method described in the previous section, there are seventeen over thirty nine parameters considered as having important impacts. Detail outcome and rationale for parameters' ranges can be found in the *Supplementary document* and *Appendix 2*.

In the baseline analysis, the population is assumed as the whole country; however, this assumption is not feasible due to some reasons: first, there are areas where condition for mosquito transmission is not favorable due to high latitude; second, some areas are isolated with the outbreak side simply because they are far away. Adjusting the population at risk to 25%, 50%, and 75% leads to significant reduction of cost, value ranges from 1.6 to 5 billion USD in the non-intervention scenario. The effectiveness is slightly affected as the proportion of the population at risk reduces, incremental costs decrease in a slower pace comparing to the health outcome. At 25% level, the total cost for non-intervention scenario is just 30% of the baseline, incremental costs decrease from 2% (S1 and S3) to 5% (S2 and S4) meanwhile incremental outcomes drop about 11% for all scenarios.

Among other epidemiological data for humans, the proportion of symptomatic infection, intrinsic infectious period, probability of getting CZS, birth rate and initial scale of outbreak significantly affect outcomes in different ways. The level of symptomatic cases will affect the transmissibility in two ways: sexual and human to mosquito transmission. Since asymptomatic patients are assumed not to contribute to spreading disease, lower levels of symptomatic cases would constrain the development of the outbreak. At 10%, cost in the non-intervention scenario drops by 17%, and regarding health outcomes, the incremental value of CZS saved and QALYs gained are up to two times lower. With regard to the infectious period in humans, using range from 5 to 10 days (Gao, Lou et al. 2016), cost data does not have a large change, while around 10% is the common level change of incremental value of health outcomes. The probability of getting CZS is having a high impact on final outcome. Using the value of 6% from one paper (Honein, Dawson et al. 2017) instead of 39% as in the base case, the number of CZS drops significantly across five scenarios to 15% of the baseline. Weekly birth rate, which might be related to pregnancy delay and abortion, has a similar effect as the probability of getting CZS to incremental cost, CZS saved and QALY gain. Initial scale of the outbreak correlates with the controllability, higher value leads to more damage in term of cost and less health outcome saved by the routine vaccination campaign.

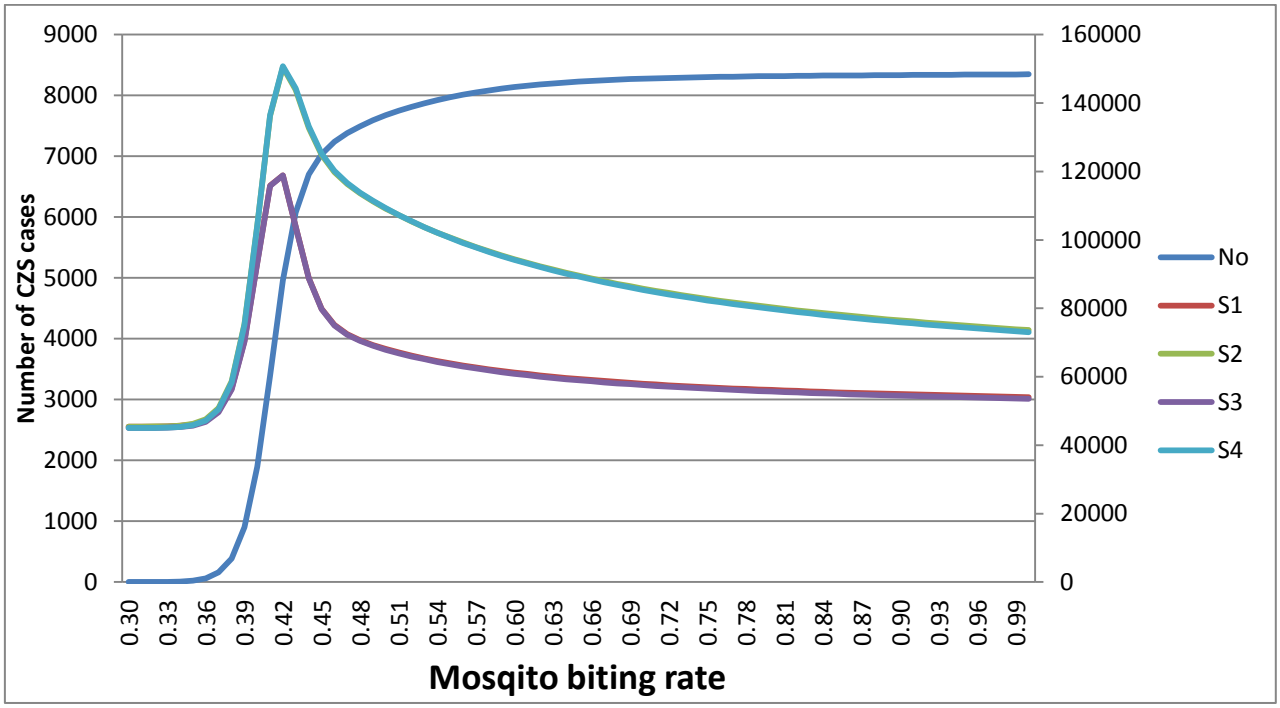

Figure 21: Number of CZS cases (for non-intervention scenario) and NHB (for vaccination scenarios corresponding with the right vertical axis) with respect to mosquito biting.

Mosquito biting rate has the biggest impact on the model among vector inputs. Dropping biting rate to 0.3 per week, we can observe from *Figure 21* that there is no effect on health outcome. From 0.36 to 0.46, the number of CZS cases increases sharply, and then become more stable with higher value. Mosquito to human ratio expresses with the similar degree of sensitivity. At 0.3 mosquito per human, the outbreak is less likely to happen, most of the health outcomes are close to zero, vaccination campaign saved most of CZS cases corresponding with 0.6 mosquito per human. As this ratio increases over 0.42, the effectiveness of the vaccination campaign decreases as described by NHB values. Mosquito lifespan, which relates to both extrinsic infectious period and mortality rate affects directly to the transmissibility of the disease. At 7.8 days, it has limited effect on non-vaccination scenario (drop about 8% for both cost and health outcome); within four intervention scenarios, there is increase from 1.3 to 1.4 times on the incremental value of CZS cases, GBS cases saved, LY and QALY gain. The extrinsic incubation period is the less influential input among mosquito epidemiological data. On its lower bound five days, values of incremental health outcomes decrease from 12% to 14%.

Relating to vaccination campaign, yearly capacity, efficacy of one-dose regime, second dose of two-dose regime are the most important inputs based on the observed change; meanwhile waning rate and first dose efficacy of two-dose scenario appear to have limited impact. Increasing yearly capacity from one million to fifteen million cases

improves significantly the cost-effectiveness of vaccination intervention, both cost and health outcome values are improved. Since cost of the non-intervention scenario is unchanged, the cost saved by vaccination campaign increases linearly with increasing of campaign's capacity, ranging from two to five billion USD at fifteen millions cases per year. On the health outcome side, CZS cases, GBS cases saved, LY and QALY gain could surge to more than thirteen times.

Vaccine efficacy of one dose scenario and the second dose of two-dose scenario have only a slight effect on the cost side, but a high impact on health outcomes. The relative change in absolute value is not large, however since this does not affect non-vaccination scenario, the incremental change is worth to mention. Within a one-dose scenario, changing efficacy from 60% to 99% results change of incremental health outcome's value from 80% to 150% of the baseline value. The scale of impact on NHB is lower, which ranges from 9% (for non-discriminate) to 15% (for high-risk focusing) with regard to 99% efficacy. In the two-dose strategy, the efficacy of the first dose appears with little impact; at the same time, the second dose efficacy sensitivity is similar to the efficacy of one-dose scenario. Waning rate does not act as an important factor on constraining the effectiveness of the campaign. Adjusting waning rate from 15% to 90% per year reduce incremental health outcome from 2% to 4% comparing with baseline result; in term of absolute value, with 90% waning rate, the total number of CZS cases increase from four to fourteen comparing to baseline within two and half year time horizon.

With regard to sensitivity analysis for cost inputs, CZS lifetime cost, loss from tourism and vaccine cost are among high impact items. As mentioned above in model input, there is high uncertainty related to these parameters. CZS lifetime cost data got from a study in US (Li, Simmons et al. 2017), and includes both direct medical and non-medical items, which used proxy method to estimate. Using 52% deviation for upper and lower bound for CZS lifetime cost, total cost changes 37% for the non-intervention scenario and 40% for vaccination scenarios. NHB of a high-risk focusing increases/decreases about 20% compared to 7% of non-discriminate vaccination campaign. Loss from dropping on tourism's income affects slightly total cost of no-intervention scenario. The total cost of non-vaccination scenario is primarily affected. Changing the baseline value with 50% deviation leads to 3.2% change in total cost, however, incremental cost change up to 40%.

Vaccine cost is a highly unpredictable variable with limited information. Using historical cost from Yellow Fever (YF) is not an optimal way, but it could be considered as a minimum value for analysis. Changing vaccine cost from 1 USD up to 200 USD, three out of four scenarios are still cost-effective. At 1 USD per dose, all four scenarios appear to be very cost-effective. Increasing vaccine price to the current level of HPV from Merck Sharpe and Dome Corp (4.5 USD), Pneumococcal vaccine from GSK (7 USD) and Rabies Vaccine from Serum Institute of India, Ltd (8 USD) (UNICEF 2017) lead to a slight change in the value of NHB. S3 has the steepest slope among four

scenarios, and as the vaccine price increases to 141 USD per dose, S3's NHB becomes negative since this strategy does not lead to cost saving anymore. This means above this level of vaccine price, the total cost in S3 would be higher than non-intervention scenario from societal perspective, or cost of the vaccination campaign overcomes cost save by reducing CZS lifetime cost and drop in tourism spending. The result of this is S3 is no longer considered as an effective intervention. From 165 USD per dose, NHB from S4 is lower than S1. Burden from the vaccine cost push S4's NHB under S1, the incremental effect of the two-dose vaccine could not offset the incremental cost anymore.

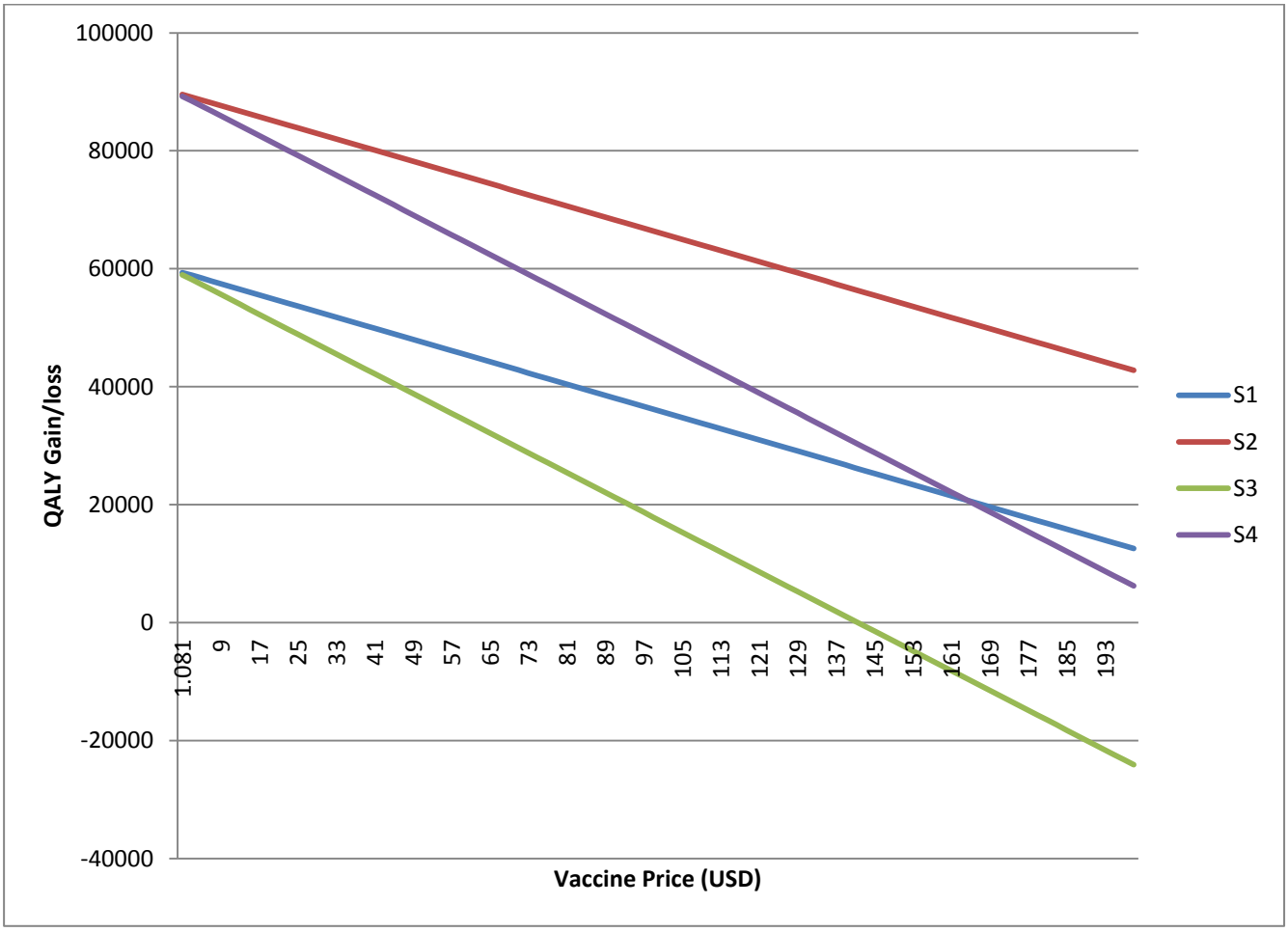

Figure 22: Sensitivity analysis's result for NHB and Cost of vaccine

The following table is used to summarize the result of sensitivity analysis with regard to the impact of each parameter on the relative change in value of NHB and NMB

NMB and NHB	**S1**	**S2**	**S3**	**S4**
Human Population	+	+	+	+
Proportion of symptomatic infection	+	+	+	+
Probability of getting CZS	++	++	++	++
Weekly birth rate	++	++	++	++
Initial scale of imported exposed	++	++	++	++

Mosquito to human	**	**	**	**
Extrinsic incubation period		+		+
Mosquito lifespan	--	--	--	--
Mosquito biting rate	**	**	**	**
Human's probability getting infected after one bite	--	--	--	--
Mosquito's probability getting infected after one bite	--	--	--	--
Yearly capacity	+++	+++	+++	+++
Proportion of vaccinated population getting second dose after the first dose				+
One dose efficacy (one dose regime)	+	++		
Second dose efficacy (two dose regime)				+
Vaccine cost	++	++	+++	++
Administration cost			-	
CZS lifetime cost	+	++	+	++
Drop in tourism	++	++	++	++

Table 15: Rating magnitude of impact from key parameters according to inputs' range from sensitivity analysis

+/-/: positive/negative/uncertain correlation between parameter value and NHB/NMB; 1st level: 5% to 10%, 2nd level: 10% to 50%, 3rd: more than 50%*

Those parameters that are not listed in *Table 16* are perceived as having little impact on changing NHB/NMB comparing to the baseline (less than 5%). Among those, which are under summary in *Table 16*, yearly capacity is with the most material influence. Administration cost, proportion of vaccinated population getting second dose after the first dose, extrinsic incubation period, proportion of symptomatic infection and human population are low impact parameters among this top ranking. High-risk scenarios' NHB are affected more than non-discriminate scenarios' with regard to changing the value of CZS lifetime cost and one dose efficacy.

4.5 Value of information analysis (EVPI and EVPPI)

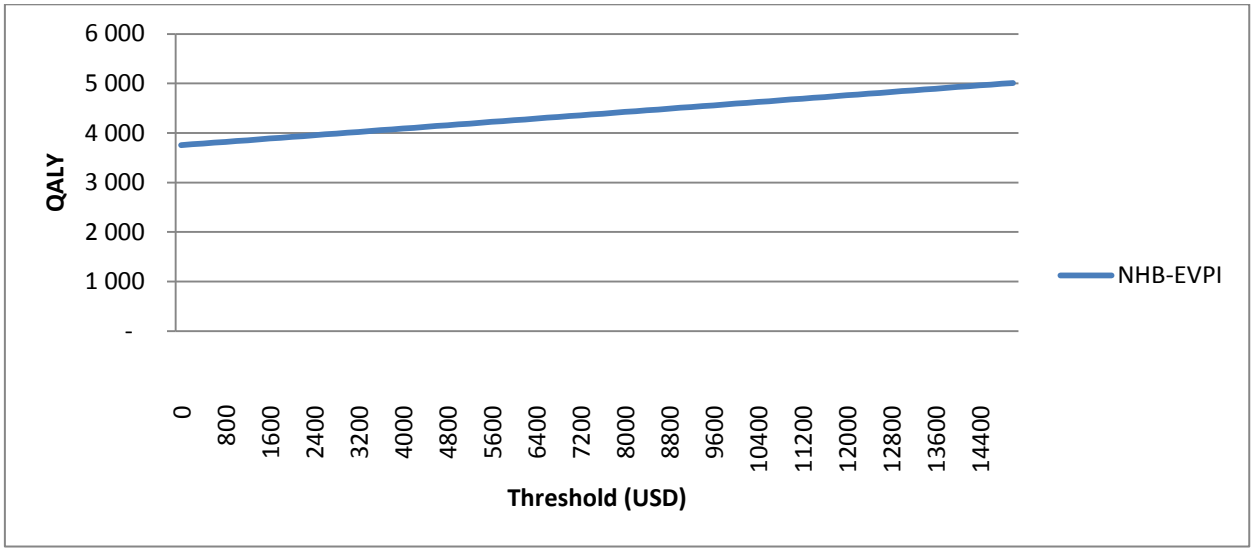

Figure 23: Expected value of perfect information

EPVI indicates the value of remaining uncertainty for all parameters. In this case, the forgone NHB could be from 3700 QALY to 5000 QALY (from 4% to 5.5% comparing to NHB of high-risk focusing scenario) as changing threshold from 100 USD to 15000 USD. The value of EVPI could also be expressed by NMB which varies from 25 million USD to 35 million USD.

24 EVPPIs (*Supplementary*) have been implemented to identify which parameter(s) is associated with the highest informational value. Among those 24 EVPPI calculations, none of them leads to any informational value. S2 is consistently having higher expected value of NHB than other scenarios.

4.6 Scenario analysis

In this part, the paper would be dedicated to scrutinizing into the events that might have happened during the last Zika outbreak. All scenarios are constructed based on less than optimal assumptions.

4.6.1 Reflecting the effect of dropping live birth rate and abortion

In the baseline model, birth rate is assumed the same in all scenarios, however, this assumption is challenged by two speculations: first, the effect of fear could lead to lower level of conception and higher rate of abortion (de Oliveira, Carmo et al. 2017); second, there is a theory about the causal effect between ZVI, early miscarriage and drop in birth rate (Coelho, Armstrong et al. 2017). The reality of abortion in Colombia is more prevalent than report from government (Prada, Singh et al. 2011, DONALD G. McNEIL Jr. 2016). The need for further investigation on those links needs to be conducted for better understanding; in the meanwhile, a scenario was constructed to reflect this potential reality. Abortion and miscarriage behave the same way on modeling meanwhile lower level of conception could be directly reflected by lower birth rate. Time difference between above two groups is up to several months. There are several basic assumptions:

- Birth rate drop is a lagging effect to the appearance of ZKV, 40 weeks would be used, starting time point is from October 2015 as first nine laboratory-confirmed cases identified (Pacheco, Beltrán et al.)
- The magnitude of drop both for lower level of conception and abortion/miscarriage is modeled directly as drop of live birth rate, data is extracted from Coelho paper (Coelho, Armstrong et al. 2017)

This scenario is constructed based on the two extremes that possibly are with a low chance of happening (dropping birth rate in the non-intervention scenario and no change in vaccination scenario).

Results discounted

Scenario	Costs	Increment	CZS	CZS save	GBS	GBS save	LY loss	LY gain	QALY loss	QALY gain
No intervention	$6 399 403 912		7041		596		2842		111577	
S1	$6 591 738 845	$192 334 933	8096	-1055	588	9	2801	41	127547	-15970
S2	$6 347 338 991	-$52 064 921	7716	-675	588	9	2801	41	121773	-10196
S3	$6 595 532 247	$196 128 335	8096	-1055	588	9	2801	41	127545	-15967
S4	$6 350 519 449	-$48 884 463	7715	-674	588	9	2801	41	121756	-10179
			NHB		**NMB**		**incremental costs/ LY gain**		**incremental costs/ QALY gain**	
ICERs:			**-$35 203**		**-$352 033 722**		**$4 662 446**		**-$12 044**	
			-$4 989		**-$49 890 160**		**-$1 262 121**		**$5 107**	
			-$35 580		**-$355 802 944**		**$4 748 293**		**-$12 283**	
			-$5 290		**-$52 901 619**		**-$1 183 499**		**$4 803**	

Figure 24: Result for dropping 15% birth rate in non-vaccination scenario

Non-discriminate vaccination strategy is no longer cost-saving, dropping from tourism spending barely save high-risk focus strategy from ineffective in term of cost. In terms of NHB and NMB, all four scenarios appear to be negative. S1 and S3's ICER fall into the northwest corner of CE plane, which is rejected area. S2 and S4 fall into the southwest area, the cost-effective could be undetermined; however, there was no incentive to conduct the campaign if it would actually deteriorate health outcome. Reducing the birth rate for both vaccination and non-vaccination strategy lead to a similar result with the baseline but with a much lower number of CZS and CZS cases saved.

Results discounted

Scenario	Costs	Increment	CZS	CZS save	GBS	GBS save	LY loss	LY gain	QALY loss	QALY gain
No intervention	$6 399 403 912		7041		596		2842		111577	
S1	$5 836 864 564	-$562 539 348	6926	115	587	10	2797	45	109754	1823
S2	$5 628 042 795	-$771 361 117	6601	440	587	10	2797	45	104821	6757
S3	$5 840 759 758	-$558 644 154	6926	115	587	10	2797	45	109754	1823
S4	$5 631 419 777	-$767 984 135	6600	441	587	10	2797	45	104808	6769
			NHB		**NMB**		**incremental costs/ LY gain**		**incremental costs/ QALY gain**	
ICERs:			**$58 077**		**$580 768 106**		**-$12 379 304**		**-$308 600**	
			$83 893		**$838 927 644**		**-$16 974 659**		**-$114 163**	
			$57 687		**$576 871 823**		**-$12 279 685**		**-$306 481**	
			$83 567		**$835 672 009**		**-$16 881 232**		**-$113 460**	

Figure 25: Result for dropping birth rate in non-vaccination scenario for both non-vaccination and vaccination scenarios

Reducing birth rate in both with and without vaccination scenarios, cost-effective results return to the similar level to the baseline. As combining birth rate changes from non-vaccination and vaccination scenarios, the result of ICER is presented in the following *Figure:*

	S1-NHB															
58076.81058	0 %	1 %	2 %	3 %	4 %	5 %	6 %	7 %	8 %	9 %	10 %	11 %	12 %	13 %	14 %	15 %
0 %	59 346	53 034	46 723	40 413	34 105	27 798	21 492	15 187	8 884	2 582	-3 719	-10 018	-16 317	-22 613	-28 909	-35 203
1 %	65 574	59 262	52 951	46 641	40 333	34 025	27 720	21 415	15 112	8 810	2 509	-3 791	-10 089	-16 386	-22 681	-28 976
2 %	71 800	65 488	59 177	52 867	46 559	40 252	33 946	27 641	21 338	15 036	8 735	2 436	-3 862	-10 159	-16 455	-22 749
3 %	78 026	71 713	65 402	59 093	52 784	46 477	40 171	33 867	27 563	21 261	14 961	8 661	2 363	-3 934	-10 230	-16 524
4 %	84 249	77 937	71 626	65 316	59 008	52 701	46 395	40 091	33 787	27 485	21 185	14 885	8 587	2 290	-4 006	-10 300
5 %	90 472	84 160	77 849	71 539	65 231	58 924	52 618	46 313	40 010	33 708	27 407	21 108	14 809	8 513	2 217	-4 077
6 %	96 693	90 381	84 070	77 760	71 452	65 145	58 839	52 534	46 231	39 929	33 628	27 329	21 031	14 734	8 438	2 144
7 %	102 913	96 601	90 290	83 980	77 672	71 365	65 059	58 754	52 451	46 149	39 848	33 549	27 251	20 954	14 658	8 364
8 %	109 132	102 820	96 509	90 199	83 891	77 583	71 278	64 973	58 670	52 368	46 067	39 768	33 469	27 172	20 877	14 583
9 %	115 349	109 037	102 726	96 416	90 108	83 801	77 495	71 190	64 887	58 585	52 284	45 985	39 687	33 390	27 094	20 800
10 %	121 565	115 253	108 942	102 632	96 324	90 017	83 711	77 406	71 103	64 801	58 500	52 201	45 903	39 606	33 310	27 016
11 %	127 780	121 468	115 157	108 847	102 539	96 232	89 926	83 621	77 318	71 016	64 715	58 416	52 118	45 821	39 525	33 231
12 %	133 994	127 681	121 370	115 061	108 752	102 445	96 139	89 835	83 531	77 229	70 929	64 629	58 331	52 034	45 739	39 444
13 %	140 206	133 894	127 583	121 273	114 964	108 657	102 351	96 047	89 744	83 442	77 141	70 841	64 543	58 246	51 951	45 656
14 %	146 417	140 104	133 793	127 484	121 175	114 868	108 562	102 258	95 954	89 652	83 352	77 052	70 754	64 457	58 162	51 867
15 %	152 626	146 314	140 003	133 693	127 385	121 078	114 772	108 467	102 164	95 862	89 561	83 262	76 964	70 667	64 371	58 077

Figure 26: Change of NHB corresponding to multiple level of live birth drop between non-vaccination (row) and S1 (column); Blue area represent for positive NHB value.

Detail of changes in incremental cost and QALY could be found in the *Supplementary*. S1 saves cost even in the most of the case, except in the higher right corner. For instance, changing drop in birth rate from 11% to 12% for non-vaccinate scenario as keeping it constant for S1 make the result no longer cost saving for S1. Meanwhile, adjusting drop on the live birth rate in non-vaccination scenario from 1% to 2% alters the status of vaccination campaign from reducing CZS cases to actually increase.

In sum, the positive effect of vaccination campaign would be eradicated if live birth rate dropped faster in non-vaccination scenario than vaccination scenarios.

4.6.2 Reflecting the risk that asymptomatic patients could contribute into the spreading of ZKV

In the baseline model, one assumption is that asymptomatic patients do not contribute to transmission. Asymptomatic cases were assumed not to transfer the disease to sex partners or mosquitos. Sexual transmission from asymptomatic patients is not well-understood and studied; in a report from France last year (Freour, Mirallie et al. 2016), transmission from "entirely asymptomatic couple" was recorded. In addition, until the moment of writing, there is no understanding about how much asymptomatic patients can contribute to the transmission from human to mosquito. Based on those uncertainties, a scenario is built to reflect the reality that asymptomatic patients might potentially contribute to the transmission mode.

In this scenario, asymptomatic patients with *factor k*, which represents for relative ability to contribute into transmission mode comparing to symptomatic patients, was analyzed in order to capture its effect on the final outcome.

Increasing contribution of asymptomatic patients leads to higher total cost, more CZS cases in all scenarios. In terms of incremental value, there is less CZS cases and cost saved by the vaccination campaign.

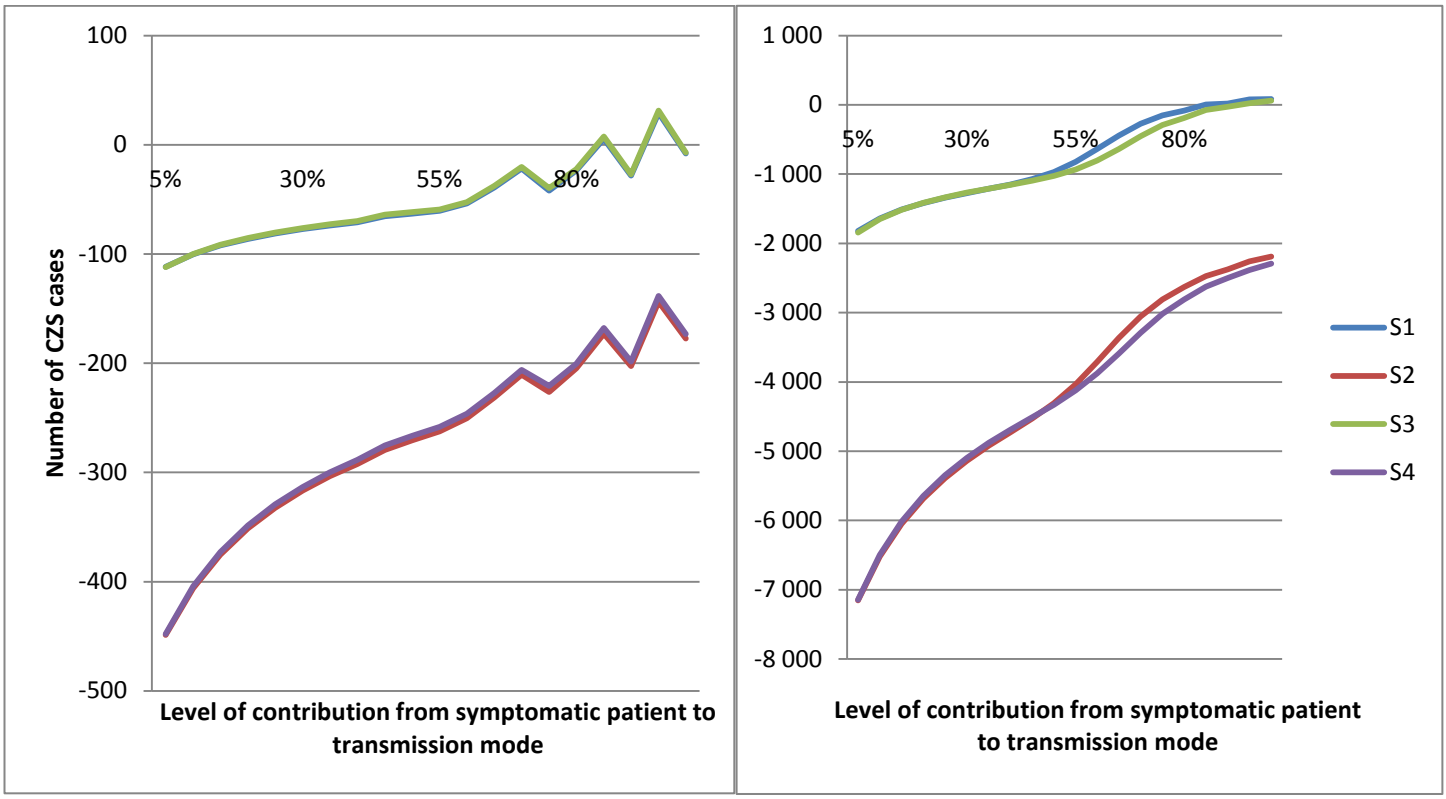

Figure 27: Incremental value of CZS cases with multiple level contributions from asymptomatic patients into transmission mode with normal (left) and mass vaccination (right) campaign.

There is a 2.5 times drop in the number of CZS cases saved in the high-risk focus strategy comparing to 14 times drop in non-discriminate campaign, with the absolute value of more than 270 and 100 cases respectively. Meanwhile, the drop in incremental cost is considerably lower, at around 14% for S1 and S3, 25% for S2 and S4. Mass vaccination campaigns in this scenario also lead to the same pattern.

4.6.3 Reflecting the reality that vaccine is not available in the beginning of the outbreak

In real world setting, available vaccines for EIDs are not always available at the beginning of the outbreak. Vaccine R&D requires heavy investment in term of capital and time. Although it has been almost sixty years since ZKV was discovered in Uganda (Hayes 2009), there is still no approved vaccine to fight against this disease. Recent effort has boosted this process, currently, there are two vaccine candidates from Vaccine Research Center/National Institute of Allergy and Infectious Diseases, and Moderna Therapeutics advanced into phase II (WHO 2017). In this case, it is too ambitious to state that vaccine was available in the beginning of the outbreak in Colombia. Since this is an explorative study, scenarios are formulated to evaluate the effect of vaccination campaign timing and its cost-

effectiveness. Time step is twelve weeks further from the beginning of the outbreak.

	Cost (Million USD)				CZS				QALY			
Weeks	S1	S2	S3	S4	S1	S2	S3	S4	S1	S2	S3	S4
0	-573	-817	-569	-814	131	511	131	512	2066	7840	2068	7857
12	-551	-746	-549	-748	106	409	109	0	1664	6279	1724	6433
24	-526	-670	-525	-671	77	301	80	309	1215	4614	1263	4734
36	-501	-593	-500	-594	49	192	51	197	765	2938	801	3026
48	-476	-517	-475	-516	20	83	22	87	317	1269	341	1327
60	-456	-456	-454	-455	-3	-3	-2	-1	-43	-49	-32	-23
72	-456	-455	-455	-454	-1	-2	-1	-2	-15	-37	-13	-34

Table 16: Timing of the vaccination campaigns and their effect on incremental outcomes

Delaying introduction of vaccination campaign could dramatically affect both cost and health outcome. In term of cost, vaccination campaign would remain cost saving due to the fact that CZS lifetime cost and dropping tourism spending is too high. 60 weeks delayed would reduce cost saving from vaccination campaign almost 120 million USD. Removing the effect of dropping tourism, at week 60 the vaccination campaign is not cost saving anymore. Health outcomes, which are represented by number of the CZS saved and QALY gain, are also affected by the effect of timing materially.

5 Discussion

Modeling result shows high cost-effectiveness potential of a vaccination campaign against ZKV in Colombia. Sensitivity analyses pointed out the importance and impact of each parameter to the final outcome, meanwhile, scenarios were built to complement for the lack of scientific evidence on the disease dynamic.

Two important components on the cost side, which boost the cost-effectiveness of the vaccinations into a very high level, are CZS lifetime cost and tourism's drop. From the deterministic result, without the appearance of those two cost items, all four vaccination scenarios still show high-cost effectiveness.

Results from sensitivity analysis highlight the number of important factors that have a high impact on either cost or health outcomes or both. In total, nineteen out of twenty four model inputs have been identified with important impact. The definition of important impact parameter is related to the change in relative value of NHB comparing to baseline scenario, in this case, it is assumed as variation higher than 5%.

To observe a clearer picture of how each model input affects the cost-effectiveness of the vaccination campaign, we need to take a step back to see the impact on absolute secondary outcomes. Human population, proportion of symptomatic infection, probability of getting CZS, weekly birth rate and mosquito biting rate are with the highest influences to all four scenarios (*Table 16*). Those five factors are observed having significant impacts on both vaccination and non-vaccination scenarios. Population at risk affects proportionally to all five scenarios, even though there is a great influence on absolute value change, the incremental value of cost and health outcomes do not change accordingly. Probability infected pregnant woman having a baby with CZS affects both absolute and incremental health outcome value with similar magnitude. Using the probability of 6% (Honein, Dawson et al. 2017), reduces more than 80% number of CZS cases and more than 60% cost comparing to baseline level in all scenarios. The result from mosquito's biting rate sensitivity analysis shows if control method could contain this parameter under 0.3 times per day, the outbreak would be less likely happening. Weekly birth rate plays a similar role as biting rate. As reducing birthrate across all five scenarios, the total number of CZS drops more than 75%, total cost drops around 60%.

Since NMB is the combination of threshold, incremental value of QALY and cost, the magnitude of parameters' impacts on absolute value does not guarantee the same result on NHB (*Table 16*). Yearly capacity of the vaccination campaign is the factor that affects NHB most. Increasing yearly capacity from one to fifteen million helps to save from 164 thousand to 544 thousand QALYs. Other factors that appear to have moderate impact to NHB could be named: probability of getting CZS, weekly birth rate, initial scale of imported cases, mosquito to human ratio, mosquito lifespan, mosquito biting rate, probability that mosquito and human get infected after one contact, vaccine cost, CZS lifetime cost and drop in tourism. 50% change on tourism drop does not lead to material adjustment comparing to baseline total cost, even though incremental cost value shifted

40. This combination makes NHB change from 25% (S2 and S4) to 40% (S1 and S3). Despite tourism spending's drop have great influence on NHB, ICER by affecting incremental cost, it has limited impact on baseline's absolute value of cost (less than 5% change).

Through sensitivity analysis, a range of parameters with limited impact was identified. Within the model, the role of human to human transmission, coverage rate, and waning rate appears with both insignificant change in absolute and incremental value in all five key primary outcomes. Human to human transmission is reported in thirteen countries (WHO 2017), the contribution of its on basic production number was calculated 0.6 comparing to total reproduction number of 2.89. However, the impact of this on health and cost outcome observed by sensitivity analysis is not material. Changing the number of contacts carried risk and probability of getting infected after one contact to lower and upper bound with 50% deviation leads to immaterial change on cost and health outcomes. Coverage rate which often regards to equality of distribution does not change any final outcome, this means as long as the total capacity still under coverage population, this parameter will not play any role. Waning rate 15% per year extracted from Dengue vaccine (Villar, Dayan et al. 2015) needs more investigating in the longer term, with two and half years horizon from the model, limited changes on outputs are observed. Cost parameters other than from drop in tourism and CZS lifetime cost shows little control on cost output. QALY loss from CZS is more influential than from GBS, QALY gains change around 10% in both absolute and incremental value as moving baseline value of QALY loss from CZS into lower and upper bound.

VOI analysis does not provide much information about the "remaining uncertainty". There are some implications for the result of EVPI and EVPPI. First, the value from EVPI indicates that there are limited uncertainties from all parameters to the choice of optimal intervention, which is one dose, high-risk focusing vaccination program (S2). Second, among those parameters with high influence identified by sensitivity analysis, there is none of them can, in fact, change the optimal choice. All four scenarios are observed highly cost-effective and mostly located in the South-East quadrant, S2 is consistently having the higher value on CEAC comparing to other scenarios, and those are explanations for the result from EVPI and EVPPI.

Three scenarios are constructed to capture potential reality might happen as conducting vaccination scenario. One is related to the design of vaccination campaign, one to social behavior and one concerning with disease dynamic. There are multiple other scenarios could also be built, however, those three are perceived as most relevant with limited resources. With regard to timing of vaccination campaign, it is reasonable to assume that there is need of time to propel the vaccination campaign from the beginning of the outbreak. Time is required for vaccine R&D, manufacturing, distributing, and local capacity preparedness. On the other hand, there is a limited amount of time that we have to combat against the outbreak.

The result from scenario in the previous section shows that vaccine intervention before week 60 is preferable in order to save CZS cases, vaccination campaign after week 60 does not appear to reduce the number of CZS cases compares to non-vaccination scenario. The effect of delaying vaccination campaign is large, varies from 110 to 362 million USD loss. Conducting vaccination campaign from week 60 even though does not have an effect on reducing the number of CZS cases, but appear to be still cost saving. However, that mainly comes from the effect of tourism drop, removing tourism spending drop from the equation will make an intervention in week 60 no longer cost-saving. Therefore, the urgency of introducing vaccine is undeniably important, preparedness and rapid response needed to be prioritized.

Currently, the mechanism that determines symptomatic and asymptomatic infections is not well studied (WHO/Unicef 2017), the role of asymptomatic patients in the transmission mode is described in an observatory study (Freour, Mirallie et al. 2016), but how much it could contribute is again not clear. Since more than 80% of cases are asymptomatic (Duffy, Chen et al. 2009, CDC 2017), the contribution from this group of patients could change model's outcomes significantly. Increasing contribution factor of asymptomatic patients on transmission mode from 0 to 100%, a routine campaign would appear to save less CZS cases.

To elaborate the understanding of asymptomatic patients' contribution and delivering capacity of a vaccination campaign, the relationship between mass vaccination campaign and contribution of asymptomatic patients to incremental value of CZS cases is described in the previous section. In the case of mass vaccination campaign with full capacity, almost eighteen millions cases per year as previously had implemented with rapid response against Rubella in 2005-2006 (Urquijo, Pastor et al. 2011), the result is similar to routine campaign with the higher number of CZS saved. The main message from this is mass vaccination campaign could save a large amount of CZS cases but still significantly affected by increasing contribution of asymptomatic patients into transmission mode.

The last scenario brought under scrutiny is the effect of fear, which is represented by delaying pregnancy, abortion and dropping live birth rate. Within its underlying assumption, fear and unfear effect might reverse the final outcome. In this scenario, non-discriminating campaign is not cost-saving and reducing the number of CZS cases anymore, meanwhile, vaccination program focusing on high-risk population hardly saves cost but still has a higher number of CZS cases. This hypothetical scenario has two implications:

- Dropping of birth rate could be a key determinant, determined health and cost outcome
- Vaccination which remove psychological fear could do more harm than good if live birth rate did not reduce in the vaccination scenarios

Observatory study has shown there was drop on live birth in Colombia (Coelho, Armstrong et al. 2017), the cause of the drop is unclear, but it must come from one of the factors: delay or avoid pregnancy, miscarriage and abortion. A report in the middle of June (PAHO 2016) showed there are 13 728 pregnant woman with ZVI in Colombia, using probability of getting CZS from Brazil (Brasil, Pereira Jr et al. 2016) or US (Honein, Dawson et al. 2017) both lead to same implication: number of CZS in Colombia has been underreported or there is other key determinant. I will discuss further latter implication with regard to birth rate drop scenario here. Abortion is well known as strictly regulated in Colombia, illegal abortion might face severe consequences; however, as report showed that there were about 400 400 abortion cases per year happened in Colombia (Prada, Singh et al. 2011), live birth rate might drop if this number increase and number of CZS might fall dramatically if woman abort as acknowledging that the fetus affected by CZS. Since abortion is illegal, the reliability of statistic is controversial (Branswell 2016). Pregnancy avoiding and delaying could also constrain the number of CZS (Li, Simmons et al. 2017), official recommendation from WHO (WHO 2016) specified the need to ensure risk information related to CZS spreading to affected areas, save sex and contraceptive methods are among recommended measures. The effect of live birth rate drop therefore is deemed to have remedy effect on the final number of CZS, lead to significant change of cost.

A vaccination campaign, which was hypothesized cover the whole population proportionally, could remove the barrier of fear. The effect of this in reality is unknown. ZKV spreading among clusters without vaccine covered would be the cause for subsequent higher number of CZS cases in the vaccination scenarios comparing to non-vaccination scenario. Therefore, removing fear factor from vaccination scenarios could even bring larger negative impact on the number of CZS cases.

Since the vaccination campaign is highly cost effective in this hypothetical model. The next question is *How much should Colombia spend on this campaign?* In order to answer this question, we might need to take a step back to see how much does it cost to introduce a vaccine for the new EID. There is a lack of empirical data summarizing total cost of preclinical, clinical and manufacturing process for the new vaccine. Total cost needed until marketing approval exceeded over 2.5 billion USD (DiMasi, Grabowski et al. 2016), development costs depend on platform technology, probability of success. R&D cost for vaccine appears with very limited information. Colombia is not the only responsible party for vaccine R&D, however they would be one of the parties benefit most from Zika vaccine. With the availability of vaccine, cost of delivery including of vaccine cost varies around four to ten million USD for routine campaign and sixty to over one hundred million USD for mass vaccination campaign, a small fraction cost saved and incremental health benefit. Sensitivity analysis pointed out that better delivering capacity will improve significantly both cost saving and health outcome of the model. The cost for the vaccination campaign itself would not be under any circumstances barrier to implementing vaccination program.

Limitations

This thesis is designed as an explorative study with the purpose to articulate the cost-effectiveness of the potential vaccine candidate in the near future. Colombia was chosen as a case study to evaluate vaccination campaign from societal perspective. However, there are limited amount of parameter extracted from Colombia, this might raise the question about paper's methodology. Lack of both epidemiological, cost and health outcome data has been remedied by using sources from other countries. This is not optimal solution, but possibly the best available evidence. On the good side, this paper could point out some main research areas that Colombian Public health should do further research in order to better understand ZVI and its catastrophic consequences.

There is another limitation in this paper is that the design of the study is more likely a retrospective paper, however, baseline vaccine intervention was constructed based more on the fact that it is not in the need for rapid response. Vaccination rate is assumed constant over time. It is counter-intuitive assumption, number of vaccinated should vary over time and reflect public sentiment, local capacity and availability of vaccine supply. However, on the other side, it is not so easy to quantify all of those elements into model.

Multiple methods are used to capture and present the uncertainty of the model: PSA, one and two way sensitivity analysis (Briggs, Weinstein et al. 2012), and scenario analysis. From Briggs's uncertainty classification, there are two forms not explicitly analyzed: stochastic uncertainty and heterogeneity. Infected pregnant woman in different trimester would most likely have different risk level and the chance that the fetus getting CZS should not be the same (Honein, Dawson et al. 2017). On the other hand, infected pregnant woman' fetuses in the same trimester would also have different probability of getting CZS (Brasil, Pereira Jr et al. 2016, Honein, Dawson et al. 2017). This might be explained by geographic, demographic and other precondition factors. In addition to that, half-cycle correction method was not applied due to the complexity of calculation.

Weekly vaccination rate is an important parameter at the heart of the model, it is assumed to be constant over time regardless of outbreak's development, local areas and public sentiment. This drawback could hardly overcome since empirical data for this is not available, assumption could be made but there is no reference for its validity.

The baseline model takes a conservative approach as putting the whole population under risk of ZVI; as analyzed above, this again is highly hypothetical and most likely not correct. There is difficulty to isolate part of the population, who are living in the areas in the absence of the vector. Even in that case, human to human transmission is still unavoidable in those areas.

Some costs were extracted indirectly by PPP conversion method. This method has some main constrains: first, it does not have theoretical foundation; second, some costs do not

normally comply with PPP conversion e.g. cost of some medical device could be the same in two countries even though PPP is not equal to 1.

Considering a big knowledge gap of understanding dynamic of ZKV, there is limited number of scenarios in study. There are still many other burning questions needed to be reflected into the model:

- What if there is rising risk with precondition and the link between ADE and CZS?
- What if the mosquito can transmit disease to next generation?
- Vaccine safety would be also a valid concern, under faster response, there is a risk of under-optimal evaluating vaccine safety before being used. What are the risk and trade-off?

6 Conclusion

In order to answer the research question how cost-effective a hypothetical vaccination campaign could be, the thesis has been designed to study multiple aspects of the outbreak: virus, disease, vector, transmission dynamic, vaccines etc. By scanning through various disciplines, the intention is to evaluate vaccination campaigns with four potential versions in the most comprehensive way and reflect from a local perspective instead of global. However, it is perceived as an ambitious intention. More research is necessary before any further conclusion can be made. The model with its explorative design raises some potential key issues that may be worth to be put under consideration.

Baseline's results of routine vaccination campaigns, which are conducted from the beginning of the outbreak among four scenarios, show very positive cost-effective outcome. Among four vaccination scenarios, one dose is more cost-effective than two doses, and a high-risk focusing campaign lead to a better result than non-discriminate strategy. All four vaccination campaigns save cost and improve health outcome. According to the model, there are multiple factors that might change the five secondary outcomes into both positive and negative direction. Increasing yearly delivering capacity could significantly offer an improvement on both total cost and health outcome. At the same time, rise on mosquito lifespan or mosquito to human ratio would deteriorate the outcomes. The timing of the vaccination campaign is a critical component, late introducing could lead to deteriorating the cost-effectiveness of the whole program exponentially. The effect of birth rate change is significant and there is a need to do further study on this area. Improving yearly delivering capacity could potentially improve the cost-effectiveness dramatically.

In sum, vaccination campaign should not be implemented independently with local factors. A thorough study on multiple aspects should be conducted prior to implementation. However, cost and impact of those studies need to be carefully evaluated before conducted. The vaccination program should be accompanied with other preventive methods (removing reproductive site, insecticide, safe sex etc.). The combination could potentially create synergy and outcome improvement.

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Appendix 1: Model input and math formula

Variables	Symbol	Value	source
Columbian population	N	47 m	(Colombia 2017)
Vector population	N^V	70m	(Flasche, Jit et al. 2016)
Vaccinated Population	N^{Vac}		
Non-Vaccinated population	N^H		
Susceptible host population	S^H		
Exposed host population	E^H		
Infected symptomatic host population	I^H		
Infected asymptomatic host population	A^H		
Recovered host population	R^H		
Guillain-Barre syndrome population	GBS^H		
Congenital Zika syndrome population	CVZ^H		
Susceptible vector population	S^V		
Exposed vector population	E^V		
Infected vector population	I^V		
Number of effective bites a human receives in a week	β_H	4.98	Dependent variable
Number of effective sexual intercourse a human has in a week	β_{HH}	0.6	Dependent variable
Number of effective bites a mosquito has in a week	β_V	2.28	Dependent variable
Host death rate	μ_H	0.00026	(UN 2017)
Vector death rate	μ_V	0.39	Dependent variable
Host birth rate	b_H	0.00046	(UN 2017)
Vector birth rate	b_V	0.39	Dependent variable
Host incubation period	$1/\kappa_H$	5.9 days	(Lessler, Ott et al. 2016)
Vector incubation period	$1/\kappa_V$	10 days	(Boorman and Porterfield 1956, Andraud, Hens et al. 2012)
Host infectiousness period	$1/y_H$	7 days	(Gao, Lou et al. 2016)
Vector infectiousness period	$1/y_V$	4 days	Dependent variable
Proportion of symptomatic patients	α	18%	(CDC 2017)
Normal birth rate	b_H	0.00046	(UN 2017)
Probability of getting CZS per infected pregnant woman	p_{CZS}	39%	(Brasil, Pereira Jr et al. 2016)
Probability of getting GBS per infected patient	p_{GBS}	0.00007213	(WHO 2017)
Weekly rate for Non-discriminate vaccination	r_{Vac1}	0.00082	Dependent variable
Weekly rate for vaccinating high-risk population	r_{Vac2}	0.00082	Dependent variable
Proportion of high-risk population	p_{hr}	40%	(CIA 2016)
Vaccine efficacy for one dose scenario	e_{1d}	70%	(Flasche, Jit et al. 2016)
Vaccine efficacy for first dose – two dose regime	$e_{1st\ 2d}$	40%	(Flasche, Jit et al. 2016)
Vaccine efficacy for second dose – two	$e_{2nd\ 2d}$	80%	(Flasche, Jit et al. 2016)

dose regime			
Coverage rate of the vaccination program	c	50%	(Flasche, Jit et al. 2016)

Scenario 0: No intervention

$$\frac{dS^H}{dt} = -\frac{\beta_H S^H I^V}{N^V} - \frac{\beta_{HH} S^H I^H}{N^H} - \mu_H S^H + b_H N^H$$

$$\frac{dE^H}{dt} = \frac{\beta_H S^H I^V}{N^V} + \beta_{HH} S^H I^H / N^H - \kappa_H E^H - \mu_H E^H$$

$$\frac{dI^H}{dt} = \alpha \kappa_H E^H - y_H I^H - \mu_H I^H$$

$$\frac{dA^H}{dt} = (1-\alpha)\kappa_H E^H - y_H A^H - \mu_H A^H$$

$$\frac{dR^H}{dt} = \gamma(I^H + A^H) - \mu_H R^H$$

$$\frac{dCZS^H}{dt} = \kappa_H E^H b_H p_{CZS}$$

$$\frac{dGBS^H}{dt} = \kappa_H E^H \alpha p_{GBS}$$

$$\frac{dS^V}{dt} = -\frac{\beta_V S^V I^H}{N^H} - \mu_V S^V + b_V N^V$$

$$\frac{dE^V}{dt} = \frac{\beta_V S^V I^H}{N^H} - (\mu_V + \kappa_V) E^V$$

$$\frac{dI^V}{dt} = \kappa_V E^V - \mu_V I^V$$

Scenario 1: Non-discriminate vaccination – 1 dose regime

$$\frac{dS^H}{dt} = -\frac{\beta_H S^H I^V}{N^V} - \frac{\beta_{HH} S^H (I^H + I^{Vac})}{N} - \mu_H S^H + b_H N - r_{Vac1} S^H c$$

$$\frac{dE^H}{dt} = \frac{\beta_H S^H I^V}{N^V} + \frac{\beta_{HH} S^H (I^H + I^{Vac})}{N} - \kappa_H E^H - \mu_H E^H - r_{Vac1} E^H c$$

$$\frac{dI^H}{dt} = \alpha \kappa_H E^H - y_H I^H - \mu_H I^H$$

$$\frac{dA^H}{dt} = (1-\alpha)\kappa_H E^H - y_H A^H - \mu_H A^H - r_{Vac1} A^H c$$

$$\frac{dR^H}{dt} = y_H (I^H + A^H) - \mu_H R^H - r_{Vac1} R^H c$$

$$\frac{dS^{Vac}}{dt} = -\frac{\beta_H S^{Vac} I^V}{N^V} - \frac{\beta_{HH} S^{Vac} (I^H + I^{Vac})}{N} + r_{Vac1} c (N^H - I^H) - \mu_H S^{Vac}$$

$$\frac{dE^{Vac}}{dt} = \frac{\beta_H S^{Vac} I^V}{N^V} + \frac{\beta_{HH} S^{Vac} (I^H + I^{Vac})}{N} - \kappa_H E^{Vac} - \mu_H E^{Vac}$$

$$\frac{dI^{Vac}}{dt} = \alpha (1 - e_{1d}) \kappa_H E^{Vac} - y_H I^{Vac} - \mu_H I^{Vac}$$

$$\frac{dA^{Vac}}{dt} = (1-\alpha)(1 - e_{1d}) \kappa_H E^{Vac} - y_H A^{Vac} - \mu_H A^{Vac}$$

$$\frac{dR^{Vac}}{dt} = \gamma (I^{Vac} + A^{Vac}) + e_{1d} \kappa_H E^{Vac} - \mu_H R^{Vac}$$

$$\frac{dCZS^H}{dt} = \kappa_H (E^H + E^{Vac}(1 - e_{1d})) b_H p_{CZS}$$

$$\frac{dGBS^H}{dt} = \kappa_H (E^H + E^{Vac}(1 - e_{1d})) \alpha p_{GBS}$$

$$\frac{dS^V}{dt} = -\frac{\beta_V S^V (I^H + I^{Vac})}{N} - \mu_V S^V + b_V N^V$$

$$\frac{dE^V}{dt} = \frac{\beta_V S^V (I^H + I^{Vac})}{N} - (\mu_V + \kappa_V) E^V$$

$$\frac{dI^V}{dt} = \kappa_V E^V - \mu_V I^V$$

Scenario 2: Vaccination high-risk population – 1 dose regime

$$\frac{dS^H}{dt} = -\frac{\beta_H S^H I^V}{N^V} - \frac{\beta_{HH} S^H (I^H + I^{Vac})}{N} - \mu_H S^H + b_H N - r_{Vac2} S^H c$$

$$\frac{dE^H}{dt} = \frac{\beta_H S^H I^V}{N^V} + \frac{\beta_{HH} S^H (I^H + I^{Vac})}{N} - \kappa_H E^H - \mu_H E^H - r_{Vac2} E^H c$$

$$\frac{dI^H}{dt} = \alpha \kappa_H E^H - y_H I^H - \mu_H I^H$$

$$\frac{dA^H}{dt} = (1-\alpha)\kappa_H E^H - y_H A^H - \mu_H A^H$$

$$\frac{dR^H}{dt} = y_H (I^H + A^H) - \mu_H R^H$$

$$\frac{dS^{Vac}}{dt} = -\frac{\beta_H S^{Vac} I^V}{N^V} - \frac{\beta_{HH} S^{Vac} (I^H + I^{Vac})}{N} + r_{Vac2} c (E^H + S^H) - \mu_H S^{Vac}$$

$$\frac{dE^{Vac}}{dt} = \frac{\beta_H S^{Vac} I^V}{N^V} + \frac{\beta_{HH} S^{Vac} (I^H + I^{Vac})}{N} - \kappa_H E^{Vac} - \mu_H E^{Vac}$$

$$\frac{dI^{Vac}}{dt} = \alpha (1 - e_{1d}) \kappa_H E^{Vac} - y_H I^{Vac} - \mu_H I^{Vac}$$

$$\frac{dA^{Vac}}{dt} = (1-\alpha)(1 - e_{1d}) \kappa_H E^{Vac} - y_H A^{Vac} - \mu_H A^{Vac}$$

$$\frac{dR^{Vac}}{dt} = \gamma (I^{Vac} + A^{Vac}) + e_{1d} \kappa_H E^{Vac} - \mu_H R^{Vac}$$

$$\frac{dCZS^H}{dt} = \frac{\kappa_H E^{Vac} (1 - e_{1d}) b_H p_{CZS}}{p_{hr}} + \frac{\kappa_H E^H b_H (p_{hr} N^H - N^{Vac}) p_{CZS}}{p_{hr} N^H}$$

$$\frac{dGBS^H}{dt} = \kappa_H (E^H + E^{Vac}(1 - e_{1d})) \alpha p_{GBS}$$

$$\frac{dS^V}{dt} = -\frac{\beta_V S^V (I^H + I^{Vac})}{N} - \mu_V S^V + b_V N^V$$

$$\frac{dE^V}{dt} = \frac{\beta_V S^V (I^H + I^{Vac})}{N} - (\mu_V + \kappa_V) E^V$$

$$\frac{dI^V}{dt} = \kappa_V E^V - \mu_V I^V$$

Scenario 3: Non-discriminate vaccination – 2 dose regime

$$\frac{dS^H}{dt} = -\frac{\beta_H S^H I^V}{N^V} - \frac{\beta_{HH} S^H (I^H + I^{Vac1} + I^{Vac2})}{N} - \mu_H S^H + b_H N - r_{Vac1} S^H c$$

$$\frac{dE^H}{dt} = \frac{\beta_H S^H I^V}{N^V} + \frac{\beta_{HH} S^H (I^H + I^{Vac1} + I^{Vac2})}{N} - \kappa_H E^H - \mu_H E^H - r_{Vac1} E^H c$$

$$\frac{dI^H}{dt} = \alpha \kappa_H E^H - y_H I^H - \mu_H I^H$$

$$\frac{dA^H}{dt} = (1-\alpha)\kappa_H E^H - y_H A^H - \mu_H A^H$$

$$\frac{dR^H}{dt} = y_H (I^H + A^H) - \mu_H R^H$$

$$\frac{dS^{Vac1}}{dt} = -\frac{\beta_H S^{Vac1} I^V}{N^V} - \frac{\beta_{HH} S^{Vac1} (I^H + I^{Vac1} + I^{Vac2})}{N} + r_{Vac1} c (E^H + S^H) - \mu_H S^{Vac1} - \int_{t-ts}^{t} S^{Vac2}$$

$$\frac{dS^{Vac2}}{dt} = -\frac{\beta_H S^{Vac2} I^V}{N^V} - \frac{\beta_{HH} S^{Vac2} (I^H + I^{Vac1} + I^{Vac2})}{N} + p_{1_2} r_{Vac1} c (E^H + S^H) - \mu_H S^{Vac2}$$

$$\frac{dE^{Vac1}}{dt} = \frac{\beta_H S^{Vac1} I^V}{N^V} + \frac{\beta_{HH} S^{Vac1} (I^H + I^{Vac1} + I^{Vac2})}{N} - \kappa_H E^{Vac1} - \mu_H E^{Vac1}$$

$$\frac{dE^{Vac2}}{dt} = \frac{\beta_H S^{Vac2} I^V}{N^V} + \frac{\beta_{HH} S^{Vac2} (I^H + I^{Vac1} + I^{Vac2})}{N} - \kappa_H E^{Vac2} - \mu_H E^{Vac2}$$

$$\frac{dI^{Vac1}}{dt} = \alpha (1 - e_{1st_2d}) \kappa_H E^{Vac1} - y_H I^{Vac1} - \mu_H I^{Vac1}$$

$$\frac{dI^{Vac2}}{dt} = \alpha (1 - e_{2nd_2d}) \kappa_H E^{Vac2} - y_H I^{Vac2} - \mu_H I^{Vac2}$$

$$\frac{dA^{Vac1}}{dt} = (1-\alpha)\left(1 - e_{1st_2d}\right) \kappa_H E^{Vac1} - y_H A^{Vac1} - \mu_H A^{Vac1}$$

$$\frac{dA^{Vac}}{dt} = (1-\alpha)(1 - e_{2nd_2d}) \kappa_H E^{Vac2} - y_H A^{Vac2} - \mu_H A^{Vac2}$$

$$\frac{dR^{Vac1}}{dt} = \gamma(I^{Vac1} + A^{Vac1}) + e_{1st_2d}\kappa_H E^{Vac1} - \mu_H R^{Vac1}$$

$$\frac{dR^{Vac2}}{dt} = \gamma(I^{Vac2} + A^{Vac2}) + e_{2nd_2d}\kappa_H E^{Vac2} - \mu_H R^{Vac2}$$

$$\frac{dCZS^H}{dt} = \kappa_H(E^H + E^{Vac1}(1 - e_{1st_{2d}}) + E^{Vac2}(1 - e_{2nd_{2d}}))b_H p_{CZS}$$

$$\frac{dGBS^H}{dt} = \kappa_H(E^H + E^{Vac1}(1 - e_{1st_{2d}}) + E^{Vac2}(1 - e_{2nd_{2d}}))\alpha p_{GBS}$$

$$\frac{dS^V}{dt} = -\frac{\beta_V S^V(I^H + I^{Vac1} + I^{Vac2})}{N} - \mu_V S^V + b_V N^V$$

$$\frac{dE^V}{dt} = \frac{\beta_V S^V(I^H + I^{Vac1} + I^{Vac2})}{N} - (\mu_V + \kappa_V)E^V$$

$$\frac{dI^V}{dt} = \kappa_V E^V - \mu_V I^V$$

Scenario 4: Vaccination high-risk population – 2 dose regime

$$\frac{dS^H}{dt} = -\frac{\beta_H S^H I^V}{N^V} - \frac{\beta_{HH} S^H(I^H + I^{Vac1} + I^{Vac2})}{N} - \mu_H S^H + b_H N - r_{Vac2} S^H c$$

$$\frac{dE^H}{dt} = \frac{\beta_H S^H I^V}{N^V} + \frac{\beta_{HH} S^H(I^H + I^{Vac1} + I^{Vac2})}{N} - \kappa_H E^H - \mu_H E^H - r_{Vac2} E^H c$$

$$\frac{dI^H}{dt} = \alpha\kappa_H E^H - y_H I^H - \mu_H I^H$$

$$\frac{dA^H}{dt} = (1 - \alpha)\kappa_H E^H - y_H A^H - \mu_H A^H$$

$$\frac{dR^H}{dt} = y_H(I^H + A^H) - \mu_H R^H$$

$$\frac{dS^{Vac1}}{dt} = -\frac{\beta_H S^{Vac1} I^V}{N^V} - \frac{\beta_{HH} S^{Vac1}(I^H + I^{Vac1} + I^{Vac2})}{N} + r_{Vac2} c(E^H + S^H) - \mu_H S^{Vac1} - \int_{t-ts}^{t} S^{Vac2}$$

$$\frac{dS^{Vac2}}{dt} = -\frac{\beta_H S^{Vac2} I^V}{N^V} - \frac{\beta_{HH} S^{Vac2}(I^H + I^{Vac1} + I^{Vac2})}{N} + p_{1_2} r_{Vac2} c(E^H + S^H) - \mu_H S^{Vac2}$$

$$\frac{dE^{Vac1}}{dt} = \frac{\beta_H S^{Vac1} I^V}{N^V} + \frac{\beta_{HH} S^{Vac1}(I^H + I^{Vac1} + I^{Vac2})}{N} - \kappa_H E^{Vac1} - \mu_H E^{Vac1}$$

$$\frac{dE^{Vac2}}{dt} = \frac{\beta_H S^{Vac2} I^V}{N^V} + \frac{\beta_{HH} S^{Vac2}(I^H + I^{Vac1} + I^{Vac2})}{N} - \kappa_H E^{Vac2} - \mu_H E^{Vac2}$$

$$\frac{dI^{Vac1}}{dt} = \alpha(1 - e_{1st_2d})\kappa_H E^{Vac1} - y_H I^{Vac1} - \mu_H I^{Vac1}$$

$$\frac{dI^{Vac2}}{dt} = \alpha(1 - e_{2nd_2d})\kappa_H E^{Vac2} - y_H I^{Vac2} - \mu_H I^{Vac2}$$

$$\frac{dA^{Vac1}}{dt} = (1 - \alpha)\left(1 - e_{1st_2d}\right)\kappa_H E^{Vac1} - y_H A^{Vac1} - \mu_H A^{Vac1}$$

$$\frac{dA^{Vac}}{dt} = (1 - \alpha)(1 - e_{2nd_2d})\kappa_H E^{Vac2} - y_H A^{Vac2} - \mu_H A^{Vac2}$$

$$\frac{dR^{Vac1}}{dt} = \gamma(I^{Vac1} + A^{Vac1}) + e_{1st_2d}\kappa_H E^{Vac1} - \mu_H R^{Vac1}$$

$$\frac{dR^{Vac2}}{dt} = \gamma(I^{Vac2} + A^{Vac2}) + e_{2nd_2d}\kappa_H E^{Vac2} - \mu_H R^{Vac2}$$

$$\frac{dCZS^H}{dt} = \frac{\kappa_H(E^{Vac1}(1 - e_{1st_{2d}}) + E^{Vac2}(1 - e_{2nd_{2d}}))b_H p_{CZS}}{p_{hr}} + \frac{\kappa_H E^H b_H(p_{hr} N^H - N^{Vac})p_{CZS}}{p_{hr} N^H}$$

$$\frac{dGBS^H}{dt} = \kappa_H(E^H + E^{Vac1}(1 - e_{1st_{2d}}) + E^{Vac2}(1 - e_{2nd_{2d}}))\alpha p_{GBS}$$

$$\frac{dS^V}{dt} = -\frac{\beta_V S^V(I^H + I^{Vac1} + I^{Vac2})}{N} - \mu_V S^V + b_V N^V$$

$$\frac{dE^V}{dt} = \frac{\beta_V S^V(I^H + I^{Vac1} + I^{Vac2})}{N} - (\mu_V + \kappa_V)E^V$$

$$\frac{dI^V}{dt} = \kappa_V E^V - \mu_V I^V$$

Appendix 2: Sensitivity analysis

Parameter	Dimension	Baseline value	Lower bound	Higher bound	Note
Discount rate	%	3	1	7	From 1% to interbank rate
Human Population	Thousand	47120	11780	47120	From 25% to 100% of population
Proportion of symptomatic infection	%	18	10	27	95% CI
Incubation period in Human	Days	5.9	4.4	7.6	95% CI
Infectiousness period in Human	Days	7	5	10	95% CI
Probability getting CZS	%	39	6	50	(Honein, Dawson et al. 2017, Reynolds, Jones et al. 2017)
Rate of appearing GBS	Per week	0.004184	0.002092	0.006276	±50%
GBS death probability	%	15	10	20	±5%
Weekly natural birth rate	Per week	0.00046	0.00012	0.00046	From 25% to 100% of baseline
Initial scale of imported exposed	Cases	10	10	10000	Assumption
Mosquito to human ratio	Per human	1.5	0.7	5	(Focks, Alexander et al. 2006, Gao, Lou et al. 2016)
Incubation period in mosquito	Days	10	5	14	(Andraud, Hens et al. 2012, Majumder, Cohn et al. 2016)
Mosquito lifespan	Days	14	7.8	27	(Andraud, Hens et al. 2012, Kucharski, Funk et al. 2016)
Mosquito biting rate	Per week	0.65	0.3	1	95% CI
Probability get infected after one contact with infected mosquito	%	73	40	90	(Andraud, Hens et al. 2012)
Probability infected human transmit ZKV to susceptible Mosquito	%	50	30	75	±20%

Number of contact carry risk (sexual contact)	Per week	1	0.5	1.5	±0.5
Human to human infected probability per contact	%	60	30	90	±30%
Coverage	%	50	30	90	
Yearly capacity	Thousand	1000	500	15000	Colombian Ministry of Health
Proportion of 1st dose population receives 2nd dose	%	80	50	90	(Flasche, Jit et al. 2016)
1 dose efficacy (1 dose regime)	%	70	60	99	Higher bound is from potential DNA vaccine (WHO 2017)
1st dose efficacy (2dose regime)	%	40	34	46	±15%
2nd dose efficacy (2dose regime)	%	80	68	99	Higher bound is from potential DNA vaccine (WHO 2017)
Waning rate	% Per year	15	10	90	Assumption
Vaccine cost	$	1.08	1.08	199	Assumption
Cost of administration	$	1	1	10	Assumption
Symptomatic patients	$	60	30	90	±50%
CZS lifetime cost	$	642967	321483	964450	±52% (Li, Simmons et al. 2017)
Cost of Zika-associated testing and monitoring of woman	$	75	37	112	±50%
Cost of Zika-associated testing among live-born infants with Zika-infected mother	$	36	18	54	±50%
Cost of testing fetus with CZS	$	56	28	84	±50%
Probability of ICU admission for GBS cases	%	69	62	76	±10%
ICU daily cost for GBS case	$	335	167	502	±50%
Average length of stay	Days	7	3.5	10.5	±50%

in ICU for GBS case					
IVIG cost	$	1243	621	1864	±50%
Hospitalized cost for GBS case	$	77	39	116	±50%
Average length of stay of hospitalization for GBS case	Days	23	9.5	36	Interquartile range (Anaya, Rodriguez et al. 2017)
Productivity loss	$	110	55	165	±50%
Loss from tourism	$ per week	7 800 404	3 900 202	11 700 606	±50%
QALY loss – CZS	QALY	15.2	13.68	16.72	±10%
QALY loss – GBS	QALY	4.13	3.72	4.54	±10%

Appendix 3: Case description from study in Brazil (Brasil, Calvet et al. 2016)

	Case	CT	MRI	TF US	Microcephaly	Small for gestational age	Cerebral calcification	Cerebral atrophy	Ventricular enlargement	Hypoplasia of cerebral structures	Parenchymal brain hemorrhages	Abnormal results on neurologic examination*	other feature **	Excessive hypersignaling ***	Total
1	3	1	0	0	1	0	1	1	0	0	0	0	1	0	**4**
2	4	0	0	1	0	0	0	0	0	0	0	1	0	0	**1**
3	7	0	1	0	0	0	0	0	0	0	0	0	0	1	**1**
4	9	0	1	1	1	1	1	1	0	0	1	1	1	0	**7**
5	10	0	1	1	0	0	0	0	0	0	0	0	0	1	**1**
6	11	0	0	1	0	0	0	0	0	0	0	1	1	0	**2**
7	12	0	1	1	0	0	0	0	0	0	0	0	0	1	**1**
8	13	0	1	1	0	0	0	0	0	0	0	0	0	1	**1**
9	14	0	1	1	0	0	0	0	0	0	0	0	0	1	**1**
10	15	0	1	1	0	0	0	0	0	1	0	0	0	1	**2**
11	16	0	0	0	0	1	0	0	0	0	0	0	0	0	**1**
12	17	0	0	0	0	0	0	0	0	0	0	0	1	0	**1**
13	18	0	0	0	0	0	0	0	0	0	0	1	0	0	**1**
14	19	0	0	1	0	0	0	0	0	0	1	0	0	0	**1**
15	21	0	0	0	0	0	0	0	0	0	0	0	1	0	**1**
16	22	0	1	1	0	0	0	0	0	0	0	0	0	1	**1**
17	23	0	1	1	0	0	0	0	0	0	0	0	0	1	**1**
18	24	0	1	1	0	0	0	0	0	0	0	0	0	1	**1**
19	25	0	0	0	0	0	0	0	0	0	0	0	1	0	**1**
20	26	0	0	1	0	0	0	0	0	1	1	0	0	0	**2**
21	27	0	1	1	0	0	0	0	0	0	0	1	0	1	**2**
22	28	0	0	0	0	0	0	0	0	0	0	1	1	0	**2**
23	29	0	1	1	0	0	0	0	0	0	1	1	0	1	**3**

24	30	0	1	1	0	0	0	0	0	0	0	0	0	1	**1**
25	31	0	0	0	0	1	0	0	0	0	0	1	1	0	**3**
26	33	0	0	0	0	0	0	0	0	0	0	1	1	0	**2**
27	34	0	0	0	0	0	0	0	0	0	0	1	1	0	**2**
28	35	0	1	0	0	0	0	0	0	0	0	1	1	1	**3**
29	36	0	0	0	0	1	0	0	0	0	0	1	1	0	**3**
30	37	0	0	1	0	1	0	0	0	0	0	1	0	0	**2**
31	38	0	1	0	0	0	0	0	0	0	0	0	0	1	**1**
32	39	0	1	0	0	0	0	0	0	0	1	0	0	1	**2**
33	40	0	1	0	0	0	0	0	0	0	0	0	0	1	**1**
34	41	0	0	0	0	0	0	0	0	0	0	1	0	0	**1**
35	43	0	1	0	0	0	0	0	0	0	1	1	1	0	**3**
36	44	0	0	0	0	0	0	0	0	0	0	1	1	0	**2**
37	45	0	0	0	0	1	0	0	0	0	0	0	0	0	**1**
38	46	1	1	1	0	0	1	0	0	0	1	1	1	0	**4**
39	47	0	0	1	0	0	1	0	0	0	0	0	0	0	**1**
40	48	0	0	0	0	0	0	0	0	0	0	1	1	0	**2**
41	49	0	0	0	1	1	0	0	0	0	0	0	1	0	**3**
42	50	0	0	0	0	0	0	0	0	0	0	1	1	0	**2**
43	52	1	0	1	0	0	1	0	0	0	0	0	1	0	**2**
44	53	0	0	0	0	0	0	0	0	0	1	1	1	0	**3**
45	54	0	0	0	0	0	0	0	0	0	0	0	1	0	**1**
46	55	0	0	0	0	0	0	0	0	0	0	1	0	0	**1**
47	56	0	0	0	0	1	0	0	0	0	0	1	1	0	**3**
48	57	0	0	0	1	1	0	0	0	0	0	1	0	0	**3**
49	58	0	0	1	0	0	0	0	0	0	1	0	0	0	**1**
		3	**19**	**21**	**4**	**9**	**5**	**2**	**0**	**2**	**9**	**23**	**22**	**16**	

Data was compiled from Brasil P et al.,

CT computed tomography, MR magnetic resonance imaging, TF US transfontanel ultrasould

** including of hypertonicity, clonus, hyperreflexia, abnormal movements, spasticity, contratures and seizures. ** cortical thumb sing, foveas in the knees or elbows, redundant scalp skin, Hemiparesis, head lag, branchycephal.*** Excessive hypersignaling in T2 in the white matter, diffuse in the peritrigonal posterior areas and less evident in the frontal parietal white matter. Hyposignaling in the diffusion sequence*

Attached files

Supplementary *includes of: Model master file, sensitivity, scenarios, EVPI and EVPPI results.*