Epidemiology of Cytomegalovirus

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ABSTRACT

Cytomegalovirus (aka CMV) is the leading cause of neurological disabilities among children causing among others mental retardation and hearing losses. This article approaches the uncertainty of CMV with the use of system dynamics to test the effect of existing and hypothesized policies in order to reduce the number of children affected by neurological disabilities because of congenital infection. A baseline system dynamics model built on deep uncertainty reveals that in the case of the USA, the spread of the epidemic can be contained by two measures: developing a vaccine currently under trials and combining existing policies.

Key words: cytomegalovirus, epidemiology, USA, public health, policy design.

1 Introduction

The prevalence, transmission modes and symptoms are presented in section 1, then system boundaries and modeling choices are developed in section 2. The third section analyzes the goodness of fit of the model while public health policies are tested under laboratory conditions in section 4.

1.1 Nature and prevalence of the virus

Congenital cytomegalovirus (CMV) is the leading cause of neurological disabilities in children (Ludwig and Hengel, 2009); therefore it represents a major public health concern. Human CMV is a large DNA virus belonging to the family *Herpes viridae* (cf Figure 1). Like all herpes viruses, CMV establishes a lifelong latency in the host, with periodic re-activations (Cheeran et al., 2009).

CMV infection is ubiquitous in the human population and most individuals are eventually infected. The overall seroprevalence in the the USA adjusted for ages is for example 60% (Cheeran et al., 2009). Seroprevalence increases among individuals with proximity to infected children or working in childcare facilities, but the virus remains invisible and undetected.

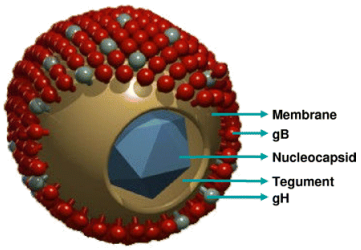

Figure 1: Schematic representation of the CMV virus (Crough and Khanna, 2009)

1.2 Transmission modes

The different modes of transmission are: close interpersonal contact (body fluids like urine and saliva), sexual activity, breastfeeding, blood transfusions and organ transplantation (Colugnati et al., 2007). So CMV is not transmitted via the respiratory system. After the initial infection, the virus stays in saliva, tears, semen, urine, cervical secretions, and blood for months to years. Seroconversion occurs at mucosal surfaces via infected urine, saliva or other bodily fluids, making children an excellent host for the virus (Cheeran et al., 2009), especially in day care settings. However all transmission modes are not equivalent in terms of risk. The most dangerous transmission mode is the congenital one, in which a pregnant mother transmits the virus via the placenta to the fetus.

1.3 Congenital infection and timing

It is well documented that the risk of congenital CMV is greatest from a primary infection of the mother during pregnancy (Cheeran et al., 2009). Seronegative women of child-bearing age (15-44 years) undergoing primary infection have the highest risk of trans-placental transmission of CMV to the fetus. The transmission rate to the fetus is 32% in the case of primary infection, contrary to 1,4% in the case of prior immunity of the mother (Kenneson and Cannon, 2007). In non-primary infection the fetus is thought to be partially protected by maternal immunity (Ludwig and Hengel, 2009). Furthermore, the timing of primary infection relative to the pregnancy is a crucial factor in establishing the risk to the fetus for in utero transmission (Cheeran et al., 2009). Congenital CMV infection during the first trimester is more likely to cause CMV disease, since organogenesis takes place in this period (Ludwig and Hengel, 2009).

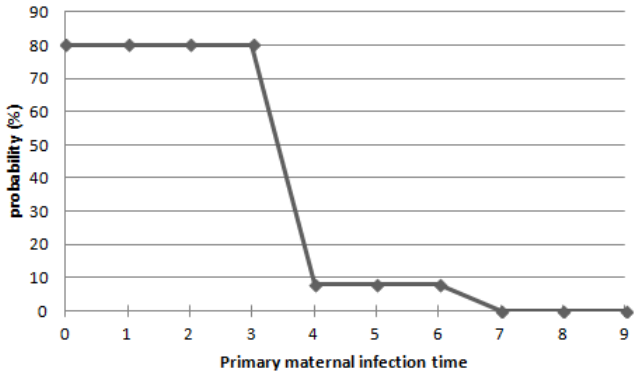

Figure 2: Chance to develop CNS sequelae as a function of primary infection time (Kenneson and Cannon, 2007)

Figure 2 illustrates that the probability to develop Central Nervous System (CNS) sequelae for the child born after a primary infection drops significantly from 80 to 8% between the first and the second pregnancy trimester. The reactivation of a CMV infection during pregnancy can still cause symptomatic congenital infection; however, the risk is lower, as preexisting maternal human CMV antibodies have a protective role against intrauterine transmission (Crough and Khanna, 2009). The two main congenital infection pathways are presented in Figure 3 . The y-axis indicates the percent chance to move from one stage to the other.

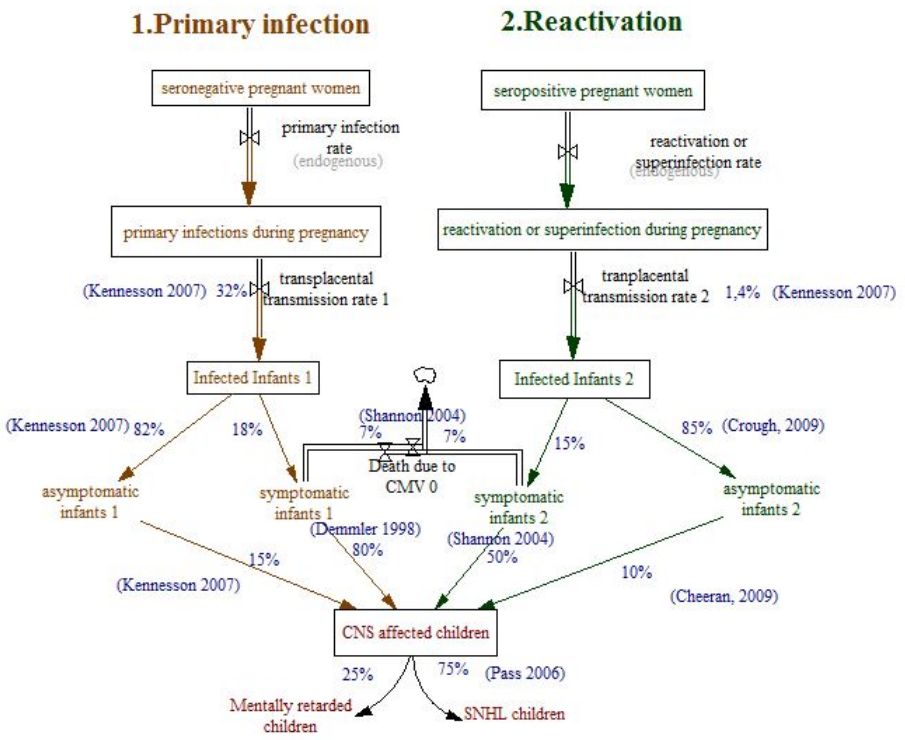

Figure 3: The congenital infection chain with 2 pathways

1.4 Symptoms

For all transmission modes, except congenital infection, CMV is a rather benign disease, whose worse symptoms are similar to those of a mild flu. While acquired infection is harmless for children, CMV can have serious consequences for immune system deficient patients, such as a HIV seropositive patient, as well as for congenitally infected infants. The latter develop serious permanent impairments which mostly affect the central nervous system and include progressive hearing loss, spastic tetraplegia , mental retardation and visual impairments (Ludwig and Hengel, 2009). The etymology of cytomegalovirus stems from *"cyto"* which stands for cell and *"megalo"* for surdimensionate, indicating that CMV infection has been associated with pro inflammatory cytokine increases (Crumpacker, 2010). Cytokines are cell-signaling protein molecules involved in inter cellular communication.

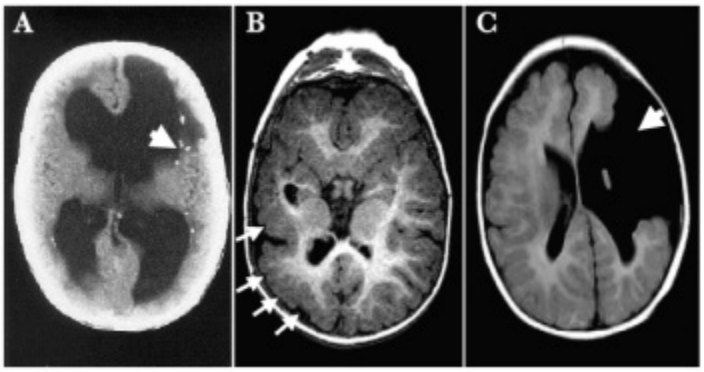

Figure 4: Central Nervous System outcomes of congenital CMV infection (Cheeran et al., 2009)

The computed tomography (A) and magnetic resonance imaging (B and C) shown in Figure 4 illustrate outcomes of congenital CMV infection in infants. These examples of CNS sequelae, ranked in severity order are periventricular calcification (A),

polymicrogyria (B), and porencephalic cysts (C), which are a profound structural abnormality (Cheeran et al., 2009).CMV-damage during the fetal period may cause spontaneous abortion or premature birth, but these cases are rare. While the majority of congenitally infected children appear asymptomatic at birth, neurological sequelae may develop after months or even years (Ludwig and Hengel, 2009).

2 Model description

"There is an urgent need for interventions that can reduce the substantial burden of this often overlooked disease." (Kenneson and Cannon, 2007)

2.1 Modeling question

Based on previous research done by Prevots et al. (1998)on the epidemic outbreak of polio in Albania in 1996, the hypotheses is that CMV follows an oscillatory pattern over time, with an inter-peak distance in the order of magnitude of 10 years (cf Figure 5).

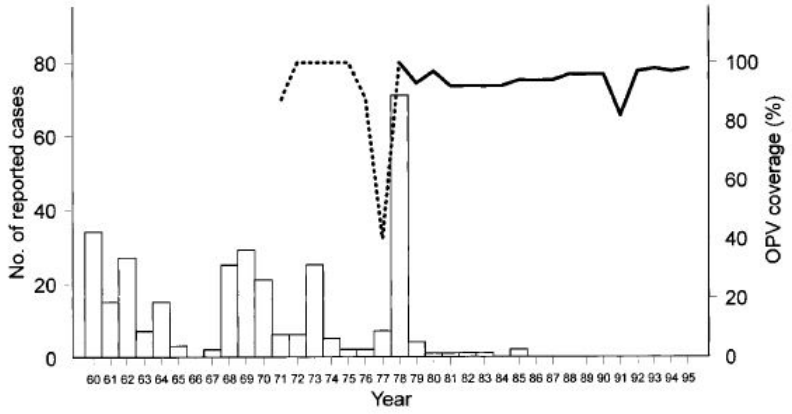

Figure 5: Reported cases of poliomyelitis in Albania (Prevots et al., 1998)

The purpose of this model is thus to first model the epidemiological behavior of the CMV virus, then test the effect of 3 types of policies: prevention, screening and therapy. Since some plausible policies are not yet implemented, the model also provides laboratory test conditions. So the modeling question is the following: *what are the effects of each health policy on the population of CMV-induced disabled children as well as on the infected fraction of the total American population?* Different modeling techniques exist, but system dynamics is an appropriate method to study the epidemiology of CMV because the system feeds back on itself, it has a dynamic character from which oscillations are expected, and the population approach is aggregated. This model could thus be used by public policy makers such as health ministries or by pharmaceutical firms during the trial phase of vaccines and therapeutic drugs. Since the epidemiology is not country specific, the parameters of the model can be changed to suit another geographic area.

2.2 System boundaries

The geographic boundary of this model is the USA, with its population of more than 314 million people in 2012. The time horizon is set at 100 years, in order to take into account the delays associated with population dynamics. Also, disabilities due to other congenital infections and genetic anomalies are ignored. For simplification reasons, the evolution of the American population is only dictated by natural growth, i.e. immigration flows are ignored (cf Figure 6). Two other simplification assumptions are made: the seroprevalence rate does not vary among ethnic origins (Colugnati et al., 2007), and the virus does not reactivate when in contact with new strains.

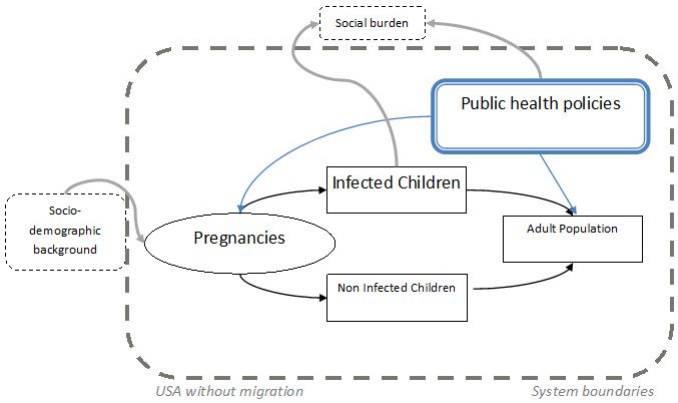

Figure 6: Conceptual model

2.3 Linking ageing and infection chains

The systems dynamic model created is built around 3 processes: population ageing, post natal infection via contact rates and infectivity, and the prenatal congenital infections. The latter infections are subdivided into 2 pathways: seropositive infections (i.e. pregnant women whose seroconversion occurred before the pregnancy) and primary infections (where seroconversion occurred during pregnancy). Only seroconversions during the first two trimesters (T1 and T2) are considered as dangerous to the fetus (cf Figure 2).

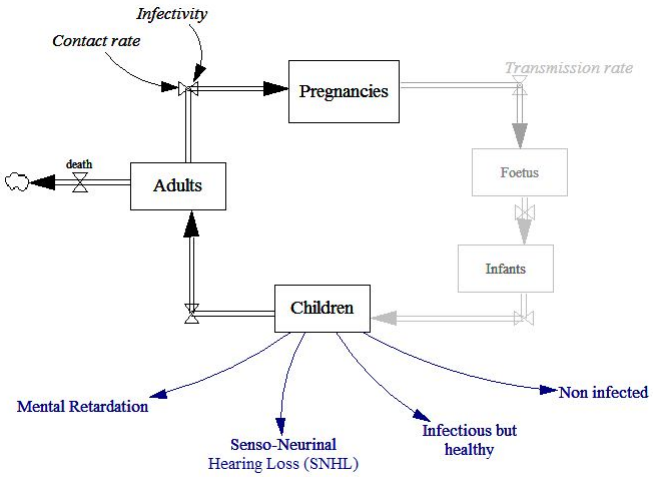

Figure 7: Simplified stock flow structure

2.3.1 The population ageing chain

Seronegative children can either grow up and become seronegative adults, or become infected at day care centers and at school. Seropositive children then grow up and become seropositive adults (cf Figure8). As a result, two death pathways exist: seropositive and seronegative deaths. A feedback loop connects the adults to the birth sub-model.

2.3.2 The post natal infection chain

Infections after birth are based on a Susceptible Infected Recovered model with deaths (Sterman, 2000), but there is no recovered population in the case of CMV (cf Figure 8) .The key variable in modeling the infections due to close interpersonal contact is the risk of acquiring infection in adults: $risk\,of\,acquiring\,infection\,in\,adults = infectivity * contact\,rate * infected\,fraction$.

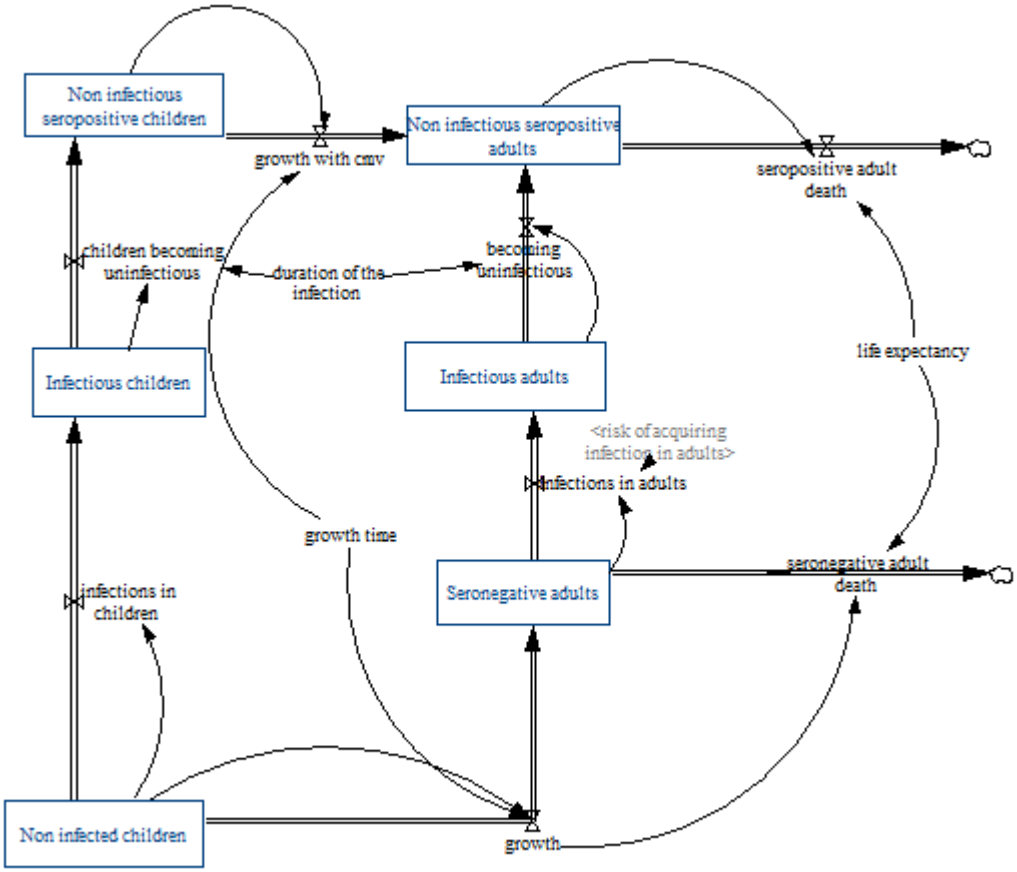

Figure 8: Population ageing chain and post natal infection chain

2.3.3 The prenatal congenital infection chain

Instead of a single "birth" inflow the entire process of congenital infection is modeled. Pregnant women are first divided into two categories according to their serology: seronegative and seropositive pregnant women. Because of the different transmission and gravity of sequelae probabilities, two congenital infection pathways can be seen in green and brown on Figure 9.

The chain of the seronegative pregnant women is modeled as an infection chain, with the pregnant women further divided into groups according to their pregnancy trimester. The reason behind this decision is that seronegative women who get infected in the first trimester present higher chances of transmission to the fetus and subsequent development of CNS sequelae (cf Figure 2). The seropositive pregnant women are modeled as a simple stock because the possibility of a virus reactivation and of a transmission to the fetus is relatively low (1,4%, cf Figure 3). Besides, reactivation with new virus strains mechanisms and the consequences on the fetus associated with their timing are currently still unknown. Also, the probability that an infected fetus in the reactivation chain develops sequelae is lower than in the case of primary infection (15 compared to 82%).

After birth, infants are not modeled as stocks in the model, because it is possible to calculate directly at the end of pregnancy, with a second order delay, the distribution of deliveries into 4 children stocks. CMV infected infants can mature and become part of the following categories according to the severity of the outcomes to:

- Children with CMV-induced mental retardation
- Children with CMV-induced SNHL sequelae.

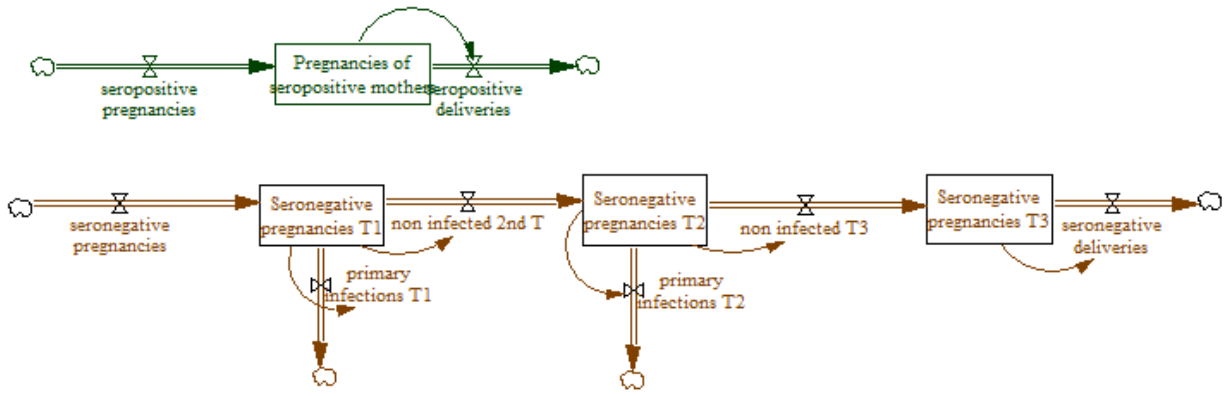

Figure 9: The congenital infection sub-model

- Infectious healthy children.They do not show any symptoms but are carriers of CMV.
- Non infected children. They are seronegative.

If a seronegative mother acquires a primary infection and the virus is transmitted to the fetus, then the fetus can be born either with symptoms or not. If it is born with symptoms then it has 80% chance to develop a CNS (central nervous system sequelae) and depending on the damage the virus caused, the child can be either mentally retarded or deaf (Senso Neurinal Hearing Loss, aka SNHL). Therefore the equation, for the inflow "MR after primary infection in T1" (annual rate of children who develop mental retardation after a primary infection in the first trimester) is a first order delay with initial value and delay time of 2,5 years:

MR after primary infection in T1=DELAY N *(primary infections T1*transmission rate after primary infection*(percentage of symptomatic infant*(1-fatality ratio of symptomatic infant)*percentage of symptomatic after T1 that shows CNS signs+(1-percentage of symptomatic infant)*percentage of asymptomatic after T1 that shows signs of CNS)*percentage of CNS that leads to serious MR,* 2.5*,*
*primary infections T1*transmission rate after primary infection*(percentage of primary symptomatic infant*(1-fatality ratio of symptomatic infant)*percentage of symptomatic after T1 that shows CNS signs+ (1-percentage of primary symptomatic infant)*percentage of asymptomatic after T1 that shows signs of CNS)*percentage of CNS that leads to serious MR, 1)*

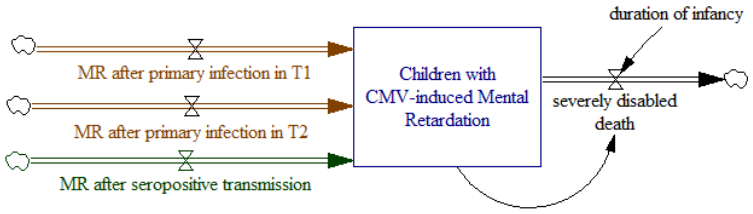

Figure 10: Stock flow diagram for children affected by Serious Mental Retardation

A second order delay is used because the levels of "fetus" and "infant"are omitted, and the probabilities that an infant is born with symptoms, the chances that it will develop CNS sequelae and also the probability that the CNS sequela lead to mental retardation or SNHL are known. The same reasoning lies behind the other inflow equations in the sub-model for the 3 other children's stocks.

The stocks of SNHL sequelae children, infectious healthy children and non infected children are emptied into the general population. Given the low severity of the SNHL handicap it is assumed that children who suffer from SNHL sequelae can also be incorporated in the general population. Because of their severe mental impairments, it is assumed in the model that children suffering from serious mental retardation do not integrate into the general population chain.

3 Behavior of the Model

The simulation of the model during 100 years is used first to verify the dynamic hypotheses and then to differentiate between two states: transient and permanent. The model was run on *Vensim* (integration method: RK 4 Auto, time step:0.0078125, units for time: years).

3.1 Similarity with polio: an oscillating pattern

In section 2.1 a comparison between CMV and polio was assumed. The oscillation behavior visible on Figure11 confirms the expectations that CMV would follow the same pattern as polio. CMV's inter peak duration is however longer than for polio: whereas the latter is 10 years (cf Figure 5) , CMV infection peaks approximately every 70 years.

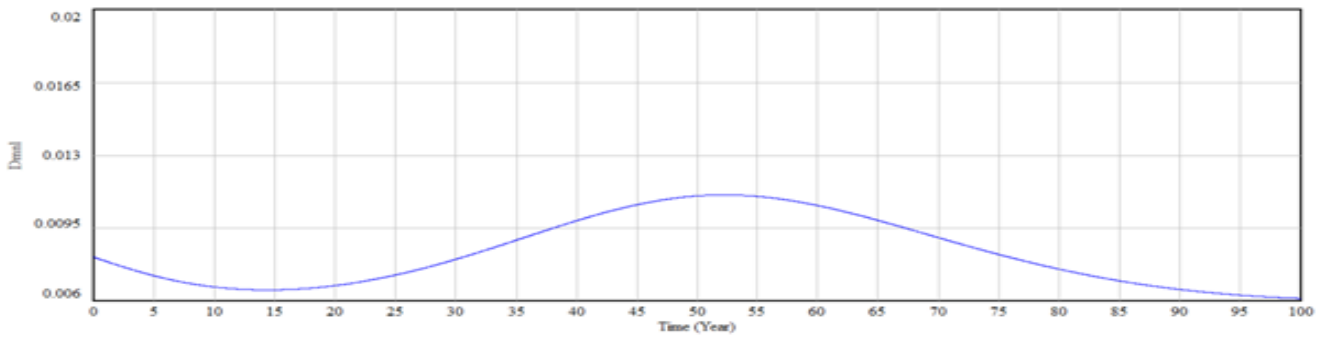

Figure 11: Infectious fraction of the population in the baseline model

3.2 Behavioral validation

The behavior of the model is coherent with expected results concerning the evolution of the American population and the number of disabled children due to CMV. First, the total American population is slowly increasing, which is justified by the fact that the birth rate (0,0135 birth/person/year) is slightly superior to the death rate (0,0133 death/person/year, corresponding to a life expectancy of 75 years). Since migration patterns are not taken into account in the model, the behavior of the ageing chain agrees with the hypotheses .

Secondly, the evolution in time of disabled children due to CMV is coherent with the structure of the model. Figure 12 displays the evolution of the number of CMV-induced mental retardation and senso-neurinal hearing losses (SNHL). The comparison of the evolutions of the infectious fraction (cf Figure 11) and the CMV-induced disabilitites among children leads to the following observation. The peak of CMV-induced disabilities is delayed of approximately 2 years after the peak of the infection in the total population., which corresponds to the structure of the model.

3.3 Sensitivity analysis on key parameters

To gain a better understanding of the roles and relative importance of several key factors, sensitivity tests were performed. Since a person infected with CMV person does not exhibit severe symptoms but mild and flu-like symptoms, the dynamics of the virus is not easily accessible. This assumption is supported by the fact that the seroprevalence of the virus in the

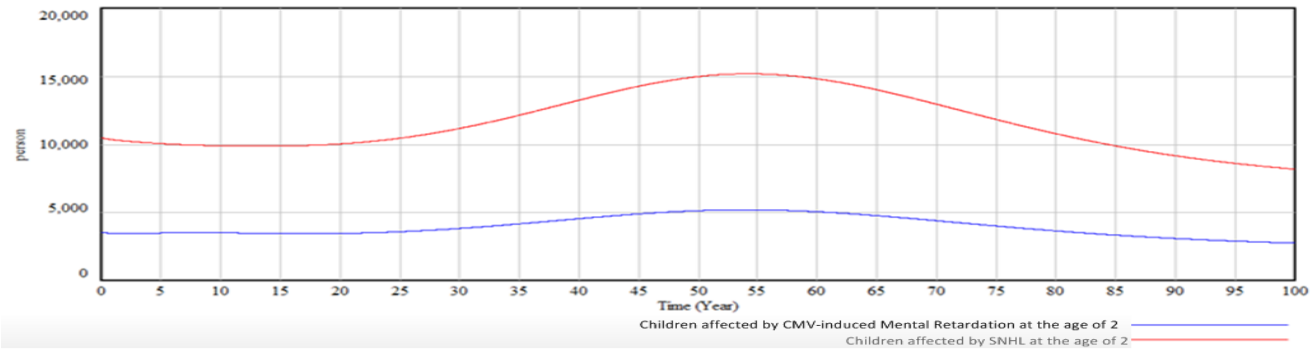

Figure 12: CMV-induced disabilities among children at the age of 2, baseline case

general population reaches the high level of 80% by the age of 60(Cheeran et al., 2009) and the social awareness still remains at a minimum level. Since the spread of the virus in the model depends on the parameters "infectivity", "contact rate" and "duration of the infection", the series of sensitivity tests addresses the uncertain values of those parameters. The baseline values are the following:
$infectivity = 0.04\, person/contact$ (Colugnati et al., 2007)

$inter\,adult\,contact\,rate = 27\, contact/year/person$

$duration\,of\,the\,infection = 1,5\, year$ (Cheeran et al., 2009)

The specifications of sensitivity analysis for the 3 parameters are : 1000 simulations, latin hypercube and a random uniform distribution of the parameter. The ranges of the parameters are the following :

- *infectivity* : [0.01 - 2]
- *contact rate* : [15 - 90] person/year
- *duration of the infection* [1 - 10] year.

As shown in Figures 15,16 and 17 presented in appendix, the infectious fraction of the population is, as expected, highly affected by the 3 parameters. For the 3 sensitive parameter's analysis, the infectious fraction of the total population demonstrates a high peak in the early years and a value above the baseline scenario in the later years. When the infectivity rate of the virus varies in the range mentioned above, the infectious fraction of the population reaches 50% instead of 1,1% in the baseline case. So the behavior of the CMV can in the worst case scenario follow the pattern of an acute disease. Consequently the number of children born with a disability due to a congenital CMV infection increases. To conclude the tests on sensitivity, the parameter *infectivity* seems to be a leverage for public health policy makers since the spread of the disease is highly sensitive to its variation.

4 Policy Testing

Existing and future measures to fight againt CMV are retrieved from litterature. Each policy tested is presented individually, and then a final comparison of all proposed policies is performed. The specifications of each policies are presented in Appendix in table 3.

4.1 Overview of prevention measures

The nature of the policies tested is inspired by the existing prevention techniques currently implemented. The overview of the range of tools available to public health decision makers reveals that there are three types of prevention measures:

1. PRIMARY PREVENTION has the aim to avoid an infection. It consists in a set of prenatal hygiene measures and change of behavior. Pregnant women, especially high risk seropositive women working in close contact with young children, are encouraged to limit close interpersonal contacts during the first two trimesters of their pregnancy.

2. SECONDARY PREVENTION has the aim to identify infected patients early, be it pregnant women or infants. Four main measures can be taken :
   2.1. Screening for maternal antibodies in the mother. Especially the avidity index of the protein Immunoglobulin G can be used to detect seroconversion among pregnant women(Kenneson and Cannon, 2007). Those maternal antibodies screenings must be done during the first trimester of pregnancy.
   2.2. Prenatal ultrasound for the presence of fetal abnormalities caused by CMV .
   2.3. Amniocentesis to detect viral genome in the amniotic fluid. Viral culture or Polymerase Chain Reaction (PCR) of the amniotic fluid can predict fetal transmission and symptomatic infection (Naessens et al., 2005). The sensitivity of PCR used to detect viral DNA is very good if amniotic fluid is collected at least six weeks after seroconversion and around the 22nd week of pregnancy (ECCI, 2012).
   2.4 Screening of all newborns for CMV shedding in the urine and monitoring of all congenitally CMV infected newborns in long-term audiologic follow-ups up to 5 years (Ludwig and Hengel, 2009).
   By combining serologic screening of IgG and IgM antibodies in the beginning of pregnancy and on cord blood with a culture of urine of the identified high risk infants, Naessens et al. reached a sensitivity of detection of congenital CMV of at least 82% (Naessens et al., 2005).

3. TERTIARY PREVENTION in the case of symptomatic disease. Tertiary prevention involves post natal treatments, which are antiviral drugs given to infected infants. The most famous drug is called Ganciclovir, and there is evidence that therapy ameliorates the severity of one of the CNS complications : SNHL(Cheeran et al., 2009). Ganciclovir therapy begun in the neonatal period in infants showing CNS symptoms prevents hearing deterioration at 6 months and may prevent hearing deterioration at 1 year (Kimberlin et al., 2003). Another promising therapy is the injection of CMV immune globulin in utero for infected fetuses. Uncontrolled studies of this method have suggested an impact on neuropathogenesis, and a decrease transmission to the fetus. Controlled trials should be conducted with pregnant women (Cheeran et al., 2009).

4.2 Testing of available policies

4.2.1 Policy 1: Prevention for pregnant women

In the first policy, which belongs to the category primary prevention, the propagation of the virus is slowed among pregnant women. If for example, a pregnant woman limits her contacts with people from the general population she can reduce the risk of infection. The "pregnant women contact rate" is reduced by 50% (from 27 to 13.5 contact/person*year). The number of disabled children alters only in a numerical and not in a behavioral way. A sensitivity analysis on the policy with values of the new contact rate ranging from 20%-80% of the initial contact rate value (ie 5.4 to 21.6 contact/person*year) results in a disappointing curb of the outbreak peak, which at year 60 is only numerically dampened.

4.2.2 Policy 2: Decrease the transmission rate to the fetus

The second policy refers to the tertiary prevention method of immunoglobulin injection in utero. The transmission rates of the virus from mother to fetus are decreased (rates for both primary infection and seropositive reactivation transmissions). Policy 2 can however only be implemented provided maternal antibodies have been analyzed beforehand. By combining maternal antibody screening and immunoglobin, Policy 2 protects the fetuses by providing them antibodies. In the model, both transmission rates from seropositive and seronegative pregnant women to fetus are reduced by 20%. The implementation of policy 2 entails a decrease of the number the disabled children changes in a numerical way. A sensitivity analysis on Policy 2 with new values for the transmission rate ranging from 30 to 95% of initial values shows that Policy 2 only has a weak numerical reducing impact.

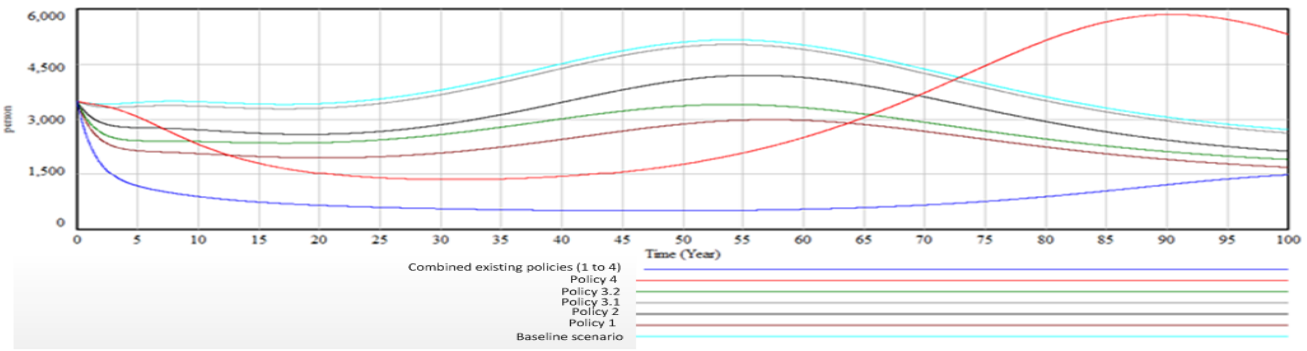

Figure 13: Comparison of existing policies on CMV-induced Mental Retardation at the age of 2

4.2.3 Policy 3: Improving screening procedures

The third policy refers to the secondary prevention methods of detection. Policy 3 is divided into Policy 3.1 and Policy 3.2.

Policy 3.1 : The choice of abortion Policy 3.1 addresses the first 3 screening methods: maternal antibody check, ultrasound and amniocentesis. Pregnant women who are confronted with a seroconversion during pregnancy are then faced with the choice of abortion. An increase in the fatality ratio of the infected fetus is then implemented. Policy3.1 brings a 50% increase of the fatality ratio. Sensitivity analysis on Policy 3 with values ranging from a 50% to 100% increase in fatality ratio reveals that it has no major influence on the number of disabled children.

Policy 3.2 : Monitoring and follow-ups of infected infants Policy 3.2 addresses particularly the last screening method: screening of all newborns for CMV shedding in the urine and monitoring of all congenitally CMV infected newborns in long-term audiologic follow-ups. It is modeled by a drop of 40% in the percentage of children (symptomatic or asymptomatic at birth) that show CNS signs. Supposing that CMV was detected at birth, those children receive extra-attention and care, thus decreasing their sequelae. The sensitivity analysis attributes values for the chances of sequelae development between 20% and 90% of the initial values. The result is similar to policies 1, 2 and 3.1 : there is a numerical impact, but not behavioral.

4.2.4 Policy 4: Prevention in the general population

The spread of the virus can also be contained in the total population. If less people get infected, then the danger for seropositive and seronegative pregnant women will be reduced. Therefore, Policy 4 reduces the contact rate among adults and also among children by 20% (from 27 to 13.5 contact/person/year). A significant numerical and behavioral difference with the baseline scenario is observed, both in the number of disabled children as well as the infectious fraction of the population. This confirms the original assumption for this policy since less contact implies that the virus does not spread easily in the population. The infectious fraction of the population reaches its lowest level at $2{,}5*10^{-3}$ (instead of $11*10^{-3}$) after 40 years. The periods during which the CMV virus is almost inactive is the longest of all policies tested so far.

However, an unexpected behavior is observed in the long-run, that is to say after 40 years. The increase of disabled children due to CMV after 40 years (cf the peak of CMV-induced Mental Retardation cases on the red curve of Figure 14) is due to a spike in primary congenital infections. The peak even exceeds the peak of the baseline scenario. Since contact rates between adults are reduced, the seronegative population of adults in reproducing age increases. Over the years, a pool of seronegative adults is created Consequently, more seronegative pregnant women undergo the chance of a seropositive conversion during their pregnancy. Policy 4 is therefore efficient in reducing the number of congenitally induced CMV diseases in the short term, but has adverse long term impacts.

Sensitivity analysis on Policy 4 with values ranging from 20%-95% down from the initial adult and children contact rates

has only a numerical effect, thus confirming that Policy 4 is highly effective in the short run, but has dangerous long term consequences.

4.2.5 Combined existing policies

If all the policies that were presented are combined, the number of CMV-induced Mental Retardation reaches the lowest point (approximately 700 children) of all tested policies at at year 60. Even if the combination of all existing policies is not feasible in reality, the drastic positive effect on the number of disabled children at the age of 2 demonstrates that room for manoeuver exists in the fight against CMV.

4.3 Policy 5: the future promising vaccine

A safe and effective CMV vaccine for seronegative women is not available so far (Ludwig and Hengel, 2009). If that vaccine, that is currently under animal-trial (Cheeran et al., 2009), were to be approved for humans and massively administered, the infectivity of the virus would be reduced by 50%. Policy 5 thus introduces a new *infectivity* rate of 0,02 person/contact. The effect on the number of disabled children is significant in the long-term : for example the number of Mental Retardation cases induced by CMV falls under 500 cases in year 100 (cf Figure 14). Such a drop in *infectivity* has a significant impact on the number of disabled children: after 100 years, the cumulative number of disabled children drops by 84 % compared to the baseline scenario.(correspoonding to 331 706 disabilities avoided, cf Table1).

The spread of the virus in the population drops exponentially and after 15 years the virus seems to be eliminated from the American population. A sensitivity analysis of policy 5 with values ranging from 20 to 80% of the initial infectivity demonstrates that even a drop of 20% of the *infectivity* (ie to 0.032 people/contact) after the introduction of a vaccine would yield a decrease of 46% of cumulative disabled children compared to the baseline scenario.

4.4 Comparison of policies

In order to evaluate the magnitude of each policy's impact, the chosen criterion is the number of disabled children due to CMV congenital infection (which includes both SNHL and Mental Retardation sequelae). The evolution of the number of Mental Retardations at the age of 2 due to CMV presented in Figure 14 emphasizes that in the long run policy 5 (vaccination) performs better than the combination of existing policies and brings the number of disabled children under 500. The difference between the base scenario and the different policy scenarios is presented in the last column of Table 1 and confirms the previous observation. The cumulative number of disabled children due to CMV is indeed dramatically reduced by vaccination: if the vaccine were to be clinically approved and distributed on a large scale, more than 330 000 child disabilities would be avoided in the time span of 100 years.

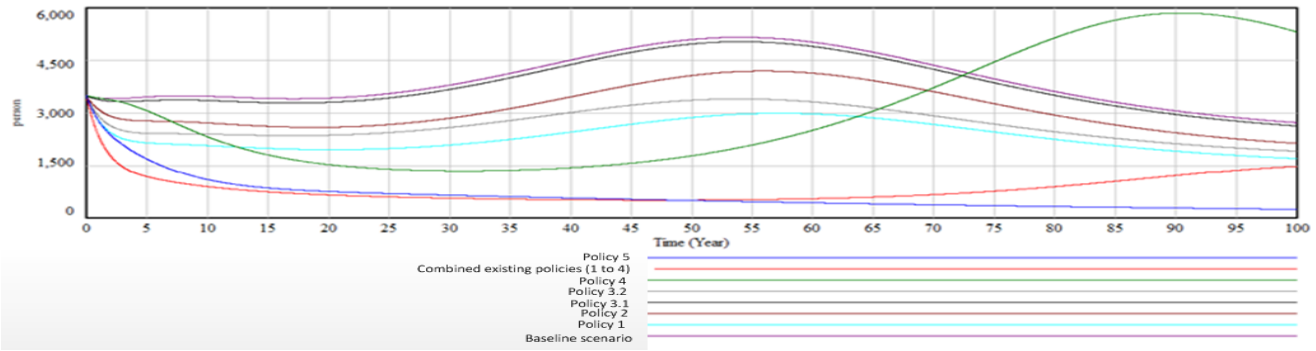

Figure 14: Comparison of policy effects on the number of CMV-induced Mental Retardation at the age of 2

Scenario	Cumulative number of disabled children	Difference with base model	% decrease
Base Model	344 992		
3.1	383 457	11 583	3 %
2	314 307	80 685	20%
4	301 543	93 449	24%
3.2	269 314	125 678	32%
1	234 256	160 736	40%
Combined existing policies (1;2;3.1;3.2;4)	81 181	313 811	***80%***
5	63 286	331 706	***84%***

Table 1: Comparison of the policies tested

5 Conclusions

The dangerous character of the cytomegalovirus stems from its "invisibility" in the general population. Since an infected individual does not manifest severe symptoms, Cytomegalo virus infections are misunderstood for a common cold. Therefore awareness about the disease is low. Even if the system dynamics model presented in this report indicates that combining existing policies offers great potential to limit the spread of the virus, this policy can only be implemented if awareness of CMV and its consequences increases.

Uncertainty remains concerning the mechanisms of transmission to the fetus, particularly in the case of reactivation with new strains of CMV. Besides, even in cases of primary infections, medical practitionners cannot predict with accuracy the development of symptoms for the infants, and the predictions are even more uncertain for the children's sequelae. Despite the ambiguity of diagnoses, the epidemiology CMV model presented here shows that there is room for maneuver to reduce the negative effects of CMV by associating different public health policies: increasing awareness among pregnant woman (policy 1), efficient screening methods in utero (Policy 3), better hygiene measures for everyone (Policy 4) and in utero antiviral treatment (Policy 2). Nevertheless the model may have oversimplified the late development of sequelae, which can appear after 2 years.

Since CMV infection is the leading infection cause of mental retardation and hearing loss among congenitally infected children (Colugnati et al., 2007), the absence of a vaccine that would prevent infection from the virus is the biggest challenge so far. The model's behavior supports the "*sense of urgency in clinical vaccine trials*" mentioned by Cheeran (2009). The vaccine presents indeed the highest potential to reduce the number of disabled children to the extent that it would bring a 84% decrease of the cumulative number of disabled children due to CMV.

Further research efforts could be directed at first evaluating the cost of the policies presented in this report on a societal level, and then finding the optimal policy mix. The model can also be refined by distinguishing different classes of pregnant women according to their seroprevalence, which is correlated to ethnic origin (Colugnati et al., 2007). Finally, Exploratory Modeling and Analysis (EMA) developed by E. Pruyt and J.H. Kwakkel at TU Delft (Pruyt and J.H., 2013) could help to explore and analyze the effectiveness and robustness of adaptative policies over time under deep uncertainty.

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Appendix

Stock	Initial value (person)
Pregnancies of seropositive mothers	$1.2*10^6$
Pregancies of seronegative mothers in trimerster 1	$4*10^6$
Children at the age of 2 with serious Mental Retardation due to CMV	3 500
Children at the age of 2 with SNHL sequelae	10 500
Infectious healthy children at the age of 2	4 800
Non infected children at the age of 2	$3*10^6$
Non infectious seropositive children at the age of 2	$12*10^6$
Infectious children at the age of 3.5	400 000
Non infected children at the age of 3.5	$15*10^6$
Non infectious seropositive adults	$115*10^6$
Infectious adults	$2*10^6$
Seronegative adults	$156*10^6$

Table 2: Stock variables and initial values

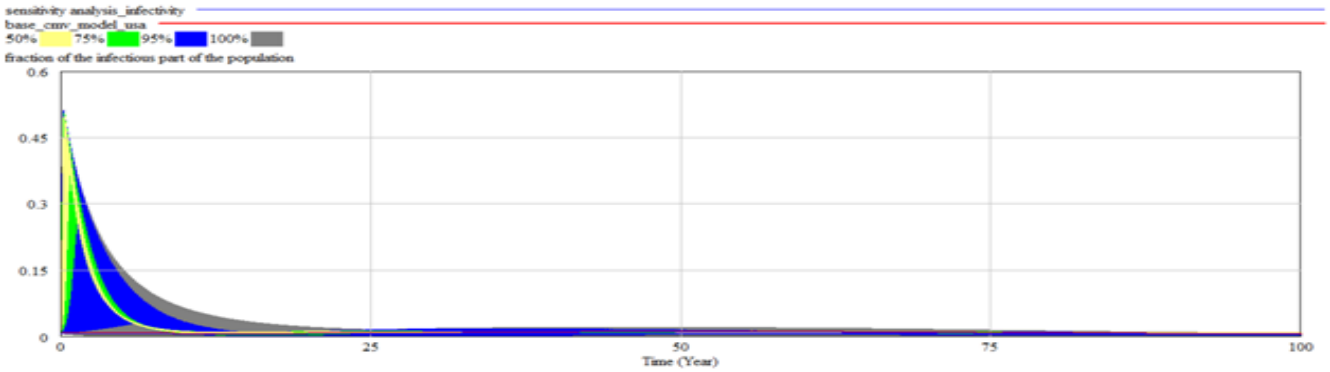

Figure 15: Sensitivity analysis of the parameter “infectivity” on the stock variable “infectious fraction of the population”

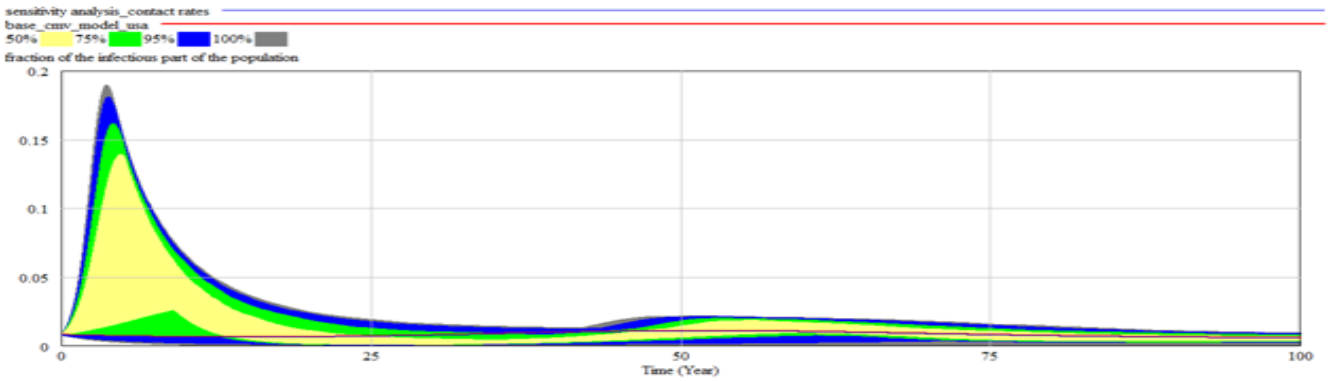

Figure 16: Sensitivity analysis of the parameter “contact rate” on the stock variable “infectious fraction of the population”

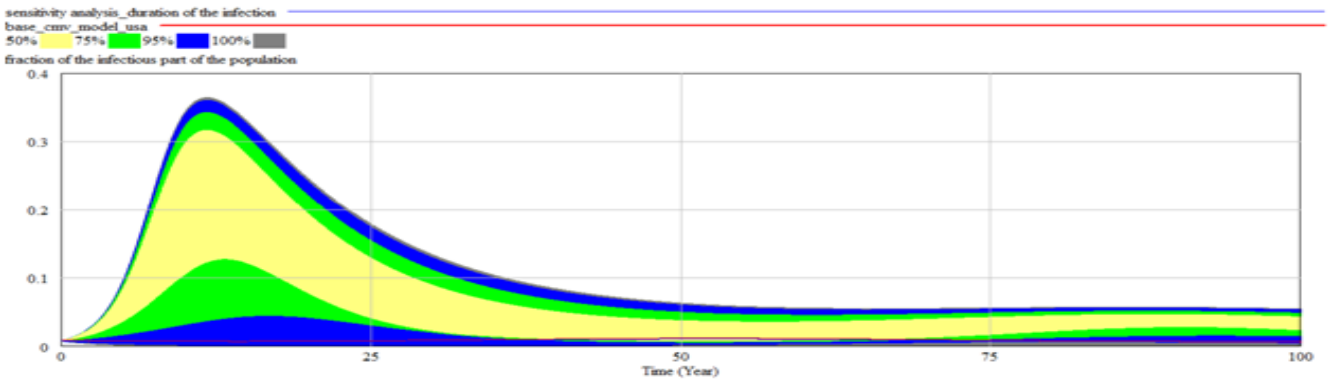

Figure 17: Sensitivity analysis of the parameter "duration of infection" on the stock variable "infectious fraction of the population"

Policy	**Parameter**	**Base value [unit]**	**Value after policy implementation**	**Sensitivity range***
1	Contact rate among pregnant women	27 [contact/person*year]	13.5	5.4-21.6
2	Transmission rate to foetus after primary infection Transmission rate to foetus for seropositive pregnancies	0.32 [Dmnl] 0.014 [Dmnl]	0.256 0.0112	0.096-0.304 0.0042-0.0133
3.1	Fatality ratio of symptomatic infant	0.07 [Dmnl]	0.14	0.105-0.14
3.2	Percentage of asymptomatic after T1 that shows signs of CNS Percentage of symptomatic after T1 that shows CNS signs Percentage of infant T2 that shows CNS signs	0.5 [Dmnl] 0.8 [Dmnl] 0.08 [Dmnl]	0.3 0.48 0.048	0.1-0.45 0.16-0.72 0.016-0.072
4	Inter-adult contact rate Children contact rate	27 [contact/person*year] 27 [contact/person*year]	13.5 13.5	5.4-21.6 5.4-21.6
Combined existing policies	all of the above	all of the above	all of the above	all of the above
5	Infectivity	0.04 [person/contact]	0.002	0.008-0.032

**** All sensitivity tests were performed with latin hypercube, 200 simulations and a random uniform parameter distribution***

Table 3: Summary of policy tests