Name: XXXXXXX

Mid-Term

Summary: The current Zika virus outbreaks and their possible association with an increase in birth malformations (cases of microcephaly) and neurological complications (cases of GBS) have caused increasing alarm in countries across the world, particularly in the Americas. Brazil is one of the severely impacted countries by zika virus and the number of microcephaly and GBS cases is growing at an exponential rate. Thereby, this study aims to develop a recommendation to the Government of Brazil in order to develop a comprehensive solution to adequately combat the situation.

In order to develop a recommendation, set of fundamental and means objectives were identified, supplemented by information from WHO situation reports. The objectives and corresponding attributes chosen for the study included 1) Minimize impacts of zika virus on human health (number of microcephaly cases) 2) Minimize economic impact (million USD) 3) Minimize funding requirement for implementation of measures (million USD) 4) Minimize duration of the epidemic (days).

A comprehensive solution to this epidemic would require attacking the problem from all possible sides which involved 1) Effective Vector Management - Control the spread of Aedes mosquitoes as well as provide access to personal protection measures 2) Public Health Risk Communication - Communicate the risks associated with zika virus to targeted audience (particularly pregnant women or travelers), general audience for increasing awareness and dispel rumors 3) Research - Public health research and development of diagnostics and vaccines

A Multi-Attribute Utility Theory model is built and used to rank the alternatives. A risk-based response has been proposed to Government of Brazil to address the crisis.

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Background Research

Fig: A biting Aedes aegypti mosquito [2]

Introduction Zika virus is an emerging viral disease that is transmitted through the bite of an infected mosquito, primarily Aedes aegypti, the same vector that transmits chikungunya, dengue and yellow fever. [1]

Signs and Symptoms Most people infected with Zika virus won't even know they have the disease because they won't have symptoms. [3] Symptoms of Zika virus disease include fever, skin rash, conjunctivitis, muscle and joint pain, malaise and headache, which normally last for 2 to 7 days. There is no specific treatment but symptoms are normally mild and can be treated with common pain and fever medicines, rest and drinking plenty of fluids.

History Zika virus was first discovered in 1947 and is named after the Zika forest in Uganda. In 1952, the first human cases of Zika were detected and since then, outbreaks of Zika have been reported in tropical Africa, Southeast Asia, and the Pacific Islands. Zika outbreaks have probably occurred in many locations. Before 2007, at least 14 cases of Zika had been documented, although other cases were likely to have occurred and were not reported. Because the symptoms of Zika are similar to those of many other diseases, many cases may not have been recognized. Local transmission has been reported in many other countries and territories. Zika virus likely will continue to spread to new areas [4]

Potential complications of Zika virus disease During large outbreaks in French Polynesia and Brazil in 2013 and 2015 respectively, national health authorities reported birth malformations and potential neurological complications of Zika virus disease.

Microcephaly There have been reports of a serious birth defect of the brain called microcephaly in some babies born to mothers infected with Zika virus during pregnancy. Microcephaly is a condition in which a baby's head is abnormally small and can be associated with incomplete brain development. Currently, it is unclear what link if any Zika infection may have to microcephaly. International research organizations are investigating. [2]

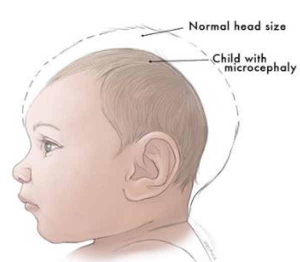


Fig: Children born with microcephaly

Guillain-Barré Syndrome (GBS) There have also been reports of in some countries where Zika transmission is occurring. GBS is a rare autoimmune disorder in which damaged nerve cells cause muscle weakness and, sometimes, paralysis. Most people do recover from GBS, but some have permanent damage and, in rare cases, GBS leads to death. It is not known if Zika virus infection causes GBS, and the U.S. Centers for Disease Control and Prevention (CDC) is working to answer this important question. [2]

Overview of the situation The situation today is dramatically different. Last year the virus was detected in the Americas, where it is now spreading explosively [1]. Possible links with neurological complications and birth malformations have rapidly changed the risk profile of Zika from a mild threat to one of very serious proportions. The Zika situation is particularly serious because of the potential for further international spread, given the wide geographical distribution of the mosquito vector, the lack of population immunity in newly affected areas, and the absence of vaccines, specific treatments and rapid diagnostic tests.

Number of Zika virus cases In February 2015, Brazil detected cases of fever and rash that were confirmed to be Zika virus in May 2015. The last official report received dated 1 December 2015, indicated 56,318 suspected cases of Zika virus disease in 29 States, with localized transmission occurring since April 2015. Due to the magnitude of the outbreak, **Brazil has stopped counting cases** of Zika virus. Today the Brazilian national authorities estimate **500,000 to 1,500,000 cases** of Zika virus disease [1]. In October 2015, both Colombia and Cape Verde, off the coast of Africa, reported their first outbreaks of the virus. As of 22 January 2016 Colombia had reported 16,419 cases, El Salvador 3,836 cases and Panama 99 cases of Zika virus disease.

Number of countries impacted From 1 January 2007 to 16 March 2016, Zika virus transmission was documented in a total of **59 countries and territories** [5]

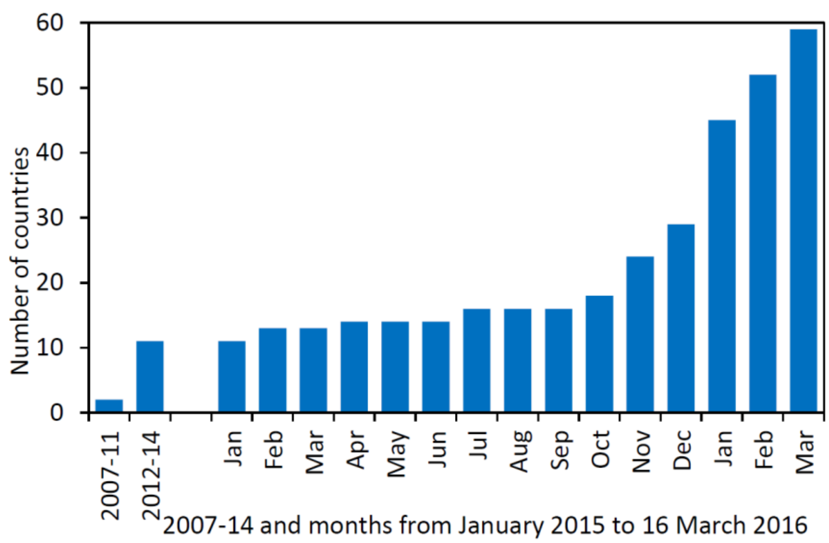


Figure: Cumulative number of countries, territories and areas reporting Zika virus transmission, 2007-2014, and monthly from 1 January 2015 to 16 March 2016. [5]

Classification	WHO Regional Office	Country/Territory/Area
Reported or indication of autochthonous Zika virus transmission AND Guillain-Barré syndrome AND microcephaly (2)	AMRO/PAHO (1)	Brazil
	WPRO (1)	French Polynesia+
Reported or indication of autochthonous Zika virus transmission, Guillain-Barré syndrome and no reports of microcephaly cases (10)	AMRO/PAHO (10)	Colombia, El Salvador, French Guiana, Haiti, Honduras, Martinique, Panama, Puerto Rico, Suriname, Venezuela (Bolivarian Republic of)
Reported or indication of autochthonous Zika virus transmission and no reports of Guillain-Barré syndrome or microcephaly cases (40)	AFRO (2)	Cabo Verde, Gabon
	AMRO/PAHO (22)	Aruba, Barbados, Bolivia (Plurinational State of), BONAIRE - Netherlands, Costa Rica, Cuba, Curaçao, Dominica, Dominican Republic, Ecuador, Guadeloupe, Guatemala, Guyana, Jamaica, Mexico, Nicaragua, Paraguay, Saint Martin, Saint Vincent and the Grenadines, Sint Maarten, Trinidad & Tobago, United States Virgin Islands
	SEARO (4)	Bangladesh, Indonesia, Maldives, Thailand
	WPRO (12)	American Samoa, Cambodia, Fiji, Lao People's Democratic Republic, Malaysia, Marshall Islands, Papua New Guinea, Philippines, Samoa, Solomon Islands, Tonga, Vanuatu
Countries/territories/areas with outbreaks terminated (4)	AMRO/PAHO (1)	ISLA DE PASCUA - Chile
	WPRO (3)	Cook Islands, New Caledonia, YAP - Micronesia (Federated States of)
Locally acquired without vector-borne transmission (3)	AMRO/PAHO (1)	United States of America
	EURO (2)	France, Italy

Table: Countries, territories and areas with autochthonous Zika virus circulation, 2007–2016. [5]

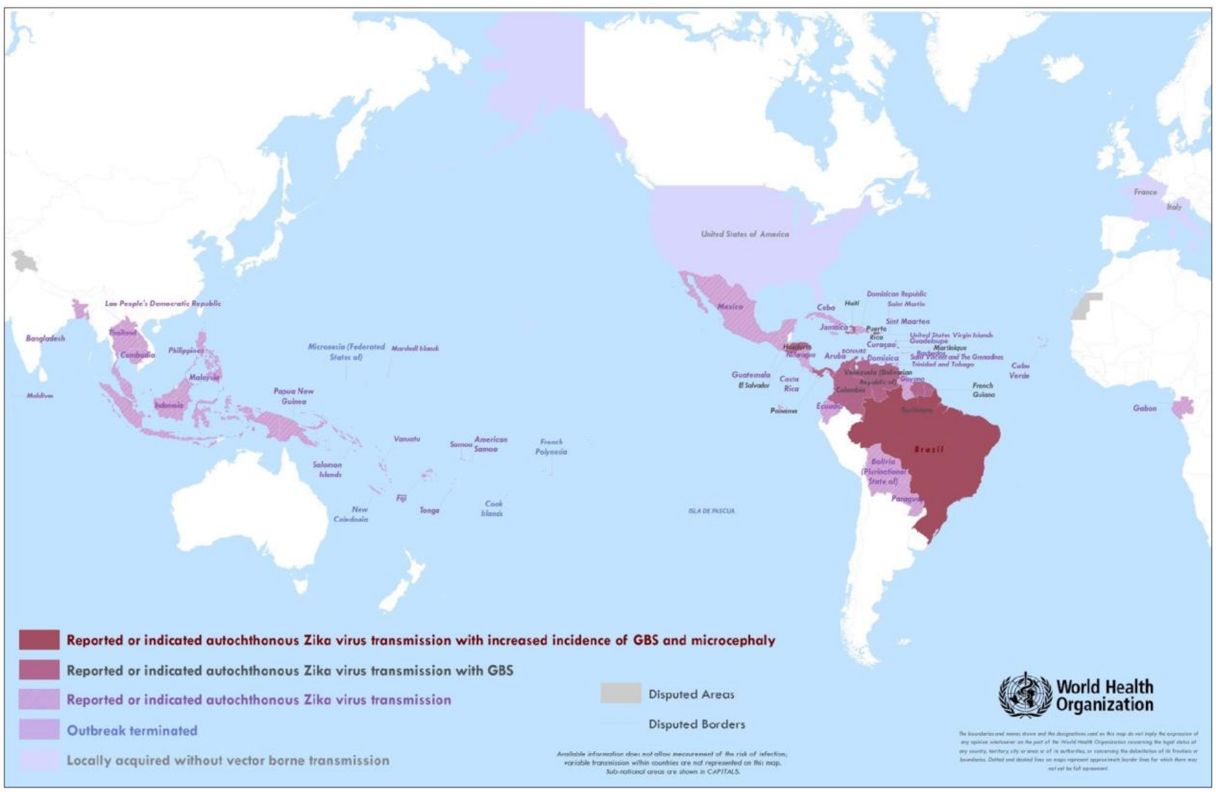


Figure: *Countries and territories reporting Zika virus, Microcephaly and Guillain-Barré syndrome, 2007-2016 [5]*

Increase in Microcephaly cases Between 22 October 2015 and 12 March 2016 **a total of 6480 cases of microcephaly** and/or central nervous system (CNS) malformation were reported by Brazil including **182 deaths** [5]. Of the 6480 cases of microcephaly reported in Brazil suspected to be associated with a Zika virus infection, investigations have been concluded for 2212 cases and **863** (~39%) were confirmed to be linked with Zika virus.

	2001-2014	22nd Oct 15-12th Mar 16
Microcephaly cases in Brazil	**163/yr**	**6480**
Confirmed with Zika virus linkage		863
Discarded		
Under investigation		4268
Child Deaths		**182**
Confirmed with Zika virus linkage		40
Under investigation		124
Discarded		18

Increase in Guillain-Barré syndrome (GBS) cases In 2015 in the Brazilian state of Bahia, 42 GBS cases were reported, among which 26 (62%) had a history of symptoms consistent with Zika virus infection [5]. A total of 1708 cases of GBS were registered between January and November 2015 nationwide, representing **a 19% increase from the previous year (1439 cases of GBS in 2014),** though not all states reported an increase in incidence. Most of Brazil's states have Zika, chikungunya and dengue virus circulation.

Classification	Country/Territory/Area
Reported increase in incidence of GBS cases, with no GBS case confirmed with Zika virus infection	Colombia, Honduras
Reported increase in incidence of GBS cases, with at least one GBS case with confirmed Zika virus infection	Brazil, El Salvador*, French Polynesia, Suriname, Venezuela (Bolivarian Republic of)
No increase in GBS incidence reported, with at least one GBS case with confirmed Zika virus infection	French Guiana, Haiti*, Martinique, Panama, Puerto Rico

Table: Countries, territories or areas reporting GBS potentially related to Zika virus infection [5]

As with microcephaly, Zika virus is highly likely to be a cause of the elevated incidence of GBS in countries and territories in the Western Pacific and Americas.

Government and public reactions In May 2015, the Pan American Health Organization (PAHO) issued an alert regarding the first confirmed Zika virus infection in Brazil. An International Health Regulations (IHR 2005) Emergency Committee met on 01 February 2016, and WHO declared the recent clusters of microcephaly and other neurological disorders in Brazil a Public Health Emergency of International Concern (PHEIC). In the absence of another explanation for the clusters of microcephaly and other neurological disorders, the IHR Emergency Committee recommended enhanced surveillance and research, and aggressive measures to reduce infection with Zika virus, particularly amongst pregnant women and women of childbearing age. [1]

WHO has activated its Emergency Operations incident management system to coordinate the international response to this outbreak. This Strategic Response and Joint Operations Plan aims to provide support to affected countries, build capacity to prevent further outbreaks and control them when they do occur. Colombia, Dominican Republic, Ecuador, El Salvador and Jamaica have all advised women to postpone getting pregnant until more is known about the virus and its rare but potentially serious complications. The US CDC has also issued a level 2 travel warning, which includes recommendations that pregnant women consider postponing travel to any area with ongoing Zika virus transmission.

WHO's Regional Office for the Americas (AMRO/PAHO) has been working closely with affected countries in the Americas on the investigation of and response to the outbreak since mid-2015. AMRO/PAHO has mobilized staff and members of the Global Outbreak Alert and Response Network (GOARN) to assist Ministries of Health in strengthening detection of Zika virus through rapid reporting and laboratory testing. A GOARN international team visited health authorities in Brazil to help assess the unprecedented increase in microcephaly cases and their possible association with Zika virus infection, as well as to provide recommendations to the Ministry of Health for surveillance, disease control measures and epidemiological research.

Decision Making

Decision Context: Given Brazil is one of the most heavily impacted countries by Zika virus, develop a recommendation for the government of Brazil to deal with the situation.

Identification and Explanation of Fundamental Objectives The higher-level objective is to develop a recommendation for a country impacted by Zika virus to minimize the impact of Zika virus. The four lower-level fundamental objectives which will enable to achieve the higher-level objective are as follows.

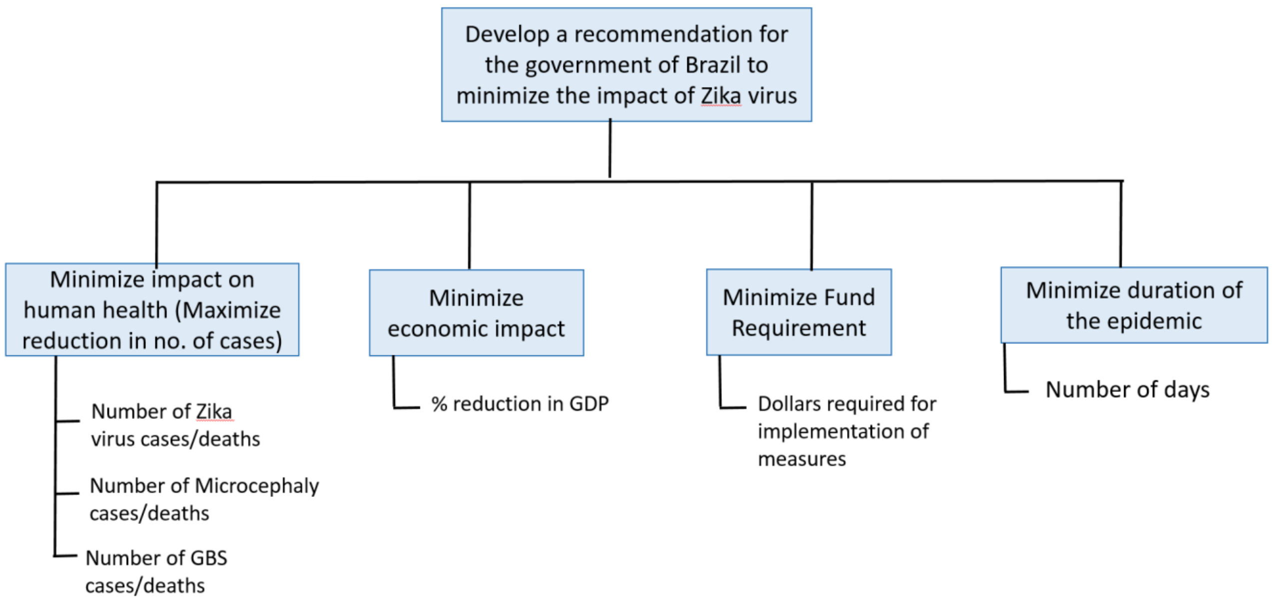


Fig: Fundamental Objectives Hierarchy

Below is a detailed explanation about what do the fundamental objectives mean and their scope:

1) **Minimize impact on human health (Maximize reduction in number of cases):** The impact of Zika virus on Brazil can be measured in terms of the following attributes:
   1) Number of Zika virus cases/deaths
   2) Number of GBS cases/deaths
   3) Number of Microcephaly cases/deaths

2) **Minimize Economic Impact:** Brazil should have been poised for a good year in 2016 as host of the summer Olympic Games but the dual impact of the Zika virus and the worst economic downturn for a century has seen the wind taken out of its sails. Apart from the health risks Zika virus posed in Brazil, it is also affecting Brazil's economy. It is expected that the tourism sector would take the biggest initial hit. Although economists are having difficulty calculating how Zika could impact tourism and the overall economy, since the virus is a relatively new phenomenon and there is uncertainty about whether it may be contained or spiral out of control. Below are few perspectives on Brazil's economy:

1) **Overall Economy:** Brazil has been in an economic downturn since the 1930s and Zika virus is making things worse. The country is already facing several economic issues, like low commodity prices, political uncertainty and the ongoing bribery scandal involving the government-run oil company, Petrobas. In fact, their economy is forecast to shrink by 3.5 percent this year. [6]

2) **Impact on Brazil's tourism sector by Zika virus compared with SARS:** Brazil is one of the countries worst affected by the Zika virus and tourism is an important component of Brazil's economy. With the current Zika situation, many tourists, not just women who are pregnant or may become pregnant, are shying away from trips to Brazil. Tourism is typically responsible for 9% of GDP but that was expected to rise to 10% in 2016 – a slight bump from its usual level of about 9%.

   Geraint Jones, an economics professor at Lancaster University, has compared the Zika epidemic with the effects of the Sars outbreak on Malaysia, Singapore, Hong Kong and China in 2003, which resulted in a 20% drop in the tourism sector for each country. In this case, the tourism industry took a hit. Measured over the year as a whole, the losses amounted to around 20% of total activity in the sector, for each of those four countries. For Brazil, a drop of 20% is a worrying prospect, he said: "A hit of 20% to tourism income – as happened with Sars – would be tantamount to a reduction of US$47bn [£32.2bn] in GDP throughout the year." [7]

   On the one hand, the fact that there is no vaccine for Zika and it may take as long as a year to develop one, the impact on tourism could last longer than with Sars. On the other hand, the fact that the virus only affects pregnant women and their families' means, only a small sector of potential tourists would cancel trips. [7]

3) **Economic Impact of Zika virus in Latin America and the Caribbean***:* The economic impact of the fast-spreading Zika virus in Latin America and the Caribbean is likely to reach 3.5 billion dollars this year, but could climb if the mosquito-borne illness is not quickly contained, the World Bank said Thursday. Across the region, the initial estimate of economic impact amounts to a "modest" 0.06 per cent of annual gross domestic product, but could be more than 1 per cent in some countries - especially in the Caribbean - that are highly dependent on tourism, the Washington-based development agency said [8]

Of all the above perspectives, we will use World Bank's analysis for capturing the economic impact of zika virus in Brazil (highlighted in point 3 above). This is explained in detail in assumptions below.

3) **Minimize Funding requirement –** The amount of money which is required for implementing the measures needs to be minimized.

4) **Minimize duration of the epidemic –** This objective involves minimizing duration of the epidemic (number of days).

Identification and Explanation of Means Objectives

Means-objectives indicate how to achieve the fundamental objectives listed in the fundamental-objectives hierarchy. For this study, the mean objectives are shown in the Means-objectives network below.

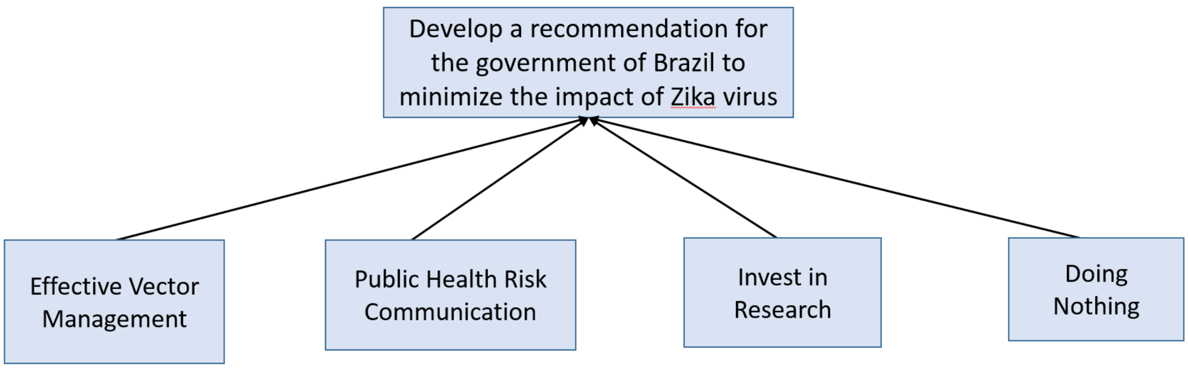


Fig: Means Objectives Network

Below is a detailed explanation about what do the means objectives mean and their scope:

1) **Effective Vector Management:** This aims to reduce the impact of Aedes mosquito bites by controlling the spread of the Aedes mosquito as well as provide access to personal protection measures. Vector management involves the following:

   a) **Measures to control the spread of Aedes mosquitoes**

   - Strong surveillance to determine changes in geographical distribution of vectors, obtain relative measurements of the vector population over time, and for facilitating appropriate and timely decisions regarding control interventions
   - Support insecticide resistance monitoring activities including assessment of the environmental consequences of the same
   - **Integrated Vector Management (IVM**) [9]: IVM principles include approaching mosquito control through careful planning and using a variety of interventions targeting both larval and adult mosquito control, and including both chemical and non-chemical methods.

     (i) *Immature and Adult Mosquito Monitoring*: It is used to determine the abundance adult vector mosquitoes, and identify areas where control measures are needed.

     (ii) *Larval Mosquito Control:* This includes the implementation of following measures

     - *Source Reduction* - Elimination of habitats that produce mosquitoes ranging from draining and scrubbing water holding containers on a weekly basis to properly disposing of discarded tires and trash containers
     - *Larvicide application* – Application of pesticides registered by EPA for larval mosquito control

     (iii) *Adult Mosquito Control:* This includes the implementation of following measures

     - *Targeted Outdoor Residual Spraying* – It should be considered in situations where long-lasting control is desired (at the case-patient household or building level, for example) an approach aimed at outdoor spraying of surfaces likely to serve as adult mosquito resting sites may be achieved.
     - *Indoor residual spraying* - It should be considered for homes that do not have adequate screening or air conditioning. Two chemicals with EPA registration allowing indoor use for mosquitoes are deltamethrin and bifenthrin. Spraying

should target sites within the home where mosquitoes rest. They include the back of closets, under furniture and other dark undisturbed sites behind furniture and in corners.

b) Personal Protection Measures

- Use of insecticidal/treated mosquito nets and insect repellent lotion.
- Implement measures to enhance personal protection measures including reducing exposed areas with long pants and shirts
- Provide proactive special care for pregnant women, such as Zika Pregnant Mother Kits (ZPMKs)

2) **Public Health Risk Communication:** This aims to communicate the risks associated with Zika virus disease and promote healthy behaviors, reduce anxiety, address stigma, dispel rumors and resolve cultural misperceptions. This empowers key populations in affected and at-risk countries to make informed decisions to protect their health. It involves the following:

a) Develop and disseminate targeted risk communication messages and material on Zika and associated complications for key audience such as women of reproductive age, pregnant women, women who are breast feeding, travel and transport sector stakeholders, healthcare workers, clinicians, and others to implement priority actions that are needed for effective prevention, detection and response to the Zika virus outbreak.

b) Ensure that advice/information is in the local language, and socially and culturally acceptable by stakeholders and in a format they can use and trust

c) News and social media channels will be monitored and analyzed to identify audience concerns, knowledge gaps, rumors and misinformation.

d) Conduct social science research to understand individual, family and community perceptions, attitudes, expectations, and behavioral responses concerning fertility decisions, contraception, abortion, pregnancy care, and care of infants with microcephaly and persons with GBS, and to inform the development of messages suited to context, and to further scale interventions

e) Potentially high-risk populations (especially pregnant women and those considering pregnancy of childbearing age) will be empowered to access medical care and given real-time information on evolving risks

f) Train Health workers to communicate risk, provide advice and specialized counselling to those affected by Zika virus disease.

3) **Research:** Research aims to investigate the etiology of microcephaly, neurological syndromes and establish the possible consequences of Zika virus infection and fast-track the research and development (R&D) of new products ((e.g. rapid diagnostics, vaccines, therapeutics)

a) Public Health Research

- Research will focus on enhancing current knowledge as well as risk factors in the transmission of Zika virus.
- Possible link between Zika virus and potential complications, such as GBS and microcephaly will be examined
- Research studies are needed in order to assess: 1) presence of the Zika virus in semen and other body fluids, including pregnancy-related fluids; and 2) potential sexual transmission, and mother-to-child transmission.
- Developing animal models that mimic Zika virus infection in people

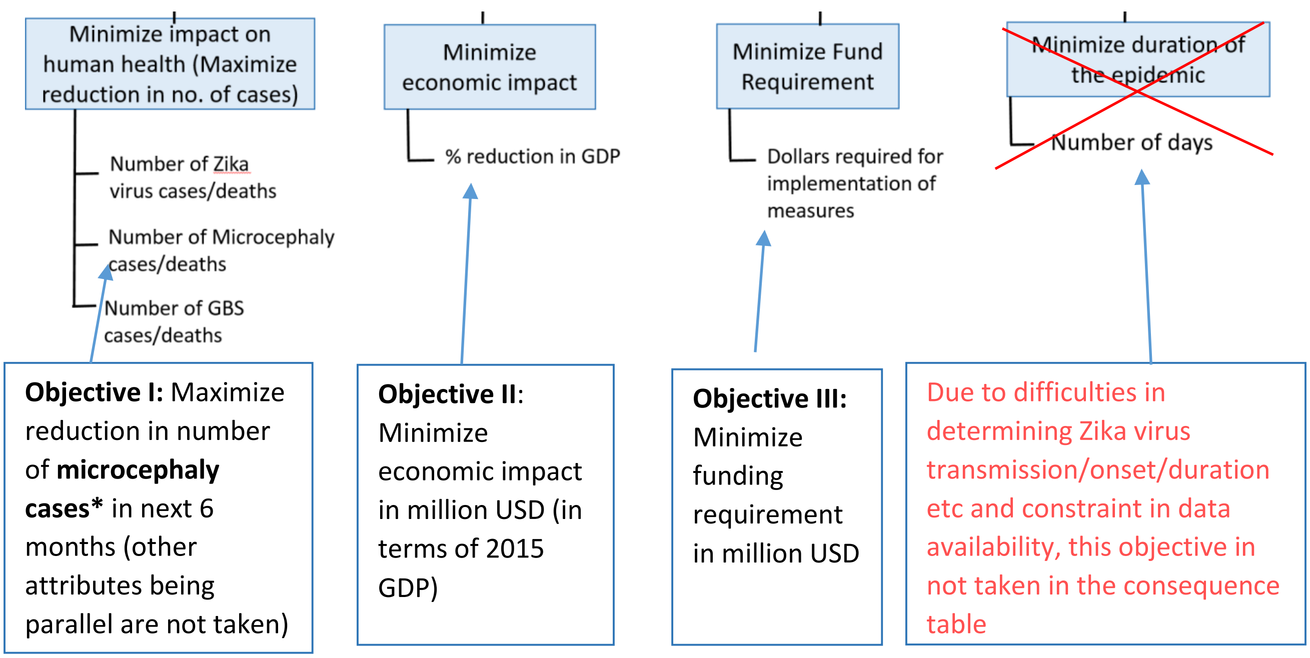
b) Diagnostics and Vaccine Development

- Addresses research and development needs for novel means of vector control, diagnostics, vaccines, and coordination of supportive research activities, such as the establishment
- Develop a master plan in line with World Health Organization's "R&D Blueprint" which aims to accelerate the availability of medical countermeasures during epidemics and limit damage as much as possible [10]
- Research related to performing definitive diagnostic testing. WHO is undertaking a landscape analysis of diagnostics under development, developing target product profiles, facilitating the preparation and characterization of reference reagents, and setting up an Emergency Use Assessment and Listing mechanism for priority Zika in vitro diagnostics. [1]

4) Doing nothing: This alternative would not have any other additional funding requirement but would not improve the situation.

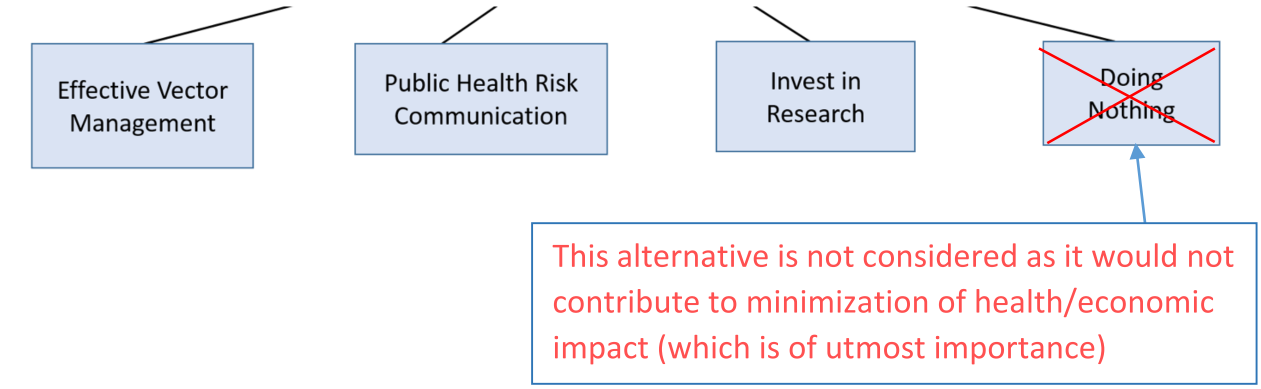
Formulation of Consequence Table

Choice of Fundamental objectives Out of the four lower-level objectives, we choose the following ones:



****Note:** Microcephaly cases/deaths could also be caused even without an infection from zika virus, however, this study only focusses those cases which are confirmed to be linked with zika virus infection.*

Choice of Means objectives Out of the four alternatives, we choose the following ones:



Identification of uncertain attributes Given the uncertain nature of all the three attributes, we have assumed a triangular probability distribution for each of the three attributes. Additionally, online sources/websites for estimating min, max and mode for each of these alternatives have been provided (wherever available), followed by detailed underlying assumptions to arrive at the below consequence table.

Final Consequence Table

Objective	***Attribute***	***Unit***	***Effective Vector Management*** *(Min, Mode, Max)**	***Public Health Risk Communication*** *(Min, Mode, Max)**	***Research*** *(Min, Mode, Max)**
Maximize	**Reduction in number of Microcephaly cases in next 6 months**	Number	207 435 621	311 518 725	104 466 828
Minimize	**Economic Impact**	Million USD	245 342 456	490 684 913	343 479 639
Minimize	**Funding requirement**	Million USD	5.1 6.4 7.7	12.3 15.4 18.5	5.1 6.4 7.7

** Refer to underlying assumptions below for the min, max and mode numbers calculation*

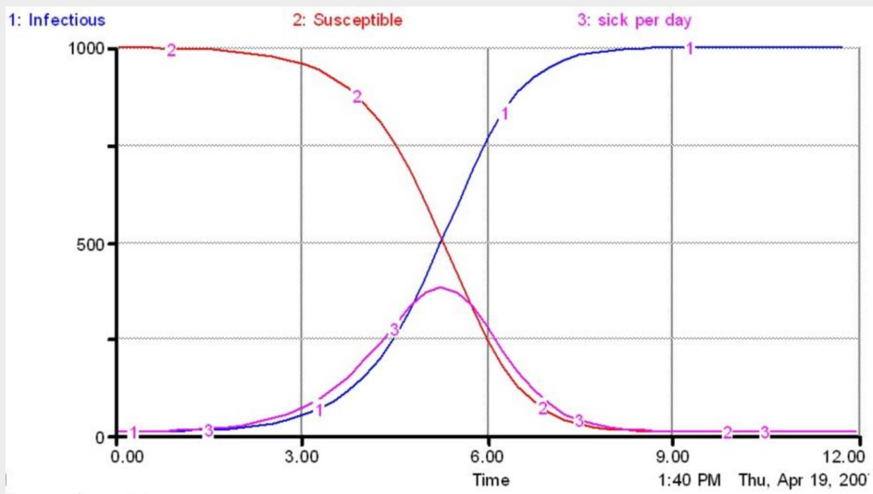
Assumption for estimates

Assumptions related to Attribute 1 (Microcephaly cases)

(a) Constant rate of new cases over the next 6 months: As per the WHO Situation report of Zika virus [5], between Oct, 22nd 2015 and March 12th 2015, out of a total 6480 microcephaly cases reported in Brazil, 863 were confirmed to be linked with Zika virus. Hence, approximately 173 (=863/5) microcephaly cases per month were reported linked to zika virus.

In order to predict the estimated number of new zika linked microcephaly cases over the next 6 months, we have assumed a constant rate*, giving 173cases/month * 6months ~ 1036 cases over the next six months.

Scope for further refinements: To further refine the above analysis, the assumption of constant rate of cases over the next 6 months should be replaced by one of the several existing models (that capture the growth of new infections of an epidemic, see [11] and [12]). As an example, the below model shows the count of people infected over a day due to spread of an epidemic:



However, given the limited amount of resolution provided in the data from WHO and other research institutes, a constant rate has been assumed (simplistically). Clearly, if the actual count of infections is of the order of ~2,500-3,000 the benefit from each alternative will also scale up accordingly.

(b) Percentage reduction in microcephaly cases due to each alternative: We assume that each of our alternative would reduce the microcephaly cases by the following percentages:

	Attribute	***Effective Vector Management***	***Public Health Risk Communication***	***Research***
Maximize	**Reduction in number of Microcephaly cases in next 6 months**	20% 40% 60%	0.3 0.5 0.7	0.1 0.5 0.8

We assume that each of these alternatives would reduce microcephaly cases most likely by ~50%. For example, public health risk communication when implemented effectively would reduce microcephaly cases by 50% of 1036 = 518 cases. However, the impact on the count of microcephaly cases would likely exhibit a much wider range (from ~100 cases to ~800 cases) owing to the uncertainty involved with the success of research.

Assumptions related to Attribute 2 (Economic impact)

We have utilized World Bank's analysis [8] to estimate the economic impact on Brazil for each of the alternatives. The estimated impact in entire Latin America and the Caribbean is likely to reach **ATLEAST USD 3.5billion** this year, but could climb further higher if the epidemic is not quickly contained.

(a) **<u>Percentage Drop in Brazil's GDP due to Zika virus</u>:** In 2015, Brazil's GDP (USD 3.26 trillion) accounted for around one-third of Latin America and Caribbean's GDP (USD 9.5 trillion) [13]. Thus, we can consider the economic impact due to Zika virus in Brazil to be a little more than its GDP contribution, say around 40% to 74% of World Bank's estimate of USD 3.5 billion (given Brazil is one of the most heavily impacted countries). This would be USD 1.4 billion to USD 2.6 billion and is around **0.043% to 0.080% of Brazil's 2015 GDP** (=1.4bn/3.26trn).

Further, as I have assumed economic impact to be an uncertain attribute in its own self, the drop in Brazil's GDP is assumed to follow a triangular distribution for each of the alternative as per below:

	Economic Impact (as % of Brazil's 2015 GDP)	**Economic impact (in million USD)**	**Impact in GDP attributed to three chosen recommendations (70% of (B) in million USD)**
	(A)	(B) = (A)*3.26 trillion	(C) = (B) * 0.7
Min	0.043	1,400	980
Mode	0.060	1,955	1,369
Max	0.080	2,607	1,825

(b) **<u>Cumulative drop in GDP attributed to three selected alternatives</u>:** Each of three alternatives when implemented, would result in lowering Brazil's GDP by different amounts. We have assumed that the cumulative drop in GDP for 2016 due to these three alternatives would be around 70% of the total GDP drop forecasted by the World Bank linked due to zika virus.

(c) **<u>Allocation of GDP drop for each alternative</u>:** The negative impact on the tourism industry of Brazil would be a major contributor in country's economic impact. Given the public health risk communication involves communication from travel advisories to travelers, this recommendation would further likely suppress travelers to Brazil. Hence public communication will be the most impactful alternative out of the three. We have assumed a split of 1:2:1 for the three recommendations respectively.

Impact in GDP attributed to three chosen recommendations (70% of (B) in million USD)	**Effective Vector Management**	**Public Health Risk Communication**	**Research**
(C) = (B) * 0.7	(D) = (C) * 0.25	(E) = (C) * 0.5	(F) = (C) * 0.25
980 1,369 1,825	245 342 456	490 684 913	343 479 639

Assumptions related to Attribute 3 (Funding Requirement)

WHO has worked out a funding requirement of 6.4, 15.4, and 6.4 million USD for the three recommendations respectively [1]. We assume that the most likely funding requirement for implementation of each alternative is the same as WHO's funding requirement numbers (taken as mode values).

We assume a margin of 20% in these funds which would give us the minimum and maximum values.

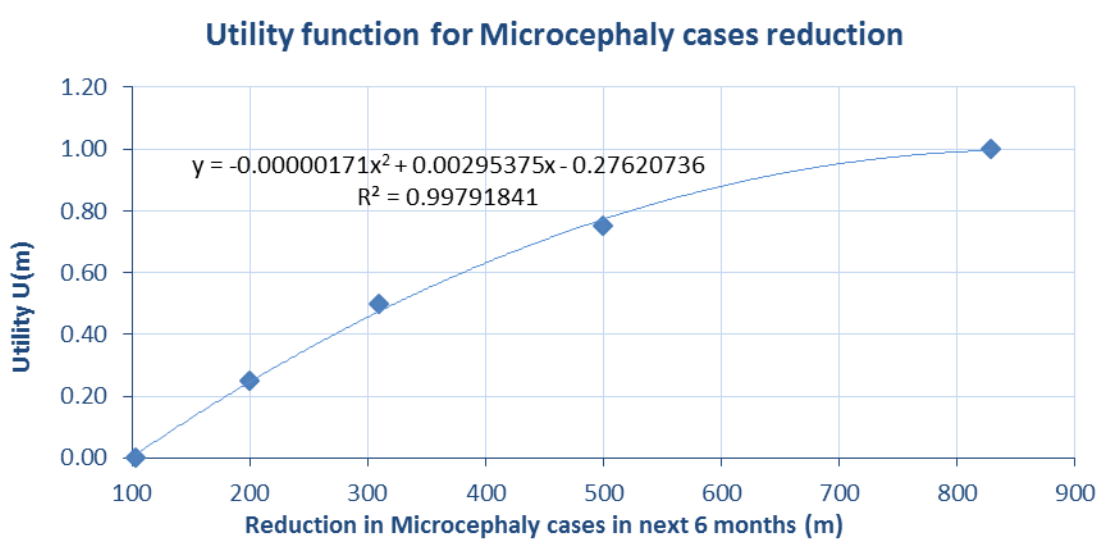
Building Multi Attribute Utility Model

Assessing Utility functions

1) Utility function for reduction in Microcephaly cases in next 6 months U(m)

For U(m), we use the Certainty Equivalent method and assign 1 to the best and 0 to the worst.

Reduction in Microcephaly cases in next 6 months (m)	U(m)
104	0.00
200	0.25
310	0.5
500	0.75
828	1



$U(m) = -0.00000171x^2 + 0.00295375x - 0.27620736$

2) Utility function for Economic Impact in million dollars U(e)

For U(e), we perform a parametric estimation of the utility function of the form: a+ b*(1-exp(-e/R))

We assess R = Risk Tolerance = 250 using a lottery

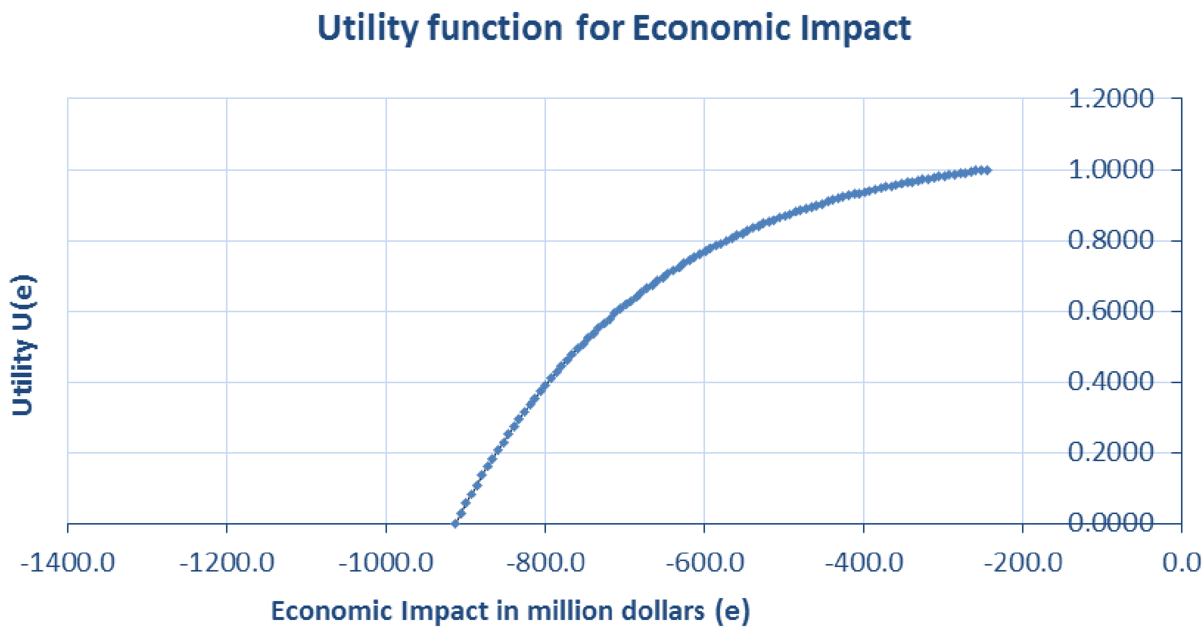
Using the following boundary conditions,

a + b*(1-exp(245/250)) = 1
a + b*(1-exp(912.5/250)) = 0

We get,

b = 0.027922597

a = 1.046475941



U(e) = 1.046475941 + 0.027922597(1-exp(-e/250)

3) Utility function for Funding requirement U(f)

For U(f), we perform a parametric estimation of the utility function of the form: a+ b*(1-exp(-f/R))

We assess R = Risk Tolerance = 10 using a lottery

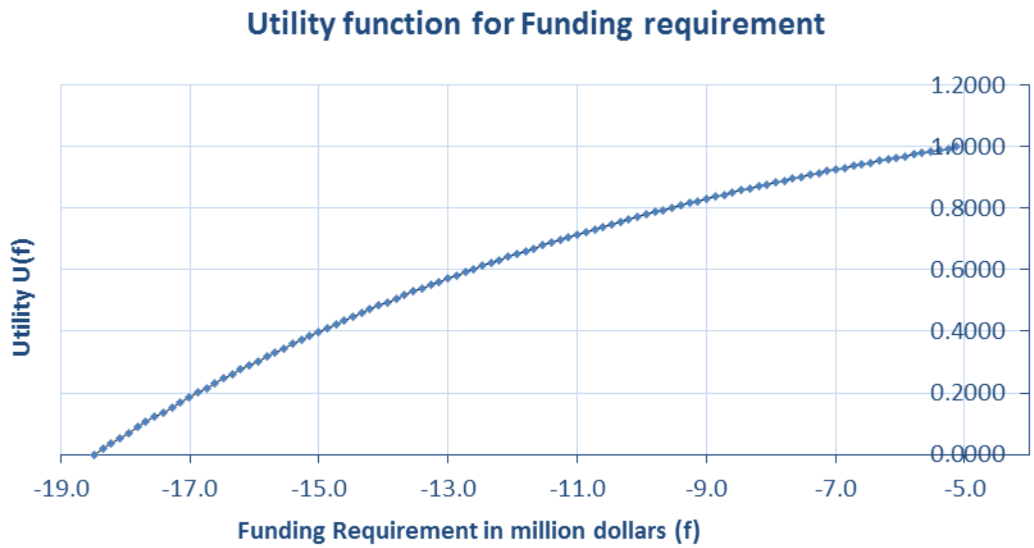
Using the following boundary conditions,

a + b*(1-exp(5.1/10)) = 1
a + b*(1-exp(18.5/10)) = 0

We get,

b = 0.21374

a = 1.14291



U(f) = 1.1429148 + 0.213744293(1-exp(-f/10)

Assessing Swing Weights

We using the swings weight method by creating a fictitious worst option and benchmark other attributes with it.

Attribute swung	Microcephaly cases	Economic Impact	Funding requirement	Rank	Rate	Weight
Benchmark	104	912.5	18.5	4	0	**0.00**
Microcephaly cases	828	912.5	18.5	1	100	**0.50**
Economic Impact	104	245	18.5	2	70	**0.35**
Funding requirement	104	912.5	5.1	3	30	**0.15**
Total					200	1.00

Finding: Highest weight on the attribute of reduction in microcephaly cases indicates that I give higher importance to this attribute in comparison to Economic impact and funding requirement, given it is directly related to the impact of zika virus on human health.

Lowest weight on Funding requirement indicates that I give lowest priority to funding needed in comparison to impact on human health and economic Impact.

Generating Additive Utility Function

Additive Utility Function U (microcephaly cases, economic impact, funding requirement) = U(m, e, f) = w_m * U(m) + w_e * U(e) + w_f * U(f)

Where,

U(m) = $-0.00000171x^2 + 0.00295375x - 0.27620736$

U(e) = 1.046475941 + 0.027922597(1-exp(-e/250)

U(f) = 1.1429148 + 0.213744293(1-exp(-f/10)

and w_m = 0.5, w_e = 0.35 and w_f = 0.15

Calculating Expected Utilities using Monte Carlo simulation

To assess the expected utility for each alternative, we perform a Monte Carlo simulation and averaged the resulting utilities
Please refer to the excel sheet "MonteCarlo_Recom 1_Vector Mgm", "MonteCarlo_Recom 2_Communicatn", "MonteCarlo_Recom 3_Research" for Monte Carlo simulation.

	Effective Vector Management	**Public Health Risk Communication**	**Research**	**Weight**
Reduction in the number of Microcephaly cases in next 6 months	0.65	0.78	0.69	0.5
Economic Impact (Million USD)	0.96	0.60	0.87	0.35
Funding requirement (Million USD)	0.95	0.37	0.95	0.15
Expected Utilities	**0.81**	**0.66**	**0.79**	

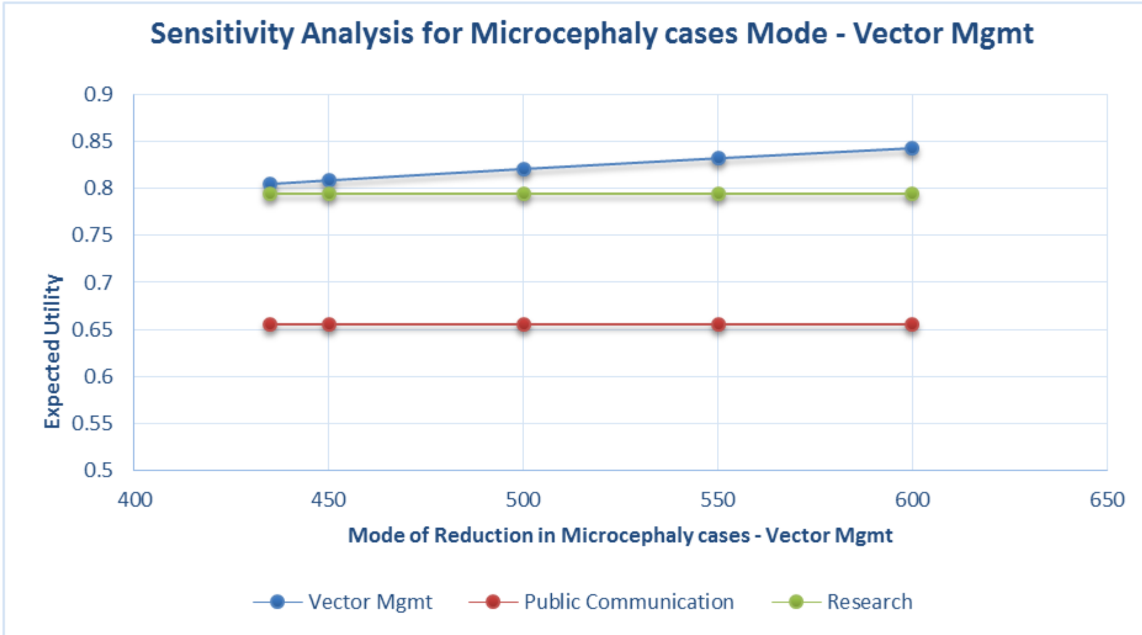
Finding: Considering the above three attributes (Reduction in Microcephaly cases, Economic Impact and Funding requirement), the expected utility for the alternative effective vector management is the highest of the expected utility for all the three alternatives. This indicates that **Effective Vector Management should be selected of the three as it is the best alternative for government of Brazil.**

Sensitivity Analysis

Given the attribute of reduction in microcephaly cases is directly related to the impact of zika virus on human health, reduction in these cases is the most important objective. A sensitivity analysis of the above model was carried out for the mode of this attribute for the best two alternatives (Vector management and Research).

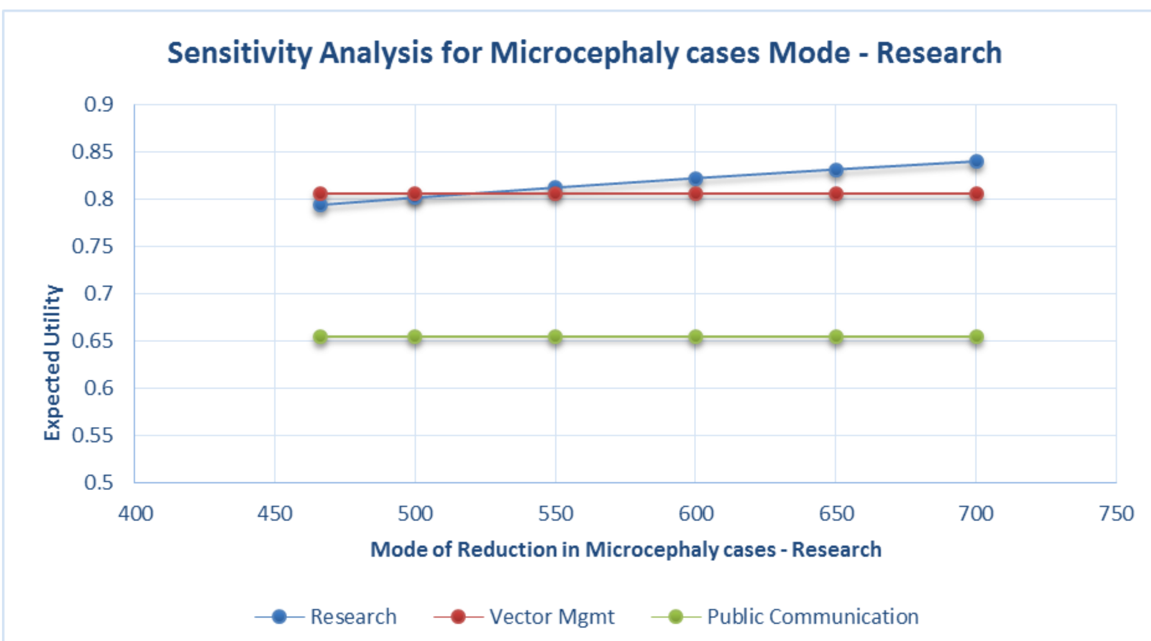
Please refer to the excel sheet for detailed calculations

1) Sensitivity Analysis for Microcephaly cases Mode for Vector Management



Finding: As the mode of reduction in Microcephaly cases for vector management is increased from current 435 to 600, the expected utility for vector management increased from 0.80 to 0.84. This indicates that it would be further effective as compared to other alternatives. These results turn out to be fairly robust.

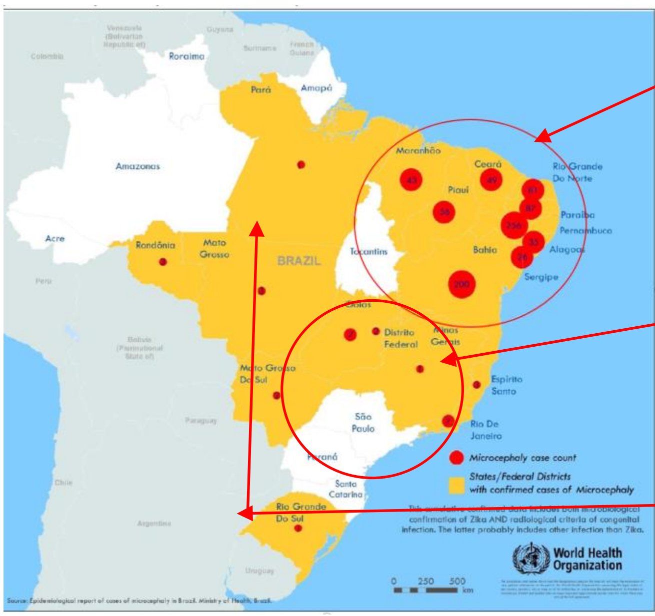
2) Sensitivity Analysis for Microcephaly cases Mode for Research



Finding: With the current consequence table, vector management is superior to research If mode of reduction in Microcephaly cases for research is increased from current 466 to 520, the expected utility for research increased from 0.79 to 0.81. Thus if the mode is more than 520, then research would be chosen oven vector management.

Final recommendation to Government of Brazil

Surveillance for Risk Based Preparedness in Brazil: An intensified surveillance is carried out to identify severely affected areas in Brazil and get an up to date and accurate information on Zika virus disease, neurological syndromes and congenital malformation. This will enable to systematically prioritize the response/alternatives to be implemented based on the degree of affectedness (as captured by the count of microcephaly cases in Brazil) and are accordingly highlighted below.



HIGH RISK: North-eastern region most impacted with highest microcephaly cases

MODERATE RISK: Other regions with lower microcephaly cases reported

LOW RISK: Other regions with lower microcephaly cases reported

Fig: Distribution of microcephaly cases associated with Zika virus in Brazil (863 cases)

Alternatives to be implemented

Region of Brazil	Risk	Alternatives to be implemented
North Eastern Region of Brazil	**HIGH**	• Effective Vector Management (Best alternative) • Research • Public Health Risk Communication
Other regions with lower number of microcephaly cases reported)	**MODERATE**	• Effective Vector Management • Public Health Risk Communication
Other regions with lowest number of microcephaly cases reported	**LOW**	• Public Health Risk Communication

Rationale behind Choice of Alternatives

- **HIGH RISK REGIONS:** Given the spread of disease has been so enormous in the north eastern region of Brazil, implementation of only Effective Vector Management (best alternative worked out) might lead to sub-optimal result. It can be best contained when all the three alternatives are implemented simultaneously so to not only contain the spread but also treat existing patients. Hence high risk regions would be better upon implementing:
    a. Effective vector management (Government to invest major amount of time, money and efforts)
    b. Research (To be simultaneously implemented for best results)
    c. Public Health Risk communication (To be simultaneously implemented for best results)

- **MODERATE RISK REGIONS:** Research is an alternative which is expected to be executed at a more centralized level and hence would be less amenable to geographical/risk based differentiation. Once a successful vaccine/drug is invented, depending on its supply, it could be made available to all the affected regions. Hence medium risk regions would be better upon implementing:
    a. Effective vector management
    b. Public Health Risk communication

- **LOW RISK REGIONS:** Considering the attributes of microcephaly cases, economic impact and funding requirement, Vector Management turned out to be the best alternative. But as the number of microcephaly cases is low in this region, it does not require implementation of Effective Vector Management. However, Public Health Risk communication is required to communicate the risks associated with zika virus to general public to keep them aware and targeted audience (particularly pregnant women or travelers) to take precautionary measures and dispel rumors. Thus, low risk region would be best catered by implementing:
    a. Public Health communication

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