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Outbreak Severity Index: The International Response to the Global Outbreaks

Mohamed A. Abofaye
University of Kentucky

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Mohamed A. Abofaye, Student

James Holsinger, Jr., MD, PhD, Committee Chair

Dr. Richard Ingram, Director of Graduate Studies

OUTBREAK SEVERITY INDEX

Mohamed A Abofaye

The College of Public Health

University of Kentucky

2015

OUTBREAK SEVERITY INDEX

THE INTERNATIONAL RESPONSE TO THE GLOBAL OUTBREAKS

ABSTRACT OF CAPSTONE

A Capstone project submitted in partial fulfillment of the
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College of Public Health
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By:
Mohamed A Abofaye

Lexington, Kentucky

Director: Dr. James W Holsinger Jr.
Lexington, Kentucky

ABSTRACT OF CAPSTONE

OUTBREAK SEVERITY INDEX

Outbreaks are emergency situations that carry hazards of death, disability, loss of home and property, and variety of other calamities. With technological advancement, not only people and commodities are easy to transfer but also disease outbreaks. However, outbreaks are dealt with by different countries based on the differences in their healthcare systems and their ability to achieve effective control of the outbreak. SARS, MERS, and Ebola are example of such outbreaks that traveled around the globe and successful control was different according to the virulence of outbreak agent and to the effectiveness of local health system control measures. This capstone project proposes an outbreak severity index as an outbreak evaluation tool. The aim of the evaluation tool is to examine the severity of any emerging outbreak and to coordinate prevention and control efforts accordingly both locally and globally. Application of the outbreak severity index of SARS, MERS, and Ebola demonstrates that the score for SARS, MERS, and Ebola are 5.42, 5.36, and 5.0 respectively on a 10.0 points scale. This result indicates that SARS, MERS, and Ebola are moderate severe

outbreaks. With this result, public health practitioners have an objective measurement tool to advocate for allocation of resources and for justifying preventive procedures. Validity and reliability are not tested, which would lead to acceptance of this evaluative approach and help in building consensus. Additional studies are needed to assess the proposed outbreak severity index.

KEYWORDS: (Outbreak, severity index, global outbreak, SARS, MERS, Ebola, healthcare system, assessment tool, WHO, advocacy, global health, international cooperation)

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Mohamed A Abofaye

College of Public Health

University of Kentucky

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First, I would like to express my sincere thanks to my advisor Dr. James Holsinger for his support and guidance since I started the DrPh program at University Of Kentucky throughout the work of this capstone. Also, I would like to extend my thanks to the committee members; Dr. Sam Matheny and Dr. Martha Riddell for their feedbacks and guidance.

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CHAPTER 1

INTRODUCTION

Background:

Global disease outbreaks are not uncommon devastating events. Some of these outbreaks have been severe enough to destroy national civilizations [1]. The known history of outbreaks goes back 25 centuries to ancient Greece with the devastating outbreak of the Plague of Athens [2]. Other more recent examples include the black death in Europe that started in the 14th century and lasted for several centuries in an on and off manner, which lead to a high mortality rate of 20% or more in some episodes [3]. The 1918-1919 flu pandemic was the most devastating disease outbreak in the modern era with more than 50 millions death around the world [4]. The list of global outbreaks is long and the outbreaks vary in severity and in their social and economic consequences.

The 21st century is no exception to history. Many global outbreaks have occurred over the last two decades such as SSRS, Mumps, the 2009 flu pandemic, MERS, Ebola, and others. The contemporary global situation provides ease of transportation, free markets policies, wide developmental gaps between regions and nation states, terrorism and potential international conflicts, availability of technologies for legal and illegal use, and other factors that make outbreak control more challenging.

Strategies for fighting outbreaks are vary widely between different national healthcare systems according to wealth, sovereignty, and scientific capabilities. However, a failure of a local healthcare system is threatening not only to the local population but also to neighbors or the entire world population. Such a potential threat requires the international community to cooperate in the outbreak controlling process. International cooperation is not straightforward intervention. Reasons that making international intervention difficult include:

1. Local systems may not able to accommodate international aid due to absence of basic infrastructure.
2. Political sensitivity to allowing foreign intervention with possible unknown hidden agendas.
3. Attitude of some poor countries to shift the cost of outbreak control to the international community.
4. Advocacy weakness in the field of outbreak control especially when outbreaks emerge in poor countries.
5. Absence of a specific international apparatus that collects and distributes aid. Despite the efforts of WHO and other international agencies, this kind of emergency may need a more robust apparatus.
6. Absence of definition and criteria for global disease outbreaks that require international involvement.

International intervention needs to be legitimized in those countries requesting support or in those countries refusing to cooperate. The road to

repairing international agencies or establishing a new international agency to serve global outbreak control starts with the definition of a global outbreak by efficient assessment tool. It is obvious that not all outbreaks need international involvement. However, public health globally does not have an efficient tool to determine if a severe outbreak requires international attention.

Purpose of the capstone:

The purpose of this capstone is to develop a disease outbreak severity index. This index will be utilized to evaluate the virulence of the outbreak agent, transmissibility, characteristic of local population, performance of local health system, and other factors. The outbreak severity index is a dynamic tool that would serve in the evaluation of an outbreak early in its emergence and during the follow-up period. The score of outbreak severity index will be used in determination if the outbreak is severe enough to launch urgent protective measures and to advocate for external intervention.

Current global public health practices depend on mortality rates and other indices that are utilized by non-professional media for evaluation of disease outbreaks. Recent history has shown that global outbreaks may be affected by many factors that need to be taken in consideration. The goal of proposing such a measurement tool is to reach a global consensus that makes public health practice function at its highest capacity in order to enhance outbreak evaluation and control. The process of assessment tool development will require more evaluation prior to its adoption. However, this proposal aims to initiate the

process of thinking about the importance of an outbreak assessment tool whether this particular measurement tool is adopted or not. The outbreak severity index will require additional development to enhance its validity and reliability prior to its adoption.

Statement of the problem:

Outbreaks as disasters that affect much larger sections of the population than most of common natural disasters have no unified or integrated assessment tools to measure the outbreak's severity and that can be utilized to initiate an appropriate mitigation process. Global public health practices depend on different models of the assessment process taking social and political circumstances into consideration. Such circumstances may delay many preventive and assistance efforts. An outbreak severity index should fill this gap in appreciation of such calamities.

Overview of project process:

This capstone project is a descriptive study. Some of the global outbreaks that occurred in the last few years were selected to be reviewed; including SARS, MERS, and Ebola. These outbreaks were selected due to their global impact and because they occurred in different areas of the world with different healthcare systems. The review of these outbreaks was from public health perspective. The next step was to review the literature to identify the factors that lead to emergence and spread of each outbreak. Identification of important factors was followed by standardization of each factor. The last step was the development of

a scoring system for these factors (indices) and evaluating these three outbreaks according the new scoring system. The end result of this evaluation is a score that is associated with each outbreak to indicate its severity in a comprehensive and integrated manner.

Scope and importance of the study:

The outbreak severity index is theoretically applicable for any outbreak. However, the assessment of an outbreak is a dynamic process and takes the evaluator's prospective into consideration. It will take the process of outbreak evaluation to higher objective and a structural level. It is not a mathematical test, but rather an appropriate model that will unify global public health activists in asking for improved processes in dealing with outbreaks that threaten the lives of an uninformed population and direct assistance to where it is mostly needed. It would also limit the effect of political and diplomatic professionals dealing with such disasters.

The outbreak severity index is a new approach that should be adopted by the global public health community to gain credibility. This process will require additional studies and efforts to build a consensus for such a measurement tool. Testing the validity and reliability of the outbreak severity index is one of the main challenges. Some of indices of the outbreak severity index may carry greater importance than others to be counted as equal. However, the outbreak severity index is an integrative approach rather than a partial evaluative approach. Interpretation and availability of information may also be considered issues

CHAPTER 2

LITERATURE REVIEW

Description of recent global outbreaks:

1- SARS:

Severe Acute Respiratory Syndrome (SARS) was recognized in Guangdong Province in China in 2002 for the first time [5]. The first known case occurred in a physician from Guangdong Province, who after visiting his family in Hong Kong, was admitted to ICU with respiratory failure after five days of symptoms [6]. The infection spread to 30 countries around the world predominantly through air travel [7][8]. The World Health Organization (WHO) issued a global health alert in March 2003. By June 2004, 8,447 cases of SARS had been identified with 813 deaths (9.6 % mortality) [5].

Symptoms:

SARS is predominantly a respiratory disease occurring as a form of atypical pneumonia [9]. The WHO defines suspected cases as a person with documented fever (temperature >38^{o}), symptoms of lower respiratory tract infection, and contact with a SARS patient or patient with travel history to an area of documented transmission. However, a probable case was defined as a suspected case plus chest radiological findings of pneumonia or Acute Respiratory Distress Syndrome (ARDS), or death from an unexplained respiratory illness with autopsy findings suggesting ARDS [9]. Fever was the

most common symptom at presentation, since all patients had a fever (>38^{o}) at the time of presentation [10][11]. The fever could reach up to 40^{o} [11]. Myalgia and weakness were also present in almost all patients. Dry cough and dyspnea were evident in most of the patients [11]. Other symptoms include headache, nausea, arthralgia, dizziness, chest pain, diarrhea, and sore throat [11]. Many patients were suffering also from anxiety and depression [10].

Mode of transmission:

The spread of SARS was mainly person-to-person [12]. The route of transmission is through direct contact with the body's mucus membranes with transmission by droplet or other fomites [13]. Transmission occurs when a person is exposed to a very ill SARS patient such as a family member or health care workers. Also intense exposure to a SARS patient in places such as airplanes or work places may carry the same hazards [13]. The arousals transmission such as the transmission of measles or influenza is another possibility. However, the reproduction number (R_0) was three, which was more consistent with direct contact or a thick and large droplet mode of transmission [13]. Another important factor was the aerosolizing procedures occurring at hospitals that might increase the risk of transmission. Other modes of transmission such as the fecal-to-oral route were suspected since significant number of SARS patients had diarrhea. However, the possibility of environmental contamination as a transmission route was another challenging and interesting factor. A study in Hong Kong had used the spatial distribution of outbreak cases and modeling of airflow dynamics to investigate the possibility of airborne

transmission of SARS [14]. The study concluded that exposure to a common source is another possibility for transmission rather than person-to-person contact; the sewage system could be the common source. The study noted that security and shopping mall workers did not register a single infection. However, many residents in other units and buildings were infected early in the peak of the outbreak.

An animal reservoir was an important issue not only to determine the source but also to control the outbreak. The SARS-coronavirus was thought to be initiated from animal origin and recently crossed from these animal reservoirs to infect humans. However, many animals including the Chinese ferret-badger, beaver, domestic cat, hog badger, Himalayan palm civet, and raccoon dog from the live-animal market in Shenzhen were tested [15]. The study focused on these animals due to early reports indicating a higher incidence among restaurant workers handling wild mammals. The study succeeded in identifying SARS- like coronaviruses from the raccoon dog and palm civet that were genetically almost identical. The possibility of transmission could not be excluded. The study concluded that these animals might represent the intermediate host but not the natural reservoir. Bats have been identified as a reservoir for many coronavirus species [16]. However, the strain of coronavirus identified in the horseshow bat (Rhinolophus) suggested that bats in general were a natural reservoir for the SARS-like coronavirus despite the slight difference, which could be explained by recombination to increase genetic diversity and fitness [16].

Diagnosis:

The diagnosis of SARS relies primarily on clinical suspicion [17]. The clinical features which suggesting the SARS diagnosis are numerous. However, the context of the outbreak's time and place plays a significant role. Following the outbreak in Canada, a directive approached was proposed. A study of 273 laboratory-confirmed SARS patients was conducted to explore the clinical manifestations and source of infection in Canada [17]. Exposure to ill patients in health care facilities occurred in 80% of confirmed cases followed by 17% in the household exposure to SARS patients. A history of travel was associated with only 3 of those exposed. Respiratory symptoms such as a cough and dyspnea were associated with less than 60% of confirmed cases. Pulmonary infiltrates and blood cell count abnormalities such as lymphopenia and thrombocytopenia at admission were associated with confirmed cases. Symptoms and signs of a common viral upper respiratory tract infection such as rhinorrhea and a sore throat were associated with excluded cases. The study concluded that in absence of a fever and a significant history of exposure, SARS was unlikely.

The incubation period for SARS is a maximum of 10 days [18]. However, it ranges from 2-10 days [19] and with a mean of 6-7 days [20]. This relatively long incubation period mandates an efficient and rapid means for early detection and diagnosis. Reverse Transcription- Polymerase Chain Reaction (RT-PCR) is a mainstay diagnostic tool during the illness [20]. However, it is affected by the type of sample (plasma, nasogastric aspiration, stool, or other) and also by the viral load. The viral load is influenced by the replication activity of the virus in the affected tissue and tends to be more evident in the second week of illness,

making a false negative result significant concern. Testing SARS antibodies in a clinical sample could be used as a screening method especially after it was made available by the WHO. Enzyme Linked ImmunoSorbant Assay (ELISA) and Immunofluorescence Assay (IFA) are examples of the antibodies detection test. The limitations of these tests are their low negative predictive value and the fact that seroconversion happened late in the course of the disease [21]. Isolation of the virus is time consuming and not widely available.

Treatment:

The treatment strategy could be divided into drugs targeting the coronavirus itself through eradication or reducing its activity, reduction of the inflammatory response by the body, and/or by general supportive measures. Antiviral drugs were utilized to deactivate the coronavirus. The usage of antiviral drugs may be more effective if it is utilized in the replicative phase before the damage occurred [22]. Ribavirin was chosen as the drug of choice due to its broad-spectrum activity against coronaviruses in general [23]. However, ribavirin did not show viral growth inhibition in laboratory tests with the dose commonly utilized [24]. Anemia and cardiac and liver toxicity were the major adverse side effects [25]. Protease inhibitors, another group of antiviral drugs, were tried. The combination of Lopinavir, and ritonavir were used, since they had shown efficacy against HIV due to synergistic characteristics [23]. This combination had better survival outcomes and lower side effects [26]. Reduction in the immunological response by corticosteroid was the second strategy during the immunopathological phase. SARS had shown a massive immunological

response that led to massive tissue damage [27]. Also, CT scan of SARS patients commonly demonstrated a Bronchiolitis obliterans organizing pneumonia (BOOP) [28], a condition that is characterized by bronchiolitis obstruction due to inflammation, which is responsive to corticosteroids. However, use of corticosteroids is almost always a controversial clinical issue. On the one hand, the use of corticosteroid would reduce the destructive immunological response, and on the other side reduce the body's resistance to the invasive microbe and thus increase its activity and replication. Many corticosteroid regimens with high and low potent steroid were tried, but it seems that the use of corticosteroids would be dictated by the individual patient's situation specially those approaching respiratory failure [23]. Convalescent plasma was also used with corticosteroids in many patients. The convalescent plasma is plasma that has been taken from recovered patients and then injected into sick patients to obtain the advantage from the antibodies that have been formed during the sickness of the donators. A retrospective study with a small group of patients produced a better outcome [29]. Intravenous immunoglobulin also has been utilized for very sick patients [30]. Supportive measures are those interventions that improve the general condition of the patient such as feeding, breathing, and circulation. SARS is mainly a respiratory disease and lung failure is the worse consequence that may lead to death. Securing efficient ventilation is crucial intervention used to prevent patient deterioration. Noninvasive positive pressure ventilation (no intubation) was shown to be effective in treating patients with acute respiratory failure and it was used particularly for health care workers [31]. However, due to fears of

spreading the infection by this aerosol procedure, it has been banned in some countries [23]. Invasive mechanical ventilation is the only choice when the patient has deteriorated and respiratory failure is evident. Other new treatment modalities such as interferon had been tried and shown some efficacy [32].

Fatality:

Six months after the emergence of this novel disease, the WHO updated the fatality rate of SARS [18]. The overall fatality rate was estimated to be from 14 to 15 %. However, this rate has a wide range from 0 to 50%. Age was the main factor affecting the fatality rate. In 24 year old or younger patients, the fatality was less than 1%, while in patients older than 64 years; the fatality rate was 50%. The presence of another disease was another determent factor. Differences occurred between health systems around the world. The Australian and American fatality rate was 0%. However, in Canada, China, and Hong Kong, fatality rates were around 15% [8].

Prevention:

The transmissibility of SARS is much less than other viral diseases with respiratory transmission such as influenza. The reproductive number of single SARS case was estimated to be around 3 cases in the presence of control efforts [33]. However, in the absence of specific control methods, SARS can spread much more widely. Early identification of cases, tracing of contacts, isolation, and quarantine are the crucial control strategies. The ideal control method would be the development of an effective vaccine, which has not been achieved [34].

In March 2003, WHO issued an emergency travel advisory [35], composed of general instructions about direct contact with SARS patients. In April 2003, WHO issued another advisory, advising postponement of travel to Hong Kong, Beijing and Shanxi Province in China and to Toronto, Canada [36]. In July 2003, WHO lifted this restrictive advisory [37].

Legislative effort was used in some countries to enforce the commitment to the quarantine individuals at home. Singapore issued the Infectious Disease Act, which prohibited breaking home quarantine [38]. Schools were also closed and all other public gatherings were postponed. Home quarantine was strict and was under continuous surveillance by cameras installed in homes. Passengers were screened at airports. Taiwan established a number of military facilities to serve as locations for isolation [38]. The definition of a SARS case was expanded early in the outbreak due to uncertainty concerning SARS. This expansion of the definition led to unnecessarily isolation [39]. In addition, restriction on personal movement and traveling between different districts was utilized as a potential way to reduce the spread of the outbreak [33].

Healthcare workers were the group most affected by the SARS outbreak and protection of this group was vital not only for it, but also for the community being served. N95-mask wearing, gloves and gowns, and hand washing were the main precautionary measures used by healthcare workers, which demonstrated their protective advantages [40]. Other strict surveillance approaches for healthcare workers were implemented. Streamlined workflow at hospitals and fever screening twice a day were examples for these measures [41]. Extra

precautions were applied for some healthcare workers, such as anesthesiologists, who were involved in invasive procedure [42].

2- MERS:

Middle East Respiratory Syndrome (MERS CoV) was diagnosed first in the United Kingdom in September 2012 for a Qatari patient transferred by air ambulance from an ICU in a Qatari hospital. The virus was given the name of Novel Coronavirus (nCoV). It was compared with another coronavirus that was almost identical isolated from the lungs of Saudi patient who died in the Netherlands [43]. The WHO thought that this novel virus was different from SARS and was concerned about the coming season of pilgrimage (Hajj) as a serious opportunity for the virus to spread [44]. Two weeks after the first case was identified, WHO failed to find any evidence of human-to-human transmission [45]. Six weeks later in November 2012, four cases were reported from Saudi Arabia and Qatar in which two were family members [46]. In May 2013, the name of disease was changed to MERS-CoV, with a total of 44 patients mainly in Saudi Arabia being identified [46].

Symptoms:

MERS-CoV is mainly a respiratory disease. Despite the severity of this disease, it has been thought that it is a part of wide spectrum of symptomatology including a much milder form. Some patients did not require admission and some did not have respiratory symptoms initially [47]. In a study of 47 patients in Saudi Arabia, 98% had fever and fever was the most prominent feature [47]. However,

in other studies including 70 patients in Saudi Arabia, fever occurred in only 61% [48]. Cough, shortness of breath, and chest pain were present in the majority of patients [47]. Other symptom such as hemoptysis, headache, and myalgia were present in some patients. Gastrointestinal symptoms such as diarrhea, nausea, and vomiting were also evident in some patients and were the initial symptoms in the case that occurred in France [47].

The majority (89%) of patients required mechanical ventilation. Also, the majority (96%) of patients had comorbid diseases [47]. In the first cluster outbreak in Al-Hasa, Saudi Arabia, the median incubation period was 5.2 days and majority of patients had an incubation period of 12.4 days [47]. Thrombocytopenia and lymphopenia, hematological abnormalities, were identified in almost one third of the patients. Also, Liver enzyme abnormalities were identified in less than half of the patients. Almost all patients had abnormal chest radiographic studies [43].

Mode of transmission:

MERS-CoV has been isolated from camels in many Middle Eastern countries including Saudi Arabia, Qatar, Egypt, and Oman. The close relationship between the geographical area of these animals and rate of disease occurrence was linked. It had been shown that people working in close contact with camels are at higher risk of infection with this novel virus [49]. Other animals such as goats, cows, sheep, water buffalo, swine and wild birds were tested for this virus with negative results [45]. However, a close strain of MERS beta-coronavirus was isolated from bats in South Africa [50]. It is interesting that less than 40% of

MERS patients reported contact with camels [51]. Also, most of infections among camels are asymptomatic or occur with mild respiratory symptoms. These facts make speculation of widespread infection among camels not only in the Arabian peninsula but even to Africa a significant concern [51]. Human-to-human transmission was limited to family members and healthcare workers, which made the assumed transmission route to be difficult between humans [52]. The role of secondary transmission in household with MERS was very limited, and estimated to be approximately 5% [53].

Diagnosis:

The WHO recommends collection of specimens from the upper and lower respiratory tracts. However, collection of sera should be performed in the first 14 days after disease onset [54]. Real Time-Reverse Transcription Polymerase Chain Reaction (qRT-PCR) is the main method to diagnose the disease among patients [50]. qRT-PCR has to be detected in at least two specific targeted genomes to be considered positive. However, serological tests are available that are mainly used for screening purposes. ELISA, or enzyme-linked ImmunoSorbant assay is the first test in the series of serological tests utilized. Positive ELISA should be confirmed by immunofluorescence assay (IFA), or by microneutralization assay [55].

The clinical picture and contact history should determine the need for screening. However, WHO defines a confirmed case as a patient with confirmatory laboratory test regardless of the clinical picture [56]. A probable case is one with suggestive for pneumonia or acute respiratory distress, and a

history of travel to the Middle East or a history of contact with a confirmed case of MERS [56]. However, other studies suggested that the onset of the disease would occur after two days of arrival from the Middle East unless a strong history of contact to MERS patient had occurred [57].

Treatment:

The treatment of MERS should begin early when suspicion of MERS is in the list differential diagnosis. The clinical features that suggest severe pneumonia or acute respiratory distress syndrome with no other explanation should be treated seriously as MERS. The first measure is the isolation of the patient with droplet precautions. Supportive measures such as oxygen and fluid therapy are the mainstay of treatment. WHO recommends prompt oxygen therapy that can be administered through invasive or noninvasive procedures. Clinicians should not hesitate to start mechanical ventilation to insure a good blood oxygen level [58]. Also, antibiotics are recommended until the diagnosis of MERS is confirmed [58]. Antiviral therapy, such as ribavirin and oseltamivir is not beneficial [58]. However, a combination of interferon and ribavirin was thought to have therapeutic and prophylactic effects [59][60]. Although ribavirin may produce the best outcome, the high prevalence of toxicity such hemolysis limits its use [61].

Fatality:

In January 5, 2015, the total incidence of MERS cases was 828 cases [62]. The total number of deaths was 357, representing a 43% mortality rate. The mortality rate was 21% in United Arab Emirates [63]. Despite the increase in the

incidence of MERS in 2014, the mortality rate decreased from 60%, a rate reported by WHO in mid 2013 [64].

Prevention:

The MERS outbreak has been dealt with mainly by containment, since there is neither an effective vaccination nor a specific treatment. Containment is centered on isolating infected patients in order to break the transmission cycle, which involves no other mode of transmission such as zoonotic transmission. CDC recommends the use of an airborne infection control room as the gold standard for treatment; otherwise, the patient should wear a facemask. Adherence to Personal Protective Equipment (PPE) should be strictly required especially during aerosol procedures such as intubation or tracheal lavage specimen collection [65]. A containment strategy among contacts is another important factor to limit the spread of this outbreak. Strict recommendations were proposed for health workers who were exposed to MERS patients especially those who did not wear PPE. Medical evaluation, and immediately stopping work are part of these recommendations. Also, screening and education of visitors were recommended [65].

3-**Ebola:**

Ebola is one of the viral hemorrhagic fever diseases. The present outbreak in West Africa is not the first Ebola outbreak, which has been preceded by several others; the first known outbreak was in 1976 in Sudan and Zaire. However, other less significant outbreaks occurred in the late seventies of the last century in Sudan, and Zaire. In 1990, the few asymptomatic cases identified

in the United States, were attributed to monkeys imported from Philippines. In 1994, Gabon was stricken by an Ebola outbreak, and outbreaks were discovered between 1995-1996 in Gabon, Congo, and the Ivory Coast. Also, many laboratory incidents occurred in England, Italy, and Russia during the same period. Ebola was undetected until another series of significant outbreaks was identified in Uganda, Republic of Congo, and South of Sudan between 2000 and 2004. Another wave of outbreaks occurred between 2007 and 2009 in the same West African countries. Succeeding outbreaks were limited and controlled in these countries until the disastrous outbreak of March 2014 in Guinea, Liberia, and Sierra Leone. This outbreak was accompanied by a relatively limited outbreak in Central Africa in the Democratic Republic Of Congo [66]. To date, the 2014 outbreak in West Africa is the most severe and long-lasting Ebola outbreak [67].

The Ebola virus is a single-strand RNA virus belonging to Filoviridae family, which contains Ebolavirus, Lloviu virus, and Marburgvirus. The Ebola virus has been divided into five strains according to genetic and antigenic properties: Sudan (EBOV-S), Zaire (EBOV-Z), Tai Forest (EBOV-TF), Reston (EBOV-R) and Bundibugyo (EBOV-B) [67].

Symptoms:

The clinical manifestations are similar to those of viral hemorrhagic fever. Generalized weakness was the most prominent clinical feature, occurring in 80% of the patients followed by fever in 78% of patients [68]. The clinical features may vary depending on the strain of the Ebola virus causative the infection [67]. Also,

the clinical features and outcomes differ according to the level of viremia. The non-survivor tend to have 100-1000 folds of viremia when compared to the survivors [69]. The clinical manifestations were divided into three phases: (1) Early onset, which presents similarly to influenza. (2) Involvement of the gastrointestinal tract. (3) The late stage is characterized by hemorrhage, multiple organ failure, and rapid clinical decline [70]. In the early stage fever, chills, and myalgia are the main symptoms. Lethargy, cough, headache, anorexia, diarrhea, abdominal pain, vomiting, and hypotension follow these symptoms [69]. . Hemorrhagic symptoms do not always occur and it was observed in only 26% of patients in an Ebola treatment center in Conakry [68]. Hemorrhagic manifestations include bruising, epistaxis, bleeding from venipuncture sites, and bleeding from the gastrointestinal and urinary tracts [69]. Tachypnea, shock, and coma are the hallmarks of the late stage along with imminent death and massive necrosis in many organs such as the liver, spleen, and kidneys [69].

Mode of transmission:

The early Ebola outbreak was thought to be transmitted by unsafe injections in Zaire in 1976 [71]. However, the major route is the exposure to the Ebola virus through mucosal surfaces, abrasions or injuries to the skin, or parental transmission [72]. The transmission of Ebola tends to occur more often in the late stage of the disease than during the incubation period and asymptomatic patients pose little threat of transmission [73]. During the outbreak in Uganda in 2000-2001, contact with patient's fluids had the strongest association with development of the disease. However, physical contact with

patients was associated with transmission of the disease more often than touching deceased patients. Also, sleeping on the same mat and participating in hand washing during funeral ceremonies were associated with transmission of the disease [74]. Another study carried out in the Democratic Republic of Congo during the 1995 outbreak demonstrated almost the same pattern of transmission. An increment of risk ratio was observed for those exposed to infected patients during the late stage of the disease. The greatest contact risk occurred by touching patients [75]. The aerosol pathway is another potential route of transmission, which was documented in an animal experimental model [76].

Tracing of transmission routes is complicated by the fact that asymptomatic individuals are present. Individuals who were exposed to an ill patient and did not develop symptoms were identified in Gabon in 1996. A study of 24 individuals with close patient contact found that 11 had a positive immunological test for Ebola [77]. Also, Ebola virus antibodies were found in asymptomatic individuals inhabiting the tropical forests of the Central African Republic. The prevalence of positive antibodies was more evident in hunter-gathers than in farmers [78].

The reproductive number (R_0) is the “average of number of successful offspring that the organism is capable of producing, in the absence of crowding and other density-dependent effects” [79]. It takes in consideration that everyone is susceptible regardless of other factors. The R_0 was estimated to be 2.7 from the two outbreaks in Africa in 1995 and 2000 [73]. The disease reservoir raises an interesting question despite knowing that the reservoir is less important than

understanding the dynamic of transmission [79]. The examination of carcasses of wild animals, which was performed between 2001 and 2003 in Gabon and Republic of Congo, found positive serological evidences that gorillas, chimpanzees, and duikers had been infected by the Ebola virus [80]. Another survey of the Ebola virus, which was performed in Cameron, Gabon, and Republic of Congo, estimated the seroprevalence rate among wild chimpanzees to be 12.9% [81]. The presence of this rate among wild animals suggests a form of non-lethal disease. However, deaths among certain species such as gorillas and chimpanzees were attributed to infection with Ebola, which was considered as the source of outbreaks in Central Africa [82]. These deaths resulted in an effort to find the real reservoir in wild species. Following the outbreak in Democratic Republic of Congo in 1995, 3066 vertebrates were tested for the Ebola virus (Zaire subtype). The selection of these animals was based on exposure history and the presence of animals in a specific habitat. The result was negative [83]. More than 400 bats among other animals were tested in Democratic Republic of Congo at the site of 1976 outbreak, and it failed to demonstrate any evidence of Ebola antibodies [84]. However, in an incremental inoculation of Ebola virus a variety of species including fruit and insectivorous bats, bats supported the replication and circulation of a high titer of the virus [85]. 1390 bats from different species were collected between 2003 and 2006 from endemic and non-endemic areas in Gabon and Democratic Republic of Congo, demonstrating that 5% of these bats were infected. That rate declined to 1% following the outbreak, indicating a role of bats in transmission of the virus [86].

Fruit bats were tested in West Africa and followed by fitting with a radio transmitter. After 13 months, the infected bats demonstrated long-term survival [87].

Diagnosis:

Ebola is a disease that shares many clinical symptoms with other diseases such as typhoid fever and malaria especially in the endemic area. Clinical suspicion of suggestive symptoms and travel history is crucial in the diagnostic process. The main limitation of many specific diagnostic tools is that they are unable to detect the virus before the onset of symptoms, which makes them useless as screening tools [88]. There are many specific diagnostic tools for Ebola hemorrhagic fever. Antigen-capture enzyme-linked immunosorbent assay (ELISA) testing, IgM ELISA, Reverse Transcription-Polymerase Chain Reaction (RT-PCR), Virus isolation, IgM and IgG antibodies, and immunohistochemistry testing are examples of these specific tools [89]. Viral isolation is the gold standard diagnostic tool. However, this procedure poses a very high level of hazard. It is also very difficult and needs a high level of expertise and technology. The shipment of infected specimens from endemic areas to well-developed laboratories demands safety procedures and certain important requirements such as cool chain. Electron microscopy is fast and sensitive especially when aggregated with immunological antigen. It can examine many types of specimen such as serum, a thin section of the infected material, and cultural fluid. The main limitation is the cost and level of expertise required. A minimum number of viruses to be visualized is also a limitation. Antigen-capture

ELISA is specific diagnostic tool. Animal antibodies, which can be used for antigenic capture, have been developed for many Ebola virus strains. ELISA is under development and appears to be a very promising diagnostic tool. Currently the most widely used diagnostic tool is the real-time RT-PCR due to its simplicity and sensitivity. It is more specific than ELISA especially when specific dye is used. Obtaining the results of the RT-PCR test takes about 2-3 hours. With the development of specific premiers and props, RT-PCR is the test of choice to confirm the diagnosis. Continuous mutation and emergence of a new viral strain may be a source of concern regarding the diagnostic use of RT-PCR [90].

Treatment:

Currently, there is no standard of treatment and the treatment occurs mainly through the use of supportive measures [91]. CDC recommends fluid and electrolyte replacement, maintenance of blood pressure and oxygen status, and treatment of secondary infections as supportive measures [92].

Antibody therapy was tried in 1995 during the outbreak in the Democratic Republic of Congo. Plasma from Ebola survivors were transfused to eight infected patients, half of them complaining of hemorrhagic manifestations. Only one of these eight patients died, a death rate much lower than that seen in previous outbreaks, which was 80% [93]. This plasma transfusion procedure contains clotting factors beside the antibodies, which could reduce the severity of hemorrhage [94]. However, the sample size was very small. Plasma transfusion carries the hazards of transfusion reaction and transmission of other pathogens. Monoclonal immunoglobulin G (IgG) was tried in animals. Six monkeys were

treated with equine IgG and showed a limited beneficial effect in viral load and delay of death [95]. Other trials of single monoclonal antibodies were unsuccessful; however, they lead to the concept of a cocktail of multiple monoclonal antibodies therapy [94]. Two IgG were administered in monkeys before and after inoculation of Ebola virus, showing protective benefits before the decline of circulating IgG [96]. This procedure indicated the need to prolong the half-life of antibodies. Unlike in the case for Ebola patients, it was administered before the infection. New generations of cocktail antibody therapy such as ZMAb and MB-003 were introduced in animal models. MB-003 had shown a protective effect approaching 70% when injected on the first day after inoculation [97]. However, ZMAb showed 100% protection when administered 24 hours after inoculation and 50% when administered 48 hours after inoculation [98]. ZMaap is a promising treatment for infected animals with a specific combination of IgG from ZMAb and MB-003, demonstrating 100% protection. The promising factor is that ZMaap was administered in animals after the appearance of symptoms such as fever, abnormal blood counts, and hemorrhage [99]. These animal trials occurred with small sample sizes and no randomized controlled clinical trials have been conducted.

Antiviral drugs are another treatment strategy. In addition to its side effects profile, ribavirin did not show activity against the Ebola virus [100], and Lamivudine did not show a decrease in mortality in Ebola patients [91]. Favipiravir, a new and promising drug, is a broad-spectrum antiviral drug,

developed in Japan for influenza. It has demonstrated100% protection against aerosol Ebola in an animal model [101].

Fatality:

By January 23, 2015, the total number of confirmed cases of Ebola was 13,602 with a total of 21,797 cases including non-confirmed cases in Guinea, Liberia, and Sierra Leone. The total number of deaths was 8,675 (64%) [102]. The outbreak in Central Africa was limited and is considered to be over. The mortality rate differs among these countries with a rate of 40% in Sierra Leone, 60% in Guinea, and 70% in Liberia [103]. Over time the fatality rate changed from a fatality rate of 47.7% to one of 31.5% [104]. The total number of cases was less than 2000 in any of the three countries in West Africa in October 2014. However, by end of January 2015, the total number of confirmed cases increased to approximately 11,000 in Sierra Leone, approximately 9,000 in Liberia, and 3000 in Guinea. The fatality rate in the previous outbreaks starting in 1976, with the exclusion of outbreaks that had single patient, had a wide range from 15% to 88% [66].

Prevention:

According to WHO, the incubation period is estimated to be between 2 and 21 days [105]. However, the incubation period appears to have shorter range. In a study in Sierra Leone, the estimated incubation period was 6 to 12 days [106]. Another larger study conducted in Guinea estimated the average incubation period to be 11.4 days [107].

Vaccination against Ebola could be a significant step in the containment strategy. However, there is no approved vaccine available. There are two candidate vaccines, cAD3 and rVSV [108]; cAD3 vaccine is in phase 1 trials and rVSV has shown protection against lethal infection of the virus in non-human primates [91]. In the absence of an effective vaccine, CDC recommends the following:

- Avoidance of contact with blood and body fluids.
- Avoidance handling items that may have come in contact with an infected person's blood or body fluids.
- Avoidance of contact with bats and nonhuman primates or blood, fluids, and raw meat prepared from these animals.
- After you return, monitor your health for 21 days and seek medical care immediately in case of Ebola symptoms have developed [109].

Common Criteria of Outbreaks:

The last decade raised the challenge of the new outbreaks that were difficult to treat and to contain. WHO defines outbreak as an "occurrence of cases of disease in excess of what would normally be expected in a defined community, geographical area or season" [110]. An outbreak is not defined by a specific number of cases; rather by the presence of an increased number of cases in a specific time and place.

Outbreaks have many factors that lead to their emergence. The Institute of Medicine Committee on Emerging Microbial Threats to Health in the 21st Century explored some of these factors [111]. The committee proposed a model of four factors interacting to produce an outbreak, including:

1. Genetic and biological factors.
2. Physical environmental factors.
3. Ecological factors.
4. Social, political, and economic factors.

These factors serve as fundamental factors that interact together in different intensities and directions. However, based on this model, the report proposed the following factors that are associated with one or more of these fundamental factors:

- *Microbial adaptation and change:*

  Microbes are widely present in the ecosystem. The relationship between humans and microbes are not always a threat, but in many instances beneficial to both parties [112]. Adaptation and change is a continuous process that assists in the survival of microbes according to the environment in which they live. One of the important examples is the influenza virus, which changes in each cycle of emergence. Such a change mandates a change in vaccine every year. The adaptation could be a result of genetic mutation or inclusion of new segments of DNA or RNA. Despite the limited size of the viral genome, the plasticity of this

genome to accommodate new segments and expand or shrink is evident in the RNA virus [113]. This accommodation could result in new genera with different characteristics. On the other hand, bacteria have many known ways of acquisition of new genetic material, including transformation, transduction, and conjugation [114]. Adaptation and change are vital methods for prokaryotic cells to survive. However, the changes accompanied by acquisition of new genetic material could be devastating to the host.

Coronavirus in general has undergone a similar genetic adaptation making them pathological to humans. No new major changes in the indigenous population in the consumption of or contact with the suspected animals were observed or reported before the emergence of SARS or MERS in East Asia or the Arabian Peninsula respectively. Ebola on other hand has a more interesting history. More than ten major outbreaks have occurred in Africa with different fatality rates and different viral strains. The adaptation process should not be ignored when trying to understand the variability in each outbreak.

- *Human susceptibility to infection:*

According to the IOM report, many factors such as impaired host immunity, genetic polymorphism, aging, and malnourishment contribute to human susceptibility to infection. Human immunity is a very complex process and it is composed of physical and chemical barriers. The immune response after passing these physical and chemical barriers is

composed of cell-mediated and humoral-mediated responses, both of which are subject to regulation that is affected by previous exposure to any specific microbes. Genetic polymorphism such as that in sickle cell anemia or thalassemia is believed to be a protective adaptation to specific exposure to malaria. The genetic adaptation makes specific populations less susceptible to certain infections. Malnutrition is associated with a higher susceptibility to infection. The reverse relationship may also be true in which an infection that causes diarrhea as an example may lead to malnutrition.

- *Climate and weather:*

  The weather plays an important role in the transmission process that involves vectors, animal reservoirs, microbes, and humans. There are many physical elements included in changes of the weather such as drought, rainfall, temperature, flood, wildfire, earthquakes, and others. The interaction of these elements at each level of the transmission cycle is different, and may lead to different outcomes. It has been predicted that influenza cases, as an example would be more prevalent in specific seasons than in others due to weather changes.

- *Change in ecosystem:*

  Environmental changes generally affect the pathogen and the host. Currently, ecology is changing at a rapid pace due to many factors such as global warming, forest loss, and other factors. These ecological changes will promote change in the population characteristics of the

pathogens and human exposure to them. Also, ecological change in the form of weather changes such as drought and increased rainfall would affect the abundance of vectors that transmit diseases and would lead to a different intensity of exposure. Although the ecological changes would affect a limited area; the effect of that change would have a widespread global effect. *Aedes aegypti* mosquito*,* which causes yellow fever and dengue fever, is an example of the change introduced to the New World through slave ships.

- *Economic development and land use*:

  Consumption of natural resources, deforestation, dam building, and other expansion projects in nature have led to increased contact between human and animal reservoirs. This change in land use by humans has resulted in the emergence of new outbreaks. Lyme disease in North America has been linked to reforestation in Northeastern and Midwestern USA, leading to an increase in the population of white-tailed dear, the definitive host of vector ticks. Another example is Schistosomiasis occurring after building dams in Senegal and Egypt for agricultural and industrial purposes.

- *Human demographics and behavior:*

  The demography of any given population plays a crucial role in the rate and susceptibility of infection. The IOM report includes four main factors that led to this increase in susceptibility due to demographic factors. Aging is one such factor. The world population is growing older due to success in

controlling many acute and chronic diseases and applying safety measures in many aspects of life. The physiological changes that accompany aging such as decreased capability of the immune system and reduction of gastric secretion makes aging people more prone to infection. The aging phenomenon is worldwide, but the developed countries represent 77% of the gain in the elderly population. Urbanization is another important demographic factor. There is a trend toward rural migration to cities in this century. 40 % the growth in the world's cities is due to migration from rural areas. Urbanization is more evident in the developed countries where 75% of the population lives in the cities. The influx of people into cities was poorly accommodated due to poor infrastructure and living arrangements. Overcrowded houses and living in a less developed part of the cities might be the only choice for the new migrants due to the cost of living. Living in such circumstances in addition to lower economic security may drive the new migrants to be exposed to higher risk behaviors such as commercial sex. Also, lower accessibility to clean water and sanitation may aggravate their living situation. Ease of transportation between rural and urban centers has been correlated with the ease of transmitting infections. An increase in the number of immune-compromised individuals is another demographic risk factor. Medical advances in treating patients with illnesses such as cancer or HIV has contributed to this increase. Also, using drugs that reduce immunity, as a treatment modality for some diseases is another way to produce an

immune-compromised population. The problem of having a significant immune-compromised population occurs not only due to their susceptibility to infection, but also due to the emergence of opportunistic infections and drug-resistant organisms. The fourth demographic factor is health behavior, which is affected by many factors including the social norm, education, economic status, age, and others. Sex behavior and illicit drug use are the main risk behaviors, which correlate with the community's demography.

- *Technology and industry:*

  Technological advancement in the medical, food safety, sanitation, and other arenas has led to eradication or reduction in the rate of many diseases. On other hand, the same technological advancement has also led to emergence of other diseases. Legionella in air-conditioning systems, E. Coli in animal husbandry practices, and toxic shock syndrome with tampons are examples of diseases that emerged with technological advancement. The wide use of antibiotics in animal husbandry and aquaculture to enhance production is correlated to the development of drug resistant bacteria. Many tools that have been developed due to the advancement of healthcare; such as endotracheal tubes, catheters, prosthetic heart valves, and hemodialysis machines, were considered to be vehicles for the transmission of many diseases. This problem of transmission of diseases was also increased by other advancements in medical procedures such as blood transfusion and organ transplant.

- *International travel and commerce:*

  Contemporary modalities of transportation have increased the average spatial mobility of humans. The ease of mobility exposes people to each other more often than previously. This exposure theoretically enhances the transmission of a disease outbreak. Modern air travel has increased the rate and speed of travel by individuals. Airplanes, ships, and trains are closed areas that contribute to the transmission process. Influenza, tuberculosis, measles, and many other infectious diseases have been linked to air travel. The increase in international commerce has resulted in 70% of the fruits and vegetables that are consumed in the United State coming from developing countries. Poultry, fish, and livestock are imported at different rates. The introduction of food from outside a country's borders introduces a significant amount of parasites, microbes, snails, and other transmission vectors. Not only living organisms, but also pathological substances such prions in the case of cow-madness disease.

- *The breakdown of public health measures:*

  Adequate sanitation and hygiene, Immunization programs, control of vector-born and zoonotic diseases, and public health legislation and enforcement were the main indicators of a quality public health system according to The IOM report. Adequate sanitation and clean drinking water were the main methods to control such diseases as cholera. Underdeveloped public health measures are not specific to developing countries. The advancement in medical technology and the survival of a

more elderly population and immune-compromised patients were not accompanied by robust public measures that would control nosocomial infections. Nosocomial infection is a leading cause of death in the USA. Immunization has proven its efficacy and has been considered one of the major public health achievements. However, due to a number reasons; such as, the cost or the perception of safety of a vaccine, vaccination for a variety of disease is in difficult. These difficulties are significant in the case of wars or famines. The application of public health practices to some programs in order to control diseases, as the use of Directly Observed Therapy (DOT) to control TB, have shown efficacy. Also public health interventions in the control of vector-born and zoonotic disease such as the use of pesticides are important programs of the public health system. Shortfalls in these interventions have been correlated to the increase in vector-borne diseases. Public health police powers such as quarantine and isolation are an important intervention in many disease outbreaks. Failure of the public health system is devastating and can contribute in the spread of outbreaks.

- *Poverty and social inequality:*

  Poverty affects accessibility to healthcare services. Low accessibility to healthcare, poverty and social inequality have been linked to the emergence to a number of infectious diseases such as TB. Education, housing, infrastructure, and the absence of social agencies are examples of factors that contribute in the emergence of disease outbreaks.

Privatization of state owned services and foreign influx of capital have contributed to financial crises in many countries. Poor countries are more sensitive to global economic fluctuation. Globalization and privatization have had a negative impact on the accessibility of healthcare in many under-developed countries.

- *War and famine:*

  The linkage between wars and the emergence of disease outbreaks is evident. Public health systems among other state and community-based systems are vulnerable to failure during wars. War and famine cannot be separated in most occasions. Battlefield casualties and the direct destructive consequences of war are not the entire story. The displacement of people forcing them to live in refugee camps with little or no infrastructure, clean water, sewage systems, sufficient food, and or healthcare creates a suitable place for outbreaks to emerge.

- *Lack of political will:*

  A disease outbreak is an exceptional situation that requires mobilization of resources to contain it. Political will is pivotal for such mobilization. Willingness means shifting available resources from other demands to the battle against the disease outbreak. It also means cooperation with local stakeholders such as the local population and private organizations to achieve containment of the outbreak. Not only domestic authorities, but also international cooperation is a key component of success. Since many outbreaks involve more than a country or world region, sensitivity to

international cooperation due to sovereignty or other reasons could theoretically affect the control of outbreaks.

- *Intent to harm:*

  Biological weapons are serious threats. Despite the Biological Weapons Convention (BWC), non-state producers add another difficulty in the control of such threats. The IOM report pointed to the fact that civilian scientists are unfamiliar with the nature of this threat. This unfamiliarity concerning biological weapons may contribute to the lack of awareness of their devastating effects. The introduction of microbes could occur by a variety of means such as direct inoculation and infecting vectors or reservoirs. Terrorism and technologic advancement make this threat a real concern.

CHAPTER 3

METHODOLOGY

In Chapter 2, the three examples of recent outbreaks require a better definition of disease outbreaks that require an international intervention. In this Chapter, a scoring system will be proposed, composed of ten indices and totaling ten points. A score of 10 will be considered the most dangerous score, mandating a prompt intervention, while 0 would not mandate any intervention by the international community. Each index would represent one point on a 10-point scale. The severity of each outbreak would be determined by comparing different disease outbreaks.

Index 1: Novelty of the disease agent:

Outbreaks are caused by a wide variety of microbial agents. Virus, bacteria, and fungi are not the only cause of disease outbreaks, but other contagious material such as prions or unsafe exposure to chemicals or radiation may be causes. Ambiguity and obscurity of the causative agent is a challenging factor in the control and containment of outbreaks. When a public health system is faced with an unknown disease with an unknown cause, it is difficult to control that outbreak and interdict its transmission cycle. The assumption here is that efforts would be exerted to identify the causative pathogen. The scoring system is dynamic and can change from time to time during the outbreak. An outbreak with an unknown etiology should become known as soon as possible. The

purpose of the scoring system is to evaluate the outbreak at any time during the outbreak.

With new technology such as the electronic microscope, PCR, and viral culture, identification of the pathogen may occur within a very short period of time. However, the identification of the pathogenic agent (microbe) is the first step but not the last. There are other important factors that would reveal an obscure pathogenic agent. These factors include knowledge about the reservoir, mode of transmission, incubation period, and availability of diagnostic methods. In this index, there are five questions/factors that determine the novelty of the disease agent:

I. Is the causative agent known?
II. Is the source or the reservoir of that agent known?
III. Is the mode of transmission known?
IV. Is the incubation period known?
V. Is there any known diagnostic procedure?

This index deals primarily with the knowledge of stakeholders about the threat that they are facing. The answer of each question is YES or NO. There may be difficulty knowing how much the stakeholders know about any one of these questions. In case there is partial knowledge such as knowing some fact about the mode of transmission but not the full picture, should this question be considered yes or no based on knowing the mode of transmission? The answer to this question should be left to the evaluating team. If the evaluating team

determines that the picture is clear enough to be considered in the plan of outbreak control, the answer should be yes. Otherwise, the answer is no when the team finds insufficient information concerning the cycle of transmission and clarity does not exist as to how to break the cycle in the effort to control the outbreak. The same principle will be applied to the other questions.

The Index Score is calculated by assigning 0.2 for each question with a NO answer. A total of 1 point is added to the total score when the investigators do not know the causative agent, the source/reservoir of the causative agent, the mode of transmission, the incubation period, and the absence/ unawareness of diagnostic tools. Thus, the total score would be 0 when the five questions had YES answers for each of them. This means that investigators are aware of the causative agent, the source/reservoir of the causative agent, the mode of transmission, the incubation period, and the presence/awareness of various diagnostic tools.

Identification of causative agent is a crucial step that leads to understanding the other properties of an outbreak. Sometimes the clinical situation suggests a specific agent/microbe; i.e., salmonella food poising, Ebola, malaria, and others. However, sometimes the causative agent may be unknown at least in the beginning of the outbreak. SARS, and MERS are good examples of this kind of outbreak. The evaluating team should consider both situations and answer the first question accordingly. The scoring process is a dynamic process and the point at which scoring occurs may change following any newly confirmed result in the identification process.

The identification of a reservoir or source of infection may be more difficult than the identification of the causative agent. MERS and Ebola are good examples. The process of reservoir/source identification is time consuming involving humans, animals, and the environment. It also carries a level of uncertainty to some extent. Despite the availability of many theories, the source of MERS as an example is not fully understood. In some instances, the reservoir may not be determined. On the other hand, some outbreaks such as HIV have no known natural reservoir. However, HIV is transmitted solely by exposure to an infected person's body fluid. In this case, the reservoir is known as the infected human being and the answer to the second question is yes. It is expected that the reservoir/source is not known for many outbreaks at least at the beginning of the outbreak.

The mode of transmission is an important factor due to concern about breaking the transmission pathway. The level of knowledge that leads to interruption of transmission should be considered as Yes to the third question. The mode of transmission includes many questions such as the source of infection, presence of a vector, transmission route, and other questions. However, the level of knowledge that is considered sufficient at least theoretically to stop or break the transmission cycle should be counted as a yes answer for this question.

The incubation period is almost always a range of days or even months. The time needed for an infected person to show the manifestation of the disease is an important aspect of this Index. It is also the time required for

isolation/quarantine that will enable investigators to determine that containment has occurred. An awareness of the incubation period is critical for directing the diagnostic and therapeutic effort especially after determination of the infection source. A new outbreak of an unknown disease will have an uncertain incubation period. However, understanding of incubation period will lead to a better understanding of an effective strategy to contain the outbreak and at the same time would lead to a decrease in the severity index of outbreak.

The fifth question regards the availability of diagnostic tools. There are primarily two types of diagnostic procedures; the screening and the confirmatory. Both are important. However, in the last few important outbreaks, the screening test seems more important. Identification of a specific virus such as Ebola or MERS was achieved by expensive and highly complicated methods such as PCR and viral culture. These methods were not widely available and required some level of expertise and were time consuming. The real need in the field was for a reasonable screening test. Having such screening test would save time and resources and would help in the containment of the outbreak by isolation or other means. The strength of screening is another question that involves some measurement such as specificity and sensitivity. There is no cut off point in the predictive value for any screening test that will be used in this proposed severity index. However, the answer to the fifth question is simply; is there a screening test that in case of negative result the team is comfortable sending suspected cases back to their community with no restriction. If the investigators have such a screening test with the required level of negative predictive value, the fifth

question can be answered Yes. The positive predictive value of the test is important also, but lack of high predictive value would be addressed by other confirmatory tests.

In this index, five questions/factors are assessed. Each factor has 0.2 point for a total index point of 1.0. It measures the awareness of public health practitioners for the outbreak that they are fighting. These factors are interconnected and some may have more importance than others. However, these factors collectively draw a picture of the outbreak agent and its movement from its source until its detection in the human body.

Index 2: Fatality rate:

The fatality rate (case-fatality ratio) may be calculated in a straightforward manner. However, the determination of the fatality rate may be a difficult task. It is the most important concern of the stakeholders. An outbreak with a 90% fatality rate would receive more attention than an outbreak with a 10% fatality rate. Including this index in the outbreak severity index is justified.

Determination of the fatality rate is an absolute number of deaths among persons who have been diagnosed with specific disease. As it has been seen in the outbreak of SARS and MERS, the fatality rate was different among various health systems and dependent on the characteristics of patients. Also, the fatality rate would be affected by the total number of diagnosed patients, which may not include all patient as in the case of the Ebola outbreak. Since the severity index is a dynamic index, the average fatality rate will be utilized and the score will

change according to use of various diagnostic processes. The fatality rate would be different among some people such immune-compromised patients, the elderly, children, and patients with comorbidities, but the severity index assesses the effect of the outbreak on any given population. The available data concerning the fatality rate of an outbreak may represent the tip of iceberg due to the issue of transparency or technical incompetence, but the severity index will include any changes in the data once it becomes available.

This index is calculated by dividing the total fatality rate by 100, with the score of this index as the result. As an example, the fatality rate of MERS was 60% at the point of emergence of the outbreak. The fatality rate score for MERS at that point would be 60/100, or 0.6 of the total score of 1. The range of deadly outbreaks that have 100% and non-fatal outbreak that have 0% fatality rates represents only 10% in the Outbreak Severity Index. This low percentage of the total index score may produce the concern of underestimating the fatality characteristic of outbreaks. For two reasons this may not be of concern: (1) Most outbreaks receiving international attention have a fairly high fatality rate; (2) Fatality is not the only negative aspect of outbreaks. Poliomyelitis is a good example of a disease that has severe non-fatal aspects.

Index 3: Incidence rate:

Incidence rate is an important index in the assessment of severity. The incidence rate "*measures the occurrence of disease onsets in a population per unit of time of follow-up"* [115]. The dominator represents persons who were at risk of disease at specific time. However, the numerator represents the number

of individuals having the disease. Both the dominator and numerator may be difficult to calculate. Counting the total number of confirmed cases may not represent the total incidence of the disease due to such reasons such as unavailability of a confirmatory test, unavailability of a screening test, unavailability of disease criteria that determines screening, unavailability of resources to test the affected population, and other reasons. On the other hand, determining the number of people at risk and the time to follow-up is almost imposable in most cases of outbreaks. These difficulties require a modification in the calculation of the incidence rate.

The aim of the Outbreak Severity Index is to have an objective tool to assess outbreaks rather than precisely calculate the incidence rate. Since the Outbreak Severity Index measurement would be of most value at the onset of an emerging outbreak, evaluating an outbreak at its onset requires modification of the incidence rate calculation. The proposed definition of incidence rate utilized in the Outbreak Severity Index is the total number of confirmed cases divided by the total population of the affected geographical area at the time of evaluation. The challenge in this definition is the determination of the representative geographic area, which can be described as the area that has a homogenous incidence of the disease. This approach leads to the possibility of having a separate Outbreak Severity Index for each geographical area; such as, cities, provinces, and countries.

As a result of the percentage of the modified incidence rate will be multiply by 1000, resulting in the value utilized for this index. The maximum difference

between the most affected area and the least affected area, which share the same value for the other indices, is 1 point on the scale of 10 (the total score of the Outbreak Severity Index).

Index 4: Ease of transmission:

The transmission property of outbreaks may be the most important index from the perspective of the public health practitioner. However, the Outbreak Severity Index deals with the ease of transmission as one index consisting of one of ten points for the total score. Influenza is an easily transmittable disease, but it does not receive the attention of the public due its fairly mild severity. Such would not be the case with HIV, a devastating disease, which requires specific contact methods of transmission. On other hand, most outbreaks having a reasonably high transmission property may be expected to get the attention of the public health system. The difference in the transmission capability of a specific disease would compensate for a lower severity of the disease when two diseases are compared. The more important issue is the fact that the Outbreak Severity Index deals with the geographic location of the disease, the people at risk, and the availability of resources.

The mode of transmission can be either contact or non-contact in nature. Contact includes direct, indirect, and droplet transmission. Non-contact includes airborne, vehicle, and vector-borne transmission [116]. Some modes of transmission have a greater ability of to transmit a disease than others. However, the ease of transmission is influenced by such factors as exposure time, availability of vaccination, and availability of precaution tools. It is also difficult to

evaluate ease of transmission by mode of transmission. The Outbreak Severity Index will use the basic reproduction number (R_0) as a measure of ease of transmission. The basic reproduction number is the number of secondary cases that are produced by one infected case in a completely susceptible population [117]. If the R_0 ranges between 0 and 10, the R_0 will be divided by 10 to calculate the score of the ease of transmission index. However, some outbreaks may have an R_0 of more than 10 such as measles [118]. Outbreaks with an R_0 of more than 10 will be score at 1.0 in this index.

Index 5: Availability of treatment:

Treatment in the proposed Outbreak Severity Index assessment has a broader meaning than usual. Treatment may equal cure in some definitions of treatment availability; however, in this proposal the definition of availability of treatment has been modified to serve as an accurate assessment of the outbreak's situation. The Outbreak Severity Index includes the following factors:

I. Is there any known curative treatment?
II. Is that treatment available in area of the outbreak?
III. Is isolation effective in controlling transmission?
IV. Is isolation available at the area of outbreak?

At the beginning of most outbreaks, broad-spectrum antibiotics and antivirals might be the logical initial treatment. However, with advancement of knowledge concerning the causative agent, a more precise treatment approach will substitute for the initial approach. At this stage, judgment

concerning the availability of treatment is used. However, on occasion the infection is self-limiting and does not require other than appropriate containment procedures. The first factor deals primarily with infections that cause death or significant disability. These types of infections require treatment to prevent devastating sequel. The answer to the first question is Yes when a fatal disease or a disease that leads to disability has a known treatment that prevents death or disability.

Despite the availability of a known treatment, it is important to assess the ability of the local healthcare system to provide that treatment, which may involve other factors such as accessibility to healthcare, willingness of people to be treated, the proper and equal distribution of treatment, and other factors that describe the integrity of the local public health system. Answering the second question depends on the general ability of the local government to provide treatment according to the judgment of the evaluating team. Other factors such as local public health integrity will be assessed in a separate index.

Isolation is an important factor for the control of outbreaks. Isolation ranges from personal isolation of patients to quarantine of the affected area. Isolation may depend on the dynamic of the disease transmission. A disease with a short incubation period and an easy transmission route may make isolation impractical. Answering the third question is based primarily on the significance of isolation in the containment of the outbreak.

The ability of local public health system to provide isolation at both the personal and community level is an important factor, which may be affected by many factors; such as, the incidence rate of the disease, the availability of resources, the strength of law enforcement, the willingness of the local authority to act, and political stability. Answering the fourth question gives a panoramic image of the ability of the local public health system to provide isolation to those cases requiring it.

This index has four factors that assess the availability of treatment of infected cases regardless of whether that treatment is medication or isolation with supportive measures. Each factor with a No answer will receive 0.25 points out of a total of 1.0 for this index.

Index 6: Geographical communication potential:

Humans' movement between different geographical areas is the nature of life. With the development of transportation methods over the last century, movement is much more rapid and easier than before. The movement between cities, countries, and continents is a daily practice of almost all human beings. The reasons for that movement are different including trading, working, education, tourism, as well as legal or illegal migration. From the point of view this proposed of Outbreak Severity Index, migration and movement of people are the same regardless of reason since the end result of that movement or migration is exposure to disease outbreaks.

Infected humans movement between different areas in the world is an important issue in transmission of diseases. Areas with the migration of people in and out results in a greater risk of the dissemination of an outbreak. However, those areas that are relatively isolated in some way or other would be at a relatively lower risk of outbreak dissemination. The direction of movement weather entering or exiting a specific area is also important. From the prospective of those residing outside the outbreak' area, the inward movement may be more concerning. On the other hand, the outward movement may pose a greater threat for those residing outside the outbreak's area. But, which one is the most important? The answer to this question should depend on the work of the evaluating team.

This proposal attempts to develop an objective measurement in this index. However, there are number of obstacles to a universal measurement scale. Obstacles include the following:

- Determining the number of people passing any geographical boundary is a difficult task. There is no method cut off the number of visitors or migrants to a specific area as high risk. It may be that the SARS outbreak in Hong Kong posed a higher risk of dissemination than Ebola in Liberia due to the number of passengers visiting Hong Kong. However, that distinction disappears when the comparison is between areas with relatively similar characteristics such as comparing Dubai with Hong Kong or comparing London with Paris. The total number of visitors are

important, but there is no critical number that poses a greater risk than another.

- Type of visitor is also an important factor. Tourists and businesspersons normally have better healthcare accessibility and better financial capability as health determinants than illegal migrants. On other hand, many countries perform screening procedure for legal migrants and visitors, which do not include illegal migrants. The type of visitor or migration is a significant factor that would not be taken in consideration if the total number of visitors and migrants were the only factor in the judgment concerning the risk of outbreak dissemination.
- The relativity of risk is another important factor. Despite globalization, some areas may pose a greater threat to their neighbors and local region than areas farther away. As an example, an outbreak in Mexico poses a threat to United States unlike an outbreak in West Africa. It also poses a greater threat to southern and southwestern states than northern states. Not only at the state level, but it also at the city level cities. San Diego may have greater threat from an outbreak in Mexico than Sacramento.

Due to these reasons, the determination of geographical potential of an outbreak should be assessed according the standpoint of the evaluating team. This score of this index will be determined by the height of the risk according to the potential of for geographical communication. A high-risk area will be given a score of 1.0 while a low-risk area will be given 0.0 points. The score may be different from place to place inside states/provinces, countries,

or continents. The global assessment of an outbreak in certain countries will be difficult. However, USA, most of Europe, China, and some places in Middle East such as Makkah (pilgrimage) may be categorized easily as having a high risk of dissemination. It is conceivable that most areas of the world could be considered as high risk of dissemination. The value of this index would become clear when the evaluating team deals with areas such West Africa (Ebola) with a relatively lower risk of dissemination to the globe than Hong Kong (SARS).

Index 7: Population density:

The density of population is playing a role in ease of transmission. It is not only due to exposure of high number of people to infection, but also due the situation of heavily populated areas. Deficiencies in clean sources of water, efficient sanitations, and good housing circumstances are often accompanying the residents of heavily populated areas.

The classification of population density from high to low could be achieved by many ways. However, the outbreak severity index will follow the classification of the United States Department of agriculture (USDA) [119] with some modification. The USDA's map of global population density is classifying the population density into six categories. For simplification and due to smallness of difference between the lowest two categories, they will be counted as one category. The classification will be as the following:

1. 0-10 persons/ square kilometer (lowest).

2. 11- 40 persons/ square kilometer.
3. 41- 100 persons/ square kilometer.
4. 101- 500 persons/ square kilometer.
5. > 500 persons/ square kilometer.

The width of each category is not equal. However, the purpose of this index is including the factor population density as outbreak dissemination factor. That purpose is clearly indicated between the two extremes of this scale. Each category will be assigned a 0.2 point of the total index score, which is 1.0. It is a cumulative score in which second category will be assigned with 0.4, third will be assigned with 0.6, fourth will be assigned with 0.8, and finally fifth score will be assigned with 1.0, the maximum score of this index.

Index 8: Political stability:

Political stability has many direct and indirect facets that affect the spread of outbreaks in communities. Outbreaks are similar to the most of other disasters that need efficient governmental interference. It is actually hard to imagine a successful outbreak's containment without governmental effort. Public health is by its nature a governmental duty despite the importance of collaboration with privet sector. Outbreak controlling involves many dimensions of work such as education, treatment, and prevention. However, police power as in isolation and quarantine is a fundamental job of public health that needs a governmental legitimacy. That leads to the conclusion of importance of efficient governmental in the process of outbreak control.

The shape of governments is different around the world. Before assessment of the efficiency of national and local government, failed states should excluded and assignment with the maximum score of this index, which is 1.0. The definition of failed state is difficult [120] and probably influenced by political agendas of the evaluators. However, the failed state in this proposal is that state, which is not able to enforce laws upon infected area. This includes civil war, insurgency, and famine. Corruption, inflation, inequality, and other similar factors would affect the government. However, these factors would not be included in the definition of failed state. Failed state is basically inability of government to manage and control outbreak due to weakness of the government.

The assessment of political stability in non-failed government would follow the United Nations' ten measures of promoting and consolidation of democracy [121]. These recommendations are:

1. Respect for human rights and fundamental freedoms.
2. Freedom of association.
3. Freedom of expression and opinion.
4. Access to power and its exercise in accordance with the rule of law.
5. The holding of periodic free and fair elections by universal suffrage and by secret ballot as the expression of the will of the people.
6. A pluralistic system of political parties and organizations.
7. The separation of powers.
8. The independence of the judiciary.

9. Transparency and accountability in public administration.
10. Free, independent and pluralistic media.

Absence of factor of these ten factors will add 0.1 point to the outbreak severity index. In case of absence of all of these ten factors will lead to a state that resembling a failed state. In other word, some totalitarians countries are equivalent to failed state. That might not be true from the political point of view. However, the political stability index is measuring the ability of governments to deal with outbreak. Absence of transparency, as an example, may be more important than many other indices since it would hinder the ability of the evaluating team to assess the situation. However, having these factors in this systemic way would provide a balance appreciation of governmental performance.

Index 9: Quality of local healthcare system:

The quality of local healthcare system is not a scale of general healthcare performance. It is solely for outbreak control ability. WHO had published an index for the world's healthcare system [122]. However, that index includes general assessment factors that might not represent the ability of outbreak control. On the other side, CDC had published with collaboration with other organizations performance standards for national, state, and local public health system based on the ten essential public health services [123]. The limitation of this performance standers tool is the difficulty of measurement especially for countries that are not following the western model of healthcare. The focus of this index requires a simple and reflective instrument tool.

WHO is following an outbreak management system in the form of *alert and response operation* [124]. The aim of that system is to manage the global outbreaks. The outbreak severity index will adopt that system for national and local assessment of public health ability of outbreak management. It is composed from the following six factors:

1. Epidemic intelligence – systemic event detection.
2. Event verification.
3. Information management and dissemination.
4. Real time alert.
5. Coordinated rapid outbreak response.
6. Public health logistic.

The assessment of these six factors will depend on the informed judgment of the evaluating team. These six factors will be turned to the following six questions:

1. Is the local health system able to detect the infected persons efficiently?
2. Is the local health system able to verify and authenticate the epidemiological information?
3. Is the flow of information from base to head of the outbreak team and vise versa performed in efficient way?
4. Is the information passed in a reasonable time that makes intervention efficient?

5. Is the response following the collected information resulting in an efficient and coordinated way?
6. Is the mobilizing of public health resources (mobilizing of stakeholders) meeting the threat of the outbreak?

The efficiency in these questions is including willingness, scientific and financial resources, and legislations. Answering of these questions might be difficult in some cases. However, in absence of information, the conservative pathway is to consider No as an answer. It is clear that answering these questions will depend on subjective rather than objective measurement. However, the limitation of this method hopefully will not limit the usefulness of this index in majority of cases. Subjective assessment of West African public health for Ebola outbreak would not be deviated from the realistic situation measured by other means. It is important here to emphasize that the aim of this index is to measure the attitude of local public health system to mitigate the outbreak situation more than measuring the success of local public in controlling the outbreak. A public health system having these six factors would be able to reflect the real situation and accommodate internal and external aids to control an emerging outbreak. The total score of this index is 1.0. The score of this index will be calculated by dividing number of No answers by 6.

Index 10: Availability of local financial and scientific resources:

This index is assessing the ability of local health system to achieve the best result in the outbreak's control. In the previous two indices, the outbreak

severity index measures the executive property of the local political system and the tendency of local health system to have effective outbreak controlling executive policy. However in this index, the ability of local public health system to control an emerging outbreak is measured by assessing the potential financial and scientific resources. Availability of resources in the presence of stable political system and effective public health policy would indeed lead to better result of outbreak containment. Assessment of resources availability as a separate index indicates that this index by itself may help in correcting political and public health policies at least partially. While in absence of financial and scientific resources, the reform of political and public health would be more difficult.

The assessment of financial and scientific resources is a difficult task. Financial resources may include national Gross Domestic Product (GDP), Gross National Product (GNP), and national income. On the other side, scientific resources may include capacity of hospital, research activity, and availability of high technology. The purpose of the outbreak severity index is developing a simple and informative assessment tool. Due to difficulty of choosing an indicator and measure it, the outbreak severity index will use the health expenditure per capita as a surrogate indicator for the following reasons:

- Outbreak is an emergency situation by its nature. The ability of local public health system to fight an emerging outbreak depends on medical infrastructures that have been built over years rather than quick mobilization of resources.

- Health expenditure represents in usually the highest ability of most countries for health. It might be true that some countries may be able to mobilize more resources in emergency case, but it would not be true for the vast majority of countries around the world especially countries that doesn't have universal healthcare converge.

The World Bank has published the health expenditure per capita per country for the last few years [125]. Health expenditure varies from 13$ in Central African Republic to 9,715 in Norway per capita in 2013. The index score will be calculated by dividing the local health expenditure by the highest health expenditure among world's countries in the same year. The result of that division will be deducted from the total score of the index, which is 1.0 and assigned as the score of this index.

CHAPTER 4

RESULTS

The purpose of this project is to develop an objective measurement for outbreak severity. This review concerns several novel outbreaks that occurred several years ago and one of them (SARS) is actually a story from the past. The intent of this severity index tool is not based on measuring the severity of outbreak in retrospective manner, but it is based on measuring any challenging new outbreak at the time it occurs. This project assumes that the evaluation was performed during the first few weeks of after the detection of the three outbreaks. This assumption is due to:

- The actual need of evaluation is most evident at the beginning of an outbreak than at a later time in the outbreak.
- The difference in severity that would result from the evaluation occurring during the early phase of an outbreak may show the need for prompt intervention.
- The outbreak severity index is a dynamic process and can be re-applied later during the progression of the outbreak.

Index 1- Novelty of the disease agent:

After the first case of the novel outbreak of SARS on November 16, 2002, the five questions of the novelty index were totally unknown until almost five months into the outbreak when the causative agent was isolated on March 24, 2003, and believed to be a new coronavirus strain [126]. During this period,

hundreds of cases were reported around the globe. The five questions of novelty were unanswered. At this point of time, the novelty score would be 1 for SARS. The exception is the mode of transmission, which was assumed to occur through arousal exposure; although tracking the transmission path was difficult without identifying the causative agent.

MERS was identified in a different scenario, being diagnosed in The Netherlands after a Saudi clinical sample was sent to Europe for examination. However, a retrospective diagnosis for another case from Jordan was performed for a deceased patient. The MERS outbreak started by identifying the causative agent. The diagnosis was performed by rt-PCR, No other diagnostic tool was available [127]. On other hand, source, mode of transmission, and the incubation period were not clear; thus the novelty score for MERS was 0.6.

The Ebola outbreak in West Africa in 2014 was preceded by more than 10 outbreaks over the last several decades. It is interesting that most of the literatures concerning Ebola was produced in the late 1990s after an outbreak in Central Africa. The diagnosis of Ebola occurred early in the course of the outbreak following the death of 50 cases [128]. Despite the severity of the disease when compared with previous outbreaks, the answers for the novelty five questions were clear. The Novelty score for Ebola at the time of detection was 0.0.

Index 2- Fatality Rate:

The overall case fatality rate for SARS was between 14% and 15%. Taking 15% as more conservative rate, the severity index for the fatality rate is 15/100=0.15. However, the fatality rate was calculated after the end of outbreak. Transparency was an important issue at the beginning of SARS outbreak in China. The fatality rate was different for the several countries involved in this outbreak and different based on the age of the patients. This project will consider this rate as the best available at the time of the evaluation, which may be the case in any similar outbreak.

The MERS fatality rate is following an up and down path with differences occurring between countries involved in the outbreak. With the confirmation of more cases of MERS, the fatality rate is increasing. However, WHO estimates the overall fatality rate to be 36% [129]. 36/100 is the outbreak severity index score for the fatality index, which results in an index of 0.36.

The Ebola fatality rate is significantly different between the three West African countries involved. However, the overall fatality rate is 64%. It has reached almost 90% in some countries in previous outbreaks. 64/100 is the outbreak severity index for the fatality rate index, which results in an index of 0.64.

Index 3- Incidence rate:

The incidence rate is a dynamic index that changes during the course of the outbreak. In this project, an arbitrary point of time will be chosen to assess it,

chosen to be at the high point of the outbreak provided that authentic information is available.

SARS occurred in several countries around the globe. Hong Kong will be used as the example in this severity index evaluation since it was one of the first affected locations outside of China and had a significant number of cases. If China were chosen instead of Hong Kong, the denominator would not be the total population, but the affected provincial population to avoid “over-dilution” of incidence rate. The total cases of SARS in Hong Kong was 1755 till the end of May 2003 [130]. The total population of Hong Kong was 6.803 millions in 2003 [131]. As proposed in this project, the total population is divided by the total number of cases to produce the index of 0.00026.

Saudi Arabia is the country of choice to calculate the incidence rate of MERS. The total number of cases of MERS in Saudi Arabia is 1033 in June 2015 [132]. The total population of Saudi Arabia is 30.8 million [133]. The result of dividing total number of cases by total population produces an index of 0.000034.

Sierra Leone is the country of choice to calculate the incidence rate for Ebola. The total number of confirmed cases of Ebola is 8692 in July 2015 [102]. The total population of Sierra Leone is 5.879 millions [134], with a resulting index of 0.0015.

The result of these calculations makes it difficult to capture the effect of the incidence of each outbreak in the outbreak severity index. To make the incidence more reflective another modification will be applied by multiplying the

result by 1000. This re-calculation of the outbreak severity index is based on producing an index score based on an incidence of 1 per 1000 population. However, what if the incidence of were significantly higher than 1/1000? An outbreak with higher incidence rate will be underestimated by this modification. However, an outbreak with a very high incidence rate is rare and other factors in the severity index would theoretically capture other important characteristics.

Index 4- Ease of transmission:

The basic reproductive number (R_0) is indicator for the ease of transmission index. The R_0 for SARS is 3, which is in consistent with direct contact or large droplet spread of the virus [13]. By dividing the SARS R_0 by 10, the result is 0.3, which will be added to outbreak severity index for the index of ease of transmission.

The basic reproductive number (R_0) for MERS is different based on the location of the outbreak. In Jeddah, the R_0 is between 3.5 and 6.7. However, in Riyadh, the R_0 is between 2.0 and 2.8 [135]. On the other hand, other studies suggest that the R_0 of MERS is less than 1.0 [136]. Taking a conservative approach, the average of the R_0 for the two main cities will be utilized in the calculation of this index. The average of 3.5, 6.7, 2.0, and 2.8 is 3.75. Dividing the average R_0 of 3.75 by 10 will result in an average of 0.38, which will be the MERS score for ease of transmission in the outbreak severity index.

The basic reproductive number (R_0) for Ebola is 2.7 [73]. Dividing this R_0 by 10 results in 0.27, and this result will be the score of Ebola ease of transmission in the outbreak severity index.

Index 5- Availability of treatment:

The answers to the following four questions will be used to calculate this index:

I. Is there any known curative treatment?
II. Is that treatment available in area of the outbreak?
III. Is the isolation procedure able to control transmission?
IV. Is that isolation procedure available at the area of outbreak?

For all of the three outbreaks, which are under evaluation in this project, there is no curative treatment. The available treatments are trials of broad-spectrum antiviral agents and interferon resulting in different rates of success. However, no one of these treatments can be claimed to be curative. The second question is not useful since there is no definitive treatment. West African countries do not have the capability to utilize the available treatment modalities or supportive measures. However, the effectiveness of supportive measures is limited. As a result, 0.5 will be added for each outbreak in the outbreak severity index.

For the third and fourth questions, the R_0 for the three outbreaks was not high and isolation demonstrated its effectiveness. Hong Kong and Saudi Arabia due to their resources were able to apply effective isolation. West African

countries on the other hand had very limited resources to apply isolation techniques. As a result 0.25 will be added to the outbreak of Ebola since isolation appears to be effective, but was not available in the area of outbreak.

Index 6- Geographical communication potential:

The evaluation of geographical communication potential needs to define the starting point of the evaluator. In this project, the starting point will be the risk of transmission of an outbreak to the USA. Hong Kong will be considered as the high point of communication due to trade and tourism and will be assigned the full score of 1.0. Saudi Arabia and the other Gulf States will be considered as a high area of communication due to Hajj, trade, and educational movement. However, West Africa will be considered as an area of low communication potential and a score of 0.0 will be assigned for this index. This evaluation is subjective in nature. Nevertheless, the perception of danger of disease spread is important in this evaluation tool.

Index 7- population density:

The population density of Hong Kong was 6,690 individuals per square kilometer in 2010, which will be utilized in considering the SARS outbreak that occurred in 2003 and it is believed that no major change has occurred subsequently. [137]. This high density of population will result in assigning the full score for this index to Hong Kong in the outbreak severity index. The population density in Saudi Arabia was 13 per square kilometer in 2013 [137], resulting in giving MERS in Saudi Arabia a score of 0.4 for this index in the outbreak severity

index. The population densities for Sierra Leone, Liberia, and Guinea are between 45 and 86 [133, which result in a score of 0.6 for this index in the outbreak severity index for Ebola.

Index 8- Political stability:

The ten measures for promotion and consolidation of democracy will be assessed for Hong Kong, Saudi Arabia, and Sierra Leone. Each No in the following table will be assigned a score of 0.1 and the result of the ten summed to calculate the score of this index. The final score will be added to the outbreak severity index for the corresponding disease outbreak. Answering these questions could be performed using information available in the public domain or even by best judgment of the evaluation team. In this project, the score for political rights and civil liberties published by the non-governmental organization of Freedom House [138] will be used to answer most of the questions. Freedom House has a specific categorization for the democracy indices. Democracy indices are divided into two categories, the first deals with political rights and the second with civil liberties. Also, Freedom house has a specific scoring process, which ranges from 7 (worst) to 1 (free). Also, each index has its own scoring point. As a general rule, any score equal to or less than half of the total score for each index will be considered as no in the ten questions table.

	Hong Kong	Saudi Arabia	Sierra Leone
1-Respect for human rights and fundamental	NO	NO	YES

freedoms.			
2-Freedom of association.	YES	NO	YES
3-Freedom of expression and opinion.	YES	NO	YES
4-Access to power and its exercise in accordance with the rule of law.	YES	NO	YES
5-The holding of periodic free and fair elections by universal suffrage and by secret ballot as the expression of the will of the people.	NO	NO	YES
6-A pluralistic system of political parties and organizations.	NO	NO	YES
7-The separation of powers.	NO	NO	YES
8-The independence of the judiciary.	YES	NO	YES
9-Transparency and accountability in public administration.	YES	NO	YES
10 Free, independent and pluralistic media.	YES	NO	YES
Total Score of **Political stability**	0.4	1.0	0.0

Table 1: Ten measures of political stability

Index 9- Quality of local healthcare system:

It should be kept in mind that answering of the six questions to calculate the quality of local healthcare system index might be controversial and debatable. The evaluating team should expect some obscurity in information and

expect to use its best judgment to determine the quality of any specific public health system. The focus of this index should concentrate on the attitudes and capabilities of the public health system to detect, monitor, and control the outbreak. In the following table, this review will attempt to answer these questions from studies and reports that have been produced following these outbreaks [139][140][141]. However, these studies and reports are not comprehensive and fully informative. Personal and team judgment should be applied using the best available resources. Judgment should also be applied in the absence of information using the best estimate such as giving the Ebola outbreak in Sierra Leone a score of 1.0 since this country is suffering from poverty and a limitation of healthcare services. Countries such as Saudi Arabia and Hong Kong, which have reasonably good resources, and a moderate level of healthcare, may be assigned a score of 0.5 in the absence of specific information. However, this judgment score should be revised once better information is available.

	Hong Kong	**Saudi Arabia**	**Sierra Leone**
Is the local health system able to detect the infected persons efficiently?	YES	YES	NO

Is the local health system able to verify and authenticate the epidemiological information?	YES	YES	NO
Is the flow of information from base to head of the outbreak team and vise versa performed in efficient way?	YES	YES	NO
Is the information passed in a reasonable time that makes intervention efficient?	YES	YES	NO
Is the response following the collected information resulting in an efficient and coordinated way?	YES	NO	NO
Is the mobilizing of public health resources (mobilizing of stakeholders) meeting the threat of the outbreak?	YES	YES	NO
Total score of quality of healthcare system = (NO/6)	0.0	0.17	1.0

Table 2: Six measures of quality of local healthcare system.

Uncertainty and arbitrariness may be an issue in this index. However, public health in West African may be considered as failing to afford reasonable protection of the population. On the other hand, public health systems in Saudi

Arabia and Hong Kong may be not adequate. Despite the uncertainty, the margin of error appears reasonable.

Index 10- Availability of local financial and scientific resources:

The Hong Kong health expenditure per capita is $ 1860 in 2015 [142], and dividing this expenditure by the highest national expenditure, Norway, ($ 9,715 in 2013) results in a ratio of 0.19. The rationale for using different expenditure years is due to the unavailability of information. Subtracting the ratio of 0.19 from the total score of this index yields a score of 0.81. Saudi Arabian health expenditures were $ 808 per capita in 2013. Dividing 808 by 9715 and subtracting the result from 1.0 results in a score of 0.92. Health expenditure in Sierra Leone was $ 96 per capita and dividing 96 by 9715 and subtracting the result from 1.0 produces a result of 0.99.

Outbreak severity index	***SARS***	***MERS***	***Ebola***
1-Novelty of the disease agent	1.0	0.6	0.0
2-Fatality rate	0.15	0.36	0.64
3-incidence rate	0.26	0.03	1.0
4- Easiness of transmission	0.3	0.38	0.27
5-Availability of treatment	0.5	0.5	0.5
6- Geographical communication potential	1.0	1.0	0.0
7- Population density	1.0	0.4	0.6

8- Political stability	0.4	1.0	0.0
9- Quality of local healthcare system	0.0	0.17	1.0
10- Availability of local financial and scientific resources	0.81	0.92	0.99
Total Score	5.42	5.36	5.0

Table 3: Summery of the final scores of Outbreak Severity Index.

Interpretation:

The result of the outbreak severity index shows that SARS has a score of 5.42, while MERS and Ebola score 5.36 and 5.0 respectively. These results demonstrate that these outbreaks were almost equal in their severity. The following table demonstrates common criteria that could be used to evaluate the severity of such outbreaks by newspapers or other media outlets in the absence of a structured tool such as the one proposed in this project:

Criteria	SARS	MERS	Ebola
Total number of cases	8098 [143]	956 [144]	12018 [145]
Case fatality rate	9.6 % [139]	37% [140]	50% [105]
Mode of transmission	Person-to	Person-to	Person-to

	person	person	person
Country/s been affected	Asia (mainly)	Middle East	West Africa

Table 4: Outbreak evaluation by general media.

This example of information that is available to the media may represent public health practitioners' knowledge concerning such outbreaks. The public health activists and the decision-making groups would be struck by these data or they may mistakenly underestimate others depending on known facts associated with each outbreak. However, the outbreak severity index indicates that the three outbreaks studied have almost the same severity despite the data available in the media. However, it is interesting that although these three outbreaks have similar outbreak severity indexes, less than 1000 individuals have died of MERS, while Ebola has produced 12,000 confirmed deaths. The fatality rate of SARS was less than 10%, while the fatality rate of Ebola exceeds 50%.

The essence of an outbreak severity index is to establish a comprehensive tool that may take into account other important factors that affect the spread of an outbreak rather than accept an out of context number. Canada has an excellent public health system and significant financial and scientific resources, but its SARS fatality rate was 17% [139] and was unable to improve on the results noted by other countries affected by SARS. This reflects that SARS was highly virulent and despite the efforts exerted in the treatment process, the fatality rate was high. On the other hand, Ebola has a very high fatality rate when compared to MERS, but in a country with an inadequate health

system and limited educational resources, it has the same danger as MERS or SARS. Funeral ceremonies for infected persons were linked to the spread of Ebola in West Africa. This mismanagement of dead bodies would be easily solved in developed countries. Lack of financial resources and support to contain Ebola cases may play a key rule in this high number of cases of West Africa rather than the virulence of disease itself. MERS seems to have less transmissibility than SARS; however, new cases of MERS continue despite the fact that the affected countries in the Arabian Peninsula are wealthy. The mismanagement of the MERS outbreak makes eradication of the disease difficult, while SARS was eradicated within a year.

Assessment of the validity and reliability of the outbreak severity index as a public health surveillance tool is a challenge. This challenge is not only due to the limited number of outbreaks that can be tested, but the end result of the outbreak severity index is vague. There are many parameters for tracking a devastating outbreak such as the number of cases, case fatality rate, mode of transmission, as well as others. However, should one of these parameters be selected for monitoring outbreaks, the question may be raised as to why such a complex tool as the outbreaks severity index should be developed to measure a simple outcome parameter. Assessment of the validity and reliability of the outbreak severity index appears premature at this stage of its development.

Weak points of this evaluation:

In the evaluation of SARS, MERS, and Ebola using the outbreak severity index, certain weaknesses were encountered. These weaknesses were due to structural, informational, and conceptual factors. It should be clear that this tool is at an early stage of development and further trials and sharpening of the various indexes comprising it are warranted. The weaknesses of the index include:

I. *Discrepancy in time of evaluation:*

SARS as one of outbreaks that was assessed in this project is an outbreak that has been resolved for more than a decade. However, MERS and Ebola are still a challenge for global health. Some of the information utilized in the severity index may not be available at the beginning of an outbreak. Retrospective evaluation of SARS may reduce the validity of the outbreak severity index when compared with MERS and Ebola, which are still occurring. However, the outbreak severity index is a dynamic assessment tool and should accommodate changes.

II. *Reference score:*

The result of the outbreak severity index demonstrates the similarity of these three outbreaks with a score of approximately 5 out of 10. On the other hand, a reference point for a previous outbreak is not available for comparison. Even historic outbreaks such as the Spanish Flu pandemic early in the 20th century would not be applicable to this assessment tool due to the advancement of technology and information systems and political change. Sequentially using the outbreak severity index in future should lead to a reference point for its use.

III. *When it would work the best:*

The outbreak severity index is a tool that should be utilized in the face of the uncertainty and chaos accompanying the onset of an outbreak. It is not primarily a tool for retrospective assessment. The severity determination of an outbreak should be followed by procedures that contain and prevent the spread of such an outbreak at the local, regional, and international level. Also, the score of any of the three outbreaks that have been reviewed in this project might be different according to the level of information available at the beginning of each outbreak.

IV. *Stakeholders' Testimonies:*

Some of the outbreaks, which were reviewed in this project, have a bulk of literature regarding many properties of each outbreak that might not available for an evaluating team facing a new threatening outbreak. This could limit the validity of this review. The quality of this assessment tool may be enhanced by reviewing the testimonies of the stakeholders who dealt with a specific outbreak. Allowing a change in the score of the outbreak severity index when more information becomes available may reveal its sensitivity.

V. *Default scores:*

Since the outbreak severity index has 10 indices, some information concerning and outbreak may not be available to the evaluating team at the time of assessment. The absence of information may lead to an inappropriate evaluation. However, the default pathway in the case of

unavailable information should be handled in a conservative manner. It is much safer to overestimate an outbreak and be prepared accordingly than to underestimate an outbreak. A full score of an index should be assigned to any of the ten sub-indexes when the evaluating team has no objective information. Also, some of outbreak severity sub-indices have a number of questions that must be answered to reach a score for that sub-index. The same conservative attitude should prevail.

VI. *Math vs. appreciation*:

The outbreak severity index has been formulated through a mathematical approach to reach a digital score. However, this mathematical approach should not obscure the fact that it is an objective measurement for an emergency situation. It is based in the most part on an appreciation for a concurrent situation utilizing the best available information. Some of this information may not be available at the time of the emergence of an outbreak. It should be understood that ambiguity is of the nature of emergencies. Emphasis should be applied on updating the outbreak severity index once new data is available. Also, it should be acceptable that an outbreak severity index score may differ from place to place and from evaluating team to evaluating team since it measures partially the perception of danger from the outbreak.

VII. Consensus building:

Severity index measurement tools are present in both medical and natural disaster arenas. Pneumonia severity index, head injury severity index, and

pancreatitis severity index are examples of medical measurement tools. Earthquake severity index [146], and hurricane severity index [147] are example of natural disaster measurement tools. A disease outbreak shares the same properties of medical and natural disaster emergencies, making consensus building a difficult task since comprehensive work of a group of professionals with different backgrounds is required. Fortunately, the public health community is the best place to start this process due to the wide differences in public health professionals' backgrounds.

The first step in developing an outbreak severity index is to propose such an efficient and useful tool based on an academic and research process. The process of establishing of such tool appears to be an important step in building consensus. In this step, a single proposal is not sufficient. It needs to be followed by other proposals to insure its usefulness and effectiveness. Examination of its reliability and validity is required in an academic setting. Building consensus is a lengthy process. However, public health professionals should initiate the process of development of such a tool.

CHAPTER 5

IMPLICATIONS FOR PUBLIC HEALTH

An outbreak severity index is a tool that is intended to evaluate disease outbreaks in anticipation of preventing or controlling the spread of disease. This measurement tool may be used at any given time period during the emergence of an outbreak. The public health community requires a better tool for assessing the severity of an outbreak and implementing that assessment in disaster preparedness. Depending on news reports about an emerging outbreak should not be the normal public health practice especially after it has been revealed in various social media. The duty of public health agencies during emergencies is to lead. The traditional definition of an outbreak does not satisfy the need for intervening and mitigating a global outbreak. The outbreak severity index is a tool that may motivate an appropriate response to a disease outbreak. The following points address the steps that follow after the determination of the severity of a disease outbreak:

1-The right of international to access the available information:

Information is a key element in fighting a disease outbreak. However, there are many barriers that prevent the flow of information. The two main barriers are the inability to obtain information and political unwillingness to release such information.

Lack of the ability to gather information such as occurred in the case of Ebola in West Africa is a major challenge. This inability occurred due to an

inefficient public health information system and interestingly enough due to the attitude of distrust by the local population. A conspiracy theory prevailed among the local population affected by Ebola based on the theory that foreigners created the disease. However, such an attitude could be alleviated by the including of key persons in the local community in the fight against Ebola. Inclusion of key persons in these communities would not only help in changing attitudes of distrust, but also in changing local customs such as funeral ceremonies.

A failure in transparency was evident in China (SARS) and Saudi Arabia (MERS) based on a political unwillingness to inform the international community of the disease outbreak. Some reports indicated that SARS was many fold worse than admitted [148]. Saudi Arabia was criticized in its effort to control MERS [149]. On other hand, the WHO was criticized for its dealing with Ebola [150]. The WHO is a product of the contemporary international political system with all of its pros and cons. Also, the WHO is affected by its level of funding and political issues. Such governmental behavior should be changed and efforts should be made to guarantee a better flow of information.

2-The right of international organizations to investigate:

Disease outbreak does not recognize political borders or national boundaries. Rather is often undetectable as it moves around the globe that acts as a small village during an age of easy and fast communication. During such global outbreaks, the number of stakeholders expanded such that an outbreak

involves every human being. SARS in Hong Kong was easily transmitted to a North American city.

Admitting that the whole population of the world are at risk of been infected should lead to accepting the right to know and to investigate. The reality of the current geopolitical situation is that it is difficult to accept such a concept of interference into national issues. However, the public health community should exert more effort to make this kind of engagement acceptable and palatable. Terrorism is a good example of how different political systems are willing to cooperate. A global disease outbreak does not pose any lesser danger than terrorism.

3- Application of the precautionary principle:

The precautionary principle should be used as an efficient way to promote cooperation between international political and public entities. It should be clear that an individual country would bear the responsibility of non-cooperative behavior. Countries that elect not cooperate should face serious consequences such as a boycott, which seem radical to propose for a country that refuses cooperation and transparency. However, quarantine is a form of boycott and has been used to contain outbreaks in the past. Public health/ global health diplomacy was almost absent in these three outbreaks, a failure should not shape the future.

4- International Preventive Task Force, sharing of costs and representation:

Alternative approaches such as an international collaborative task force has been shown to be highly effective in the eradication of smallpox. Building similar collaborative task forces for fighting emergent disease outbreaks may produce improved results. This task force should include both governmental and public cadres, with a vision and mission to mitigate a specific international disease outbreak. The purpose of this task force is not to undermine the work of the WHO or other international agencies, but rather to support their efforts and to reduce bureaucratic and political issues.

One of the main deterrents to form such a task force is its funding. However, a disease outbreak does not solely happen in poor countries as has been experienced in the case of SARS and MERS. Volunteers should be encouraged to join such a task force. The other deterrent is political acceptance of the efforts of such a task force. Preemption authority of such task force would a source of dispute, but such disputes may be solved by fair representation on the task force including local involvement. The establishment of such a task force would promote international cooperation, the exchange of information, and limit the bureaucracy inherent in a disease outbreak. It would provide a platform for accepting funding and volunteers and serve as a distribution point to areas that are in need of support.

5- Application of public health police power:

Public health police power such as quarantine and closed boarders and/or boycotts should not be underestimated as a procedure for outbreak containment. However, the actual situation may make this choice very difficult provoking a

political response. Also, historically boycotts have been misused for unjustified reasons. At the beginning of an outbreak, this choice would be too extreme to be considered. Nevertheless, with an increase in the number of cases, many states may resort to this choice.

Public health and global health professionals should initiate the discussion regarding the regulation of the concept of an international quarantine. A preset announcement of such a regulation would serve to legitimize this kind of procedure. It should be fair, equitable, and supportive for countries that are engaged in fighting a disease outbreak.

6- Sustainable intervention:

The use of the outbreak severity index should not only be a defense mechanism against outbreak, but it should be used as a tool to direct support and intervention in the area of the outbreak especially in areas that are underdeveloped and under-resourced. The outbreak severity index is a tool for evaluating the virulence of an outbreak agent and the local capabilities of fighting the outbreak. Utilizing the outbreak severity index in a local social, political, and demographic approach should mitigate deficiencies and scarcities in fighting the disease outbreak.

A sustainable intervention is based on involving the local population rather than depending only on external aid. Sustainable intervention includes developing local community resources, education, training, and advocating. West Africa as an example is in great need of engagement that promotes community

resources. Building trust by engaging the local population in rebuilding of community's resources is a key factor for success in an atmosphere of doubt.

Conclusion:

The outbreak severity index is a measurement tool that is useful in public health practice to justify precaution and to justify interference. The review of the last several disease outbreaks, SARS, MERS, and Ebola, demonstrated moderate global outbreaks. Public health needs an assessment tool for local and global outbreaks that would direct the best international intervention. The score of the outbreak severity index could be used for such a purpose. This measurement tool is still in the early stages of development and more effort is needed to make it a more useful and reliable tool.

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