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«Stochastic epidemic models and their usage in the analysis of the recent  
measles outbreak in Greece»

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## ABSTRACT

Measles was considered to be a largely eradicated disease in the developed world, including in Greece. However, recently there has been a resurgence of measles outbreaks essentially due to the decreasing uptake of the MMR vaccine. This thesis is concerned with the application of nonlinear stochastic epidemic models for the analysis of the outbreak in Greece during the years 2017-2018. In particular, the class of chain-binomial stochastic processes has been extended and the new models are fitted to the data using Bayesian inference via suitable Monte Carlo methodology. Deterministic models are not well suited in this scenario since relatively few measles cases were confirmed within a population of approximately ten million people. We used a number of epidemic models taking into consideration different age groups which include children, adults up to the age of sixty five and individuals over sixty five years old. The rate of susceptibility in the population was allowed to vary as part of a sensitivity analysis. The main limitations of this work stem from missing data with respect to different age groups, pre-existing immunity, vaccination status and contact rates.

Η ιλαρά θεωρήθηκε ως μια ασθένεια που είχε εξαλειφθεί σε μεγάλο βαθμό στον αναπτυγμένο κόσμο, συμπεριλαμβανομένης και της Ελλάδας. Παρόλα αυτά, πρόσφατα υπήρξε μια αναζωπύρωση επιδημιών ιλαράς κυρίως λόγω της μειωμένης πρόσληψης του εμβολίου MMR. Η παρούσα διπλωματική εργασία ασχολείται με την εφαρμογή έντονα μη γραμμικών στοχαστικών επιδημιολογικών μοντέλων για την ανάλυση της επιδημίας στην Ελλάδα κατά τα έτη 2017-2018. Συγκεκριμένα, έχει επεκταθεί η τάξη των αλυσιδωτών διωνυμικών στοχαστικών διαδικασιών και τα νέα μοντέλα προσαρμόζονται στα δεδομένα χρησιμοποιώντας Μπεϋζιανή συμπερασματολογία μέσω κατάλληλης Μόντε Κάρλο μεθοδολογίας. Τα ντετερμινιστικά μοντέλα δεν είναι αποτελεσματικά στη συγκεκριμένη περίπτωση, εφόσον τα επιβεβαιωμένα κρούσματα ιλαράς είναι σχετικά λίγα σε έναν πληθυσμό προσεγγιστικά δέκα εκατομμυρίων ανθρώπων. Χρησιμοποιήσαμε ορισμένα επιδημιολογικά μοντέλα λαμβάνοντας υπόψη διαφορετικές ηλικιακές ομάδες που περιλαμβάνουν παιδιά, ενήλικες μέχρι την ηλικία των εξήντα πέντε και άτομα ηλικίας άνω των εξήντα πέντε ετών. Η αναλογία των ευπαθών ατόμων στον πληθυσμό επιτράπηκε να μεταβληθεί ως μέρος μιας ανάλυσης ευαισθησίας. Οι κύριοι περιορισμοί αυτής της εργασίας απορρέουν από την έλλειψη δεδομένων αναφορικά με τις

διαφορετικές ηλικιακές ομάδες, την προϋπάρχουσα ανοσία, την κατάσταση εμβολιασμού και τα ποσοστά επαφών.





## CHAPTER 1: Introduction

### 1.1 MEASLES OVER TIME

Sixteenth century Aztec drawing of a measles victim (Oldstone M, 2009)



The Antonine Plague of 165 to 180 AD, also known as the Plague of Galen (from the name of the Greek physician living in the Roman Empire who described it), was an ancient pandemic brought back to the Roman Empire by troops returning from campaigns in the Near East. Scholars have suspected it to have been either smallpox or measles. The disease killed about one-third of the population in some areas and decimated the Roman army (Littman RJ, Littman ML, 1973). Estimates of the time of measles evolution seem to indicate that the plague was something other than measles. Modern molecular biology places the emergence of measles as a human disease sometime after 500 AD (Furuse Y. et al<sup>a</sup>, 2010). The first systematic description of measles, and its distinction from smallpox and chickenpox, is credited to the Persian physician Rhazes (860–932), who published *The Book of Smallpox and Measles*. (Cohen SG, 2008) Given what is now known about the evolution of measles, Rhazes' account is remarkably timely, as recent work that examined the mutation rate of the virus indicates the measles virus emerged from rinderpest (cattle plague) as a zoonotic disease between 1100 and 1200 AD, a period that may have been preceded by limited outbreaks involving a virus not yet fully acclimated to humans. (Furuse et al<sup>b</sup>, 2010) This agrees with the observation that measles requires a

susceptible population of >500,000 to sustain an epidemic, a situation that occurred in historic times following the growth of medieval European cities (Black FL, 1966).

Measles is an endemic disease, meaning it has been continually present in a community, and many people develop resistance. In populations not exposed to measles, exposure to a new disease can be devastating. In 1657, according to the Historical Medical Library of The College of Physicians of Philadelphia<sup>a,b</sup> the earliest recorded measles epidemic breaks out in Boston. In the diary of John Hull (the leading merchant and mintmaster of the Massachusetts Bay Colony) was written that “the disease of measles went through the town”. However, it seems that the disease caused very few deaths. In 1676, English doctor Thomas Sydenham, MD, published *Medical observations on the history and cure of acute diseases*. He attempted to distinguish smallpox from measles in a more efficient way than the Persian physician Rhazes did in the past.

It wasn't until 1757 when a Scottish physician Francis Home demonstrated the infectious nature of measles through the transmission of the disease from infected patients to healthy individuals via blood. His experiment clearly showed the presence of the virus in human blood as mentioned in CDC'S chapter about Measles History. Almost a century later (1846) a Danish physician Peter Panum who was sent to the Faroe Islands in order to study a measles epidemic noted that the disease attacked almost the entire population without respect to age, even though it was considered to be a disease of childhood globally. The most important part of his observations was that he managed to describe the incubation period of measles (14 days after being exposed) and lifelong immunity after recovery from the disease, as it is reported by CDC in the unit Epidemiology and Prevention of Vaccine-Preventable Diseases. A reference from the College of Physicians of Philadelphia<sup>c,d</sup> mentions that in the duration of American Civil War (1861) over 67,000 soldiers in the Union Army had measles and more than 4,000 eventually died. A decade later Native American Tribes of southern Arizona suffered from measles outbreaks causing the death of many kids from 1878-1879.

Approaching the 19th century measles became a nationally notifiable disease in the United States (1912) leading in the major requiring of reporting all diagnosed cases. Only in the first decade of reporting, an average of 6,000 measles-related deaths were reported each year by U.S. healthcare providers and laboratories, pursuant to CDC's unit History of Measles. Meanwhile in France of 1916 a scientific development was achieved by the researchers Charles Nicolle and Ernest

Conseil, since they managed the first successful immunization against measles by means of convalescent serum. In 1951, the population of southern Greenland was threatened by measles virus carried by a traveler from Denmark. The disease had a final attack rate of 99.9%. Denmark rapidly provided gamma globulin (a type of blood protein—in this case, rich in antibodies) to Greenland succeeding a lower case fatality rate from the disease to patients who received it than those who did not. Overall, 1.8% of the population died during this epidemic in accordance with the College of Physicians of Philadelphia <sup>e,f</sup>. According to statistics and reports about seven to eight million children are thought to have died from measles each year before the vaccine was introduced (Ludlow M. et al, 2015).

Regarding the development of the vaccine John F. Enders and Dr. Thomas C. Peebles collected blood samples from several ill students during a measles outbreak in Boston, Massachusetts in 1954. They succeeded in isolating the virus in human (13-year-old David Edmonston) and monkey kidney tissue culture. As a result, the first live attenuated vaccine was licensed for use in the United States in 1963. Five years later, Maurice Hilleman and colleagues managed to develop the first successful vaccine which was improved and weaker than the previous one. Measles vaccine is usually combined with mumps and rubella (MMR), or combined with mumps, rubella and varicella (MMRV). In the following years Centers for Disease Control and Prevention (CDC) in cooperation with the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP) who recommended a second dose of MMR vaccine for all children made a huge effort in measles elimination till 2000 when they succeeded the absence of continuous disease transmission for greater than 12 months from the United States as it is reported in CDC's unit of History of Measles.

## 1.2 CAUSALITY- PREVENTION OF THE DISEASE

### 1.2.1 Signs and Symptoms

Measles is a highly contagious infectious viral disease responsible for a huge rate of mortality among young children globally, despite the availability of a safe and effective vaccine. Alternatively, in the medical literature, the disease is referred to as morbilli, rubeola, red measles or English measles (Milner D.A., 2015, Stanley J, 2002) and it is caused by the measles virus (meV).

There are specified clinical features for the recognition of the disease registered by CDC and WHO. The incubation period of measles from exposure to prodrome is ten to twelve days. It takes an average of fourteen (7-18) days from exposure to the virus to the onset of the rash. The prodrome lasts 2–4 days (range 1–7 days) (Hamborsky J. et al, 2017). Initial symptoms include high fever with a peak of 103°F –105°F, cough, runny nose (coryza) and bloodshot eyes (tarsal conjunctivitis). Koplik spots, a rash present on mucous membranes, is considered to be pathognomonic, highly predictive of confirmed measles and essential for prompt diagnosis (Biesbroeck L, Sidbury R, 2013) before the patient reaches maximum infectivity (Baxby D, 1997). It appears as punctate blue-white spots on the buccal mucosa that “resemble grains of salt and have a reddish background” (Steichen O, Dautheville S, 2009) followed by a maculopapular rash. The morbilliform eruption usually lasts five to six days and progresses in a cephalocaudal direction, which means from the head to the trunk to the lower extremities. The maculopapular lesions are generally discrete, but may become confluent, particularly on the upper body. Initially, lesions blanch with fingertip pressure. By 3–4 days, most do not blanch with pressure. Fine desquamation occurs over more severely involved areas. The rash fades in the same order that it appears. Immunocompromised patients may not have a rash and can develop severe, progressive giant cell pneumonia (Tesini B. L, 2018). A patient is considered to be contagious from 4 days before to 4 days after the rash appears. Other symptoms of measles include anorexia, diarrhea, especially in infants and generalized lymphadenopathy. There is an acceptable case classification which includes three stages: possible case meeting the clinical criteria, probable

case meeting the clinical criteria and epidemiological link with laboratory confirmed cases and laboratory confirmed case with serological test and/or PCR in pharyngeal swab.

### **1.2.2 Complications**

Organizations as WHO, PAHO and NHS refer that a noteworthy percent of 30% of measles cases suffer from one or more complications which are especially common in fragile groups of people as babies under the age of 1, children with poor diet or weakened immune system by leukemia/ hiv/ aids and adults over the age of twenty. The most serious complications include diarrhea and vomiting which often lead to dehydration, ear infections (otitis media), inflammation of the voice box (laryngitis), infections of the airways and lungs (pneumonia) and seizures. Pneumonia is possibly the most common cause of death related to measles. Less common complications may be liver infection (hepatitis), misalignment of the eyes, meningitis or infection of the brain (encephalitis) with a fatality rate of 15%. Rare but notable complications include blindness (mostly in African children), heart and nervous system problems and subacute sclerosing panencephalitis (SSPE) which is a fatal brain complication occurred several years after measles and observed once at 25000 reported cases. However, SSPE is considered to be extremely rare since the early 1980s. In addition, pregnancy is mentioned as high risk period since measles can result in miscarriage or stillbirth. The possibility of giving birth prematurely or having a low-birth weight baby is higher. Unvaccinated young children, unvaccinated pregnant women and any non-immune person are at higher risk of measles and its complications. Countries with low per person incomes and weak health services or countries recovering from a natural disaster present the majority of measles deaths.

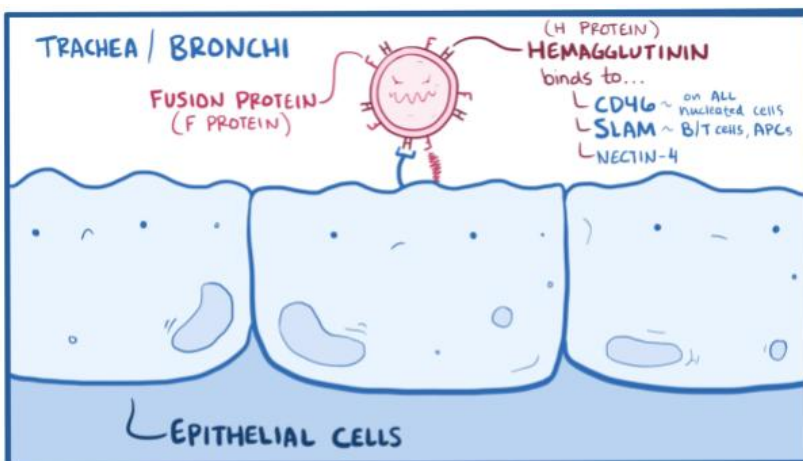
### 1.2.3 Cause

#### Pathogen - Host

Measles is a viral infection caused by the measles virus. The measles virus is an RNA virus integrated into paramyxovirus group of the genus *Morbillivirus*. It has a diameter of 120-250 nm containing six structural proteins. Three of them form a complex with RNA, while the other three proteins are associated with the virus envelope. Two of the latter membrane envelope proteins are of great importance in the pathogenesis of the virus. These are the F (fusion) protein and the H (hemagglutinin) protein. The F protein is responsible for virus attachment to cell membranes, viral penetration and hemolysis, whereas the H protein is responsible for adsorption of virus to cells. Despite the fact that studies have declared alterations in the H protein, they do not seem to be epidemiologically important. As far as the vaccine efficacy no change has been observed, fortunately, because there is only one antigenic type of measles virus. Another remarkable issue it that the only host of the disease is humans, since there is no known animal reservoir or any documented asymptomatic carrier state.

### 1.2.4 Pathophysiology

#### Pathogenesis



Measles virus enters the body through the respiratory system. More specifically the primary site of infection is the respiratory epithelium of the nasopharynx. The virus is installed on the respiratory mucosa and the adjacent lymph nodes where it replicates. A primary viremia occurs two to three days later resulting to reticuloendothelial system's infection. A second viremia occurs five to seven days after initial infection and further viral replication affecting the respiratory tract. The virus is transported by the lymphatic system into the bloodstream and coincidentally into various organs. Measles virus is quickly inactivated by heat, sunlight, acidic pH, ether and trypsin. It survives in the air or on objects surfaces. However, its survival time is less than two hours.

### **1.2.5 Transmission - Infectious period**

Measles transmission is primarily from person to person via large respiratory droplets which are eliminated by patients and rarely via objects recently infected by nasal and throat secretions (coughing, sneezing). Measles disease occurs mainly in late winter and spring. Measles is highly contagious with up to 90% secondary attack rates among susceptible persons (e.g. people who have not been immunized). It can be transmitted by an infected person from four days before to four days after rash onset. The maximum transmission occurs from the beginning of prodrome through three to four days of rash. Vaccine's virus is not considered to be contagious.

### **1.2.6 Prevention**

Vaccination is the most crucial fact in the prevention strategy of measles. The vaccine in circulation contains a live attenuated measles virus cultured in chick embryo cells. It is recommended to be subcutaneous in two doses at the age of twelve-fifteen months and at the age of four-six years in the form of a triplet (Measles-Mumps-Rubella, MMR) or a quadruple vaccine (Measles-Mumps-Rubella-Varicella or Chickenpox, MMRV). MMR vaccine is given later than other childhood vaccines because antibodies transferred from the mother to the baby may make it less effective for children under the age of one. People born during or after 1957



should have documentation of at least one dose of MMR or other evidence of immunity to the disease. All the adults should have received both doses of MMR.

The second dose of the vaccine should have a time gap of at least four weeks from the first dose. It is a necessity for those who failed to produce immunity after the first dose and it should be administered before a child enters kindergarten. Children without documentation or other acceptable evidence of immunity to measles, mumps and rubella should be admitted at school after receipt of the first dose of MMR. Needless to say that only written documentation of the date of the receipt should be considered as valid, while self or parental- reported doses should be judged as inadequate proof. A visit at the age of eleven-twelve years is recommended by doctors so that a vaccination status verification can be done or the administration of the second dose to those who have not received it yet.

Healthcare providers should not grant immunization records for patients unless they have administered the vaccine themselves or have seen the appropriate documentation of its reception. Every patient's vaccination status should have been documented in their permanent medical record and also in a vaccination record held by the individual.

The quadruple vaccine MMRV as being approved by the Food and Drug Administration can be used in children who are in the age of twelve months through twelve years but not in older than that age. Vaccination options should be discussed with parents or caregivers. Unless they express a preference for MMRV vaccine, CDC recommends that MMR vaccine and the vaccine for chickenpox should be administered separately for the primary dose in this specific age group due to adverse reactions. For the second dose of vaccine using MMRV is often more preferable over separate injections of MMR vaccine and varicella vaccine which include equivalent components.

Measles vaccine successes long standing immunization. It has been observed that immunization reaches the level of 98% when the child has been vaccinated in the age of fifteen months or the level of 95% when in the age of twelve months. About 2-5% of the vaccinated children with one dose of vaccine fail to produce primary antibody response. The majority of children who failed to produce antibodies after primary vaccination have adequately responded to the second dose of vaccine. Studies indicate that 99% of children who received two doses of vaccine finally

developed measles immunization. In developing countries where measles is a major cause of infant mortality WHO recommends Edmonston-Zagreb vaccine with increased content of attenuated viruses which is proven to be more effective in infants at the age of six months. Children must be vaccinated through the age of twelve months, especially in areas where measles cases have occurred. In case of a measles outbreak children can be vaccinated earlier than usual. However, revaccination with MMR vaccine may be necessary in the age of fifteen months.

Administration of vaccine with live attenuated measles virus is strongly contraindicated in some cases:

- In patients with immunosuppression. HIV infection is not an absolute contraindication.
- Concrete instructions should be given to susceptible women of reproductive age in order to avoid pregnancy for at least one month after their vaccination with MMR because of the theoretical risk of harming the embryo.
- In individuals who had a hypersensitivity reaction to previous dose of the vaccine, gelatin or neomycin. Egg allergy is not a contraindication.
- The vaccine should be administered at least fourteen days prior to administration of  $\gamma$ -globulin or blood transfusions or three months later.

Control of cases, carriers and close environment is quite important: (Heymann DL, 2008, Hamborsky J. et al, 2017)

- The case should be reported to the competent health authorities.
- Children infected by measles should be moved away from school the first four-five days of rash onset. In case of children from the close environment of the cases occurring prodrome coryza symptoms, their contact with susceptible individuals as infants and pregnant women should be restricted.
- Quarantine is practically not applied
- Simultaneous disinfection is not applied.
- Close contacts should be vaccinated through the first seventy two hours after exposure to the virus in order to develop an adequate response.

- Human normal immunoglobulin (HNIG) is a special concentration of antibodies which results in short-term but immediate protection against measles and should be given within six days of exposure to susceptible individuals as babies under one year of age or non fully vaccinated pregnant women or people with weak immune systems in the close environment of the infected person. All the above cases should be vaccinated with measles vaccine five to six months after HNIG reception.
- The source of infection should be detected and searching for other possible cases in the wide patient's environment should be performed too. Close contacts with family members, coworkers, school, society and people who work in medical facilities should be investigated during the whole infectious period.
- There is not a special treatment for infected individuals. Administration of vitamin A is recommended in developing countries and especially in children suffering from malnutrition in order to prevent complications and reduce mortality.

## **1.3 DIAGNOSIS**

Measles diagnosis is mainly clinical. Virus isolation is not recommended as a routine diagnostic test for measles. However, virus isolates are extremely important for surveillance. The specific applied methods are virus isolation and serological testing.

### **1.3.1 Virus isolation**

Virus can be isolated from urine, nasopharyngeal secretions and heparinized blood of infected individuals by culture. Measles virus RNA can be detected with real time Polymerase Chain Reaction (RT-PCR). Virus can be more possibly isolated in specimens collected within three days and not more than ten days of rash onset. Clinical specimens should be obtained from every person with a clinically suspected case of measles and should be sent for laboratory testing. Specimens' collection should be managed at the same time while samples for serologic testing are taken.

### **1.3.2 Serologic testing**

The simplest and most common measles diagnostic method is the definition of antibodies by enzyme-linked Immunosorbent Assay (ELISA or EIA) as long as it is applied at the appropriate time. Certain types of antibodies are found in body fluids when human body fights a new infection. Such kind of antibodies may be IgM (Immunoglobulin M) or IgG (Immunoglobulin G). Presence of IgM antibodies is temporary and lasts approximately one to two months. However, IgG antibodies remain detectable for many years following disease resolution. Measles uninfected individuals should be IgM negative. Detection of IgM antibodies requires only one serum specimen and is diagnostic if it is found positive. IgM tests for measles are often positive on the day of rash onset. However, in the first seventy two hours after rash onset, up to 20% of them may be false-negative, fact that requires their repetition. IgM antibodies are detectable for more than twenty eight days after rash onset. Acute measles diagnosis through IgG testing requires two serum specimens and demonstration of a four-fold rise in titer of antibody against measles virus. The first specimen should be taken as soon after the rash occurs as possible. The second specimen should be collected ten to thirty days later. The same type of test should be used on both specimens. A confirmed diagnosis cannot be made in case of the second specimen has not been obtained. That is mainly the reason why IgM tests are preferable for measles diagnosis confirmation.

### **1.4 TREATMENT**

Unfortunately, there is no specific treatment for measles because viral infections are not sensitive to antibiotics. Supportive care is able to reduce severe complications focusing on nutrition, adequate fluid intakes and oral rehydration as recommended by the WHO. These interventions aim in replacing fluids and strictly necessary elements that are lost through diarrhea or vomiting. Antibiotics should be prescribed as far as other complications are concerned such as eye and ear infections or pneumonia. Additionally, doctors may recommend acetaminophen or ibuprofen in order to reduce fever and pain. If it is required, a humidifier may be effective in easing cough and sore throat. Vitamin A supplements reception is crucial for children diagnosed with measles, especially in malnourished ones, since it is proven to act as immunomodulation. The specific

vitamin decreases the risk of severe complications such as eye damage or blindness and even reduces measles mortality. Resting is always recommended in order to help boost patients' immune system.

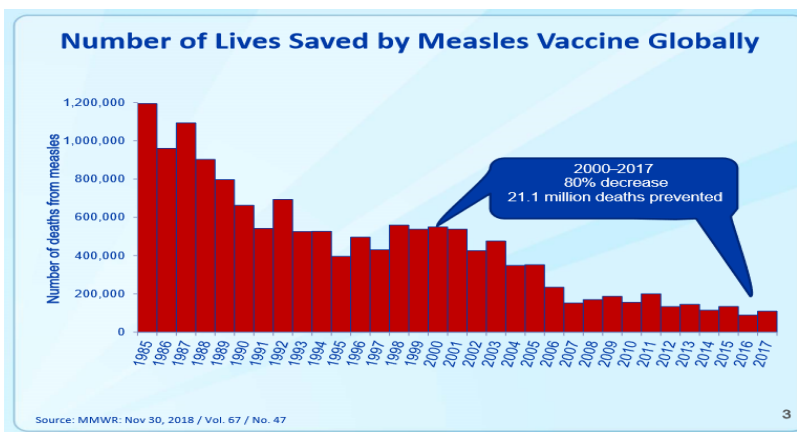
## 1.5 EPIDEMIOLOGY

*“Measles will always show you if someone isn't doing a good job on vaccinations. Kids will start dying of measles.”* – Bill Gates, 2011

### 1.5.1 Recent measles data in the U.S.A and worldwide

Although measles vaccine is totally available, safe and cost-effective, according to the WHO approximately 145700 people worldwide died from the disease in 2013 and 110000 in 2017, the majority of whom was children under the age of five years. The fact that measles vaccination reduced disease's mortality rates up to 80% between the years 2000 and 2017 is remarkable. Health services made an outstanding effort in administration of the primary dose of the vaccine to children by the age of one increasing the rate of vaccination from 72% in 2000 to 85% in 2017. During these years measles vaccination prevented an estimated 21.1 million deaths making measles vaccine a huge success in public health (Figure 1).

*Figure 1:* Number of lives saved by Measles vaccine globally (CDC, Measles data and statistics, 2019)



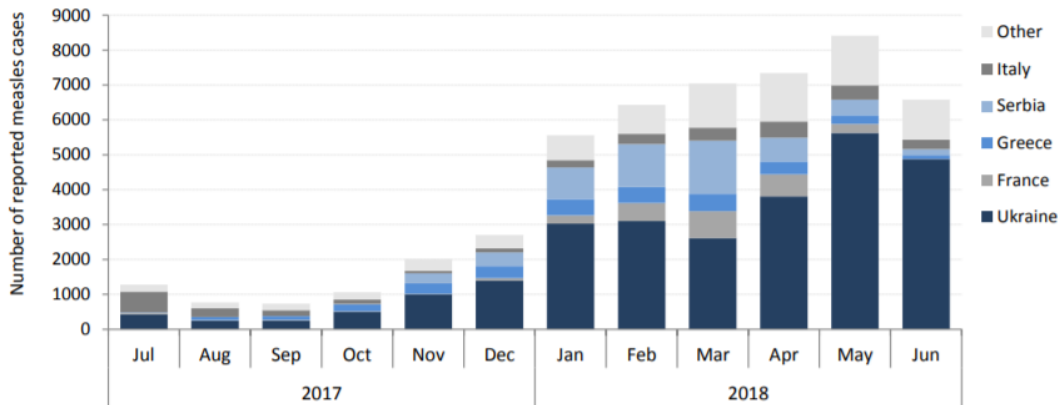
In 2016, according to CDC Yellowbook implementation of measles elimination strategies in cooperation with high vaccination coverage resulted in the Americas becoming the first region

globally to be certified as having verified elimination of endemic measles virus transmission. Elimination actually means the absence of virus transmission in a defined geographic area for greater than twelve months in the presence of an efficient surveillance system. However, measles virus importations from other parts of the world result in recent protracted outbreaks challenging maintaining elimination. Travelers are often at risk of being exposed to the virus, especially in countries where measles is still endemic or large outbreaks are occurring. In the United States outbreaks are often caused by unvaccinated residents who became infected while traveling abroad and became symptomatic after returning to the U.S. transmitting the disease to their communities. Immunization services can be severely disrupted by natural disasters, war or extensive population movements creating permanent reservoirs for vaccine-preventable diseases such as measles. Rudimentary health services, including the delivery of vaccinations to children, may be not provided to locals in countries facing armed conflicts or absence of centralized government.

### **1.5.2 Recent measles data in Europe**

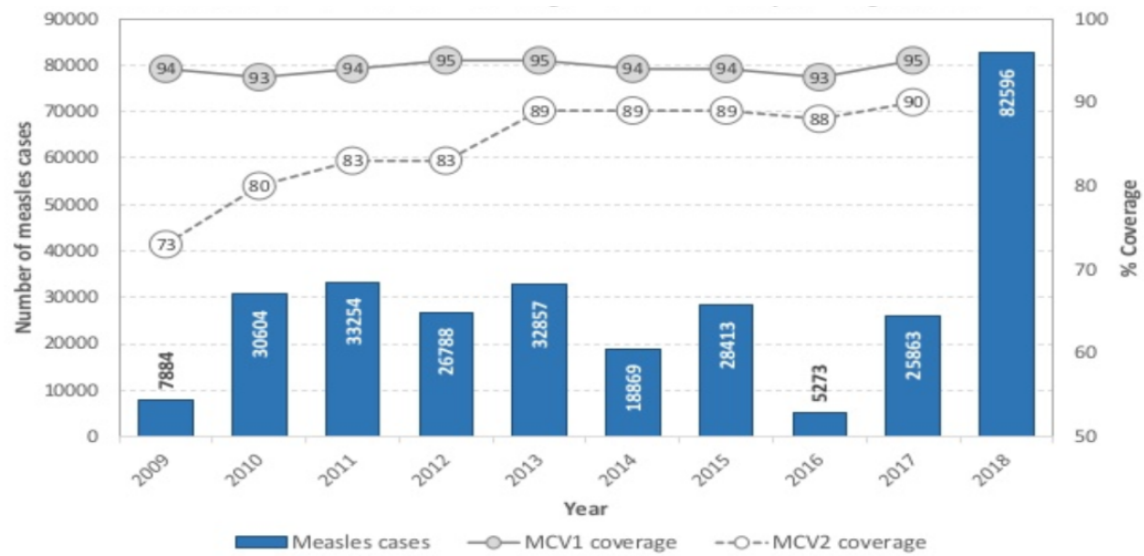
In 2017, the World Health Organization reported that thirty five deaths were caused by measles in Europe during the last year. The majority of them (thirty one) occurred in Romania, where measles-containing vaccine (MCV) coverage has been declined for years. In most countries outbreaks occurred in 2017 due to the fact that measles immunization rates are quite lower than the 95% vaccination coverage needed to support herd immunity. Specifically, only four countries achieved that target compared to fourteen countries ten years ago. In Italy, 3300 cases of measles were confirmed and one death in the first half of 2017. These numbers led to the making of immunization against twelve childhood diseases mandatory in order for the children to attend public schools. By the end of 2017, 1000 measles cases were reported in Ukraine (Figure 2), whereas in France eleven childhood vaccines including measles-containing vaccine became mandatory by health officials one year later (The College of Physicians of Philadelphia, 2017).

*Figure 2:* Measles cases by month in the WHO European Region, 1 July 2017- 30 June 2018 (n=51636) (WHO EpiBrief, 2018)



Even though the progress in vaccination status of the WHO European Region is remarkable, it is hardly equal between and within countries. This fact results in a record number of people affected by measles virus even in 2018. Particularly, in European Region the disease killed seventy two people, 61% of reported measles cases were hospitalized and the total number of infected people in 2018 was three times the total number reported in 2017 and fifteen times the number of affected people in 2016. In 2017, the highly increased number of measles cases resulted in a slight increase of the first dose of measles-containing vaccine coverage to 95%, which is actually the highest level reached since 2013. Moreover, European Region achieved 90% estimated coverage for the second dose of measles-containing vaccine, which is highest than ever (Figure 3). However, at a subnational level there are definitely gaps in immunization coverage, which allow the occurrence of outbreaks (WHO, Regional office for Europe, 2019)

*Figure 3: Measles cases and MCV1 & MCV2 coverage in the WHO European Region, 2009-2018 (WHO, Regional office for Europe)*



\*Data sources: 1) Measles cases – monthly aggregated and case-based data reported by Member States to WHO/Europe or via ECDC/TESSy as of 01 Feb 2019, 2) MCV1 and MCV2 coverage - WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) as of 08 Nov 2018.

MCV1 = first dose of measles-containing vaccine; MCV2 = second dose of measles-containing vaccine

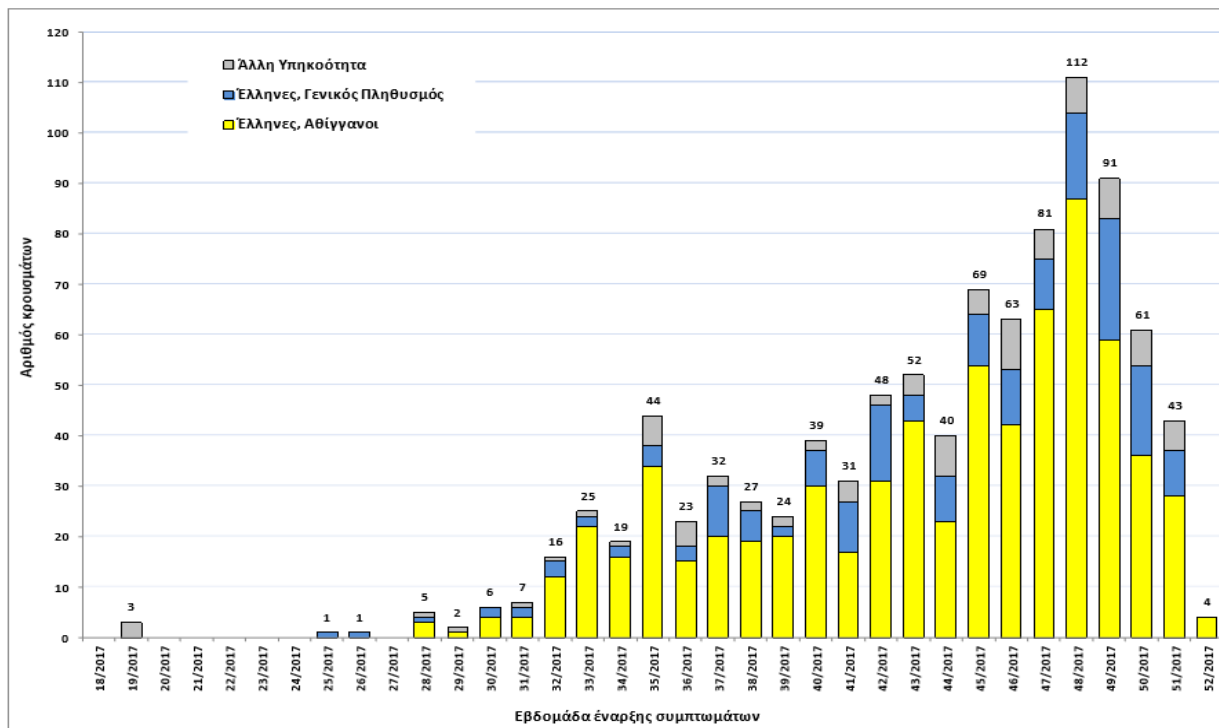
### 1.5.3 Recent measles data in Greece

Meanwhile in Greece, according to the Department of Epidemiological Surveillance and Intervention of National Public Health Organization, during the years 2014 and 2015 the number of reported measles cases was equal to one each year, while in 2016 no measles case was reported. A total number of 968 measles cases were reported through the Compulsory Statement System Disease by January 1st to December 31st 2017, which stands for 8.98 cases per 100000 population. Primary cases were reported on May 2017, which constitutes the beginning of measles epidemic in Greece. A systematic investigation of measles cases is carried out through the first twenty four hours of their report by contact with physicians in order to define the possible location of case exposure to measles virus, characteristics of the disease, its complications and risk factors.



At the following epidemic curve (Figure 4) the reported measles cases are represented as contributed by week of symptoms onset and population group. Population groups consist of people of Greek nationality from the non-minority general population (color blue), Roma (color yellow) and people of other nationalities (color grey). Thirty three cases from the total reported were healthcare professionals, who were probably unvaccinated or inadequately vaccinated.

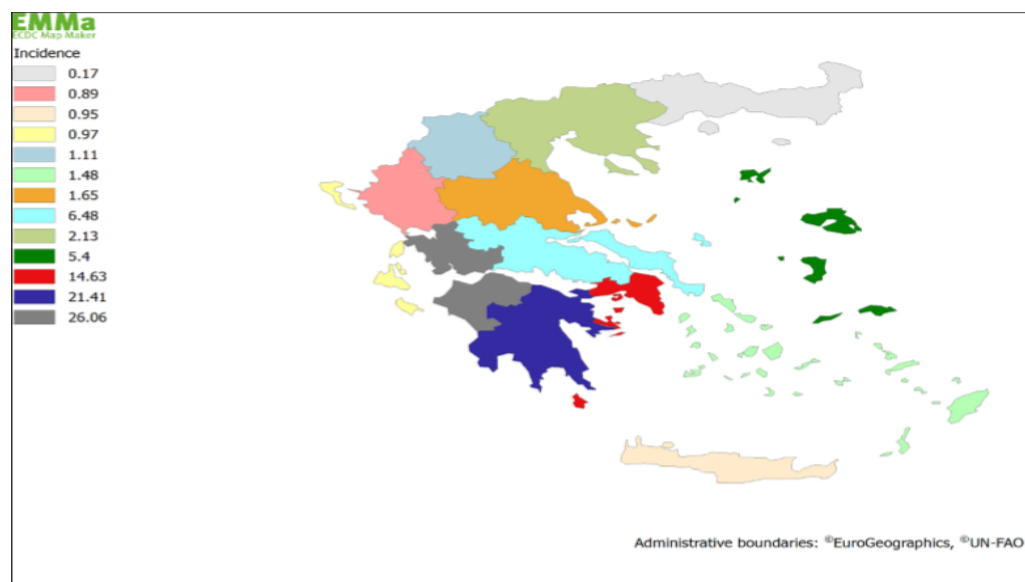
*Figure 4:* Epidemic curve - Reported measles cases per week of symptoms onset and population group, Greece, 2017 (n=968) (NPHO)



Nationality was a known factor for all reported measles cases. As notified by NPHO, 71.2% of measles cases were Roma, 19% were Greeks from general population and 9.8% were immigrants. The majority of measles cases (77%) were children aged 0-14 years old but mostly in the age of one to four years (33%), while 12% of cases were infants under the age of one. The majority of cases belonging to Roma families were children aged 0-14 years (91%) and mainly children in the age of one to nine years (65%), while 12% were infants under the age of one. On the contrary, most of the cases belonged to the greek general population were adults aged greater than twenty five years (60%). The annual reported incidence in men was 9.4 cases per 100000 population instead of 8.6 cases per 100000 population in women. The disease occurred the

highest annual reported incidence in the region of Western Greece (26.06/100000 population), while in the region of Peloponnese it was a little lower (21.41/100000 population) (Figure 5). As far as the other regions concerned, incidence fluctuated up to 14.63 cases/100000 population. The large majority of cases occurred in the Attica region.

*Figure 5:* Annual incidence of measles cases per 100000 population per Region, Greece, 2017 (NPHO)



As far as the measles cases classification concerned, 59.3% of them were laboratory confirmed cases with serological test and/or PCR in pharyngeal swab, 33.9% were probable cases meeting the clinical criteria and epidemiological link with laboratory confirmed cases and 6.8% were possible cases meeting the clinical criteria. Measles virus genotype B3 has been isolated by the national reference laboratory for measles in Greece (Hellenic Pasteur Institute) in sixty laboratory confirmed cases. Vaccination status was known for about 95% of measles cases. Particularly, 84.3% of cases were unvaccinated and 10.7% were vaccinated but mainly had received one dose of the vaccine. More than half the cases (55.9%) were hospitalized and 13% of the total number occurred complications such as pneumonia, otitis, liver infections or encephalitis. Two deaths have been reported in laboratory confirmed measles cases. The first case concerned an 11-months old unvaccinated Roma infant, with underlying dystrophy, who

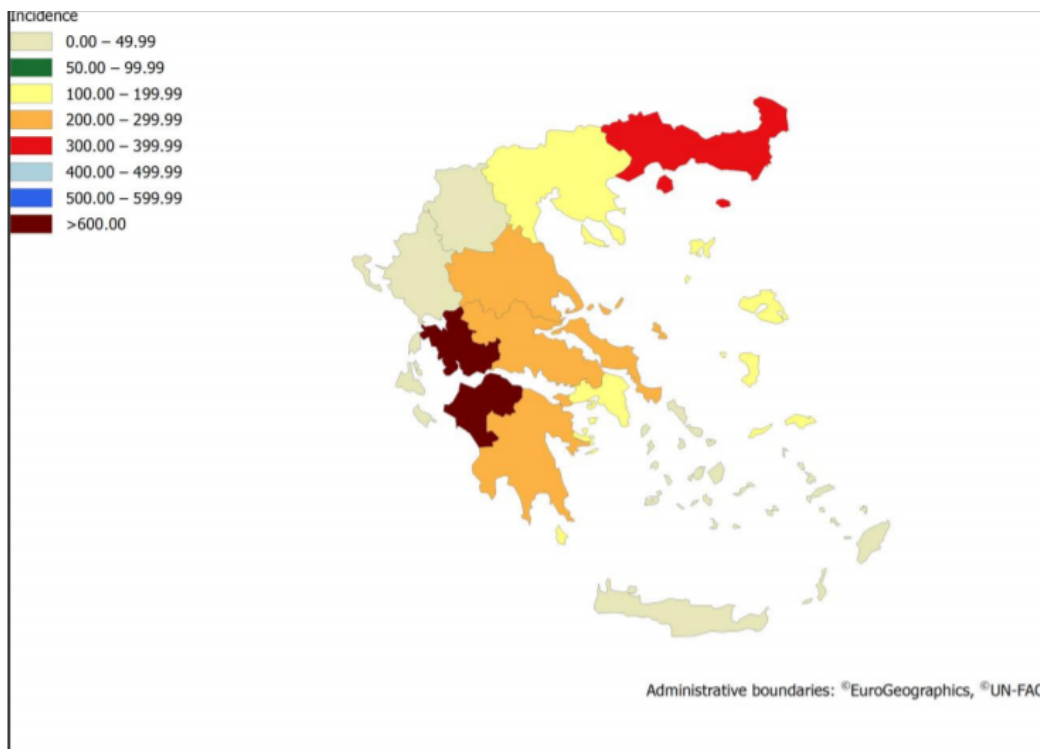
died of septicemia. The second case concerned a 17-year-old unvaccinated Roma, who died of encephalitis (NPHO, 2017).

Moreover, the Department of Epidemiological Surveillance and Intervention of NPHO in Greece aims to the overview of reported measles cases through the first six months of 2018. Data of epidemiological surveillance are collected from the reports, which physicians send to NPHO through the Compulsory Statement System Disease, and through daily contact with the national reference laboratory for measles -Hellenic Pasteur Institute and other microbiology laboratories in Greece. From 1/1/2018 up to 30/6/2018 2228 measles cases have been notified in Greece, which stands for 20.69 cases per 100000 population. Seventy cases from the total reported were healthcare professionals. As far as the measles cases classification concerned, 57.5% of them were laboratory confirmed cases with serological test and/or PCR in pharyngeal swab, 36.1% were probable cases meeting the clinical criteria and epidemiological link with laboratory confirmed cases and 6.4% were possible cases meeting the clinical criteria. Measles virus genotype B3 has been isolated by the national reference laboratory for measles in Greece (Hellenic Pasteur Institute) in thirty laboratory confirmed cases. However, standardization for more laboratory confirmed cases is still expected.

As notified by NPHO, 62.6% of measles cases were Roma, 37.4% were Greeks from general population and 10% were immigrants. The majority of measles cases has been occurred in Roma families, which indicates that the dispersion of the disease is mainly observed in population groups with low vaccination coverage. The majority of measles cases (59%) were children aged 0-14 years old but mostly in the age of one to four years (22.1%) followed by the age of five to nine years (16.5%), while 10.8% of cases were infants under the age of one. The majority of cases belonging to Roma families were children aged 0-14 years (86%) and mainly children in the age of one to nine years (57.9%), while 12.6% were infants under the age of one. On the contrary, most of the cases belonged to the greek general population were adults aged greater than twenty five years (72.5%). Vaccination status was known for about 89.4% of measles cases. Particularly, 78.7% of cases were unvaccinated and 10.7% were inadequately vaccinated. 64.1% of total reported measles cases were hospitalized and 18.8% of the total number occurred complications such as pneumonia, otitis, liver infections or encephalitis. In 2018, two deaths have been reported in laboratory confirmed measles cases. The first case concerned a 35-year-old

female, from the general population, partially vaccinated as reported, who died of pneumonia and Acute Respiratory Distress Syndrome (ARDS). The second case concerned an 18-year-old male, from the general population, with underlying immunodeficiency, fully vaccinated, who died of the same complications as the first case. The outcome of all the other measles cases was cure. The incidence of notified cases of measles per 1000000 population by district in Greece from 1/1/2018 up to 30/6/2018 is illustrated by Figure 6.

*Figure 6:* The incidence of notified cases of measles per 1000000 population by district in Greece, 1/1/2018-30/6/2018 (NPHO)



Taking into consideration the current measles outbreak in the European region, the health needs resulting from the refugee crisis management and the low vaccination coverage in Roma families, NPHO achieved a massive vaccination of refugees/immigrants children and Roma children in the age of nine months up to eighteen years against measles. Particularly, 44257 doses of MMR vaccine were administered in refugees staying in hotspots of mainland and islands of Greece and 5164 doses of measles virus vaccine were administered in Roma families

by NPHO, european program PHILOS and non-governmental organizations in cooperation with the Ministry of Health (NPHO, 2018).

## **1.6 AIM OF THE THESIS**

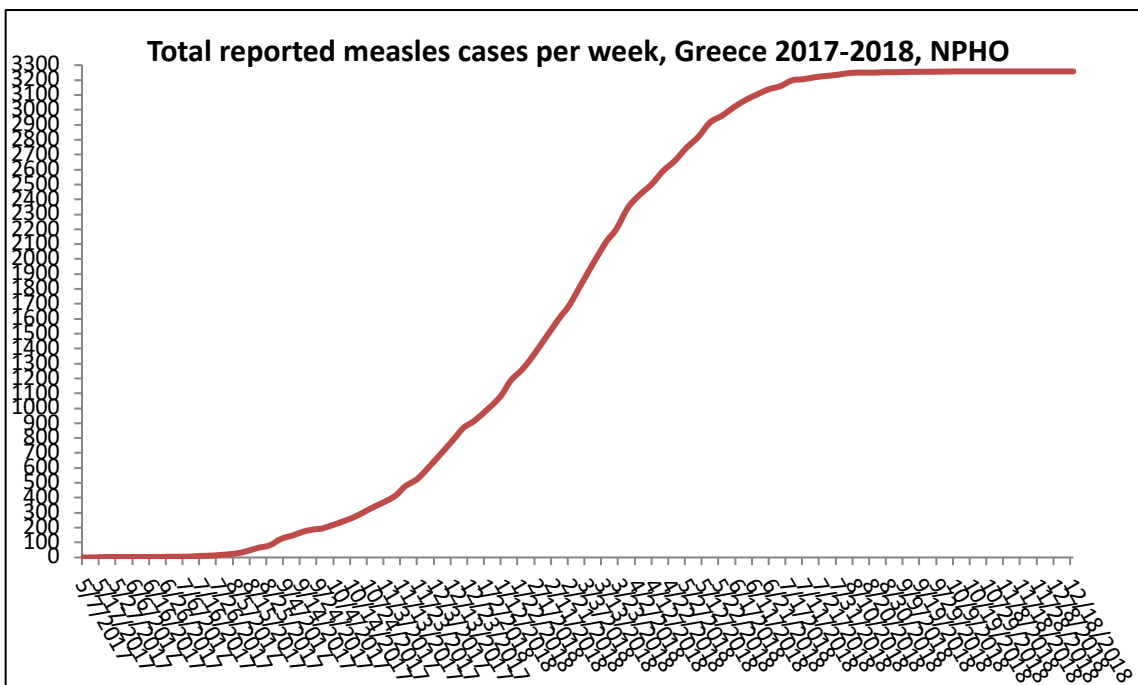
The aim of this thesis is to clarify the usage of stochastic epidemic models in the analysis of the recent measles outbreak in Greece in terms of estimating the probability of infection and forecasting forthcoming epidemics or pandemics by constructing a transmission model to understand the spread of measles in the Greek population. Specifically, the applied models are three Single type epidemic models (Greenwood, Reed-Frost and Generalised Reed Frost) and one Multitype epidemic model with age groups. A great achievement nowadays is understanding the mechanism of disease spread which leads hopefully to its control and eradication. This kind of models provide the framework for control measures by calculating the critical vaccination coverage and the optimal vaccination policy and manage to evaluate the cost-effectiveness of different interventions.

## CHAPTER 2: MATERIAL AND METHODOLOGY

### 2.1. STUDY POPULATION

The very first reported measles case was introduced in 27/05/2017 (NPHO, 2017). The sample of this study contains reported measles cases from 25/06/2017 up to 20/12/2018 collected by NPHO and classified in three categories as mentioned above: laboratory confirmed cases with serological test and/or PCR in pharyngeal swab, probable cases meeting the clinical criteria and epidemiological link with laboratory confirmed cases and possible cases meeting the clinical criteria. The study is based on data for a period of seventy three weeks. In reference to the year 2018 the new measles cases per week were calculated by the notified almost weekly updates from NPHO. However, concerning the year 2017, weekly or monthly updates cannot be found for the whole year. In that case, data were collected by reported charts from the same source including aggregated data for large time periods. Particularly, during 2017-2018, 3258 consecutive patients were recorded with measles mainly in Southern Greece, as it is demonstrated at the Graph 2.1.

*Graph 2.1:*



The majority of them were young children from Roma families and adults from the general Greek population mainly in the age group of 25 to 44 years who have not achieved measles immunization, including healthcare professionals probably unvaccinated or inadequately vaccinated. As it is reported by the Hellenic Statistical Authority, Greece is a country with an approximately 10800000 population, which is also distributed in various age groups. Almost twenty percent of this population constitutes the age group of 0-20 years, fifty five percent is between 20 and 65 years old and twenty five percent are adults over the age of sixty five.

For the particular study, it was necessary to collect data or at least estimates of the number of contacts each individual makes with another individual from the same age group or from a different one. Concerning contact data, an evidence synthesis was necessary to be made, since little information is given by NPHO. A contact matrix for Greece which was previously constructed by estimates and reported (Prem K. et al, 2017<sup>a</sup>) applied to our data. Estimates of mixing patterns have been provided for many countries for which contact data such as POLYMOD are not yet available (Mossong J. et al, 2008, Mossong J. et al 2017). The contact matrix included sixteen age groups: 0-5, 5-10, 10-15, ..., 70-75, 75-80, so it was necessary to merge them to three specific age groups in order to fit in our analysis. The selected age groups were children in the age of 0-20 years, adults in the age of 20-65 years and individuals over 65 years old.

## **2.2.THEORETICAL BACKGROUND OF THE STUDY**

### **2.2.1 The nature and the challenges of Epidemic Models**

The desired effect of using a stochastic epidemic model is to describe the spread of a viral infection with a person-to person transmission mechanism such as measles or generally to describe the transmission of infectious diseases in a population of individuals such as animals, computers or plants. These models being modified can also be used in social sciences in order to describe the spread of knowledge, rumors or information, in host-vector diseases, in financial crises and even over power-law-type networks. However, the modelling of infectious diseases may include some challenges. The primary reason which makes that kind of modelling different is that strong dependencies naturally occur, since the hazard of an individual getting infected depends on the status of others in their vicinity. This feature complicates the model analysis and makes the statistical inference really hard even for a very small number of individuals. As far as the statistical analysis concerned, another existing challenge is that the epidemic process is never fully observed, so it is rarely known who infected whom or at what time an individual was infected or during what period they were infectious. Actually, only the times that symptoms appear are observed, resulting to a non-trivial statistical analysis.

The most natural way to describe the spread of disease is stochastic. Through stochastic models the probability of disease transmission between two individuals can be defined, while deterministic models are stating certainly whether or not transmission will occur relying on the law of large numbers. However, there are cases where a law of large numbers is not satisfied. Particularly, in a large community, a minor outbreak infecting few individuals or a major outbreak infecting a more or less deterministic positive proportion of the susceptible individuals may occur. In order to calculate the probability of the two cases, applying a stochastic model is crucial. Moreover, analysis with stochastic models is appropriate when extinction of endemic diseases is taken into consideration, since it occurs when the epidemic process deviates from the expected level. As far as the estimation is concerned, it is not really useful without knowledge of its uncertainty, which requires a stochastic model.



### 2.2.2 The deterministic General Epidemic (Kermack and McKendrick 1927)

The first complete mathematical model for the spread of an infectious disease was a deterministic model of Kermack and McKendrick, 1927, known as the deterministic general epidemic. There are three possible compartments between which an individual can move. These are susceptible (S), infective (I) and removed (R) individuals. An individual is at first susceptible to the disease. If they become infected, they will be infectious for some time and called infective. The removed individuals represent the recovered and immune or the dead ones (permanent immunity), playing no further part in the epidemic spread. The symbolic pattern which describes this movement between stages is:  $S \rightarrow I \rightarrow R$ . The system of differential equations which defines the SIR model is:

$$\frac{dS}{dt} = -\lambda S(t)I(t)$$

$$\frac{dI}{dt} = \lambda S(t)I(t) - \gamma I(t)$$

$$\frac{dR}{dt} = \gamma I(t),$$

noting that  $\frac{dS}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = 0$ , since there is no demography and the population size is considered to be closed, homogeneous and homogeneously mixing (Demiris N, 2016).

The factor  $\lambda S(t)I(t)$  is the crucial nonlinear term, indicating that infections occur at high rate only when there are many susceptible and infective individuals. Dividing the first and third equations it follows that:  $\frac{dS}{dR} = -R_0 S$ , where  $R_0 = \frac{\lambda}{\gamma}$ .  $R_0$  is a threshold parameter that largely determines the system behavior, particularly, it defines how infectious the disease tends to be. This is the reason the parameter  $R_0$  is called the basic reproduction number and represents the average number of new infections caused by a typical infective during the early stages of an epidemic. The value of this parameter for measles fluctuates between fifteen and eighteen. By integrating we get:  $S(t) = S(0)e^{-R_0[R(t)-R(0)]}$ . For large populations when  $t \rightarrow \infty$  we have  $1 - \tau = e^{-\tau R_0}$ , where  $\tau$  represents the

proportion of individuals who got infected in a historical outbreak. A crude  $R_0$  estimate can be obtained from  $\tau=1-e^{-\tau R_0}$ , so  $R_0=\frac{-\log(1-\tau)}{\tau}$ . This transcendental equation has a non-trivial solution if and only if  $R_0>1$ , whence  $\tau\uparrow$  with  $R_0$ . Otherwise,  $\tau=0$ . It is shown that  $I(t)$  is decreasing unless  $I(t)[\lambda S(t)-\gamma]=\frac{dI}{dt}>0$  or equivalently  $R_0>1/S(0)$ . In this latter case there will be a major epidemic. This observation suggests a threshold theorem, which means that a completely different behavior will occur depending on whether  $R_0>1$  or not. There will be a major epidemic iff (if and only if)  $R_0>1$  instead of a minor epidemic iff  $R_0<1$ .

Now supposing that there is a perfect available vaccine against an infectious disease, it may be considered the key of developing dynamic health policy. Our interest focuses on estimating the proportion, let  $\omega$ , to be immunized in order to avoid a large outbreak. Thus, the effective transmission rate falls to  $\lambda(1-\omega)$ , so  $R_0(\omega)=\frac{\lambda(1-\omega)}{\gamma}=(1-\omega)R_0$ . We call  $\omega_c$  the *critical vaccination coverage*. Supposing that  $(1-\omega_c)R_0=1$ , we get  $\omega_c=1-\frac{1}{R_0}$ . The more infectious the disease is, the more people must be vaccinated in order to control the spread. Generally, the aim is to achieve  $R_0(\omega)<1$  or equivalently  $\omega>\omega_c=1-\frac{1}{R_0}$ . For example,  $\omega_c=\{0.8,0.9,0.93\}$  for  $R_0=\{5,10,15\}$ , respectively. The state where  $\omega>\omega_c$  is referred to as *herd immunity*. However, this process is appropriate only under the assumption that the vaccine offers perfect immunity. There is, also, the case that the available vaccine is imperfect with efficacy  $\psi$ . Under this assumption, we have

$R_0(\omega,\psi)=(1-\omega)R_0+\omega(1-\psi)R_0$ . Supposing that  $(1-\omega_c)R_0+\omega_c(1-\psi)R_0=1$ , we get  $\omega_c(\psi)=\frac{1-\frac{1}{R_0}}{\psi}$ . Here,

the aim is to achieve  $R_0(\omega,\psi)<1$  or equivalently  $\omega(\psi)>\omega_c(\psi)=\frac{1-\frac{1}{R_0}}{\psi}$ . As  $\omega_c$  increases, even more people must be vaccinated in order the spread to be controlled. As long as vaccination coverage needed is greater than vaccination's efficacy, which stands for  $\psi<1-\frac{1}{R_0}$ , herd immunity is impossible. For example, for a disease with basic reproduction number equal to ten, vaccination coverage equal to 90% is needed. Any available vaccine with efficacy lower than 90% cannot achieve that aim, even if everybody is vaccinated (Andersson H., Britton T.,2000).

## 2.2.3 Chain Binomial Epidemic Models

### 2.2.3.1 The Generalized Reed-Frost model (Reed Frost and Greenwood model)

The simplest possible epidemic model describing the spread of an infectious disease in a small group of individuals is known as Reed-Frost model and is a chain-binomial model. The model is an SIR epidemic model. It is actually a Markovian process defined in discrete time or in generations. It posits independent reproduction, which means that the event probabilities in the current generation depend only on the state of the epidemic in the previous generation and these events are specified by binomial probabilities. Particularly,  $Y_{t+1} \sim \text{Bin}(x_t, 1 - q^{y_t})$ , where  $x_t$  and  $y_t$  denote the number of susceptible and infected individuals respectively, at time  $t$ , while  $q^{y_t}$  defines the probability with which each of  $x_t$  individuals avoid getting infected by anyone of the  $y_t$  individuals. The necessary assumption of this model is that each individual becomes infected if they have contact with an infective with probability  $p=1-q$  and all such contacts are independent. It is a density dependent process; since as more individuals are infected, it is more possible a susceptible individual to become infected. The probability of getting infected increases really quickly. The length of a chain cannot be longer than the total number infected, since new infections may occur as far as there are infectious individuals. Thus, the number of possible chains is finite. The Greenwood model assumes that  $Y_{t+1} \sim \text{Bin}(x_t, 1-q)$ . Both Reed Frost and Greenwood model are special cases of the Generalized Reed Frost model (GRF) when  $a=1$  and  $a=0$  respectively. GRF model indicates that  $Y_{t+1} \sim \text{Bin}(x_t, 1 - q^{y_t^a})$ .

### 2.2.3.2 The standard SIR epidemic model

Simplifying assumptions made for this model are the same as in the deterministic General Epidemic. Factors such as the effects of latent periods, changes in behavior time varying infectivity temporary or partial immunity are excluded from this model. There are initially  $m$  infectious individuals and  $n$  susceptible individuals. Each individual, while infectious, makes contacts according to the time points of a time homogeneous Poisson process with intensity  $\lambda/n$ . During the infectious period, the rate at which a given infective makes contact with other initially susceptible individuals is constant and equals to  $\lambda$  (close contact rate) independently of the

population size. The Poisson processes are independent of each other and independent of the infectious periods. The infectious periods, let  $I_j$ , are independent and identically distributed (i.i.d.) having a specified distribution. We denote the process by  $E_{n,m}(\lambda, I)$ . The mean and the variance of the infectious period  $I$  are denoted by  $\tau$  and  $\sigma^2$ , respectively. The final size of the epidemic, let  $Z$ , is defined as the number of initially susceptible individuals that ultimately become infected and takes values between 0 and  $n$ . The basic reproduction number,  $R_0$ , declares the expected number of infections generated by one infectious individual in a large susceptible population and equals  $\lambda\tau$ .

We assume now that the stochastic process is Markovian iff the infectious period has the lack-of-memory property and, thus, the infectious period  $I$  is exponentially distributed with intensity  $\gamma$ . Then, based on the definition of the model, the process is represented by the following table:

From	To	At rate
$(i,j)$	$(i-1,j+1)$	$\frac{\lambda_{ij}}{n}$
	$(i,j-1)$	$\gamma_j$

, so this version of the model, as introduced by Bartlett (1949), is called *general stochastic epidemic*.

### 2.2.3.3 The Generalized Stochastic Epidemic

It seems that there is also the case where  $I_j$ 's are not necessarily exponential; In this case the model is known as Generalized Stochastic Epidemic (GSE). Here,  $R_0$  is given by the equation  $R_0 = \lambda E(I)$ . It is shown that the number of infectious individuals in a large population initially behaves like a (BGW) branching process, where the initial ancestors in the latter process correspond to the initial infectives in the epidemic. Meanwhile, birth is equivalent with a new infection whereas death is equivalent with a removal. Particularly, a contact in the epidemic process occurs whenever a birth occurs in the branching process. The individual contacted at the  $i$ th contact is labelled as  $C_i = [nU_i] + 1$ , where  $U_i, i \geq 1$  are independent and identically distributed random variables, each uniformly distributed on the interval  $(0,1)$ . If this individual is still

susceptible, then the individual becomes infected in the epidemic, otherwise the individual and all of her descendants in the branching process are ignored in the epidemic process. Using a coupling method, it is clarified that the life span of ancestor  $j$  is  $I_j$  and  $I_j$  is independent. During their lifetime, each ancestor gives birth at the time points of a Poisson process with intensity  $\frac{\lambda}{N}$ . The two processes agree until time  $C \log(N)$  (Ball F., Donnelly P., 1995). Applying the machinery of branching processes (Jagers, 1975), we are able to derive results for the initial behavior of epidemics. Particularly, let  $\{Y(t); t \geq 0\}$  be the number of individuals alive at time  $t$  and  $D$  the number of offspring of a given individual. If the initial population size is  $m$  then there will be on average  $mE(D)^v$  individuals in the  $v$ -th generation, so it is clear that the process will become extinct iff  $E(D) \leq 1$ . Turning into the case where  $E(D) > 1$  and letting  $q$  to be the extinction probability of the branching process, it is shown that there will be extinction with probability  $q^m$  (when  $m$  ancestors exist) and explosion otherwise and that  $q$  is the smallest solution of the equation  $\theta = E(\theta^D)$ . Summarizing, two outcomes occur in the branching process:

- $E(D) \leq 1 \rightarrow$  extinction with probability 1
- $E(D) > 1 \rightarrow$  extinction with probability  $q^m$ , where  $q$  is the smallest solution of the equation  $\theta = E(\theta^D)$  or explosion with probability  $1 - q^m$ .

It is noted that when given  $I=i$ , the number of children  $D$  has a Poisson distribution with intensity  $\lambda i$  resulting in the equation  $E(D) = \lambda E(I) = R_0$ . Consequently,  $E(D) \leq 1$  leads to  $R_0 \leq 1$ , whereas  $E(D) > 1$  leads to  $R_0 > 1$ . The final size of the GSE is the number of initially susceptible individuals that ultimately become infected. For  $\theta \geq 0$ , let  $\varphi(\theta) = E[\exp(-\theta I)]$  be the moment generating function of the infectious period  $I$  (Laplace transform of  $I$ ), let  $p_k$  be the probability that  $k$  individuals are ultimately infected,  $0 \leq k \leq n$  and let  $m$  denote the number of initial infective individuals. According to Ball (1986),

$$\sum_{\kappa=0}^l \binom{n-\kappa}{l-\kappa} p_\kappa / [\varphi\left(\frac{\lambda(n-l)}{n}\right)]^{k+m} = \binom{n}{l}, \quad 0 \leq l \leq n.$$

The system of equations is triangular in the  $p_k$ 's and thus, in principle, it is straightforward to calculate the final size probabilities recursively, starting with  $p_0$ , then  $p_1$ ,  $p_2$  and so on (Demiris N, O'Neill P.D., 2006).

## 2.3 STATISTICAL ANALYSIS

We demonstrate some highly nonlinear stochastic models with autocorrelation whom statistical inference is a quite difficult procedure accomplished through Winbugs or Openbugs, programs for Bayesian analysis of complex statistical models using Markov chain Monte Carlo (MCMC) techniques. The initial models for which we made long runs up to 1000000 iterations are Greenwood, Reed-Frost and Generalised Reed-Frost model. They are single type epidemic models. The final model that has been constructed is a multitype epidemic model. The analysis is based on a dynamic transmission model (Shubin et al, 2016). However, it is a totally different version of it due to the lack of data and the decision to merge the available contact data in three age groups (children, adults and over sixty five years old). This procedure has been succeeded manually. The age groups 0-5, 5-10, 10-15 and 15-20 from the given contact matrix have been merged in one group (the children's group), the age groups 20-25, 25-30,...,55-60,60-65 in the adults' group and finally the age groups 65-70, 70-75 and 75-80 in the group with the individuals over sixty five years old (Table 2.3.1). The average of the diagonal elements and the mean of the off-diagonal elements of the given contact matrix have been computed for each of the three new age groups, in order to produce a new 3x3 contact matrix for Greece, which will be appropriate to use in the analysis of this study.

*Table 2.3.1:* Estimated Contact matrix for Greece

Age groups	0-20	20-65	65+
0-20	6.052654199	0.452087528	0.070578658
20-65	0.618203914	2.510121839	0.132812
65+	0.365193299	0.499080819	1.12955688

In this study we run some stochastic epidemic models aiming to estimate each time the probability of infection. Primarily, we assume that the proportion of non-vaccinated individuals is twenty percent of the population size. Then, we run variants of the three initial models Greenwood, Reed-Frost and Generalised Reed-Frost changing the proportion of non-vaccinated

individuals to 10% or 30% of the population size, so that we can obtain the differences in the estimated parameters of each model. The final model includes a contact matrix with the mean numbers of potentially infectious contacts produced by a single individual from age group a to individuals in age group b during one week, where a, b=1,2,3. The model uses data for 73 weeks distributed already in the three age groups. Initially, it works out the first week for the three age groups and later it draws the weekly infected per age group. Models' assumptions are that all infected are infectious and that during the modeled period there is no population dynamics such as births, deaths or ageing. At the first week the number of susceptible individuals equals twenty percent of the population size,  $S_{a,t=0}=0,2*N$  and  $I_{a,0}=0$ . Susceptibles at week t-1 can be infected at week t with probability  $r_{a,t}$ .

$$I_{a,t} \sim \text{Bin}(S_{a,t=0}, r_{a,t})$$

$$r_{a,t} = 1 - \left(1 - \frac{p}{N}\right)^M$$

$$S_{a,t} = S_{a,t-1} - I_{a,t},$$

where p is the susceptibility, which stands for the probability to get infected per contact with an infectious individual within the population,  $M = \sum_{b=1}^3 CI$  is the total number of infectious contacts by age group a and C is the contact matrix.

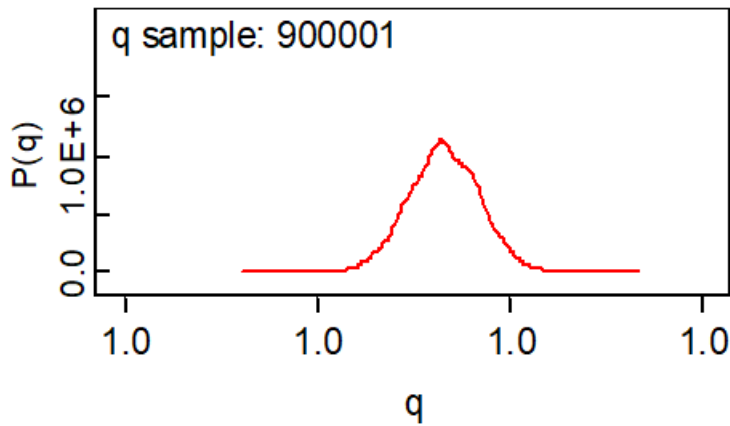
We estimate the posterior distribution of model parameters using Markov Chain Monte Carlo computation (MCMC) with particle Gibbs sampler step for each of the variants of the model. We change the number of susceptible individuals from 20% to 10% or 30% of the population size as in the initial models in favor of sensitivity analysis.

## CHAPTER 3: RESULTS

The outcomes for the Greenwood model (Appendix 1) are represented below. It runs up to 1000000 iterations with thin 1 while the first 100000 iterations have been excluded. It should be mentioned that for a given sample size, the accuracy of our inferences is dependent on the efficiency of our posterior sample, which decreases with an increasing level of autocorrelation. Hence, we perform a process known as thinning (“thin”) whereby only every  $\nu$ -th value from the Gibbs sampler is actually retained for inference (the rest are still generated but are subsequently discarded) in order to improve efficiency. Each time the model runs, the number of susceptible individuals is changed from 20% of the whole population to 10% or to 30%. That procedure aims to clarify the impact on the parameter  $q$ , which is the probability of a healthy individual to avoid getting infected by contact with any other given individual. All such contacts occur independently. The posterior density of the parameter  $q$  (probability of avoiding infection) from Greenwood model is represented in the case where the number of susceptibles is equal to  $0.2 \cdot N$  (Graph 3.1). This is the only graphically represented case due to the fact that the level on which the alternatives in the number of susceptibles affected the posterior density of the parameter  $q$  was very similar. However, in order to be inclusive, the statistics for parameter  $q$  from Greenwood model have been presented for every chosen number of susceptibles (Table 3.1). This model is frequency independent. In a large population of approximately ten million people, obtaining the infection of three thousand people does not have a serious effect. Model’s assumption is that each individual who becomes infected has an infectious contact with another individual with probability  $p=1-q$ ,  $Y_{t+1} \sim \text{Bin}(x_t, 1-q)$ . It assumes that even if an individual is exposed to two or more infectious people at the same time, it is equivalent to be exposed to one. The probability is constant and independent from the number of infected individuals. This scenario is more possible to succeed in a big city.



*Graph 3.1:* Posterior density of the parameter  $q$  (probability of avoiding infection) from Greenwood model with number of susceptibles equal to  $0.2*N$



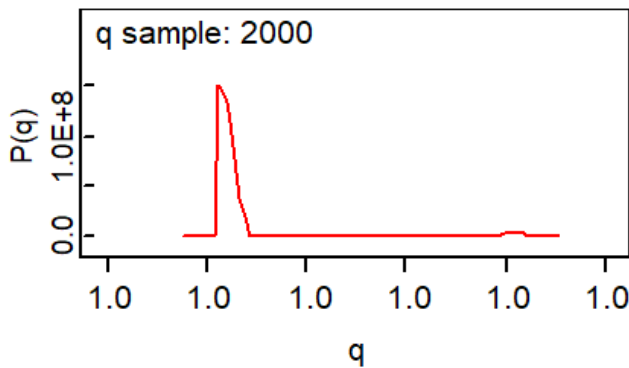
*Table 3.1:* Statistics for parameter  $q$  from Greenwood model

Number of susceptibles	Parameter	mean	sd	MC-error	median	start	sample
$0.2*N$	$q$	1.0	3.269E-6	3.892E-10	1.0	100000	900001
$0.1*N$	$q$	1.0	4.244E-7	7.612E-10	1.0	100000	900001
$0.3*N$	$q$	1.0	3.697E-6	2.582E-10	1.0	100000	900001

The outcomes for the Reed Frost model (Appendix 1) are represented below. Reed Frost is a simplest version of Generalised Reed Frost with  $a=1$ . It runs up to 1000000 iterations with thin 1 while the first 100000 iterations have been excluded. Each time the model runs, the number of susceptible individuals is changed from 20% of the whole population to 10% or 30%. Reed Frost indicates that  $Y_{t+1} \sim \text{Bin}(x_t, 1-q^{y_t})$ , where  $x_t$  and  $y_t$  denote the number of susceptible and infected individuals respectively, at time  $t$ , while  $q^{y_t}$  defines the probability with which each of  $x_t$  individuals avoid getting infected by anyone of the  $y_t$  individuals. This model is density dependent. In Graph 3.2 the posterior density of the parameter  $q$  (probability of avoiding infection) from Reed Frost model is represented in the case where the number of susceptibles is equal to  $0.2*N$ . According to this model the probability of an individual becoming infected

increases really fast. This is the result of the model’s assumption that the more people have the disease, the more possible is a susceptible individual to get infected through “infectious” contacts with any other individual.

*Graph 3.2:* Posterior density of the parameter  $q$  (probability of avoiding infection) from Reed Frost model with number of susceptibles equal to  $0.2*N$



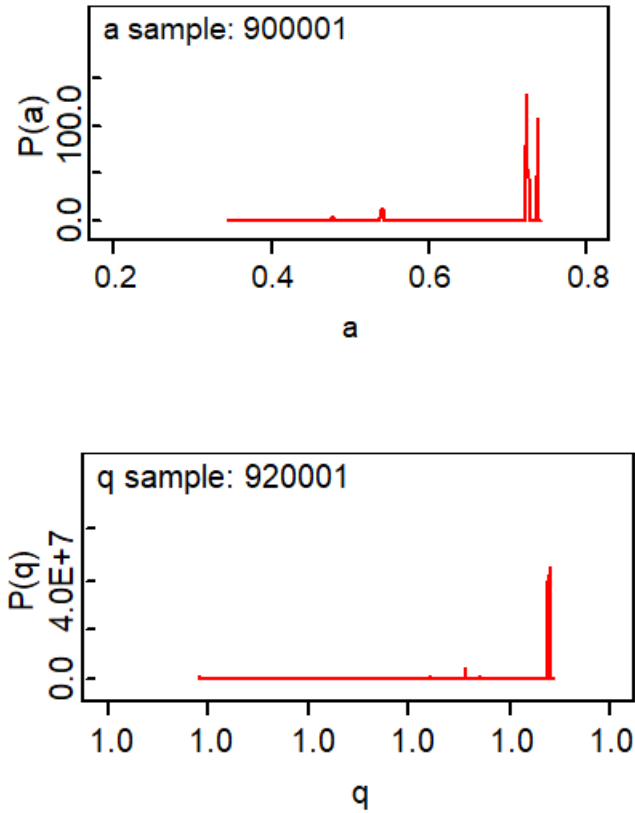
It is important to mention that the graphic representation of the posterior density of the parameter  $q$  from Reed Frost model or Generalised Reed Frost model with number of susceptibles equal to  $0.1*N$  or  $0.3*N$  has been investigated, too. However, it has not been included in the thesis because there is not a distinguishable difference at the graphs compared to Graph 3.2. Furthermore, the statistics for parameter  $q$  from Reed Frost model have been presented for every chosen number of susceptibles (Table 3.2) with the aim of featuring its impact on the parameter  $q$  and making comparisons.

*Table 3.2:* Statistics for parameter  $q$  from Reed Frost model

Number of susceptibles	Parameter	mean	sd	MC_error	median	start	sample
$0.2*N$	<b>q</b>	1.0	0.0	1.177E-11	1.0	100000	900001
$0.1*N$	<b>q</b>	1.0	0.0	3.194E-11	1.0	100000	900001
$0.3*N$	<b>q</b>	1.0	0.0	9.971E-13	1.0	100000	900001

The outcomes for the Generalised Reed Frost model (Appendix 1) are represented below. It runs up to 1000000 iterations with thin 1 while the first 100000 iterations have been excluded. Each time the model runs, the number of susceptible individuals is changed from 20% of the whole population to 10% or 30%. Generalised Reed Frost indicates that  $Y_{t+1} \sim \text{Bin}(x_t, 1 - q^{y_t^a})$ , where  $x_t$  and  $y_t$  denote the number of susceptible and infected individuals respectively, at time  $t$ , while  $q^{y_t^a}$  defines the probability with which each of  $x_t$  individuals avoid getting infected by any one of the  $y_t$  individuals. This model is density dependent. The probability of an individual becoming infected increases really fast. This is the result of model's assumption that the more people have the disease, the more possible is a susceptible individual to get infected through "infectious" contacts with any other individual. It is essential to include this model in the analysis, since parameter  $a$  takes values between 0-1. As a result, it does not lead neither to Greenwood Model ( $a=0$ ) nor to Reed Frost ( $a=1$ ). The posterior densities of the parameters  $q$  (probability of avoiding infection) and  $a$  from Generalised Reed Frost model are represented in the case where the number of susceptible individuals is equal to  $0.2 * N$  (Graph 3.3). The term "beg" specifies the iterations we want to use for posterior summaries. As we increase the number in beg, we discard the "burn-in", which stands for the initial, non-stationary portion of the chain. Here we select  $\text{beg}=80,000$  to discard the first 79,999 out of a total of 1,000,000 iterations for posterior summary of parameter  $q$  and  $\text{beg}=100,000$  to discard the first 99,999 out of a total of 1,000,000 iterations for posterior summary of parameter  $a$ . In addition, as the number of susceptible individuals changes from 20% to 10% or 30% of the population size, we can obtain the statistics for parameters  $q$  and  $a$  from Generalised Reed Frost model and the autocorrelation between them in each case (Table 3.3). Finally, we summarize the mean values of the parameters through the different models while the number of susceptibles changes (Table 3.4).

*Graph 3.3:* Posterior densities of parameters  $q$  (probability of avoiding infection) and  $a$  from Generalised Reed Frost model with number of susceptibles equal to  $0.2*N$  with  $beg=80.000$  for  $q$ 's posterior and  $beg=100000$  for  $a$ 's posterior density



*Table 3.3:* Statistics for parameters  $q$  and  $a$  from Generalised Reed Frost model

Number of susceptibles	Parameters	mean	sd	MC_error	median	start	sample	Autocorrelation between $q$ and $a$
0.2*N	$q$	1.0	0.0	2.527E-8	1.0	100000	920001	0.9792
	$a$	0.713	0.06352	0.002062	0.7266	100000	900001	
0.1*N	$q$	1.0	0.0	5.02E-8	1.0	100000	900001	0.9593
	$a$	0.7265	0.07466	0.002424	0.7504	100000	900001	
0.3*N	$q$	1.0	5.486E-7	3.884E-8	1.0	100000	900001	0.9757
	$a$	0.684	0.1195	0.003879	0.7318	100000	900001	

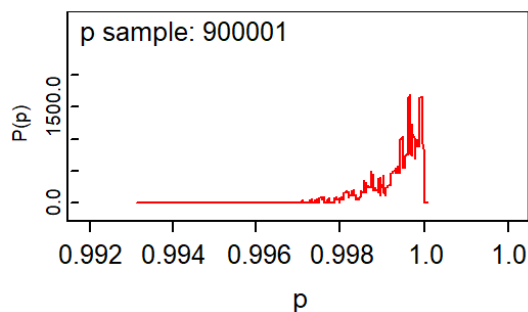
*Table 3.4:* Representation of the mean values of parameters  $q$  and  $a$  through the different models

Number of Susceptibles	Models			
	Greenwood	Reed-Frost	Generalised Frost	Reed- Frost
$S=0.1*N$	$q=1.0$	$q=1.0$	$q=1.0$	$a=0.7265$
$S=0.2*N$	$q=1.0$	$q=1.0$	$q=1.0$	$a=0.713$
$S=0.3*N$	$q=1.0$	$q=1.0$	$q=1.0$	$a=0.684$

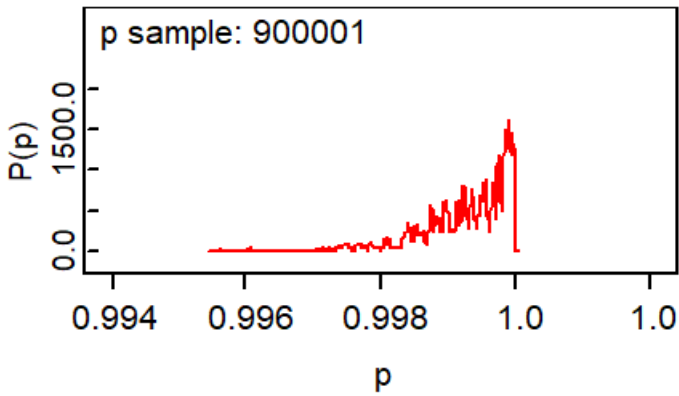
In each case, the probability of an individual becoming infected is quite low. As the number of susceptible individuals increases, we observe a slight decrease at the value of parameter  $a$ . This can be interpreted intuitively by a movement from a small village to a big city.

The outcomes for the multitype stochastic epidemic model (Appendix 2), where data are distributed in three age groups, are represented below. It runs up to 1000000 iterations with thin 100 while the first 100000 iterations have been excluded. Each time the model runs, the number of susceptible individuals is changed from 20% of the whole population to 10% or 30%. The posterior density of parameter  $p$  from multitype epidemic model is represented in the case where the number of susceptibles is equal to  $0.2*N$  (Graph 3.4),  $0.3*N$  (Graph 3.5) and  $0.1*N$  (Graph 3.6). Finally, we summarize the mean value of the parameter  $p$  for the latter model while the number of susceptibles is changed from 20% of the whole population to 10% or 30% (Table 3.6).

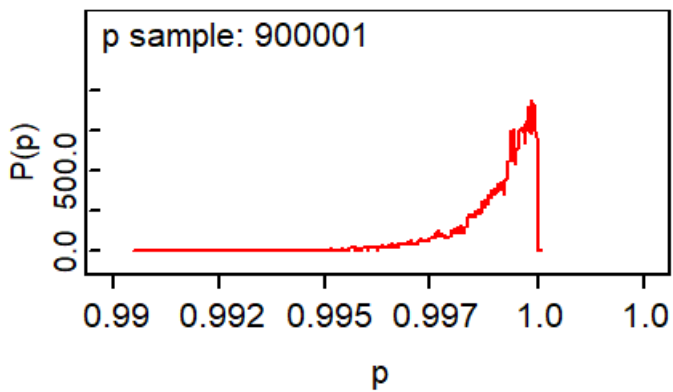
*Graph 3.4:* Posterior density of parameter  $p$  from multitype epidemic model with number of susceptibles equal to  $0.2*N$  with  $beg=100000$



*Graph 3.5:* Posterior density for parameter  $p$  from multitype epidemic model with number of susceptibles equal to  $0.3*N$  with  $beg=100000$



*Graph 3.6:* Posterior density for parameter  $p$  from multitype epidemic model with number of susceptibles equal to  $0.1*N$  with  $beg=100000$



*Table 3.5:* Statistics for parameter p from multitype epidemic model

Number of susceptibles	Parameter	mean	sd	MC_error	median	start	sample
0.2*N	p	0.9993	6.938E-4	1.809E-5	0.9995	100000	900001
0.3*N	p	0.9992	7.097E-4	2.065E-5	0.9994	100000	900001
0.1*N	p	0.999	0.001015	1.863E-5	0.9993	100000	900001

*Table 3.6:* Representation of the mean values of parameter p through the different versions of the multitype epidemic model

Number of Susceptible	Multitype epidemic model's parameter p
S=0.1*N	p=0.999
S=0.2*N	p=0.9993
S=0.3*N	p=0.9992

In each case, both posterior densities and statistics of parameter p are underlying the fact that if a susceptible individual has an infectious contact with any other individual, the probability of transmission is really high. As a result, it is of great importance that the social contacts of individuals be reduced.

## CHAPTER 4: DISCUSSION

During the current measles outbreak in Greece, 3258 individuals got infected from May 2017 till the 20<sup>th</sup> December 2018 in a population of 10,800,000 persons when the epidemic was thought to be extinguished. In this study, a dynamic transmission model has been used in order to estimate the probability of infection, while conditions related to study population vary. We illustrate indicatively some posterior densities of the estimated probabilities and we present their statistics making comparisons between the potential quantitative different results of each model. According to the social mixing matrix, produced by the given contact matrix for Greece, children's age group (0-20 years old) is the main transmission group for such an infection which spreads through droplets in close contact, especially between individuals from the same age group. Moreover, it is clear from the 3x3 contact matrix that the second group with the most contacts is adults with contacts mainly with individuals from the same age group and last but not least comes the age group of people over sixty five years old while contacting with individuals from the same age group.

In our final model, the spread of infection is modulated by some quantities as susceptibility to infection (parameter  $p$ ), which stands for the probability to get infected per contact with an infectious individual within the population and the pattern of contacts (contact matrix  $C$ ). The contact matrix was based on a survey of social contacts (Prem K. et al, 2017<sup>b</sup>), where data from the POLYMOD study were projected to 144 other countries using a Bayesian hierarchical model that estimated the trend of age and location specific contact patterns for the countries, using Markov chain Monte Carlo simulation.

As it is reported by NPHO, vaccination played an important role in mitigating measles transmission. In our analysis, we initially made the assumption that 80% of the population is vaccine-protected. However, we checked the scenario of 70% of the population being vaccine-protected and also 90% of the population being vaccine-protected. Susceptibility to infection was estimated to slightly decrease with the percent of non-vaccinated individuals. Additionally, we did not use informative prior on the model parameter for the susceptibility to infection ( $p$ ).



Our study is quite important and useful, since there is not a similar one which is related to the measles transmission in Greece. We managed to separate the problem in two components: the social and the biological one, while there was an evidence synthesis (contacts). Furthermore, the measles outbreak is a hot topic nowadays not only in Greece but worldwide. Many European countries are still trying to cope with measles transmission and its effects in humans' health and communities' immunization. There are a lot of factors that we could have included in our analysis if we had not such a strong limitation of data. Further sensitivity analysis could have been made in order to observe the impact of the choice of the prior distributions. We could have distributed study's population in more (or different) age groups or count the pre-existing immunity among older individuals as a factor which affects the probability of infection. Other limitations of this work stem from missing data with respect to vaccination status and contact rates. Since literature (NPHO) mentions that the largest infection sites have been noticed in Greek Roma families, further research is needed to investigate the transmission of the disease in and between Roma and non Roma population groups.

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## APPENDIX 1

### Greenwood model

```
model{
  y[1] ~ dbin(p[1], x[1])      # Likelihood
  p[1] <- 1 - pow(q, InInf)
  N <- 10800000    #Population size
  x[1] <- 0.2*N
  InInf <- 1
  for(j in 2:73){
    y[j] ~ dbin(p[2], x[j])    # Likelihood of Greenwood model
    x[j] <- x[j-1] - y[j]
  }
  # Prior
  p[2] <- 1 - q
  q ~ dbeta(1, 1)
}

#INITIAL VALUES
Inits list(q=0.5)

#DATA
Data list(y=c(1,1,1,4,2,6,7,16,23,17,44,23,28,14,6,54,34,42,79,72,47,80,176,91,51,146,
117,77,100,226,103,138,270,101,145,86,69,91,68,88,72,97,44,56,49,38,35,21,39,8,14,8,9,
11,2,0,3,0,2,1,0,1,1,0,0,0,0,0,0,0,0,0,0))
```

## Reed-Frost model

```
model{
  y[1] ~ dbin(p[1], x[1])      # Likelihood
  p[1] <- 1 - pow(q, InInf)
  N <- 10800000      #Population size
  x[1] <- 0.2*N
  InInf <- 1
  for(j in 2:73){
    y[j] ~ dbin(p[j], x[j])    # Likelihood of Reed-Frost model
    p[j] <- 1 - pow(q, y[j-1])
    x[j] <- x[j-1] - y[j]
  }
  # Prior
  q ~ dbeta(1, 1)
}

#INITIAL VALUES
Inits list(q=0.5)

#DATA
Data list(y=c(1,1,1,4,2,6,7,16,23,17,44,23,28,14,6,54,34,42,79,72,47,80,176,91,51,146,
117,77,100,226,103,138,270,101,145,86,69,91,68,88,72,97,44,56,49,38,35,21,39,8,14,8,9,
11,2,0,3,0,2,1,0,1,1,0,0,0,0,0,0,0,0,0,0))
```





## APPENDIX 2

### Multitype epidemic model with age groups

```
model{
  N <- 10800000          #Population size
  for(i in 1:3){        # Work out the first week for the three age groups
    S[i,1] <- qq[i] * 0.2 * N          #0.2 is the proportion of non-vaccinated
    Ii[i,1] ~ dbin(r[i,1],S[i,1])      #Likelihood
    r[i,1]<- 1-pow(1-p/N,M[i,1])
    M[i,1]<- inprod(C[i,i], Ii[i,1])
  }
  for(i in 1:3){        # Double loop required for the 3 age groups
    for(j in 2:73){    #Draw the weekly infected per age group
      M[i,j] <- inprod(C[i,i], Ii[i,j])
      Ii[i,j] ~ dbin(r[i,j],S[i,j])    #likelihood
      r[i,j]<- 1-pow(1-p/N,M[i,j])
      S[i, j] <- S[i, j-1] - Ii[i,j]
    }
  }
  # Prior
  p ~ dunif(0,1)
}

#INITIAL VALUES
Inits list(p=0.2)
```



## **ABBREVIATION TABLE**

AAFP: American Academy of Family Physicians

AAP: American Academy of Pediatrics

ACIP: Advisory Committee on Immunization Practices

ARDS: Acute Respiratory Distress Syndrome

BGW: Bienamyé-Galton-Watson Branching Process

CDC: Centers for Disease Control and Prevention

ELISA or EIA: Enzyme-linked Immunosorbent Assay

GRF: Generalized Reed Frost model

GSE: Generalized Stochastic Epidemic

HNIG: Human Normal Immunoglobulin

IgG: Immunoglobulin G

IgM: Immunoglobulin M

MCMC: Markov Chain Monte Carlo

MCV: Measles-Containing Vaccine

MMR: Measles-Mumps-Rubella

MMRV: Measles-Mumps-Rubella-Varicella or Chickenpox

NHS: National Health Service in United Kingdom

NPHO: National Public Health Organization

PCR: Polymerase Chain Reaction

PAHO: Pan American Health Organization

RNA: Ribonucleic acid

RT-PCR: Real Time - Polymerase Chain Reaction

SSPE: Subacute Sclerosing Panencephalitis

WHO: World Health Organization