

# **Modeling Large Scale Epidemics of Meningococcal Disease in Europe**

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## ABSTRACT

Meningococcal disease is a severe acute infectious disease caused by the bacterium *Neisseria meningitidis* (aka meningococcus). The infectious agent affects mainly children and young adults. *Neisseria meningitidis* belongs to a specific class of pathogens, accidental pathogens, since the disease results in the death of both the host and the infectious agent. Epidemics of meningococcal disease happen sporadically, in small clusters, and disease incidence has been reported from all the European countries. Since 1999, a surveillance network for meningococcal disease is monitoring the activity of the infectious agent in 17 of these countries. In our study, we combine empirical information on the incidence and death rate due to meningococcal disease with data on demographics, socio-economics and health care resources in an attempt to develop a statistical model that can describe the patterns observed. Furthermore, we expand an already developed model for meningococcal disease to a metacommunity to theoretically study how patch dynamics change when more than one patch is connected in a network topology. The results of our study can have important implications in the control and prevention of future epidemics in newly built networks such as that of the European Union.

## **RESUME**

La méningite est une maladie infectieuse aiguë et sévère causée, entre autres, par la bactérie *Neisseria meningitidis* (le méningocoque). Cet agent infectieux touche principalement les enfants et les jeunes adultes. *Neisseria meningitidis* appartient à une classe particulière de pathogènes, pathogènes accidentels, puisque la maladie entraîne tant la mort de l'hôte que de l'agent infectieux. Les épidémies de méningites apparaissent sporadiquement, sous formes de petits groupes de cas, et son incidence est rapportée par tous les pays européens. Depuis 1999, un réseau de surveillance international sur la méningite assure le monitorage de l'activité de l'agent infectieux parmi 17 de ces pays. Dans notre étude, nous combinons l'information empirique sur l'incidence et le taux de mortalité par méningite avec des données démographiques, socio-économiques et les ressources de santé en vue de développer un modèle qui décrit les profils observés. De plus, nous adaptons un modèle déjà existant pour la méningite à une métapopulation pour étudier théoriquement comment la dynamique des petits groupes change lorsque plus d'un groupe est connecté dans un réseau topologique. Les résultats de notre étude auront des retombées importantes pour le contrôle et la prévention d'épidémies futures dans de nouveaux réseaux tels que celui de l'Union européenne.

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## INTRODUCTION

Few infections can cause the social stress that meningococcal disease causes when entering a community. The ability of *Neisseria meningitidis* to kill a healthy child within a few hours is the major reason for this fear. Even with antimicrobial therapy, the introduction of a vaccine against serogroup C meningococcal disease and the availability of advanced intensive care, the overall case fatality rates have remained relatively stable, at around 10% over the past 20 years, with a rate of up to 40% among cases with meningococcal sepsis (Rosenstein et al., 2001). Between 10 and 20% of the survivors develop permanent sequelae, such as epilepsy, mental retardation, or sensorineural deafness (Wilder-Smith & Memish, 2003).

The World Health Organization (WHO) characterized meningococcal disease as a serious infectious illness that causes over 500,000 cases annually worldwide, a number that is frequently accentuated when large epidemic outbreaks occur (Tikhomirov et al., 1997).

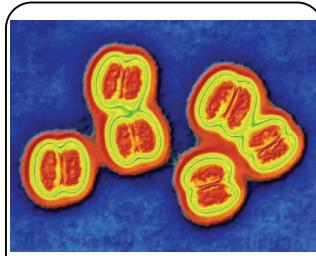


Figure I.1. False colour electron micro-graph of *N. meningitidis*. ©Google Images



Figure I.2. Political map of Europe. © Google Images

## **CASE STUDY: 17 EUROPEAN COUNTRIES**

In my study I will monitor and model the epidemics in the following European countries: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Malta, Netherlands, Norway, Portugal, Spain, Switzerland, and United Kingdom of Great Britain and Northern Ireland, from 1999 to 2004. The thesis will include two chapters, one focused on an epidemiological surveillance of meningococcal disease and the other on the development of a theoretical model that aims to simulate the spatiotemporal patterns of the disease at a larger scale.

## **ETIOLOGIC AGENT**

The *Neisseria* family consists of more than ten species. Only two of them are of great clinical importance: *Neisseria gonorrhoeae*, responsible for gonorrhea, and *Neisseria meningitidis*, responsible for meningococcal disease. *Neisseria meningitidis* (also known as meningococcus) is an aerobic, gram negative,  $\beta$ -proteobacterial, encapsulated species with a coccoid shape that is restricted to human reservoirs, and can not survive in the environment (Rosenstein et al., 2001). Meningococci are highly susceptible against dry heat, light and disinfectants.

Outbreaks of meningococcal infection are known to have occurred during all wars since Vieusseaux in Switzerland first described the illness in 1805 (Vieusseaux, 1805). Anton Weichselbaum, from Geneva, Switzerland, was the first to isolate the causative

agent, *Neisseria meningitidis*, from the cerebrospinal fluid of a patient and identified it as the cause of meningitis in 1887 (Brandtzaeg & van Deuren, 2005).

Meningococci are traditionally classified into serogroups by serological typing based on antigenic variation of the capsular polysaccharide; into serotypes by the PorB outer-membrane (OMP); and into serosubtypes by the PorA OMP and immunotypes, by the lipopolysaccharide (LPS) (Brandtzaeg & van Deuren, 2005). Each of these characteristics can be determined by specific antisera and monoclonal antibodies. The capsule of the bacterium plays an important role in determining the virulence since non-encapsulated strains rarely produce clinical disease (Frasch, 1987). At least 13 main serogroups of meningococci have been identified so far: A, B, C, D, E29, H, I, K, L, W135, X, Y and Z. Only five of these serogroups (A, B, C, W135 and Y) are of clinical importance as they cause more than 90% of the invasive disease worldwide. Serogroup A causes meningitis in almost all cases, with or without meningococcemia and other manifestations. Serogroups B and C are mainly responsible for meningococcemia with or without meningitis and other manifestations such as petechial rash, pericarditis and myocarditis. Serogroup W135 is more frequently associated with acute and fulminant meningococcemia, as well as other severe complications than other serogroups. Serogroup Y causes most cases meningococcal pneumonia but is more rarely involved in meningitis and severe forms of meningococcemia.

## **MODES OF TRANSMISSION**

Meningococci are obligate commensals in man and colonize the nasopharyngeal mucosa without affecting the host, also known as carriage. *N. meningitidis* exhibits age-dependent levels of asymptomatic carriage ranging from 5 to 40% in all human populations examined to date. The nasopharynx is the primary site of meningococcal colonization. The microorganism must adhere to the mucosal surface, utilize locally available nutrients and evade the human immune system.

Meningococcus produces a number of structures and molecules that are important in its relation to the human host: adhesion molecules, receptors capable of binding to human transferring and lactoferrin, and an extracellular IgA<sub>1</sub> protease with the capability to cleave human IgA<sub>1</sub> (Tzeng & Stephens 2000; Brandtzaeg & van Deuren, 2005).

*Neisseria meningitidis* spreads from person to person by contact with upper respiratory secretions of nasopharyngeal carriers, such as by kissing, and less efficiently by aerolised droplets. The bacteria attach to and multiply on the mucosal cells of the nasopharynx. Colonization of the nasopharynx is mediated by pili and outer membrane proteins such as Opc and Opa which interact with epithelial cells (Tzeng & Stephens 2000). In a small proportion (less than 1%) of colonized persons, the organism penetrates the mucosal cells and enters the blood stream. Carriage may last a long time (at months) in about 25% of carriers, is intermittent in another third, and is transient or infrequent in the remaining 40% (Anderson et al., 1998). Asymptomatic carriage is an age-dependent phenomenon. Carriage may induce a strain specific immunity directed against a variety of targets such as capsular polysaccharides, lipopolysaccharides, and porins. Frequent

encounter of human population with a circulating pathogenic strain has been reported to induce herd immunity.

## ***CLINICAL DESCRIPTION AND TREATMENT***

Clinical descriptions of meningitis were documented as long ago as the 16<sup>th</sup> century. Invasive infection with *N. meningitidis* may cause several clinical syndromes, including meningitis, bacteremia, sepsis and pneumonia. Other manifestations of meningococcal disease include septic arthritis, purulent pericarditis, conjunctivitis, otitis, sinusitis, and urethritis. Symptoms of meningitis typically include the sudden onset of a stiff neck, high fever and headache. A petechial rash may be present. Nausea, vomiting and mental confusion are often also present. Nearly one-fifth of survivors experience debilitating sequelae, including hearing or visual loss, learning disabilities or mental retardation, seizures, and amputation of limbs.

The major impact of meningococcal disease is among children. Community-based studies have shown that the attack rate and case fatality ratio can be up to twenty times that of the adult population. Peltola et al. (1982) reported a



Figure I.3. Clinical symptoms of meningococcal disease © Google Images

shift in the age distribution of the disease towards older children, although the highest incidence rate was among children under the age of 5 years old.

Due to the rapidity and severity of the disease, urgent measures must be taken for any patient displaying signs of meningococcal infection. Treatment of meningococcal disease has two facets: antibiotic therapy and supportive care are emergency measures for any case. A range of antibiotics may be used for treatment including penicillin, ampicillin, chloramphenicol, and ceftriaxone. Before the discovery and use of sulfonamides and antibiotics, meningococcal disease was fatal in about 70-80% of cases. Meningococci do not seem to be particularly efficient in developing resistance to antimicrobial agents (Vázquez et al., 2007).

## ***EPIDEMIOLOGY***

The spatial patterns of the disease vary considerably, occurring sporadically in small clusters throughout the world with seasonal variations. Major epidemics arise very rapidly, reaching a peak within a few weeks. Incidence rates often remain elevated for 1 to 2 years after the appearance of an epidemic. Wherever this disease is endemic, there is a risk of periodic epidemics.

In Europe, approximately two thirds (63%) of the reported cases of meningococcal disease are caused by serogroup B, and about one third (30.4%) are caused by serogroup C. A small number of remaining cases are serogroup Y (1.5%), serogroup W-135 (1.4%) and serogroup A (0.7%). The proportion of group B strains is especially high in Norway, The Netherlands, Germany, and Denmark, and high or increasing proportions of group C strains are reported from the Czech Republic, Slovakia, Greece, Republic of Ireland, Spain, and the UK.

When we compared distributions per serogroup by analyzing the average number of meningococcal cases in each age group (data from 17 European countries; results are shown

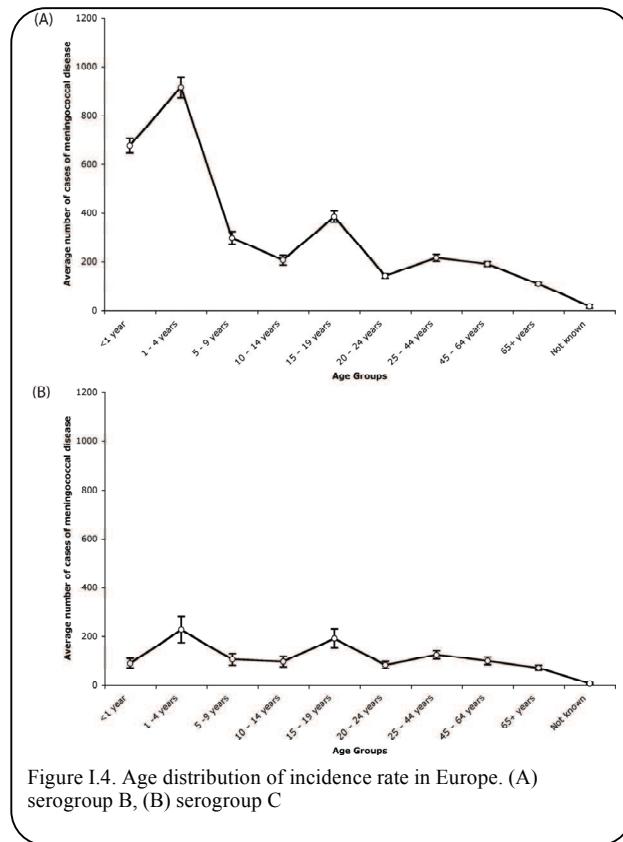


Figure I.4. Age distribution of incidence rate in Europe. (A) serogroup B, (B) serogroup C

in the figure I.6), it was shown that young children (0–4 years of age), and adolescents (15–19 years of age) accounted for the highest percentages of cases of serogroup B infections. When serogroup C was compared with serogroup B, the percentage of cases was lower for infants (1–11 months of age) and higher in adolescents. The distribution of cases of serogroup Y was markedly higher in older individuals (>65 years of age). For serogroup W-135 the distribution of cases reported higher percentages for infants and the elderly (results not shown).

## **RISK GROUPS**

***Close contacts of infected individuals*** – meningococcal disease is usually spread by airborne droplets. Crowding therefore, facilitates transmission. This is confirmed by the observed number of cases among the families and close contacts of patients with meningococcal disease. Munford et al. (1974) studied rates of carriage of serogroup C meningococcal disease during an epidemic in Sao Paolo, Brazil, and they reported higher rates of carriage in households with a case of meningococcal disease than in households without a case. They also reported that within households with case higher rates were reported for the people living in the house than for other people having household contact with the patient (Munford et al., 1974). More recently, Deutch et al. (2004) performed a nationwide registry-based case-control study in Denmark and found that the risk for meningococcal disease increased with increasing household density.

***Travelers*** – in certain countries of the world, meningococcal illness is known to be epidemic or hyper-endemic. Travelers from low endemic areas traveling to large parts of Africa, Asia, the Middle East and parts of South America may unwittingly place themselves at increased risk of meningococcal infection. The annual pilgrimage to Mecca (Hajj), which attracts more than two million pilgrims from all over the world, is also a situation providing ideal conditions for transmission of meningococci as a consequence of overcrowding. Returning pilgrims may spread the bacteria to their household contacts or to the community at large. In 2000, W135, a previously rare meningococcal serogroup

strain was identified as the cause of an outbreak among returning Hajj pilgrims from Saudi Arabia (Taha et al., 2000). Taha et al. (2000) reported that the strain caused hyperendemic disease activity, outbreaks and small epidemics in diverse countries (UK, France, Netherlands, Oman, Kuwait, Indonesia, Singapore and the USA).

***Incoming university students/college freshmen, particularly when living in dormitories*** – the increased risk of these groups has been confirmed by several studies in the U.K. and the U.S (Imrey et al., 1995).

***Military recruits*** – the routine use of meningococcal vaccines has largely reduced the incidence of meningococcal disease in recruits serving in the army of many European countries (Blackwell et al., 1992).

***Occupational hazard to microbiologists*** – in 2000, two cases of fatal laboratory-acquired meningococcal disease have been reported from Alabama and Michigan, U.S.

***Individuals at higher health risks for disease*** – patients suffering from some immunodeficiency states, asplenia, respiratory track infections, malnutrition and anaemia may be at increased risk of developing single or recurrent clinical meningococcal infections (Pollard et al., 2000).

***Smoking (including passive smoking)*** may also increase the risk of infection. Coen et al. (2006) reported that exposure to cigarette smoke or to smokers increased the

risk of meningococcal disease in adolescents, in a population-based case-control study they carried in six regions in UK. In a different study, Blackwell et al. (1992) examined Greek military recruits and they reported that carriage of meningococcal disease was associated with smoking.

***Age and gender*** – meningococcal disease is typically related to age and gender. Even though it may occur at any time of life, it is mainly a childhood disease that tends to affect males slightly more frequently than females (Caugant et al., 2007). In endemic conditions, incidence is generally the highest in young children and shows a gradual decrease afterwards. However, the age distribution of meningococcal disease varies from area to area. Differences are related to serogroup and epidemiological pattern: serogroup B affects younger children than do serogroups A and C, and epidemics are clearly characterized by a shift towards older age groups.

***Seasonally varying environmental conditions*** – have been related to meningococcal disease. In many tropical countries, most cases occur during the dry season, as for instance in Meningitis Belt (area in sub-Saharan Africa, from Senegal to West Ethiopia), where outbreaks usually begin in the second half of the dry period and have been associated with the Hamantan, a dusty wind from the desert (Sultan et al., 2005). In temperate climates, most cases occur at the end of the winter. In Europe and the United States of America, meningococcal meningitis is most common in the late winter and early spring. These seasonal patterns are related to the overall severity of the climatic conditions, particularly harmful for the integrity of the respiratory mucosa. Seasonal

changes in social habits, including increased crowding, and nutritional status may also play a role.

In 2003, Jensen et al. conducted a study in the County of North Jutland, Denmark, to examine the seasonal variation in meningococcal disease, its magnitude and how it is related to age, gender and meningococcal phenotype. Their results showed a sinusoidal seasonal variation of case numbers with a peak-to-trough ratio of two. They also reported differences between age groups (the most pronounced seasonality being in 5-14 years old), but no differences were found between genders (Jensen et al., 2003).

A year later, Jensen et al. (2004) published a 20-year population study examining whether fluctuations in occurrence of influenza were associated with changes in the incidence rate of meningococcal disease in the County of North Jutland, Denmark. They concluded that the influenza detection rate is associated with the number of meningococcal disease cases in the population during the same week (Jensen et al., 2004).

**Socioeconomic status** – the socioeconomic setting appears as an environmental factor of the disease. Davies et al. (1996) reported that the risk for carriage in some populations appeared to be increased due to low socioeconomic status.

**Air-travel associated meningococcal disease** – commercial aircrafts are suitable environments for the spread of airborne pathogens, including *N. meningitidis*. During the period February 1999 to May 2001, the Centers for Disease Prevention and Control (CDC) received 21 reports. The mean time interval between the completion of the flight

and the onset of illness was 1.9 days. Five patients had onset of illness before arrival. No cases of secondary meningococcal disease among air-travel contacts have been reported.

***Genetic predisposition*** – Several genetic disorders have been reported to increase susceptibility to meningococcal disease. Genetic polymorphisms among components of pathways such as the complement system, the inflammatory response, the coagulation and fibrinolysis pathways, have been shown to be involved in the susceptibility, severity and outcome of meningococcal disease (Emonts et al., 2003). The most profound role in genetically established susceptibility is due to complement deficiencies and defects in sensing and opsonophagocytic pathways as well as combinations of inefficient variants of Fc $\gamma$ -receptors.

Mannose-binding lectin (MBL), a serum protein characterized by both collagenous regions and lectin domains, plays an important role in innate immune defense (Kilpatrick, 2002). MBL deficiency seems to predispose to infections in the general population only during the vulnerable period of life from the ages of 6–18 months of age after the disappearance of the placental transferred maternal antibodies and before the maturation of the child's own adaptive immune system is established. Nevertheless, numerous studies have shown that MBL deficiency may increase the risk for infections in individuals with a concomitant disease or immunodeficiency (Eisen & Minchinton, 2003). However, Dahl et al. (2004) conducted a large population-based study in Denmark where they reported that in ethnically homogeneous Caucasian population, there was no evidence for significant differences in infectious disease or mortality in MBL deficient individuals versus controls. Based on their results MBL deficiency is not a major risk

factor for morbidity or mortality in the Danish adult Caucasian population (Dahl et al., 2004).

Furthermore it has been indicated both in hospital-based and community-based studies that MBL deficiency may increase the risk for meningococcal disease (Hobbs, 1986; Hibberd et al., 1999; Bax et al., 1999; Hermans et al., 1999; Eisen & Minchinton, 2003). Hibberd et al. (1999) stressed the importance of the MBL pathway as a critical determinant of meningococcal disease susceptibility and concluded that genetic variants of MBL might account for a third of all disease cases. Inherited functional deficiency of MBL is observed in as much as 5% of the general population, while as much as 35% of the population carries variant alleles which may cause a dominant decrease in the serum concentration. An important question to be answered is whether vaccination is justified in MBL deficient individuals (Bax et al., 1999).

## **IMMUNIZATION**

Short-term immunity to meningococcal infection due to serogroups A, C, Y and W-135 can be obtained by vaccination with polysaccharide vaccines. Polysaccharide vaccines for these serogroups have been available since 1978 when the first quadrivalent A, C, Y and W-135 polysaccharide vaccine was licensed. These vaccines are not immunogenic in young children (<18 months of age), who represent about 25% of all cases, and induce only short-lived protection (3 years) (Balmer & Miller 2002).

Conjugate vaccines have previously shown that the immunogenicity of polysaccharides can be improved by chemical conjugation to a protein carrier, thereby

eliciting a T-cell dependent antisaccharide antibody response. Meningococcal conjugated vaccine for serogroups A, C, Y and W-135 was first licensed in the U.S. in 2005.

The major challenge in the prevention of meningococcal disease by vaccination is the development of an effective serogroups B meningococcal vaccine. Serogroup B disease is endemic in most industrialized countries, with the burden of disease occurring mainly in young children (>2 years of age). The serogroup B capsular polysaccharide is poorly immunogenic, possibly because it shares homology with glycopeptides of neural cell adhesion molecules. This results in immunological tolerance to the serogroup B polysaccharide, which prevents the production of autoimmune antibodies. It has been proposed that chemical modification of the serogroup B capsular polysaccharide may overcome the observed immunological tolerance. Levy-Bruhl (2006) stated that the hyper-endemicity of meningococcal B invasive disease in Northern France re-emphasizes the need for generic vaccines against meningococcal disease of serogroup B. Getsios et al. (2004) reported that routine vaccination of children and adolescents in Europe was predicted to be cost effective. In Europe as at March of 2004, conjugate meningococcal disease serogroup C vaccination programs had been routinely implemented in Belgium, Iceland, Ireland, the Netherlands, Spain and the UK (EU-IBIS). Austria, Greece and Portugal were following a voluntary vaccination schedule (EU-IBIS).

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# **CHAPTER I**

## **Epidemiological analysis of meningococcal disease in Europe**

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Keywords: review, epidemics, incidence rate, standard death rate, Europe, model,  
sensitivity analysis, uncertainty, databases

## ***ABSTRACT***

Meningococcal disease is a severe acute infectious disease caused by the bacterium *Neisseria meningitidis* (aka meningococcus). The infectious agent affects mainly children and young adults. *Neisseria meningitidis* belongs to a specific class of pathogens, accidental pathogens, since disease is a dead end for both the host and the infectious agent. Epidemics of meningococcal disease happen sporadically, in small clusters, and disease incidence has been reported from all the European countries. Since 1999, a surveillance network for meningococcal disease is monitoring the activity of the infectious agent in 17 of these countries. In our study we combine empirical information on the incidence and death rate due to meningococcal disease with data on demographics, socio-economics and health care resources to develop statistical models that can describe the patterns observed. Our study confirms that meningococcal disease is primarily a childhood disease. We also show that serogroups B and C of meningococcal disease are the main causal agents of disease in Europe. The results of our regression and sensitivity analyses elucidate the importance of overcrowding as a risk for increase in the incidence rate. In addition, average population density per km<sup>2</sup> (crowding) and number of physicians per 100,000 (health care resources) are important factors influencing the death rate due to meningococcal disease.

## **INTRODUCTION**

Few infections can cause the social stress that meningococcal disease causes when entering a community. The ability of *Neisseria meningitidis* to kill a healthy child within a few hours is the major reason for this fear. *Neisseria meningitidis* (aka. meningococcus) is a commensal bacterium of the human nasopharyngeal cavity that accidentally causes invasive meningococcal disease. Meningococcal disease remains an important cause of childhood morbidity and mortality in both more and less developed countries (Hermans et al., 1999). More than 700,000 meningitis cases were reported to the WHO between 1995 and 2003 (Aguado et al., 2005).

Europe has been the focus of many community-based studies on meningococcal disease. The literature shows that epidemics of meningococcal disease have happened in most of the European countries. The European Union, in a recent decision, established a surveillance network to monitor the activity of *Neisseria meningitidis* in the area.

*Neisseria meningitidis* (also known as meningococcus) is an aerobic, gram negative,  $\beta$ -proteobacterial, encapsulated species with a coccoid shape. Strains of meningococci have been classified into twelve serogroups based on the immune specificity of their capsule. Only five of these serogroups (A, B, C, Y, and W135) are frequently isolated from patients with invasive infections. In Europe, serogroup A accounts for 0.7% of the total number of cases (no distinct age-dependent distribution), B for 63% (mainly affecting infants 0-4 years old and teenagers 15-19 years old), C for 30.4% (mainly affecting teenagers), Y for 1.5% (mainly affecting elderly people, >65 years old), and W135 for 1.4% (affecting infants and elderly) (EU-IBIS).

*Neisseria meningitidis* is transmitted from person to person by upper-respiratory tract secretions. The meningococci colonize the nasopharyngeal mucosa without causing harm to the host. This phenomenon is called asymptomatic carriage and it is a characteristic of a certain class of pathogens called accidental pathogens. Asymptomatic carriage of meningococci is an age-dependent phenomenon, with carriage rates usually ranging from 10 to 35% in young adults in Europe at any time (Caugant et al., 2007). Studies performed in Europe have shown that carriage rates are very low in infants, increase in teenagers, peak in adults between 20 and 24 years of age and then decrease to less than 10% in older people (Cartwright et al., 1987; Caugant et al., 1994; Claus et al., 2005).

Occasionally after the onset of colonization (establishment of meningococci in the nasopharyngeal mucosa), meningococci may penetrate the mucosa and enter the bloodstream. For meningococci to evade the human immune system they must retain their polysaccharide capsule, otherwise they will not survive. They also have to survive either the host-cell cytokine production or the complement pathway to make it to the meninges (Rosenstein et al., 2001).

After the bacteria cross the blood-brain barrier endothelium, they reproduce in the subarachnoid space and then they infect the meninges causing their inflammation. Then various forms of meningococcal disease may develop such as meningitis, meningococcemia, and more rarely septic arthritis, pneumonia, purulent pericarditis, conjunctivitis, otitis, sinusitis, and urethritis (Tzeng & Stephens, 2000). The development of disease is considered to be a dead-end for accidental pathogens and is disadvantageous to the spread of the bacteria. Treatment of meningococcal disease has two facets:

antibiotic therapy and supportive care are emergency measures for any suspected case. A range of antibiotics may be used for treatment including penicillin, ampicillin, chloramphenicol, and ceftriaxone.

The spatial patterns of the disease vary considerably, occurring sporadically in small clusters around the world with seasonal variations (Jensen et al., 2003; Pascual & Dobson, 2005). Major epidemics arise rapidly, reaching a peak within a few weeks. Incidence rates remain high for 1 to 2 years after the outbreak.

The incidence of meningococcal disease varies across Europe from less than 1 to up to 6 cases per 100,000 population. In addition, the case fatality rate between European countries ranges between 4 and 20%, with the overall case fatality rate being around 8% (Trotter et al., 2005). Despite the successful vaccination programs against meningococcal disease of serogroup C, meningococcal disease remains a significant problem. In Europe the majority of cases are caused by serogroup B, for which strain there is no efficacious vaccine to protect the population from bacterial infection (Coen et al., 2006).

Past studies have identified an array of factors influencing the carriage rate of meningococci. Such factors include closeness of social contacts, crowding (in closed and semi-closed populations), environmental seasonality, upper-respiratory track infections, smoking (both active and passive), low socioeconomic status, travelling, age and gender, and others (Olcen et al., 1981; Caugant et al., 1992, Stephens, 1999; Stuart et al., 1989; Blackwell et al., 1992; Kremastinou et al., 1994; Davies et al., 1996; McLennan et al., 2006). However, most of these studies were based on local (city or town) or regional (region or district) populations and, so far, no one has considered these factors at the multi-regional (national) to continental level.

Here we will develop a robust statistical model to describe the mortality and incidence of meningococcal disease at a larger scale by quantifying the previously mentioned factors. We will try to elucidate parameters that are important in a larger scale and explore how they affect the incidence and the mortality due to meningococcal disease. Towards this goal we will analyze data and examine patterns from 17 European countries from 1999 to 2004.

## ***METHODS***

### **Study site and Databases**

For the purpose of our study we will attempt to statistically model the occurrence of meningococcal disease in Europe using data from the WHO – Regional Office for Europe and EU-IBIS databases. The countries included in our study are Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Malta, Norway, the Netherlands, Portugal, Spain, Switzerland and the United Kingdom of Great Britain and Northern Ireland. The selection of the countries was based on the availability of data in the above-mentioned databases. The window frame of our study includes 6 years and it spans from 1999 to 2004.

The European Union Invasive Bacterial Infections Surveillance Network (EU-IBIS) began in 1999 and is funded by the European Commission DG Sanco. The European Commission Decision No 2119/98/EC on setting up a network for the epidemiological surveillance and control of communicable diseases in the European

Union (EU) stated as a priority "Diseases prevented by vaccination". *Haemophilus influenzae* and *Neisseria meningitidis* are infectious agents that come within this category. The *N. meningitidis* network was built upon two existing networks: (1) the European Monitoring Group on Meningococci (EMGM), a consortium of reference for microbiologists and epidemiologists working in Europe to exchange information on meningococcal infection; (2) the Bacterial Meningitis in Europe surveillance network (also known as European Bacterial Meningitis Surveillance Project, or EBMS), which was established in 1988 by Norman Noah and colleagues with the aim of describing how the epidemiology of meningococcal disease varied across Europe, to inform best practice in vaccine and chemoprophylactic policy and to facilitate contacts between epidemiologists and microbiologists.

The World Health Organization (WHO) is a specialized agency of the United Nations (UN) that acts as a coordinating authority on issues of international public health. The WHO Regional office for Europe has developed the European Health for All database (HFA-DB), a database that contains data on about 600 health indicators, including basic demographic and socioeconomic indicators; some lifestyle- and environment-related indicators; mortality, morbidity and disability; hospital discharges; and health care resources, utilization and expenditure.

## **Response Variables and Parameters**

The mortality rate due to meningococcal disease was measured as 'standardized death rate per 100,000 population', for each country. The incidence rate for each country

was defined as the incidence rate (per 100,000 population) of laboratory-diagnosed confirmed and probable cases of invasive meningococcal disease. We have data on the total incidence rate as well as on the age-specific and serogroup-specific incidence rates. The datasets we used include data from 1999 to 2004.

We have also compiled data on demographics, socio-economics, and health care resources. Since meningococcal disease can be triggered by over-crowding, we assumed that two important demographic parameters should be the average population density per  $\text{km}^2$ , and the percent of urban population. Other reports have shown that most cases of the disease occurred in populations of low socio-economic status. Here we quantify the status of each country using the Human Development Index (HDI), which represents the average of the following three indices: Life Expectancy Index, Education Index (Adult Literacy Index, Gross Enrolment Index) and GDP Index, and is published annually by the United Nations. Finally, we used the number of hospital beds per 100,000 population, as well as the number of physicians per 100,000 population as indicators of health care resources, based on previous studies. Our parameter list is highly dependent on the quality of the databases. Datasets with incomplete values were not included in the analysis. Many potentially important factors could not be included in the statistical analysis because no reliable data are available for them.

## **Statistical Analysis**

The purpose of our study is to identify key empirical parameters for a robust statistical model that can explain the incidence and mortality (per 100,000 population) among Europeans at an inter-regional scale.

First, we examined time-series data from the countries of our dataset to explore qualitatively the dynamics of the incidence rate of the disease. One of our main questions here is whether the disease dynamics occur in or out of phase among countries. The World Health Organization (WHO) has stated that since the 1980's no evident periodicity has been observed and that intervals between epidemics became more irregular (WHO, 1998). Therefore, the answer to this question will have important implications in the robustness of the statistical model.

Meningococcal disease incidence is age-dependent with infants (0 – 4 years old) and teenagers (15 – 19 years old) reporting most of the cases. Incidence rate should not be confused with carriage rate, as social habits and the status of the human immune system play important role in the incidence of the disease. Meningococcal disease serogroups B and C are responsible for most of the cases, with serogroup B causing more cases than C (Rosenstein et al., 2001). To explore whether these patterns are observed among European countries we collected age-specific and serogroup-specific data from the EU-IBIS database. We calculated the average number of cases of meningococcal disease for each age group.

Finally, we performed two step-wise linear regression analyses, with either incidence rate per 100,000 population or standardized death rate per 100,000 population as dependent variables. Our independent variables entered the analyses in a forward

manner (the probability of F for entry is 0.05 and for removal is 0.10) and included the demographic, socio-economic and health care resource parameters presented previously. For the regression analysis we used the average of the variable over time, due to the out-of-phase occurrence of the disease.

Age-standardization facilitates comparisons across geographical areas by controlling for differences in the age structure of local populations. We used the direct method of age-standardization, where the mortality or incidence rate is the number of events that would occur in a standard population (per 100,000) if that population had the age-specific rates of a given area. The rates are standardized to the European Standard Population (Table 1.1). The age-standardized rate for an area is defined as follows: *Age-*

$$\text{standardized rate for an area} = \frac{\sum S_i r_{ia}}{\sum S_i}, \text{ where } S_i \text{ are the standard population sizes in the}$$

relevant age groups (*i*) and  $r_{ia}$  are the age-specific rates in age groups *i* in area *a*. The age groups used for deriving the standardized rates are as defined in the European Standard Population (Table 1.1).

We also performed a simple sensitivity analysis to test the robustness of models obtained from the stepwise linear regression. Sensitivity analysis is used to determine how “sensitive” a model is to changes in the value of the parameters of the model and to changes in the structure of the model (Salteli et al., 2004). Empirical data are subject to many sources of uncertainty such as errors of measurement or absence of information. This uncertainty imposes a limit on our confidence in the response of the model. In our sensitivity analysis we tested both the incidence rate and death rate models to individual uncertainty of each parameter up to 50%. For the performance of all statistical calculations we used the SPSS statistical package.

## **RESULTS**

Incidence rate was highly variable among the 17 European countries studied from 1999 to 2004, with Iceland, Ireland, Malta, the Netherlands and the United Kingdom reporting the highest rates (Figure 1.1). Dynamics can also be characterized as being out of phase, i.e. years of maximum and minimum incidence do not coincide among most countries (Figure 1.1).

Death rate was highly variable among the 17 countries, ranging from zero to almost 1.2 deaths per 100,000 population (Figure 1.2). Higher death rates were observed for Iceland, Ireland, Malta and the Netherlands. Dynamics of death rate can also be characterized as out of phase.

Infants (0 to 4 years of age) and teenagers (15 to 19 years of age) report most of the cases (Figure 1.3). The average age-standardized number of cases for infants below 1 year of age across all countries from 1999 to 2004 was 866 (674 for serogroup B and 87 for serogroup C); for infants between 1 and 4 years of age the average number of cases was 1303 (914 for serogroup B and 226 for serogroup C); and for teenagers (15 to 19 years old) the average number of cases due to meningococcal disease was 672 (384 for serogroup B and 190 for serogroup C). Figure 1.3 summarizes the results and the standard error for all age groups.

The results of our stepwise linear regression analysis have shown that the urbanization rate of a country has a great impact on incidence rate per 100,000 of meningococcal disease ( $p<0.001$ ,  $R^2= 0.351$ ; Table 1.2I). An increase in the percent of urban population will lead to a corresponding increase in the number of cases observed

annually (Figure 1.4). When the sensitivity of the model was tested, the results showed that the model is robust enough, in the range of uncertainty of each parameter separately.

With standardized death rate per 100,000 population as dependent variable the selected parameters explain a higher proportion of the variability ( $R^2 = 0.586$ ) than in the previous case. The significant parameters ( $p < 0.0001$ ) for this model are the average population density per  $\text{km}^2$ , and the number of physicians per 100,000 population (Table 1.2II). An increase in the average population density will lead to an increase of death rate while an increase in the number of physicians per 100,000 population will lead to a corresponding decrease in the death rate (Figure 1.5). The results of the sensitivity analysis for this model suggest that the model is robust to individual uncertainty of each parameter in the range of -50% to +50%.

Finally, our analyses constantly identified the countries Ireland, Iceland, Malta and the United Kingdom as outliers, i.e patterns of mortality and incidence in these four islands were not well described by the selected parameters. These results suggest that factors absent from our analyses may have an effect on the incidence and mortality due to meningococcal in these countries.

## **DISCUSSION**

Meningococcal disease in Europe appears to be endemic in all countries examined in our study with incidence rates ranging from below 1 to almost 12 cases per 100,000 population in certain years. Ireland, Iceland, Malta, the Netherlands and the United Kingdom show rates above the threshold of epidemics ( $> 3$  cases per 100,000 population).

Our results confirm that meningococcal disease is primarily a childhood disease affecting infants and young adults (ages 15 to 19); however, cases have been reported in other age groups. Serogroup B is the dominant serogroup of *Neisseria meningitidis* causing most of the cases recorded during the 6 years we studied the disease. Serogroup C seems to cause fewer cases than B in our analysis, which is probably due to the intense vaccination strategy against serogroup C disease that was introduced in 1999 in most European countries.

The quality of the ascertainment of the incidence rate of meningococcal disease varies across the different countries in Europe. It has been recently noticed that the percentage of cases ascertained in the various surveillance systems varies from 96% in Denmark to 40% in the UK (Trotter et al., 2005), making the incidence rate record incomplete, and unreliable. Death rate records appear to be more complete. Trotter et al. (2005) estimated that around 85% of the deaths are reported in a capture-recapture analysis they performed. The results from our regression and sensitivity analyses elucidate the importance of overcrowding as a risk for increase in the incidence rate. Even at a large scale (national and continental) an increase in the urbanization rate can trigger a larger number of cases of meningococcal disease. In addition, average population density per km<sup>2</sup> (crowding) and number of physicians per 100,000 (health care resources) are important factors influencing the death rate due to meningococcal disease.

Our study is one of the very few studies to explore epidemics of infectious diseases at a larger scale, pooling data from 17 European countries. It is also one of the first ones in trying to quantify important non-clinical factors that affect the spread of

meningococcal disease at a larger scale and to develop robust statistical models for the incidence and standard death rate per 100,000 population for Europe. Research towards a more continental evaluation of the disease should elucidate distributions of other key parameters in order to build stronger models with forecasting ability based on empirical data.

Furthermore, future studies should try to explain the high risk of meningococcal disease in Ireland, Iceland, Malta, and the United Kingdom. Particular focus should be placed on underlying genetic predisposition to infectious diseases (Kilpatrick DC, 2002). The current literature lacks information on the distribution of important genetic polymorphisms that have been clinically shown to predispose individuals to meningococcal disease.

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**TABLE 1.1: European Standard Population (WHO, 1998)**

<b>Age group</b>	<b>European Standard Population</b>
0	1,600
1-4	6,400
5-9	7,000
10-14	7,000
15-19	7,000
20-24	7,000
25-29	7,000
30-34	7,000
35-39	7,000
40-44	7,000
45-49	7,000
50-54	7,000
55-59	6,000
60-64	5,000
65-69	4,000
70-74	3,000
75-79	2,000
80-84	1,000
85+	1,000
<b>Total</b>	<b>100,000</b>

**TABLE 1.2: Regression analysis models**

I. Incidence rate per 100,000

Parameters	$\beta$	Standard error	Standardized $\beta$	$R^2$
<b>Used</b>				
Average population density per km <sup>2</sup>				
Percent of urban population				
Human Development Index				
Hospital beds per 100,000				
Physicians per 100,000				
<b>Selected</b>				
Percent of urban population	0.59	0.21	0.598	0.357

II. Standardized death rate per 100,000

Parameters	$\beta$	Standard error	Standardized $\beta$	$R^2$
<b>Used</b>				
Average population density per km <sup>2</sup>				
Percent of urban population				
Human Development Index				
Hospital beds per 100,000				
Physicians per 100,000				
<b>Selected</b>				
Average population density per km <sup>2</sup>	0.0001	0.00001	0.557	0.586
Physicians per 100,000	0.001	0.0001	-0.439	

## ***LIST OF FIGURES***

**Figure 1.1:** Incidence rates per 100,000 population due to meningococcal disease of 17 European countries, from 1999 to 2004.

**Figure 1.2:** Standardized death rates per 100,000 population due to meningococcal disease of 17 European countries, from 1999 to 2004.

**Figure 1.3:** Average age-dependent distribution of number of cases of 17 European countries. (A) Total incidence rate, (B) Serogroup B incidence rate, and (C) Serogroup C incidence rate.

**Figure 1.4:** Scatter plots of the incidence rate per 100,000 against each independent variable of our dataset.

**Figure 1.5:** Scatter plots of the standardized death rate per 100,000 against each independent variable of our dataset.

## FIGURES

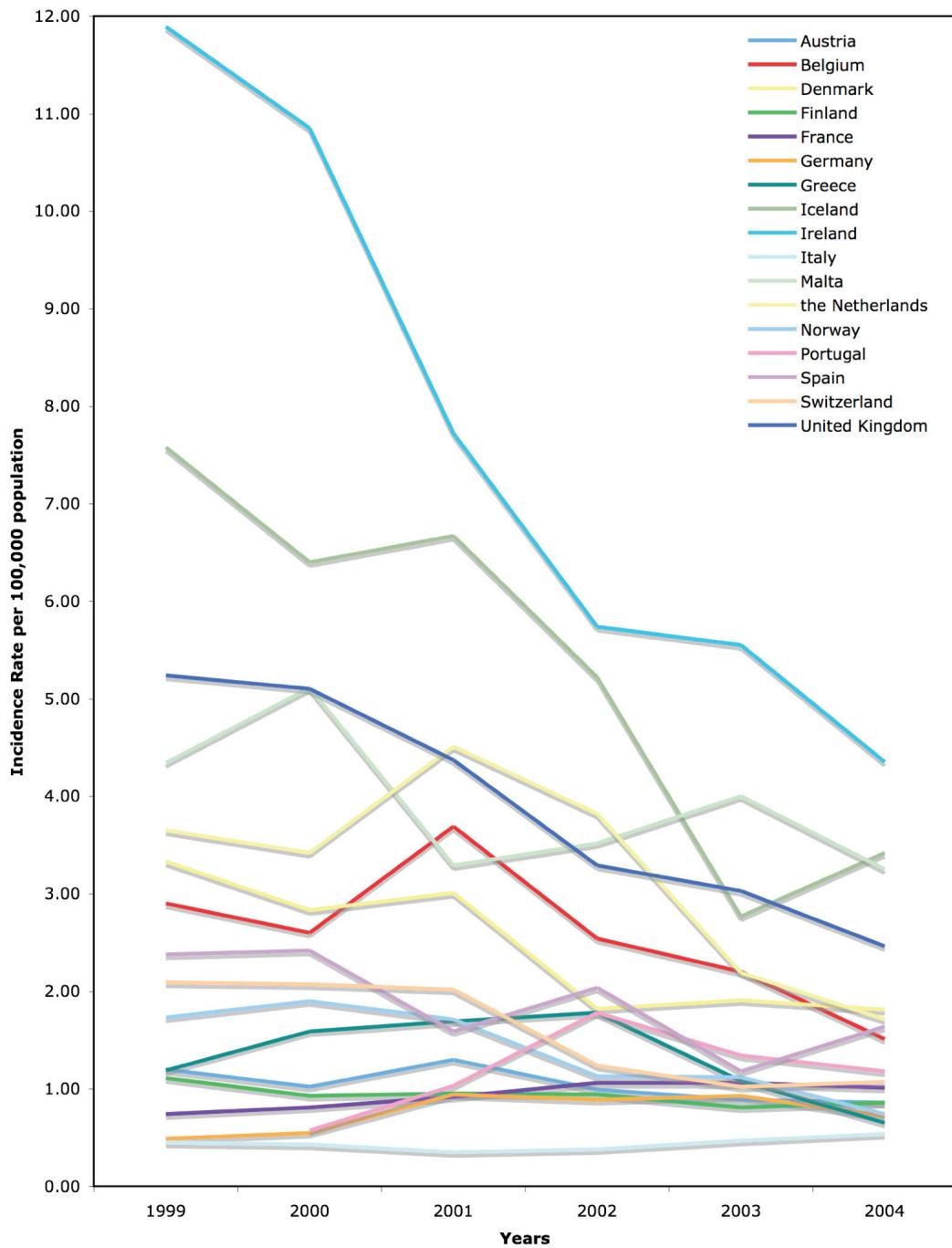
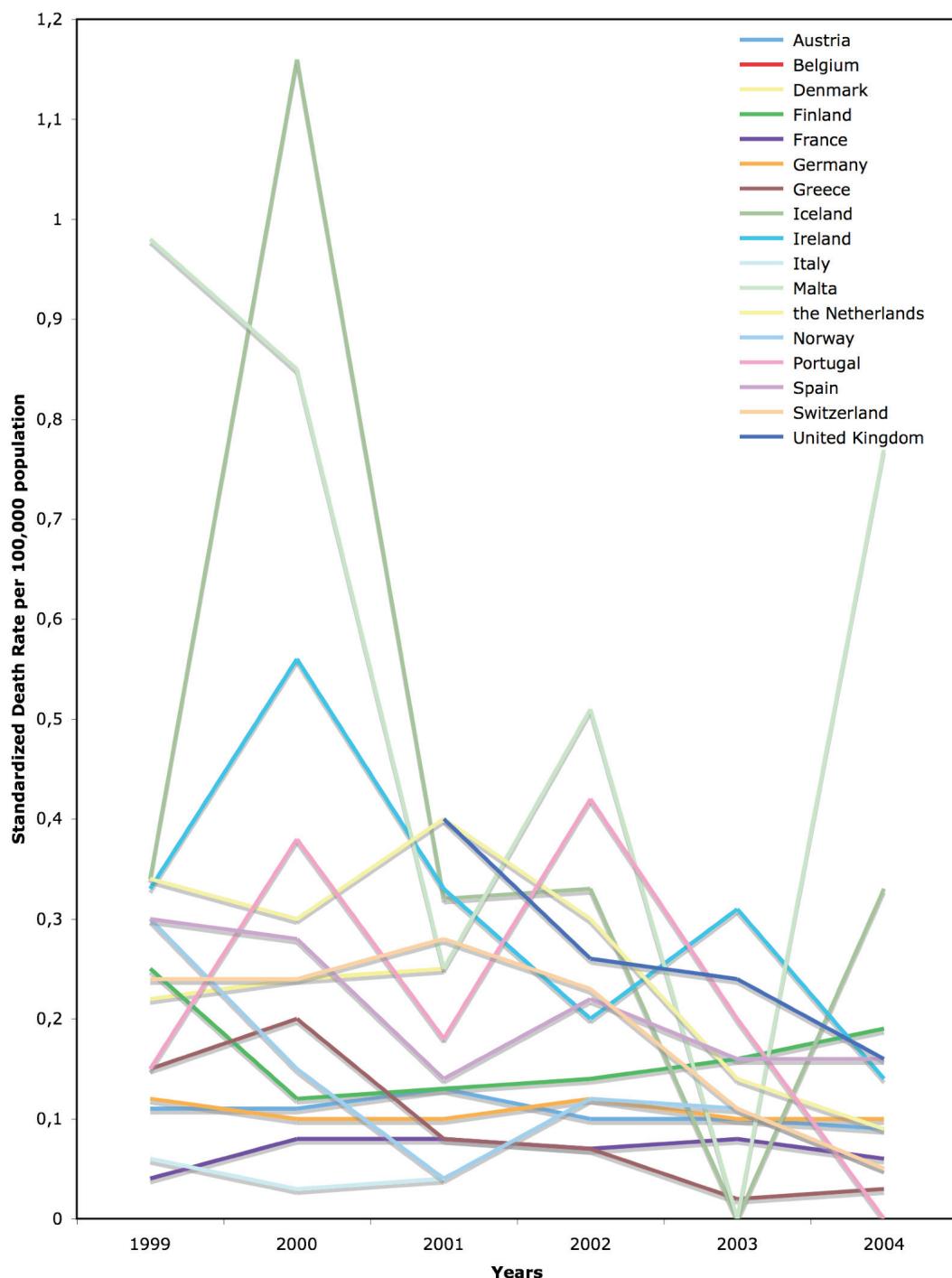
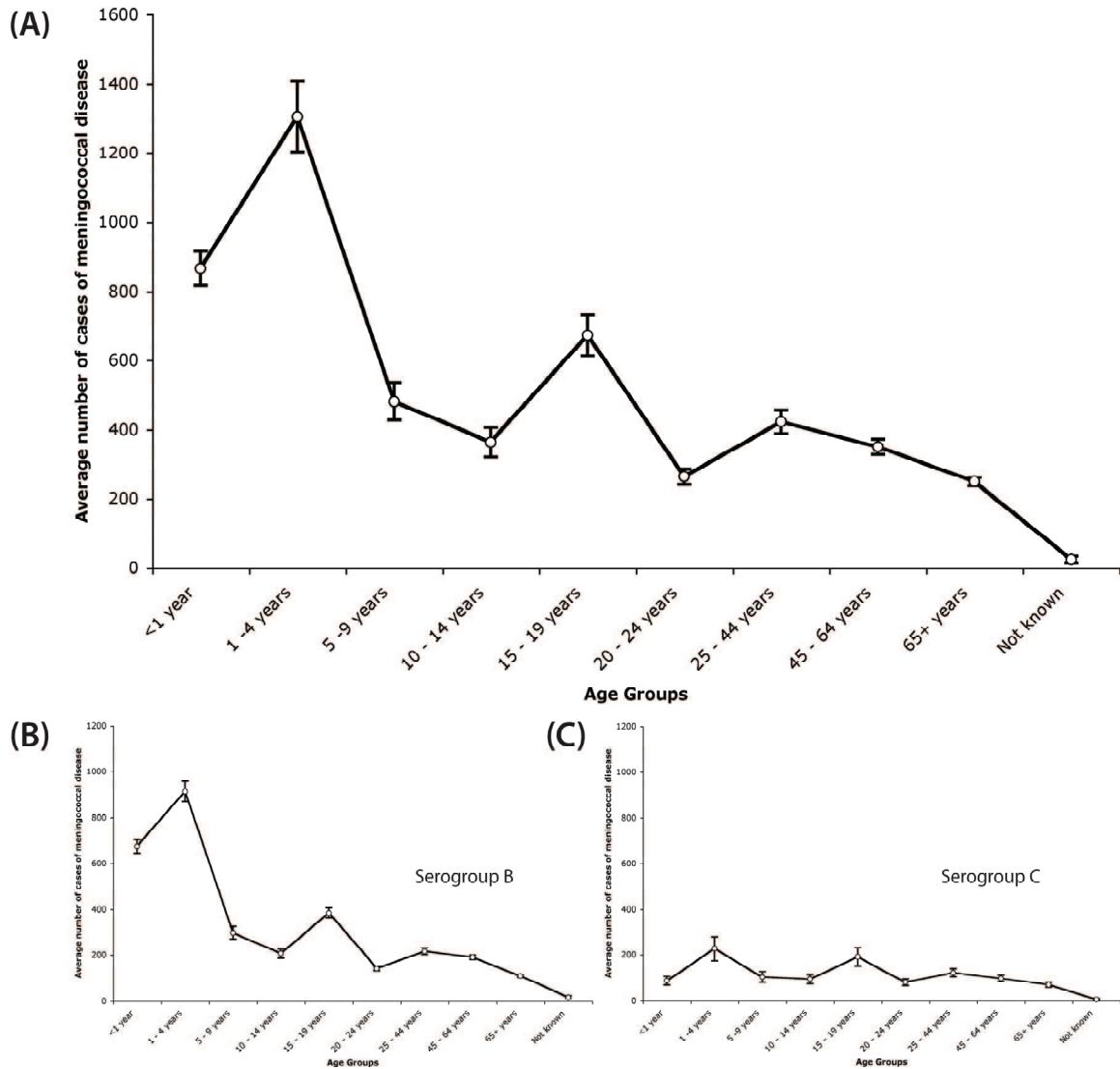


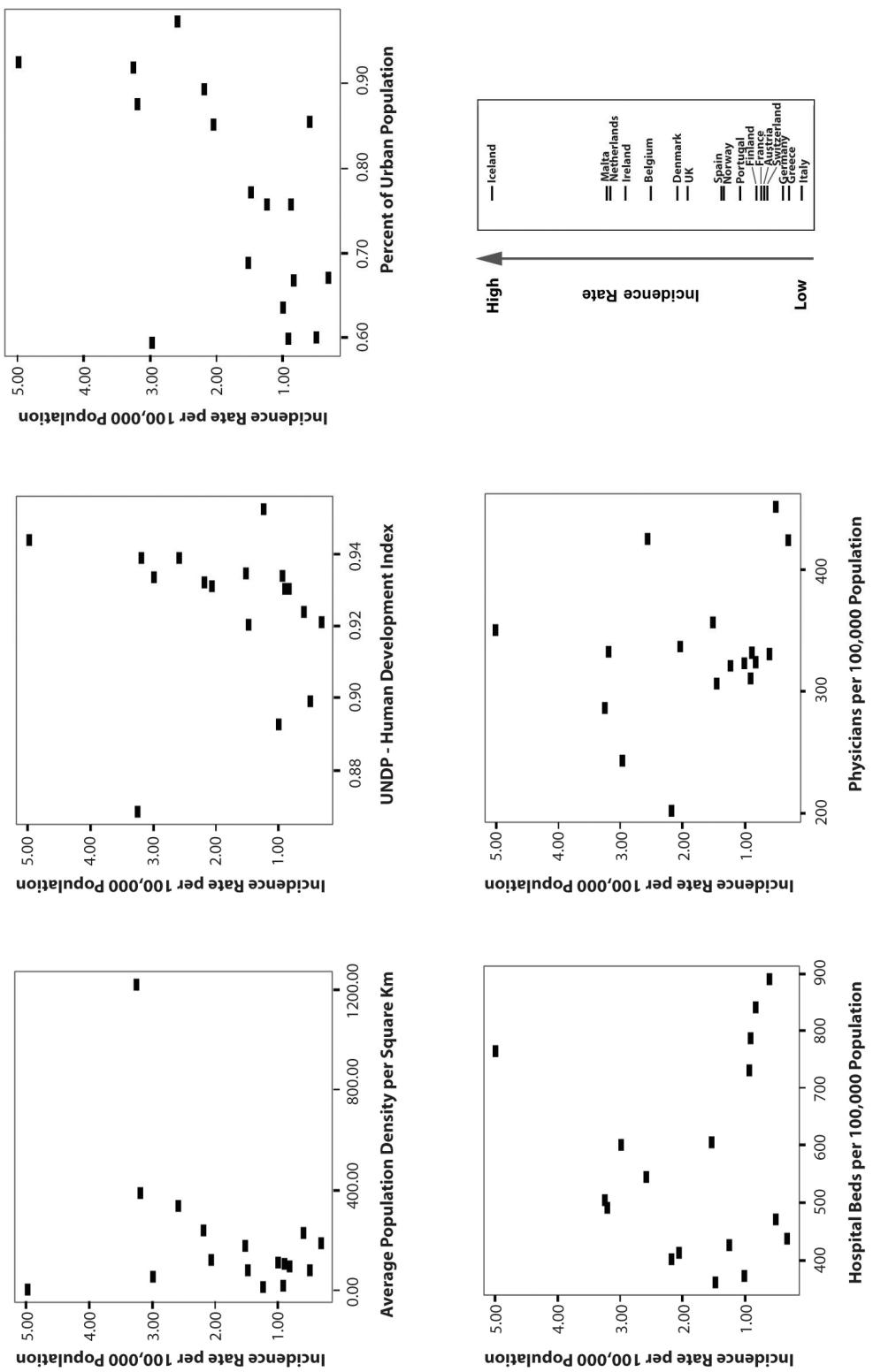
Figure 1.1



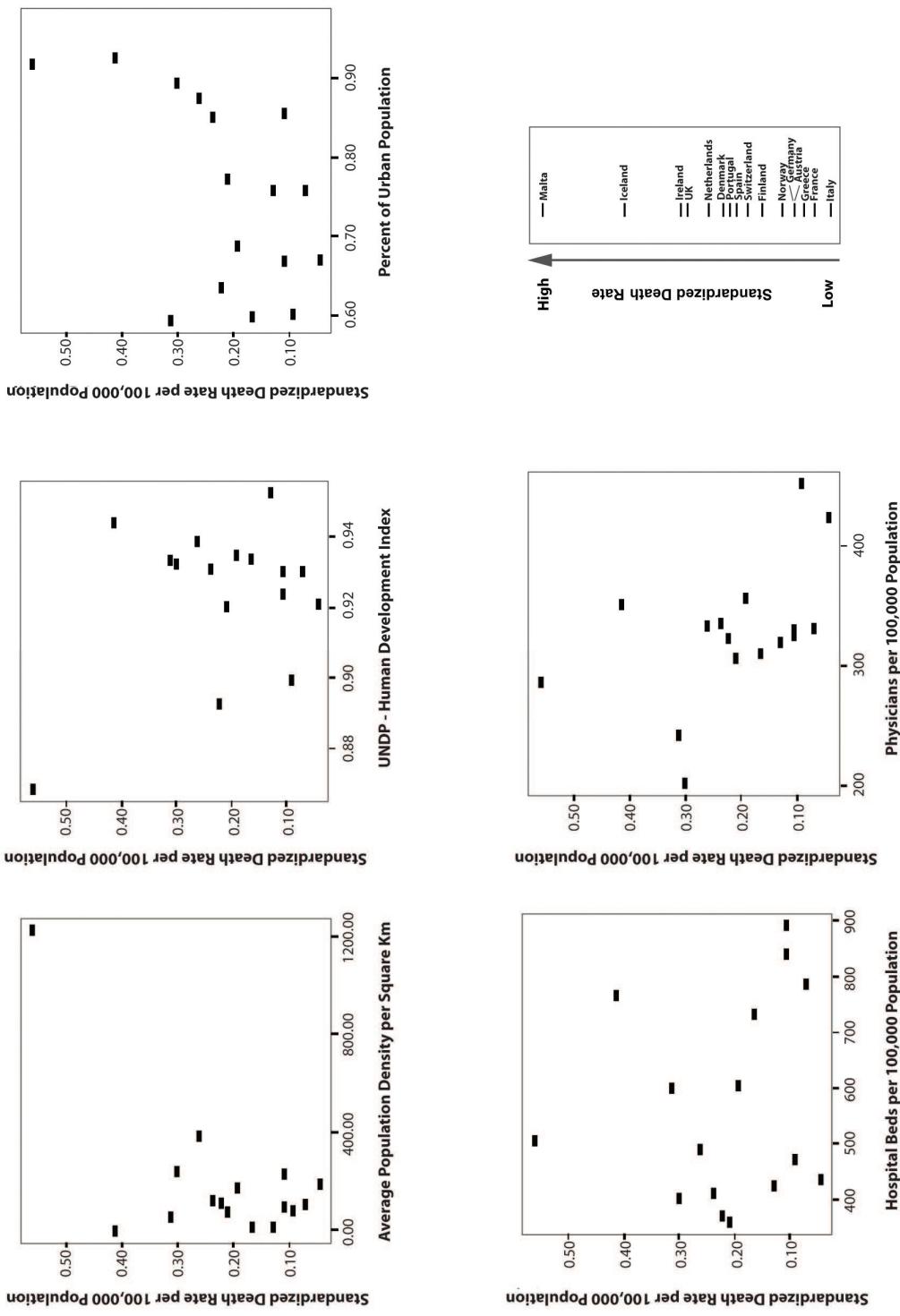
**Figure 1.2**



**Figure 1.3**



**Figure 1.4**



**Figure 1.5**

## **LINKING PARAGRAPH**

In the first chapter we tried to get a statistical grasp of the factors determining the occurrence of the disease in a spatially extended network such as the European Union. Meningococcal disease has received recent interest from a theoretical epidemiology perspective as a model for diseases caused by accidental pathogens. In the second chapter we try to understand the dynamics of the disease in a spatial structure network that can be understood as an abstraction of a multi-country network. At the local scale, patch dynamics are dictated by a standard model (specific to meningococcal disease). At the inter-regional scale patches are linked to simulate transmission of the disease across larger scales.

## **CHAPTER II**

# **An infectious disease model for meningococcal disease in a metacommunity framework**

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Keywords: SIRYX, metacommunity, epidemiological coupling, network topology,  
disease persistence, deterministic model

## ***ABSTRACT***

Meningococcal disease is a severe acute infectious disease caused by the bacterium *Neisseria meningitidis* (aka meningococcus). Meningococci belong to a specific class of pathogens, accidental pathogens, because disease is a dead end for both the host and the infectious agent. Epidemics of meningococcal disease happen sporadically, in small clusters, and disease incidence has been reported from all the European countries. Recently, Stollenwerk et al., (2004) developed a theoretical formulation based on the standard SIR model to describe the dynamics of meningococcal disease. In our study, we expand Stollenwerk's et al. (2004) theoretical formulation for meningococcal disease to a metacommunity to theoretically study how patch dynamics change when more than one patch is connected in a network topology. Our results show that connectivity prevents the infectious agent from undergoing extinction. Our results confirm potential negative effects of metacommunities on epidemics. Furthermore, we showed the importance of topological features of a network in determining how fast an epidemic will spread among patches. The results of our study will have important implications in the control and prevention of future epidemics in newly built networks such as that of the European Union.

## **INTRODUCTION**

Infectious diseases have been part of the ecological theory since Bernoulli's work on smallpox in 1760, an attempt to forecast and control the fate of pathogenic agents in human populations. In the middle of 20<sup>th</sup> century, and after intense research on vaccines and antibiotics, scientists and public health managers believed that the eradication of most major epidemics would be achievable (Cohen, 2000). Unfortunately, changes in the lifestyle and migration patterns of the human population in late 20<sup>th</sup> and early 21<sup>st</sup> century have triggered the emergence and re-emergence of infectious disease causing more than 13 million deaths each year worldwide (Morens et al., 2004).

Infectious diseases that are endemic in their host population undergo extinction when the chain of transmission events terminates by chance (Hagenaars et al., 2004). Often infectious diseases avoid extinction and persist in their host population; it has been hypothesized that persistence depends on the transmission characteristics of the infectious disease and the patterns of mixing between hosts (Hagenaars et al., 2004).

*Neisseria meningitidis* (a.k.a. meningococcus) is the main cause of meningococcal disease, an acute, potentially lethal illness. Meningococcus is a human commensal of nasopharyngeal mucosa, without causing harm to the host (asymptomatic carriage). Up to 10-15% of a population may be asymptomatic carriers at any given time. These carriers are crucial to the spread of the disease as most cases are acquired through exposure to asymptomatic carriers. For many unknown reasons, meningococci may lose their outer lipopolysaccharide capsule, and invade the blood stream, causing septicemia. Rarely meningococci cross the blood-brain barrier, reach the meninges and cause an acute inflammation, which is commonly known as meningococcal disease/meningitis.

Meningococcal disease incidence occurs along a continuum with temporal and spatial fluctuations (cases are observed throughout the year; in temperate countries cases peak in late winter and early spring). *Neisseria meningitidis*, with its small but hyperdynamic genome, has achieved high levels of genetic variability in order to evade the human immune system and colonize new hosts. It has evolved a strategy to alter the surface structures that are essential for adhesion and colonization of mucosa without having to cause disease to the host. Invasion is not essential to survival; instead, it is an evolutionary end-point for these bacteria. Virulence emerges as an accidental by-product of the immune forces that select out genes coding for transmissibility. Meningococci have not evolved to cause disease but they do so as “accidental pathogens” (Stollenwerk & Jensen, 2003a & b).

Understanding the dynamics of the disease is important from a public health point of view. However, epidemics happen at a larger scale than the local scale that most theoretical models concentrate on (Watts et al., 2005; Cohen ML, 2000). Epidemiological models indicate that increased contact among human populations enhances the spread of disease and can trigger epidemics.

It is difficult to determine actual rates of immigration and emigration from empirical data so that quantifying human dispersal at inter-regional scales is a major challenge in epidemiology. Bolker & Grenfell (1993) suggested a measure of connectivity, which is the ratio of between- and within-patch contacts that they termed epidemiological coupling. Epidemiological couplings can range between zero and one with zero indicating no connectivity and one indicating homogeneous mixing (Grenfell et al., 1995; Xia et al., 2004). More recent studies (Hufnagel et al., 2004) incorporated

human dispersal on the aviation network to forecast the dynamics of the recent SARS global epidemic. Their results show a good fit with disease notification data.

The concept of metacommunities, sets of ecological communities that are linked by dispersal (Leibold et al., 2004), is useful in explaining patterns of distribution and abundance of interacting species at a larger scale. Results of theoretical studies have elucidated the importance of connectivity in avoiding extinction (Leibold et al., 2004). However, very little is known about the potential negative implications that connectivity might have when diseases are more easily spread among highly connected human populations.

Here we investigate the potential of a mathematical model to describe features of meningococcal disease epidemiology when an individual patch model is extended to a metacommunity framework. First, we hypothesize that the dynamics of the extended SIRYX model (Stollenwerk et al., 2004) will be different from those of the standard SIR model, establishing the latter one as incapable of explaining dynamics of diseases caused by the general class of accidental pathogens. We suggest that an explanation for the persistence of disease lies in the ability of carriers to move within a closed network, come in contact with susceptible individuals of another patch and enhance this patch's disease incidence rate. Towards this goal we will test the role of transmission and epidemiological coupling on topologically different networks. Finally, we hypothesize that the disease persists longer and with a greater impact in topologies when patches have greater numbers of links with the rest of the patches.

## MODEL

We explored disease dynamics on a network of patches with a standard compartmental model for meningococcal disease: the SIRYX model (Figure 2.1; Stollenwerk et al., 2004). We divided the constant total host community into five equal sub-communities ( $N_i = 1, \dots, 5$ ). The deterministic dynamics of infection in sub-community  $i$ , when two communities ( $i$  and  $j$ ) are epidemiologically coupled (Grenfell et al., 1995; Grenfell & Bolker, 1998; ), are then described by the following equations:

$$\begin{aligned}\frac{dS_i}{dt} &= \alpha R_i + \varphi X_i - \left[ \beta_i I_i + \beta_i Y_i + (1-\varepsilon) \sum_{j \neq i} (\mu_{ji} \beta_j Y_j) \right] \frac{S_i}{N_i} \\ \frac{dI_i}{dt} &= \beta_i (1-\psi) I_i \frac{S_i}{N_i} - \gamma I_i \\ \frac{dR_i}{dt} &= \gamma (I_i + Y_i) - \alpha R_i \\ \frac{dY_i}{dt} &= \left[ (1-\varepsilon) \left( \beta_i Y_i + \sum_{j \neq i} (\mu_{ji} \beta_j Y_j) \right) + \beta_i \psi I_i \right] \frac{S_i}{N_i} - \gamma Y_i \\ \frac{dX_i}{dt} &= \varepsilon \beta_i Y \frac{S_i}{N_i} - \varphi X_i\end{aligned}$$

$$i = 1, \dots, 5$$

$S_i$ ,  $I_i$ ,  $R_i$ ,  $Y_i$  and  $X_i$  represent the density of susceptibles, carriers of the benign strain, recovered/immunes, asymptomatic carriers of the invasive strain and hosts with meningococcal disease, respectively. The infection process within sub-community  $i$  is controlled by a per capita infection parameter  $\beta_i$ , with a cross-infection rate from carriers of the invasive strain in sub-community  $j$  determined by a coupling proportion,  $\mu_{ji}$ . Bolker (1993) suggested that  $10^{-4}$  to  $10^{-1}$  is a plausible range of epidemiological coupling

constants although there is no accepted way of quantifying epidemiological couplings between different regions. The pathogenicity,  $\varepsilon$ , is the probability of disease to develop upon acquisition of the invasive strain, while asymptomatic carriage develops with probability  $(1 - \varepsilon)$ . Hosts who carry the bacterium can lose it and become immune with probability  $\gamma$ . Hosts can also lose their immunity and return to the susceptible pool with probability  $\alpha$ . Finally, hosts who developed meningococcal disease can either recover or die, and replenish the susceptibles with a probability  $\varphi$ . It has been noticed that meningococci and other encapsulated bacteria use an ingenious strategy to evade natural or vaccine-induced immunity directed at their capsule, known in the literature as capsule switching. Stollenwerk et al. (2004) incorporated this characteristic strategy in their model as an indirect transition from carriers of the benign strain to carriers of the invasive strain with probability  $\psi$  ( $\psi \ll \varepsilon$ ). They further parameterized the model using data for the United Kingdom and obtained a good fit to the empirical data.

First, we are interested in comparing the SIRYX model that Stollewerk et al. (2004) developed specifically for meningococcal disease, to the standard SIR infectious disease model. For this set of simulations we compare the behavior of the susceptible individuals between the two versions of the model. The parameterization is shown in Table 2.1. To keep the size constant, the ‘I’ individuals of the SIR are equal to the ‘I’+‘Y’+‘X’ individuals of the SIRYX model. In this set of simulations we allow only the ‘I’ individuals to get epidemiologically coupled, so that our results from the simulations are comparable.

At the inter-regional level, patch arrangements are specified by a connectivity matrix. For the purpose of initial simulations we adopted two common network

topologies seen in human-dominated networks (“star” and full connectivity; Hess G, 1996) and we examined the effect of patch arrangement on the dynamics of disease spread (Hess, 1996).

In a first set of simulations we are interested to explore how transmission affects the general dynamics of the model. Towards this goal we progressively increased the transmission probability  $\beta_i$  from 1.0 to 1.8, and let the model run for 360 time steps (according to our parameterization a time step is equivalent to a calendar month).

In a second set of simulations we connected two patches and we varied the level of epidemiological coupling between them from  $10^{-4}$  to  $10^{-1}$ . The purpose of these series of simulations was to identify the effect of epidemiological coupling on the disease incidence. Theoretically, meningococcal disease is dependent on the number of asymptomatic carriers  $Y$  who are capable of spreading the invasive strain and trigger outbreaks. For this reason, only ‘Y’ individuals were allowed to get epidemiologically coupled in this set of simulations (Figure 2.2A).

In the third set of simulation we are interested in exploring the effect of topological arrangement on the disease dynamics. We increased the total number of patches to five ( $n = 5$ ). In the star topology, four patches were added around a central hub, whereas in the full connectivity model, patch arrangement is not important, since all patches are connected with each other.

In a following set of simulations we concentrate on exploring differences in the dynamics of the metacommunity when only the benign strain is allowed to get epidemiologically coupled (Figure 2.2B), instead of the invasive one. For this set of simulations all the parameters are kept constant, except for the coupling parameter of the

benign strain that is varied according to the previous range of coupling values. In addition, to explore whether there are cumulative effects when both strains are being epidemiologically coupled, we ran a set of simulations where we coupled both ‘I’ and ‘Y’ individuals.

For the simulations of the model, the code was written in MATLAB. The model is described by a set of Ordinary Differential Equations (ODE) for each patch that are parameterized to describe monthly dynamics of the disease. The number of individuals in each class of the model is saved for each time step of the simulations. For most of the simulation the code is iterated for 360 time steps.

## **RESULTS**

The standard SIR model and the SIRYX model (which includes asymptomatic carriers) showed comparable dynamics only at the lowest rates of coupling. For higher coupling intensity  $\nu$  between two patches the two model formulations differed in their equilibrium predictions (Figure 2.3). Susceptibles reached considerably higher equilibrium densities in the SIRYX framework than in the SIR simulations. Equilibrium densities were also reached more rapidly in the SIRYX simulations. Although we were primarily interested in the size of the diseased population, we used Susceptibles as a benchmark for the SIR/SIRYX comparison. A straightforward comparison of disease incidence between the two formulations is difficult because diseased individuals are “I” in the SIR framework and “X” in the SIRYX framework, respectively. Since the two classes are locally coupled in a completely different fashion we preferred to compare

Susceptibles as a benchmark. For the following SIRYX simulations, however, we use diseased hosts X as the variable of interest.

Figure 2.4 shows patterns of extinction in a single-patch framework from simulations at a range of transmission intensities. A systematic change in transmission rate led to a corresponding change in the number of cases of the disease. As we increase the transmission intensity of the disease within a community, we observe a corresponding increase in the number of individuals that die due to meningococcal disease. In addition, due to the deterministic formulation of the model, infection process is not stochastic, and the disease dynamics do not show fluctuations as usually observed in time-series.

Figure 2.5 examines the effect of different levels of epidemic coupling between two patches on the number of cases. Epidemiological coupling at very low levels ( $\mu=10^{-4}$ ) promoted global extinction of the disease. At higher levels of epidemiological coupling the disease persisted in the community, and became endemic. We were able to identify a threshold range, which lies between  $10^{-3}$  and  $10^{-2}$ , where the disease escapes extinction and persists in the host sub-communities.

In Figure 2.6A, we focus on changes in the dynamics of the model in the case where the benign strain gets coupled. Since the ‘I’ individuals do not affect directly the number of the ‘X’ individuals, we observed a slight decrease in the number of individuals who develop the disease (compare with Figure 2.5). The same type of dynamics is observed when both strains get coupled between patches (Figure 2.6B). This suggests a “dilution effect” on the number of disease cases since there are more carriers of the benign strain in the community than carriers of the invasive one.

The two 5-patch topologies tested are different in how the number of links increases as patch number increases. In the star topology the number of links between patches increases linearly as patches are added around a central hub. In a full connectivity network, where all patches are connected with each other, the increase in number of links follows a power law with the addition of patches (Figure 2.7). This difference affects how fast an epidemic can spread in a network as the dynamics of a patch become dependent on the dynamics of the patches that are connected to it. From this set of simulations we observe that in full connectivity models disease spreads and becomes endemic faster than the star topology (Figure 2.8). Using the exact same parameterization, we see that going from the peripheral patches in the star network to the hub and then to a full connectivity topology the number of X individuals increases and the disease reaches equilibrium faster (Figure 2.8).

## ***DISCUSSION***

The SIR model is a standard formulation in theoretical epidemiology. Here we used a modification of this general model that can model diseases caused by pathogens that only accidentally cause harm to their host and are transmitted in a network topology. The SIRYX model (Stollenwerk et al., 2004) includes two different classes of infected individuals based on the pathogenicity of the infectious agent, as well as a class of individuals that symptomatically develop the disease and die. When we compare the dynamics of the two models our results show that Susceptibles reach higher equilibrium densities in the SIRYX framework. We conclude that the inclusion of a benign strain,

which competes with the virulent strain for hosts, leads to a higher proportion of undiseased individuals. The traditional SIR model cannot account for this type of interaction because all carriers are diseased “I” individuals. Given that SIRYX model has already been parameterized for the United Kingdom and given its ability to show a good fit with empirical we suggest that the SIR is unsuitable to capture the dynamics caused by this class of pathogens (Stollenwerk et al., 2004). For this reason we used the SIRYX formulation to describe dynamics of meningococcal disease at the metacommunity level.

Most metacommunity models suggest that increased movement among communities reduces the probability of metacommunity extinction (Hess G., 1996; Hagenaars et al., 2004). We showed that, through the same mechanism, increased contact among sub-communities universally increases the prevalence, incidence, and rate of spread of disease in the overall community. Interaction among sub-communities can enable a disease to persist when it would have been unable to persist in any of the isolated sub-communities. Our results show that disease endemism is achieved at low levels of epidemiological coupling between patches. A corresponding increase in the coupling intensity leads to a corresponding increase in disease persistence.

The topology of a network is very important for detecting the rate of disease spread in a metacommunity. The number of links between patches and the intensity of the linkage determines the vulnerability of a patch in a network. In our simulations we concentrated on two different topologies that have been identified in human dominated networks, the star and full connectivity models (Hess G., 1996). The difference between the two is the number of links between sub-communities. The central hub in the star topology shows a linear correlation between number of patches and number of links

whereas the full connectivity model shows a power correlation. The disease agent has a bigger impact as the number of links increases among patches.

In our study we revealed changes in the dynamics of a patch model when it is extended to a metacommunity. We also showed differences in the disease dynamics as we changed the topological features of a network of sub-communities. Finally, we compared our results with those of the general SIR infectious disease model and we showed that diversity in pathogenicity could be important when modeling meningococcal disease. However, our model should be understood as a generalized approach to meningococcal disease dynamics on network topologies rather than a predictive model of concrete epidemiologic scenarios. Our deterministic approach allowed us to identify important patterns of disease spread and persistence but real-world epidemic outbreaks are stochastic and highly depend on seasonality of the transmission (Rohani et al., 2002). Other factors that make spatial meningococcal disease dynamics difficult to predict are the occurrence of multiple strains ( $>2$ ), unknown patterns of regional resistance to and vaccination against these strains, and uncertain transition pathways.

In a globalized world, where individuals can travel around, and come in contact with diverse sub-communities, the issue of re-emergence of epidemics is of extreme importance (Cohen, 2000; MacLehose et al., 2002; Hufnagel et al., 2004). The recent epidemics of SARS and influenza showed that the probability of an infectious strain to spread around the world in a very small amount of time is indeed high (Becker et al., 2005; Cooper et al., 2006). Public health organizations focusing on the control strategies and prevention are in need of models that can explain dynamics beyond the patch level.

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**TABLE 2.1: Model parameterization**

Sim.	Model	Figure	Parameter values									Initial population size				
			$\alpha$	$\beta$	$\gamma$	$\varepsilon$	$\varphi$	$\psi$	$\mu$	$\nu$	$t$	S	I	R	Y	X
1	a	2.3A	1	1.35	1	0.0013	2.5	$8 \cdot 10^{-6}$	0	[...]	360	80000	7998	6000	6000	3
	b	2.3B	1	1.35	1	0	0	0	0	[...]	360	80000	14000	6000	0	0
2	a	2.4	1	[...]	1	0.0013	2.5	$8 \cdot 10^{-6}$	0	0	10000	80000	7998	6000	6000	3
3	a	2.5	1	1.35	1	0.0013	2.5	$8 \cdot 10^{-6}$	[...]	0	360	80000	7998	6000	6000	3
4	a	2.6A	1	1.35	1	0.0013	2.5	$8 \cdot 10^{-6}$	0	[...]	360	80000	7998	6000	6000	3
5	a	2.6B	1	1.35	1	0.0013	2.5	$8 \cdot 10^{-6}$	[...]	[...]	360	80000	7998	6000	6000	3
6	a	2.8	1	1.35	1	0.0013	2.5	$8 \cdot 10^{-6}$	[...]	0	360	80000	7998	6000	6000	3

1. SIRYX versus SIR,
2. SIRYX response to a range of  $\beta$  values,
3. SIRYX response to a range of  $\mu$  values,
4. SIRYX response to a range of  $\nu$  values,
5. SIRYX response to a range of  $\mu$  and  $\nu$  values.
6. SIRYX in “star” and full connectivity topology
  - a. SIRYX model, b. SIR model, [...] range of values.

## **LIST OF FIGURES**

**Figure 2.1:** Schematic representation of the SIRYX model for meningococcal disease, as it appears in Stollenwerk et al. (2004) study. The transition rate equations are shown for each individual patch.

**Figure 2.2:** Schematic representation of epidemiological coupling between two patches when (A) the ‘Y’ individuals are coupled at a rate  $\mu$  and (B) the ‘I’ individuals are coupled at a rate  $\nu$ .

**Figure 2.3:** SIRYX model versus SIR model. Number of susceptible individuals after 360 time steps for (A) SIRYX and (B) SIR models at different levels of connectivity.

**Figure 2.4:** Dynamics of a single patch at a range of transmission probability ( $\beta$ ) values. Dynamics over 10,000 time steps. The inset shows a detailed view of the first 360 time steps.

**Figure 2.5:** SIRYX model in a 2-patch metacommunity framework. Results of simulations when the ‘Y’ individuals of two identical patches are epidemiologically coupled at various levels.

**Figure 2.6:** Results from simulations when (A) only ‘I’ individuals and (B) both ‘I’ and ‘Y’ individuals are coupled at various intensities.

**Figure 2.7:** “Star” and “Full Connectivity” topological models. Differences in the rate of increase of the number of links as a function of patch number.

**Figure 2.8:** Results of simulations when the SIRYX model is embedded in a star or full connectivity network of 5 patches. (A) dynamics of the X individuals of a hub in a star topology. (B) dynamics of the X individuals of a patch in one peripheral patch of the star. (C) dynamics of the X individuals of a patch that is part of a fully connected network.

## FIGURES

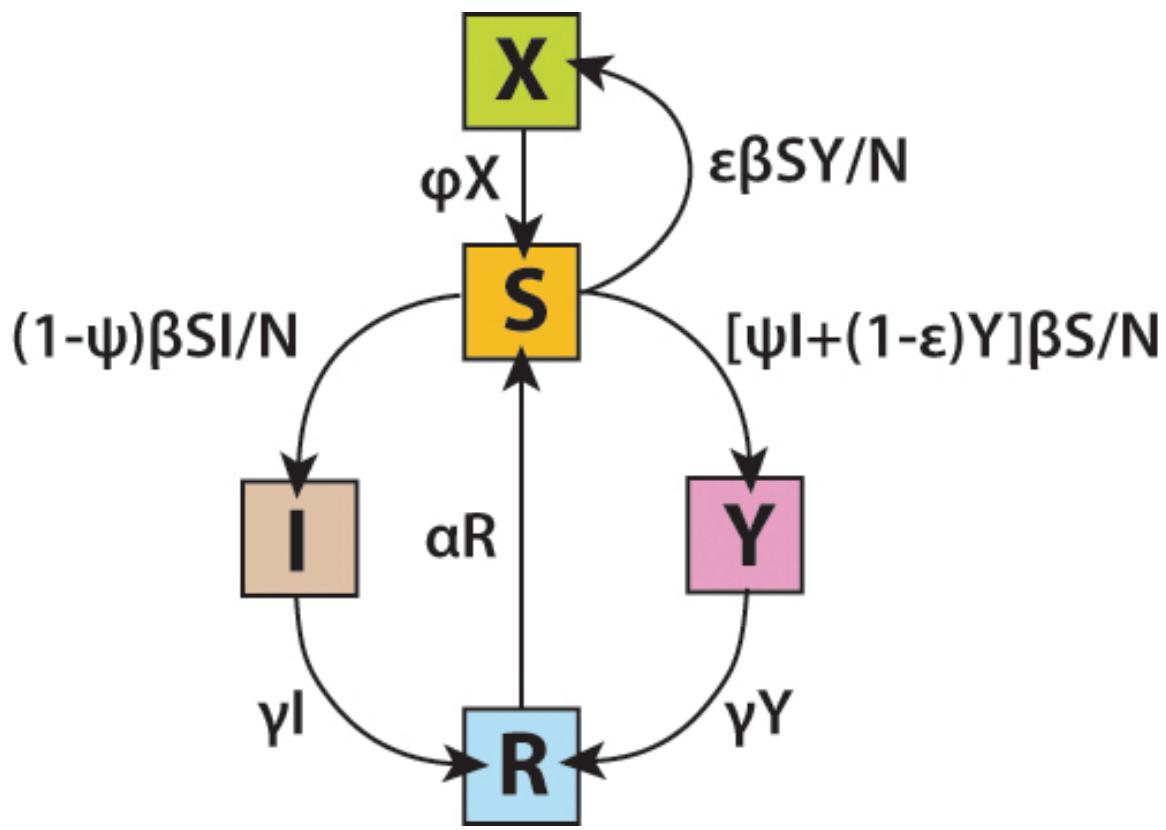
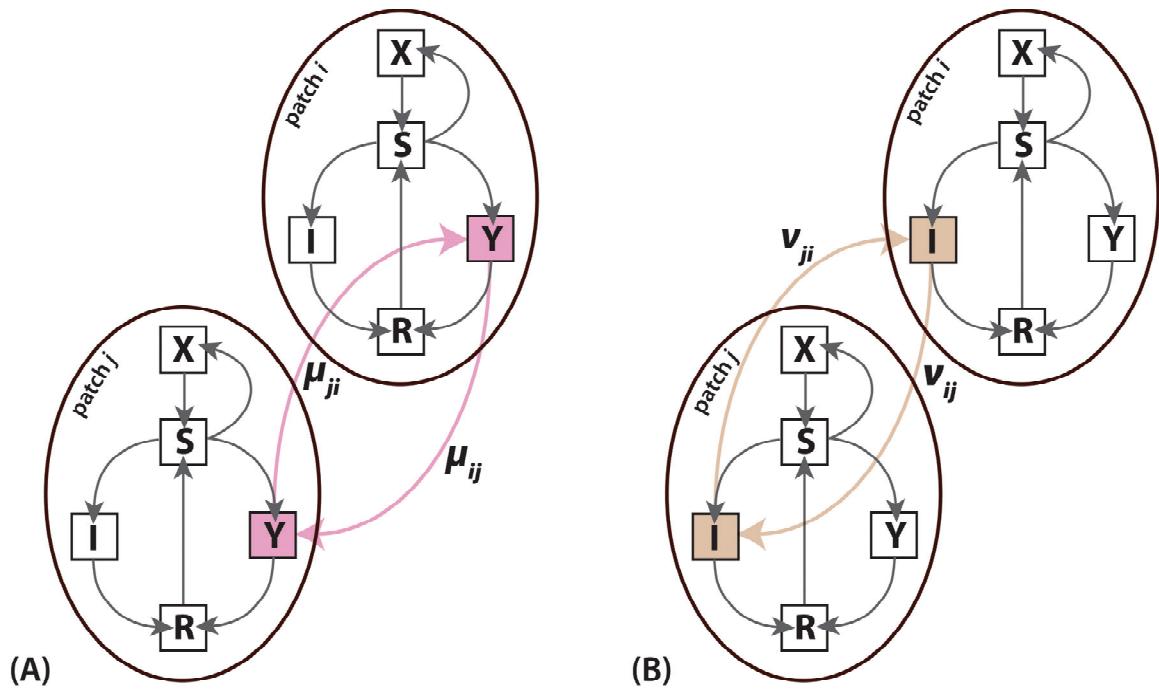


Figure 2.1



**Figure 2.2**

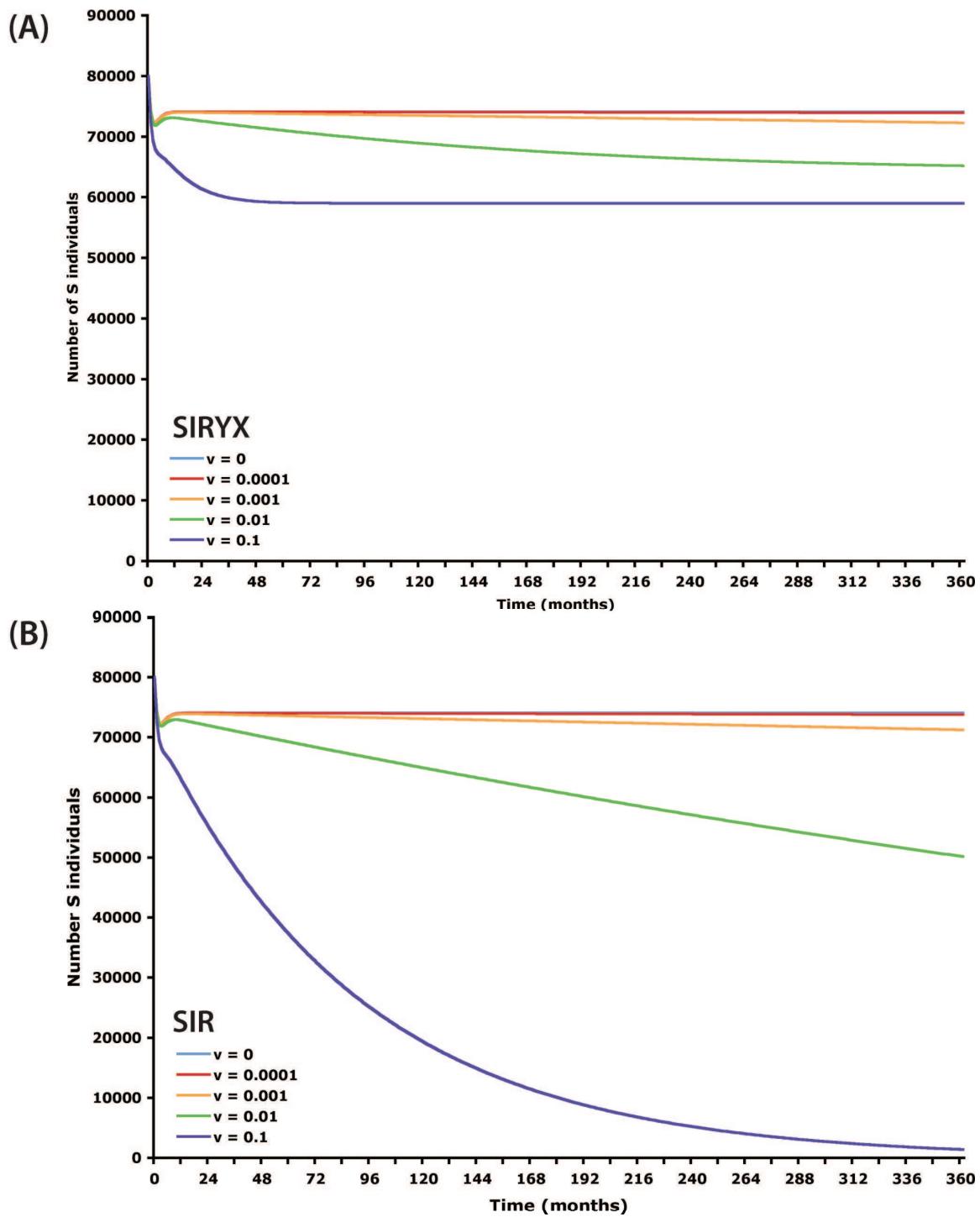


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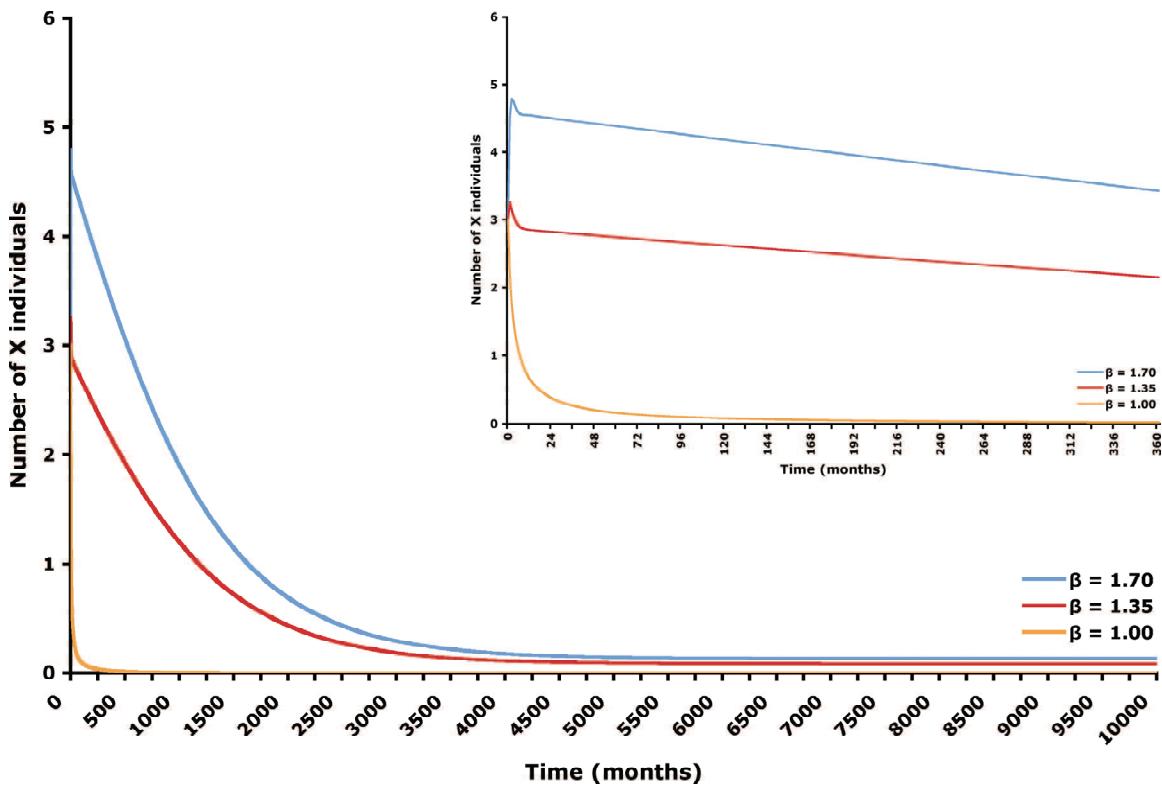


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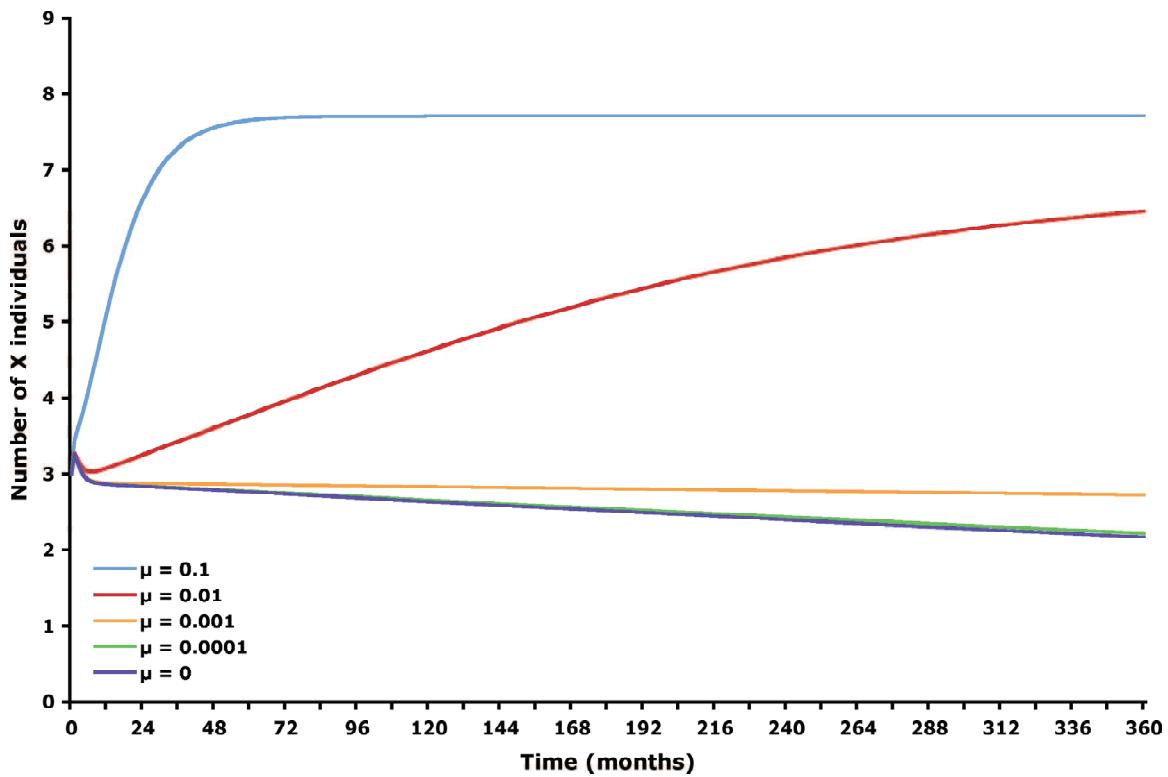


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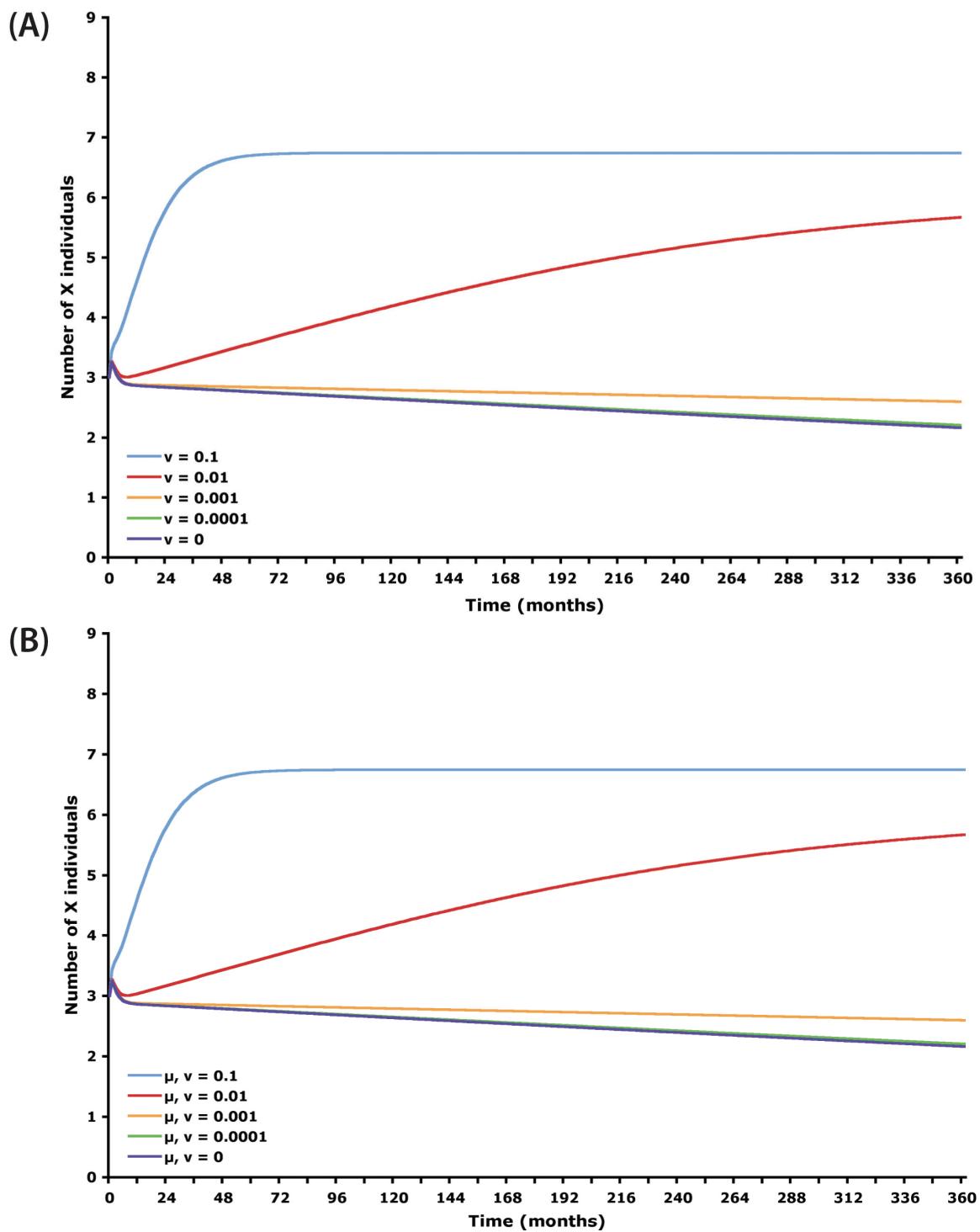


Figure 2.6

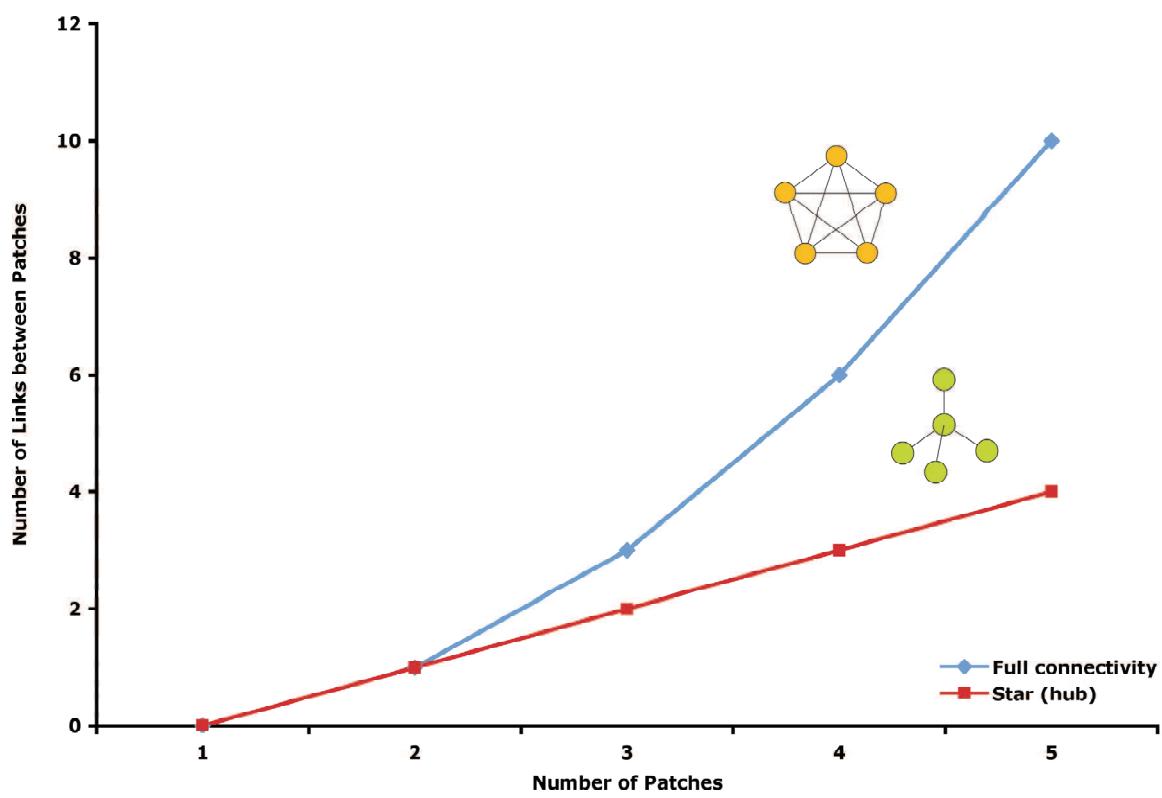
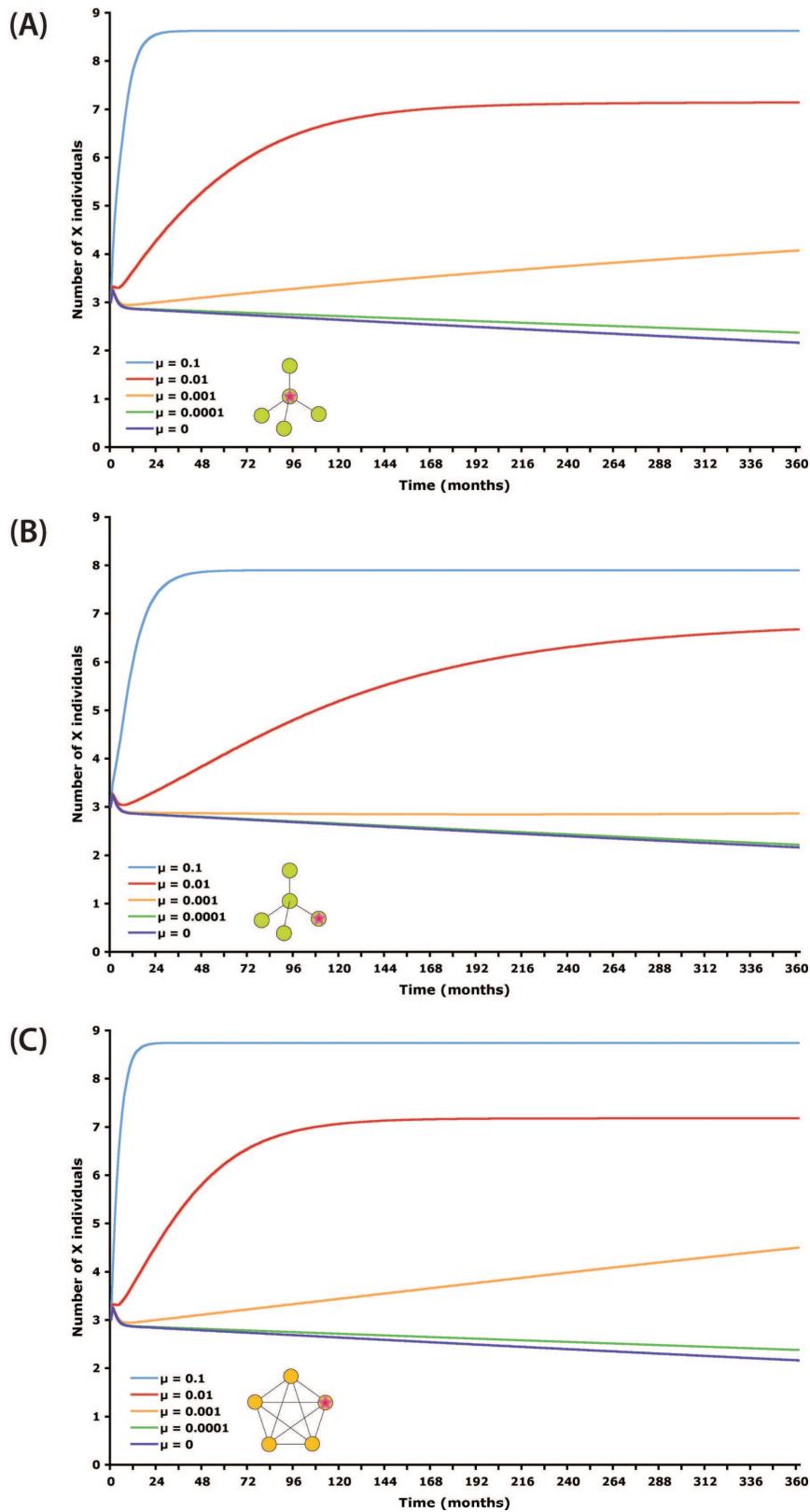


Figure 2.7



**Figure 2.8**

## CONCLUSIONS

In our study we revealed patterns of distribution and spread of meningococcal disease. We explored data from 17 European countries from 1999 to 2004. Meningococcal disease is endemic in this region, and incidence rate varies from 1 to 12 cases per 100,000 population. Our results confirm that meningococcal disease is primarily a childhood disease. High incidence rate was observed in infants and young adults. Our analysis of factors affecting the spread of the disease at a continental level confirms the potential of development robust models to forecast the incidence and death rate of the disease using databases of demographic, socio-economic and health care resource data.

In our study we also explored meningococcal disease as a model for accidental pathogens. Adopting the theoretical formulation of Stollenwerk and colleagues, and the idea of epidemiological coupling developed by Bolker and Grenfell we were able to elucidate changes in the deterministic dynamics of the disease in a network of patches. We confirmed the difficulty of the standard SIR formulation to describe dynamics of agents with strains of different pathogenicity. Our results showed negative effects in terms of disease prevalence when patches were epidemiologically coupled. A disease, which would fade out in isolation could persist in a metacommunity and increase in the number of cases observed.

Changes in the lifestyle and patterns of movement of humans have triggered the re-emergence of epidemics. Nowadays epidemics affect more areas. Recent outbreaks have shown the emergency of predictive models. Both of our statistical and theoretical models have important implications in issues concerning public health.

The European Union (EU) has been an informative study case from a theoretical epidemiology perspective. It is a network of 20 member countries where movement of individuals has reached different levels of freedom, and individuals travel freely within its borders. In theoretical epidemiology words, it is a fully connected network of 20 patches where coupling happens at different levels between members of the network.

Recent reports of annual notifications of meningococcal disease for EU have shown that the disease is endemic in all the countries, at different levels. As our results suggest, eradication of the disease is very difficult. With the opening of borders between countries and the freedom of movement of individuals, countries with high disease incidence rate will dramatically affect the dynamics of the rest in the network. The level of coupling between the countries will determine the spread of the disease.

The European Union, for instance, has been lately enlarging its borders, accepting new member countries in its network. Enlarging the network and incorporating new members with higher degrees of endemism than current EU members may cause outbreaks of the disease that depend on the increase in coupling to the EU that these countries obtain as a consequence of their new member status.

The record on epidemics is incomplete. Each country has its own registering system, which makes it difficult to have a clear picture of their state. For many countries records are not available at all. It is very important that authorities have a better idea of the state of infectious disease of candidate countries in order to avoid the issue of re-emergence of infectious disease in members that have already controlled them.

In a globalized world where distances have a different meaning than decades ago it is important to explore patterns at larger scales. A more detailed formulation and

parameterization of our models for the European Union can enable the authorities to evaluate the risk of expansion from an epidemiological point of view.

## APPENDIX

Table: Empirical data

Countries	Years	Incidence Rate per 100,000 Population (EU-IBIS)	Standardized Death Rate per 100,000 Population (WHO)	Average Population Density per square Km (WHO)	UNDP – Human Development Index (WHO)	Percent of Urban Population (WHO)	Hospital Beds per 100,000 Population (WHO)	Physicians per 100,000 Population (WHO)
Austria	1999	1.20	0.11	96.5	0.908	67.21	877.36	302.82
	2000	1.02	0.11	96.71	0.931	67.28	861.27	312.35
	2001	1.30	0.13	95.91	0.929	67.4	861.86	326.82
	2002	0.99	0.1	96.4	0.934	65.8	841.15	330.43
	2003	0.89	0.1	96.8	0.936	68	834.07	337.69
	2004	0.86	0.09	97.48	0.944	65.9	773.19	345.25
Belgium	1999	2.90	...	332.55	0.925	97.26	559.19	407.12
	2000	2.60	...	332.84	0.94	97.33	556.53	413.7
	2001	3.69	...	336.18	0.937	97.4	548.41	418.77
	2002	2.54	...	338.47	0.942	97.2	541.78	447.78
	2003	2.20	...	339.89	0.945	98	536.68	443.24
	2004	1.51	...	340.87	0.945	97.2	534.59	...
Denmark	1999	3.33	0.22	123.44	0.911	85.09	434.23	324.73
	2000	2.83	0.24	123.87	0.929	85.1	429.56	327.26
	2001	3.01	0.25	124.28	0.93	85.1	422.1	332.04
	2002	1.82	...	124.72	0.932	85.2	413.55	338.67
	2003	1.91	...	125.02	0.941	85	398.72	343.28
	2004	1.81	...	125.35	0.943	85.5	382.25	357.09
Finland	1999	1.11	0.25	15.28	0.917	59.96	760.53	305.76
	2000	0.93	0.12	15.31	0.933	58.97	753.58	307.27
	2001	0.95	0.13	15.34	0.93	59	736.8	310.52
	2002	0.94	0.14	15.38	0.935	61	731.17	316.23
	2003	0.81	0.16	15.42	0.941	59	724.86	319.07
	2004	0.86	0.19	15.46	0.947	61.1	690.15	...
France	1999	0.74	0.04	106.3	0.917	75.24	828.69	329.57
	2000	0.81	0.08	106.79	0.929	75.37	809.16	329.4
	2001	0.92	0.08	107.33	0.925	75.5	796.66	331.12
	2002	1.06	0.07	108.21	0.932	76.1	780.01	332.95
	2003	1.06	0.08	109.07	0.938	76	759.89	334.8
	2004	1.01	...	109.26	0.942	76.5	747.99	337.7
Germany	1999	0.49	0.12	229.92	0.911	87.33	919.6	320.94
	2000	0.55	0.1	230.2	0.925	87.54	911.91	326.04

	2001	0.94	0.1	230.62	0.921	87.7	901.06	330.7
	2002	0.89	0.12	231.02	0.925	87.9	887.36	333.61
	2003	0.93	0.1	231.13	0.93	88	874.56	336.75
	2004	0.72	0.1	231.08	0.932	75.1	857.93	339.05
Greece	1999	1.19	0.15	82.47	0.875	59.93	472.35	423.83
	2000	1.59	0.2	82.73	0.894	60.1	471.72	432.8
	2001	1.69	0.08	82.98	0.892	60.4	477.41	437.85
	2002	1.78	0.07	83.26	0.902	60.6	471.27	458.22
	2003	1.08	0.02	83.54	0.912	61	469.56	474.67
	2004	0.65	0.03	83.85	0.921	58.9	468.82	487.54
Iceland	1999	7.58	0.34	2.69	0.927	92.32	...	338.4
	2000	6.40	1.16	2.73	0.939	92.5	...	344.3
	2001	6.67	0.32	2.77	0.942	92.6	781.61	347.3
	2002	5.22	0.33	2.79	0.941	92.7	750.8	357.84
	2003	2.77	0	2.81	0.956	...	...	361.94
	2004	3.42	0.33	2.84	0.96	92.7	...	360.92
Ireland	1999	11.89	0.33	53.25	0.907	58.79	638.06	226.34
	2000	10.85	0.56	53.93	0.926	59.01	626.99	222.67
	2001	7.72	0.33	54.75	0.93	59.3	603.71	238.25
	2002	5.74	0.2	55.75	0.936	59.6	590.37	241.09
	2003	5.55	0.31	56.62	0.946	60	579.26	258.11
	2004	4.35	0.14	57.55	0.956	60.2	571.97	275.51
Italy	1999	0.45	0.06	188.85	0.903	66.87	475.8	423.48
	2000	0.43	0.03	188.9	0.915	66.94	456.16	416.35
	2001	0.35	0.04	189.02	0.916	67.1	447.09	437.14
	2002	0.38	...	189.68	0.92	67.3	430.18	442.64
	2003	0.47	...	191.16	0.934	67	411.8	411.43
	2004	0.54	...	192.58	0.94	67.5	399.63	415.28
Malta	1999	4.34	0.98	1185.31	0.865	90.61	557.34	263.12
	2000	5.11	0.85	1205.65	0.873	90.92	547.68	265.42
	2001	3.29	0.25	1228.21	0.856	91.2	496.15	...
	2002	3.52	0.51	1237.4	0.875	91.4	487.92	267.19
	2003	4.00	0	1245.57	0.867	...	482.21	314.62
	2004	3.25	0.77	1253.96	0.875	95	464.28	324.47
Netherlands	1999	3.65	0.34	380.74	0.925	89.39	503.98	309.81
	2000	3.42	0.3	383.47	0.938	89.49	482.62	319.34
	2001	4.51	0.4	386.38	0.938	89.6	466.02	327.82
	2002	3.82	0.3	388.85	0.942	...	503.38	338.25
	2003	2.19	0.14	390.69	0.943	90	497.75	348.47
	2004	1.71	0.09	392.05	0.947	79.6	...	360.37
Norway	1999	1.73	0.3	13.78	0.934	74.43	396	328.67
	2000	1.90	0.15	13.8	0.954	74.71	433.18	292.15
	2001	1.71	0.04	13.94	0.944	75	437.31	290.29
	2002	1.13	0.12	14.01	0.956	77.6	433.55	330.49
	2003	1.12	0.11	14.09	0.963	76	434.76	338.26
	2004	0.74	0.05	14.18	0.965	77.3	429.34	348.29
Portugal	1999		0.15	110.59	0.864	62.74	384.9	312.21
	2000	0.57	0.38	111.17	0.892	64.43	380.49	317.8
	2001	1.03	0.18	111.9	0.896	65.6	373.57	322.87
	2002	1.78	0.42	112.72	0.897	...	363.69	325.52

	2003	1.34	0.2	113.88	0.904	68	363.9	328.79
	2004	1.18	0	114.18	0.904	57	374.61	335.3
Spain	1999	2.38	0.3	78.31	0.899	77.39	377.63	295.76
	2000	2.42	0.28	79.4	0.917	77.61	368.6	316.38
	2001	1.59	0.14	80.27	0.918	77.8	360.57	307.53
	2002	2.04	0.22	81.65	0.922	76.4	353.64	290.94
	2003	1.18	0.16	83.01	0.928	78	345	322.11
	2004	1.64	0.16	84.37	0.938	76.6	...	...
	1999	2.09	0.24	173.02	0.915	67.47	660.82	336.31
Switzerland	2000	2.07	0.24	173.99	0.932	67.41	626.31	350.99
	2001	2.02	0.28	175.02	0.932	67.5	605.07	351.41
	2002	1.24	0.23	176.43	0.936	67.6	595.61	355.83
	2003	1.02	0.11	177.74	0.947	68	582.4	371.55
	2004	1.07	0.05	178.97	0.947	74.8	566.97	375.42
	1999	5.24	0.44	241.02	0.918	89.43	416.38	196.12
United Kingdom	2000	5.10	...	241.85	0.932	89.48	411.62	199.67
	2001	4.37	0.4	242.79	0.93	89.5	405.41	204.54
	2002	3.29	0.26	243.64	0.936	89	400.03	212.61
	2003	3.03	0.24	244.59	0.939	90	397.65	...
	2004	2.46	0.16	245.75	0.94	89.6	389.79	...

[...]: no available data