



Universidad Pública de Navarra  
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# **Trends in Mortality Associated with Infectious Diseases in European Union, 2000-2010.**

Doctoral Thesis

**Department of Health Sciences - Public Health  
Public University of Navarra**

By:

**Moad Jamal Saad Al-Rahamneh**

Supervisor:

**Dr. Prof. Francisco Guillén Grima**

Co- supervisor:

**Dr. Prof. Inés Aguinaga Ontoso**

**Pamplona - 2017**

# Dedication

To my idols ... my parents, for their  
sacrifice and support.

To my right-hand man ... my brother,  
for his concern and patience with me.

To coffee and sugar ... my  
companions through many a long  
nights of writing.

*"I hated every minute of training,  
but I said, don't quit, suffer now  
and live the rest of your life as a  
champion."*

Muhammad Ali Clay

# Acknowledgment

First and foremost, I would like to express my sincere gratitude and appreciation to my supervisor Dr. Prof. Francisco Guillén Grima for the continuous support of my Ph.D study and related research, for his patience, concern, advices, motivation, and immense knowledge. His guidance helped me in all the time of research and writing of this thesis. I could not have imagined having a better supervisor and mentor for my Ph.D study. It has been an honor to be a student of such a great Epidemiologist like him.

Also, I would like to thank my co-supervisor Dr. Prof. Inés Aguinaga Ontoso for her supervision and encouragement.

Especial thanks from all my heart for Dr. Raquel Saenz for her support, advices and concern that made my last moments of my study period clear and easy.

Besides my supervisors, I would like to thank the members of the department of Preventive Medicine and Public Health for their help to facilitate everything during my study.

Also, I would like to thank the staff of Preventive Medicine and Infection control department in Clínica Universitaria de Navarra (CUN) for their well receiving, cooperation and for the knowledge that they gave me.

And I would not forget to thank the Epidemiological Surveillance department of the Jordanian Ministry of Health represented by Dr. Sultan Al-Qasrawi for his concern, support and believing in me to participate in a national and international acts and duties.

Thanks are also attached to the Eastern Mediterranean Public Health Network (EMPHNET) for having faith in me to participate and represent them in various national and international events.

On the other hand, I would express my thanks to my family for their support always and especially during my study period.

For my best friend Khaled in my country Jordan, for his concern and motivation all the time.

And finally, for all whose supported my here in Spain, my friend, colleagues, flat mates and above all for Spain and their people, that country that made me see the life and the world in a different way. It has been an unforgettable experience.

From all of my heart .. THANKS!!!

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# 1 Introduction

The 20th century saw a series of social, scientific and medical developments that freed the people of Europe from the ravages of infectious disease to an extent that would have been unimaginable to their great-grandparents. By the end of the 1950s it had begun to appear that a combination of public health measures, vaccination and antibiotics would soon render most infectious illnesses a distant memory.

Infectious disease worldwide accounts for about one-quarter of all deaths. Estimates suggest that communicable diseases currently represent about 10% of the total burden of disease in Europe,[1] although this is based on limited data for selected countries and diseases and comprehensive, more robust evidence should be collected.[2]

Infectious diseases are a leading cause of illness and death worldwide. According to the World Health Organization (WHO) data in 2012, infectious (including parasitic) diseases were together responsible for the death of more than 8.7 million people worldwide in 2008.[1]

Globally, infections cause over a fifth of all deaths and a quarter of all illnesses, disproportionately affecting poorer communities and resource-poor countries.[3] It is estimated that worldwide each year around 5.5 million people die from malaria, Tuberculosis and human immunodeficiency virus (HIV)-related infections, 1.8 million die from diarrheal disease and more than a million children die from other diseases that are preventable through vaccines.[4] The vast majority of these deaths are in the developing world, and similarly it has been suggested that in the case of an influenza pandemic up to 96% of deaths could occur in developing countries.[5]

While prevention and control of many infectious diseases has improved in recent decades, they continue to pose major challenges to public health. These stem from, for example, the emergence of new infections in humans such as HIV and SARS (severe acute respiratory syndrome).[6] The emergence of old disease problems with new complexities and the continued periodic occurrence of worldwide epidemics of influenza resulting from new strains of the virus.[7]

The range of prevention and control strategies that may be used is wide, depending in part on the nature of the infectious agent and its mode of spread. It includes, for example, advice about safer sex, regulations on food hygiene, advice about hand-washing, and precautions taken in hospitals to prevent infections spreading between individuals, as well as vaccines.

National surveillance for notifiable infectious diseases has been a cornerstone of the public health system in many developed countries,[8] but such surveillance systems have been harder to establish and maintain in developing countries. Establishment of effective surveillance is precluded in many countries by scarcity of resources and inadequate infrastructure, as well as by an imperative to focus on other basic services, such as immunization. Yet it is precisely in developing countries, where infectious diseases still account for the majority of morbidity and mortality,[9] that such surveillance systems can be most valuable today in recognizing outbreaks, tracking emerging diseases, and setting public health priorities for important infectious diseases.

Socio-economic status plays a very important role in incidence and prevalence of Infectious diseases. Infectious diseases can undermine economic and commercial viability by placing extraordinary demands on the healthcare system, sapping business confidence, reducing the productive labor force, and destroying individual livelihoods.

The impact of infectious diseases on economic growth is visible, encompassing both the direct cost of medical care and the reduction in years of healthy life expectancy and productivity because of early death and chronic illnesses. This, in return, leads to a reduction to business and infrastructure investment, social cooperation and social stability.

Many countries in the European Union (EU) and the European Economic Area (EEA) are in an economic recession. It is acknowledged that a recession or economic crisis can have an effect on the population's health, especially with respect to infectious diseases.[10] There are two main mechanisms through which an economic crisis can have an effect on infectious diseases. Firstly, if due to a decrease in country and individual income, less money is spent on healthcare and social welfare. And secondly, if due to an increase in poverty and stress, the number of people belonging to risk groups for infectious diseases increases.

National experts of EU/EEA countries who participated in a scoping study that assessed the effects of the current global crisis on communicable diseases expect that there will be budget cuts especially in prevention services and in services targeted at vulnerable and hard-to-reach population groups.[11]

Marked rises in infectious disease incidence during previous economic crisis and downturns raise concerns about the current situation. During the 1990s, countries of the former Soviet Union (FSU) and Eastern Europe experienced a devastating economic crisis, as Gross Domestic Product (GDP) fell by one-third on average. Concurrently, the incidence, prevalence and mortality of Tuberculosis rose markedly, and worsening treatment led to the emergence of drug-resistant strains.[12][13] HIV also increased from relatively low pre-crisis levels; outbreaks of diphtheria[14] and tick-borne encephalitis[15][16] and leptospirosis[17] also occurred. These effects outlasted the immediate crisis period; today, some countries from central and Eastern Europe and former Soviet Union have not been able to achieve Millennium Development Goal (MDG) number 6, 'to halt or reverse the spread of Tuberculosis and HIV.[18]

The level and distribution of wealth within a society plays a significant role in determining vulnerabilities to infectious diseases. Even in the absence of economic crisis or downturn, infectious diseases disproportionately affect vulnerable groups. In every European Union (EU) Member State, vulnerable groups are disproportionately affected by infectious diseases.[19] A clear association between social welfare spending and mortality across European Union countries has been reported.[20]. In a review of the European literature, this effect could be found in every single European Union Member State.[19] A separate study comparing wealth distribution and Tuberculosis rates across European Union Member States demonstrated a strong correlation between income equality and lower Tuberculosis rates.[21] Thus, health inequalities, whose importance has been thoroughly documented by the WHO Commission on the Social Determinants of Health,[22] may be as relevant for communicable diseases as they are for non-communicable diseases.

Actually, social determinants of infectious diseases are a significant public health issue throughout Europe, thus, addressing social determinants of infectious diseases in



Europe becomes a public health priority. It is not purely an issue of solidarity and social justice. Elevated infectious disease incidence/prevalence rates in vulnerable populations pose a health threat not only to them, but also to society at large. Last but not least, the control of infectious diseases is a strong driving force in the acceleration of demographic transition, by modifying the 'quantity-to-quality trade off' paradigm of parents.

The impacts of climate change on human health will not be evenly distributed globally. Populations in developing countries are considered to be particularly vulnerable.[23] However, WHO emphasizes that climate change is also likely to cause changes in ecological systems that will affect the risk of infectious diseases in the European region, including the seasonal activity of local vectors and the establishment of sub-tropical species.[24] Climate change can also pose a threat to health security. Failure to respond could be very costly in terms of disease, health care expenditure and lost productivity.

Infectious diseases are natural components of ecosystems, contributing to biodiversity and to their dynamic stability over time. However, when natural ecosystems are stressed, disease outbreaks may become more frequent and may have longer-term negative impacts, both on the ecosystems and potentially on society, as most natural ecosystems provide services, such as clean water and air, recreation, tourism, and the 'existence value' of biodiversity.

The greatest hazard to ecosystems arises when diseases affect keystone species that are important to ecosystem function, such as top predators, whose removal may lead to population explosion of herbivores and the overexploitation of plants. In an already stressed ecosystem, these effects may be aggravated, and a capacity to return to pre-disease structure and function reduced. Examples of stressed ecosystems today include over-fished marine systems; overgrazed grasslands and overexploited forests.

During the next 20 years, environmental degradation is likely to continue due to pollution, overproduction, habitat fragmentation and alien species invasions, while the economic value placed on natural ecosystems, particularly in developed countries, will increase.

Perhaps the greatest potential ecosystem-level impact of a new disease would be to undermine global water and geochemical cycles by disrupting the key plant and microbial systems that support them. The probability of this is regarded as very low at present. It is much more likely that new diseases in natural ecosystems will reduce the local abundance and diversity of species and the ecosystem services they provide. Natural ecosystems will, on the other hand, continue to be a major source of wildlife diseases that may threaten agricultural systems and human health.

Climate plays a role in the transmission of many infectious diseases, of which some are among the most important causes of mortality and morbidity in developing countries. Often these diseases occur as epidemics which may be triggered by variability in climatic conditions that favor higher transmission rates. With increasing demand for operational disease early warning systems, recent advances in the availability of climate and environmental data and increased use of geographical information systems (GIS) and remote sensing make climate-based early warning systems increasingly feasible from a technical point of view.

Early identification of an infectious disease outbreak is an important first step towards implementing effective disease interventions and reducing resulting mortality and morbidity in human populations. In the majority of cases, however, epidemics are generally well under way before authorities are notified and able to control the epidemic or mitigate its effects.

Both geographical and seasonal distributions of many infectious diseases are linked to climate, therefore the possibility of using seasonal climate forecasts as predictive indicators in disease early warning systems has long been a focus of interest. During the 1990s, however, a number of factors led to increased activity in this field: significant advances in data availability, epidemiological modeling and information technology, and the implementation of successful early warning systems outside the health sector. In addition, convincing evidence that anthropogenic influences are causing the world's climate to change has provided an added incentive to improve understanding of climate-disease interactions. Projections indicate an approximate average global warming of 2-5 °C within the twenty-first century,[25] accompanied by an increase in the frequency

of extreme and anomalous weather events such as heat-waves, floods and droughts.[26] It has been widely speculated that these projected changes may have significant impacts on the timing and severity of infectious disease outbreaks.

A range of infectious (particularly vector-borne) diseases are geographically and temporally limited by environmental variables such as climate and vegetation patterns. Climatic factors' impact on infectious diseases can be divided into three main effects: on human behavior; on the disease pathogen; on the disease vector, where relevant:

#### **a) Human behavior**

Climate variability directly influences human behavior, which in turn can determine disease transmission patterns. The strong seasonal pattern of influenza infections in Europe, for example, is thought to reflect humans' increased tendency to spend more time indoors during winter months.[27] Also, the peak of gastroenteritis in temperate developed countries during summer months can be related to changes in human behavior (e.g. more picnics and barbecues) associated with warmer temperatures.[28]

#### **b) Disease pathogens**

For infectious diseases where the pathogen replicates outside the final host (i.e. in the environment or an intermediate host or vector), climate factors can have a direct impact on the development of the pathogen. Most viruses, bacteria and parasites do not replicate below a certain temperature threshold (e.g. 18 °C for the malaria parasite *Plasmodium falciparum* and 20 °C for the Japanese encephalitis virus).[29][30] Ambient temperature increases above this threshold will shorten the development time of the pathogen.

#### **c) Disease vectors**

The geographical distribution and development rate of insect vectors is strongly related to temperature, rainfall and humidity. A rise in temperature accelerates the insect metabolic rate, increases egg production and makes blood feeding more frequent.[30] The influence of rainfall also is significant, although less easy to predict. Rainfall has an indirect effect on vector longevity through its effect on humidity; relatively wet conditions may create favorable insect habitats, thereby increasing the geographical distribution and seasonal abundance of disease vectors. In other cases excess rainfall may

have catastrophic effects on local vector populations if flooding washes away breeding sites.

Even where linkages between disease and climate are relatively strong, other non-climatic factors also may have a significant impact on the timing and severity of disease outbreaks. One such factor is population vulnerability (e.g. influenced by herd immunity and malnutrition). In Kenya, for example,[31] have argued that malaria epidemics in the western highlands may occur only when the non-immune proportion of the population has grown by recovery, births and immigration because local children surviving to adulthood develop immunity. When developing an early warning systems, factors influencing the population dynamics of the pathogen (e.g. drug resistance) also may have to be considered. Human-related factors such as population movements and agricultural practices also can have considerable impact on disease patterns at various spatial scales. For example, the prevalence of Malaria and Leishmaniasis sometimes is strongly related to irrigation schemes and deforestation.[32][33]

Arguably, the importance of non-climatic factors should be assessed and compared to that of climate variability in order to justify the development of climate-based early warning systems for infectious diseases. The relative contributions of climatic and non-climatic risk factors in explaining temporal variability in disease incidence will, to a large degree, determine the practical utility of climate-based early warning systems.

As long as climate change is not too rapid or strong, many of the health effects can be controlled by strengthening health systems. This may include strengthening preparedness, public health services and health security, advocating action in other sectors to benefit health, better informing citizens and leading by example. Health systems need to strengthen their capacity to assess potential climate-related health effects, to review their capacities to cope, and develop and implement adaptation and mitigation strategies, and to strengthen a range of key areas of work - from disease surveillance and control to disaster risk reduction - that are essential for rapid detection of and action against climate-related risks.

The reductions in the capacity of the health service to deal with other conditions and restrictions or changes affecting the lives of individuals and their businesses where an

outbreak occurs considers as another potential costs of infectious diseases. Higher levels of international travel and trade increase the risk of infectious agents spreading rapidly around the world, causing epidemics and pandemics; many factors create new ecological niches for the multiplication and spread of infectious agents like meanwhile, changing behavioral, environmental, economic and migration patterns.[34]

## 1.1 Tuberculosis (TB)

### 1.1.1 Epidemiology, Surveillance and Burden

Tuberculosis (TB) remains a major global health problem, is a challenging disease to diagnose, treat, and control. Despite notable progress in the past decade, Tuberculosis is still a public health concern in most of the countries within the WHO European Region.

One third of the world's population is estimated to be infected with *Mycobacterium Tuberculosis*, representing a huge reservoir of potential Tuberculosis disease. In 1997, there were an estimated 7.96 million new cases of Tuberculosis worldwide and 16.2 million prevalent cases.[35] In 2008, there were an estimated 9.4 (range, 8.9–9.9 million) million incident cases of Tuberculosis globally. This is an increase from the 9.3 million Tuberculosis cases estimated to have occurred in 2007, as slow reductions in incidence rates per capita continue to be outweighed by increases in population.

Tuberculosis is no longer among the 10 leading causes of death, but is still among the top 15 killing one million people in 2011.[36] It causes ill-health among millions of people each year and ranks as the second leading cause of death from an infectious disease worldwide after the human immunodeficiency virus (HIV). The latest estimates are that there were 8.6 million new Tuberculosis cases in 2012 and 1.3 million Tuberculosis deaths (just under 1.0 million among HIV-negative people and 0.3 million HIV-associated Tuberculosis deaths).[37]

In the European Union, Tuberculosis case notification rates are among the lowest in the world. However, the epidemiological pattern varies considerably from country to country, with some countries showing steady progress towards eliminating the disease, while others still face unacceptably high case notification rates. In all countries, control efforts have to deal with the challenges of multidrug-resistant (MDR) and extensively drug-resistant (XDR) Tuberculosis, co-infection of Tuberculosis and human immunodeficiency virus (HIV) infection, and the concentration of cases in vulnerable groups.

In 2012, an estimated 353 000 new (incident) Tuberculosis cases (range 330 000–376 000) occurred in the WHO European Region, equivalent to an average of 39.4 cases (36.9–41.9) per 100 000 population. This represents about 4% of the total burden of incident Tuberculosis cases in the world.[38]

Globally, there were an estimated 0.5 million cases of multidrug-resistant Tuberculosis (MDR-Tuberculosis) in 2007. In 2011, there were about 310, 000 cases among patients with pulmonary Tuberculosis. In the same year, of an estimated 78 000 multidrug-resistant Tuberculosis (MDR-Tuberculosis) cases in the European Region, 29 473 (38%) were detected. The prevalence of MDR among new Tuberculosis cases in the Region amounted to 14% and 47.7% among previously treated cases.[39] In 2012, there were an estimated 450 000 new MDR-Tuberculosis cases in the world according to WHO.[40]

In 1997, there were 10.7 million people co-infected with Tuberculosis and HIV.[35] A person who is HIV-positive and infected with Tuberculosis is 30 times more likely to develop clinical symptoms than is an infected person who is HIV-negative, because their weakened immune systems allow the bacteria to develop unchecked.[41] A person who is HIV-positive and develops Tuberculosis can expect to survive only five to six weeks, although chemotherapy can increase such an individual's life expectancy by two to five years.[42] In sum, the HIV epidemic has produced more Tuberculosis cases that are more difficult to diagnose and more expensive to treat.[43]

In 2008, there were an estimated 0.5 million deaths among incident Tuberculosis cases who were HIV-positive. In 2011, 12 751 Tuberculosis cases with HIV co-infection (56.5%) were detected from the 22 500 estimated cases in the European Region. The estimated prevalence of HIV infection among Tuberculosis patients was 6%. The fact that prevalence among all tested Tuberculosis cases was very similar (6.2%) gives an indication of the accuracy of Tuberculosis-HIV surveillance in the Region. However, since HIV testing coverage is at 60%, the status was only known for 205 578 new and previous Tuberculosis cases, 12 751 of which had an HIV co-infection.[39]

The great majority of the Tuberculosis burden occurs in the 18 high-priority countries of the European Region (87% of the Tuberculosis incidence, 87% of the

prevalence, 92% of the mortality caused by Tuberculosis, 91% of Tuberculosis/HIV co-infections, and 99% of the MDR-Tuberculosis), it must focus the main efforts to combat and prevent Tuberculosis in the Region there.[39]

Because there is currently no completely effective vaccine, control of the disease relies heavily on detecting infectious cases and treating them for at least six months with a combination of antibiotics. The aim of treatment is to cure the patient and achieve non-infectiousness, hence interrupting transmission of the disease, while avoiding the emergence of drug resistance.

The Millennium Development Goal target to halt and reverse the Tuberculosis epidemic by 2015 has already been achieved. The Tuberculosis mortality rate decreased by 41% between 1990 and 2011.[44]

### **1.1.2 Social, economic and psychological impact**

Although much is known about the epidemiology of Tuberculosis, relatively little is known of its economic and social impacts. The illness and death caused by the disease have far-reaching economic, psychological, and social consequences.

Tuberculosis places an extraordinary burden on those afflicted by the disease, their families, and communities and on government budgets. The greatest burden of Tuberculosis falls on productive adults who, once infected, are weakened and often unable to work. The burden of taking care of sick individuals usually falls to other family members and, in addition to putting them at greater risk of infection, can lower their productivity. Besides loss of productivity, the cost of treating Tuberculosis also can be significant. Mean household spending on Tuberculosis can account for as much as 8–20% of annual household income, varying by region.[45] Children also are affected. Each year, a significant proportion of children from families in which the primary breadwinner has Tuberculosis are forced to drop out of school or seek employment.

In many regions of the world, Tuberculosis is a growing problem. Because of a combination of economic decline, insufficient application of control measures (case detection and chemotherapy), and the HIV/AIDS epidemic, Tuberculosis is on the rise in developing and transitional economies.



The economic impact of Tuberculosis comes both from the size of the problem in the community and from the fact that, in developing countries, the majority of such patients come from the most economically productive segment of the population: more than 75% among those 15 to 54 years of age.[46] Tuberculosis accounts for almost 20% of all deaths in this age group and 26% of preventable deaths.[47]

The impact of Tuberculosis is most often measured as the direct costs of treatment to the health service, that is, the costs of medicines, personnel, and facilities used. However, the economic impacts are considerably more far-reaching. Often patients seek costly treatment from traditional healers or the private sector before an accurate diagnosis is made. Only then, they may shift to the public sector. The costs to patients and their families that can be quantified are principally in the form of lost earnings from loss of work due to illness or death. Additional costs come from food required while in hospital and the costs of travel to hospital or clinic for care. In addition to these direct treatment and non-treatment costs, Tuberculosis imposes intangible costs in the form of pain, suffering, grief and discrimination.

Conventional treatments for Tuberculosis are often expensive and have low cure rates. They tend to impose particularly large indirect costs on individuals and households. Meanwhile, the substantial non-treatment costs of Tuberculosis are borne by the patients and their families. These are often greater than the costs of treatment to the health sector. The largest indirect cost of Tuberculosis for a patient is income lost by being too sick to work. Studies suggest that on average three to four months of work time are lost, resulting in average lost potential earnings of 20% to 30% of annual household income. For the families of those that die from the disease, there is the further loss of about 15 years of income because of the premature death of the Tuberculosis sufferer. When a woman suffers from Tuberculosis, additional losses may result. The household loses the activities that the woman routinely performs in the household: cooking, cleaning, childcare, and managing the activities of the household.

Women who suffer from Tuberculosis are often less likely to be detected and treated than men. Although Tuberculosis is commonly thought to be a disease of the poor, this is not exclusively the case. Although the poor are more likely to suffer from the

disease, a significant proportion of those infected are literate, have considerable education, and earn good incomes.[48] Had found in a study conducted in Pakistan on socio-cultural constraints in treatment that while both male and female Tuberculosis patients face social and economic problems, female patients are more affected.

By diverting resources from other forms of health care, reducing other forms of consumption, withdrawing children from school, borrowing or selling assets, and the like, the households attempt to cope with the large immediate costs of Tuberculosis. Some of these short-term coping strategies can have significant long-term costs for household members. Such costs are rarely taken into account in studies of the impacts of Tuberculosis.

Psychological impact is one of the most important impacts of Tuberculosis. Discrimination may consider a major psychological impact of Tuberculosis, additional costs, both monetary and psychological, can occur due to discrimination against those infected with Tuberculosis and members of their households. Family and friends may reject Tuberculosis patients, they may receive less social support during treatment, or they may lose their jobs.

In some developing countries, discrimination against Tuberculosis sufferers has taken particularly damaging forms, such as divorce or lowered prospects of marriage. Such discrimination represents significant costs because the economic prospects for divorced or unmarriageable women in many societies are bleak.

Furthermore of discrimination, psychological costs such as attendant anxiety, depression and lower life satisfaction, add to the costs of Tuberculosis.

Treatment process plays an important role in the psychological impact, the isolation process is necessary while the client remains infectious to maintain safety and prevent possible further spread of disease. Infection control and protective masks are important but the initial psychological impact of their use is significant. Isolation creates problems for the client with difficulties around communication and financial problems and is recognized as an issue by staff. Visiting times are restricted and children are not permitted to visit Tuberculosis cases. Many may choose not to visit at all.

The quality of life assessed for the cases when compared with that of the control group helped in the evaluation of the impact of Tuberculosis on quality of life of patients. Quality of life is defined as a person's perception of his or her physical and mental health and covers broad domains including physical, psychological, economic, spiritual and social well-being.[49] Health care to be comprehensive in true sense must include not only the indicators of changes in frequency and severity of disease but also an estimation of well-being.

Tuberculosis is a disease with social implications due to the stigma attached to it which is evident from the lower scores of cases in psychological and social domains. This is in coherence with the other studies.[50][51] which point out that Tuberculosis affects all the predicted domains of quality of life such as psychological, general health perception and social role functioning.

Addressing the MDR-Tuberculosis public health crisis is the top priority for Tuberculosis control. Countries with a high burden of MDR-Tuberculosis should recognize it as a public health crisis and address it as an emergency. Adequate treatment of drug-susceptible Tuberculosis, expansion of early and rapid detection of all MDR-Tuberculosis cases, and immediate and proper treatment and care must all be prioritized. Support the accelerated scale up of services to prevent, diagnose, treat and care for MDR-Tuberculosis comes only if all stakeholders work together. To ensure that the increasing capacity to diagnose MDR-Tuberculosis is matched with an adequate supply of quality drugs and scaled-up country capacity to deliver effective treatment and care, high-level dialogue and refocused commitment must be done.

Tuberculosis has long been a disease associated with poverty and developing countries, and in the nineteenth and early twentieth centuries was a significant issue across what is today the developed world. This high incidence of disease dropped steadily as incomes. A financial crisis can increase the size of groups with a high risk for Tuberculosis. Experts from EU/EEA countries predict that there will be an impact of the current global crisis on the financial and human resources available for the control of communicable diseases.[11]

For instance, tuberculosis prevalence in European Union Member States is inversely correlated with wealth and its distribution at an ecological level, with increasing socio-economic equality; Tuberculosis rates drop.[52]

There is evidence that an economic crisis can impact on access to care and quality of care and on the number of individuals that are exposed to risk factors for Tuberculosis, a study about the impact of the New York City's fiscal crisis in 1975,[53] found that the number of homeless people (well known risk group for Tuberculosis) increased by 300%. Overall, risks of contracting Tuberculosis were greatest among those who had experienced reductions in income, involuntary unemployment, and were unable to afford health care.[54][55] In European Union it seems that the previous study doesn't really keeping with another study conducted in European Union countries that did not show any significant effects.[10] In that study, data for social protections, i.e. availability of social welfare programs and for job insecurity was missing for many countries, which makes the detection of immediate changes in mortality difficult. And it must take into accounts that study was conducted before the current economic crisis started and do therefore not provide direct information about the effect of the current situation on tuberculosis. So, that keeps the doubts and concerns about the real impact of economic crisis on Tuberculosis incidence and prevalence.

Over the five reporting years (2006 - 2010) of the European Centre for Disease Prevention and Control (ECDC) and the World Health Organization Regional Office for Europe, the EU/EEA has experienced a constant annual decline of 4.4% in Tuberculosis notification rates, from 17.5 per 100,000 population in 2006 to 14.6 in 2010.[56] Thus, the European data do not show an effect of the current economic crisis on Tuberculosis at this moment.

Tackling the MDR-Tuberculosis public health crisis is the first priority for Tuberculosis control in the European region. Of the 27 high MDR-Tuberculosis burden countries, 15 are in the European region. The leadership of the WHO Regional Office has already been developed a regional MDR-Tuberculosis action plan for Europe and approved by all Member States to reduce the proportion of previously treated patients who have MDR-Tuberculosis by 20% (compared with 2011), to diagnose at least 85% of

all estimated cases of MDR-Tuberculosis among Tuberculosis patients and to successfully treat at least 75% of all Tuberculosis patients with confirmed MDR-Tuberculosis.[57]

Because Tuberculosis is a slow disease with a minimum incubation period of eight weeks it may take time to see a significant increase in the number of cases. Because the healthcare system may experience difficulties in diagnosing and notifying, it is possible that we will initially see a further decrease in the number of Tuberculosis cases. However, it has been shown that in Europe, Tuberculosis notifications are higher where national incomes are lower and/or income inequalities are higher.[52] If the current financial crisis affects these two variables, then Tuberculosis rates may well rise.

### The economic burden

The global burden of tuberculosis is estimated at hundreds of billions of dollars every year. The annual economic loss is 0.52% of the world's gross national income.

The economic burden of Tuberculosis in the European Union amounts to a total of €5,898 million per year, according to a conservative calculation,[58] did a systematic review of literature and institutional websites for the direct costs (medication, hospitalization and outpatient cost) and indirect costs (loss of productivity and the monetary equivalent of Disability-Adjusted Life-Years (DALYs) (overall disease burden)), the direct costs of Tuberculosis in the European Union add up to about €537 million per year. The cost of treatment of susceptible Tuberculosis cases in the 18 wealthier European Union countries (Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Malta, Netherlands, Portugal, Slovenia, Spain, Sweden, United Kingdom) is estimated at €7,848 per case, whereas the costs to treat MDR-Tuberculosis cases and XDR-Tuberculosis cases are estimated at €54,779 and €168,310 respectively. Due to lack of data the cost of treatment of susceptible Tuberculosis patients in the 9 remaining 'new' European Union member states (Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia)) are estimated at one third of the mean in the 'wealthier' European Union member states: €2,616. The cost of treatment of MDR-Tuberculosis and XDR-Tuberculosis patients in these countries are estimated at € 24,166.

The loss of productivity is calculated at €2,434 per patient, regardless of drug susceptibility, for the 18 wealthier European Union countries, and €811 for the remaining 9 countries. Combined with the direct costs and the monetary equivalent of Disability-Adjusted Life-Years due to Tuberculosis of €5,361 million this adds up to about €5.9 billion overall cost for Tuberculosis in the European Union.

It is expected that the current economic crisis will have an effect on the Tuberculosis situation in EU/EEA countries given the likely influence of an economic crisis on the functioning of healthcare systems and on factors that affect the epidemiology of Tuberculosis. This will be especially true in countries that were already experiencing problems with Tuberculosis control before.[59] Also, control of MDR- and extensively drug-resistant (XDR-) Tuberculosis requires a well-established and functioning healthcare system that is able to diagnose cases and provide them with expensive treatment and long-term care.

While tuberculosis is on the increase, economic difficulties in some countries are putting pressure on health budgets. In these circumstances, health departments need to use the most cost-effective treatments for tuberculosis, that is, those approaches that provide effective treatment or a cure for the lowest cost. In many cases, the most cost effective treatments are not being used. Furthermore, decisions on what treatment regimens to follow are often based only on costs to the health ministry. The costs borne by patients have largely been ignored, even though such costs often exceed the costs to the health ministry.

When the costs and benefits of investments in health are being considered, the total social costs (public costs plus those borne by individuals), and not just the government costs, should be taken into account in order that efficient choices in health care may be made.[60] If private costs are ignored, too little investment may be made and it may be allocated in a way that does not minimize the burden of disease.

### 1.1.3 The Lungs, Anatomy and physiology

The anatomy and physiology of the respiratory tract is quite complex. Each anatomic segment performs in concert with the others and is accountable for a wide variety of physiological responsibilities. These responsibilities vary with rest or exercise, disease or health.

The lungs are the two sponge-like organs which expand with diaphragmatic contraction to admit air and house the alveoli where oxygen and carbon dioxide diffusion regenerates blood cells. The lungs are divided into right and left halves, which have three and two lobes, respectively. Each half is anchored by the mediastinum and rests on the diaphragm below. The medial surface of each half features an aperture, called a hilus, through which the bronchus, nerves and blood vessels pass. (Figure 1)

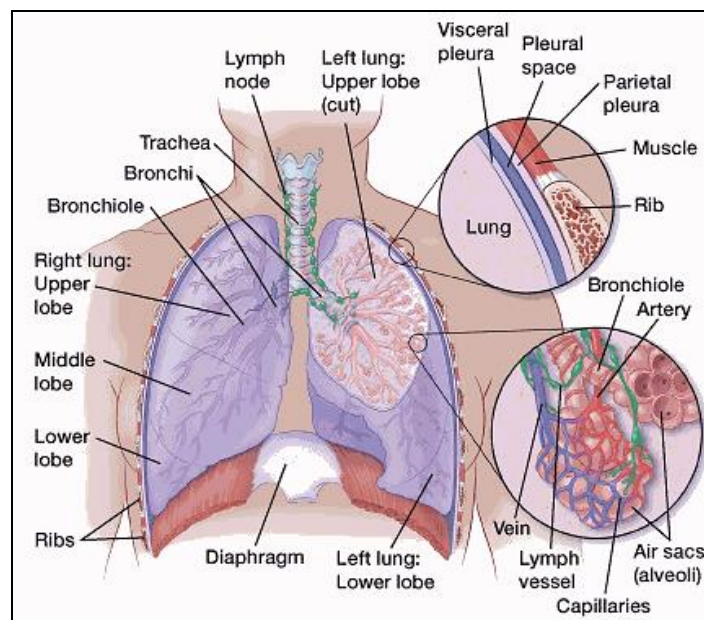


Figure 1: Anatomy of the Lung.

At the lower end of the trachea, there are two primary bronchi. The right is slightly larger than the left. These bronchi enter their corresponding lung, where they branch into secondary and then tertiary bronchi. The tertiary bronchi branch into even smaller airways, the bronchioles. Because the primary bronchi and their respective branches resemble an upside down tree, they are known as the bronchial tree. The bronchioles keep dividing into smaller and smaller tubes that eventually become

microscopic. Once the tubes become microscopic, they are known as the alveoli ducts. These ducts enter into alveolar sacs. Diffusion of gases occurs in the alveoli.[61]

Because the alveoli are truly the functional gas exchanging units of the lungs, they deserve to be described in more detail. There are approximately 300 million alveoli in the lungs. This is equivalent to approximately 85 square meters if opened up and laid out flat.[61] The walls of the alveoli are very thin and lie right next to a bed of capillaries. This barrier between the incoming air and the blood is known as the respiratory membrane. Oxygen travels across this membrane into the bloodstream and carbon dioxide travels from the bloodstream, across the membrane and into the alveoli, where it can be exhaled. Within the alveoli is a substance known as surfactant. Surfactant is responsible for keeping the alveoli open during exhalation, so they do not collapse completely.[61][62]

#### 1.1.4 Definition

Tuberculosis is an airborne disease caused by the bacterium *Mycobacterium tuberculosis* (*M. tuberculosis*) (Figure 2) *M. tuberculosis* and seven very closely related mycobacterial species (*M. bovis*, *M. africanum*, *M. microti*, *M. caprae*, *M. pinnipedii*, *M. canetti* and *M. mungi*) together comprise what is known as the *M. tuberculosis* complex. Most, but not all, of these species have been found to cause disease in humans. *M. tuberculosis* organisms are also called tubercle bacilli. The majority of cases involve the respiratory system; however, the organism may infect any part of the body.

The *Mycobacterium tuberculosis* is a rod-shaped, non-spore-forming, aerobic bacterium.[63] The well-developed cell wall contains a considerable amount of a fatty acid, mycolic acid, covalently attached to the underlying peptidoglycan-bound polysaccharide arabinogalactan, providing an extraordinary lipid barrier.

This barrier is responsible for many of the medically challenging physiological characteristics of Tuberculosis, including resistance to antibiotics and host defense mechanisms. The composition and quantity of the cell wall components affect the bacteria's virulence and growth rate.[64] The peptidoglycan polymer confers cell wall rigidity and is just external to the bacterial cell membrane, another contributor to the permeability barrier of mycobacteria.



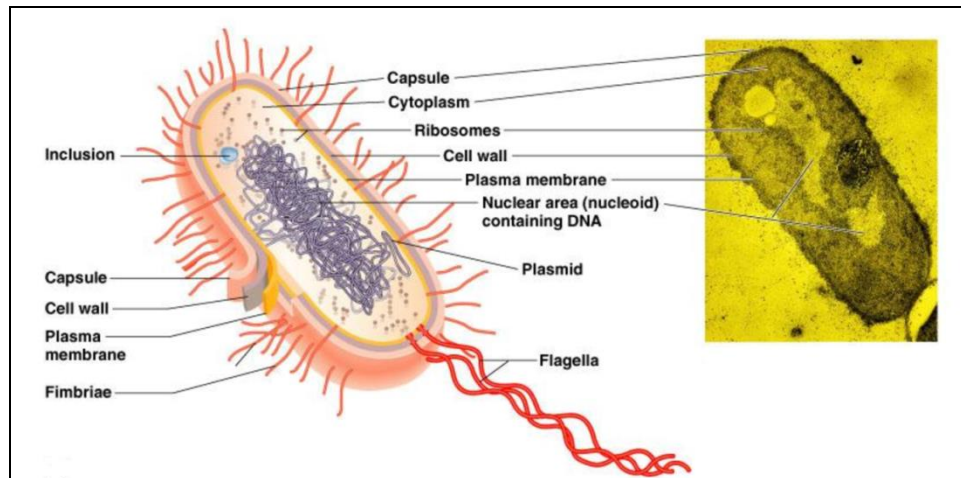


Figure 2: Bacterium *Mycobacterium Tuberculosis*.

Another important component of the cell wall is lipoarabinomannan, a carbohydrate structural antigen on the outside of the organism that is immunogenic and facilitates the survival of mycobacteria within macrophages.[64][65] The cell wall is key to the survival of mycobacteria and a more complete understanding of the biosynthetic pathways and gene functions and the development of antibiotics to prevent formation of the cell wall are areas of great interest.[65]

### 1.1.5 Pathophysiology

Once inhaled, the infectious droplets settle throughout the airways. The majority of the bacilli are trapped in the upper parts of the airways where the mucus-secreting goblet cells exist. The mucus produced catches foreign substances, and the cilia on the surface of the cells constantly beat the mucus and its entrapped particles upward for removal.[66] This system provides the body with an initial physical defense that prevents infection in most persons exposed to Tuberculosis.[67]

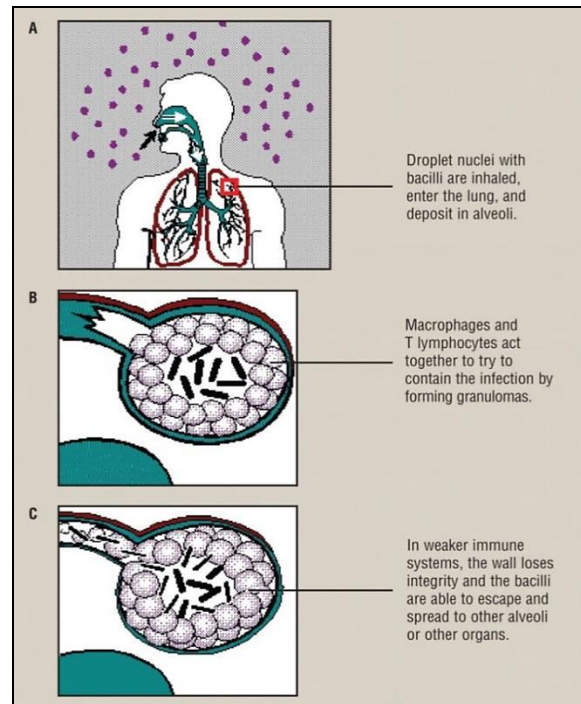
Bacteria in droplets that bypass the mucociliary system and reach the alveoli are quickly surrounded and engulfed by alveolar macrophages,[68][66] the most abundant immune effector cells present in alveolar spaces.[69] These macrophages, the next line of host defense, are part of the innate immune system and provide an opportunity for the body to destroy the invading mycobacteria and prevent infection.[70] Macrophages are readily available phagocytic cells that combat many pathogens without requiring previous exposure to the pathogens. Several mechanisms and macrophage receptors are involved

in uptake of the mycobacteria.[70] The mycobacterial lipoarabinomannan is a key ligand for a macrophage receptor.[71] The complement system also plays a role in the phagocytosis of the bacteria.[72] The complement protein C3 binds to the cell wall and enhances recognition of the mycobacteria by macrophages. Opsonization by C3 is rapid, even in the air spaces of a host with no previous exposure to *M. tuberculosis*. [73] The subsequent phagocytosis by macrophages initiates a cascade of events that results in either successful control of the infection, followed by latent Tuberculosis, or progression to active disease, called primary progressive Tuberculosis. The outcome is essentially determined by the quality of the host defenses and the balance that occurs between host defenses and the invading mycobacteria.[70][74]

After being ingested by macrophages, the mycobacteria continue to multiply slowly,[66] with bacterial cell division occurring every 25 to 32 hours. [63][68] Regardless of whether the infection becomes controlled or progresses, initial development involves production of proteolytic enzymes and cytokines by macrophages in an attempt to degrade the bacteria.[70][71] Released cytokines attract T lymphocytes to the site, the cells that constitute cell-mediated immunity. Macrophages then present mycobacterial antigens on their surface to the T cells.[70] This initial immune process continues for 2 to 12 weeks; the microorganisms continue to grow until they reach sufficient numbers to fully elicit the cell-mediated immune response, which can be detected by a skin test.[63][66][70]

For persons with intact cell-mediated immunity, the next defensive step is formation of granulomas around the *M. tuberculosis* organisms (Figure 3[75]). These nodular-type lesions form from an accumulation of activated T lymphocytes and macrophages, which creates a micro-environment that limits replication and the spread of the mycobacteria.[66][71] This environment destroys macrophages and produces early solid necrosis at the center of the lesion; however, the bacilli are able to adapt to survive.[76] In fact, *M. tuberculosis* organisms can change their phenotypic expression, such as protein regulation, to enhance survival.[72] By 2 or 3 weeks, the necrotic environment resembles soft cheese, often referred to caseous necrosis, and is characterized by low oxygen levels, low pH, and limited nutrients. This condition restricts further growth and establishes latency. Lesions in persons with an adequate immune system

generally undergo fibrosis and calcification, successfully controlling the infection so that the bacilli are contained in the dormant, healed lesions.[76] Lesions in persons with less effective immune systems progress to primary progressive Tuberculosis.[63][66][72][76].



**Figure 3: Pathophysiology of Tuberculosis.**

For less immunocompetent persons, granuloma formation is initiated yet ultimately is unsuccessful in containing the bacilli. The necrotic tissue undergoes liquefaction, and the fibrous wall loses structural integrity. The semiliquid necrotic material can then drain into a bronchus or nearby blood vessel, leaving an air-filled cavity at the original site. In patients infected with *M. tuberculosis*, droplets can be coughed up from the bronchus and infect other persons. If discharge into a vessel occurs, occurrence of extra pulmonary Tuberculosis is likely. Bacilli can also drain into the lymphatic system and collect in the tracheobronchial lymph nodes of the affected lung, where the organisms can form new caseous granulomas.[76]

### 1.1.6 Transmission

*Mycobacterium tuberculosis* is spread by small airborne droplets, called droplet nuclei, generated by the coughing, sneezing, talking, or singing of a person with pulmonary or laryngeal Tuberculosis. These minuscule droplets can remain airborne for

minutes to hours after expectoration.[64] The number of bacilli in the droplets, the virulence of the bacilli, exposure of the bacilli to UV light, degree of ventilation, and occasions for aerosolization all influence transmission.[68] Introduction of *M. tuberculosis* into the lungs leads to infection of the respiratory system; however, the organisms can spread to other organs, such as the lymphatics, pleura, bones/joints, or meninges, and cause extrapulmonary Tuberculosis.

### 1.1.7 Stage classification

#### a) Latent Tuberculosis

*Mycobacterium tuberculosis* organisms can be enclosed, as previously described, but are difficult to completely eliminate.[74] Persons with latent Tuberculosis have no signs or symptoms of the disease, do not feel sick, and are not infectious.[77] However, viable bacilli can persist in the necrotic material for years or even a lifetime,[67] and if the immune system later becomes compromised, as it does in many critically ill patients, the disease can be reactivated. Although co-infection with human immunodeficiency virus is the most notable cause for progression to active disease, other factors, such as uncontrolled diabetes mellitus, sepsis, renal failure, malnutrition, smoking, chemotherapy, organ transplantation, and long-term corticosteroid usage, that can trigger reactivation of a remote infection are more common in the critical care setting.[66][77] Additionally, persons 65 years or older have a disproportionately higher rate of disease than any does other age group[77] often because of diminishing immunity and reactivation of disease.[78]

#### b) Primary Disease

Primary pulmonary Tuberculosis is often asymptomatic, so that the results of diagnostic tests are the only evidence of the disease. Although primary disease essentially exists subclinically, some self-limiting findings might be noticed in an assessment. Associated paratracheal lymphadenopathy may occur because the bacilli spread from the lungs through the lymphatic system. If the primary lesion enlarges, pleural effusion is a distinguishing finding. This effusion develops because the bacilli infiltrate the pleural space from an adjacent area. The effusion may remain small and resolve spontaneously, or it

may become large enough to induce symptoms such as fever, pleuritic chest pain, and dyspnea. Dyspnea is due to poor gas exchange in the areas of affected lung tissue. Dullness to percussion and a lack of breath sounds are physical findings indicative of a pleural effusion because excess fluid has entered the pleural space.[68]

### c) Primary Progressive Tuberculosis

Active Tuberculosis develops in only 5% to 10% of persons exposed to *M. tuberculosis*. When a patient progresses to active Tuberculosis, early signs and symptoms are often nonspecific. Manifestations often include progressive fatigue, malaise, weight loss, and a low-grade fever accompanied by chills and night sweats.[79] Wasting, a classic feature of Tuberculosis is due to the lack of appetite and the altered metabolism associated with the inflammatory and immune responses. Wasting involves the loss of both fat and lean tissue; the decreased muscle mass contributes to the fatigue.[80] Finger clubbing, a late sign of poor oxygenation, may occur; however, it does not indicate the extent of disease.[81] A cough eventually develops in most patients. Although the cough may initially be nonproductive, it advances to a productive cough of purulent sputum. The sputum may also be streaked with blood. Hemoptysis can be due to destruction of a patent vessel located in the wall of the cavity, the rupture of a dilated vessel in a cavity, or the formation of an aspergilloma in an old cavity. The inflamed parenchyma may cause pleuritic chest pain. Extensive disease may lead to dyspnea or orthopnea because the increased interstitial volume leads to a decrease in lung diffusion capacity. Although many patients with active disease have few physical findings, rales may be detected over involved areas during inspiration, particularly after a cough. Hematologic studies might reveal anemia, which is the cause of the weakness and fatigue. Leukocytosis may also occur because of the large increase in the number of leukocytes, or white blood cells, in response to the infection.[68]

## 1.1.8 Extrapulmonary Tuberculosis

Although the pulmonary system is the most common location for Tuberculosis, extrapulmonary disease occurs in more than 20% of immunocompetent patients, and the risk for extrapulmonary disease increases with immunosuppression.[82] The most serious location is the central nervous system, where infection may result in meningitis or space-

occupying tuberculomas. If not treated, tubercular meningitis is fatal in most cases, making rapid detection of the mycobacteria essential.[66] Headaches and change in mental status after possible exposure to Tuberculosis or in high risk groups should prompt consideration of this disease as a differential diagnosis. Another fatal form of Extrapulmonary Tuberculosis is infection of the bloodstream by *mycobacteria*; this form of the disease is called disseminated or Miliary Tuberculosis. The bacilli can then spread throughout the body, leading to multiorgan involvement.[83] Miliary Tuberculosis progresses rapidly and can be difficult to diagnose because of its systemic and nonspecific signs and symptoms, such as fever, weight loss, and weakness.[68] This is prevalent in one third of Tuberculosis cases. Rarely Miliary Tuberculosis may appear in a single organ (<5%), in many organs, or throughout the body (>90%). If undiagnosed (up to 50% of cases antemortum), the infection could be fatal. Miliary Tuberculosis may mimic many other diseases depending on the organ system(s) involved.[84] Lymphatic Tuberculosis is the most common extrapulmonary Tuberculosis, and cervical adenopathy occurs most often. Other possible locations include bones, joints, pleura, and genitourinary system.[85]

### 1.1.9 Clinical Manifestations

As the cellular processes occur, Tuberculosis may develop differently in each patient, according to the status of the patient's immune system. As previously mentioned, Tuberculosis stages include latency, primary disease, primary progressive disease, and extrapulmonary disease. Each stage has different clinical manifestations (Table 1).

#### 1.1.10 Diagnosis: Clinical and laboratory

Despite rapid advances in molecular diagnosis and drug therapies, Tuberculosis remains among the leading causes of death in the world today.

Early and accurate diagnosis is critical to Tuberculosis care and control. There is substantial evidence that failure to identify cases early is a major weak link in efforts to control the disease, resulting in ongoing transmission in the community and in more severe, progressive disease in the affected person. However, it must be emphasized that the major delays in diagnosing Tuberculosis result from the patient not seeking care and/or the provider not suspecting the disease, rather than technological limitations.[86]

While improving the performance of diagnostic tests is important, improving patients' and providers' awareness of the disease and their understanding of approaches to diagnosis is at least equally important.

<b>Early infection</b>	<b>Early primary progressive (active)</b>	<b>Late primary progressive (active)</b>	<b>Latent</b>
Immune system fights infection.	Immune system does not control initial infection.	Cough becomes Productive.	Mycobacteria persist in the body.
Infection generally proceeds without signs or symptoms.	Inflammation of tissues ensues.	More signs and symptoms as disease progresses	No signs or symptoms occur. Patients do not feel sick.
Patients may have fever, paratracheal lymphadenopathy, or dyspnea.	Patients often have nonspecific signs or symptoms (eg, fatigue, weight loss, fever).	More signs and symptoms as disease progresses.	Patients are susceptible to reactivation of disease.
Infection may be only subclinical and may not advance to active disease.	Nonproductive cough develops.	Findings on chest radiograph are normal.	Granulomatous lesions calcify and become fibrotic, become apparent on chest radiographs.
	Diagnosis can be difficult: findings on chest radiographs may be normal and sputum smears maybe negative for mycobacteria.	Diagnosis is via cultures of sputum.	Infection can reappear when immunosuppression occurs.

**Table 1: Clinical manifestation in each stage of Tuberculosis.**

A complete medical evaluation for Tuberculosis includes the following:

➤ **Medical History**

It is important to ask individuals suspected of having Tuberculosis about their history of Tuberculosis exposure, infection, or disease. Clinicians may also contact the local health department for information about whether a patient has received Tuberculosis treatment in the past. If the treatment regimen was inadequate, or if the patient did not adhere to therapy, Tuberculosis may recur and may be drug-resistant.

It is also important to consider demographic factors (e.g., country of origin, age, ethnic or racial group, occupation) that may increase the patient's risk for exposure to Tuberculosis or to drug-resistant Tuberculosis. Also, clinicians should determine whether the patient has medical conditions, especially HIV infection, that increases the risk of latent Tuberculosis infection progressing to Tuberculosis disease.

➤ **Physical Examination**

A physical examination is an essential part of the evaluation of any patient. It cannot be used to confirm or rule out Tuberculosis, but it can provide valuable information about the patient's overall condition and other factors that may affect how Tuberculosis is treated, such as HIV infection or other illnesses.[85]

Physical findings in pulmonary Tuberculosis are not generally helpful in defining the disease. A physical examination may reveal symptoms of Tuberculosis, including persistent cough, hemoptysis, fever, chills, or adventitious breath sounds. In the absence of a physical examination, a patient's Tuberculosis symptoms may be subclinical and go unrecognized for a long time.[41]

Certain manifestations of Tuberculosis, such as erythema nodosum, can be diagnosed on the basis of physical examination alone since the cutaneous nodules that extend to the layer of subcutaneous tissue are very distinctive.[87]



## ➤ Chest Radiograph

Active Tuberculosis may be considered as a possible diagnosis when findings on a chest radiograph of a patient being evaluated for respiratory symptoms are abnormal, as occurs in most patients with pulmonary Tuberculosis. Pulmonary Tuberculosis nearly always causes abnormalities on the chest film, although an endobronchial lesion may not be associated with a radiographic finding. In addition, in patients with pulmonary Tuberculosis disease and HIV infection, a normal chest film is more common than in persons with Tuberculosis disease without immune suppression. In primary Tuberculosis occurring as a result of recent infection, the process is generally seen as middle or lower lung zone infiltrate, often associated with ipsilateral hilar adenopathy. Atelectasis may result from compression of airways by enlarged lymph nodes.[88] Those lesions may appear anywhere in the lungs and may differ in size, shape, density, and cavitation. These abnormalities may suggest Tuberculosis, but cannot be used to definitively diagnose Tuberculosis.[89] If the primary process persists beyond the time when specific cell-mediated immunity develops, cavitation may occur (so-called “progressive primary” Tuberculosis).[88]

However, a chest radiograph may be used to rule out the possibility of pulmonary Tuberculosis in a person who has had a positive reaction to a Tuberculin Skin Test (TST) or Tuberculosis blood test and no symptoms of disease. However, a chest radiograph may be used to rule out the possibility of pulmonary Tuberculosis in a person who has had a positive reaction to a TST or Tuberculosis blood test and no symptoms of disease.

## ➤ Laboratory and Diagnostic Studies

### • Tuberculosis Testing

Targeted testing for Tuberculosis infection is done to identify individuals who are at high risk of developing Tuberculosis disease and who would benefit from treatment. All testing activities should be accompanied by a plan for follow-up medical evaluation and treatment for individuals with Tuberculosis infection or Tuberculosis disease. Individuals with a positive test for Tuberculosis infection should be evaluated for

Tuberculosis disease and, if disease is ruled out, considered for treatment for latent Tuberculosis infection.[90]

- **Diagnosis of active Tuberculosis infection**

For active Tuberculosis, serological tests have been attempted for decades. Two meta-analyses have convincingly shown that existing commercial antibody-based tests have poor accuracy and limited clinical utility. [91][92] Despite this evidence, dozens of commercial serological tests continue to be marketed, mostly in private sectors of countries that lack diagnostic regulatory bodies.[93]

Nucleic acid amplification tests (NAATs) were considered to be a major breakthrough in Tuberculosis diagnosis when they were first introduced. A series of meta-analyses have shown that NAATs have high specificity and positive predictive value, but modest and highly variable sensitivity, especially in smear-negative and extrapulmonary Tuberculosis.[94][95][96]

- **Diagnosis of latent Tuberculosis infection**

For diagnosis of latent Tuberculosis, clinicians have used the tuberculin skin test (TST) for decades. Recently, interferon-gamma release assays (IGRAs) have emerged as attractive alternatives. While the TST is known to have poor specificity in populations vaccinated with Bacille Calmette-Guérin (BCG), [97] meta-analyses have shown that IGRAs have much higher specificity for Tuberculosis infection than the TST, and IGRA specificity is unaffected by BCG vaccination.[98][99][100] However, another meta-analysis showed that BCG vaccination received in infancy has a minimal effect on the TST, whereas BCG received after infancy produces more frequent, more persistent, and larger TST reactions.[101] Thus, the TST might retain high specificity in some populations, whereas it may perform poorly in others. IGRAs are particularly attractive in the latter setting. However, meta-analyses on IGRAs have highlighted the lack of evidence on the predictive ability of these assays in identifying those individuals with Tuberculosis infection who are at highest risk for progressing to active disease. Several cohort studies are ongoing,[102] and these should provide useful evidence on this unresolved issue.

Conventional tests such as smears and cultures perform poorly in Extrapulmonary Tuberculosis. A series of reviews have shown that biomarkers such as Adenosine Deaminase (ADA) and interferon-gamma (IFN- $\gamma$ ) have excellent accuracy for tuberculous pleural effusion.[103][104] These biomarkers, especially ADA, are easy to measure and inexpensive. Despite this evidence, these tests appear to be underutilized.[105]

- **Diagnosis of Multidrug-resistant Tuberculosis (MDR-Tuberculosis) infection**

For the diagnosis of multidrug-resistant Tuberculosis (MDR-Tuberculosis), available data suggest that phage-based assays do not perform well when directly applied to clinical specimens.[100] Line probe assays show great promise for rapid detection of Rifampicin resistance in settings with high MDR-Tuberculosis prevalence.[106][107] Simple tests such as colorimetric redox methods and nitrate reductase assays appear to perform very well, but require culture isolation.[108][109]. More evidence is needed on rapid tests for drug resistance, especially since the Global Extensively Drug-Resistant Tuberculosis (XDR-Tuberculosis) Response Plan calls for wide-scale implementation of rapid methods to screen patients at risk of XDR-Tuberculosis and MDR-Tuberculosis.[110]

For laboratory practice, systematic reviews provide strong evidence that fluorescence microscopy is more sensitive than conventional light microscopy (with no significant loss in specificity),[111] that sputum processing methods (e.g., bleach or centrifugation) can be effective in increasing the yield of smear microscopy,[112] and that liquid cultures are more rapid and sensitive than solid cultures.[113] Tuberculosis diagnosis is summarized in the (Table 2).

The confirmation of a single case of Tuberculosis often involves a complex network of laboratories performing a wide range of tests. This is because multiple methods are required to recover, identify, and determine drug resistance for *Mycobacteria*, including *M. tuberculosis*, not all of which are available in every laboratory. Existing methods for detection range from simple smear microscopy and slow culture methods to advanced, costly, or technically demanding molecular assays. Average turnaround times for reporting results, even in state-of-the-art laboratories, are often measured in days to weeks.

Variable	Sputum smear	Sputum culture	Polymerase chain reaction	Tuberculin skin test	Tuberculin skin test	Chest radiography
<b>Purpose of test or study.</b>	Time required for results.	Identify <i>Mycobacterium tuberculosis</i> .	Identify <i>M. tuberculosis</i>	Detect exposure to mycobacteria	Measure immune reactivity to <i>M. tuberculosis</i> .	Visualize lobar infiltrates with cavitation.
<b>Time required for results.</b>	<24 hours	3-6 weeks with solid media, 4-14 days with high-pressure liquid chromatography.	Hours	48-72 hours	12-24 hours	Minutes

**Table 2: A summary of Tuberculosis diagnosis.**

### 1.1.11 Treatment

Persons with latent *M. tuberculosis* infection who are at increased risk for active Tuberculosis require preventive treatment.[114][115] The preferred regimen is Isoniazid alone for 9 months or for a longer duration in HIV-infected persons in areas with a high prevalence of Tuberculosis.[116][117] Recently, directly observed weekly administration of Isoniazid and Rifampine for 12 weeks has been shown to be as effective as Isoniazid alone in adults without HIV infection in countries with a low burden of Tuberculosis. This regimen was associated with fewer serious adverse events than 9 months of Isoniazid alone, although treatment discontinuation because of an adverse event was more common.[118] The trial is continuing to assess safety and effectiveness in children and HIV-infected persons.

Current WHO guidelines[117] recommend that all HIV-infected persons with positive or unknown results on the Tuberculin Skin Test and without active Tuberculosis who are living in resource constrained, high-burden countries receive preventive therapy with Isoniazid for at least 6 months. Three regimens are effective for the prevention of active Tuberculosis in HIV-infected persons: daily Isoniazid for 6 to 9 months, daily Rifampin and isoniazid for 3 months, and Rifampin and Isoniazid twice weekly for 3 months.[116][117] Rifampin containing regimens have higher rates of drug toxicity than those that do not include Rifampin.[117][118][119] The difficulty of diagnosing active

Tuberculosis in patients with HIV co-infection accounts in part for the slow adoption of Isoniazid preventive therapy in clinical practice. Only patients with a positive Tuberculin Skin Test who are receiving preventive therapy with Isoniazid have decreased rates of active Tuberculosis and death,[119] and protection against Tuberculosis wanes within a few months after cessation of Isoniazid therapy. A trial in Botswana recently showed that 36 months of preventive therapy with Isoniazid, as compared with 6 months of therapy, reduced the subsequent rate of Tuberculosis by 43%.[120] However, compliance with such a long-term regimen may be poor.[117] A daily regimen of Rifapentine and Isoniazid for 1 month is also being studied. Studies have been suggested to investigate targeted use of preventive therapy with isoniazid on a continuous or recurring basis in persons with HIV infection who have a positive tuberculin skin test.[121]

### Treatment during Pregnancy and Breastfeeding in Women

Women of childbearing age should be asked about pregnancy status before starting Tuberculosis treatment. Untreated Tuberculosis represents a greater hazard to a pregnant woman and her fetus than dose treatment of the disease. Treatment of a pregnant woman with suspected Tuberculosis should be started if the probability of Tuberculosis is moderate to high. Rarely, a baby may be born with Tuberculosis.[122]

In general, administration of antituberculosis drugs is not an indication for termination of pregnancy. However, in women who are being treated for drug-resistant Tuberculosis, counseling concerning the risk to the fetus should be provided because of the known and unknown risks of the second-line antituberculosis drugs. Timely and properly applied chemotherapy is the best way to prevent transmission of Tuberculosis to the baby. After active Tuberculosis in the baby is ruled out, the baby should be given six months of Isoniazid (Isonicotinylhydrazine (INH)) preventive therapy, followed by BCG vaccination.[123]

Breastfeeding should not be discouraged for women being treated with first-line antituberculosis drugs because the small concentrations of these drugs in breast milk do not produce toxic effects in the nursing infant. Conversely, drugs in breast milk should not be considered to serve as effective treatment for active Tuberculosis or latent Tuberculosis infection in a nursing infant.

Supplementary pyridoxine (vitamin B6) is recommended both for the nursing mother and her infant. Due to the potential ototoxicity to the newborn, the administration of fluoroquinolones during breastfeeding is not recommended.[122]

## Extrapulmonary Tuberculosis Treatment

As a general rule, principles that underlie the treatment of pulmonary Tuberculosis also apply to extrapulmonary forms of the disease. Pulmonary and extrapulmonary disease should be treated with the same regimens.[123]

Extrapulmonary Tuberculosis can be treated using the same combination of antibiotics as those used to treat pulmonary Tuberculosis. However, you may need to take them for 12 months.

If Tuberculosis affects the brain, it may also be prescribed a corticosteroid, such as prednisolone, for several weeks to take at the same time as the antibiotics. This will help reduce any swelling in the affected areas.

## Treatment for Drug-resistant Tuberculosis

Tuberculosis that is resistant to at least two of the best anti-Tuberculosis drugs, Isoniazid (INH) and Rifampin (Rifadin), is called multidrug-resistant Tuberculosis (MDR Tuberculosis). Because these drugs are considered first-line drugs, they are used to treat all persons with Tuberculosis disease.

There are two types of drug resistance: primary and secondary. Primary resistance develops in individuals who are initially infected with resistant organisms. Secondary resistance, or acquired resistance, develops during Tuberculosis therapy, either because the patient was treated with an inadequate regimen or because the patient did not take the prescribed regimen appropriately.

Patients at increased risk for drug resistance include those with:

- Cultures those remain positive despite two months of therapy with Tuberculosis drugs.
- Inadequate treatment regimens for >2 weeks.

- A history of treatment with Tuberculosis drugs.
- Contact with an individual known to have drug-resistant Tuberculosis.
- Ethnic origin from foreign areas where the prevalence of drug-resistant Tuberculosis is high.[85]

### 1.1.12 Prevention and Infection control

The major public health objective of Tuberculosis control is to stop transmission of tubercle bacilli. The most important means of reducing transmission is the treatment of infectious cases with antituberculosis drugs. However, treatment of cases alone will not benefit those persons who have already been infected; therefore, the prevention of disease among infected persons at high risk of becoming infectious is a desirable second step.

Although Tuberculosis cure rates have improved markedly over the last few years, it is quite clear that Tuberculosis diagnosis and treatment programs alone are insufficient to control or reduce the burden of Tuberculosis disease (epidemic). New Tuberculosis infections should be prevented.

Some of the reasons for the increasing incidence of Tuberculosis are: inadequate access to health care, migration, deterioration of Tuberculosis control programs, low compliance with Tuberculosis treatment, multidrug-resistant strains, and the acquired immunodeficiency syndrome (AIDS) epidemic.

The means used to prevent and control Tuberculosis are improvement of socioeconomic conditions, case finding and treatment, chemoprophylaxis, and vaccination.[124] Improving socioeconomic conditions has proven to be slow and difficult in a world of social and political instability. Case finding and treatment, and chemoprophylaxis require an organized control program, which many countries do not yet have.

Prevention and control of Tuberculosis in a population requires a multidimensional approach whose major emphasis is to minimize risk of transmission by the early identification of people with active infectious disease and the treatment of each

case until cured using Directly Observed Therapy Shortcourse (DOTS).[125] Secondly, preventive treatment for those with latent infection but without active disease should be given, when appropriate, to prevent progression to active Tuberculosis disease. This preventive treatment is also known as treatment of latent Tuberculosis infection or Tuberculosis prophylaxis. Infection control measures should be used in health care facilities and other institutions to prevent nosocomial/institutional spread. Finally, BCG vaccination of selected population groups is used to prevent serious complications of infection.

Anything which increases the number of infectious people, such as the presence of Tuberculosis and HIV infection together, or which increases the number of people infected by each infectious person, such as ineffective treatment because of drug resistant Tuberculosis, reduces the overall effect of the main Tuberculosis prevention efforts. As a result it is then more likely that the number of people globally developing active Tuberculosis will increase rather than decrease.

## THE difference between Tuberculosis infection and Tuberculosis disease

### Tuberculosis Infection

Tuberculosis infection is when a person has *M. tuberculosis* in the body but does not have any symptoms of the Tuberculosis disease. The bacilli are inactive, but remain alive in the body and can become active later. This condition is also referred to as latent Tuberculosis infection.

Only one out of ten people with latent Tuberculosis will develop Tuberculosis disease in their lifetime. However this risk increases in persons with dual HIV and Tuberculosis infection in whom one out of ten will develop Tuberculosis disease in a year. Isoniazid preventive therapy reduces the risk of developing Tuberculosis disease.



## Tuberculosis Disease

A person is said to have Tuberculosis disease when he or she is infected with *M. tuberculosis* and shows signs and symptoms of the disease. Tuberculosis disease mostly occurs in the lungs. A person with Tuberculosis disease of the lungs (pulmonary Tuberculosis) usually has persistent cough lasting three weeks or more. With standard treatment, Tuberculosis can be cured, even in persons with HIV infection. Untreated, Tuberculosis is often fatal, especially in persons infected with HIV.

In general, a person with Tuberculosis disease of the lungs or larynx should be considered infectious until his/her sputum smear tests negative on microscopy. A Tuberculosis suspect should be considered infectious until Tuberculosis is ruled out through sputum smear microscopic examination.

As one of key targets in Tuberculosis prevention, BCG is used in Tuberculosis control programs primarily to prevent serious complications of infection (e.g. meningitis, military disease) in persons with undiagnosed disease who do not have access to early identification and treatment or where Tuberculosis control programs have been tried and not been successful.

### Bacillus Calmette-Guérin vaccine (BCG) vaccine

Bacillus Calmette-Guérin vaccine (BCG) is an alternative preventive measure that can be achieved in newborns in a single visit. It is an attenuated strain of *Mycobacterium bovis*, applied in 1921 in France by Albert Calmette and Camille Guérin as a vaccine against Tuberculosis.[126] The mechanism of protection from BCG vaccination involves a reduction of the haematogenous spread of bacilli from the site of primary infection. It protects against the acute manifestations of the disease, and reduces the lifelong risk of endogenous reactivation and dissemination associated with foci acquired from prior infection.[127][128]

BCG vaccine is one of the most widely used vaccines in the world and is currently given at or soon after birth to children in over 100 countries to minimize the potential for serious forms of Tuberculosis disease.[129] It reaches more than 80% of all new born

children and infants in countries where it is part of the national childhood immunization program.[130] However, it is also one of the most variable vaccines in routine use. As Tuberculosis rates have fallen many countries have discontinued routine BCG programs.[129] Because of their high cost: benefit ratio, adverse reactions associated with BCG immunization or because such programs have hindered investigation of Tuberculosis transmission through tuberculin skin testing.

## Recommendations

- **Children:** BCG vaccination should only be considered for children who have a negative tuberculin skin test and who are continually exposed, and cannot be separated from, adults who;
  - Are untreated or ineffectively treated for Tuberculosis disease (if the child cannot be given long-term treatment for infection); or
  - Have Tuberculosis caused by strains resistant to Isoniazid and Rifampin.
  
- **Health Care Workers:** BCG vaccination of health care workers should be considered on an individual basis in settings in which:
  - A high percentage of Tuberculosis patients are infected with *M. tuberculosis* strains resistant to both Isoniazid and Rifampin;
  - There is ongoing transmission of such drug-resistant *M. tuberculosis* strains to health care workers and subsequent infection is likely; or
  - Comprehensive Tuberculosis infection-control precautions have been implemented, but have not been successful.

Health care workers considered for BCG vaccination should be counseled regarding the risks and benefits associated with both BCG vaccination and treatment of Latent Tuberculosis Infection.

## Contraindications

- **Immunosuppression:** BCG vaccination should not be given to persons who are immunosuppressed (e.g., persons who are HIV infected) or who are likely to become immunocompromised (e.g., persons who are candidates for organ transplant).
- **Pregnancy:** BCG vaccination should not be given during pregnancy. Even though no harmful effects of BCG vaccination on the fetus have been observed, further studies are needed to prove its safety.

Mortality due to Tuberculosis disease in people living with HIV infection will not be reduced simply by treating Tuberculosis. The WHO Stop Tuberculosis Strategy 2006 emphasizes collaboration between Tuberculosis and HIV programs in order to effect Tuberculosis prevention. WHO Stop Tuberculosis programs Tuberculosis prevention strategies[131] include the 'Three 'I's of Tuberculosis prevention:

- Isonicotinylhydrazine (INH) prophylactic therapy – INH (a Tuberculosis drug) given for 6 months to people living with HIV infection who are well, without Tuberculosis disease can prevent reactivation of latent Tuberculosis.
- Intensified case finding – early detection of new cases of Tuberculosis will reduce the number of secondary cases that each infectious case generates.
- Infection control – prevents new infections by reducing the risk of acquiring Tuberculosis in health care institutions.

It's supposed that these three interventions will result in improvements in the National Tuberculosis Control Program (NTCP) (through improved case finding and, decreased numbers of Tuberculosis cases) and in care for people living with HIV/AIDS (by early diagnosis and prevention of Tuberculosis).

To address the factors that increase the risk of developing Tuberculosis, Tuberculosis control demands a comprehensive and sustained response and complementing measures. For that, The Stop Tuberculosis Strategy should therefore be viewed as a comprehensive strategy to control and stop Tuberculosis by gathering

medical, social, economic and political aspects. The Stop Tuberculosis Strategy has six principal components:[131]

**1. Pursue high-quality DOTS expansion and enhancement**

- a) Secure political commitment, with adequate and sustained financing.
- b) Ensure early case detection, and diagnosis through quality-assured bacteriology.
- c) Provide standardized treatment with supervision, and patient support.
- d) Ensure effective drug supply and management.
- e) Monitor and evaluate performance and impact.

**2. Address Tuberculosis/HIV, MDR-Tuberculosis, and other challenges**

- a) Scale-up collaborative Tuberculosis/HIV activities.
- b) Scale-up prevention and management of multidrug-resistant Tuberculosis (MDR-Tuberculosis).
- c) Address the needs of Tuberculosis contacts, and of poor and vulnerable populations.

**3. Contribute to health system strengthening**

- a) Help improve health policies, human resource development, financing, supplies, service delivery, and information.
- b) Strengthen infection control in health services, other congregate settings and households.
- c) Upgrade laboratory networks, and implement the Practical Approach to Lung Health (PAL).
- d) Adapt successful approaches from other fields and sectors, and foster action on the social determinants of health.

**4. Engage all care providers**

- a) Involve all public, voluntary, corporate and private providers through Public-Private Mix (PPM) approaches.
- b) Promote use of the International Standards for Tuberculosis Care (ISTC).

## 5. Empower people with Tuberculosis, and communities

- a) Pursue advocacy, communication and social mobilization.
- b) Foster community participation in Tuberculosis care, prevention and health promotion.
- c) Promote use of the Patients' Charter for Tuberculosis Care.

## 6. Enable and promote research

- a) Conduct program-based operational research.
- b) Advocate for and participate in research to develop new diagnostics, drugs and vaccines.

### Directly Observed Therapy Short Course (DOTS)

Directly Observed Therapy Short Course (DOTS) remains at the heart of the Stop Tuberculosis Strategy. DOTS is one method of ensuring adherence. Simply, it means that a supervisor watches the client swallowing the medication for all doses over the course of treatment. This ensures that a Tuberculosis client takes the correct drugs, the correct dose, and at the correct times. According to WHO, "The most cost-effective way to stop the spread of Tuberculosis in communities with a high incidence is by curing it. The best curative method for Tuberculosis is known as DOTS.[41]

DOTS is composed of five distinct elements:

- **Political commitment with increased and sustained financing:** Clear and sustained political commitment by national governments is crucial. Political commitment is needed to foster national and international partnerships, which should be linked to long-term strategic action plans. Meanwhile, adequate funding is essential. Current resources are inadequate, and further effort is required to mobilize additional resources from domestic as well as international sources, with a progressive increase in domestic funding.
- **Case detection through quality-assured bacteriology:** Bacteriology remains the recommended method of Tuberculosis case detection. First using sputum smear microscopy and then culture and Drug Susceptibility Testing (DST). To ensure

access to quality-assured sputum smear microscopy; a wide network of properly equipped laboratories with trained personnel is necessary.

- **Standardized treatment, with supervision and patient support:** Organizing and administering standardized treatment across the country for all adult and pediatric Tuberculosis cases – sputum smear-positive, smear-negative, and extrapulmonary is the mainstay of Tuberculosis control. Supervision of Tuberculosis Services by identify and address factors that may make patients interrupt or stop treatment, helps patients to take their drugs regularly and complete treatment, thus achieving cure and preventing the development of drug resistance. To improve the treatment access, identify and address physical, financial, social and cultural barriers – as well as health system – barriers to accessing Tuberculosis treatment services, locally appropriate measures should be undertaken. To the poorest and most vulnerable population groups particular attention should be given.
- **An effective drug supply and management system:** It is fundamental to Tuberculosis control the uninterrupted and sustained supply of quality-assured anti-Tuberculosis drugs. Anti-Tuberculosis drugs should be available free of charge to all Tuberculosis patients, both because many patients are poor and may find them difficult to afford, and because treatment has benefits that extend to society as a whole (cure prevents transmission to others).
- **Monitoring and evaluation system and impact measurement:** It is really vital establish a reliable monitoring and evaluation system with regular communication between the central and peripheral levels of the health system. These data, when compiled and analyzed, can be used at the facility level to monitor treatment outcomes. The additional diagnostic information from both of developed and developing countries that now have can be used to guide patient management by making the best use of data at all levels. All of that lead to enhance recording and reporting.

The difference in the way the term 'DOTS' as defined by WHO and interpreted by many observers has led to some misunderstanding. WHO generally uses the term to mean the five components of DOTS. But the word 'DOTS' is an acronym for Directly Observed Therapy Shortcourse. Many workers therefore interpret DOTS purely as direct supervision

of therapy. DOTS is not an end in itself but a means to an end. In fact it has two purposes, to ensure that the patient with Tuberculosis completes therapy to cure and to prevent drug resistance from developing in the community. The main criticism of DOTS rightly derives from the fact that some properly conducted randomized, controlled trials of directly observed therapy with or without the other components have shown no benefit from it. The problem is that it is impossible to design a study of modern directly observed therapy against the previous self-administered, poorly-resourced programs.

A number of studies of the DOTS strategy showed that the introduction of DOTS considerably lowered the indirect costs of Tuberculosis to patients and their families. Estimates suggest that the introduction of DOTS could halve the current potential national economic loss from Tuberculosis. DOTS is very cost-effective and its introduction does not imply that more funds are needed: at least some of the funding could come from the reallocation of funds away from poorer, less cost-effective strategy.

## **Tuberculosis Infection Control**

### **Health-care settings**

Tuberculosis is a big problem in health care settings. This is because persons with undiagnosed and potentially infectious Tuberculosis mix with others including those with HIV infection. In high Tuberculosis burden settings, surveys have shown that up to 10% of persons with HIV infection may have previously undiagnosed Tuberculosis at the time of HIV Testing and Counseling (HTC), including at centers providing prevention-of mother-to-child transmission (PMTCT) services. Up to half of these may be infectious Tuberculosis cases.

Every health-care setting should have a Tuberculosis infection-control plan that is part of an overall infection-control program. All health-care settings need a Tuberculosis infection-control program designed to ensure prompt detection, airborne precautions, and treatment of persons who have suspected or confirmed Tuberculosis disease (or prompt referral of persons who have suspected Tuberculosis disease for settings in which persons with Tuberculosis disease are not expected to be encountered). Such a program is

based on a three-level hierarchy of controls, including administrative, environmental, and respiratory protection.[132][133][134]

Persons with HIV-associated immuno-suppression may become infected or re-infected with Tuberculosis if they are exposed to someone with infectious Tuberculosis disease. They can progress rapidly from Tuberculosis infection to disease. Health care workers and other staff are also at particularly high risk of infection with Tuberculosis because of frequent exposure to patients with infectious Tuberculosis disease.

### Among health care workers and other staff

Tuberculosis prevention in health care settings for staff, guardians and other patients is very essential. Patients or health workers and other staff who are HIV infected are at a greater risk of Tuberculosis infection than those that are HIV negative. The following are measures to follow in an attempt to prevent Tuberculosis infection in different settings:

- **The general outpatient clinic**

Tuberculosis patients attending the general outpatient clinic need to be identified early enough by health workers so that they are given a priority for Tuberculosis (triage). All chronic coughers in out patients' clinics need to be screened for pulmonary Tuberculosis as soon as possible.

- **The hospital wards**

Tuberculosis suspects are a potential source of Tuberculosis infection. All Tuberculosis suspects should rapidly have their sputum collected and sent to the laboratory for microscopy. The pulmonary Tuberculosis suspects should be placed in one part of the general ward near a window for good ventilation. Wherever possible, these Tuberculosis suspects should spend daylight hours outside the ward. Education on proper cough hygiene for pulmonary Tuberculosis suspects should be given on regular basis. For all Tuberculosis wards, windows should be kept open wherever possible. Visitors to the Tuberculosis wards should be kept to a minimum.



## Administrative control measures

Administrative control measures have the greatest impact on preventing Tuberculosis transmission within health care facilities. They serve as the first line of defense for preventing the spread of Tuberculosis in health care settings. Their goals are; to prevent Tuberculosis exposure to staff and patients, and to reduce the spread of infection by ensuring rapid diagnosis and treatment.

An infection prevention and control plan, administrative support for procedures in the plan including quality assurance, training of staff, education of patients and increasing community awareness, and coordination and communication with the Tuberculosis program are the components to good administrative controls.

## Environmental Controls

Environmental controls used to prevent the spread and reduce the concentration of infectious droplet nuclei in ambient air.

Ventilation can reduce the risk of infection through dilution and removal. When clean or fresh air enters a room, by either natural or mechanical ventilation, it dilutes the concentration of airborne particles, such as droplet nuclei, in room air. This is similar to opening doors and windows to dilute objectionable odors. Dilution reduces the likelihood that a person in the room will breathe air that may contain infectious droplet nuclei.

Primary environmental controls consist of controlling the source of infection by using local exhaust ventilation (e.g., hoods, tents, or booths) and diluting and removing contaminated air by using general ventilation.

Secondary environmental controls consist of controlling the airflow to prevent contamination of air in areas adjacent to the source (All rooms) and cleaning the air by using High Efficiency Particulate Air (HEPA) filtration or UVGI.

## Isolation

On identification of any hospitalized patients with suspected or confirmed Tuberculosis a decision will be made about appropriate placement, based on a risk assessment, by the Infection Prevention and Control Team. If a patient has suspected or confirmed pulmonary Tuberculosis they must be isolated in a side room on the isolation ward. Whilst the highest risk of transmission occurs with smear positive patients, smear negative patients with pulmonary Tuberculosis may present a risk to certain patient groups and should be isolated on the isolation ward where possible. Except for MDR Tuberculosis, patients should be considered infectious until two weeks of appropriate antituberculous drug therapy have been completed, and be showing clinical improvement e.g. free from fever for a week and/or cough resolving. If the patient has 3 consecutive sputum smear negative samples and is asymptomatic as outlined above he/she will not need to be isolated. A patient who has suspected or confirmed MDR Tuberculosis must be isolated immediately in a single room (on the isolation ward) with the door closed, until transfer to a specialist center with facilities for isolation in a negative pressure room can be arranged. This should be arranged without delay.

An anteroom should be provided between the Airborne Infection Isolation Room (AIIR) and the corridor. This will help prevent infectious particles in the AIIR from escaping into the corridor. When an AIIR door is open, negative pressure is immediately lost. If there is an anteroom that is negative to the corridor, then the overall integrity of the suite is maintained. The anteroom provides an “air lock” between the AIIR and the rest of the facility. An anteroom should be at positive pressure with respect to the AIIR, and at either neutral or negative pressure with respect to the corridor. However, in practice this is very difficult to accomplish. It is not easy to balance airflow to a space so that it will be positive at one door and neutral at the other. Furthermore, air pressure in the corridor will vary due to external factors such as elevators and corridor doors to the outside.

## Education of patients and community awareness

Educating communities and patients to recognize symptoms of Tuberculosis and to seek health care should be routine in all settings providing care for patients. In addition, patients should be taught how to protect themselves, and others, from exposure to Tuberculosis.

In the entire world, identifying and reaching all those in need of care, especially the poorest of the poor, poses a major challenge. Efforts to control Tuberculosis must progress hand-in-hand with efforts to strengthen health systems as a whole. The ultimate goal of eliminating Tuberculosis depends on new diagnostics, drugs and vaccines. New approaches to overcoming the obstacles to Tuberculosis control have been developed, but greater resources are needed to allow these approaches to be widely implemented.

## 1.2 Human Immunodeficiency Virus (HIV) Infection/ Acquired Immunodeficiency Syndrome (AIDS)

### 1.2.1 Epidemiology, Surveillance and Burden

Infection with Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) is a major global public health issue that affects all countries, it remains one of the world's most significant public health challenges, particularly in low- and middle-income countries, it affects both sexes, all ages and cultural and also socio-economic levels.[135][136]

Human immunodeficiency virus (HIV) dates back to at least the late 1950s and possibly earlier.[137] Sporadic cases of AIDS-like illnesses were first reported in the 1950s,[138] but the epidemic is generally considered to have gained momentum in the early 1980s, coinciding with the first reports of disease in US populations.[139] Although several theories exist as to the origination of HIV infection in humans, it is largely believed that HIV began as a zoonotic infection. The bushmeat theory of HIV posits that zoonotic transmission occurred when non-human primates were slaughtered for food thus exposing hunters to infected blood.[140] Different regions of Africa had different strains of Simian immunodeficiency virus (SIV) in the nonhuman primate populations and consequently, the serotypes of HIV in the human populations in these regions also differ. HIV-1 has been traced to chimpanzees and gorillas in West-Central Africa, while HIV-2 has been traced to sooty mangabeys in West Africa.[141] HIV-1 is largely responsible for the global pandemic of AIDS; HIV-2 has mostly been limited to Western Africa, is less pathogenic compared with HIV-1, and less likely to cause AIDS.[142][143][144]

With more than 27 million dead and upward of 60 million infected worldwide the history of the HIV epidemic is entering its third decade.[145] Every day, over 6,800 persons become infected with HIV and over 5,700 persons die from AIDS, mostly

because of inadequate access to HIV prevention and treatment services. The HIV pandemic remains the most serious of infectious disease challenges to public health.

In 2000, the global HIV/AIDS epidemic has killed an estimated 21.8 million people and another 36.1 million are living with HIV infection.[146]

At the beginning of 2001, more than 36 million people lived with HIV/AIDS worldwide 50% more than were predicted a decade ago. About 14 million women of childbearing age are currently infected with HIV, the virus that causes AIDS, increasing the risk of children being born with HIV. Over 21 million people including 4.3 million children have already died of AIDS since the start of the epidemic, leaving behind a legacy of more than 13 million orphans.[147]

An estimated 38.6 million [33.4 million–46 million] people worldwide were living with HIV at the end of 2005. An estimated 4.1 million [3.4 million–6.2 million] became newly infected with HIV and an estimated 2.8 million [2.4 million–3.3 million] lost their lives to AIDS. Overall, the HIV incidence rate (the proportion of people who have become infected with HIV) is believed to have peaked in the late 1990s and to have stabilized subsequently, notwithstanding increasing incidence in several countries.[148]

Favorable trends in incidence in several countries are related to changes in behavior and prevention programmes. Changes in incidence along with rising AIDS mortality have caused global HIV prevalence (the proportion of people living with HIV) to level off. However, the numbers of people living with HIV have continued to rise, due to population growth and, more recently, the life-prolonging effects of antiretroviral therapy. In sub-Saharan Africa, the region with the largest burden of the AIDS epidemic, data also indicate that the HIV incidence rate has peaked in most countries. However, the epidemics in this region are highly diverse and especially severe in Southern Africa, where some of the epidemics are still expanding.[148]

According to the 2008 Report on Global AIDS epidemic by the Joint United Nations Programme on HIV/AIDS and World Health Organization (UNAIDS/WHO), the total estimated number of people living with AIDS at the end of 2007 is 33.2 million, with 2.5 million new infections and 2.1 million deaths.[148]

In 2009, there were an estimated 2.6 million [2.3 million–2.8 million] people who became newly infected with HIV. This is nearly one fifth (19%) fewer than the 3.1 million [2.9 million–3.4 million] people newly infected in 1999, and more than one fifth (21%) fewer than the estimated 3.2 million [3.0 million–3.5 million] in 1997, the year in which annual new infections peaked. [149]

Worldwide, an estimated 14,000 new HIV infections occur every day. Most HIV carriers are asymptomatic and unaware of the risk to their partners and children.

In the European Union and European Economic Area (EU/EEA), 27,116 new HIV infections were diagnosed in 2010 and reported by 28 countries, a rate of 5.7 per 100,000 population. The overall rate for men was 8.6 per 100,000 population and for women 2.9 per 100,000 population. Of the reported newly diagnosed HIV infections, 11% were aged 15–24 years.[150]

According to the UNAIDS/WHO Global Report Epidemiology 2013, it is estimated that 35.3 (32.2–38.8) million people were living with HIV in 2012, with 2.3 million [1.9 million – 2.7 million] as a people newly infected with HIV and 1.6 million [1.4 million – 1.9 million] AIDS deaths.[151]

At the end of 2013, an estimated 35 million [33.2–37.2 million] people were living with HIV globally, and 3.2 million [2.9–3.5 million] of these were children, 240,000 new infections among children, and 190,000 AIDS deaths from the total 1.5 million people died of AIDS in 2013. The vast majority of people living with HIV are in low- and middle-income countries. An estimated 2.1 million [1.9–2.4 million] people were newly infected with the virus in 2013 about 6,000 new infections per day.[152] In spite of the overall number of cases has continued to decline, HIV infection remains a major public health concern in EU/EEA countries, characterized by a significant number of new infections. In some eastern European Union countries, the number of AIDS cases continues to rise.

According to UNAIDS estimates, around 2.3 million people were living with HIV in the European region at the end of 2010.[153] Estimated adult HIV prevalence varies from below 0.2% in parts of Central Europe to above 1% in parts of Eastern Europe.[154]

In 2011, a total of 28,038 new HIV diagnoses were reported by European Union and European Economic Area countries, a rate of 6.3 per 100,000 population when adjusted for reporting delay. The overall rate for men was 8.7 per 100,000 population and 2.8 per 100,000 population for women.[155] In Western and Central Europe 860,000 people were living with HIV in 2012. 29,000 people newly infected with HIV, and 7,600 deaths due to AIDS.[151]

In 2012, 29,306 diagnosed cases of HIV infection were reported in 29 EU/EEA countries, a rate of 5.7 per 100,000 population. This number is likely to be an underestimation due to the delay in reporting HIV diagnoses in a number of countries.

The overall rate ranged from 6 cases per 100,000 population in 2008 to 5.7 per 100,000 in 2012. When adjusted for reporting delay, the rate was 6.2 cases per 100,000 in 2012, indicating a relatively stable rate over the period.[156]

## Surveillance

Global surveillance of HIV and sexually transmitted infections is a joint effort of the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS). The UNAIDS/WHO Working Group on Global HIV/AIDS and Sexually Transmitted Infections (STI) Surveillance, initiated in November 1996, is the main coordination and implementation mechanism for UNAIDS and WHO to compile the best information available and to improve the quality of data needed for informed decision-making and planning at the national, regional and global levels.

Surveillance data are usually drawn from official sources. The two most common types of data are:

1. AIDS case data – that is, the number of AIDS cases by age, gender, and transmission category. The value of such data is limited because, in most countries, only a small number of cases reach official reports.

2. HIV data drawn from surveys of specific groups. Typically these will include blood donors, people who attend Sexually Transmitted Disease (STD) clinics, people with Tuberculosis, and women who attend Antenatal Clinics (ANCs). Women who attend

ANCs provide the most useful data at present: such data are usually based on surveys done at regular intervals and have fewer and more predictable biases than other data.

It is very important to remember that all data are subject to bias. When examining HIV data, one should assess bias by considering the following issues: (1) How representative of the general population is the group for which data have been collected? Typical groups in decreasing representativeness are: women who attend antenatal clinics, blood donors, Commercial Sex Workers (CSWs), and Injecting Drug Users (IDUs). (2) What differences might exist between urban and rural prevalence rates? Data are usually collected from urban areas, and rural rates are often lower than these. (3) HIV infection suppresses fertility, which means that prevalence data derived from women who attend antenatal clinics may underrepresent prevalence. (4) There are differences in male-female ratios at various points in the epidemic:  $>1$  for early, 1 or less for later once again leading to selectivity in the HIV prevalence data obtained from women who attend ANCs (depending on the stage of the epidemic).

Until recently the only way to test for HIV was by using blood samples, which made carrying out population-based sample surveys very difficult. The development of saliva testing will result in a wider range of data becoming available.

The first source for surveillance data should be the national AIDS control programme of the country under study. Such programmes should have all available information on AIDS cases and serosurvey data. If such data exist, they should be used to obtain as much detailed information as possible. In addition, any subsequent projections made on the basis of the data should be noted. If annual reports of the AIDS control programme are available, the researcher should assemble or gain access to as many years as possible to gain a perspective of the epidemic. It is important to note carefully what categories of people from what regions and districts of the country are being used as the main source of information, and how the data are being collected.

When the main outline and method of the published official figures have been established, the researcher should see whether there are any more detailed unpublished data that could be of use. It is important to note which geographical areas and social groups are most likely to be absent from the official figures, and to consider how this



might influence the official view of the epidemic. Some thought should be given to why and how the data came to be constructed in the way that they were. What does that construction reveal about biases and lacunae in the processes of data production? Does this suggest anything about how the next stages of the impact analysis need to be approached? It is also important to remember that aggregate data, even down to the regional and district levels, may not reflect particular communities, which may be much better or worse than the average.

The purpose of HIV/AIDS surveillance is to enable evidence-based development of prevention and control programmes, and to promote the most effective use of health resources. In the late 1990s a framework termed the second generation HIV/AIDS surveillance was developed by WHO and UNAIDS with the aim to tailor surveillance systems to needs of the specific epidemic states. HIV and AIDS case reporting, sero-surveillance, STI surveillance and behavioral surveillance are indispensable for monitoring epidemic trends and evaluating the effects of prevention interventions. The surveillance of HIV requires the collection of demographic and behavioral data because of the unique link between HIV epidemiology and behaviors. Biological and behavioral data collected by the HIV surveillance system should be used to validate one another.

### The Concept of “Second Generation Surveillance”

In response to the need to adapt surveillance tools to the epidemiologic state and to the need for tracking not only the disease but also its risk factors, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and WHO have together developed the concept of second generation surveillance.[157][158] This is defined as the “regular, systematic collection, analysis and interpretation of information for use in tracking and describing changes in the HIV/AIDS epidemic over time”. Acknowledging that no single data source can fully explain the status and trends of the epidemic. Second generation surveillance combines various sources of information including biological HIV/AIDS surveillance and behavioral surveillance, and the surveillance of other STI. These data allow monitoring of risks related to HIV transmission and provide a key source of information not only to understand the drivers of epidemics, but also for advocacy and for the planning and evaluation of prevention interventions.

To adapt surveillance to specific contexts, UNAIDS and WHO have developed a typology that classifies countries in terms of HIV epidemiologic states, which should guide the choice of surveillance tools and the methods for making incidence and prevalence estimates. Three categories have been defined as generalized, concentrated, and low level epidemics. “Generalized epidemics” are those in which HIV infection is firmly established in the population and in which sexual networking in the general population is sufficient to sustain the epidemic; operationally, they are defined as epidemics where the HIV prevalence among pregnant women is consistently greater than 1%. “Concentrated epidemics” are those in which infection is firmly established in at least one subpopulation but not in the general population; operationally, they are defined as epidemics in which HIV prevalence is consistently over 5% in at least one subpopulation but is below 1% among pregnant women in urban areas. “Low-level epidemics” are those in which the epidemic has not spread to a significant degree in any subpopulation; operationally, they are defined as epidemics in which HIV prevalence both has never been consistently greater than 5% in any subpopulation and is below 1% among pregnant women in urban areas.

European countries generally have concentrated epidemics, with perhaps a few exceptions, mostly in Central Europe where the epidemic can still be classified as low-level. However, classifying a country into one single category in the UNAIDS typology is not that straightforward because of uncertainties in the estimates of HIV prevalence in subpopulations.[159]

Second generation HIV surveillance grew out of the complexity inherent in measuring the full spectrum of populations’ experiences with HIV infection. To fully understand the HIV epidemic, national programmes needed to understand the modes of transmission using behavioral data, the prevalence using HIV test data, and the prevalence of other sexually transmitted infections. Collection and use of these data constitute second generation surveillance. With the rise in treatment availability, additional data collection systems have arisen and merged with traditional second generation surveillance. Treatment availability has also changed the ethical dynamic between surveillance practitioner and respondent.

In 2000, the UNAIDS/WHO published the Guidelines for second generation HIV surveillance.[160] The guidelines are a series of modules released over the past decade, designed to address the complexity of different HIV epidemic contexts and meet the planning needs of national programmes.

The earlier surveillance systems were focused on strategies for determining the prevalence of both asymptomatic and symptomatic HIV infection. While they helped to generate a response to the HIV epidemic and served to monitor the successes and failures of national responses to HIV, they were inadequate to meet the evolving challenges of the epidemic.

Second generation surveillance aims to build on the strengths of earlier efforts but with more focus on the importance of providing early warning signs of the spread of HIV. To achieve this goal, second generation surveillance seeks to integrate a wide range of resources including: HIV and advanced HIV (AIDS) case reports, serological studies of the prevalence of HIV infection, analyses of trends in Sexually Transmitted Infections (STIs), general morbidity and mortality reports and, most critically, studies of the behavior of individuals most at risk for acquiring and transmitting HIV. To ensure that surveillance efforts would make effective contributions to the control of the spread of HIV and the provision of services to those already infected second generation surveillance distinguishes among the efforts necessary to control the spread of HIV in countries at very different epidemic stages.

Low-level epidemics are those in which HIV infection exists at low levels in some populations whose social circumstances increase the likelihood of behaviors that carry a high risk of contracting or transmitting HIV, but in which infection is not widespread in the general population. In concentrated epidemics, relatively high levels of infections exist in selected subpopulations. The goals of surveillance are to understand the social and structural factors shaping behaviors that expose certain groups to risk, the prospect of increased infection in those groups, and the probability of the spread of HIV to the broader population. In generalized epidemics, HIV is already established in the population of sexually active adults with >1% of pregnant women infected. While heterosexual transmission is always the dominant mode of HIV spread in generalized

epidemics, HIV may also be overrepresented in some groups whose position in society and behavior places them at increased risk for acquiring and transmitting HIV. In such epidemics, the goal of surveillance is to understand both the sociostructural and behavioral dynamics that account for trends in HIV prevalence and the impact of interventions designed to reduce the level of incident infection.[160] European HIV/AIDS surveillance started in 1984 with the European Centre for the Epidemiological Surveillance of AIDS (EuroHIV) and the reporting of AIDS cases by 17 countries. It aims at understanding, improving and sharing HIV/AIDS surveillance data to optimize the prevention, control and management of the disease. This network gradually extended to the 51 member countries of the World Health Organization European Region. After reporting AIDS cases, most European countries have implemented the notification of HIV seropositivity at different dates.[161]

Since January 2008 onwards, ECDC and the WHO Regional Office for Europe jointly coordinated HIV/AIDS surveillance in Europe. Together they work to ensure a high quality of HIV/AIDS surveillance data covering all 53 countries in the European region.

The surveillance data on HIV and AIDS diagnoses is collected annually and is submitted by the national HIV/AIDS surveillance contact points in the Member States to The European Surveillance System (TESSy). The HIV/AIDS surveillance report is published annually on World AIDS Day, 1 December.

HIV/AIDS surveillance for Europe is carried out by the ECDC in cooperation with the WHO Regional Office for Europe, and by UNAIDS. National surveillance systems should become fully compatible with international requirements and all countries should report regularly on their HIV/AIDS epidemics. Second generation and behavioral surveillance must be intensified to better understand the dynamics of the epidemic in Europe. Policy development and implementation need solid and quality data, hence more behavioral studies would be needed. Policy makers need better evidence on what drives the epidemic. The contribution of Sexually Transmitted Infections (STIs) to the transmission of HIV should be assessed to inform policies and result in improved prevention, diagnosis, treatment and monitoring.

Surveillance of HIV infection and AIDS in Europe is essential to describe the HIV epidemic in this region and its main characteristics. It is important to monitor the epidemic and guide the public health response in order to reduce HIV transmission. Ensuring that the data are of high quality is of utmost importance to follow up the epidemic response and international commitments.[162]

AIDS data reported at the European level include: reporting country; age at diagnosis; sex; date of diagnosis; date of report; transmission category; AIDS indicative disease(s) at diagnosis; type of virus (HIV-1 or HIV-2); date of first HIV-positive test; vital status; date of death; date of death report. Not all countries are able to provide all the information for all cases, particularly date of first HIV-positive test. Conversely, some information may be available at country level but not at European level. For example, information on pre-AIDS treatment is recorded (in different ways) in some countries but is not, at this point, reported at the European level.

The HIV epidemic has challenged the traditional approach to public health in general and to the control of communicable diseases in particular. The response to this challenge has been termed exceptionalism.[163] It was characterized by enhanced communication between doctors and patients, increased emphasis on the respect of informed consent and confidentiality and a strong involvement of affected communities, particularly gay men, in designing prevention interventions and public health policies. Exceptionalism also applies to HIV/AIDS surveillance, which was handled differently from that of other communicable diseases. The use of unlinked anonymous surveys to monitor HIV prevalence in specific populations is just one example of this exceptionalism. The challenge presented by HIV led to more open discussion and involved the recording (and careful handling) of very private and sensitive information (such as risk behavior, country of origin or ethnic origin) seldom seen in the surveillance of other diseases. HIV/AIDS surveillance merged different approaches and combined biological and behavioral surveillance, paving the way for risk-behavioral surveillance pertaining to health in general.

## 1.2.2 Social, psychological and economic impact

HIV is a priority for all health authorities in all countries over the world as one of the main dangers for individual's health. Although the situation for developed and developing countries is quite different, this disease generates quite a lot of pressure in the Health System according to the amount of resources needed. This implies quite a lot of relevant questions for decision makers.

According to the United Nations Development Programme (UNDP) in the Human Development Report 2005, HIV has inflicted the “single greatest reversal in human development” in modern history.[164]

At the same time, the epidemic has heightened global consciousness of health disparities, and catalyzed unprecedented action to confront some of the world's most serious development challenges. No disease in history has prompted a comparable mobilization of political, financial, and human resources, and no development challenge has led to such a strong level of leadership and ownership by the communities and countries most heavily affected. In large part due to the impact of HIV, people throughout the world have become less willing to tolerate inequities in global health and economic status that have long gone unaddressed.

Just as the spread of HIV has been greater than was predicted a decade ago, so too has been its demographic, social and economic impact. But the impact witnessed so far is only a fraction of the impact to come, given the rapid spread of HIV over the past 20 years together with the long lag time between infection and the onset of severe HIV-related disease and symptoms. The course of HIV disease in those already infected, even with the most optimistic scenarios about the efficacy and accessibility of treatment will have a profound high impact not only on populations' health but on future rates of life expectancy and economic growth. AIDS constitutes one of the most serious crises currently facing human development, and threatens to reverse progress in the most severely affected countries by decades.

Implementation of effective preventive and risk reduction policies against sexual and intravenous transmission of the virus has certainly contributed to the emergence of

this new epidemiological trend. But the decrease in AIDS-related mortality and morbidity that has been observed in most Western European countries during the same period is also due to significant advances in clinical care of people infected with HIV. The diffusion of Highly Active Antiretroviral Therapies (HAART), including protease inhibitors (PIs), has clearly proved to be effective for obtaining substantial and sustained suppression of HIV viral replication and reducing the incidence of opportunistic infections among HIV-infected patients in short-term studies, and has provided a rationale for earlier initiation of antiretroviral treatment.[165]

These epidemiological and therapeutic positive changes in HIV/AIDS prevention and care have, however, not created technical “magic bullets” that would be able to solve all the questions raised by the epidemic for European societies, and from now on, to ignore their social, economic, psychological and political dimensions. Other realities, that have recently emerged, confirm that AIDS is largely a disease of human behaviors, and that it will remain so in the future. In spite of medical progress, HIV is still spreading very quickly in marginalized and socially deprived groups of Western European countries. As discussed by Delor and Hubert[166] in this issue, the epidemic has become one of the major focal point for the multiple forms of social exclusion which persist and even flourish in European “welfare states”. As also described in this issue by Atlani and others[167], a dramatic rise in the epidemic is observed in Eastern European countries, where rapid diffusion of HIV seems to be one of the price to pay for the liberalization of societies after the end of the communist era.

The characteristics of HIV/AIDS and its mode of transmission are the principal determinants of its impact on society. This impact can be divided into four broad areas, namely demographic, economic, social and developmental.

The demographic impact of HIV/AIDS has implications for the age structure of the population, for household composition, and for the dependency and care burden on different sections of the population. HIV/AIDS affects the population in a number of ways; HIV/AIDS increases morbidity (more people will die) and many of these people will be in their reproductive years. This could reduce fertility rates. The epidemic, however, will not stop population growth, nor will it cause populations to fall. Thus, any

idea that “AIDS is the solution to the population problem” is unfounded. What it will do, in some regions, is slow the rate of population growth and alter the structure of the population. The number of 20-40 year olds as a proportion of the entire population will decline; resulting in increased dependency ratios (This is particularly important as these are the most productive members of society. Collectively this cohort embodies a substantial human capital investment, much of which will be lost). The number of orphaned children will increase and they will have special needs, especially as the numbers grow and extended families are no longer able to cope. The phenomenon of AIDS orphans has brought to the attention of communities the work of women in rearing children. While extended family structures have, in some instances, been able to absorb these children, in many cases, they are already overstretched by other economic and social pressures.[168]

These issues have also been picked up in some micro-level studies of the impact of HIV/AIDS on women and gender relations[169][170], emphasising women’s role as carers and issues of home-based care, as well as access to resources and socio-economic status, including of female headed households.

### Social Burden

The HIV/AIDS epidemic threatens the social fabric of the most affected countries. Of all units affected by the HIV/AIDS epidemic, individuals, households and families are the most affected. The evidence shows that the AIDS epidemic is having severe effects on households.

The social or household impact begins as soon as a member of a household starts suffering from HIV-related diseases. In addition to social and psychological consequences, three kinds of economic impacts can be distinguished. The first is the loss of the income of the family member, in particular if he or she is the breadwinner. The second impact is the increase in household expenditures to cover the medical costs. The third impact is the indirect cost resulting from the absenteeism of members of the family from work or school to care for the AIDS patient.



Households experience the immediate impact of HIV/AIDS, because families are the main caregivers for the sick and suffer AIDS-related financial hardships. During the long period of illness caused by AIDS, the loss of income and cost of caring for a dying family member can impoverish households. When a parent dies, the household may dissolve and the children are sent to live with relatives or left to fend for themselves.

The social impact of HIV infection will result from the illness and death of individuals and the consequent effect on the family, community and broader society. Obviously critical to this impact will be who falls ill and dies in terms of their role in the family and community. The death of an adult male, who is an income earner, will affect the family's access to resources. The death of an adult female may result in children receiving less care and females being taken out of school.[171]

HIV/AIDS reverses gains in building basic human capabilities, and denies people opportunities for living long, healthy, creative and productive lives. The epidemic impoverishes families, places burdens on families and communities to care for the sick and dying, results in social exclusion and affects people's psychological well-being. Women and girls are particularly vulnerable to the epidemic and its impacts, and bear the burden of caring for families affected by HIV/AIDS.[172]

The long-term human development impact is felt in all sectors of public and private life. The epidemic strains national and local budgets, deprives sectors such as education and health of skilled workers as a result of illness and death, and inhibits the capacity of various sectors to sustain previous levels of productivity and services. While the long-term consequences may not yet be visible in some countries, the dynamics of the spread of the epidemic can be indicative of the potential magnitude of its impact.[171]

Applying the human development approach to HIV/AIDS helps to focus the analysis and policy recommendations on people rather than on the virus—a prerequisite for mobilizing effective action to reverse the epidemic. The value added of analyzing HIV/AIDS through a human development lens is that it lends itself to a more inclusive and people-centered approach to addressing the impact of the epidemic and promoting effective action.[173]

## Economic Burden

The impact of the HIV/AIDS epidemic on the economy has been a concern since the beginning of the pandemic. Some believe that the HIV/AIDS epidemic is responsible for slowing the rate of growth of the Gross National Product (GNP) of many heavily affected countries and that in some cases, GNP growth could decrease by more than 1 percentage point for every 10 per cent HIV prevalence. Others take the view that HIV/AIDS has had little impact on the macroeconomy so far.

Once HIV begins to spread in a society, certain consequences are inevitable, although initially they are invisible. The extent of these consequences and the speed with which they occur will depend on the effectiveness of prevention programmes and the degree to which the society is willing and able to plan for the impact.[174]

The HIV/AIDS epidemic can affect the economy in a number of ways:

1. The AIDS epidemic will slow or reverse growth in the labor supply. The economic impact can vary according to the sector of the economy, the degree to which HIV/AIDS affects hard-to-replace skilled labor and whether or not there is a substantial pool of “surplus labor”.

2. Savings and investments of families will be reduced owing to the increase in HIV/AIDS-related health expenditures. If children’s education, health and nutrition suffer as a result, prospects for longer-run economic growth and development will decline.

3. The AIDS epidemic may also divert public spending from investments in physical and human capital to health expenditures, leading over time to slower growth of the Gross Domestic Product (GDP). Foreign and domestic private investment might also decline if potential investors become convinced that the epidemic is seriously undermining the rate of return to investment.

4. The HIV/AIDS epidemic may also deepen the poverty of the most affected countries by decreasing the growth rate of per capita income and by selectively impoverishing the individuals and families that are directly affected.

Cohen [175], among others, stresses the effect of HIV on the size of the working population, which tends to reduce total output and worsen the dependency ratio. More

children and elderly people may have to be supported by a smaller active labor force. In addition, the composition of the labor force may change with respect to skills, education and experience, which would decrease the productivity of labor.

People living with HIV/AIDS will not only be unable to work, but will also require significant medical care. The forecast is that this will probably cause a collapse of economies and societies in countries with a significant AIDS population. In some heavily infected areas, the epidemic has left behind many orphans cared for by elderly grandparents.[176] The increased mortality in this region will result in a smaller skilled population and labor force.[176] This smaller labor force will be predominantly young people, with reduced knowledge and work experience leading to reduced productivity. An increase in workers' time off to look after sick family members or for sick leave will also lower productivity. Increased mortality will also weaken the mechanisms that generate human capital and investment in people, through loss of income and the death of parents. As the epidemic progresses, the age profile of those infected will increase, though the peak is expected to stay within the working age population. HIV disproportionately infects and impacts on women, so those sectors employing large numbers of women e.g. education, may be disproportionately economically impacted by HIV.[177][178] In a model applied to several Caribbean countries, identified four channels through which HIV/AIDS may affect the economy: the production channel; the allocation channel; the distribution channel; and the regeneration channel. The production channel refers to the mechanisms through which HIV/AIDS affects the main factors of production—labor and capital—causing the production process to be less fruitful than it would have been in the absence of HIV/AIDS. The second channel through which HIV/AIDS may affect the economy is the allocation channel. One of the most important functions of the economic system is to ensure an efficient allocation of resources. HIV/AIDS reroutes some of those resources to medical expenses and away from other productive uses. The third assumed channel through which HIV/AIDS affects the economy is the distribution channel, specifically, the distribution of income. In the face of an epidemic that increases health expenditures and weakens the income base, the lowest income groups may fare the worst. While the rich may have other assets—savings, land or capital—often the only productive asset of the poor is their own labor, which HIV/AIDS attacks. The upper income groups, though they are also affected, may be better placed to

protect themselves and better able to afford treatment. Thus, the HIV/AIDS epidemic has the potential not only to affect all groups but also to widen the gap between different social strata. The fourth channel, the regeneration channel, refers to the investments in human capital, physical capital and new technology that are needed to keep the economy growing. If the HIV/AIDS epidemic compromises the saving capacity and the human capital of the economy, it will undercut the process of economic development.

The macroeconomic impact of AIDS is difficult to assess. Most studies have found that estimates of the macroeconomic impacts are sensitive to assumptions about how AIDS affects savings and investment rates and whether AIDS affects the best educated employees more than others. Few studies have been able to incorporate the impacts at the household and firm level into macroeconomic projections. Some studies have found that the impacts may be small, especially if there is a plentiful supply of labor and worker benefits are small. Other studies have found significant macroeconomic impacts. The magnitude of the impact depends partly on the structure of the economy. Economies based on extractive industries or export agriculture are likely to be most severely affected. Unless highly qualified economists are to spend time trying to assess the impact of AIDS, it is likely that the output of the Spectrum model will be sufficient for the study.[174]

The macroeconomic effects of HIV/AIDS are explored below in terms of the differences in projected annual growth rates between “with-AIDS” and “no-AIDS” scenarios. It should be borne in mind that the effects of lower growth rates will cumulate over time since, unlike epidemics of such contagious diseases as influenza, HIV/AIDS will continue to exert its effects for many years into the future.[174]

A socioeconomic impact study may be expected to look at various sectors or government services, depending on the terms of reference. The health sector sees the first impact of AIDS. This is hardly surprising, as people who are experiencing periods of ill-health will seek medical care. In assessing the impact of AIDS, the emphasis is on the public-sector health care system. For the private sector, in the short term, increased illness will present an opportunity rather than a threat. However, it should be noted that in some settings the private sector provides a significant percentage of treatment, usually through employment-linked health insurance. As the epidemic develops and individuals use up their resources or become eligible for medical insurance because they lose their

employment, they have the choice of going without care or seeking it in the public sector. Although the private sector may offer a way of mobilizing resources, it is driven by profit motives and so may not be the most efficient or cost-effective way of providing the type of services wanted.

Although economic evaluations of High Activity Antiretroviral Treatment (HAART) have revealed being a cost-effective treatment compared to the treatments before [179][180], this does not really imply that the cost of these treatments does not worry the decision makers. Indeed, the appearance of new and more expensive drugs highlights the importance for decision makers to study and put more effort into the resources assignment due to the spread of costs generated. The HAART treatment is not considered the solution of this disease, but has increased considerably the expectancy and quality of life from seropositive persons.

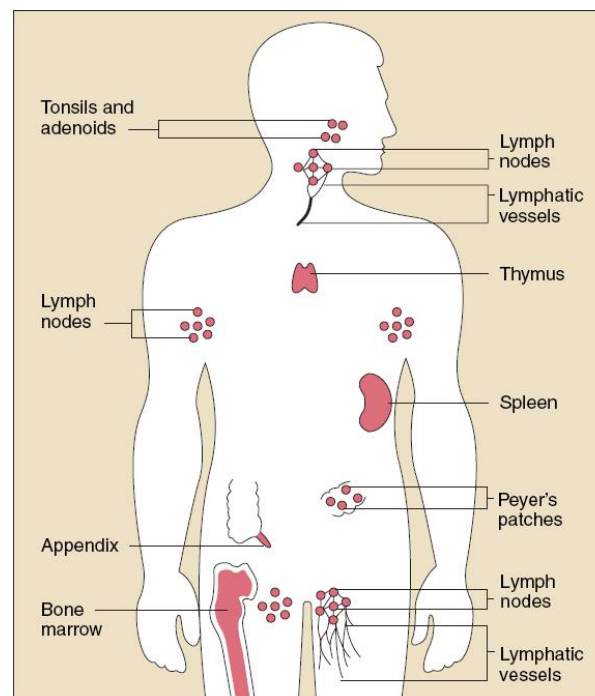
From the economic point of view, the introduction of the HAART has supposed an increase in the total treatment cost. Not really because the annual cost of treating is more expensive but because the increase on the life expectancy in patients. [180][181][182][183][184] The cost of treating a patient along their life period notably increases. [185][186] However, unlike what happens with other diseases such as Ischemic Heart Disease (IHD), stroke, mental illness or Alzheimer's disease, there are few studies of HIV costs in European countries. So, important doubts still exist regarding the annual treatment costs per patient and the heterogeneity of these costs among the different European countries and the impact of those on the health budget. In addition, it is also an element of interest the distribution of the total healthcare costs and the patient cost according the disease stage and the defenses (lymphocytes) level across patients.

### **1.2.3 Immune (Lymphatic) system, Anatomy and Physiology**

The immune and lymphatic systems are two closely related organ systems that share several organs and physiological functions. The immune system is our body's defense system against infectious pathogenic viruses, bacteria, and fungi as well as parasitic animals and protists. The immune system works to keep these harmful agents out of the body and attacks those that manage to enter.

## Definition

Immune (Lymphatic) System -- The immune or lymphatic system consists of a complex network of specialized cells and organs designed to protect and defend the body against attacks by "foreign" invaders such as bacteria and viruses (Figure 4).[187]



**Figure 4: Immune System.**

The immune system is generally divided into two large categories, innate and acquired. Innate immunity, also called natural immunity, is present at birth and functions similarly regardless of the pathogen earning it the designation, "nonspecific." Acquired immunity refers to immunity that is not present at birth and develops either as a result of exposure or through an external source such as colostrum or injection of immunoglobulin. Acquired immunity is also called adaptive or specific, because the immune response develops and changes in response to the specific pathogen. Adaptive immune responses are considered either humoral mediated or cell-mediated. Humoral mediated immunity refers to immunity that is mediated by B - lymphocytes, plasma cells, and antibodies. Cell-mediated immunity refers to immunity that is mediated by T-lymphocytes.[188]

The human body is constantly surrounded by pathogens in the air, on solid surfaces, and in water. Pathogens are ingested with every meal and inspired with every breath. Before ever encountering an immune system cell, a pathogen must penetrate the body's outer defenses. These consist of barriers—mechanical, chemical, and microbial—that are considered to be part of the innate immune system. In addition to the barriers themselves, each of these areas is populated with members of the innate immune system and often with lymphoid tissue.[189]

Non-specific defenses include the skin, internal and externalized secretions, and an army of natural (innate) immune cells, chemicals and defenses. The innate immune system is bolstered by the inflammatory response, which increases blood flow to damaged areas and encourages phagocytic leucocytes to move there to engulf potential pathogens. Non-specific immune responses are complemented by specific responses. These develop more gradually yet more definitively, targeting individual pathogens and ridding the body of malignant cells. With increasing age, the homeostatic mechanisms normally invoked when a foreign agent enters the body are severely disrupted, and the immune system is less able to respond well. While there are profound changes to innate defenses, it is the flexible and adaptable immune system that deteriorates more severely with age. [188]

## The innate immune system

Innate immunity consists of pattern recognition receptors, antimicrobial peptides, cells, complement components and different cytokines. It is the fast, nonspecific response and does not generate any memory against the attacking antigens. The skin, mucous membranes and secretions along with several non-specific cells, comprise the innate immune system.[190]

## The skin

The skin is the human body's first defense against infection. Intact skin is virtually impermeable to microorganisms.[191] Skin inhibits bacteria because it is dry and has a Low pH and antibacterial in sebum (oily secretions) and sweat. The skin consists of multiple layers of tightly packed dead cells filled with waxy keratin, shed regularly to prevent buildup of bacterial communities. The sebaceous glands provide protective film

over skin. Also, the acidity of skin secretions (acid mantle) inhibits bacterial & fungal growth. Skin also contains bactericidal chemicals.

## Mucous membranes

Mucosal surfaces or mucosa of the gastrointestinal tract, respiratory tract, reproductive tract, eyes, ears, and nose as they are continually bathed in the mucus that they secrete. The mucosa produces antimicrobial secretions such as Acid, Lysozyme and Mucus. This thick fluid layer contains glycoproteins, proteoglycans, and enzymes that protect the epithelial cells from damage, help to limit infection, traps both microbes and debris, and facilitates their removal. [187]

## Innate cellular and chemical defenses

Once a pathogen has breached a barrier and invaded deeper tissues, the internal innate immune defenses must act. The first cells to arrive at the site of infection are neutrophils, closely followed by macrophages. It is their job to try and clear the infection, for example by phagocytosis, initiation of the inflammatory response, recruitment of natural killer cells and activation of the complement system. In addition, dendritic cells mature and migrate to the site where they will later help in the adaptive immune response. [190]

## Phagocytes: Macrophages and Neutrophils

Many of the cells of the immune system have a phagocytic ability, at least at some point during their life cycles. Phagocytosis is an important and effective mechanism of destroying pathogens during innate immune responses. The phagocyte takes the organism inside itself as a phagosome, which subsequently fuses with a lysosome and its digestive enzymes, effectively killing many pathogens. On the other hand, some bacteria including *Mycobacteria tuberculosis*, the cause of Tuberculosis, may be resistant to these enzymes and are therefore much more difficult to clear from the body.[192]



Macrophages and neutrophils are the major phagocytes of the immune system. A Macrophage is an irregularly shaped phagocyte that is amoeboid in nature and is the most versatile of the phagocytes in the body. Macrophages move through tissues and squeeze through capillary walls using pseudopodia. They not only participate in innate immune responses but have also evolved to cooperate with lymphocytes as part of the adaptive immune response. Macrophages exist in many tissues of the body, either freely roaming through connective tissues or fixed to reticular fibers within specific tissues such as lymph nodes. When pathogens breach the body's barrier defenses, macrophages are the first line of defense. They are called different names, depending on the tissue: Kupffer cells in the liver, histiocytes in connective tissue, and alveolar macrophages in the lungs.[193]

A Neutrophil is a phagocytic cell that is attracted via chemotaxis from the bloodstream to infected tissues. These spherical cells are granulocytes. A granulocyte contains cytoplasmic granules, which in turn contain a variety of vasoactive mediators such as histamine. In contrast, macrophages are agranulocytes. An agranulocyte has few or no cytoplasmic granules. Whereas macrophages act like sentries, always on guard against infection, neutrophils can be thought of as military reinforcements that are called into a battle to hasten the destruction of the enemy. Although, usually thought of as the primary pathogen-killing cell of the inflammatory process of the innate immune response, new research has suggested that neutrophils play a role in the adaptive immune response as well, just as macrophages do.[194]

### Natural killer cells

A Natural Killer cell (NK) is a circulating blood cell that contains cytotoxic (cell-killing) granules in its extensive cytoplasm. It shares this mechanism with the cytotoxic T cells of the adaptive immune response. NK cells are among the body's first lines of defense against viruses and certain types of cancer.[195]

### The complement system

This consists of a cascade of potent plasma proteins (a group of 20 or more globulins that aid in nonspecific resistance and specific immunity). Triggered by microorganisms, to lyse bacteria and activate inflammation. These proteins are continually

present in the blood plasma but must be activated by pathogens to exert their effects.[187]

## Dendritic cells

So called because their surface membrane looks like neuron dendrites, these are keys in activating T-lymphocytes.[196]

## The adaptive immune system

It is so called because it is organized around an ongoing infection and adapts to the nuances of the infecting pathogen. Consequently, the long-lasting adaptive immunity that develops against one pathogen provides a highly specialized defense that is of little use against infection by a different pathogen. The main weapons of the adaptive (acquired) immune system are two types of lymphocytes (B cells and T cells), which create and 'acquire' immunity to specific antigens. [187]

## Bone Marrow

In the embryo, blood cells are made in the yolk sac. As development proceeds, this function is taken over by the spleen, lymph nodes, and liver. Later, the bone marrow takes over most hematopoietic functions, although the final stages of the differentiation of some cells may take place in other organs. The red bone marrow is a loose collection of cells where hematopoiesis occurs, and the yellow bone marrow is a site of energy storage, which consists largely of fat cells. The B cell undergoes nearly all of its development in the red bone marrow, whereas the immature T cell, called a Thymocyte, leaves the bone marrow and matures largely in the thymus gland.[197]

## Thymus

The thymus is a large and very active organ in early childhood, which regresses rapidly until middle age. This 'thymic wasting' may play a major role in immune senescence. As well as a reduced thymic output of T cells and thus a decrease in the number of naive lymphocytes, production of immunoregulator hormones that affect the differentiation and activities of T and B lymphocytes also decreases.[198]

## Lymphocytes

There are two broad sub-types of lymphocyte. These are known as B cells and T cells. All of them are derived from the bone marrow but T cells undergo a process of maturation in the thymus gland. Mature lymphocytes all have a similar appearance. They are small cells with a deeply basophilic nucleus and scanty cytoplasm.[196]

### T-lymphocytes and cell-mediated

Immunity T cells leaving the thymus is stimulated to proliferate once they have bound with an antigen. It performs a variety of functions in the adaptive immune response. They can differentiate into:

- Cytotoxic T cells, which mediate the direct cellular killing of target cells;
- Helper T cells, which help other cells, usually via the production of cytokines;
- Suppressor T cells, which work by controlling the immune system;
- Memory T cells, which store encounters with antigens.[187]

### B-lymphocytes and antibody mediated (humoral) immunity

B-lymphocytes originate and mature in the bone marrow. They are activated by antigens, and then become antibody-secreting plasma cells. These antibodies are known as immunoglobulins. They neutralize antigens and assist other components of the immune system in destroying non-self-antigens.

Some mature B cells become memory B cells, capable of 'remembering' their specific antigen that triggered antibody production. [187]

## Lymph vessels

There are 3 main types of lymph vessels:

- Lymphatic capillaries – microscopic, closed-ended tubes where fluid from body tissues enters the lymphatic system.
- Lymph vessels – tubes that move lymph to and from the lymph nodes.
- Collecting ducts – tubes that return lymph to the bloodstream.[199]

## Lymph nodes

Lymph nodes are small, bean-shaped organs that filter lymph. Lymph nodes vary in size, but are usually less than 2.5 cm (1 inch) across. There are many lymph nodes throughout the body. The number of lymph nodes varies from one part of the body to another.

Lymph nodes contain 2 types of white blood cells that fight invading micro-organisms:

- Lymphocytes – attack viruses, bacteria and other micro-organisms.
- Macrophages – engulf and destroy foreign substances, damaged cells and bits of broken cells.

Lymph nodes are located in groups in the following major locations:

- Neck – cervical nodes.
- Chest (thoracic) cavity – thoracic and mediastinal nodes.
- Armpit – axillary nodes.
- Abdominal cavity – para-aortic (peri-aortic) and mesenteric nodes.
- Groin – inguinal nodes.

The main functions of the lymph nodes are to:

- Filter harmful particles, such as bacteria, viruses and foreign substances, from the lymph before returning it to the bloodstream.
- Activate the immune system.

If a large number of particles are filtered through a lymph node or group of nodes, they may swell and become tender to the touch. For example, a sore throat may cause the lymph nodes under the jaw and in the neck to swell. [199][200][201]

## Spleen

The spleen is a fist-sized organ located on the left side of the body, behind the stomach. It acts as a filter, collecting antigen from the blood and destroying senescent red blood cells. Most of the spleen is made up of tissue called red pulp which primarily serves as the site of red blood cell destruction and also houses macrophages. Interspersed throughout the red pulp, lymphocytes surround arterioles forming pockets called white pulp. The organization of white pulp consists of two layers, the periarteriolar sheath, consisting mainly of T lymphocytes, and the B-cell corona, consisting of mainly B lymphocytes. The white pulp is responsible for generating immune responses to blood borne immunogens and plays an important role in preventing septicemia.[202][203]

## Autoimmune conditions

Although the overall immune response to antigens decreases with age, autoimmune reactivity increases. The percentage of auto reactive T-lymphocytes and auto-antibodies increase with age, indicating a loss of tolerance to self. This is associated with common age-associated autoimmune conditions, such as rheumatoid arthritis.[204]

### 1.2.4 Definition

**HIV:** stands for human immunodeficiency virus, a virus that infects cells of the human immune system and destroys or impairs their function. Infection with this virus results in the progressive depletion of the immune system, leading to immune deficiency.

Immunodeficient people are much more vulnerable to a wide range of infections, most of which are very rare among people without immune deficiency.

**AIDS:** stands for acquired immunodeficiency syndrome and describes the collection of symptoms and infections associated with acquired deficiency of the immune system. Infection with HIV has been established as the underlying cause of AIDS.

Human Immunodeficiency Virus (HIV) and its subtypes are retroviruses and the etiologic agents of AIDS. Human retroviruses were unknown until the 1980's, though animal retroviruses such as feline leukemia virus had been detected previously. HIV belongs to a large family of ribonucleic acid (RNA) lentiviruses.[205] These viruses are

characterized by association with diseases of immunosuppression or central nervous system involvement and with long incubation periods following infection before manifestations of illness become apparent.[206][207]

**Origins of HIV:** Lentiviruses similar to HIV have been found in a variety of primate species, and some of these are associated with a disease process called simian AIDS. Unlike other retroviruses, the primate lentiviruses are not transmitted through the germ line, and no endogenous copies of the virus exist in the genome of susceptible species.[208] Molecular epidemiologic data suggest that HIV type 1 (HIV-1), the most common subtype of HIV that infects humans, has been derived from the simian immunodeficiency virus, called SIVcpz, of the Pan troglodytes troglodytes subspecies of chimpanzee. The lentivirus strain SIVcpz is highly homologous with HIV-1, and another form of simian immunodeficiency virus found in sooty mangabeys (SIVsm) has similarities as well and likely gave rise to HIV-2.[209]

**Structure of HIV:** The mature virus consists of a bar-shaped electron dense core containing the viral genome--two short strands of ribonucleic acid (RNA) about 9200 nucleotide bases long--along with the enzymes reverse transcriptase, protease, ribonuclease, and integrase, all encased in an outer lipid envelope derived from a host cell (Figure 5). This envelope has 72 surface projections, or spikes, containing an antigen, gp120 that aids in the binding of the virus to the target cells with CD4 receptors. A second glycoprotein, gp41, binds gp120 to the lipid envelope.[207][210][211]

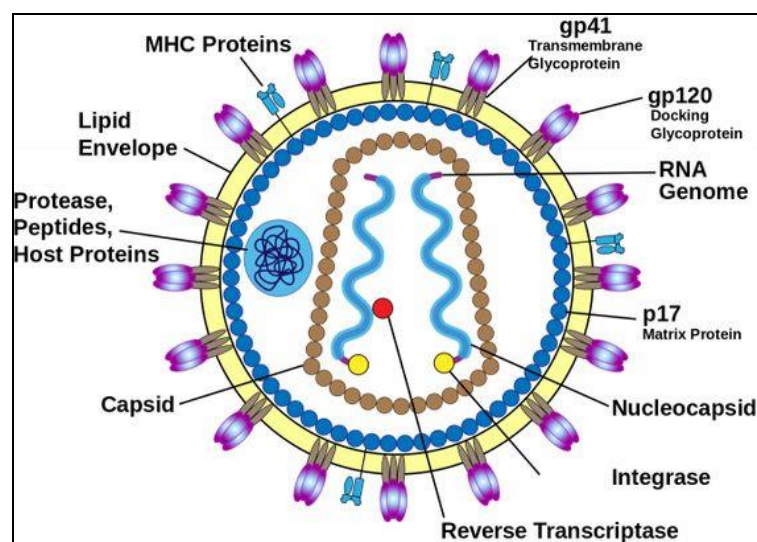


Figure 5: Human immunodeficiency virus

### 1.2.5 Pathophysiology

When first identified, the new syndrome lacked an agreed-upon, accurate definition, and its causative agent was unknown. In 1983, and 1984, respectively, U.S. and French researchers isolated and described the causative agent of AIDS, with each group calling the virus a different name: human T-cell lymphotropic virus type III (HTLV-III) or lymphadenopathy-associated virus (LAV).[212][213] Therefore, the U.S. Centers for Disease Control and Prevention (CDC) named the causative agent HIV and suggested that a combination of opportunistic infections and immunosuppression were indicative of AIDS. Once the causative agent HIV was identified, the definition was revised appropriately. This definition was based on the presence of certain “indicator” diseases, backed by laboratory evidence of HIV infection.[214][215]

The HIV-1 life cycle is complex and its duration and outcome is dependent on target cell type and cell activation.[216] In the early steps, HIV-1 gains access to cells without causing immediate lethal damages but the entry process can stimulate intracellular signal cascades, which in turn might facilitate viral replication.[217][218] The two molecules on the HIV-1 envelope, the external glycoprotein (gp120) and the transmembrane protein (gp41), form the spikes on the virion’s surface.[219] During the entry process, gp120 attaches to the cell membrane by first binding to the CD4+ receptor. Subsequent interactions between virus and chemokine co-receptors (eg, CCR5, CXCR4) trigger irreversible conformational changes.[219][220] The actual fusion event takes place within minutes by pore formation,[220][221] and releases the viral core into the cell cytoplasm. After the core disassembles, the viral genome is reverse transcribed into DNA by the virus’ own reverse transcriptase enzyme. [216] Related yet distinct viral variants can be generated during this process since reverse transcriptase is error prone and has no proofreading activity.[216] At the midpoint of infection, the viral protein integrase in conjunction with host DNA repair enzymes inserts the viral genome into gene-rich, transcriptionally active domains of the host’s chromosomal DNA.[222][223][224] An integrase binding host factor, LEDGF/p75 (lens epithelium-derived growth factor), facilitates integration,[225][226] which marks the turning point by irreversibly transforming the cell into a potential virus producer. In the late steps, production of viral particles needs host driven as well as virus driven transcription.[216] Viral proteins are transported to and assemble in proximity to the cell membrane. Virus egress from the cell

is not lytic and takes advantage of the vesicular sorting pathway (ESCRT-I, II, III), which normally mediates the budding of endosomes into multivesicular bodies.[227][228] HIV-1 accesses this protein-sorting pathway by binding TSG101 via its late domain, a short sequence motif in p6 of Gag.[229][230] Cleavage of the Gag-Pol poly-protein by the viral protease produces mature infectious virions.[216][231]

Since cytoplasmic molecules of the producer cell and components from its cell surface lipid bilayer are incorporated into the new viral particle, virions bear characteristics of the cells in which they were produced.[232] Incorporated host molecules can determine the virus' phenotype in diverse ways (eg, shape the replicative features in the next cycle of infection or mediate immune activation of bystander cells.[233]

Studies of the early events that happen after HIV-1 breaches the mucosal barrier suggest the existence of a window period in which viral propagation is not yet established and host defences could potentially control viral expansion.[234] The important co-receptors for HIV-1 infection are two chemokine receptors—CCR5 and CXCR4. Independently of the transmission route, most new infections are established by viral variants that rely on CCR5 usage.[235] CXCR4-tropic viruses generally appear in late stages of infection and have been associated with increased pathogenicity and disease progression.[236]

### 1.2.6 Transmission

HIV is known to be transmitted only through:

- Contact of infected sexual fluids, blood, or vaginal and cervical secretions with mucous membranes.
- Injection of infected blood or blood products.
- Vertical transmission (that is, from infected mother to fetus) and from mother to infant via breast milk.



## Contact of Sexual Fluids or Blood with Mucous Membranes

The virus cannot pass through undamaged skin. HIV can enter the body through the mucous membranes that line the vagina, rectum, urethra, and possibly, on rare occasions, the mouth. Damage to a mucous membrane may increase the risk of transmission of HIV but is not necessary for transmission to occur. Almost all cases of sexually transmitted HIV have been caused by anal or vaginal intercourse without a condom.

HIV has consistently been isolated in varying concentrations from blood, semen, vaginal and cervical secretions, and breast milk. It has occasionally (and in low levels) been isolated from saliva and tears.[237][238][239] Antibodies to HIV have been detected in urine. Two studies have isolated HIV in pre-ejaculatory fluid.[240][241] Epidemiological evidence implicates only blood, semen, vaginal and cervical secretions, and breast milk as sources of transmission.[242][243] Infection through contact of semen, blood, or vaginal or cervical secretions with mucous membranes occurs during anal or vaginal intercourse and only rarely during oral-genital sex. A component of saliva helps inactivate HIV.[244]

## Injection of Infected Blood

HIV can be transmitted by infected blood getting directly into the bloodstream through intravenous, intramuscular, or subcutaneous injection. Blood-to-blood transmission occurs in the following ways:

- Sharing of unsterilized hypodermic needles and syringes.
- Transfusion of contaminated blood and blood products to hemophiliacs and other blood recipients. However, the risk of infection from transfusion is now extremely small, for example, since March 1985; the U.S. blood supply has been screened for contaminated blood. Risk of becoming infected with HIV from a single transfusion is less than one in two million.[245]

## Vertical transmission (Mother-to-child)

HIV can be transmitted from an infected woman to her fetus during pregnancy and during delivery also during breastfeeding. This is referred to as vertical or perinatal

transmission. Mother-to-child transmission of HIV is responsible for more than 90% of HIV infection in children worldwide.[168]

### 1.2.7 Stage Classification (Course of HIV disease)

There is a typical course of HIV disease without treatment, when the majority of HIV-infected people will develop AIDS within 10-15 years after being infected, though some people who have been infected longer than this remain healthy even without treatment.[246]

Without treatment, the average time from seroconversion to symptoms severe enough to meet the definition of AIDS is 10-12 years. Sex, race, and risk category do not affect rate of progression if data are adjusted for quality of care.

Both the 2008 and 2014 HIV case definitions were used to classify HIV infection among adults and adolescents and among children.[247][248]

The 2008 case definition was used to classify cases diagnosed from the beginning of the epidemic through 2013. For adults and adolescents, this definition incorporates an HIV infection staging system that includes AIDS (HIV infection, stage 3). The 2008 stages of HIV infection are defined as follows:

**HIV infection, stage 1** (No AIDS-defining condition and either CD4 count of  $\geq 500$  cells/ $\mu\text{L}$  or CD4 percentage of total lymphocytes of  $\geq 29$ )

- **Primary HIV infection**

HIV is disseminated to the brain and central nervous system and lymphatic tissue (lymph nodes, spleen, tonsils, and adenoids). Lymphatic tissue is the major reservoir of HIV in the body. Ten to thirty days after infection (median 2-4 weeks), about 80 to 90% of people develop what is called “acute retroviral syndrome” or “primary HIV infection.” This is an illness that resembles the flu and usually lasts about 1-2 weeks. Symptoms include fever, swollen glands, sore throat, faint rash that generally starts in the torso, sores on the mouth and sometimes around the anus, weight loss, and muscle or joint pain. Remember that many of these symptoms are common in a variety of illnesses other than acute HIV infection. During the first two to three months of HIV infection, viral load may be high and the CD4 count drops below normal. After a few months, the CD4 count

generally rises close to normal levels and viral load drops. Viral load stabilizes at about 3 to 9 months to what is known as a viral “set point.” A higher viral set point and more severe acute retroviral syndrome symptoms are considered predictors of more rapid progression to AIDS. It is important that people who might have acute HIV infection seek medical attention because most experts recommend at least short term treatment during this period.[249][250] The management of acute HIV infection remains an area of research and current guidelines recommend referral to a research center for evaluation and possible treatment. Most people become positive on an antibody test at about three weeks after infection. However, the way to diagnose acute infection is with the simultaneous use of viral load testing with antibody testing and sometimes p24 antigen testing. It is important to understand that during the first three weeks after infection – acute infection – the antibody test may be negative while the viral load is very high. During this period, the newly infected person may be asymptomatic but infectious to others.

**HIV infection, stage 2** (No AIDS-defining condition and either CD4 count of 200–499 cells/  $\mu$ L or CD4 percentage of total lymphocytes of 14–28)

- **Asymptomatic infection**

During the next two to six years, most people remain asymptomatic, although they may have chronic swollen glands (lymphadenopathy). Despite lack of symptoms, HIV disease is progressing. On average, CD4 cells decline at a rate of approximately sixty points per year, while viral load gradually increases.

- **Symptomatic HIV infection**

After some years, a variety of medical symptoms may develop, often involving skin and gastrointestinal disorders. Viral load continues to rise, and the CD4 count shows a more accelerated decline about 1.5 to 2 years before development of AIDS-defining illness.

**HIV infection, stage 3** (Documentation of an AIDS-defining condition or either a CD4 count of  $<200$  cells/ $\mu$ L or CD4 percentage of total lymphocytes of  $<14$ )

- AIDS

CD4 cells drop below 200. Opportunistic infections develop.[251] The clear categorization of HIV into stages has become blurred by the ability of HAART to restore immune function, elevate T cells, and permit AIDS-related infections and conditions to be cured, thus halting or even reversing this course.

## 1.2.8 Clinical Manifestations

We can resume the clinical manifestations of HIV-AIDS in the next table (Table 3)

Clinical Stage	Clinical Manifestations
<b>Clinical Stage I</b>	<b>Asymptomatic disease</b>  Asymptomatic/acute HIV infection, persistent generalized lymphadenopathy.
<b>Clinical Stage II</b>	<b>Early (mild) disease</b>  Weight loss $\geq$ 10% of body weight; minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infection, recurrent oral ulceration, and angular cheilitis); recurrent respiratory tract infections, such as bacterial sinusitis.
<b>Clinical Stage III</b>	<b>Intermediate (moderate) disease</b>  Weight loss $\geq$ 10% of body weight; chronic unexplained diarrhea $\geq$ one month; oral candidiasis (thrush); oral hairy leukoplakia; pulmonary Tuberculosis within the past year; severe bacterial infection, such as pneumonia and pyomyositis.
<b>Clinical Stage IV</b>	<b>Late (severe) disease AIDS</b>  HIV-wasting syndrome; Pneumocystis carinii pneumonia; toxoplasmosis of the brain; cryptosporidiosis with diarrhea $\geq$ one month; extrapulmonary cryptosporidiosis; cytomegalovirus disease other than in liver, spleen, or lymph nodes; herpes simplex virus infection; mucocutaneous $\geq$ one month or visdermal of any duration; progressive multifocal leukoencephalopathy; disseminated endemic mycosis, such as histoplasmosis and coccidioidomycosis; candidiasis of the esophagus, trachea, bronchi, or lungs; atypical mycobacteriosis; disseminated, nontyphoidal salmonella septicemia; extrapulmonary Tuberculosis; lymphoma, Kaposi's sarcoma; HIV encephalopathy.

**Table 3: Clinical Manifestations of HIV infection.** [252][215]

## 1.2.9 Diagnosis

### 1. Serological Diagnosis of HIV Infection

Laboratory diagnosis by HIV testing is the only method of determining the HIV status of an infected individual's infected blood, blood products, organs, and tissues. HIV diagnosis at Integrated Counselling and Testing Centres (ICTCs) and other laboratories is based on the demonstration of antibodies. Antibody detection can be done using an Enzyme Linked Immunosorbent Assay (ELISA) test, rapid test, and western blot test. These tests are used as screening tests and/or confirmatory tests. All tests should be performed and interpreted as per test instruction manuals that are supplied with the kit. HIV testing should be based on testing strategy and algorithm.

A number of moral, legal, ethical, and psychological issues are related to a positive HIV status; hence, any laboratory attempting to assess the HIV status of an individual should be conversant with these issues. Testing laboratories should ensure pre and post-test counselling for every individual and confidentiality to be maintained.

#### Detection of Anti-HIV Antibodies

The central component in the diagnosis of HIV infection is the detection of anti-HIV antibodies in serum, plasma, or whole blood. Urine and saliva may be tested using specific kits. HIV antibody assays are commercially available in various formats.

Some of these assays can differentiate between HIV-1 and HIV-2 infections. However, the occurrence of antibody-cross reactivity makes differentiation difficult between HIV-1 and HIV-2. Differentiation between HIV-1 and HIV-2 is required since the treatment varies for the two types.

Technical errors and interference from other medical conditions may compromise the accuracy of HIV tests. Antigens used in HIV diagnostic tests must be appropriately specific and are usually purified antigens from viral lysates or antigens produced through recombinant, or synthetic, peptide technology. Such antigens help to improve the sensitivity (true positives) and specificity (true negatives) of HIV assays. Along with the testing process, there is the requirement for a dedicated quality system in the laboratory to ensure accuracy and reproducibility of test result.

## Screening Tests

Serological tests for the detection of HIV are classified as first to fourth generation tests based on the type of antigens used and principle of the assays. National AIDS Control Organisation (NACO) recommends the use of rapid test kits, which detect >99.5% of all HIV-infected individuals and have false-positive results in <2% of all those who are tested.

Commonly used screening tests are:

- Enzyme Linked Immunosorbent Assay (ELISA)
- Rapid tests
  - Immunoconcentration/Dot Blot assay (vertical flow)
  - Agglutination assay
  - Immunochromatographic assay (lateral flow)
  - Dipstick and comb assay based on Enzyme Immune Assay (EIA)

### Enzyme Linked Immunosorbent Assay (ELISA)

All ELISAs consist of either HIV antigens or antibodies (depending upon the principle), attached to a solid phase (matrix or support), and incorporated with a conjugate and substrate detection system. Viral antigens may be whole viral lysates, recombinant, or synthetic peptides. The matrix can be “wells” or “strips” of a microplate, plastic beads, or nitrocellulose paper. Conjugates are most often antibodies (IgG, sometimes IgM and IgA) coupled to enzymes (alkaline phosphatase or horseradish peroxidase), fluorochromes, or other reagents that will subsequently bring about a reaction that can be detected. In case of enzyme conjugates, the signal generated is a colour reaction and in case of fluorochrome, it is fluorescence. The substrates used are 4-nitrophenylphosphate – for alkaline phosphatase and ophenylenediamine dihydrochloride (OPD) and Tetramethylbenzidine (TMB) – for horseradish peroxidase, which produce colour on being acted upon by the respective enzymes. The colour can be measured on an ELISA Reader as optical density (OD) values. ELISAs are suitable for use in laboratories where the specimen load is high.

## 2. Molecular & Other Assays for the Diagnosis of HIV Infection

Serological assays for the detection of HIV antibodies are predominantly used for the diagnosis of HIV infections. Diagnosis in a child less than 18 months cannot be done using antibody based assays as maternal antibodies may be present in the infant's circulation. Therefore, up to the age of 18 months, the diagnosis of HIV infection can only be reliably made by DNA PCR.[253] In these situations, the diagnosis of HIV infections is established using molecular assays to detect viral genomes.

### Diagnosis of Pediatric HIV Infection (< 18 months)

The standard diagnostic method for HIV infection in adults (i.e., testing for antibodies) has limited utility in newborns, infants, and children less than 18 months of age. This is due to the transplacental transfer of maternal IgG (including HIV-specific antibodies) from infected mothers to their babies during pregnancy. HIV antibody tests are reactive in most infants born to HIV positive mothers, though the infection is transmitted to less than half of such infants (even in the absence of Antiretroviral Therapy (ART)). HIV antibodies can also be transferred through the breast milk of infected mothers. Maternal antibodies may persist in an infant's blood until 18 months after birth, and are difficult to differentiate from those produced by an infected infant. Therefore, antibody tests cannot produce a definitive diagnosis of HIV infection until 18 months of age. Waiting until this time delays specific treatment. In this situation, Nucleic Acid Testing (NAT) can facilitate early infant diagnosis. NACO recommends the use of a qualitative HIV-1 DNA PCR.[254]

### Detection of Acute HIV Infection

Virological tests can be used for the detection of acute HIV infection during the "window period," before HIV antibodies become detectable. Though positive NAT results confirm the HIV diagnosis, the NAT result may turn out negative if tested within 7 to 10 days of exposure. NAT tests may be successfully employed for the detection of HIV infection if appropriate infrastructure and technical expertise is available. At present, NACO does not recommend the use of NAT for the diagnosis of acute HIV infection.

NATs include tests for the qualitative detection of HIV-1 DNA or RNA, as well as the quantitative detection of HIV-1 RNA (viral load determination) through various assays.

### Qualitative Polymerase Chain Reaction for HIV DNA

In infants, the sensitivity of a traditional PCR test – for the diagnosis of HIV infection and the qualitative detection of HIV DNA – is as high as 90 to 100% by the age of 4- 6 weeks. An example of a commercially available test, approved by the Drug Controller General of India (DCGI), is the qualitative AMPLICOR HIV-1 DNA PCR Test, ver. 1.5 (Roche), which can be used to test dried blood spots or whole blood collected in Ethylenediamine Tetraacetic Acid (EDTA). This test has a reported 99.3% sensitivity and 96% specificity. NACO's first choice for the diagnosis of HIV-1 infection in infants and children less than 18 months of age (starting at 6 weeks of age or at the earliest opportunity thereafter) is the HIV-1 DNA PCR test.

### 1.2.10 Treatment

At some point in the future, there may be a cure for HIV disease, perhaps a way to eradicate the virus from the body. At the present time, the goal of treatment is to halt or at least significantly slow the process described above. If the virus can be controlled with antiretroviral drugs, the immune system can function competently and no opportunistic infections will develop. This is the purpose of antiretroviral treatment. One AIDS expert summarizes large medication studies in the following way: “The results from these –“studies”- have been astonishingly consistent, when HAART is introduced, opportunistic infections and deaths drop.”[255]

Most people who start HAART for the first time reach the goal of becoming undetectable on viral load tests. In studies of these regimens, up to 90% of people who take the medications as directed, every day, without fail, achieve an undetectable viral load. This typically takes about four to six months. You can remain healthy even if your viral load does not become undetectable. However, because reducing viral load to undetectable predicts a more durable response, this is generally the goal of first-time treatment. CD4 levels gradually rise as viral load drops. On the average, the CD4 count



will rise 100 to 200 in the first year after the virus becomes undetectable. After one year on treatment, it continues to rise at a more gradual rate.

HAART involves treatment with multiple drugs, most typically a total of three drugs. Multiple drugs are necessary to suppress HIV replication and to prevent the virus from becoming resistant to the medication.

Each stage of the reproductive cycle of the virus—attachment, uncoating, reverse transcription, protein synthesis, particle assembly, and budding--provides an opportunity for anti-HIV drugs to halt the reproduction and spread of the virus. As our understanding of HIV grows, additional categories of antiretroviral drugs are discovered. All current antiviral agents work by preventing both reproduction of the virus and infection of susceptible cells. They do not kill the virus nor do they kill cells that are already infected. Effective treatment requires the use of drugs from at least two classes of medication.

Following are the classes of medication currently available:

- Nucleoside reverse transcriptase inhibitors (NRTIs; also known as nucleoside.nucleotide analogues) inhibit a viral enzyme (reverse transcriptase) that converts the RNA in HIV into DNA allows it to reproduce.
- Nonnucleoside reverse transcriptase inhibitors (NNRTIs) also inhibit the viral enzyme (reverse transcriptase) that converts the RNA in HIV into DNA and allows it to reproduce. However, it does so with a different mechanism than the NRTIs,
- Protease inhibitors (PIs) disable a chemical necessary for the effective organization of the structure of new copies of HIV.
- Fusion or entry inhibitors prevent the virus from entering susceptible cells. These drugs are also known as chemokine co-receptor antagonists and include two subclasses (CCR5 antagonist and CXCR4 antagonist) prevent the entry of HIV into target cells. They bind to co-receptors (either CCR5 or CXCR4) on the surface of CD4 cells. By doing so, they block a required step in viral entry.
- Integrase inhibitors bind a viral enzyme known as integrase and thereby interfere with the incorporation of reverse-transcribed HIV DNA into the chromosomes of host cells.

All HIV treatment involves use of at least three medications. If fewer than three are used, you are likely to develop resistance to a drug or even the whole class of medications to which that drug belongs. Sometimes, three different types of medication are combined in one or two pills.

### Viral resistance

A major problem in the use of antiretroviral drugs has been the ability of the virus to become resistant to medication, rendering the drug ineffective. HIV is very active in the body even when no clinical problems exist. In fact, billions of new viral particles can be made and cleared from the body every day. This level of reproduction allows for rapid mutation of the virus. If the medication is taken but the reproduction of the virus is not completely blocked, the virus can become resistant to the medication you are taking. At the present time, no single drug is effective enough to lower reproduction of the virus to a level that will prevent resistance. This is the reason a combination of medication is used.

### 1.2.11 Prevention and Infection Control

At the onset of the epidemic, effective treatments were not available for AIDS, and its exact mechanisms of infection were unclear. These circumstances provoked considerable debate about social, legal, and medical responses to the disease. To be sure, the world had experienced epidemics of infectious and communicable disease before but the sudden onset of this disease put questions about healthcare ethics into sharp focus. The resources that countries have available to treat and prevent AIDS differ starkly which was true at the onset of the epidemic and remains so now. When looked at from a global perspective, many of the ethics questions associated with AIDS are also questions of global healthcare ethics in general.

Today, HIV/AIDS is recognized as a global emergency demanding the attention of all public sectors – not just health. Millions of people around the world die from it every year, and millions more become newly infected. That is why combating it is one of the eight Millennium Development Goals and a top priority in bilateral and multilateral development aid.

In Europe, HIV/AIDS prevention, treatment and care are needed more than ever. More than two million people now live with the disease in the WHO European Region, where no country has been spared. Though this figure is low compared to that in the worst affected area, Sub-Saharan Africa, it represents an unprecedented increase in new cases. In particular, the accelerating incidence of HIV in Eastern Europe poses one of the Region's most important public health challenges today. In the last 10 years, three countries in Eastern Europe have gone from a few reported cases to an estimated HIV prevalence greater than 1% among people aged 15–49. For the poor, the vulnerable and the marginalized, the rates are much higher – and rising.

During the last years, the picture of HIV infection in Europe has been greatly modified. For the first time since the beginning of the epidemic, in three consecutive years (1996/98), the incidence of new AIDS cases has decreased in Western Europe. Implementation of effective preventive and risk reduction policies against sexual and intravenous transmission of the virus has certainly contributed to the emergence of this new epidemiological trend. But the decrease in AIDS-related mortality and morbidity that has been observed in most western European countries during the same period is also due to significant advances in clinical care of people infected with HIV. The diffusion of Highly Active Antiretroviral Therapies (HAART), including protease inhibitors (PIs), has clearly proved to be effective for obtaining substantial and sustained suppression of HIV viral replication and reducing the incidence of opportunistic infections among HIV-infected patients in short-term studies, and has provided a rationale for earlier initiation of antiretroviral treatment.[165]

Prevention of HIV/AIDS would benefit all regions and countries, irrespective of the prevalence or incidence of HIV/AIDS in the population as all social and economic life in the early twenty-first century is interconnected. HIV/AIDS in one part of the world is bound to affect the health, economy, and security of countries everywhere. The health of all people is affected by modern travel and migration patterns. HIV/AIDS, and the interconnected epidemics of Tuberculosis, sexually transmitted diseases, and drug dependency, can spread across countries and regions.[256] The economy of all countries is affected because of the complex economic and trade relationships that exist within the modern world. Countries and regions with a heavy burden of HIV/AIDS often have

weaker economies, impeding their ability to import and export essential products and services.[257] This has a cascading effect on the economies of other countries.

### General Interventions Relevant for All Modes of Transmission

The following are general interventions not specifically targeting the mode of transmission:

**Information, education, and communication (IEC).** This intervention includes education on HIV/AIDS and condom use through pamphlets, brochures, and other promotional materials in classroom or clinic settings or through the radio, television, or press. In general, discerning the effectiveness of IEC alone is difficult, because IEC is often included in condom promotion and distribution interventions. Here we consider the effectiveness of IEC in concert with condom promotion and distribution. Of all available prevention interventions, providing information and education about HIV/AIDS is perhaps the most difficult to assess for cost-effectiveness. Numerous studies have shown that information alone is typically insufficient to change risk behavior. Accurate information, however, is indisputably the basis for informed policy discourse—a vital ingredient in the fight against fear-based stigma and discrimination. In the absence of studies to guide the level of investment in IEC, the only reasonable alternative seems to be to implement IEC on the basis of data derived from relative levels of knowledge and understanding in the population. For example, if only 25% of the sexually active population were able to describe how HIV is transmitted and prevented, clearly more IEC would be needed, but if 75% of the population understood the basic facts about HIV/AIDS, the need for additional funding would be diminished.

**School-based sex education.** School-based sex education programmes, an aspect of IEC, provide information to young people and reinforce healthy norms in a school setting.[258] In light of more recent controlled studies that sex education, including condom promotion, does not encourage or increase sexual activity.[259] Sex education reduces risk and positively affects sexual behaviors. In general, sex education programmes increase knowledge about AIDS and related issues, increase intention to use condoms, and increase condom use among sexually active youths.[260] Abstinence-only education is not effective in promoting healthy sexual behaviors. Programmes that promote both postponement of intercourse and contraceptive use were more effective in changing

behaviors than those that stressed abstinence alone. None of the abstinence only programmes that have been evaluated demonstrated an overall positive effect on sexual behavior, nor did they affect contraceptive use among sexually active participants.[261]

**Voluntary counseling and testing.** This intervention enables people to know their HIV status and provides counseling support to help them cope with the outcome. Knowledge of serostatus may lead individuals to avoid engaging in risky behaviors.[262] Cost-effectiveness estimates of voluntary counseling and testing vary widely, and as with many other prevention interventions, these estimates are extremely sensitive to the prevalence of HIV in the population that is seeking testing.

The following are interventions specifically targeting the mode of transmission:

#### **Prevention of Sexual Transmission of HIV:**

- **Condom promotion, distribution, and social marketing.** Condom promotion, distribution, and social marketing vary by epidemic profile. The evidence on condom promotion and distribution programmes indicates that such programmes result in significantly higher condom use and significantly lower STI incidence.[263]

#### **Prevention of Mother-to-Child Transmission:**

- **Avoidance of unwanted pregnancies among infected mothers.** One of the most effective strategies to reduce HIV among infants is to provide better contraception services.[264][265][266]
- **Use of antiretroviral therapy.** Evidence indicates that the provision of antiretroviral drugs to infected mothers significantly reduces vertical transmission.[267][268][269]
- **Feeding substitution.** Whereas in high-income countries the health community recommends complete avoidance of breastfeeding for HIV-infected mothers to prevent postnatal HIV transmission, in developing countries the feasibility of this approach is often limited by such factors as cost, sustainability, lack of safe water, health, and child spacing and by sociocultural factors.[270] Prolonged breastfeeding more than doubles the likelihood of Mother-to-Child Transmission.[271] Because evidence indicates that mixed feeding (breast milk and

formula or other substance) has a higher risk of transmission than exclusive breastfeeding.[272] mothers should be counseled on the superiority of early weaning over mixed feeding.

### Prevention of Bloodborne Transmission:

- **Harm reduction for injecting drug users.** Harm reduction involves a combination of health promotion strategies for users, including needle and syringe exchange programmes, ready access to effective drug treatment and substitution, and provision of counseling and condoms. For example, Brazil, which has reduced the incidence of HIV and kept HIV prevalence from reaching projected levels, has relied on strong official support for harm reduction as a cornerstone of its national prevention program.[273]
- **Implementation of blood safety practices.** Transmission of HIV can be virtually eliminated in health care settings through a blood safety programme that ensures (a) a national blood transfusion service; (b) the recruitment of voluntary, low-risk donors; (c) the screening of all donated blood for HIV; and (d) the reduction of unnecessary and inappropriate transfusions.[274] Available evidence indicates that HIV screening is effective in reducing HIV infections.[275][276][277] Blood screening for HIV is costly but has been shown to be cost-effective in numerous studies in developing countries.[278][276][279] The evidence appears to support the WHO and UNAIDS recommendations that all countries, regardless of the nature of the epidemic in the country, should implement a comprehensive blood safety programme.
- **Universal precautions.** To prevent bloodborne transmission of HIV and other diseases, health care workers, emergency personnel, and others who might experience occupational exposure to blood or body fluids are advised to take universal precautions. This approach, which treats all bodily fluids as potentially infectious, includes the use of gloves, gowns, and goggles; the proper disposal of waste; and the use of sterile injection and other infection control practices.[280] Studies have demonstrated that the use of protective gear, such as gloves, reduces the likelihood of blood exposure in health care settings.

## 2 Background and Objectives

Tuberculosis can represent an important clinical and public health in developing and developed countries. Low- and middle-income countries are facing an epidemic which is difficult to address because of the drug-resistance spread and the association of Tuberculosis with HIV/AIDS. High-income countries, whose Tuberculosis incidence has decreased in the last decades, can be involved in new Tuberculosis epidemic waves owing to social, healthcare, and economic hurdles and challenges.

Today, HIV infections are recognized as a global emergency demanding the attention of all public sectors – not just health. As the HIV/AIDS epidemic enters its third decade, much of the sense of urgency that accompanied discussions of AIDS only 10 or 15 years ago seems to be disappearing.[281] In the WHO European Region, almost 2 million people live with HIV, it represents an unprecedented increase in new cases, especially in Eastern Europe where the accelerating incidence of HIV poses one of the Region's most important public health challenges nowadays.

Tuberculosis remains the leading cause of death among people living with HIV, accounting for around one in three AIDS-related deaths. Tuberculosis and Tuberculosis/HIV co-infection partially reflects the income and development level of a country, with medium incidence rates at least 20 times higher in low-income countries than in high-income countries.[282]

Infectious diseases control demands a strong public health infrastructure to detect and treat infected people.[283] Many countries in the European Union are in an economic recession, and it is acknowledged that a recession or economic crisis can have an effect on the population's health, especially with respect to infectious diseases.[284] Budgets for healthcare are cut in times of economic hardship.[285] Economic recessions are often accompanied by an increase in drug use, homelessness, migration of vulnerable groups and other factors affecting the transmission of Tuberculosis.[286]

One of the main challenges for health policy makers is recognising the increasing inequalities in health between socio-economic groups.[22] Health inequalities are

substantial almost everywhere in Europe according to studies comparing different European countries, but that there are important variations in the magnitude of these inequalities between countries, suggesting a greater scope for reducing these inequalities.[287][288][289]

The main condition for the cause of death may not always be clear, sometimes there is a kind of ambiguity, besides the illness leading directly to death, and the medical data on the death certificate should also contain a causal chain linked to the suffering of the deceased. Other substantial health conditions may be indicated, which did not have a link to the illness leading directly to death, but may have unfavourably affected the course of a disease and thus contributed to the fatal outcome.

Some studies have investigated the actual causes of death among Tuberculosis patients[290][291][292][293][294][295], and most relied on vital statistics registration or death certificates. [290][291][293][294][295] However, they may not completely reflect the actual causes of death because of reporting bias due to inaccurate certificates in the registration system and the imprecise design in large population-based surveys.[296][297][298][299] Moreover, these studies were conducted in areas with a high prevalence of either HIV infection or MDR-Tuberculosis. [300][290][291][292][293] Research evidence shows that, at least in England, use the underlying cause alone, for Tuberculosis, captures only about half of all deaths with Tuberculosis as a certified cause of death.[301]

Patterns of morbidity and mortality among patients infected with human immunodeficiency virus (HIV) have significantly changed over the last two decades. A number of prior studies have documented the effectiveness of different HIV therapies in reducing mortality and the incidence of AIDS in different populations[302][303][304][305][306][307][308][309] as well as increasing the time after an AIDS diagnosis.[310][311]

With the introduction of Highly Active Antiretroviral Therapy (HAART), an increase in the life expectancy among subjects infected with HIV has been reported in developed countries. [312][313][314]



Immigrant populations have been acknowledged by the European Centre for Disease Prevention and Control (ECDC) and the European Commission as one of the priority groups for HIV prevention and care.[315][316][317]

Immigrants include very diverse populations with different immigration drivers—cultural, economic, social, environmental, and political—as well as distinct risk contexts for HIV infection. According to a previous analysis in EU/EEA countries between 1999 and 2006 revealed the large contribution of people from high-endemic countries of Sub-Saharan Africa to reported HIV cases predominantly in Western Europe.[318]

Trends in observed rates provide invaluable information for needs assessment, program planning, program evaluation, and policy development activities. Examining data over time also permits making predictions about future frequencies and rates of occurrence. Trend data provide a dynamic rather than a fixed view of the health status of the population and of the services and systems that can have an impact on that health status. Since long-term trends provide useful information in order to understand recent patterns, the objectives of this study are:

1. To conduct a systematic and updated analysis of the evolution of the trends in Tuberculosis mortality rates and the association between them and factors such as underlying cause of death, economic situation, economic recession and health inequalities.
2. To conduct a systematic and updated analysis of the evolution of the trends in Human Immunodeficiency Virus infections mortality rates and the association between them and factors such as economic situation, economic recession, health inequalities, immigration and Highly Active Antiretroviral Therapies (HAART).

## 3 Material and Methods

### 3.1 Data source

#### WHO Database

For this study, Age-standardised mortality rates data were used. The data have been extracted from the WHO Database (World Health Organization Regional Office for Europe. European Detailed Mortality Database.[319] WHO European Health for All database (HFA-DB) provides a selection of core health statistics covering basic demographics, health status, health determinants and risk factors, and health-care resources, utilization and expenditure in the 53 countries in the WHO European Region. It allows queries for country, inter-country and regional analysis, and displays the results in tables, graphs or maps, which can be exported for further use.

The data are compiled from various sources, including a network of country experts, WHO/Europe's technical programs and partner organizations, such as agencies of the United Nations system, the statistical office of the European Union (Eurostat) and the Organization for Economic Cooperation and Development (OECD). HFA-DB is updated twice a year. WHO/Europe uses the results of the joint data collection with Eurostat and OECD to update the data on health care resources and selected health care activities. HFA-DB can be used online or downloaded for work on a personal computer.

In particular, historical data on hospital discharges, outpatient contacts and caesarean sections are now collected through the joint data collection for a subset of WHO member states that submit data to Eurostat and/or OECD, as well as WHO. WHO/Europe updated DMDB with the latest available cause of death data, adding functionality to calculate Potential Years of Life Lost (PYLL).

For this research, European detailed mortality database (DMDB) was used. Comparability data has been made possible world-wide through the development and revisions of the international Statistical Classification of Diseases and Related Health Problems (ICD).

By using the development and revisions of the International Statistical Classification of Diseases and Related Health Problems (ICD), during the calendar periods considered, two revisions of ICD were used (ICD9 and ICD10).[320][321]

Data is subsequently forwarded to the regional mortality registries where causes of death are coded according to ICD guidelines. According to WHO recommendations, the cause of death that is ICD coded should be taken as the underlying cause of death.[322]

### Missing Data

The WHO data source showed that data was missing from some countries for certain periods of time; no imputation was done for Tuberculosis, while for Human Immunodeficiency Virus imputation was computed by using IBM SPSS (Statistical Package for the Social Sciences) software version 22.0. We have assumed that this missing data of Tuberculosis and the imputation for HIV data are not a huge problem and that it has not affected our interpretations and conclusions. For HIV, there were no data at all for Greece, so it was not included in the HIV part.

### The International Classification of Diseases (ICD)

The International Classification of Diseases (ICD) is the standard diagnostic tool for epidemiology, health management and clinical.[323] This includes the analysis of the general health situation of population groups. It is used to monitor the incidence and prevalence of diseases and other health problems, providing a picture of the general health situation of countries and populations.

The ICD is the foundation for the identification of health trends and statistics globally. It is the international standard for defining and reporting diseases and health conditions. It allows the world to compare and share health information using a common language.

ICD is used by physicians, nurses, other providers, researchers, health information managers and coders, health information technology workers, policy-makers, insurers and patient organizations to classify diseases and other health problems recorded on many types of health and vital records, including death certificates and health records. In addition to enabling the storage and retrieval of diagnostic information for clinical,

epidemiological and quality purposes, these records also provide the basis for the compilation of national mortality and morbidity statistics by WHO Member States.

The ICD defines the universe of diseases, disorders, injuries and other related health conditions. These entities are listed in a comprehensive way so that everything is covered. It organizes information into standard groupings of diseases, which allows for easy storage, retrieval and analysis of health information for reimbursement and resource allocation decision-making by countries. Also, the ICD allows sharing and comparing health information between hospitals, regions, settings and countries; and data comparisons in the same location across different time periods.

It is the diagnostic classification standard for all clinical and research purposes. These include monitoring of the incidence and prevalence of diseases, observing reimbursements and resource allocation trends, and keeping track of safety and quality guidelines.

ICD allows the counting of deaths as well as diseases, injuries, symptoms, reasons for encounter, factors that influence health status, and external causes of disease.

The ICD divided into many versions; the most versions used nowadays are ICD-9 and ICD-10, many developments and updates was happened between each version, like adding more classifications and new diseases. The last version until now is the ICD-10, while the version ICD-11 is due by 2018.

Work on ICD-10 began in 1983, and the new revision was endorsed by the Forty-third World Health Assembly in May 1990. The latest version came into use in WHO Member States starting in 1994.[323] The classification system allows more than 155,000 different codes and permits tracking of many new diagnoses and procedures, a significant expansion on the 17,000 codes available in ICD-9.[324] Adoption was relatively swift in most of the world. Several materials are made available online by WHO to facilitate its use, including a manual, training guidelines, a browser, and files for download.

### European detailed mortality database (DMDB)

The data for Mortality have been extracted from the WHO European detailed mortality database (DMDB). This access contains mortality data by cause of death, age and sex, submitted to the WHO by the European Member States. The DMDB allows

flexible and user-friendly access to the mortality data at the 3-character ICD code level. It supplements the European Mortality Database (MDB), which provides mortality data only for predefined, aggregated causes of death. The data are official national statistics in the sense that they have been transmitted to the World Health Organization by the competent authorities of the countries concerned. It comprises deaths registered in national vital registration systems, with underlying cause of death as coded by the relevant national .Underlying cause of death is defined as "the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury" in accordance with the rules of the International Classification of Diseases.

DMDB was developed in 2007 to provide user-friendly access to detailed data on mortality. It allows users to define and retrieve data by any combination of three-digit codes used in the International Classification of Diseases, ninth or tenth revisions (ICD-9 or ICD-10) and five-year age groups. It supplements the European Health for All Database (HFA-DB) and the mortality indicators by 86 causes of death, age and sex (HFA-MDB), which provide data only for a predefined, limited set of aggregated causes of death.

All the data in DMDB are uploaded from the raw detailed data files of the global WHO mortality database, which is maintained at WHO headquarters, but are limited to the 53 countries in the WHO European Region and to the data files that have been submitted to WHO using three- or four-digit ICD-9 or ICD-10 coding or ICD-10 mortality tabulation list 1.

The current ICD, the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10), includes definitions, instructions and rules for coding and tabulating cause of death. To understand and interpret ICD-10 coded mortality statistics some basic facts about how cause of death information is collected and classified are needed.

Statistics on the causes of death are based on two pillars: medical information contained on death certificates, which may be used as a basis for ascertaining the cause of death; and the coding of causes of death following the WHO-ICD system. All deaths in the population are identified by the underlying cause of death.

The information provided on the medical certificates of cause of death is to be coded into the International Statistical Classification of Diseases and Related Health Problems (ICD). The purpose of coding is to select the underlying cause of death. Depending on the country, coding is done manually or using automated coding systems. In most countries, coding is done centrally in the cause of death statistics office. Cause of death statistics also require information on sex, age, place of residence and occurrence etc. of the deceased. Depending on the country, this information is either collected through the death certificate or taken from other sources. The data are collected annually by Eurostat from countries via eDamis.

In all European Union countries, the medical certification of death is an obligation. Most countries already use WHO's international standard model for all but perinatal deaths (0 to 1 week). The objective of the medical certificate of cause of death is to allow the certifier to enter as clearly and completely as possible the causes of death, i.e. describing the sequence of diseases and conditions leading to the death, mentioning other contributing conditions etc. In most countries, the medical certificates of cause of death are forwarded to cause of death statistics offices for centralized coding. Cause of death statistics also requires information on sex, age, place of residence etc. of the deceased. Depending on the country, this information is either collected through the death certificate or taken from other sources.

For calculating crude and standardized death rates, the annual average population available in Eurostat's demography database is used.

However, national legal requirements as well as national practices concerning the registration of residents dying abroad and domestic deaths of non-residents are far from being harmonized across European countries. Therefore, information about residents dying abroad might not be included in all countries, while deaths of non-residents are mandatory information.

For data validation, countries submit data for the underlying causes of death either at the ICD 4-digit level or according to the "European shortlist" for causes of death (86 causes, based on ICD). A number of consistency checks (on age, sex, cause of death) are applied on the data at the level of the European shortlist. After validation of the cause of death total number data, the derived indicators (crude death rates, standardized death

rates) are calculated and stored in Eurostat's database. Countries are encouraged to apply a standard validation tool (i.e. a list of standard checks that each country should perform on their cause of death data) before submitting data to Eurostat.

The absolute numbers for European Union aggregates are the sum of country numbers. It is noted that when data of a member state are missing, the latest available number for this country is used to compute European Union aggregate. Hence, the EU-28 aggregate might not correspond to the sum of the published data of the 28 member states. European aggregates calculated for crude death rates and standardized death rates are weighted averages.

Sometimes there is ambiguity in the cause of death: besides the illness leading directly to death, the medical data on the death certificate should also contain a causal chain linked to the suffering of the deceased. Other substantial health conditions may be indicated, which did not have a link to the illness leading directly to death, but may have unfavorably affected the course of a disease and thus contributed to the fatal outcome. Indeed, there is sometimes criticism that the coding of only one illness as a cause of death appears more and more unrealistic in view of the increasing life expectancy and associated changes in morbidity. For the majority of the deceased of 65 years and older the selection of just one out of a number of possible causes of death may be somewhat misleading. For this reason, some of the European Union Member States have started to consider multiple-cause coding. Eurostat has supported European Union Member States in their efforts to develop a joint automated coding system called IRIS for the improvement and better comparability of causes of death data in Europe. However, the quality of the European death certificate has been studied and validated.[325][326][327]

## Eurostat Database

We collected unemployment rates of 2010, GINI index of 2009 (GINI index is a statistical dispersion measure purposed to represent the income or wealth distribution of a residents of the nation, and it is considered as the most commonly used measure of inequality)[328][329], Gross Domestic Product (GDP) per capita of 2013, evolution of the GDP before and after the crisis (2010-2006) and (immigration (2006-2015 average) for HIV infection) from Eurostat (Eurostat is the statistical office of the European Union situated in Luxembourg. Its mission is to provide high quality statistics (such as, general

and regional statistics, economy and finance, population and social conditions. etc.) for the institutions of the European Union.) [330] [331][332][333] [334] to do a correlation test between them and the age-standardised mortality rates of Tuberculosis and HIV.

## 3.2 Variables

Our variables for this study were the Age-standardised Mortality Rates of two Infectious Diseases:

1. Tuberculosis (TB).
2. Human immunodeficiency virus/Acute Immunodeficiency Syndrome (HIV/AIDS).

## 3.3 Study Period

For this study, we studied two different periods:

1. Tuberculosis (TB). From 2000 to 2010.
2. Human immunodeficiency virus/Acute Immunodeficiency Syndrome (HIV/AIDS). From 2000 to 2014.

## 3.4 Study Population

### 3.4.1 Geographic Zone of Study

This study included all the European Union countries (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and United Kingdom) (Figure 6).





Figure 6: European Union map.

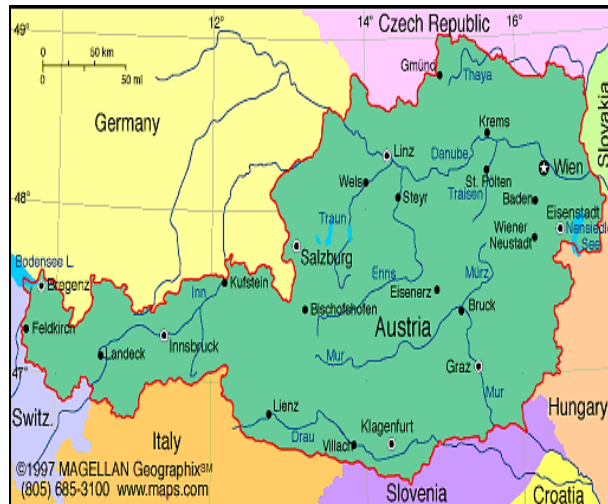
The following (Table 4) shows some major interesting socio-demographic indicators of the region of study (Surface, Total population, Population density, Political administrative organization, Total fertility rate and Life expectancy at birth) were extracted Eurostat [335](Data were Updated: April 2014), the data were used as found at their respective sources.

Country	Surface km <sup>2</sup>	Total population	Population density Inhabit/Km <sup>2</sup>	Total life expectancy at birth in years
<b>Austria</b>	83879	8361069	99.68	80.88 (M: 77.96 / F: 83.63)
Belgium	30530	10839905	355.06	80.31 (M: 77.96 / F: 82.99)
<b>Bulgaria</b>	111000	7534289	67.88	73.82 (M: 70.3 / F: 77.42)
Croatia	56590	4417781	78.07	76.86 (M: 73.62 / F: 80.01)
<b>Cyprus</b>	9250	834454	90.21	82.19 (M: 79.85 / F: 84.46)
Czech Republic	78870	10517247	133.35	77.81 (M: 74.58 / F: 80.98)
<b>Denmark</b>	43090	5543819	128.66	78.51 *2006 (M: 76.21 / F: 80.76)
Estonia	45230	1340160	29.63	76.03 (M: 70.7 / F: 80.84)
<b>Finland</b>	338420	5363352	15.85	80.34 (M: 76.97 / F: 83.66)
France	549190	62932344	114.59	81.98 (M: 78.39 / F: 85.42)
<b>Germany</b>	357127	81757472	228.93	80.64 (M: 78.14 / F: 83.09)
Greece	131960	11307557	85.69	80.69 (M: 78.48 / F: 82.93)
<b>Hungary</b>	93030	10000024	107.49	74.78 (M: 70.77 / F: 78.62)
Ireland	70280	4489305	63.45	80.8 (M: 78.5 / F: 83.03)
<b>Italy</b>	301340	60483384	200.71	82.5 (M: 79.75 / F: 85.04)
Latvia	64510	2239008	34.71	73.7 (M: 68.64 / F: 78.4)
<b>Lithuania</b>	65300	3286820	50.33	73.57 (M: 68 / F: 78.97)
Luxembourg	2590	506966	195.74	81.49 (M: 78.78 / F: 83.94)
<b>Malta</b>	320	415990	1299.97	81.51 (M: 79.27 / F: 83.62)
Netherlands	41540	16615394	399.99	81.15 (M: 79.05 / F: 83.1)
<b>Poland</b>	312680	38516688	123.18	76.58 (M: 72.3 / F: 80.83)
Portugal	92090	10573100	114.81	80.13 (M: 76.84 / F: 83.27)
<b>Romania</b>	238390	21431298	89.9	73.83 (M: 70.15 / F: 77.62)
Slovakia	49037	5431024	110.75	75.66 (M: 71.81 / F: 79.4)
<b>Slovenia</b>	20270	2049261	101.1	79.96 (M: 76.56 / F: 83.21)
Spain	505600	46072832	91.13	82.32 (M: 79.16 / F: 85.43)
<b>Sweden</b>	450300	9378126	20.83	81.77 (M: 79.73 / F: 83.74)
United Kingdom	243610	62261968	255.58	80.78 (M: 78.75 / F: 82.73)

**Table 4: Major interesting socio-demographic indicators of the region of study.**

The indicators with its correspondent map can also be seen in the following map figures [314]

## Austria



- ✚ **Surface:** 83879 km<sup>2</sup>
- ✚ **Total population:** 8361069 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 99.68
- ✚ **Total life expectancy at birth in years:** Total population 80.88, Male: 77.96, Female: 83.63
- ✚ **Total fertility rate:** 1.44 per woman
- ✚ **Political-administrative organization:** Federal republic, consisting of nine states. Capital City: Vienna.

## Belgium



- ✚ **Surface:** 30530 km<sup>2</sup>
- ✚ **Total population:** 10839905 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 355.06
- ✚ **Total life expectancy at birth in years:** Total population: 80.31, Male: 77.96, Female: 82.99.
- ✚ **Total fertility rate:** 1.8 per woman
- ✚ **Political-administrative organization:** Federal state, divided into 3 regions. Capital City: Brussels.

## Bulgaria



- ✚ **Surface:** 111000 km<sup>2</sup>
- ✚ **Total population:** 7534289 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 67.88
- ✚ **Total life expectancy at birth in years:** Total population: 73.82, Male: 70.3, Female: 77.42.
- ✚ **Total fertility rate:** 1.49 per woman
- ✚ **Political-administrative organization:** Republic, divided into 28 provinces. Capital City: Sofia.

## Croatia



- ✚ **Surface:** 56590 km<sup>2</sup>
- ✚ **Total population:** 4417781 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 78.07
- ✚ **Total life expectancy at birth in years:** Total population: 76.86, Male: 73.62, Female: 80.01.
- ✚ **Total fertility rate:** 1.46 per woman
- ✚ **Political-administrative organization:** Republic, divided into 20 counties. Capital City: Zagreb.

## Cyprus



- ✚ **Surface:** 9250 km<sup>2</sup>
- ✚ **Total population:** 834454 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 90.21
- ✚ **Total life expectancy at birth in years:** Total population: 82.19, Male: 79.85, Female: 84.46.
- ✚ **Total fertility rate:** 1.44 per woman
- ✚ **Political-administrative organization:** Republic, divided into 6 districts. Capital City: Nicosia.

## Czech Republic



- ✚ **Surface:** 78870 km<sup>2</sup>
- ✚ **Total population:** 10517247 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 133.35
- ✚ **Total life expectancy at birth in years:** Total population: 77.81, Male: 74.58, Female: 80.98.
- ✚ **Total fertility rate:** 1.49 per woman
- ✚ **Political-administrative organization:** Republic, divided into 13 regions. Capital City: Prague.

## Denmark



- ✚ **Surface:** 43090 km<sup>2</sup>
- ✚ **Total population:** 5543819 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 128.66
- ✚ **Total life expectancy at birth in years:** Total population: 78.51 \*2006, Male: 76.21, Female: 80.76.
- ✚ **Total fertility rate:** 1.88 per woman
- ✚ **Political-administrative organization:** Kingdom, divided into 5 administrative regions. Capital City: Copenhagen.

## Estonia



- ✚ **Surface:** 45230 km<sup>2</sup>
- ✚ **Total population:** 1340160 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 29.63
- ✚ **Total life expectancy at birth in years:** Total population: 76.03, Male: 70.7, Female: 80.84.
- ✚ **Total fertility rate:** 1.64 per woman
- ✚ **Political-administrative organization:** Republic, divided into 15 counties. Capital City: Tallinn.

## Finland



- ✚ **Surface:** 338420 km<sup>2</sup>
- ✚ **Total population:** 5363352 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 15.85
- ✚ **Total life expectancy at birth in years:** Total population: 80.34, Male: 76.97, Female: 83.66.
- ✚ **Total fertility rate:** 1.87 per woman
- ✚ **Political-administrative organization:** Republic, consists of 19 regions. Capital City: Helsinki.

## France



- ✚ **Surface:** 549190 km<sup>2</sup>
- ✚ **Total population:** 62932344 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 114.59
- ✚ **Total life expectancy at birth in years:** Total population: 81.98, Male: 78.39, Female: 85.42.
- ✚ **Total fertility rate:** 2 per woman
- ✚ **Political-administrative organization:** Republic, divided into 27 administrative regions. Capital City: Paris.

## Germany



- ✚ **Surface:** 357127 km<sup>2</sup>
- ✚ **Total population:** 81757472 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 228.93
- ✚ **Total life expectancy at birth in years:** Total population: 80.64, Male: 78.14, Female: 83.09.
- ✚ **Total fertility rate:** 1.39 per woman
- ✚ **Political-administrative organization:** Federal Republic, comprises 16 states. Capital City: Berlin.

## Greece



- ✚ **Surface:** 131960 km<sup>2</sup>
- ✚ **Total population:** 11307557 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 85.69
- ✚ **Total life expectancy at birth in years:** Total population: 80.69, Male: 78.48, Female: 82.93.
- ✚ **Total fertility rate:** 1.51 per woman
- ✚ **Political-administrative organization:** Republic consisted of 13 regions. Capital City: Athens.



## Hungary



- ✚ **Surface:** 93030 km<sup>2</sup>
- ✚ **Total population:** 10000024 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 107.49
- ✚ **Total life expectancy at birth in years:** Total population: 74.78, Male: 70.77, Female: 78.62.
- ✚ **Total fertility rate:** 1.26 per woman
- ✚ **Political-administrative organization:** Republic divided into 19 counties. Capital City: Budapest.

## Ireland



- ✚ **Surface:** 70280 km<sup>2</sup>
- ✚ **Total population:** 4459305 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 63.45
- ✚ **Total life expectancy at birth in years:** Total population: 80.8, Male: 78.5, Female: 83.03.
- ✚ **Total fertility rate:** 2.06 per woman
- ✚ **Political-administrative organization:** Republic, divided into 31 local authorities. Capital City: Dublin

## Italy



- ✚ **Surface:** 301340 km<sup>2</sup>
- ✚ **Total population:** 60483384 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 200.71
- ✚ **Total life expectancy at birth in years:** Total population: 82.5, Male: 79.75, Female: 85.04.
- ✚ **Total fertility rate:** 1.41 \*(2008) per woman
- ✚ **Political-administrative organization:** Republic, subdivided into 20 regions. Capital City: Rome.

## Latvia



- ✚ **Surface:** 64510 km<sup>2</sup>
- ✚ **Total population:** 2239008 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 34.71
- ✚ **Total life expectancy at birth in years:** Total population: 73.7, Male: 68.64, Female: 78.4.
- ✚ **Total fertility rate:** 1.36 per woman
- ✚ **Political-administrative organization:** Republic, unitary state, currently divided into 110 one-level municipalities and 9 republican cities. Capital City: Riga.

## Lithuania



- ✚ **Surface:** 65300 km<sup>2</sup>
- ✚ **Total population:** 3286820 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 50.33
- ✚ **Total life expectancy at birth in years:** Total population: 73.57, Male: 68, Female: 78.97.
- ✚ **Total fertility rate:** 1.5 per woman
- ✚ **Political-administrative organization:** Republic, divided into 10 counties. Capital City: Vilnius.

## Luxembourg



- ✚ **Surface:** 2590 km<sup>2</sup>
- ✚ **Total population:** 506966 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 195.74
- ✚ **Total life expectancy at birth in years:** Total population: 81.49, Male: 78.78, Female: 83.94.
- ✚ **Total fertility rate:** 1.63 per woman
- ✚ **Political-administrative organization:** Grand Duchy, divided into 3 districts (12 cantons). Capital City: Luxembourg.

## Malta



- ✚ **Surface:** 320 km<sup>2</sup>
- ✚ **Total population:** 415990 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 1299.97
- ✚ **Total life expectancy at birth in years:** Total population: 81.51, Male: 79.27, Female: 83.62.
- ✚ **Total fertility rate:** 1.4 per woman
- ✚ **Political-administrative organization:** Republic, 3 statistical regions (present 68 local councils). Capital City: Valletta.

## Netherlands



- ✚ **Surface:** 41540 km<sup>2</sup>
- ✚ **Total population:** 16615394 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 399.99
- ✚ **Total life expectancy at birth in years:** Total population: 81.15, Male: 79.05, Female: 83.1.
- ✚ **Total fertility rate:** 1.8 per woman
- ✚ **Political-administrative organization:** Kingdom, divided into 12 provinces. Capital City: Amsterdam.

## Poland



- ✚ **Surface:** 312680 km<sup>2</sup>
- ✚ **Total population:** 38516688 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 123.18
- ✚ **Total life expectancy at birth in years:** Total population: 76.58, Male: 72.3, Female: 80.83.
- ✚ **Total fertility rate:** 1.38 per woman
- ✚ **Political-administrative organization:** Republic, divided into 16 provinces. Capital City: Warsaw.

## Portugal



- ✚ **Surface:** 92090 km<sup>2</sup>
- ✚ **Total population:** 10573100 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 114.81
- ✚ **Total life expectancy at birth in years:** Total population: 80.13, Male: 76.84, Female: 83.27.
- ✚ **Total fertility rate:** 1.39 per woman
- ✚ **Political-administrative organization:** Republic, agglomerated into 18 districts. Capital City: Lisbon.

## Romania



- ✚ **Surface:** 238390 km<sup>2</sup>
- ✚ **Total population:** 21431298 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 89.9
- ✚ **Total life expectancy at birth in years:** Total population: 73.83, Male: 70.15, Female: 77.62.
- ✚ **Total fertility rate:** 1.3 per woman
- ✚ **Political-administrative organization:** Unitary semi-presidential republic, divided into 41 counties. Capital City: Bucharest.

## Slovakia



- ✚ **Surface:** 49037 km<sup>2</sup>
- ✚ **Total population:** 5431024 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 110.75
- ✚ **Total life expectancy at birth in years:** Total population: 75.66, Male: 71.81, Female: 79.4.
- ✚ **Total fertility rate:** 1.41 per woman
- ✚ **Political-administrative organization:** Republic, subdivided into 8 regions. Capital City: Bratislava.

## Slovenia



- ✚ **Surface:** 20270 km<sup>2</sup>
- ✚ **Total population:** 2049261 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 101.1
- ✚ **Total life expectancy at birth in years:** Total population: 79.96, Male: 76.56, Female: 83.21.
- ✚ **Total fertility rate:** 1.57 per woman
- ✚ **Political-administrative organization:** Republic, subdivided 62 administrative districts. Capital City: Ljubljana.

## Spain



- ✚ **Surface:** 505600 km<sup>2</sup>
- ✚ **Total population:** 46072832 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 91.13
- ✚ **Total life expectancy at birth in years:** Total population: 82.32, Male: 79.16, Female: 85.43.
- ✚ **Total fertility rate:** 1.37 per woman
- ✚ **Political-administrative organization:** Kingdom, divided into 17 autonomous communities and 2 autonomous cities. Capital City: Madrid.

## Sweden



- ✚ **Surface:** 450300 km<sup>2</sup>
- ✚ **Total population:** 9378126 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 20.83
- ✚ **Total life expectancy at birth in years:** Total population: 81.77, Male: 79.73, Female: 83.74.
- ✚ **Total fertility rate:** 1.98 per woman
- ✚ **Political-administrative organization:** Kingdom, divided into 21 counties. Capital City: Stockholm.

## United Kingdom



- ✚ **Surface:** 243610 km<sup>2</sup>
- ✚ **Total population:** 62261968 inhabitants
- ✚ **Population density Inhabit/Km<sup>2</sup>:** 255.58
- ✚ **Total life expectancy at birth in years:** Total population: 80.78, Male: 78.75, Female: 82.73.
- ✚ **Total fertility rate:** 1.8 \*(2005) per woman
- ✚ **Political-administrative organization:** Kingdom, there is no common stratum of administrative unit encompassing the United Kingdom. Capital City: London.



### 3.4.2 Group of Age

This study included one age group, from 20 years old to more than 85 years old, separated for male and female. To collect this data, we used the age-standardised Tuberculosis mortality rates of this age group, but separately for men and women within each country for every year studied, using the European standard population as the reference [336], giving our findings as number of deaths per 100,000 persons per year.

#### For trends in Mortality:

The database contains the data with underlying cause of death coded in one of the following three coding systems:

1. ICD-10 3-digit codes. The data records, which are coded using 4- digit codes, are aggregated into 3-digit codes when loading the data into the DMDB.
2. ICD-9 3-digit codes. Four-digit codes are aggregated into 3-digit codes.
3. Mortality tabulation list 1 (MTL1) of ICD-10, containing 103 categories.

In this study Mortality tabulation list 1 (MTL1) of ICD-10 was used for the both Infectious Diseases.

#### Mortality tabulation lists 1 (MTL1)

The ICD-10 mortality tabulation lists 1 (MTL1) were created by a team of health statisticians and medical officers following several steps. First, a complete one-to-one mapping of each category at the 4-digit level of both ICD-9 and ICD-10 was completed to identify the structure of ICD-10 and to highlight changes from ICD-9. The mapping indicated that many categories were subdivided into multiple codes in ICD-10 and that other codes in ICD-10 did not match any ICD-9 codes. Second, the ICD-10 codes were aggregated into groups that were most comparable with ICD-9, except when medical or public health requirements and concerns warranted new combinations or groups of codes. The current ICD-9 tabulation lists were used as a starting point to create the ICD-10 tabulation lists. Third, draft lists were sent for review to key federal and state health agencies for comment. The comments and suggestions were analyzed carefully to make decisions on which causes or cause groups should be included in the final tabulation lists.

Greece used the ICD9 and other countries like Poland, Spain and the United Kingdom used the ICD10, while countries such as Bulgaria, Italy and Portugal used both versions, switching from ICD9 to ICD10 in different years. So we used the data file containing the DMDB for the MTL1 (Mortality tabulation list 1 of the ICD-10) version of ICD when available data in ICD-9 and ICD-10 was aggregated and used as well to include all European Union countries in all years of the study. Some eastern European countries are using this tabulation list when reporting aggregated mortality data to the WHO. Data can be converted into MTL1 codes by grouping relevant ICD-10 or ICD-9. Complete conversion between ICD-9 and ICD-10 codes is not possible. Therefore, the international comparisons are available only between countries using the same ICD version. However, for the majority of MTL1 categories, comparisons are also possible between ICD-9 and ICD-10.

The tabulation list has been developed to maintain continuity with the lists from the Ninth Revision of the International Classification of Diseases (ICD-9); to facilitate trend analysis; and to separately identify causes of death that are of public health and medical importance.

### Mortality tabulation lists 1 (MTL1) codes

- ❖ Tuberculosis:
  - MTL1 1-005 ... A15-A16 Respiratory Tuberculosis
  - MTL1 1-006 ... A17-A19 Other Tuberculosis
- ❖ Human immunodeficiency virus (HIV):
  - MTL1 1-020 ... B20-B24

## 3.5 Statistical Analysis

From this data, age specific rates for each 5-year age group amalgamated into one age group and calendar period were obtained for men and women. Age-standardised mortality rates per 100,000 at (20–85+) years for men and women were calculated using the direct method on the basis of the European standard population [336], which was agreed amongst all European member states, including all twenty-nine European Union member states and the countries of the European Free Trade Association (EFTA).

The identification of changes in the recent trend is an important issue in the analysis of Infectious diseases mortality data, and in order to describe such continuous changes joinpoint regression model is currently being applied. [337][338]

Like the least squares regression method, the Joinpoint program is used to find the best-fit line through several years of data. However, the Joinpoint program uses an algorithm that tests whether a multi-segmented line is a significantly better fit than a straight or less-segmented line. The Joinpoint regression analysis involves fitting a series of joined straight line on a log scale to the trends in the annual age-adjusted disease incidence and mortality rates. Line segments are joined at points called Joinpoint. Each Joinpoint denotes a statistically significant ( $P = .05$ ) change in trend. P-value was estimated using Monte Carlo methods, and the overall asymptotic significance level is maintained through a Bonferroni correction. These tests are extended to the situation with non-constant variance to handle rates with Poisson variation and possibly auto correlated errors.[339]

The Joinpoint regression model, which is composed of a few continuous linear phases, is often useful to changes in trend data. The Joinpoint regression model for the observation,  $(x_1, y_1), \dots, (x_n, y_n)$ , where  $x_1 \leq \dots \leq x_n$  without loss of generality, may be written as

$$E[y|x] = \beta_0 + \beta_1 x + \delta_1(x - \tau_1)^+ + \dots + \delta_K(x - \tau_K)^+$$

Where that  $\tau_K$ 's are the unknown joinpoints and  $a^+ = a$  for  $a > 0$  and 0 otherwise. This type of non-linear regression model has been studied by many authors and has been named in the literature as piecewise regression, segmented regression, broken line regression, and multi-phase regression with the continuity constraint.

Assuming that  $k = 1$ , Sprent derived the likelihood ratio statistic for testing  $H_0: \tau_1 = \tau_{1,0}$  with application in biometry. Hinkley studied asymptotic properties of the maximum likelihood estimators of the parameters and developed a procedure to construct confidence region. For a general case where the model allows polynomial segments, Lerman proposed a grid search method to fit segmented regression curves. He assumed the distribution of the likelihood ratio statistic to be an F-distribution, and used it to test hypotheses and to construct an approximate confidence region for the joinpoint.

Knowles and Siegmund applied the method suggested by hotelling to make an inference on joinpoint in regression.

They derived an approximate upper bound for the  $p$ -value of the likelihood ratio test and constructed confidence regions based on the likelihood ratio statistic. Their approximation is the first analytic solution to approximate the distribution of the likelihood ratio statistic, but it only provides an upper bound and the accuracy is reasonable only when the regression parameters are assumed to be known. Furthermore it is not known how accurate the approximation would be when the underlying distribution is not normal, such as Poisson.

In this analysis, joinpoint regression analyses was used identify point where a significant change in the liner slope of the trend occurred.[340] In joinpoint analysis, the best fitting points -the "joinpoint"- where the rate changes significantly -increases or decreases- are chosen. The analysis starts with the minimum number of joinpoint (*e.g.*, 0 joinpoint, which is a straight line), and tests whether one or more joinpoint—up to 3, corresponding to 4 distinct period segments identified by trend 1 to trend 4- are significant and must be added to the model. In the final model each joinpoint -if any- informs of a significant change in the slope. The Estimated Annual Percentage Change (EAPC) was then computed for each of those trends by fitting a regression line to the natural logarithm of the rates using calendar year as regressor variable (i.e., given  $y = a + bx$ , where  $y = \ln(\text{rate})$  and  $x = \text{calendar year}$ , the EAPC is estimated as  $100*(e^b-1)$ ). The joinpoint analyses were performed using the "Joinpoint Trend Analysis Software" from the surveillance Research Program of the U.S. National Cancer Institute.[339]

Pearson correlation between age-standardised mortality rates of (Tuberculosis and HIV/AIDS) and unemployment rates of 2010, GINI index of 2009, Gross Domestic Product (GDP) per capita of 2013, evolution of the GDP before and after the crisis (2010-2006) and immigration 2006-2015 (average) -just for HIV/AIDS- was computed by using IBM SPSS (Statistical Package for the Social Sciences) software version 22.0.

We collected unemployment rates of 2010, GINI index of 2009 (GINI index is a statistical dispersion measure purposed to represent the income or wealth distribution of a residents of the nation, and it is considered as the most commonly used measure of

inequality)[328][329], Gross Domestic Product (GDP) per capita of 2013, evolution of the GDP before and after the crisis (2010-2006) and (immigration (2006-2015 average) for HIV infection) from Eurostat. Pearson correlation for these factors (immigration just for HIV infection) was computed, as well as multiple linear regression from each country.[330] [331][332][333] [334]

ArcGIS software was used to draw maps of distribution (Figure 8 and Figure 10). In each gender for each Tuberculosis and HIV/AIDS, we made 2 ranges of values divide into 5 equal categories for each one (Tuberculosis age-standardised mortality rates average and GDP 2013) for Tuberculosis and (HIV age-standardised mortality rates average and GINI index 2009) for HIV/AIDS.

## 4 Results

### 4.1 Tuberculosis

Between 2000 and 2010, there were 68,771 recorded Tuberculosis deaths in the European Union, 50,599 in men (73.5%) and 18,172 in women (26.5%).

Figure 7: TB age-standardised mortality rates in each European Union country and in European Union overall, 2000-2010. gives general view of the Tuberculosis age-standardised mortality rates trends in each European Union country and in European Union overall between 2000 and 2010. In this figure, we can see that the gap between Tuberculosis age-standardised mortality rates for men and women is clear in European Union for general and in all countries of study and even greater in countries of Eastern Europe (Bulgaria, Croatia, Poland, Romania) and of Baltic (Estonia, Latvia, Lithuania). For European Union, overall (last graphic in figure 1), the men-to-women ratio in age-standardised mortality rates increased from 3.96 in 2000 to 5.08 in 2010, which means that even the mortality rates declined in both genders, but it declined more so in women than men in relative terms.

Table 5 and Table 6 show the Tuberculosis age-standardised mortality rates in all European Union countries, for both men and women. Tuberculosis age-standardised mortality rates decreased in men and women linearly in European Union as a whole, despite there being variability between countries. However, we can see that the downward trend over the same period is greater in women in the majority of countries, and it is also clear that men have higher age-standardised mortality rates of Tuberculosis, which highlights a big gap between men and women (figure 1, table 1 and table 2). The higher age-standardised mortality rates for both genders correspond to East Europe and Baltic countries (Bulgaria, Croatia, Romania, Estonia, Lithuania, and Latvia). The lower age-standardised mortality rates for both genders correspond to Western European countries (Sweden and Netherlands).

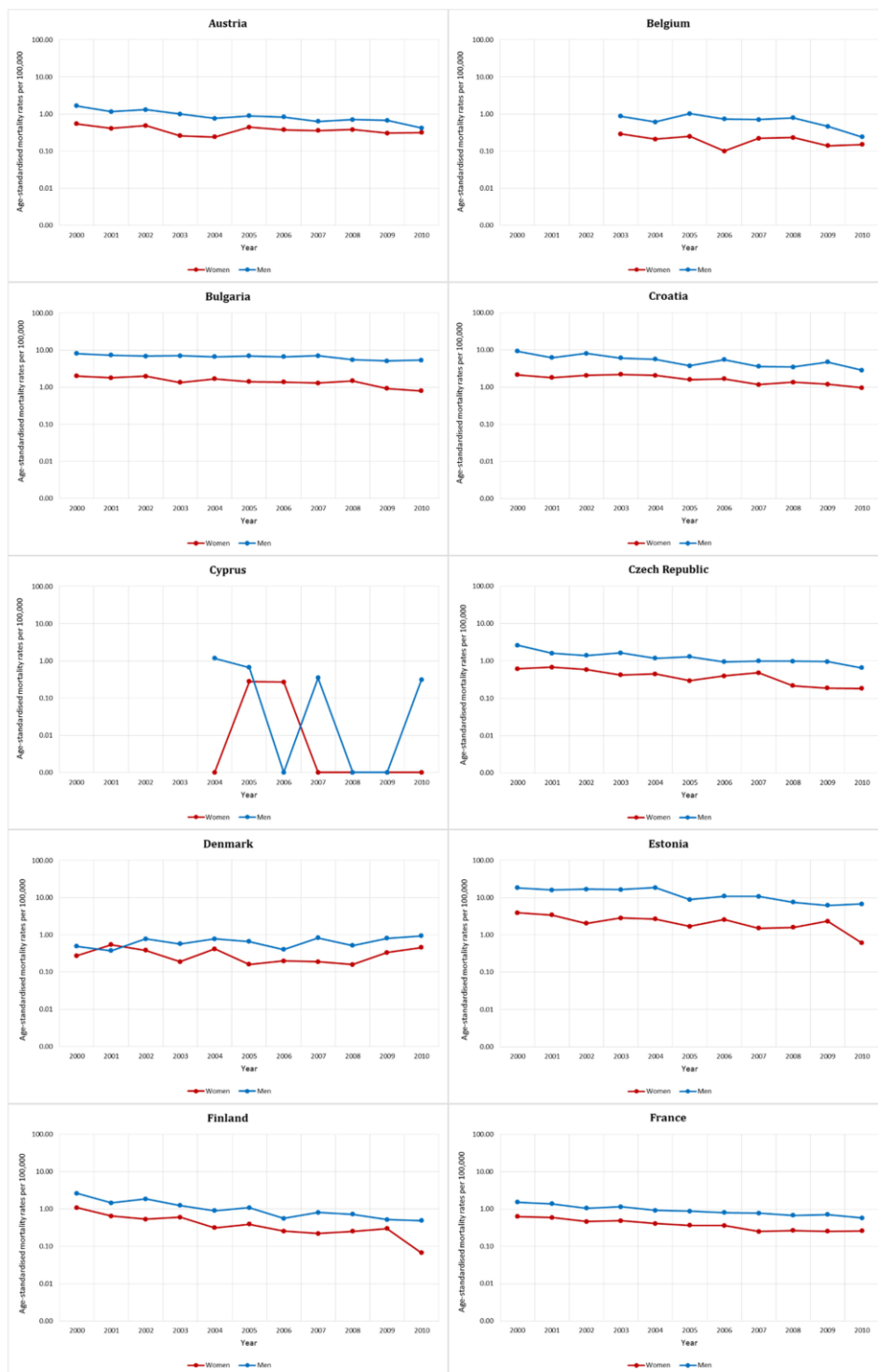


Figure 7: TB age-standardised mortality rates in each European Union country and in European Union overall, 2000-2010.

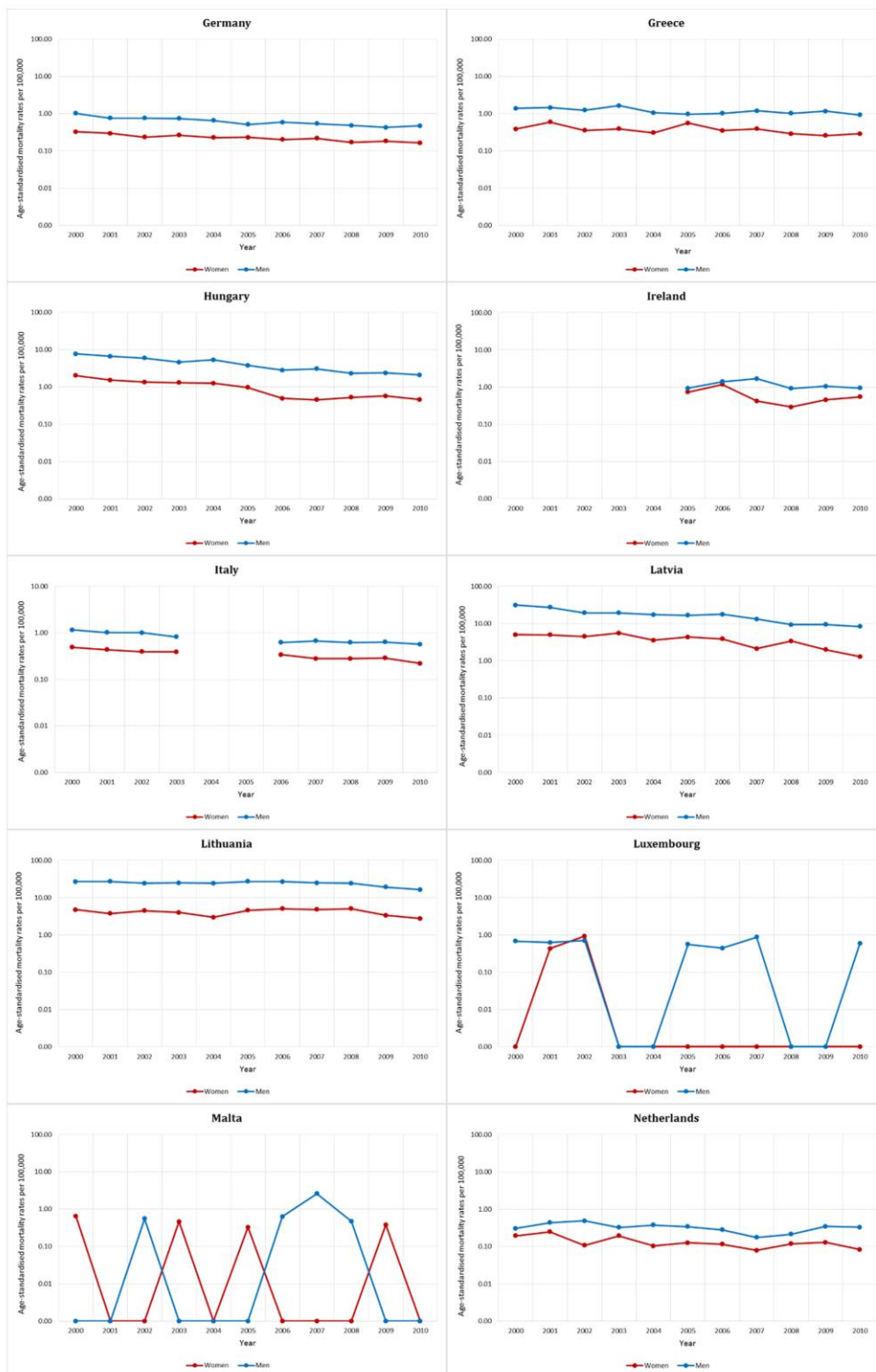


Figure 7: TB age-standardised mortality rates in each European Union country and in European Union overall, 2000-2010. continue



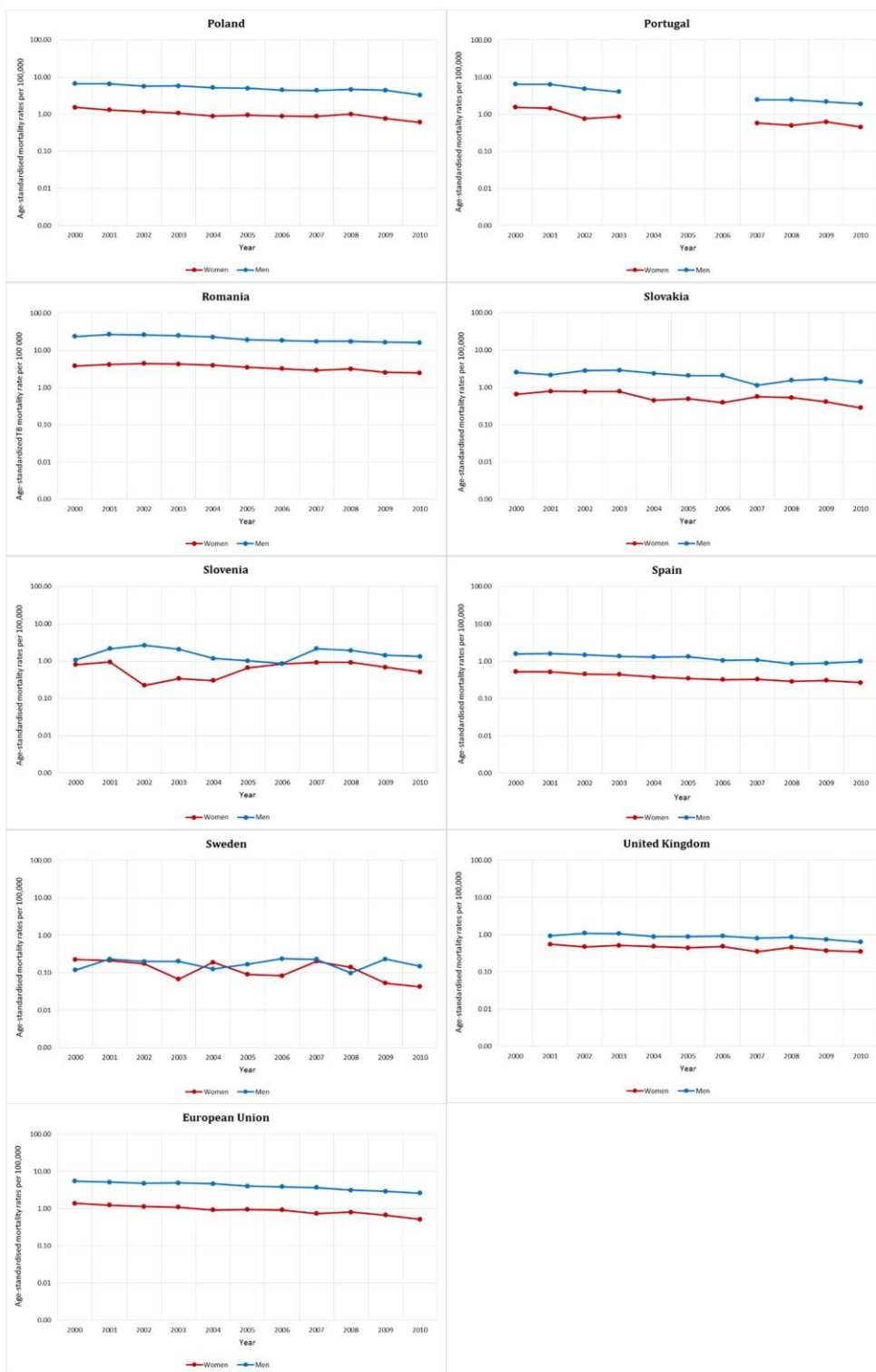


Figure 7: TB age-standardised mortality rates in each European Union country and in European Union overall, 2000-2010.continue

Country	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	Average 2000-2010
Austria	1.66	1.15	1.31	1.00	0.76	0.89	0.83	0.63	0.70	0.67	0.42	<b>0.91</b>
Belgium	...	...	...	0.87	0.61	1.02	0.73	0.70	0.79	0.46	0.24	<b>0.49</b>
Bulgaria	8.09	7.28	6.87	7.07	6.58	6.93	6.64	7.02	5.46	5.10	5.37	<b>6.58</b>
Croatia	9.25	6.26	8.14	6.10	5.69	3.74	5.51	3.64	3.51	4.78	2.88	<b>5.41</b>
Cyprus	...	...	...	...	1.17	0.66	0.00	0.35	0.00	0.00	0.31	<b>0.25</b>
Czech Republic	2.62	1.60	1.41	1.64	1.18	1.30	0.95	1.00	0.99	0.96	0.66	<b>1.30</b>
Denmark	0.49	0.38	0.78	0.57	0.78	0.67	0.40	0.83	0.51	0.81	0.94	<b>0.65</b>
Estonia	18.29	15.97	16.82	16.32	18.51	8.84	10.87	10.68	7.46	6.13	6.75	<b>12.42</b>
Finland	2.64	1.47	1.87	1.24	0.91	1.09	0.56	0.80	0.73	0.52	0.49	<b>1.12</b>
France	1.53	1.38	1.05	1.15	0.92	0.88	0.81	0.77	0.68	0.72	0.58	<b>0.95</b>
Germany	1.02	0.76	0.76	0.75	0.66	0.51	0.59	0.54	0.48	0.43	0.47	<b>0.63</b>
Greece	1.38	1.46	1.25	1.65	1.06	0.98	1.02	1.20	1.02	1.17	0.93	<b>1.19</b>
Hungary	7.68	6.70	5.95	4.61	5.36	3.80	2.83	3.09	2.31	2.38	2.11	<b>4.26</b>
Ireland	...	...	...	...	...	0.93	1.39	1.68	0.91	1.04	0.94	<b>0.77</b>
Italy	1.15	1.02	1.00	0.82	...	...	0.62	0.67	0.62	0.63	0.57	<b>0.79</b>
Latvia	31.19	27.22	19.28	19.13	17.09	16.56	17.67	13.11	9.23	9.32	8.25	<b>17.09</b>
Lithuania	26.81	26.88	24.27	24.81	24.24	27.18	26.67	24.94	24.28	19.17	16.21	<b>24.13</b>
Luxembourg	0.68	0.62	0.70	0.00	0.00	0.56	0.44	0.87	0.00	0.00	0.59	<b>0.41</b>
Malta	0.00	0.00	0.55	0.00	0.00	0.00	0.64	2.60	0.47	0.00	0.00	<b>0.39</b>
Netherlands	0.31	0.44	0.49	0.32	0.38	0.34	0.28	0.17	0.21	0.34	0.33	<b>0.33</b>
Poland	6.67	6.56	5.63	5.81	5.19	5.00	4.47	4.36	4.61	4.42	3.27	<b>5.09</b>
Portugal	6.41	6.33	4.87	4.03	...	...	...	2.45	2.45	2.17	1.90	<b>3.83</b>
Romania	23.51	26.42	25.85	24.61	22.56	19.15	18.30	17.33	17.28	16.52	16.08	<b>20.69</b>
Slovakia	2.55	2.16	2.84	2.90	2.38	2.07	2.07	1.15	1.56	1.69	1.40	<b>2.07</b>
Slovenia	1.06	2.15	2.67	2.08	1.18	1.02	0.86	2.15	1.93	1.43	1.33	<b>1.62</b>
Spain	1.57	1.60	1.48	1.37	1.29	1.33	1.06	1.08	0.86	0.88	0.99	<b>1.23</b>
Sweden	0.12	0.23	0.20	0.20	0.12	0.17	0.23	0.23	0.10	0.23	0.15	<b>0.18</b>
United Kingdom	...	0.93	1.09	1.06	0.88	0.88	0.91	0.80	0.85	0.74	0.63	<b>0.80</b>
European Union	<b>5.43</b>	<b>5.09</b>	<b>4.74</b>	<b>4.83</b>	<b>4.61</b>	<b>3.96</b>	<b>3.85</b>	<b>3.63</b>	<b>3.11</b>	<b>2.87</b>	<b>2.59</b>	<b>4.06</b>

Table 5: Age-standardised TB mortality rates per 100,000 in European Union for men.

Country	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	Average 2000-2010
Austria	0.54	0.41	0.48	0.26	0.24	0.44	0.38	0.36	0.38	0.30	0.32	<b>0.37</b>
Belgium	...	...	...	0.29	0.21	0.25	0.10	0.22	0.23	0.14	0.15	<b>0.20</b>
Bulgaria	1.99	1.78	1.97	1.35	1.67	1.40	1.37	1.30	1.48	0.92	0.79	<b>1.46</b>
Croatia	2.16	1.80	2.07	2.21	2.09	1.60	1.68	1.17	1.36	1.20	0.96	<b>1.66</b>
Cyprus	...	...	...	...	0.00	0.28	0.27	0.00	0.00	0.00	0.00	<b>0.08</b>
Czech Republic	0.62	0.68	0.59	0.42	0.45	0.30	0.40	0.48	0.22	0.19	0.18	<b>0.41</b>
Denmark	0.27	0.55	0.38	0.19	0.42	0.16	0.20	0.19	0.16	0.34	0.46	<b>0.30</b>
Estonia	3.92	3.42	2.02	2.84	2.66	1.69	2.56	1.51	1.59	2.32	0.61	<b>2.28</b>
Finland	1.08	0.65	0.53	0.60	0.31	0.39	0.26	0.22	0.25	0.30	0.07	<b>0.43</b>
France	0.63	0.59	0.46	0.49	0.41	0.37	0.36	0.25	0.27	0.25	0.26	<b>0.39</b>
Germany	0.33	0.30	0.24	0.27	0.23	0.23	0.20	0.22	0.17	0.18	0.16	<b>0.23</b>
Greece	0.39	0.60	0.35	0.39	0.31	0.56	0.35	0.39	0.29	0.26	0.29	<b>0.38</b>
Hungary	2.03	1.54	1.35	1.30	1.25	0.97	0.49	0.46	0.53	0.57	0.46	<b>1.00</b>
Ireland	...	...	...	...	...	0.73	1.17	0.42	0.29	0.45	0.54	<b>0.60</b>
Italy	0.49	0.43	0.39	0.39	...	...	0.34	0.28	0.28	0.29	0.22	<b>0.34</b>
Latvia	4.98	4.94	4.46	5.48	3.55	4.33	3.84	2.11	3.37	1.97	1.28	<b>3.66</b>
Lithuania	4.75	3.72	4.44	3.97	2.95	4.58	5.01	4.78	5.06	3.35	2.74	<b>4.12</b>
Luxembourg	0.00	0.43	0.93	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	<b>0.12</b>
Malta	0.64	0.00	0.00	0.46	0.00	0.33	0.00	0.00	0.00	0.38	0.00	<b>0.16</b>
Netherlands	0.19	0.25	0.11	0.19	0.10	0.13	0.12	0.08	0.12	0.13	0.08	<b>0.14</b>
Poland	1.53	1.31	1.17	1.06	0.89	0.94	0.88	0.88	1.00	0.76	0.61	<b>1.00</b>
Portugal	1.54	1.44	0.76	0.86	...	...	...	0.58	0.50	0.62	0.45	<b>0.84</b>
Romania	3.79	4.15	4.38	4.26	3.93	3.50	3.19	2.91	3.15	2.53	2.47	<b>3.48</b>
Slovakia	0.66	0.79	0.77	0.78	0.45	0.49	0.39	0.57	0.53	0.41	0.29	<b>0.56</b>
Slovenia	0.81	0.94	0.22	0.34	0.30	0.66	0.84	0.93	0.93	0.69	0.51	<b>0.65</b>
Spain	0.52	0.52	0.45	0.44	0.37	0.35	0.32	0.33	0.29	0.30	0.27	<b>0.38</b>
Sweden	0.22	0.21	0.17	0.07	0.19	0.09	0.08	0.20	0.14	0.05	0.04	<b>0.13</b>
United Kingdom	...	0.55	0.47	0.51	0.48	0.44	0.48	0.35	0.45	0.37	0.35	<b>0.44</b>
European Union	<b>1.37</b>	<b>1.23</b>	<b>1.13</b>	<b>1.09</b>	<b>0.91</b>	<b>0.94</b>	<b>0.91</b>	<b>0.73</b>	<b>0.80</b>	<b>0.66</b>	<b>0.51</b>	<b>0.94</b>

Table 6: Age-standardised TB mortality rates per 100,000 in European Union for women.

Table 7 shows that there is a significant decline in European Union in men, by a significant EAPC (-7%) when ( $p < 0.05$ ) and with 95% confidence interval. It also shows that in all countries except Denmark, the trend in Tuberculosis for men declined during study period. In addition, the majority of countries had a significant decrement in the trend in Tuberculosis. In countries such as Finland (EAPC = -14.1%), Hungary (EAPC = -12.7%), Belgium (EAPC = -12.4%), the age-standardised mortality rates of Tuberculosis fell more than in other countries. Bulgaria (EAPC = -3.7%), Greece (EAPC = -3.7%) and Romania (EAPC = -3.9%) had the lowest significant decline in Tuberculosis age-standardised mortality rates, while countries such as Ireland, Netherlands, Slovenia and Sweden did not have a significant decline. Denmark (EAPC 4.8%) is the only country that showed an upward trend in Tuberculosis age-standardised mortality rates.

Table 8 shows that there is a significant decline in Tuberculosis age-standardised mortality rates in European Union in women, by a significant EAPC (-8.1%) when ( $p < 0.05$ ) and with 95% confidence interval. It also shows that in all countries except Slovenia, the trend in Tuberculosis for women also declined, and the majority of countries had a significant decrement but in fewer countries than in men. Countries such as Finland (EAPC = -17.7%), Hungary (EAPC = -14.5%), Czech Republic (EAPC = -12%) showed a greater decline than the other countries. Greece (EACP = -4.8%), UK (EACP = -4.3%) and Romania (EACP = -4.3%) had lowest significant decline, while some countries had not significant decline. Slovenia (EACP = 3.5%) is the only country that showed an upward but not significant.

By observing EAPC data for men and women in European Union (Tables 3 and 4) when the EAPC for all period of study in women is -8.1 and it is more than in men -7, whereby the decrease Tuberculosis age-standardised mortality rates is slightly more in women, it is demonstrated why the men-to-women ratio increased from 3.96 in 2000 to 5.08 in 2010.

Figure 8 presents the distribution the Tuberculosis age-standardised mortality rates average and GDP 2013 distribution in European Union for men and women. There was a negative correlation between GDP and Tuberculosis ( $r = -0.378$   $p = 0.003$ ) and positive with GINI index ( $r = 0.482$   $p < 0.0005$ ) and unemployment ( $r = 0.402$   $p = 0.002$ ). We did not find any association with the evolution of the GDP.

Country	Trend all study period		Trend 1		Trend 2		Trend 3		Trend 4	
	Year	EAPC	Year	EAPC	Year	EAPC	Year	EAPC	Year	EAPC
Austria	2000-2010	-10.1*	2000-2002	-13.9	2002-2005	-11.4	2005-2008	-3.7	2008-2010	-20
Belgium	2003-2010	-12.4*	2003-2005	3.7	2005-2008	-3.2	2008-2010	-41.9	...	...
Bulgaria	2000-2010	-3.7*	2000-2002	-7.9	2002-2005	1.2	2005-2008	-6.5	2008-2010	-5.1
Croatia	2000-2010	-9.1*	2000-2002	-5.6	2002-2005	-15.6	2005-2008	-3.3	2008-2010	-9.3
Cyprus	...	...	...	...	...	...	...	...	...	...
Czech Republic	2000-2010	-9.7*	2000-2002	-22.6	2002-2005	-6.7	2005-2008	-5.9	2008-2010	-15.2
Denmark	2000-2010	4.8	2000-2002	24.9	2002-2005	-1.4	2005-2008	-2.5	2008-2010	29.8
Estonia	2000-2010	-10.9*	2000-2002	2.1	2002-2005	-1.3	2005-2008	-12.8	2008-2010	-10.7
Finland	2000-2010	-14.1*	2000-2002	-18.1	2002-2005	-18.9	2005-2008	-6.8	2008-2010	-16.5
France	2000-2010	-8.4*	2000-2002	-14.8	2002-2005	-8	2005-2008	-6.7	2008-2010	-8.1
Germany	2000-2010	-7.3*	2000-2002	-11.1	2002-2005	-8.8	2005-2008	-5.4	2008-2010	-3.9
Greece	2000-2010	-3.7*	2000-2002	1.7	2002-2005	-11.1	2005-2008	3.5	2008-2010	-6.7
Hungary	2000-2010	-12.7*	2000-2002	-12.4	2002-2005	-13.1	2005-2008	-14.7	2008-2010	-5.1
Ireland	2005-2010	-4	2005-2007	21.6	2007-2010	-16.6	...	...	...	...
Italy	2000-2010	-6.7*	2000-2003	-11	2003-2008	-5.8	2008-2010	-2.3	...	...
Latvia	2000-2010	-11.8*	2000-2002	-22.3	2002-2005	-2.8	2005-2008	-17.1	2008-2010	-9.9
Lithuania	2000-2010	-4.9*	2000-2002	-6	2002-2005	3.2	2005-2008	-3.1	2008-2010	-18.7
Luxembourg	2000-2010	-0.6	2000-2005	-3.6	2005-2010	2.6	...	...	...	...
Malta	...	...	...	...	...	...	...	...	...	...
Netherlands	2000-2010	-4.1	2000-2002	18.5	2002-2005	-12.3	2005-2008	-13.3	2008-2010	35.2
Poland	2000-2010	-5.7*	2000-2002	-6.5	2002-2005	-6.7	2005-2008	-1.7	2008-2010	-13.1
Portugal	2000-2010	-11.7*	2000-2002	-15.5	2002-2008	-11.4	2008-2010	-9.1	...	...
Romania	2000-2010	-3.9*	2000-2002	6.2	2002-2005	-10.4	2005-2008	-4.5	2008-2010	-2.5
Slovakia	2000-2010	-6.8*	2000-2002	10.3	2002-2005	9.4	2005-2008	-12.9	2008-2010	4.1
Slovenia	2000-2010	-1.6	2000-2002	58.9	2002-2005	-32.9	2005-2008	32.6	2008-2010	-21.6
Spain	2000-2010	-6.1*	2000-2002	-4.1	2002-2005	-4.7	2005-2008	-11.9	2008-2010	5.8
Sweden	2000-2010	-0.1	2000-2002	22.4	2002-2005	-4.8	2005-2008	-3.6	2008-2010	4.7
United Kingdom	2001-2010	-4.6*	2001-2003	1.5	2003-2008	-4.3	2008-2010	-11.4	...	...
European Union	2000-2010	-7*	2000-2002	-4.7	2002-2005	-5.1	2005-2008	-8.7	2008-2010	-10

\*EAPC: The estimated Annual Percent Change. Significantly different from Zero at Alpha = 0.05

Table 7: Joinpoint analysis for TB mortality in European Union for men, 2000-2010.

Country	Trend all study period		Trend 1		Trend 2		Trend 3		Trend 4	
	Year	EAPC	Year	EAPC	Year	EAPC	Year	EAPC	Year	EAPC
Austria	2000-2010	-3.2	2000-2002	-1.9	2002-2005	-1.2	2005-2008	3.2	2008-2010	-9.7
Belgium	2003-2010	-7	2003-2005	-22.2	2005-2008	4.8	2008-2010	-16.5	...	...
Bulgaria	2000-2010	-7.3*	2000-2002	-4.8	2002-2005	-7.8	2005-2008	-0.6	2008-2010	-25.5
Croatia	2000-2010	-7.4	2000-2002	3	2002-2005	-6.5	2005-2008	-10.2	2008-2010	-11.3
Cyprus	...	...	...	...	...	...	...	...	...	...
Czech Republic	2000-2010	-12*	2000-2002	-6.8	2002-2005	-13.4	2005-2008	-8.3	2008-2010	-22.8
Denmark	2000-2010	-5	2000-2002	8.8	2002-2005	-20.4	2005-2008	-4.3	2008-2010	67.5
Estonia	2000-2010	-11.1*	2000-2002	-21.5	2002-2005	-5.4	2005-2008	-3.2	2008-2010	-34.6
Finland	2000-2010	-17.7*	2000-2002	-25.7	2002-2005	-17.6	2005-2008	-4	2008-2010	-42.3
France	2000-2010	-9.5*	2000-2004	-9.2	2004-2007	-13.6	2007-2009	-3.4	...	...
Germany	2000-2010	-6	2000-2002	-13.1	2002-2005	-2.5	2005-2008	-7.4	2008-2010	-4.4
Greece	2000-2010	-4.8*	2000-2003	-9.6	2003-2005	5.4	2005-2009	-12.3	...	...
Hungary	2000-2010	-14.5*	2000-2002	-13.6	2002-2005	-16.3	2005-2008	-19	2008-2010	5.6
Ireland	2005-2010	-12.6	2005-2008	-31.1	2008-2010	30.6	...	...	...	...
Italy	2000-2010	-6.5*	2000-2002	-8.6	2002-2008	-5.5	2008-2010	-10.1	...	...
Latvia	2000-2010	-11.3*	2000-2002	-1.6	2002-2005	-6.9	2005-2008	-10.9	2008-2010	-31.2
Lithuania	2000-2010	-1.7	2000-2002	-7.7	2002-2005	2.3	2005-2008	7.5	2008-2010	-28.2
Luxembourg	...	...	...	...	...	...	...	...	...	...
Malta	...	...	...	...	...	...	...	...	...	...
Netherlands	2000-2010	-7.2*	2000-2002	-18.7	2002-2005	-8.3	2005-2008	-2	2008-2010	-6.7
Poland	2000-2010	-8.8*	2000-2002	-13.2	2002-2005	-8.7	2005-2008	3.1	2008-2010	-20.5
Portugal	2000-2010	-10.2*	2000-2002	-28	2002-2008	-7.5	2008-2010	-5.6	...	...
Romania	2000-2010	-4.3*	2000-2002	9.2	2002-2005	-8.4	2005-2008	-5.6	2008-2010	-9.2
Slovakia	2000-2010	-7.6*	2000-2002	11	2002-2005	-19.8	2005-2008	8.6	2008-2010	-27.2
Slovenia	2000-2010	3.5	2000-2002	-50.9	2002-2005	31.1	2005-2008	20.4	2008-2010	-30.1
Spain	2000-2010	-6.7*	2000-2002	-6.4	2002-2005	-9.6	2005-2008	-4.5	2008-2010	-4.3
Sweden	2000-2010	-11.3*	2000-2002	-22.2	2002-2005	-12.1	2005-2008	14.2	2008-2010	-50.3
United Kingdom	2001-2010	-4.3*	2001-2005	-4.2	2005-2008	-3.2	2008-2010	-7.6	...	...
European Union	2000-2010	-8.1*	2000-2002	-9.1	2002-2005	-7.1	2005-2008	5	2008-2010	-18.3

\*EAPC: The estimated Annual Percent Change. Significantly different from Zero at Alpha = 0.05

Table 8: Joinpoint analysis for TB mortality in European Union for women, 2000-2010.

In a multiple lineal regression, the model of Tuberculosis Age-standardised Mortality Rate will be:

$TMR = -13.735 + 3.092 (\text{Gender Male}) + 0.449 (\text{GINI}) + 0.234 (\text{Unemployment}) - 0.00003 (\text{GDP})$ . That means that Tuberculosis mortality is higher in men by (3.092), increase with inequities (GINI) by (0.449) and unemployment by (0.234) and decrease with GDP by (0.00003).

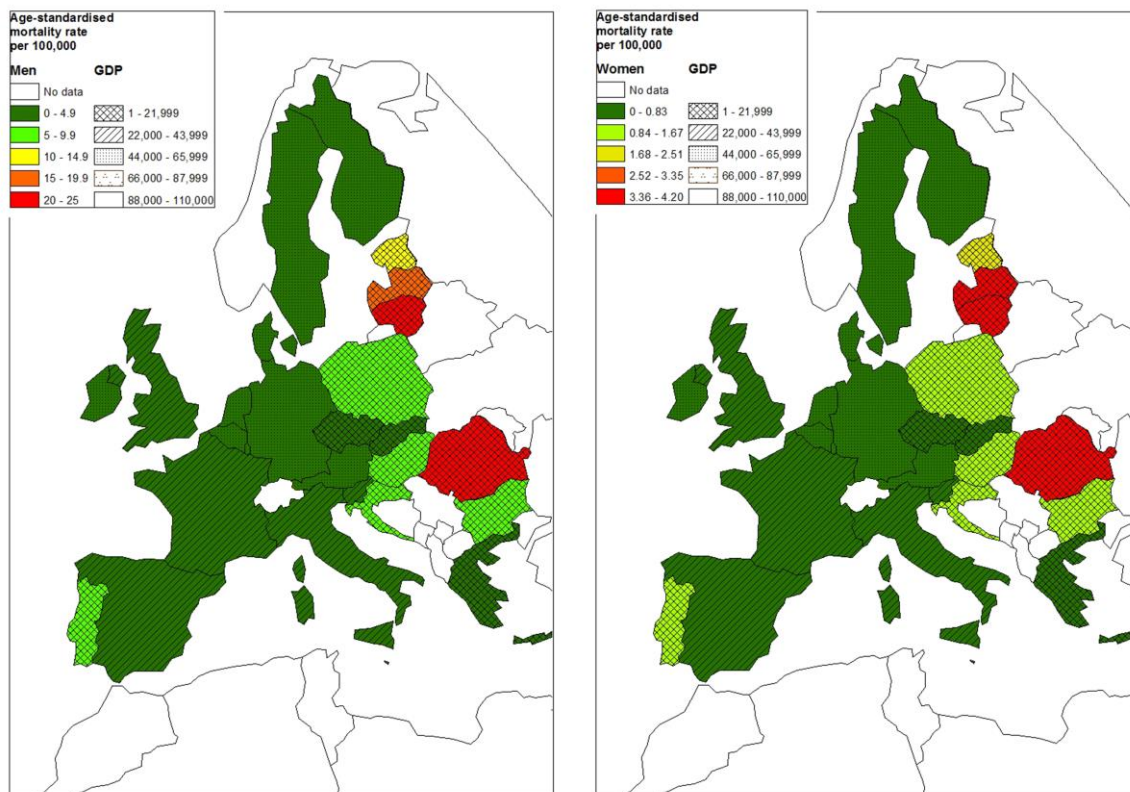


Figure 8: Distribution of TB age-standardised mortality rates average 2000-2010 and GDP of 2013 in European Union for men and women separately.

## 4.2 Human Immunodeficiency Virus Infection/Acquired Immunodeficiency Syndrome

It is estimated that between 2000-2014 there were 53518 deaths due to HIV/AIDS infection in European Union overall, 41294 in men (77.2%) and 12224 in women (22.8%). The HIV age-standardised mortality rates per 100,000 in European Union overall during 2000-2014 were higher in men than women, with an average of 1.83 for men and 0.54 for women and with a 3.38:1 of ratio.

Figure 9 displays the HIV age-standardised mortality rates in each European Union country and in European Union overall between 2000-2014 for men and women. It shows the corresponding trends over the whole period of study 2000-2014. We can see that men had a higher HIV age-standardised mortality rates during all years of the study period. The men-to-women ratio in HIV age-standardised mortality rates decreased slightly from 3.82:1 in 2000 to 3:1 in 2014. By observing the figure 4, we can see that age-standardized mortality rate of HIV in in European Union overall rose in both genders, but more in women than in men.

Table 9 and 6 (Table 5 for men and table 6 for women) present the HIV age-standardised mortality rate in each country of European Union and for European Union overall in men and in women. The countries which had a higher HIV age-standardised mortality rates were Portugal (13.7 for men, 3.52 for women), Spain (5.99 for men, 1.48 for women), Estonia (5.37 for men, 1.73 for women), Latvia (4.48 for men, 1.92 for women), Italy (3.28 for men, 0.91 for women) and France (2.52 for men, 0.72 for women), while The countries which had lower age-standardised mortality rate per 100,000 were Slovakia (0.08 for men, 0.009 for women), Czech Republic (0.09 for men, 0.03 for women), Bulgaria (0.18 for men, 0.03 for women), Hungary (0.22 for men 0.03), Finland (0.28 for men, 0.07 for women), Croatia (0.05 for women), and Slovenia (0.29 for men).



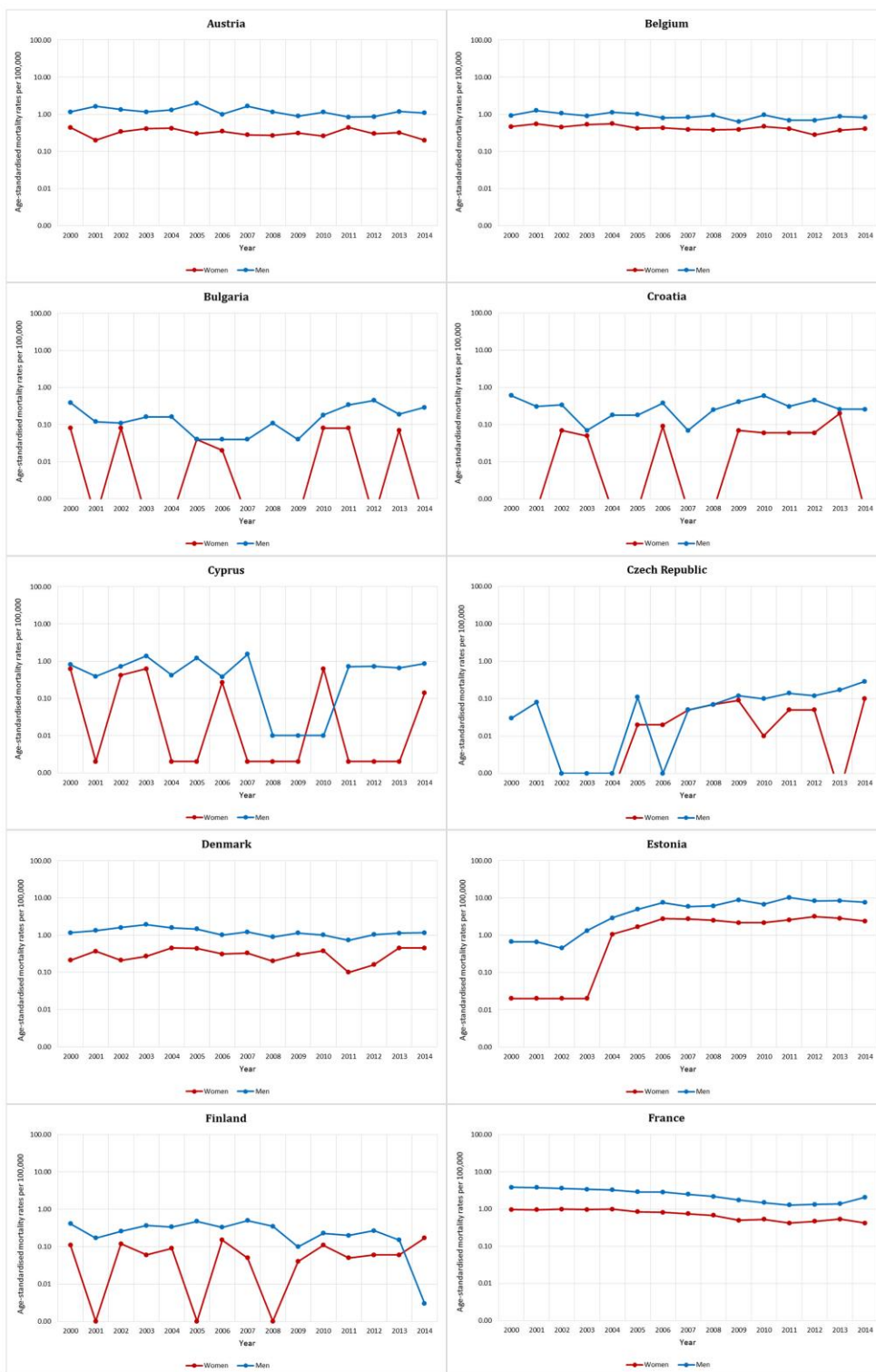


Figure 9: HIV age-standardised mortality rates in each European Union country and in European Union overall, 2000-2014.

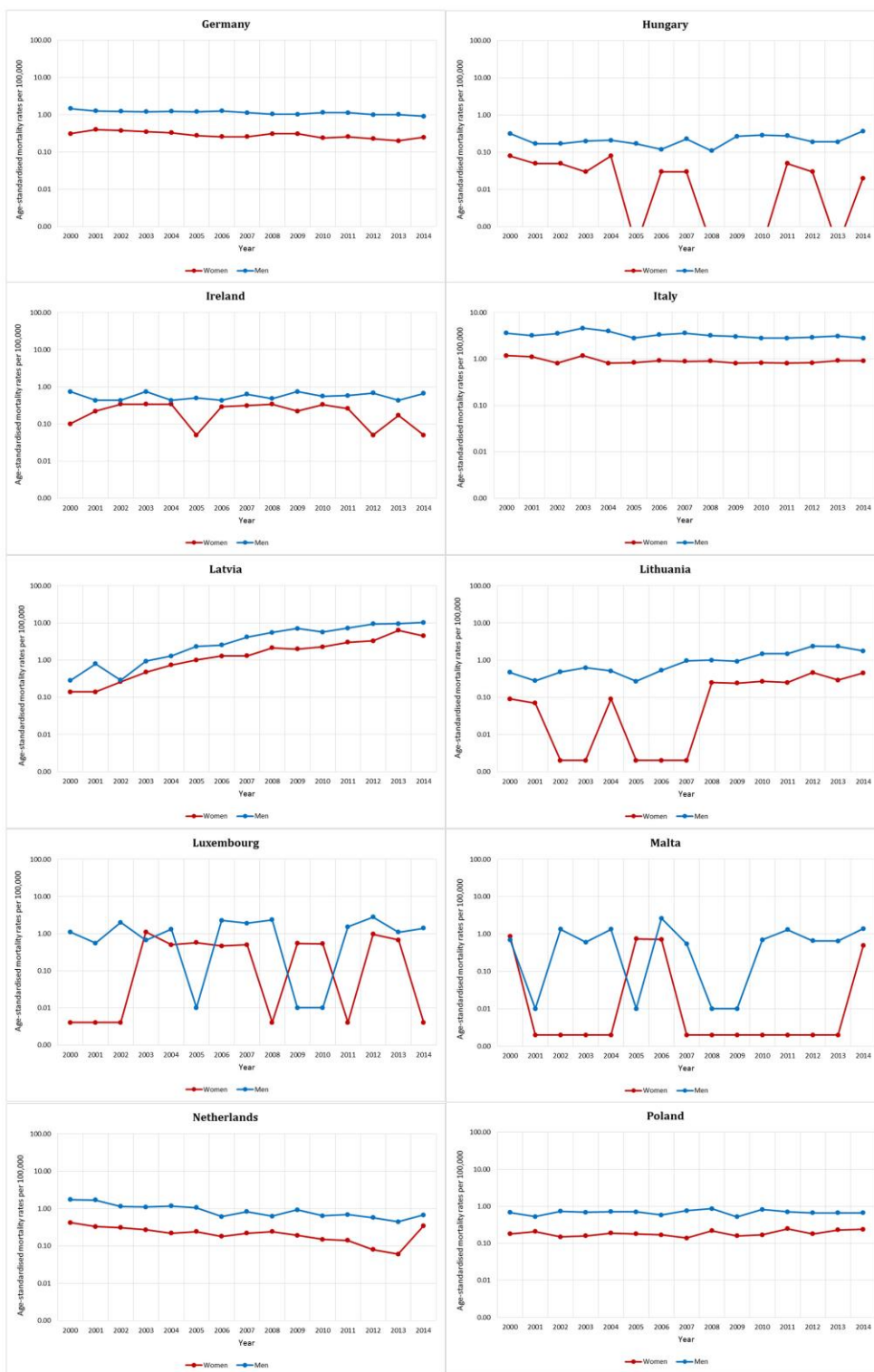


Figure 9: HIV age-standardised mortality rates in each European Union country and in European Union overall, 2000-2014. continue

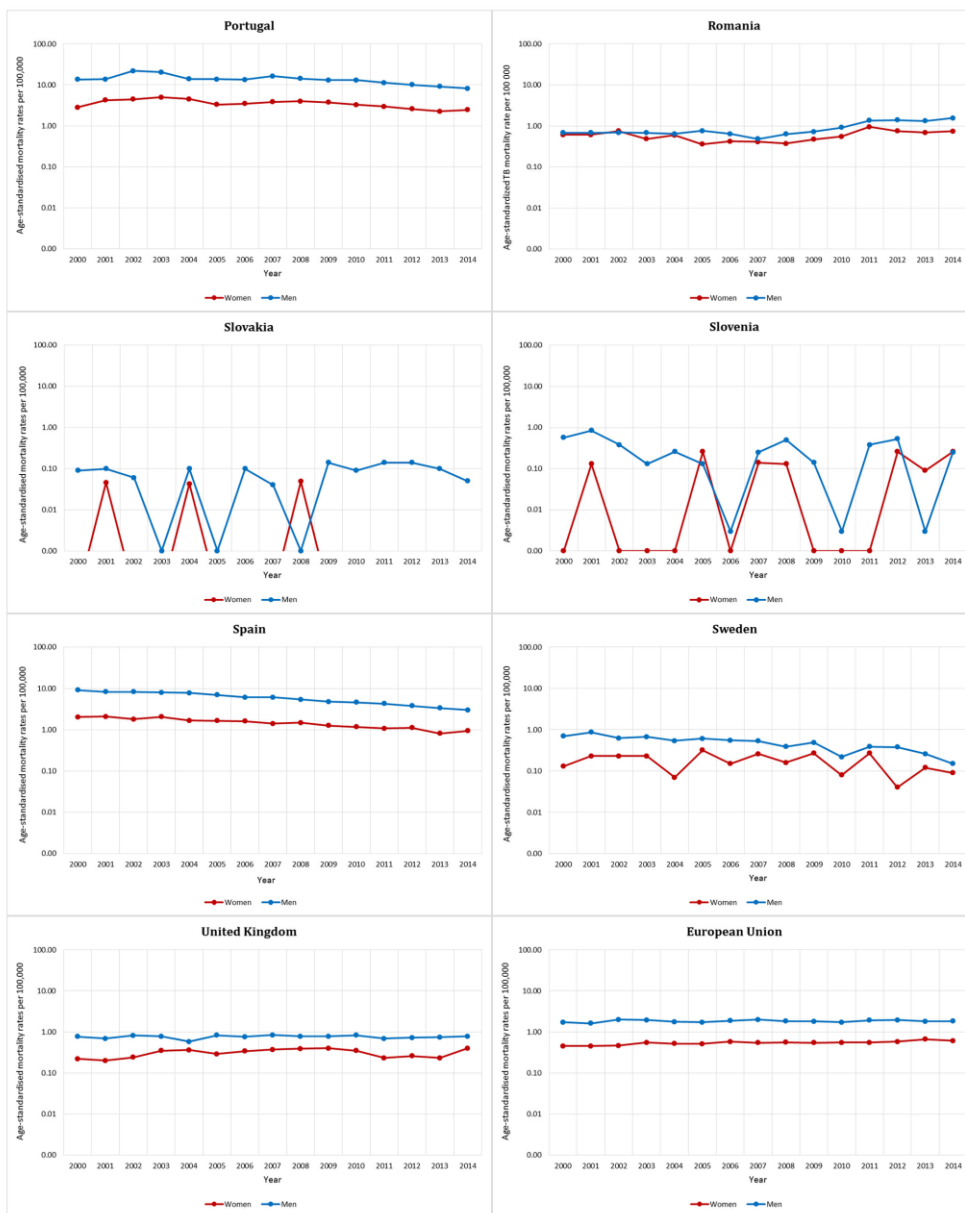


Figure 9: HIV age-standardised mortality rates in each European Union country and in European Union overall, 2000-2014. continue

Country	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Average 2000-2014
Austria	1.16	1.63	1.34	1.15	1.31	1.98	1.00	1.65	1.16	0.89	1.14	0.84	0.86	1.19	1.08	1.22
Belgium	0.92	1.26	1.06	0.90	1.13	1.02	0.80	0.83	0.94	0.63	0.96	0.69	0.69	0.87	0.83	0.90
Bulgaria	0.39	0.12	0.11	0.16	0.16	0.04	0.04	0.04	0.11	0.04	0.18	0.34	0.45	0.19	0.29	0.18
Croatia	0.61	0.31	0.34	0.07	0.18	0.18	0.38	0.07	0.25	0.41	0.60	0.31	0.46	0.26	0.26	0.31
Cyprus	0.81	0.39	0.72	1.37	0.42	1.22	0.38	1.53	0.01	0.01	0.01	0.71	0.72	0.65	0.86	0.65
Czech Republic	0.03	0.08	0.001	0.001	0.001	0.11	0.001	0.05	0.07	0.12	0.10	0.14	0.12	0.17	0.29	0.09
Denmark	1.16	1.32	1.59	1.92	1.57	1.47	1.01	1.21	0.89	1.14	1.01	0.73	1.03	1.13	1.16	1.22
Estonia	0.67	0.66	0.45	1.32	2.90	4.96	7.55	5.89	6.07	8.80	6.74	10.19	8.31	8.39	7.63	5.37
Finland	0.41	0.17	0.26	0.37	0.34	0.48	0.33	0.50	0.35	0.10	0.23	0.20	0.27	0.15	0.003	0.28
France	3.83	3.81	3.63	3.41	3.29	2.91	2.87	2.51	2.18	1.76	1.50	1.28	1.33	1.39	2.09	2.52
Germany	1.48	1.28	1.24	1.21	1.24	1.21	1.28	1.14	1.05	1.03	1.15	1.14	1.01	1.02	0.92	1.16
Hungary	0.32	0.17	0.17	0.20	0.21	0.17	0.12	0.23	0.11	0.27	0.29	0.28	0.19	0.19	0.37	0.22
Ireland	0.74	0.43	0.43	0.74	0.43	0.50	0.43	0.63	0.48	0.74	0.56	0.58	0.68	0.43	0.66	0.56
Italy	3.60	3.18	3.51	4.59	3.97	2.80	3.31	3.58	3.19	3.02	2.81	2.80	2.93	3.10	2.80	3.28
Latvia	0.28	0.79	0.29	0.93	1.29	2.33	2.53	4.17	5.54	7.05	5.68	7.22	9.35	9.54	10.24	4.48
Lithuania	0.47	0.28	0.48	0.62	0.51	0.27	0.53	0.96	1.00	0.92	1.47	1.48	2.36	2.35	1.75	1.03
Luxembourg	1.10	0.55	2.00	0.66	1.31	0.01	2.26	1.89	2.34	0.01	0.01	1.52	2.78	1.09	1.39	1.26
Malta	0.70	0.01	1.34	0.60	1.34	0.01	2.63	0.55	0.01	0.01	0.70	1.30	0.66	0.65	1.39	0.79
Netherlands	1.73	1.69	1.14	1.10	1.16	1.06	0.61	0.83	0.62	0.92	0.64	0.69	0.57	0.44	0.67	0.93
Poland	0.68	0.53	0.74	0.69	0.72	0.71	0.58	0.76	0.86	0.52	0.82	0.71	0.67	0.67	0.67	0.69
Portugal	13.48	13.65	21.88	20.39	13.82	13.68	13.43	16.21	14.26	13.09	12.97	11.28	10.01	9.14	8.14	13.70
Romania	0.68	0.68	0.69	0.68	0.64	0.76	0.64	0.48	0.63	0.72	0.91	1.35	1.38	1.32	1.55	0.87
Slovakia	0.09	0.10	0.06	0.001	0.10	0.001	0.10	0.04	0.001	0.14	0.09	0.14	0.14	0.10	0.05	0.08
Slovenia	0.57	0.85	0.38	0.13	0.25	0.13	0.003	0.25	0.50	0.14	0.003	0.38	0.53	0.003	0.25	0.29
Spain	9.17	8.33	8.33	7.94	7.76	6.96	6.11	6.12	5.37	4.80	4.61	4.29	3.77	3.35	3.00	5.99
Sweden	0.70	0.87	0.62	0.67	0.54	0.61	0.55	0.53	0.39	0.49	0.22	0.39	0.38	0.26	0.15	0.49
United Kingdom	0.77	0.69	0.82	0.78	0.58	0.83	0.76	0.84	0.78	0.78	0.83	0.69	0.72	0.74	0.78	0.76
Europe overall	1.72	1.62	1.99	1.95	1.75	1.72	1.86	1.98	1.82	1.80	1.71	1.91	1.94	1.81	1.83	1.83

Table 9: Age-standardised HIV mortality rates per 100,000 in European Union for men.

Country	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Average 2000-2014
Austria	0.44	0.20	0.34	0.41	0.42	0.30	0.35	0.28	0.27	0.31	0.26	0.44	0.30	0.32	0.20	0.32
Belgium	0.46	0.55	0.45	0.53	0.56	0.42	0.43	0.39	0.38	0.39	0.47	0.41	0.28	0.37	0.41	0.43
Bulgaria	0.08	0.0003	0.08	0.0003	0.0003	0.04	0.02	0.0003	0.0003	0.0003	0.08	0.08	0.0003	0.07	0.0003	0.03
Croatia	0.0005	0.0005	0.07	0.05	0.0005	0.0005	0.09	0.0005	0.0005	0.07	0.06	0.06	0.06	0.20	0.0005	0.05
Cyprus	0.62	0.002	0.42	0.6199	0.002	0.002	0.27	0.002	0.002	0.62	0.62	0.002	0.002	0.002	0.14	0.18
Czech Republic	0.0003	0.0003	0.0003	0.0003	0.0003	0.02	0.02	0.05	0.07	0.09	0.01	0.05	0.05	0.0003	0.10	0.03
Denmark	0.21	0.37	0.21	0.27	0.45	0.44	0.31	0.33	0.20	0.30	0.38	0.10	0.16	0.45	0.45	0.31
Estonia	0.02	0.02	0.02	0.02	1.06	1.66	2.75	2.73	2.51	2.15	2.15	2.56	3.18	2.83	2.37	1.73
Finland	0.11	0.001	0.12	0.06	0.09	0.001	0.15	0.05	0.001	0.04	0.11	0.05	0.06	0.06	0.17	0.07
France	0.97	0.96	1.00	0.97	0.99	0.85	0.82	0.75	0.68	0.50	0.53	0.42	0.47	0.54	0.42	0.72
Germany	0.31	0.40	0.38	0.35	0.33	0.28	0.26	0.26	0.31	0.31	0.24	0.26	0.23	0.20	0.25	0.29
Hungary	0.08	0.05	0.05	0.03	0.08	0.0003	0.03	0.03	0.0003	0.0003	0.0003	0.05	0.03	0.0003	0.02	0.03
Ireland	0.10	0.22	0.34	0.34	0.34	0.05	0.29	0.31	0.34	0.22	0.33	0.26	0.05	0.17	0.05	0.23
Italy	1.18	1.11	0.81	1.18	0.81	0.83	0.92	0.88	0.90	0.81	0.82	0.81	0.82	0.92	0.91	0.91
Latvia	0.14	0.14	0.26	0.47	0.74	1.00	1.29	1.30	2.12	1.99	2.26	3.02	3.28	6.28	4.47	1.92
Lithuania	0.09	0.07	0.002	0.002	0.09	0.002	0.002	0.002	0.25	0.24	0.27	0.25	0.46	0.29	0.45	0.17
Luxembourg	0.004	0.004	0.004	1.10	0.50	0.57	0.46	0.50	0.004	0.54	0.53	0.004	0.96	0.67	0.004	0.39
Malta	0.87	0.002	0.002	0.002	0.002	0.74	0.72	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.49	0.19
Netherlands	0.42	0.33	0.31	0.27	0.22	0.24	0.18	0.22	0.24	0.19	0.15	0.14	0.08	0.06	0.34	0.23
Poland	0.18	0.21	0.15	0.16	0.19	0.18	0.17	0.14	0.22	0.16	0.17	0.25	0.18	0.23	0.24	0.19
Portugal	2.80	4.25	4.42	4.96	4.50	3.30	3.47	3.83	3.99	3.75	3.27	2.97	2.59	2.25	2.44	3.52
Romania	0.61	0.61	0.75	0.48	0.59	0.36	0.42	0.41	0.37	0.47	0.55	0.95	0.75	0.69	0.74	0.58
Slovakia	0.0001	0.0457	0.0001	0.0001	0.0429	0.0001	0.0001	0.0001	0.0489	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.009
Slovenia	0.001	0.13	0.001	0.001	0.001	0.26	0.001	0.14	0.13	0.001	0.001	0.001	0.26	0.09	0.26	0.09
Spain	2.04	2.08	1.80	2.06	1.67	1.65	1.61	1.41	1.47	1.26	1.17	1.08	1.12	0.81	0.94	1.48
Sweden	0.13	0.23	0.23	0.23	0.07	0.32	0.15	0.26	0.16	0.27	0.08	0.27	0.04	0.12	0.09	0.18
United Kingdom	0.22	0.20	0.24	0.35	0.36	0.29	0.34	0.37	0.39	0.40	0.35	0.23	0.26	0.23	0.40	0.31
<b>EUROPEAN EUROPE overall</b>	<b>0.45</b>	<b>0.45</b>	<b>0.46</b>	<b>0.55</b>	<b>0.52</b>	<b>0.51</b>	<b>0.58</b>	<b>0.54</b>	<b>0.56</b>	<b>0.54</b>	<b>0.55</b>	<b>0.55</b>	<b>0.58</b>	<b>0.66</b>	<b>0.61</b>	<b>0.54</b>

Table 10: Age-standardised HIV mortality rates per 100,000 in European Union for women.

Findings from our Joinpoint regression analysis, assessing HIV trend changes over time (2000-2014) are shown in table 7 for men and table 8 for women. Tables 7 and 8 report the calendar period during which mortality trends changed significantly and the corresponding EACP for men and women are reported separately.

Table 11 shows that there is no significant rise in European Union overall during 2000-2014 in men, by an Estimated Annual Percentage Change (EAPC) ( $P= 0.3$ ) when ( $p<0.05$ ) and with 95% confidence interval. However, it shows a variety of EAPC among the European Union countries where some countries had a significant rise and others had a significant decline in HIV age-standardised mortality rates. The countries that had a higher significant rise when ( $p<0.05$ ) and with 95% confidence interval in the trend in HIV in men were; Czech Republic (EAPC= 35.4), Latvia (EAPC= 29.9), Estonia (EAPC= 23.2) and Lithuania (EAPC= 15.2). The countries that had a higher significant decline when ( $p<0.05$ ) and with 95% confidence interval in the trend in HIV in men were; Sweden (EAPC= -8.9), France (EAPC= -7.8), Netherlands and Spain (EAPC= -7.6).

Table 12 shows that there is a significant rise in European Union overall during 2000-2014 in women, by an EACP (2.1) when ( $p<0.05$ ) and with 95% confidence interval. However, it shows a variety of EAPC among the European Union countries where some countries had a significant rise and others had a significant decline in HIV age-standardised mortality rates. The countries that had a higher significant rise when ( $p<0.05$ ) and with 95% confidence interval in the trend in HIV in women were; Estonia (EAPC= 48.4), Czech Republic (EAPC= 43.5), Lithuania (EAPC= 35) and Latvia (EAPC= 29.5), and. The countries that had a higher significant decline when ( $p<0.05$ ) and with 95% confidence interval in the trend in HIV in were; Netherlands (EAPC= -7.7), France (EAPC= -6.7), Spain (EAPC= -6.1), Germany and Portugal (EAPC= -3.5).

By observing EAPC data for men and women in European Union overall in tables 7 and 8, we can note that HIV age-standardised mortality rates per 100,000 in European Union overall during 2000-2014 rose in both genders; in women rose more and it was a significant rise.

Country	Trend for all period			Trend 1		Trend2		Trend 3		
	Year	EACP	Year	EACP	Year	EACP	Year	EACP	Year	EACP
Austria	2000-2014	-2.7	2000-2005	3.8	2005-2011	-8.6	2011-2014	9		
Belgium	2000-2014	-2.6*	2000-2002	3.6	2002-2012	-4.2	2012-2014	11.3		
Bulgaria	2000-2014	4.4	2000-2007	-24.7*	2007-2012	61.3	2012-2014	-24.3		
Croatia	2000-2014	1.9	2000-2005	-44.8	2003-2010	21.3	2010-2014	-11.4		
Cyprus	2000-2014	-8.1	2000-2006	6.7	2006-2009	-76.6	2009-2014	186.9*		
Czech Republic	2000-2014	35.4*	2000-2005	-76.4	2003-2008	149.1	2008-2014	20.8		
Denmark	2000-2014	-3.1*	2000-2005	13.6	2003-2011	-8.9*	2011-2014	15		
Estonia	2000-2014	23.2*	2000-2002	-13.9	2002-2005	127.4*	2005-2014	4.2		
Finland	2000-2014	-13.8*	2000-2009	-4	2009-2012	13.2	2012-2014	-87.5*		
France	2000-2014	-7.8*	2000-2006	-5.3*	2006-2012	-13.9 <sup>v</sup>	2012-2014	30.8 <sup>v</sup>		
Germany	2000-2014	-2.4*	2000-2002	-7.3	2002-2007	-1.5	2007-2014	-5		
Hungary	2000-2014	1.9	2000-2002	-8.9	2006-2010	14.9	2010-2014	1.3		
Ireland	2000-2014	0.8	2000-2002	-16.4	2002-2009	3.9	2009-2010	-1		
Italy	2000-2014	-2.0*	2000-2005	7.5	2003-2006	-7.9	2006-2014	-1.4		
Latvia	2000-2014	29.9*	2000-2002	14.1	2002-2007	57.1*	2007-2014	12.4*		
Lithuania	2000-2014	15.2*	2000-2002	0.4	2005-2012	26.6*	2012-2014	-9.2		
Luxembourg	2000-2014	-1.4	2000-2007	-0.5	2007-2010	-59.3	2010-2014	214.1		
Malta	2000-2014	8.1	2000-2006	14.4	2006-2009	-54.2	2009-2014	132.2		
Netherlands	2000-2014	-7.5*	2000-2006	-13.4*	2006-2009	-0.1	2009-2014	-6.7		
Poland	2000-2014	0.4	2000-2002	4.5	2002-2008	1	2008-2014	-1.2		
Portugal	2000-2014	-4.3*	2000-2002	20.4	2002-2010	-4.8	2010-2014	-10		
Romania	2000-2014	6.2*	2000-2008	-2.6	2008-2011	29.7	2011-2014	5.7		
Slovakia	2000-2014	9.8	2000-2005	-69.1	2003-2012	43.1	2012-2014	-35.4		
Slovenia	2000-2014	-13.8	2000-2006	-41.8	2006-2009	45.8	2009-2014	-13.5		
Spain	2000-2014	-7.6*	2000-2004	-4.2*	2004-2011	-8.1*	2011-2014	-10.7*		
Sweden	2000-2014	-8.9*	2000-2009	-7.7*	2009-2012	-4	2012-2014	-32.8		
United Kingdom	2000-2014	0.1	2000-2004	-2.9	2004-2007	5.7	2007-2014	-1.7		
Europe overall	2000-2014	0.3	2000-2002	8	2002-2005	-2	2005-2014	0.3		

\*EACP: The estimated Annual Percent Change. Significantly different from Zero at Alpha = 0.05

Table 11: Joinpoint analysis for HIV/AIDS mortality in European Union for men, 2000-2014.

Country	Trend for all period		Trend 1		Trend2		Trend 3	
	Year	EACP	Year	EACP	Year	EACP	Year	EACP
Austria	2000-2014	-1.7	2000-2008	-2.7	2008-2011	9	2011-2014	-15.9
Belgium	2000-2014	-2.6*	2000-2003	2.2	2003-2012	-4.4	2012-2014	9.4
Bulgaria	2000-2014	-3.2	2000-2008	-31.9	2008-2011	319	2011-2014	-73.5
Croatia	2000-2014	22	2000-2008	3.9	2008-2012	203.3	2012-2014	-92.9
Cyprus	2000-2014	-15.8	2000-2005	-41.9	2005-2012	-14.8	2012-2014	270.1
Czech Republic	2000-2014	43.5	2000-2003	-4.7	2003-2007	325.7	2007-2014	-27.3
Denmark	2000-2014	-0.2	2000-2005	12.1	2005-2012	-11.9	2012-2014	81.7
Estonia	2000-2014	48.4*	2000-2002	-23.8	2002-2005	468.9*	2005-2014	1.5
Finland	2000-2014	10.8	2000-2003	37.1	2003-2008	-25	2008-2014	62.2
France	2000-2014	-6.7*	2000-2004	0.8	2004-2011	-10.6 <sup>^</sup>	2011-2014	1.1
Germany	2000-2014	-3.5	2000-2002	10.3	2002-2005	-9.9	2005-2014	-2.6
Hungary	2000-2014	-20.1	2000-2009	-45.0*	2009-2012	180.8	2012-2014	-48.5
Ireland	2000-2014	-4.9	2000-2002	51.1	2002-2010	-0.1	2010-2014	-30.8
Italy	2000-2014	-1.6*	2000-2002	-11.8	2002-2011	-1.6	2011-2014	4.4
Latvia	2000-2014	29.5*	2000-2002	44.9	2002-2005	59.5	2005-2014	19.4*
Lithuania	2000-2014	35.0*	2000-2006	-4.4	2006-2009	478.3	2009-2014	4
Luxembourg	2000-2014	11.7	2000-2003	528.2	2003-2012	-6.7	2012-2014	-69.1
Malta	2000-2014	-7.5	2000-2006	13	2006-2012	-47.4	2012-2014	1875.8
Netherlands	2000-2014	-7.7*	2000-2009	-6.3 <sup>^</sup>	2009-2012	-28.4	2012-2014	81.1*
Poland	2000-2014	1.8	2000-2002	-7.2	2002-2009	0.7	2009-2014	6.4
Portugal	2000-2014	-3.5*	2000-2002	23.9	2002-2009	-3.8	2009-2014	-8.6
Romania	2000-2014	1.8	2000-2008	-7.7*	2008-2011	32.3	2011-2014	-5.5
Slovakia	2000-2014	-16.2	2000-2008	4.4	2008-2011	-58.3	2011-2014	22.8
Slovenia	2000-2014	24.3	2000-2007	56	2007-2010	-70.9	2010-2014	407.9
Spain	2000-2014	-6.1*	2000-2003	-2.7	2003-2008	-6	2008-2014	-7.4*
Sweden	2000-2014	-5	2000-2009	2.5	2009-2012	-29.9	2012-2014	20.6
United Kingdom	2000-2014	1.6	2000-2009	7.3 <sup>^</sup>	2009-2012	-20.1	2012-2014	29.9
Europe overall	2000-2014	2.1*	2000-2006	3.9 <sup>^</sup>	2006-2010	-0.9	2010-2014	4.1

\*EACP: The estimated Annual Percent Change. Significantly different from Zero at Alpha = 0.05

Table 12: Joinpoint analysis for HIV/AIDS mortality in European Union for women, 2000-2014.



Figure 10 presents the distribution of HIV age-standardised mortality rates average 2000-2014 and GINI index of 2009 in European Union for men and women during 2000-2014. There was a positive correlation between GINI index and HIV ( $r = -0.436$   $p = 0.001$ ) and with unemployment ( $r = 0.338$   $p = 0.012$ ). We did not find any association with the evolution of the GDP nor with the immigration.

In a multiple lineal regression the model of Tuberculosis Age-standardised Mortality Rate will be:

$TMR = -6.823 + 1.286 (\text{Gender Male}) + 0.233 (\text{GINI}) + 0.063 (\text{Unemployment})$ .  
That means that Tuberculosis mortality is higher in men, increase with inequities (GINI) by (0.233) and unemployment by (0.063).

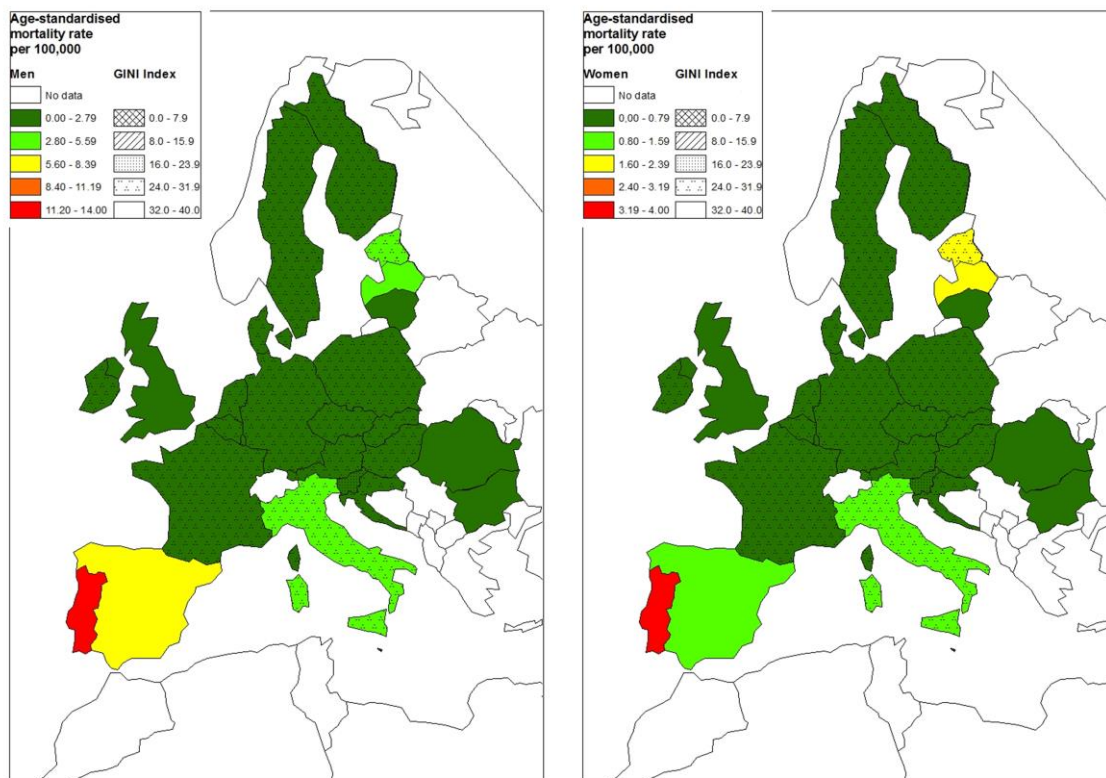


Figure 10: Distribution of HIV age-standardised mortality rates average 2000-2014 and GINI index of 2009 in European Union for men and women separately.

## 5 Discussion

### 5.1 Tuberculosis

The fall European age-standardised mortality rates of Tuberculosis are a global trend. The decrease in age-standardised mortality rates of Tuberculosis has some notable key features. First, although men have a higher age-standardised mortality rates than women in all countries, the trend in European Union overall and by country, is a fall in the mortality rates for both genders, with higher decreases for women than men. The difference in mortality rates between men and women is commonly attributed to biological, including hormonal and immunity differences, behavioral habits such as cigarette smoking or alcoholism, and epidemiological characteristics as well as socio-economic and cultural barriers in access to health care. [341][342] Second, these mortality trends differ between countries and gender, with some countries having higher mortality rates than the European Union average. Third, the joinpoint analysis allowed identification of time-points at which trends changed in different countries. The multiple regression lineal model found that Tuberculosis age-standardised mortality rates is higher in the countries with lower economic resources and more inequalities.

Our results showed that Eastern European and Baltic countries (Bulgaria, Romania, Lithuania, Latvia, and Estonia) present higher age-standardised mortality rates of Tuberculosis in both gender than Western European countries. In addition, two Eastern European countries (Bulgaria and Romania) presented had the lowest significant decline in age-standardised mortality rates of Tuberculosis for men, and Romania for women. The gap between age-standardised mortality rates of Tuberculosis for men and women is observed in all countries, but this gap in countries such as Bulgaria, Lithuania, Poland and Romania is more notable, taking into account that these countries have lower income compared with other European Union countries, the high age-standardised mortality rates of Tuberculosis in those countries are consistent with global studies that demonstrates that Tuberculosis is a disease that thrives where social and economic determinants of ill health and poverty prevail.[282][343] In these countries, a higher mortality of MDR-Tuberculosis patients, including MDR-Tuberculosis HIV patients, have been observed with some shortcomings in the management and treatment. [344][345] On the other hand,

health inequalities from studies of mortality in Europe are more prenominated in Eastern Europe and Baltic countries. [288]

Factors associated with the prevalence of Tuberculosis including low access to health-care, longer delays in the diagnosis of Tuberculosis, insufficient quality treatment, and increase of homeless population, migrant groups and prison population.[346][347] In addition, unemployment and job insecurity appear to lead to behaviour that increases the risk for Tuberculosis, e.g. increase tobacco consumption, substance abuse and hazardous drinking, all of which could impair immunity. Alcohol can increase susceptibility to some infectious diseases, such as Pneumonia and Tuberculosis[348]. A study[349] demonstrated that during the economic recession (2008-2011) in the European Union, the detection rates declined by a mean of 5.2%. A recently published systematic review[10] showed that an economic crisis indeed led to increased incidence, prevalence or mortality of Tuberculosis.

Since the onset of the recession, several European Union countries have introduced user fees or budget cuts to infectious disease programs, including charges for prescription drugs, shifted approximately 50% of the costs of diagnostic testing to patients and reduced spending on disease control and surveillance. Even in the absence of an economic crisis, infectious diseases disproportionately affect vulnerable groups. A study comparing wealth distribution and Tuberculosis rates across European Union member states demonstrated a strong correlation between income equality and lower Tuberculosis rates[21]. The association between economic deprivation and Tuberculosis is well established and widespread. Socio-economic inequalities have extended in Eastern Europe in particular[289].

The global Tuberculosis case-fatality rates are reported to be between 7% and 35% and risk factors for death may include non-infective comorbidities, human immunodeficiency virus (HIV) infection, multi-drug resistant Tuberculosis MDR-Tuberculosis, and malnutrition.[350] In addition, old age, alcohol consumption, intravenous drug, and unemployment are other risk factors.[351][352] The higher Tuberculosis mortality in Eastern Europe and Baltic countries have been associated with lower education level,[289][353] higher prevalence of HIV and MDR-Tuberculosis, and differences in relation of health care of HIV subjects such as deficiencies in drug

susceptibility testing and initial Tuberculosis treatment[354]. In addition, the prevalence of smoking habit is higher in the Eastern Europe and Baltic countries than the Western countries, but only for men and not for women. This may explain some gender differences in Tuberculosis morbidity and mortality in these countries. [355][356]

Since WHO defined Tuberculosis deaths as the number of Tuberculosis patients dying during treatment, irrespective of cause,[357] most studies have used all-cause mortality as a surrogate marker of mortality attributable to Tuberculosis. Nevertheless, knowing the actual underlying cause of death, especially whether it was Tuberculosis-related or not, is valuable in monitoring Tuberculosis control and may help in identifying effective interventions. Research evidence shows that, at least in England, use the underlying cause alone, for Tuberculosis, captures only about half of all deaths with Tuberculosis as a certified cause of death.[301] However, the quality of the European death certificate has been studied.[358] The Tuberculosis death certificate quality has been also validated.[326][327] Based on that, we supposed that in general, Tuberculosis as cause of death is well included in the official statistics.

Data on Tuberculosis as the underlying cause of death for European Union countries were retrieved from Eurostat (updated: October 2010). ICD-10 codes A15–19 and B90 were captured. For other countries data were obtained from the European mortality database (MDB) or alternatively from Centralized Information System for Infectious Diseases (CISID) (updated: August 2010), if MDB did not contain the necessary information. These data are coded and reported via national vital registration authorities, or National Tuberculosis Program Managers. In any event, we suppose, that use of underlying cause alone for Tuberculosis probably does not fundamentally undermine our findings.

During the late 1990s and early 2000s, nearly all European Union countries switched from using the 9<sup>th</sup> to using the 10<sup>th</sup> revision of ICD. Converting between the “old” and “new” versions of ICD is complicated by significant differences between the versions. Whilst the quality of the mortality data collection in European countries is generally high, coding of death certificates has some problems. Then comparisons between countries, and over time, may not be counting the same causes of death as different practitioners may assign the same cause of death to different codes. Impact of

switching between ICD9 and ICD10 existed in just three countries of the twenty-nine countries. Additionally, some of the apparent changes in trends may be due to artefact, but that is unlikely to affect the general conclusion that for both countries and sexes, Tuberculosis mortality rates are continuing to decline in European Union.

Our results are consistent with trends previously described in several countries, including the United States (US), China and Mexico.[359][360][361] In the US, overall, the number of Tuberculosis deaths reported annually has decreased by 67% since 1992. In China, from 2004 to 2010, the mortality rates due to all Tuberculosis and pulmonary Tuberculosis decreased by 36.02% and 37.70%, respectively. In Mexico, the age-standardised mortality rates per 100,000 inhabitants who died from Pulmonary Tuberculosis decreased from 4.1 to 2 between 2000 and 2009. About 75% of total Tuberculosis deaths occurred in the African and South-East Asia Regions in 2012 (both including and excluding Tuberculosis deaths among HIV-positive people). India and South Africa accounted for about 30% of global Tuberculosis deaths. Studying the trends in Tuberculosis as a cause of death in Africa is quite complex since Africa has a high incidence, prevalence and mortality of HIV. The Tuberculosis HIV co-infection therefore is high and the worldwide spread of HIV infection has undermined human defenses against *Mycobacterium tuberculosis*.

Reducing inequalities in health between socio-economic groups within a country is one of the greatest challenges for public health, even in the highly developed welfare states of Europe. Several European countries—such as England, Finland, and Lithuania—have adopted national targets for the reduction of socio-economic inequalities in mortality. In a context of declining mortality, where baseline levels of mortality are higher in lower socio-economic groups than in higher socio-economic groups, the only way to reduce inequalities in mortality is to achieve stronger reductions in lower socio-economic groups than in higher socio-economic groups.[289] Given the likely influence of an economic crisis on the functioning of healthcare systems and on factors that affect the epidemiology of Tuberculosis, it is expected that the current economic crisis will have an effect on the Tuberculosis situation in European Union countries. This will be especially true in countries that were already experiencing problems with Tuberculosis control before.[59]

Demographic changes in essence slow the progress of Tuberculosis control, a factor that should be built into considerations for funding and program strategies. The established links between alcohol, diabetes, tobacco smoking and Tuberculosis also mean that trends in these risk factors can modulate trends in Tuberculosis.[362] New strategies, better diagnostic tests, new drug regimes, and more broadly protective vaccines are all urgently needed.

The 2013 Report on Tuberculosis Research Funding Trends 2005–2012 shows that funding for Tuberculosis research and development dropped by \$30.4 million in 2012 compared with 2011. A study showed, that each European country needs its own tailored strategy for tackling health inequalities and no one country had the smallest inequalities in all determinants of health inequalities.[363] Tuberculosis mortality is influenced by other diseases, especially HIV, a specific and deep study must be done to explore a joint mortality rates of both diseases Tuberculosis and HIV. On another hand, modeling studies have shown that under specific circumstances MDR-Tuberculosis could reverse important gains made in combating Tuberculosis.[364] Future revisions of the burden of disease should examine more carefully the evidence on the levels and trends in MDR-Tuberculosis.

## 5.2 Human Immunodeficiency Virus Infection/Acquired Immunodeficiency Syndrome

Our data showed a slightly rise in HIV/AIDS age-standardised mortality rates in European Union, significant in women but not in men. The rise in HIV/AIDS Age-standardised mortality rates has some major outstanding characteristics.

Frist, the trends in HIV/AIDS age-standardised mortality rates in European Union do not consistent with the global trends. From 2000 to 2015, the global mortality peaked in 2005, at 1.8 million (95% UI 1.7–1.9 million) and subsequently fell by 5.5% (95% UI 5.0–5.9) per year to 1.2 million (1.1–1.3 million) in 2015.[365] However, the trends in HIV/AIDS mortality rates around the world are varied. According to the CDC report which studied the trends in HIV infection and AIDS in the United States during 1981–2008. HIV/AIDS diagnoses and deaths declined substantially from 1995 to 1998 and remained stable from 1999 to 2008 at an average of 38,279 AIDS diagnoses and 17,489 deaths per

year, respectively.[366] Models for the HIV epidemic for Latin America (LA) have shown a 21% increment in HIV annual mortality between 2001 and 2004 and a drop to 16% in the year 2008.[367] The decline between 2004 and 2008 has been associated with increased availability and access to ART throughout the Latin American region.[367] Yet, differences both among and within countries exist and treatment coverage continues to be suboptimal in many areas.[368][369][370] Increase access to ART has resulted in decrease mortality due to HIV/AIDS in the Latin America and the Caribbean region at least 50% between 2001 and 2010.[371] In China, the number of HIV/AIDS-related deaths increased from 5544 in 2007 to 21,234 in 2011.[372] Zheng H et al. showed in their study that the actual annual number of HIV/AIDS deaths after verifying cause of death from 2006 to 2010 was 7,013; 9,298; 11,921; 13,832; and 13,981, respectively, showing a relatively upward trend.[373] Especially, in 2008 and 2009, HIV/AIDS had become the leading cause of death from infectious disease in China [374], killing nearly 7000 people during the first nine months of that year. [375][373] A study from south India has reported a dramatic decrease in mortality from 25 to 5 deaths per 100 person years in HIV infected individuals between 1997 and 2003 after initiation of HAART.[376] However, a retrospective study from Andhra Pradesh in southern India reported more deaths in HAART era as compared to pre HAART era.[377] Overall, India's HIV epidemic is slowing down, with a 54% decline in AIDS-related deaths between 2007 and 2015.[378] HIV/AIDS mortality rates had increased in Iran from 1990 to 2010. The majority of individuals who died of HIV were between 15 to 49 years old. The estimated rank of HIV/AIDS burden compared with the burden of other leading disease was 152nd in 1990 and considerably increased to 37th in 2010.[379] In Southern Africa, there were a dramatically decreased HIV incidence and HIV mortality rates. In South Africa alone, it is estimated that more than 2.1 million of the 6.1 million HIV-positive people were receiving ART by the end of 2012, and that this resulted in more than 2.7 million life years saved, and hundreds of thousands of HIV infections averted.[380]

Second, Men have a higher average of HIV/AIDS Age-standardised mortality rates than women in all European Union countries during 2000-2014. The difference in mortality rates between men and women mostly imputed to biological differences beside another factors like the HIV/AIDS risk groups and epidemiological characteristics. The impact of biological difference between men and women on HIV infection and on

response of HAART is unclear. Despite reports to the contrary [381][382], recent findings of sex-based differences in circulating human immunodeficiency virus type 1 (HIV-1) RNA levels (virus load) and lymphocyte subsets have generated renewed interest in the effects of sex on the course of HIV infection.[383][384][385][386]

Anyways, we assume that the difference of the HIV/AIDS age-standardised mortality rates between men and women in European Union is most likely due to HIV/AIDS risk group. Men having sex with men (MSM) remain the group at highest risk of contracting HIV in most European Union countries [387], especially in Western Europe. Studies reveal considerable HIV incidence among MSM: around 3% per year in the UK, Amsterdam, and Valencia, and up to 12 per year in Rome. In Valencia and Rome, HIV incidence in MSM has been rising overall, but in Amsterdam, this trend can only be seen in MSM over 34 years old, and not in younger men. In many high-income settings—including Australia, France, the UK, and the USA—overall HIV epidemic trends are in decline except in MSM, where they have been expanding in the era of HAART in what have been described as re-emergent epidemics in MSM.[388][389] HIV prevalence among IDU varies greatly between, as well as within, countries, but mainly concentrated in Eastern Europe, in some countries has remained very high, over 25%.[390]

On the other hand, according to our results, a significant rise in HIV/AIDS age-standardised mortality rates in European Union during 2000-2014 was in women but not in men. A gender-based approach to HIV/AIDS involves examining how these biological and gender factors come together to increase a woman's risk of becoming infected. Women lack power and economic independence to negotiate safe sex and insist on condom use. Indeed, those who exchange sex for income can seldom mention safe sex at all. Women face domestic violence, at times made much worse by conflict or insecurity and most often bear the brunt of social stigma and discrimination.

There is no doubt that the number of infections among women is growing faster than in men.[391] In the early stages of the HIV/AIDS pandemic, infection was predominantly among men. This situation has changed dramatically. In 2002, 5 million people became infected with HIV with women representing 48% of all new infections.



More alarmingly, women are becoming infected at younger ages than men. In developing countries, an estimated 67% of all newly infected individuals are between 15 and 24 years old.[257]

Furthermore, HIV infected women and minorities are more likely to have a lower socioeconomic status [392], which may have a number of consequences affecting the access to health care, the effectiveness of HAART, including lower adherence to treatment [393] and different utilisation patterns of HARRT. [394]

Our results showed that in some Western Europe countries (Portugal, Spain, Italy and France), Estonia and Latvia had the higher HIV/AIDS age-standardised mortality rates in both genders among European Union, this could be justified if we took in account that Western Europe countries has the highest number of immigrants.[334] Immigrants include very diverse populations with different immigration drivers cultural, economic, social, environmental, and political as well as distinct risk contexts for HIV infection. According to a previous analysis in EU/EEA countries between 1999 and 2006 revealed the large contribution of people from high-endemic countries of Sub-Saharan Africa to reported HIV cases predominantly in Western Europe.[318] Despite the decline over the last decade, immigrants still constitute a considerable proportion (37%) of new HIV diagnoses in the EU/EEA in 2014, reaching more than half in some countries. There is growing evidence that a substantial proportion of immigrants, even those originating from HIV-endemic areas, acquire HIV after arrival in the EU/EEA, indicating the need for targeted interventions directed at this vulnerable population.[395][396][397][398]

In European Union/European Economic Area between 2007 and 2012, 60,446 out of 156,817 new cases of HIV (38%) were in people who were not native to the country where they were diagnosed. Nearly all HIV-positive immigrants are concentrated in the richer countries of Western Europe, with only 5% of diagnoses in central Europe and 1% in Eastern Europe being immigrants. Of these, 53% were from Sub-Saharan Africa, 12% from Latin America. Male and female migrants from Sub-Saharan Africa and Latin America had higher odds of late HIV presentation than native men and women. Migrants accounted for 40% of all HIV notifications in 2007 versus 35% in 2012. HIV

diagnoses in migrant men who have sex with men increased from 1927 in 2007 to 2459 in 2012. [399]

According to our results, Baltic countries (Estonia, Latvia and Lithuania) and Czech Republic had the highest significant rise in HIV/AIDS mortality rate. This rise is commonly attributed to increment in Injecting Drug Users (IDUs), socio-economic and health care (especially in HAART) inequalities.

IDUs is an important HIV infection risk group, as we mentioned before, HIV prevalence among IDUs is mainly concentrated in Eastern Europe.[390]

Inequalities continue to fuel the HIV infection in all societies regardless of their degree of development or prosperity, and HIV infection has increasingly been concentrated in the poorest, most marginalized sectors of society in all countries, people living in situations characterized by diverse forms of structural violence.[400] Low access to health-care, longer delays in the diagnosis of HIV/AIDS, insufficient quality treatment, and increase of homeless population, migrant groups and prison population are a HIV/AIDS associated factors.[346][401][402] In addition, unemployment and job insecurity appear to lead to behaviour that increases the risk for HIV infection and death [403], substance abuse and hazardous drinking, all of which could impair immunity. [404][405][406][407][408]

The multiple regression lineal model found that HIV/AIDS age-standardised mortality rates in European Union is higher in the countries with more unemployment and more inequalities.

The financial crisis affects directly the HIV infection prevention, detection and treatment. Since the onset of the recession, several EU countries and other countries have introduced user fees or budget cuts to infectious disease programs, including charges for prescription drugs, shifted approximately 50% of the costs of diagnostic testing to patients and reduced spending on disease control and surveillance.[409] The effects of the financial crisis will almost certainly linger beyond any economic recovery. Inevitably, therefore, concerns have been raised that control of infectious diseases could have been and will continue to be adversely affected by budgetary constraints as well as the social effects of recession.[410][411][412]

The burden of HIV infection in Baltic countries is the highest in Estonia in 2006 followed by Latvia and then Lithuania.[413] The use of illicit drugs has grown rapidly in Estonia in the past 15 years. The upward trend has been confirmed by the findings of the European School Survey Project on Alcohol and Other Drugs (ESPAD) 1995, 1999, 2003 and 2007 surveys.[414][415][416][417]

From 1987 to 2007, the main risk group was IDUs who account for 63% of all newly diagnosed HIV infections registered cases in Latvia. An open cohort study of Kaupe and Trapencieris in Latvia in 2014 among drug users shows that the prevalence of opioid use and injecting drug use in Latvia is among the highest in Europe, the majority of high-risk drug users are non-Latvian born males, the educational level amongst problem drug users is low and prevalence of HIV and HCV infection among people who inject drugs is high and rising, suggesting that the current response in Latvia is insufficient.[418] While absolute numbers of HIV cases among MSM in Latvia are low, as a share of new HIV cases, it is growing, and has increased since 2000 from around 1% to above 5% in 2006.[419]

In Lithuania in 1997, HIV entered the IDUs community.[420] In 2003, HIV was still predominantly transmitted through sharing contaminated needles while injecting drugs. However since 2003, the number of heterosexually transmitted HIV cases has been increasing.[421] In 2007, a total of 106 new HIV cases were identified and 44% of them reported heterosexual transmission. All in all, 77% of all HIV cases have been diagnosed among IDUs. According to social characteristics, 67% of all HIV infected individuals are former convicts, some of whom have served more than one term.[422]

A number of prior studies have documented the effectiveness of different HIV therapies in reducing mortality and the incidence of AIDS in different populations [302][303][304][305][306][307][308][309] as well as increasing the time after an AIDS diagnosis.[310][311]

Donoghoe MC et al. mentioned in their study that IDUs in Europe have poor and inequitable access to HAART, with only a relatively small improvement in access between 2002 and 2004. Regional and country comparisons reveal that inequities in IDUs access to HAART are worst in eastern European countries.[423] A WHO report for HIV/AIDS treatment and care in Estonia shows that among HIV/AIDS diagnosed people in 2013,

only about 1 in 4 are retained in care.[424] In 2007, only 5–12% of HIV-infected IDUs have reported currently receiving ART.[425] This means that the majority of those infected – the reservoir of further transmission – are still outside the treatment and care system, which explains the continued relatively high onward transmission. Furthermore, for those already diagnosed, it means that they start treatment very late, straining the hospital system, as they have already developed life-threatening AIDS related diseases.

On the other hand, in the developed countries, ample treatment options and accessibility have significantly improved overall survival and increased the life expectancy of HIV-positive individuals.[426] A number of studies have reported the dramatic decreases in mortality among individuals infected with HIV since the widespread introduction of HAART in developed countries.[427][428]

In the Czech Republic, sexual route of HIV transmission has long been the most frequent route. The homosexual/bisexual transmission clearly prevail and cumulatively accounts for 65.0 % of the diagnosed HIV cases, with additional 2.1 % of HIV cases in homosexual intravenous drug users. Up to 70 %-75 % of newly diagnosed HIV cases in the Czech Republic occur in men having sex with men over the last years. The population group with the highest HIV prevalence and the most rapidly increasing rates of new cases are men having sex with men who accounted for 210 (78.9 %) newly diagnosed HIV cases, with five of these cases occurring in intravenous drug users. In spite of the Czech Republic still remains a low prevalence country at both the global and European levels, the trend in HIV/AIDS in this country is unfavourable, and the proportional increase is among the most rapid in Europe. Alarmingly, new cases are continuously on the rise since 2002, particularly in men having sex with men.[429]

Countries need to live up their commitment to end the AIDS epidemic - as a public health threat by 2030 - a target included in the 2030 Agenda for Sustainable Development adopted by the United Nations General Assembly in September 2015. The immediate challenge is to reach the Fast-Track targets for 2020, as HIV-related deaths are still unacceptably high. by ensuring more accessibility to HAART and reducing inequalities in health between socio-economic groups within a country these objectives can be reached.

## 6 Conclusions

- 1) The trends in Tuberculosis mortality declined in Europe overall (not all countries) in both genders during the period of study (2000-2010), consenting with the Tuberculosis downward trends in many other countries globally.
- 2) Trends in Tuberculosis mortality declined slightly in women more than men during the period of study (2000-2010).
- 3) Eastern Europe Union countries have a higher Tuberculosis age-standardised mortality rates than other Europe Union countries during the period of study (2000-2010).
- 4) Tuberculosis age-standardised mortality rates are higher with more inequalities and lower economic resources.
- 5) The trends in Human Immunodeficiency Virus Infection/Acquired Immunodeficiency Syndrome mortality rose in Europe overall (not all countries) in both genders during the period of study (2000-2014); these trends are not consenting with the global downward trends.
- 6) Trends in Human Immunodeficiency Virus Infection/Acquired Immunodeficiency Syndrome mortality rose significantly more in women than men during the period of study (2000-2014). (Rise in men was not significant).
- 7) Western Europe Union countries has a higher Human Immunodeficiency Virus Infection/Acquired Immunodeficiency Syndrome age-standardised mortality rates than other Europe Union countries during the period of study (2000-2014) while these countries (Western Europe Union countries) had a decline in Human Immunodeficiency Virus Infection/Acquired Immunodeficiency Syndrome age-standardised mortality rates during the period of study (2000-2014).
- 8) Eastern Europe Union countries had a rise in Human Immunodeficiency Virus Infection/Acquired Immunodeficiency Syndrome age-standardised mortality rates during the period of study (2000-2014).
- 9) Human Immunodeficiency Virus Infection/Acquired Immunodeficiency Syndrome age-standardised mortality rates are higher with more inequalities and more unemployment.

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## 8 Appendixes

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## 8.3 Published article



## ORIGINAL ARTICLE

## Trends of mortality from Alzheimer's disease in the European Union, 1994–2013

H. Niu<sup>a</sup>, I. Alvarez-Alvarez<sup>a</sup>, F. Guillen-Grima<sup>a,b,c</sup>, M. J. Al-Rahamneh<sup>a</sup> and I. Aguinaga-Ontoso<sup>a</sup><sup>a</sup>Department of Health Sciences, Public University of Navarre, Pamplona, Navarre; <sup>b</sup>Navarre's Institute for Health Research (IDISNA), Pamplona, Navarre; and <sup>c</sup>Preventive Medicine, University of Navarre Clinic, Pamplona, Navarre, Spain**Keywords:**

Alzheimer's disease, European Union, joinpoint analysis, mortality, trends

Received 21 November 2016  
Accepted 23 March 2017*European Journal of Neurology* 2017, **24**: 858–866

doi:10.1111/ene.13302

**Background and purpose:** In many countries, Alzheimer's disease (AD) has gradually become a common disease in elderly populations. The aim of this study was to analyse trends of mortality caused by AD in the 28 member countries in the European Union (EU) over the last two decades.**Methods:** We extracted data for AD deaths for the period 1994–2013 in the EU from the Eurostat and World Health Organization database. Age-standardized mortality rates per 100 000 were computed. Joinpoint regression was used to analyse the trends and compute the annual percent change in the EU as a whole and by country. Analyses by gender and by European regions were conducted.**Results:** Mortality from AD has risen in the EU throughout the study period. Most of the countries showed upward trends, with the sharpest increases in Slovakia, Lithuania and Romania. We recorded statistically significant increases of 4.7% and 6.0% in mortality rates in men and women, respectively, in the whole EU. Several countries showed changing trends during the study period. According to the regional analysis, northern and eastern countries showed the steepest increases, whereas in the latter years mortality has declined in western countries.**Conclusions:** Our findings provide evidence that AD mortality has increased in the EU, especially in eastern and northern European countries and in the female population. Our results could be a reference for the development of primary prevention policies.**Introduction**

Alzheimer's disease (AD) is defined by the World Health Organization as a degenerative cerebral disease of unknown etiology, with characteristic neuropathological and neurochemical features [1].

With the progressive increase in life expectancy, AD has become an increasing public health issue. In 2013, the Global Burden of Disease Study found that AD was one of the top 50 global causes of years of life lost, which experienced a pronounced increase in the past few years [2], and it has been estimated that

the disease will be the seventh highest cause of death in high-income countries in the year 2030 [3].

Previous studies described increasing trends in mortality from AD in the USA, where the mortality rate rose from 45.3 per 100 000 in 1999 to 50.0 per 100 000 in 2008 [4], and in Canada, where the crude mortality rate for men and women increased from 10.1 to 11.5 per 100 000 and 24.4 to 25.4 per 100 000, respectively, between 2004 and 2011 [5].

However, to date, no studies have been conducted at a European level, using a consistent methodology, estimating significant changes in trends. Therefore, the aim of this study was to analyse trends of mortality caused by AD in the European Union (EU) in the period 1994–2013.

Correspondence: H. Niu, Department of Health Sciences, Public University of Navarre, Avenida Burzaiain s/n, 31005 Pamplona, Navarre, Spain (tel.: +34 622795847; fax: +34 948270902; e-mail: niu.74609@ie.unavarra.es).

## 8.4 Article in second revision

### TRENDS IN MORTALITY IN TUBERCULOSIS IN THE EUROPEAN UNION COUNTRIES, 2000–2010

Ref. EIMC-D-17-00004 (**REVISADO**) Revista de Enfermedades Infecciosas y Microbiología Clínica

Moad J. Al-Rahamneh *BSN MSc*<sup>1</sup>, Anas Al-Rahamneh *BCS MSc*<sup>2</sup>, Francisco Guillén-Grima *MD MBA MPH MSc PhD*<sup>1,3,4</sup>, Alberto Arnedo-Pena *MD MPH PhD*<sup>1</sup>, Inés Aguinaga-Ontoso *BA MD MPH PhD*<sup>1</sup>

Public University of Navarra, Department of Health Sciences. Avda. Barañain s/n. Pamplona, Navarra, 31008. Spain

Citius- Center for Research on Information Technologies. Santiago de Compostela, A Coruña, Spain

Clínica Universitaria de Navarra, Department of Preventive Medicine. Pamplona, Navarra, Spain

Servicio Navarro de Salud-Osasunbidea-IdiSNA, Navarra Institute for Health Research, 31002 Pamplona, Spain

Moad J. Al-Rahamneh [moad.rahamneh@gmail.com](mailto:moad.rahamneh@gmail.com). Anas Al-Rahamneh: [anas.abbadi@gmail.com](mailto:anas.abbadi@gmail.com). Francisco Guillén-Grima: [f.guillen.grima@unavarra.es](mailto:f.guillen.grima@unavarra.es). Alberto Arnedo-Pena (Corresponding Author): [albertoarnedopena@gmail.com](mailto:albertoarnedopena@gmail.com). Inés Aguinaga-Ontoso: [ines.aguinaga@unavarra.es](mailto:ines.aguinaga@unavarra.es)

#### ABSTRACT

**Background:** The objective of this study was to update and analyze Tuberculosis mortality data in European Union between 2000 and 2010 for men and women separately and try to detect if there have been changes in trends in each country and the association with economic situation and inequalities.

**Methods:** Data was extracted for Tuberculosis deaths during 2000-2010 for the twenty-nine countries of the European Union, and for Switzerland, from the World Health Organization (WHO) European detailed mortality database (DMDB), using the Mortality tabulation list 1 (MTL1) codes for men and women separately for one age group (20 – 85+). We estimated age-standardised mortality rates, and analyzed data using Joinpoint Regression programme for men and women separately in European Union overall and by individual country for each year.

**Results:** Between 2000-2010, there were 68,771 recorded Tuberculosis deaths in European Union and the mortality rates were higher in men than in women across the zone of study. Overall, the TB mortality rates declined linearly in both genders, but more so in women than men (from 5.43/100,000 in 2000 to 2.59/100,000 in 2010 in men and from 1.37/100,000 in 2000 to 0.51/100,000 in 2010 in women). There was decline in both genders for the whole period of study, by a significant Estimated Annual Percentage Change (EAPC) -8.1 for women and -7 for men when (Alpha < 0.05) and with 95% confidence interval (CI). A higher Tuberculosis mortality was associated with lower economic resources and more inequalities.

**Conclusions:** TB mortality rates in European Union decreased overall during 2000-2010 in both genders. Men have a higher TB mortality rates than women in all countries. Our findings were consistent with the downward TB mortality trend in many other countries globally.