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Analysis and individual-based modelling of the tuberculosis epidemiology in Barcelona. The role of age, gender and origin.

TREBALL FINAL DE GRAU D'ENGINYERIA DE SISTEMES BIOLÒGICS
BIOSYSTEMS ENGINEERING BACHELOR'S THESIS

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Abstract

Tuberculosis (TB) has existed for millennia and remains a major global health problem. The best estimate is that there were 1.8 million TB deaths and 10.4 million new TB cases in 2015. It is one of the top 10 causes of death worldwide, ranking above HIV/AIDS as one of the leading causes of death from an infectious disease. In particular, the Ciutat Vella neighbourhood in Barcelona has a tuberculosis incidence which is comparable to the incidence in countries like Sudan.

Data provided by the *Agència de Salut Pública de Barcelona* has been key to this project. It has enabled us to describe and analyse the tuberculosis transmission patterns in Ciutat Vella. We have characterized the strongest TB transmission channels between collectives (i.e. an immigrant male adult will be most likely infected by another immigrant male adult). The age, gender and origin of the TB sick population in Ciutat Vella have been observed to be relevant variables for the determination of transmission patterns.

These findings have allowed us to improve a previous Individual-based Model which is used to simulate the tuberculosis dynamics in Ciutat Vella. The model was implemented in NetLogo, a free and open source simulation tool that incorporates a helpful user-friendly interface. To improve the model, age, gender and origin (native/immigrant) have been introduced as new properties of the individuals. The tuberculosis infection and sickening process have now been simulated taking into account the analysed transmission patterns and sickening probabilities, which differ for each different individual profile. This has allowed to observe simulation results closer to reality.

Finally, the distributions of ages, gender and origin for the TB cases in Ciutat Vella have been compared to the ones obtained with the simulations. Similar distributions were observed with a reasonably satisfactory agreement in quantitative terms, but further work is required to increase the quality of such agreement.

As conclusions, we have seen that the distribution of ages, gender and origin amongst the TB sick population in Ciutat Vella is far from homogenous. The profile of the individuals has a significant effect on the way the disease is developed and transmitted. Depending on the profile, the risk of becoming infected and the risk of progressing to disease varies greatly and special attention must be brought to those collectives which are most susceptible. Immigrant male adults appear to be the hotspot for TB in Ciutat Vella, accounting for over 50% of the total cases and infecting almost 80% of the times individuals with the same profile. Knowing which are the most susceptible collectives and the transmission patterns will allow to apply optimized and more efficient TB control strategies.

Resum

La Tuberculosi (TB) està present al planeta des de fa milers d'anys i segueix sent un greu problema de salut global. El número estimat de morts per TB durant el 2015 va ser de 1.8 milions, i el nombre de nous casos va ser de 10.4 milions. És una de les principals 10 causes de mort per malaltia infecciosa mundialment, per sobre del nombre de morts causades pel virus del VIH. Concretament, al districte de Ciutat Vella a Barcelona s'hi observa una incidència de la tuberculosi comparable a la incidència de països com Sudan.

Les dades de l'Agència de Salut Pública de Barcelona han sigut claus per aquest projecte. Ens han permès descriure i analitzar els patrons de transmissió de la tuberculosis a Ciutat Vella. Hem caracteritzat els canals de transmissió més importants entre grups de gent (per exemple, un home adult i immigrant haurà estat infectat molt probablement per un altre home adult i immigrant). S'ha trobat que l'edat, el gènere i l'origen dels malalts de TB són variables molt rellevants a l'hora de determinar els patrons de transmissió.

Aquests descobriments ens han permès millorar un Model basat en l'Individu, que s'ha utilitzat per simular la dinàmica de la tuberculosi a Ciutat Vella. El model ha estat implementat a NetLogo, una plataforma d'accés i codi lliure que incorpora una interfície d'ús versàtil. Per a millorar el model, característiques com l'edat, el gènere i l'origen (autòctons/immigrants) dels individus s'han inclòs com a propietats en les simulacions. El procés d'infectar-se i d'emmalaltir a causa de la tuberculosi s'ha simulat tenint en compte els patrons de transmissió i el risc d'emmalaltir analitzats, característiques que dependran del perfil dels individus. Això ha permès observar resultats més similars a la realitat.

Finalment, les distribucions d'edat, gènere i origen dels malalts de tuberculosi a Ciutat Vella s'han comparat amb les distribucions obtingudes a partir de les simulacions. Distribucions similars a nivell qualitatiu han sigut observades, però és necessari seguir-hi treballant per incrementar la qualitat de les simulacions a nivell quantitatiu.

S'ha conclòs que les distribucions d'edats, gènere i origen entre els malalts de tuberculosi a Ciutat Vella són molt heterogènies. El perfil dels individus alterarà significativament la manera en la que la malaltia es desenvolupa i es transmet. Segons el perfil de la persona, el risc que tingui tant d'infectar-se com d'emmalaltir variarà molt i s'ha de prestar especial atenció als col·lectius més susceptibles. Els homes adults i immigrants són el col·lectiu més nombrós entre els malalts de tuberculosi a Ciutat Vella i representen més del 50% dels casos totals. A més, segons els nostres resultats, els homes adults i immigrants infectaran un 80% de les vegades a un altre individu del mateix perfil. Si es coneixen els grups de gent més susceptibles a tenir la malaltia i es coneixen els patrons de transmissió, es podran aplicar estratègies de control de TB més eficaces i eficients.

Resumen

La tuberculosis (TB) está presente en el planeta desde hace miles de años y sigue siendo un grave problema de salud global. El número estimado de muertes por TB durante el 2015 fue de 1.8 millones y el número de nuevos cases fue de 10.4 millones. Es una de las principales 10 causas de muerte por enfermedad infecciosa mundialmente por encima del número de muertes causadas por el VIH. Concretamente en el distrito de Ciutat Vella en Barcelona se observa una incidencia de la tuberculosis comparable a la incidencia de países como Sudan.

Los datos proporcionados por l'Agència de Salut Pública de Barcelona han sido claves para este proyecto. Nos han permitido describir y analizar los patrones de transmisión de la tuberculosis en Ciutat Vella. Hemos caracterizado los canales de transmisión más importantes entre distintos grupos de personas (por ejemplo, un hombre adulto e inmigrante habrá sido infectado muy probablemente por otro hombre adulto e inmigrante). Se ha observado que la edad, el género y el origen de los enfermos de TB son variables muy relevantes a la hora de determinar los patrones de transmisión.

Estos hallazgos nos han permitido mejorar un Modelo basado en el Individuo. La utilidad de dicho modelo ha sido simular la dinámica de la tuberculosis en Ciutat Vella. El modelo ha estado implementado en NetLogo, una plataforma de acceso y código libre que además incorpora una interface de uso versátil. Para mejorar el modelo, características como la edad, el género y el origen (autóctonos/inmigrantes) de los individuos se han incorporado como propiedades en las simulaciones. El proceso de infectarse y enfermar debido a la tuberculosis se ha simulado tomando en consideración los patrones de transmisión y el riesgo de enfermar analizados anteriormente, los cuales dependen del perfil de los individuos. Este cambio ha permitido observar resultados más similares a la realidad.

Finalmente, las distribuciones de edad, género y origen de los enfermos de tuberculosis en Ciutat Vella se han comparado con las distribuciones obtenidas a partir de simulaciones. Distribuciones similares a nivel cualitativo han sido observadas, pero es necesario continuar con el trabajo hecho para aumentar la calidad de las simulaciones a nivel cuantitativo.

Se ha concluido que las distribuciones de edad, género y origen entre los enfermos de tuberculosis en Ciutat Vella son muy heterogenias. El perfil de los individuos alterará significativamente la manera en la que la enfermedad se desarrolla y se transmite. Según el perfil de la persona, el riesgo tanto de infectarse como de enfermar variará mucho y se deberá prestar especial atención a aquellos colectivos más susceptibles. Los hombres adultos e inmigrantes son el perfil más común entre los enfermos de tuberculosis en Ciutat Vella y representan más del 50% del total de casos. Además, según nuestros resultados, los hombres adultos e inmigrantes infectaran un 80% de las veces a otro individuo con el mismo perfil. El conocer los colectivos más susceptibles a tener esta enfermedad y se conocen también los patrones de transmisión, se podrán aplicar estrategias de control de TB más eficaces y más eficientes.

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LIST OF SYMBOLS AND ACRONYMS

TB: Tuberculosis
LTBI: Latent tuberculosis infection
HIV: Human Immunodeficiency Virus
AIDS: Acquired Immune Deficiency Syndrome
WHO: World Health Organization
FDA: Food and Drug Administration
INH: Isoniazid
RIF: Rifampicin
EMB: Ethambutol
PZA: Pyrazinamide
MDR: Multiple-drug resistant
XDR: Extremely-drug resistant
IBM: Individual-based Model
GII: Gender Inequality Index
HDI: Human Development Index
ASPB: Agència de Salut Pública de Barcelona
ODD: Overview Design Details protocol
MDD: Mean diagnosis delay
λ: Specific infection-rate
ϒ: Recovery-rate

The sick child, by Edvard Munch (1885)

A moment before the death of Munch's older sister Johanne Sophie (1862–1877), who died at the age of 14 from tuberculosis, also known as the White Plague.

1. INTRODUCTION

Tuberculosis (TB) is an infectious disease that has co-evolved with humanity since ancient times. The first evidence of tuberculosis was found in Egyptian skeletons which dated 3500 B.C. (Chalke, 1962), and although it might come as a surprise to many, it still remains a major global health problem. The Global Tuberculosis Report 2016 from the World Health Organization (WHO) estimates that one third of the population is infected by the pathogen; from those, a 10% will develop a TB active disease the next years. It estimates that 10.4 million new TB cases were developed during 2015, and 1.8 million died from the disease during that year. The incidence of the disease is distributed worldwide as shown in Figure 1.1. (WHO, 2016)

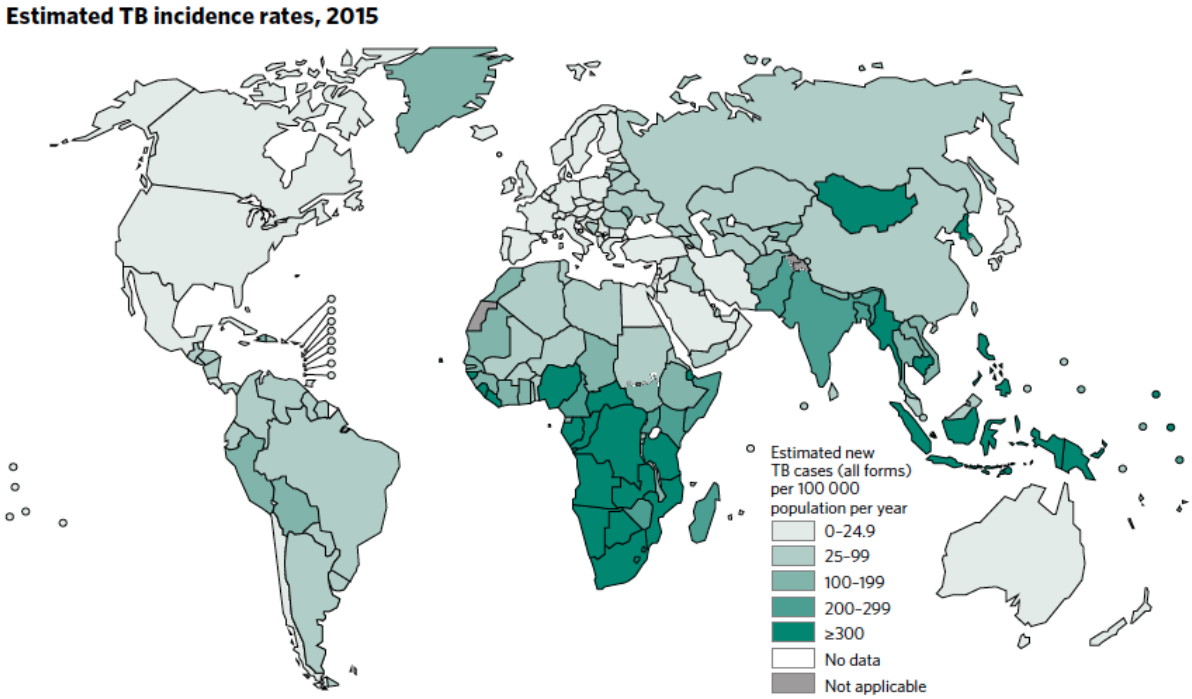

Figure 1.1: Map of the tuberculosis incidence worldwide in 2015, data corresponding to the *Global Tuberculosis Report 2016* (WHO, 2016)

1.1 THE TUBERCULOSIS DISEASE

Tuberculosis is caused by the bacillus *Mycobacterium tuberculosis* and it typically affects the lungs; 85% of the cases are pulmonary. The disease is spread when people who are sick with pulmonary TB expel bacteria into the air through airborne droplets, for example by coughing or sneezing. If a susceptible individual inhales these droplets, bacteria may reach the alveoli in the lungs. Once in the alveoli, bacteria are absorbed by macrophages through phagocytosis, and they start growing and dividing inside them. This is the starting point of the tuberculosis infection. Depending on the immune reaction of the individual, this initial infection will remain controlled or it will evolve towards an active disease, when the person will sicken.

Therefore, two stages of the disease can be differentiated; the latent stage (latent tuberculosis infection or LTBI) and the active stage (active tuberculosis). During the latent stage bacteria are present in the lungs but the bacterial load remains controlled and the individual does not experiment any symptoms; therefore, the individual does not infect others, it is the silent stage. During the active stage the sick individual will infect other people and will suffer from symptoms such as cough with blood, fever, weight loss, weakness... Overall, a relatively small proportion (5–15%) of the estimated 2–3 billion people infected with *M. tuberculosis* will develop TB disease during their lifetime (WHO, 2016). The state of the lungs throughout the active stage of the disease can be observed in Figure 1.2.

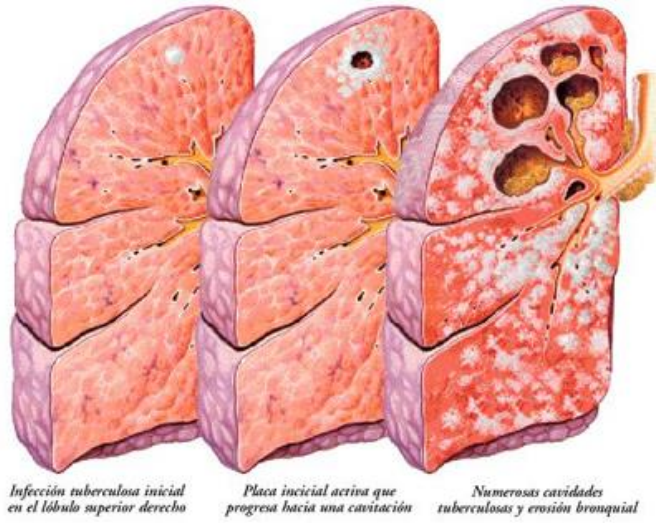

Figure 1.2. Progression of the cavities formed in the right lung by *M. tuberculosis* throughout an active tuberculosis disease.

Diagnosis & treatment

Latent tuberculosis can be rapidly diagnosed with a tuberculin skin test (Mantoux test). In case someone has been exposed to the TB bacillus, a skin reaction to the antigens will appear in less than 2 days after the test (see Figure 1.3). It is a bit more expensive to diagnose active TB, since it is necessary to carry out a chest X-ray (Figure 1.4) or a microscopic examination of sputum. A cultivation of a clinical sample allows to identify antibiotic resistant TB strains. It is of great importance to test the sensitivity to drugs to identify drug resistant strains before starting the treatment to be able to plan the optimal treatment in each situation (Nahid *et al.*, 2016).

Standard tuberculosis treatment usually lasts for about 6 to 9 months and consists of a combination of 4 antibiotics. Currently there are 10 drugs approved by the FDA, but the first-line anti-TB agents that form the core of treatment are: isoniazid (INH), rifampicin (RIF), ethambutol (EMB) and pyrazinamide (PZA). Nevertheless, when resistant strains appear the standard treatment has to be adjusted (Nahid *et al.*, 2016). Unfortunately, the 6-month period under treatment is difficult to commit to for some, therefore there are cases of treatment abandonment. The treatment must always go hand in hand with a health worker who supervises and makes sure the patient completes the treatment.

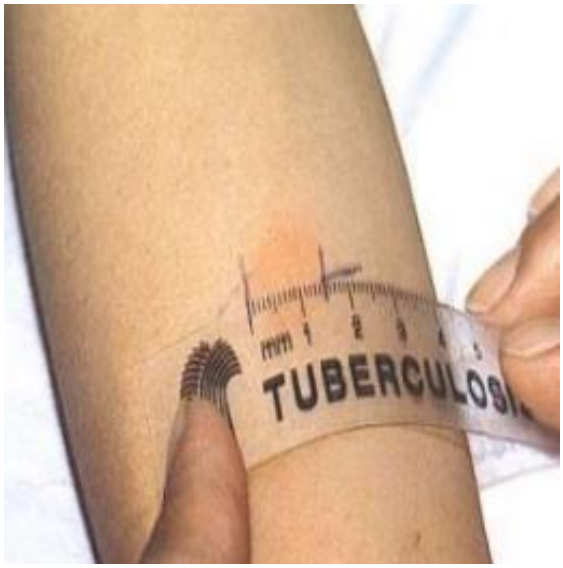

Figure 1.3. Skin reaction to the TB antigens during the Mantoux test

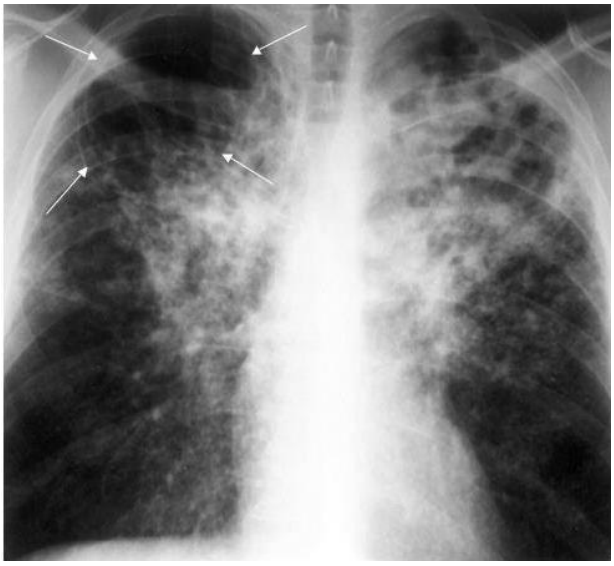

Figure 1.4. Chest X-ray with a large cavity in the right upper lobe of the lung

Even though tuberculosis has always had a very successful strategy of surviving by means of remaining hidden and acting slowly, some new challenges are arising nowadays. The following risk factors have been identified as crucial from the epidemiological point of view since they increase the difficulty when trying to control and eradicate the disease.

People with depressed immune systems have a much higher chance of sickening from TB, once infected. Back in 1959 the first case of HIV in a human was detected from a man in Kinshasa, Congo (Faria et al., 2014). During this past 50 years HIV has turned into a global pandemic of transcendent importance, peaking in 2005 when it killed 2.2 million people worldwide. The appearance of an HIV-TB co-infection has complicated the control strategy for tuberculosis. People living with HIV accounted for 11% of all new TB cases and 22% of the TB-deaths in 2015 (WHO, 2016). Other immunodeficiency disorders like malnutrition, diabetes, tobacco and alcohol consumption are also a risk factor for the development of an active TB.

Another challenge that has recently risen is the appearance of drug resistant tuberculosis strains. The extensive use of antibiotics and the occasional treatment abandonment fact has brought the world to a point where multidrug-resistant TB strains (MDR-TB) and extremely drug-resistant TB strains (XDR-TB) are becoming an alarming concern. In 2015, there were an estimated 580 000 new cases of MDR-TB, which represent a 6% of the total new cases. The treatment then becomes longer, more expensive and more difficult (WHO, 2016).

When assessing epidemiological risk factors, it is also worth noting that approximately 22% (Prats et al., 2016) of the sick tuberculosis patients are smear-positive. Some of the smear-positive cases develop cavities in their lungs which increases the spreading rate.
The risk factors described above are only a few of the several characteristics of the disease that are prolonging the fight against it.

1.2 TUBERCULOSIS IN BARCELONA

As it has been mentioned, tuberculosis is transmitted through air. Therefore, a higher incidence in urban areas is expected, since people live more crowded. The city of Barcelona is not an exception. Barcelona hosts approximately 16% of immigrant population which is mostly confined in the district of Ciutat Vella, where the immigrants represent up to 43% of the total people in the district. A significant group of the immigrants in Ciutat Vella come from countries stricken by high TB incidences such as Pakistan, the Philippines or Bangladesh (Ajuntament de Barcelona, 2017). Hence, it is not surprising to find out that the city of Barcelona registered over 300 new TB cases in 2014 (incidence of 18.6/100000 population). Figure 1.5 shows the evolution of the incidence of TB in Barcelona from the 90's until now, with an observable decreasing tendency. This city is an interesting case of study when looking at the incidence disaggregated by districts. From its 10 districts, in 2014, Ciutat Vella was the one with the highest incidence rate (60.5/100000 population) and Eixample was the one with the lowest (9.6/100000 population). The incidence rates for each district range in a spectrum with vast differences from end to end. The social inequalities within the districts of the city correspond to the inequalities observed in the TB incidence rates. There is a health gradient that corresponds with the social ladder (Marmot, 2015). The particular characteristics of the Ciutat Vella district is what brought us to centre the following study around it. Also, the high incidences given in this district enabled us to work with a larger data set.

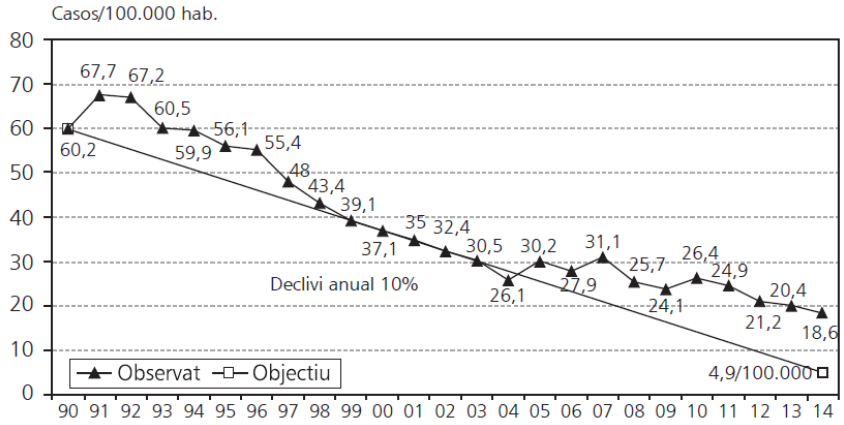

Figure 1.5: Evolution of the TB incidence (new cases/100.000 habitants) in Barcelona. Straight line shows the targeted TB incidence (ASPB, 2014)

All the data used in this bachelor's thesis has been collected by the *Agència de Salut Pública de Barcelona*, which has been putting together extensive information on the main characteristics of TB for the past 30 years. The key tasks of the programme developed are the surveillance of the active cases and their treatment as well as a study on their contacts. In contrast to other Spanish cities that are not carrying out TB prevention and control programmes, Barcelona is now more capable to face new challenges regarding TB.

1.3 MODELS IN EPIDEMIOLOGY

The ultimate goal when assessing an infectious disease is to control and eradicate the disease. To do that, control strategies have to be applied, and the better the disease is understood, the more accurate those control strategies will be, hence more efficient. To better understand the dynamics of a disease, its transmission rates, its distribution amongst a population, its risk factors… epidemiology models are used.

Epidemiology is the study of the factors responsible for the spread of the diseases. To fully understand the mechanisms of transmission of the infectious agents, tools need to be developed and used. Models are a simplification of reality, a conceptual representation of a complex system. Models allow people to understand a complex phenomenon by spotting the main aspects of a problem and ignoring the secondary. Models are a very powerful tool to better understand epidemiology.

Two strategies can be used when modelling a system: The Top-Down and the Bottom-Up approach. As an example, let us say the flow of a tide has to be simulated; a Top-Down approach would start by understanding the movement of a wave, it would then formulate a differential equation able to predict the position of each water molecule at each time. Instead, a Bottom-Up approach would assign each water molecule a trajectory to then observe the general pattern, the wave.

Therefore, the Top-Down approach is based on applying a general qualitative theory to the specific, in order to generate quantitative conclusions. Mathematicians inclined themselves to use this strategy and they developed several models that have been extensively used, such as the compartmental models based on differential equations (SIR, SEIRS, SIS...). S for susceptible, E for exposed, I for infected and R for recovered are the different categories population moves through, depending on differential equations with a specific infection-rate (λ) and a recovery-rate (ϒ) that determine the flow of individuals between categories (Rock *et al*., 2014). Figure 1.6 shows the evolution of the disease when approached with different continuous models such as the ones mentioned now.

On the other hand, the Bottom-Up approach has been gaining importance recently. This strategy consists on modelling the low-level interactions, the behaviour of the elements to observe the dynamics of the global system. The Bottom-Up approach allows to include heterogeneity in the elements, obtaining more realistic results (Diekmann and Heesterbeek, 2000). Examples of such strategy are the individual-based models (IBM).

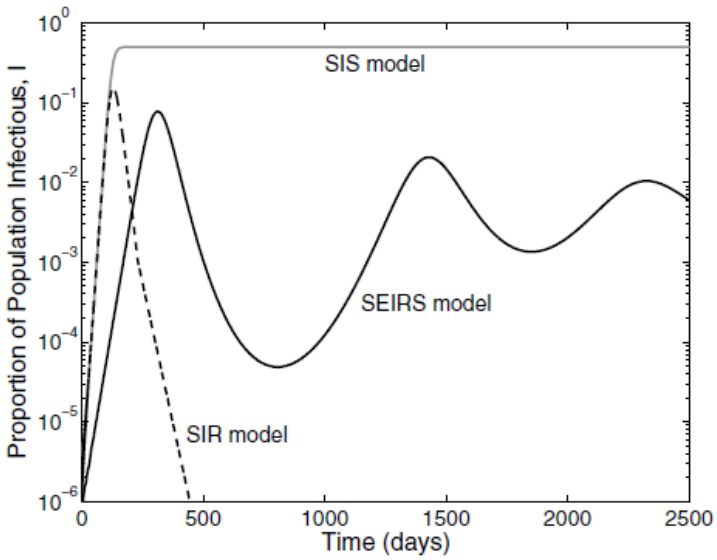

Figure 1.6. Comparison of the basic infectious models. The three curves show the proportion of infectious individuals in the population for the standard SIS, SIR and SEIRS model (Rock *et al.,* 2014).

1.3.1 Individual-based Models

The traditional mathematical models discussed above all use a differential calculus approach and are therefore limited to face big populations where heterogeneity is not relevant. With the increase of powerful computing machines, the computational limiting barrier disappeared giving rise to the IBMs. IBMs have been defined by Grimm *et al.* (2012) as simulation models that describe autonomous individual organisms, which are discrete entities that interact with each other and with their environment locally. It is clear that these models are more complex than the traditional ones, since they have to represent every individual component of the system separately, instead of describing the whole system with only a few global mean variables. Nevertheless, the drawback of requiring more powerful computation is balanced by the advantages an IBM presents.

IBMs allow to assign each individual different characteristics. Each entity may have a specific size, location, gender or age, among others. Each individual will act independently and will pursue their set objectives regardless of the others. They will interact with the environment that surrounds them and with the other individuals near them. IBMs allow the modellers to simulate the evolution of a heterogeneous population. It enables us to observe a system's dynamics emerge from the interaction of the individual components. Hence, with IBMs, modellers can study questions of how a system's behaviour arises from, and is linked to the characteristics and behaviours of its individual components (Railsback and Grimm, 2012).

Tuberculosis is a social disease, its incidence is very different for male and female, for children and for the elders, for Japanese and Indians (WHO, 2016). It is even significantly different for people living in the same city, as it has been shown above for the ones living in Ciutat Vella and for the ones living in Eixample, both districts in Barcelona.

The population with tuberculosis is extremely heterogeneous. If a model has to be used to simulate the evolution of the tuberculosis disease in Barcelona, it seems like an IBM would be a wise election.

1.3.2 An Individual-based Model of TB calibrated for Ciutat Vella, Barcelona

An IBM which simulates the evolution of tuberculosis in Barcelona was developed by Prats *et al*. (2016). The simulator was developed in the NetLogo platform, an Individual-based programming language with an integrated modelling environment that includes a user-friendly interface for simulations. NetLogo is an open access platform with also an open source, so it is possible to add and include new parameters to enhance the performance of the simulations (Tisue and Wilensky, 2004).

This particular model simulates the evolution of a population confined in a geographical space of variable size. The individuals in the model change states as shown in Figure 1.7.

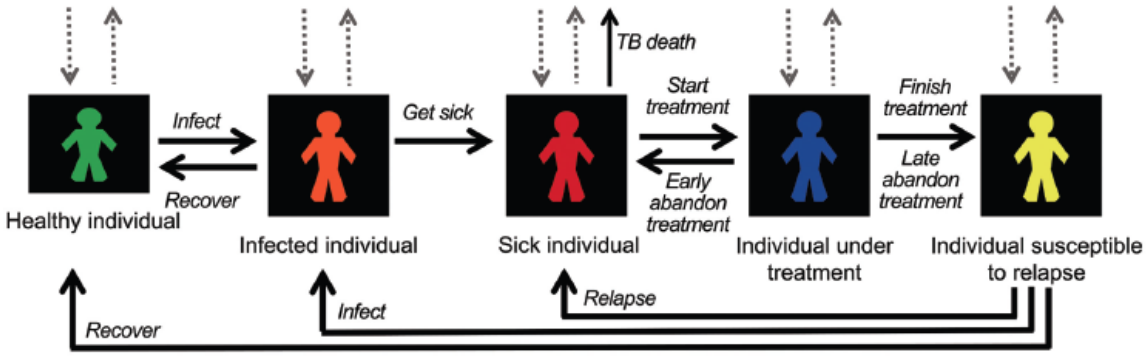

Figure 1.7: State diagram of the model, where the five states of individuals and possible transitions are shown. Output grey dotted arrows refer to deaths (Prats *et al.,* 2016).

As it can be seen, the discrete entities in this model are born, grow old, move and in case of encountering someone infectious, they might become infected. Once infected, they might sicken or recover, and once sick they start treatment and might finish it or abandon it. The model was calibrated and parameterized for the district of Ciutat Vella in Barcelona, but the core code of it could be recalibrated to be used in any other place, since the disease would have the same dynamics.

The individuals in this IBM differ by their location and their "disease state"; nevertheless, they are not heterogeneous for other factors such as gender or age. The following study will intend to determine if further characteristics should be included to the individuals in the model. An assessment on the social factors of tuberculosis in Ciutat Vella will be carried out to resolve the need for more accuracy in the simulator exposed above.

1.4 SOCIAL DETERMINANTS OF TB

Why is it important to study the social determinants of a disease? Wouldn't it be more useful to invest in better technology and medicine? What is it that keeps us from eradicating tuberculosis worldwide, the lack of an efficient treatment or the lack of access to treatment? Social determinants are of fundamental importance, as it is shown by a study carried out in England and Wales that noted the tuberculosis mortality over the years (Gérvas and Pérez Fernández, 2013). The study showed a significant decrease of over a quarter of the cases from 1861 to 1947 by which time there were no antibiotics or vaccines. It was back in 1948 that streptomycin went out to the market, and surprisingly enough the number of TB-deaths did not decrease as significantly as it had the years before that. Moreover, similar studies with the same results were carried out in Finland and Sweden. It seems that the key element to fight an infectious disease was the improvement of the social lifestyle. An increase in food safety, less overcrowding, better hygiene, education and work conditions, smaller households and a better wealth distribution is what determined the spread of the infectious disease. It appears that the incidence of tuberculosis depends on many more factors than simply the health care system.

If the incidence of tuberculosis depends greatly on the social lifestyle, the characteristics of the disease will vary a great deal depending on the group of people. People in different countries, of different ages, different genders, different cultures or habits will have completely different risk factors, distribution of diseases, health care, treatment availability…

1.5 THE ROLE OF AGE, GENDER AND ORIGIN

As it was being discussed above, more factors have to be taken into account when simulating the evolution of TB besides the treatment. Let us start by assessing the role of the age, gender and origin and how their distribution in the district of Ciutat Vella might affect the incidence of TB.

1.5.1 The role of origin in Barcelona

The country of origin will clearly determine the risk of infection of tuberculosis. The natural resources, the distribution of wealth, the weather, the public health systems differ depending on the geographical areas. In theory, all habitants of Barcelona have the same access to public health services, the streets are equally cleaned, there is public education, there is drinkable water and edible food available… Why should there be a different TB distribution amongst people coming from different countries then?

As it has been mentioned, the neighbourhood of Ciutat Vella is the one with the highest percentage of immigrant population (43%) in Barcelona. In Ciutat Vella, 57% of the people are Spanish, 4% are from Africa (mostly Morocco), 7% are from America (mostly Brazil and Argentina), 17% are from Asia (mostly Pakistan and Philippines) and the remaining 15% corresponds to non-Spanish Europeans as it can be observed in Figure 1.8 (Ajuntament de Barcelona, 2017).

It was at the beginning of the 21st century that international immigration arrived at Barcelona, bringing in a large number of people from countries highly burdened by the tuberculosis disease. Hence, most of the people coming from Pakistan for example, (current TB incidence of 270 /100000 population) (WHO, 2016) arrived less than 17 years ago. Most of them were born and lived in their country for a while, so that coming to Barcelona already with a higher chance of a latent TB infection. In addition, immigrants suffer from social exclusion; difficulties to obtain a work and a residence permit leads to an even more complicated situation, in which they are more likely to live in crowded houses, to not have the same access to health care and to be employed in jobs with higher risk factors (Sarasa Urdiola, Sales i Campos and Plana i Arrasa, 2004).

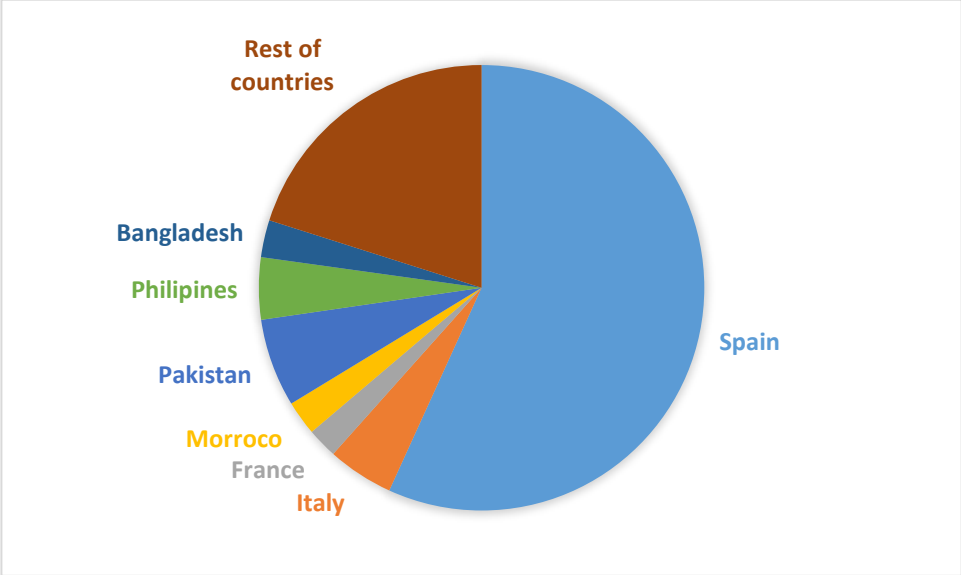

Figure 1.8. Distribution of nationalities amongst the population in Ciutat Vella (Ajuntament de Barcelona, 2017)

1.5.2 The role of gender bias in TB

In 2015, there were an estimated 10.4 million new tuberculosis cases worldwide: 5.9 million among men, 3.5 million among women and 1.0 million among children. (WHO, 2016). The male:female ratio stands at around 1.7:1. There is a strong difference between the male and the female TB incidence and many have wondered what the possible reasons are. Nhamoyebonde and Leslie (2014) argue there are two different hypotheses, the behavioural and the physiological, that could explain this gender bias.

The behavioural hypothesis

The behavioural hypothesis considers the gender bias to be due to different social conducts between the male and the female population. Women still suffer from large societal inequities such as insufficient access to income, legal rights, social status and education, which could have an impact on the data results of tuberculosis cases. In some cultures, those differences might be less significant, but gender inequalities are still

present worldwide. Although it is very obvious in some cultures, it might be surprising to realise that behavioural patterns between genders differ in every single country.

The United Nations Development Programme has made an assessment on the gender inequalities worldwide. The Gender Inequality Index (GII) is a parameter calculated according to the dimensions of health, empowerment and labour market. The GII ranges between 0, where women and men fare equally, and 1, where one gender fares as poorly as possible in all measured dimensions. A map of the of the GII index 2014 worldwide is shown in Figure 1.9. Overall, the world's GII stands at 0.45 (United Nations Development Programme, 2016).

Different genders have different roles in society. The extent to which men relate to other men, women to the elderly or to children, the extent to which each gender has increased risk factors such as smoking and drinking will vary for each culture. Because of the immigration, Ciutat Vella has a very diverse population and many different cultures, hence we expect to observe different patterns for the native population and for the immigrant as well as for the female and male population.

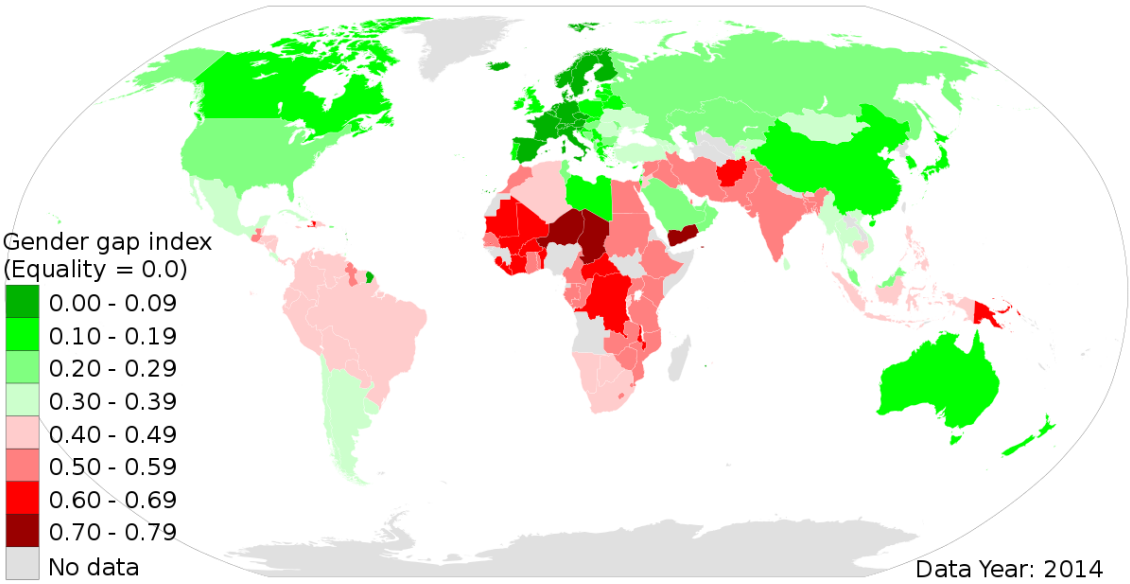

Figure 1.9: Gender Inequality Index 2014 (United Nations Development Programme, 2016)

The physiological hypothesis

Physiological differences between the female body and the male body have also been looked at as a cause of the TB gender bias. Neyrolles *et al*., (2009) made an assessment on how sex hormones modulate the immune response to *Mycobacterium tuberculosis*. Simple experiments in castrated animals were carried out. It was observed that when male mice where castrated and deprived from testosterone, the number of T-lymphocyte cells increased and also the proliferation of cells following antigen recognition. Experiments reveal that estradiol enhances macrophage activation while testosterone inhibits it.

Another hypothesis considered by Neyrolles, although it requires further research, explains that the male bias in TB includes X-linked genetics that code for TB susceptibility. As a result, males are at the mercy of the X-chromosome inherited and females express the beneficial X-linked polymorphism.

Features of nutrition and metabolism could also be associated with susceptibility to *M. tuberculosis*. Evidence has suggested that iron is critical for *Mycobacterium tuberculosis* growth in macrophages. Since iron deficiency is common amongst women in countries with a high Human Development Index (HDI) it may be correlated with greater resistance to TB (Neyrolles *et al.,* 2009). Data collected by the *Agència Pública de Salut de Barcelona* shows greater bias on TB incidences during the years women menstruate (years in which iron-deficiency gains importance amongst women), therefore supporting the explanation above.

The importance and magnitude of each cause for the gender bias can only be hypothesised, since it is a synergy of all the causes that produces this outcome. The distribution of TB amongst male and female differs indeed; to conduct an accurate study TB models in Ciutat Vella will need to take into account the origin and gender of the habitants.

1.5.3 The role of age bias in TB

The distribution of ages in Ciutat Vella is remarkably different for the native and the immigrant population as it can be seen in the Figure 1.10. Since the immigrant population accounts for almost half of the total population, it is worth noting the differences. The highest incidences in this district are consistently found in the age group 25-35, clearly due to the age distribution of the immigrants that currently account for 75% of the total TB cases in Ciutat Vella (ASPB, 2014).

It is not a surprise that the distribution of ages of the population infers in the distribution of ages of the TB sick patients, as it will be shown in Chapter 2, but there are other factors that need to be looked into. People at different ages behave differently, and their bodies also work differently. How does this affect the distribution of TB in Ciutat Vella? Which are the important age factors?

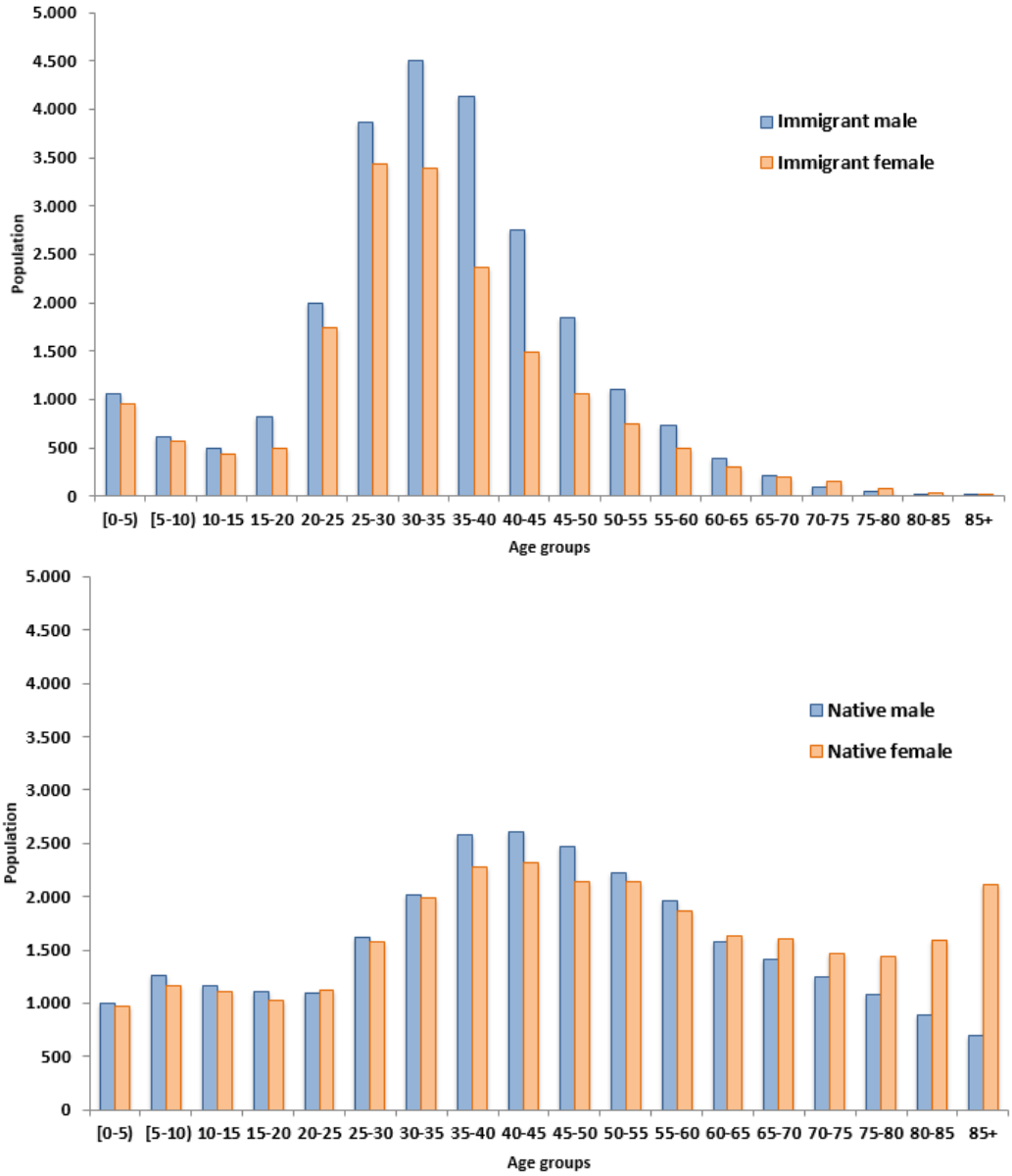

Figure 1.10: Age distribution in Ciutat Vella in 2015 for immigrants (top) and native (bottom) population (Ajuntament de Barcelona, 2017).

Tuberculosis among children

It appears that much of the morbidity and mortality of TB occurs during childhood and it is a major contributor to the future reservoir of cases. One would reasonably think that a child's weak immune system is the cause of that. It appears that the risk of progression from a TB infection to disease depends greatly on the age of the child. Most of the children under 10 who progress to disease do so within 12 months of primary infection, and are therefore a high-risk group (Cruz and Starke, 2010). Because of the rapidity with which disease progression occurs in this group it is essential to work on preventing exposure and infection. An assessment on the progression risk stratified by children's ages is shown in Table 1.1. It can be observed that new-borns have a 15-fold greater risk of progressing to disease than children between 5-10 years.

On the other hand, as described by Cruz and Starke (2010), infants (0 to 5) are easier to diagnose than children (5 to 10) since they are more likely to be symptomatic for pulmonary TB. Fever, decreased breath sounds, wheezing and rales are commonly observed in toddlers and not so easily in grown children. Usually, any child suspected of having the disease is started on TB therapy.

Table 1.1 Risk of progression from TB infection to disease
Adapted from Marais *et al*., 2006.

Age at primary infection (years)	Risk to progress to pulmonary TB	Risk to progress to extrapulmonary TB
< 1	30 - 40 %	10 - 20 %
1-2	10 - 20 %	2,50%
2-5	5%	0,50%
5-10	2%	< 0,5 %

Tuberculosis among older adults

The demographic global curves are shifting, as it is well known; the world is facing an ageing global population. Since tuberculosis amongst older people is notoriously challenging we can see how this can turn into a situation that needs to be addressed.

The proportion of tuberculosis deaths among people aged 50+ is the highest in high-income countries, representing 93% of total TB deaths in Western Europe (Institute for Health Metrics and Evaluation, 2017). Despite increased attention on vulnerable groups, there has been on-going neglect of older adults. It has been argued that co-infection of TB-HIV has diverted attention from TB in older adults, who are less able to access health care than younger people.

Undetected cases among older people are very common. It appears the major component of the immune system affected by ageing is the T-cell mediated response. Results of the tuberculin test, which relies on a dermal reactivity to activated T-cells, are often misleading (Rajagopalan, 2001). In addition, older people are often unable to produce a high-quality sputum sample, which complicates the process of diagnosing a smear-positive tuberculosis case (Negin *et al.,* 2014).

Older population is more likely to develop atypical forms of tuberculosis, which are harder to diagnose than the common pulmonary tuberculosis. Older patients may not show the classical symptoms of tuberculosis such as cough, weight loss or fever. Therefore, non-specific symptoms that persist for a long period of time have to be noticed by doctors and assessed as possible un-recognized tuberculosis.

On top of the already mentioned decline in T-cell response, which increases the risk of infection by *M. tuberculosis*, other risks are present amongst the elderly population. There are many age-associated diseases, which include poor nutrition, immunosuppression, renal failure, diabetes and also co-morbidity and a higher rate of poverty than younger adults especially in countries with a low HDI (Rajagopalan, 2001).

Another problem arising is the increased propagation of the bacteria in institutions and residencies for the elderly. In high-income countries, older people are clustered in aged-care facilities. A lack of adequate sanitation, ventilation or overcrowding creates the perfect set for the bacteria to spread. In addition, social marginalisation and reduced mobility discourage health care seeking (Negin *et al.,* 2014). A 3-fold increase in the incidence of active tuberculosis in nursing residents has been found (Stead *et al.,* 1985). This has raised concerns for the institutionalized elderly population.

1.6 AIM OF THE WORK

There are yet many questions to answer regarding the tuberculosis epidemiology. The distribution of the disease and its transmission patterns are of difficult determination. Tuberculosis transmission depends on many factors; either biological or social factors as it has been described above. The aim of this analysis is to look into specific characteristics of the tuberculosis transmission in Barcelona and its social implications, in order to determine the most susceptible collectives.

Hence, the purpose of this study is to characterize the pattern of transmission of tuberculosis in Ciutat Vella (Chapter 2), to later include the results in the improvement of an individual-based model (Chapter 3). The model simulations are expected to provide accurate predictions that will help when deciding the correct TB control strategy in Barcelona to be applied.

Some linked questions rose when the study was set-up; Do people who suffer from active TB infect other people randomly? If not, what type of people do they infect? Although we expected to observe specific patterns of transmission in TB depending on the profile of the sick patient, the ultimate goal of the study is to confirm if the gender, age and origin of a patient will be related somehow to the profile of the people they infect. If it is related, the study should allow answering one more question: What is the pattern that can be observed? Finally, if the answer is consistent enough, a preventive action can be recommended to reduce the spread of TB and the number of active patients.

The structure of the study can be summarised into the questions stated in Table 1.2, where *profile* stands for age, gender and origin of the individuals.

Table 1.2. Core questions raised which the study will assess

	Questions
1.	*What is the profile of the people infected by a TB case, depending on the profile of the case itself?*
2.	*What is the probability of sickening for someone with latent TB depending on their profile?*
3.	*How can the results be quantitatively evaluated to be included in the epidemiology model?*
4.	*Do the simulation results obtained faithfully represent the epidemiological results?*
5.	*How will comprehending these patterns help us towards the goal of controlling and preventing the tuberculosis disease?*

2. ANALYSIS OF THE TUBERCULOSIS TRANSMISSION PATTERN IN CIUTAT VELLA

Point two of this project will attempt to find an answer to questions 1, 2 and 3 stated in Table 1.2. A deep analysis of data collected by the *Agència de Salut Pública de Barcelona* (ASPB) will allow to infer and describe a pattern of TB transmission in Ciutat Vella.

2.1 SURVEILLANCE DATA FROM THE PUBLIC HEALTH AGENCY OF BARCELONA

The *Agència de Salut Pública de Barcelona* carried out a contact tracing study for the city of Barcelona between 2010-2015 which consists of the following:

a) For each active TB case reported in Barcelona, a number of their closest friends and relatives where surveyed and tested for latent and active TB.
b) The ones who tested positive for either active or latent TB where added to a list of "contacts" of the case.
c) Every new contact was noted along with their age, gender, nationality, type of TB, neighbourhood they lived in, relation to the original case, etcetera.

The contact tracing study allows to analyse the transmission patterns, since it gathers information about the profile of the infectious agent and the profile of the newly infected individuals.

The contact tracing study was done about 60% the cases that were diagnosed in Barcelona during those 5 years. It is also worth noting that many contacts who were actually infected might have been missed, since only a fraction of the case's close relatives could be surveyed and tested. The contacts who were found infected did not know they were, and the ones who were found sick had not yet found out it was because of tuberculosis. It is therefore assumed that the original case is the source of the disease amongst the group of friends and relatives.

The contact tracing study does not provide complete and exact information about the transmission patterns in Barcelona, but it allows to draw general conclusions and infer the population pattern.

Aside from the contact tracing study, the ASPB also gathered data for the city of Barcelona between 2005-2015 for all the diagnosed TB sick cases. Although it is expected that the majority of TB sick cases will be diagnosed, there still are a few miss outs from individuals who are not in the census or who do not have access to medical care, therefore we can not assume that the number of diagnosed cases is equal to the number of total cases.

It has to be taken into account that all conclusions drawn from these data will be an approximation to reality. Sampling from a population will always be subjected to sampling error, but a close enough idea can be extracted from the study.

2.2 DATA TREATMENT

The raw data was obtained in an excel file format. An overview of the excel spreadsheet can be seen in Figure 2.1. Each row contained a case file and its contacts' information; Each column contained different parameters such as age, neighbourhood, type of TB...

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
1	No identificad	No ider	Data naixeme	Edat del contac	Sexe cc	Intensi	Ambit	Conviver	Prova tube	Vacun	Pais d'o	Prova tuberculina actual				
2	REGISTRE	NID	DNAIX	EDAD	SEXE	INT	AMB	CONV	PPDANT	BCG	PAIS	PPDACT	PPD2M	RX	RESULT	CONCLU
3	0900259	006		79	1	2	3	2	9	9	108	2	2	1	1	5
4	0900259	001		35	1	2	1	1	9	9	426	1	0	1	2	1
5	0900259	004		36	1	2	1	1	9	9	426	2	1	1	2	5
6	0900259	005		32	1	2	1	1	9	9	426	1	0	1	2	1
7	0900259	003		0	1	2	1	1	9	9	426	2	2	1	1	5
8	0900259	002		32	1	2	1	1	9	9	426	2	2	1	1	5
9	1000003	001		58	2	1	1	1	0	9	108	2	2	1	1	5
10	1000004	008	18-Sep-1948	62	1	3	3	2	0	2	108	1	0	1	2.2	5
11	1000004	016	29-Jan-2008	2	1	3	3	2	2	2	108	2	2	4	1	5
12	1000004	002		20	2	1	1	1	1	9	108	0	0	1	4.1	5
13	1000004	013	12-Jun-1978	32	1	3	3	2	0	2	108	2	2	4	1	5
14	1000004	018	5-Apr-1982	28	2	3	3	2	0	2	108	2	2	4	1	5
15	1000004	024	29-Oct-1978	32	2	3	3	2	0	2	108	2	2	4	1	5
16	1000004	025	29-May-1982	28	2	3	3	2	0	2	108	2	2	4	1	5
17	1000004	001		54	2	1	1	1	1	9	108	0	0	1	2.3	5
18	1000004	004		56	1	3	1	2	9	9	108	2	0	1	1	5
19	1000004	007	19-Nov-1950	59	1	3	3	2	1	2	108	0	0	1	2.3	5
20	1000004	012	7-Jan-1967	43	2	3	3	2	0	2	108	2	2	4	1	5
21	1000004	014	13-Jan-1963	47	1	3	3	2	0	2	108	2	2	4	1	5
22	1000004	017	8-May-1951	59	2	3	3	2	0	2	108	2	2	4	1	5
23	1000004	019	19-Feb-1955	55	2	3	3	2	0	2	108	2	2	4	1	5
24	1000004	022	13-May-1960	50	2	3	3	2	0	2	108	2	2	4	1	5
25	1000004	023	18-Jun-1955	55	2	3	3	2	2	2	108	2	2	4	1	5
26	1000004	003		80	2	1	1	1	1	9	108	0	0	1	2.3	5
27	1000004	010	10-May-1983	27	2	3	3	2	9	1	123	1	0	1	2.2	1

Figure 2.1. Overview of the excel file obtained with the raw data from the TB cases and contacts from Barcelona from 2010-2015.

For this project, the age, gender and origin factors for Ciutat Vella where studied, although further factors should also be looked at since they contain important hidden information that can help understand the dynamics of the disease. Parameters such as the intensity of contact needed to infect someone, or the type of space (house, work, bar) where people get infected more often can be inferred from the data collected by the ASPB. Comparison with other neighbourhoods of Barcelona can also be useful. The fact that the data correlates the information of the cases with the information of the positive contacts found from that case, it allows to have a general idea on how, when or why the disease is spread.

Therefore, columns that contained the ID of the case, ID of its contacts, the type of TB (latent or active), the age, the country of origin and the sex of the cases and its contacts where extracted from the source document. From there, different correlations where plotted as it will be seen below. It should be noted that some individuals were missing some information, so they were eliminated from the study. The sample size of the study was as follows: In Barcelona, 11970 contacts were surveyed from 1285 cases during the 5-year span 2010-2015. That represents a mean of 9 contacts studied per case followed. From those, only 2871 contacts tested positive for the Mantoux test, hence they either had latent or active TB. The 2871 contacts where found from 863 cases, therefore a mean of 3 positive contacts found per case followed. From all those contacts in Barcelona, 591 where from Ciutat Vella which were found from 193 cases. In conclusion, the resulting plots are drawn from a sample size of 591 contacts in Ciutat Vella.

2.3 RESULTS AND DISCUSSION

Let us bring back to question 1 from Table 1.2 presented before:

1. *What is the profile of the people infected by a TB case, depending on the profile of the case itself?*

2.3.1 Profile of the contacts

A better understanding of the relationship between the case profiles and their relevant contact profiles can be gathered from the following plots. Let it be reminded that all plots are drawn using data from the Ciutat Vella neighbourhood in Barcelona, from 2010-2015.

Age

The age relationship between cases and positive contacts can be observed in Figure 2.2.

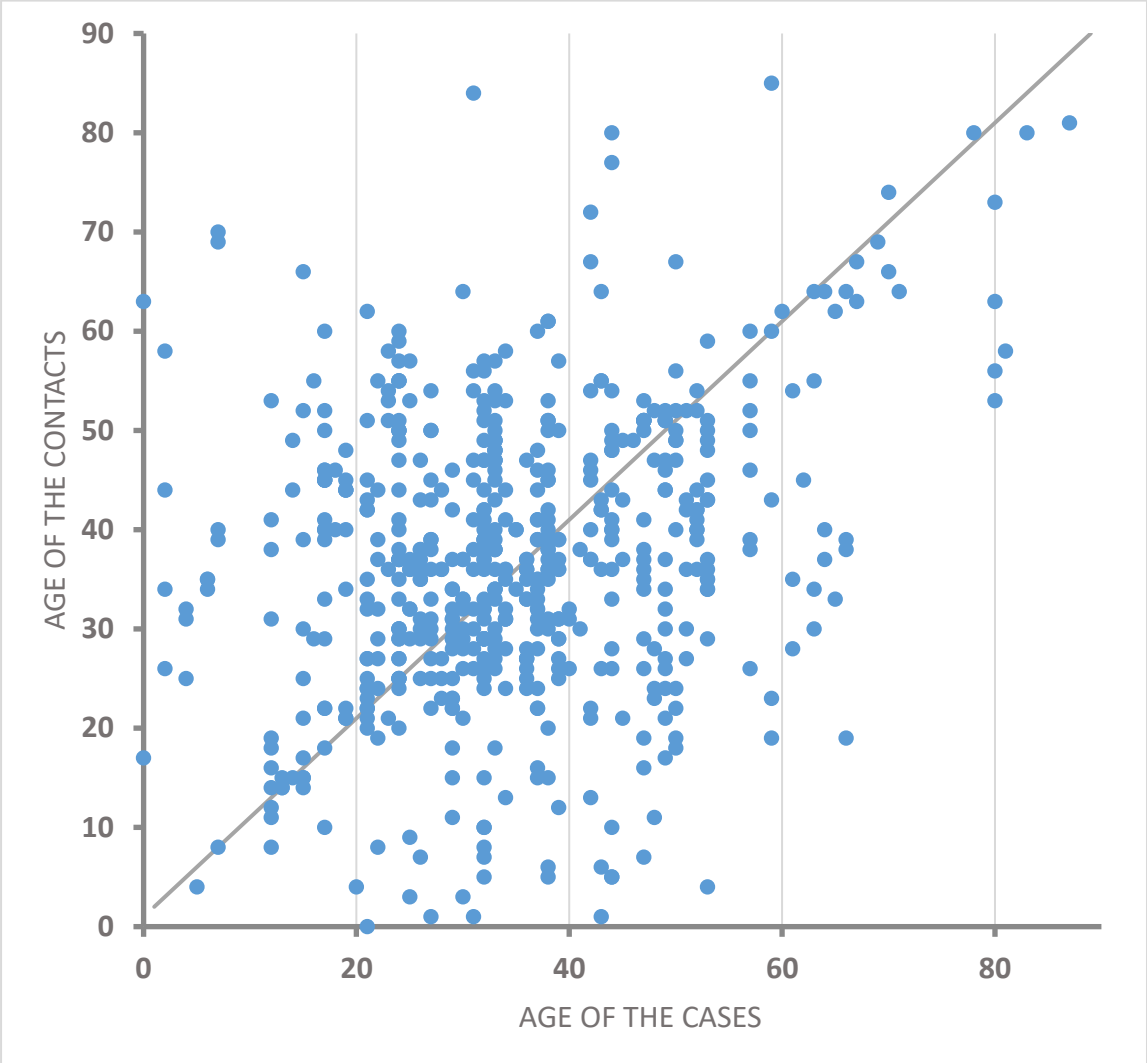

Figure 2.2: Age relationship between TB cases and their contacts. Each of the dots shows the age of one positive contact with regards to the age of the causing case.

In the plot above (Figure 2.2), the x-axis represents the age of the different cases that were reported during the time period of study. For each case studied, the positive contacts' age was noted.

To understand the logics of the social behaviours behind this plot, it has to be looked at closely. From the analysis of Figure 2.2, it can be concluded that:

- There is a strong correlation between the ages of 20 and 60. A very dense cloud seems to describe the working society. We can therefore conclude that cases in this age group (20-60) will most likely infect people who are also in this age group.

- There are also a few contacts of the cases aged 20-60, who are children (aged under 10). Only cases who are aged 20-45 infect children, therefore we deduce this transmission mainly derives from the parent-children contact.

- The elderly (aged 60+) seem to infect mostly other elderly, with some exceptions on old adults, but definitely no contacts aged under 50. It could be deduced that aged-care facilities have a strong effect.

- Children (0-10) seem to infect a few other children, but mostly people in the parenting age. Very few elderly seem to get infected due to children.

Figures 2.3 and 2.4 show a similar data treatment, but separating the male cases and the female cases both for causing agents (infectious male individuals: Fig. 2.3; infectious female individuals: Fig. 2.4) and resulting positive contacts (new infected male cases: blue dots in both figures; new infected female cases: orange dots in both figures). The plots were drawn separately for male and female in order to study possible interactions between age and gender when dealing with new infections. It was determined that the results of the correlation between age groups differed significantly for different genders, especially for the 20-60 age group when the gender of the case was taken into consideration, as described below.

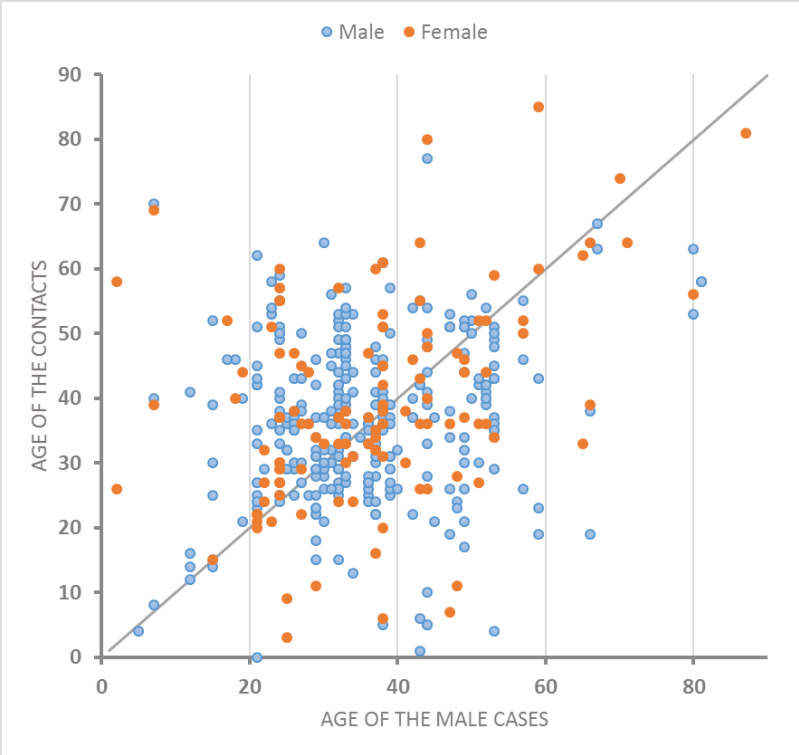

Figure 2.3: Age relationship between male TB cases and their contacts. Orange dots represent resulting positive female contacts, while blue dots represent resulting positive male cases.

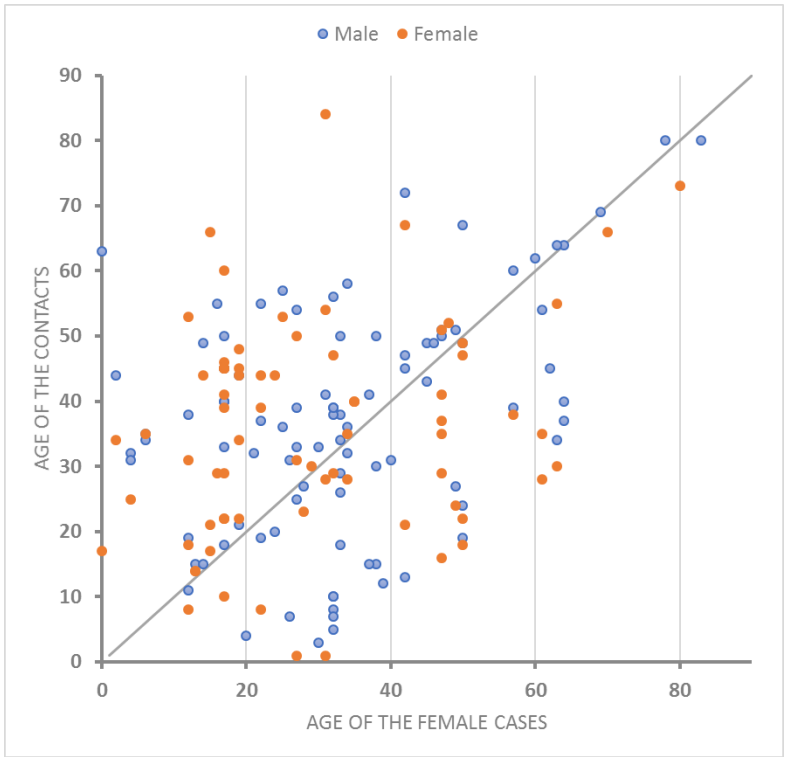

Figure 2.4: Age relationship between female TB cases and their contacts. Orange dots represent resulting positive female contacts, while blue dots represent resulting positive male cases.

When looking at the male cases aged 20-60 it can be seen that approximately 95% of their contacts are also aged 20-60, leaving the children and elderly group with very little significance in terms of the chance of getting infected by a man aged 20-60. However, when looking at the same plot for the female cases aged 20-60, we can see they relate more to the elderly and to children than men did. A rough approximation would suggest that around 10% of the female contacts are children, and 5% old people, therefore 85% of their contacts will be aged 20-60. This suggests that female adults relate more to children and elderly than male adults do.

Gender and origin

After addressing the age relationship between cases and contacts, further characteristics were looked into. The gender relationship and the origin relationship were also assessed, as shown in Figures 2.5-2.8.

Figure 2.5 analyses the relationship between the origin of the cases (immigrant/native) and the origin of the resulting infected contacts.

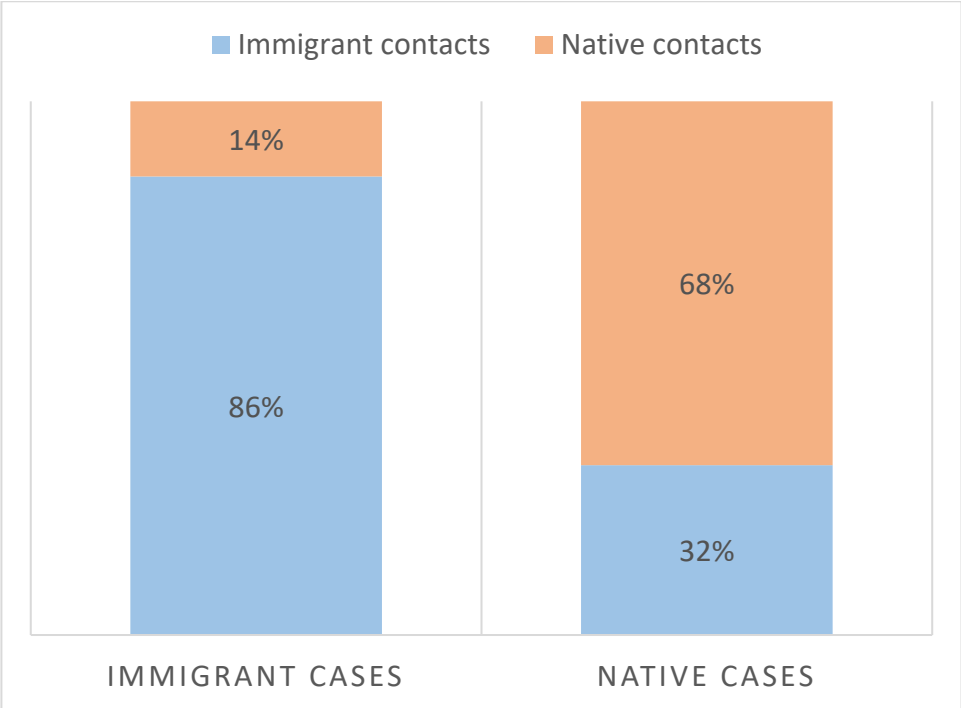

Figure 2.5: Origin relationship between TB cases (left: immigrant causative agents; right: native causative agents) and their positive contacts (blue: infected immigrant individuals; orange: native infected individuals).

A very strong correlation can be observed in Figure 2.5. Almost 90% of the people an immigrant case infects will also be immigrant. A very high percentage for the case of native people is also observed (almost 70%). We can infer from this information a pattern on how people in Ciutat Vella relate to each other; it seems there is a more intense contact between those of the same group: Spanish or coming from abroad.

Figure 2.6 assesses the intensity of the relationship between genders; i.e., for male and female cases, the percentage of contacts that where also female or male.

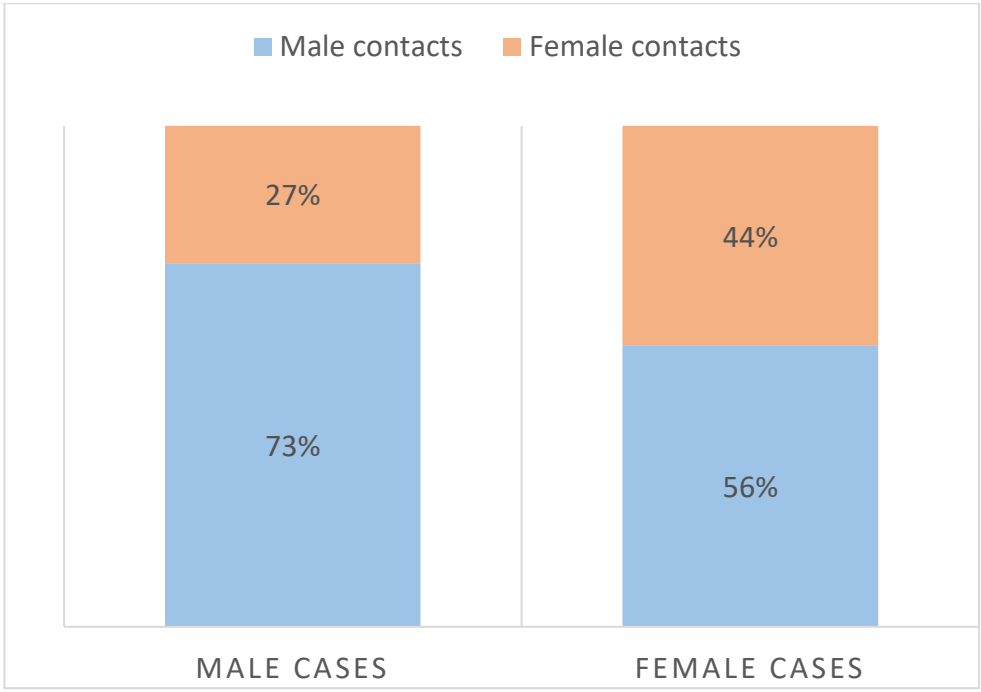

Figure 2.6: Gender relationship between TB cases (left: male causative agents; right: female causative agents) and their positive contacts (blue: infected male individuals; orange: female infected individuals).

What can be deduced from Figure 2.6 is that men infect many more men than women. We do not see such a clear correlation for the female cases collective. Do we therefore deduce that intra-gender social contacts are higher in the case of men, or could it be that female do relate more to female but men have a higher risk of becoming infected? Several questions arise when looking at the plots that should be addressed.

Since the importance of the influence of different cultures was argued when assessing the behaviour of the population, Figure 2.6 above was disaggregated by origin (native vs immigrant). Differences on the intensity of contact between female and male is expected to be seen when looking at the immigrant population or the native population. Figure 2.7 (infections caused by immigrant TB cases) and Figure 2.8 (infections caused by native TB cases) clearly state that the distributions for the native and the immigrant population differ. It seems that in the native population both genders relate more equally to the opposite gender than amongst the immigrant population, where male to male social contacts are more frequent.

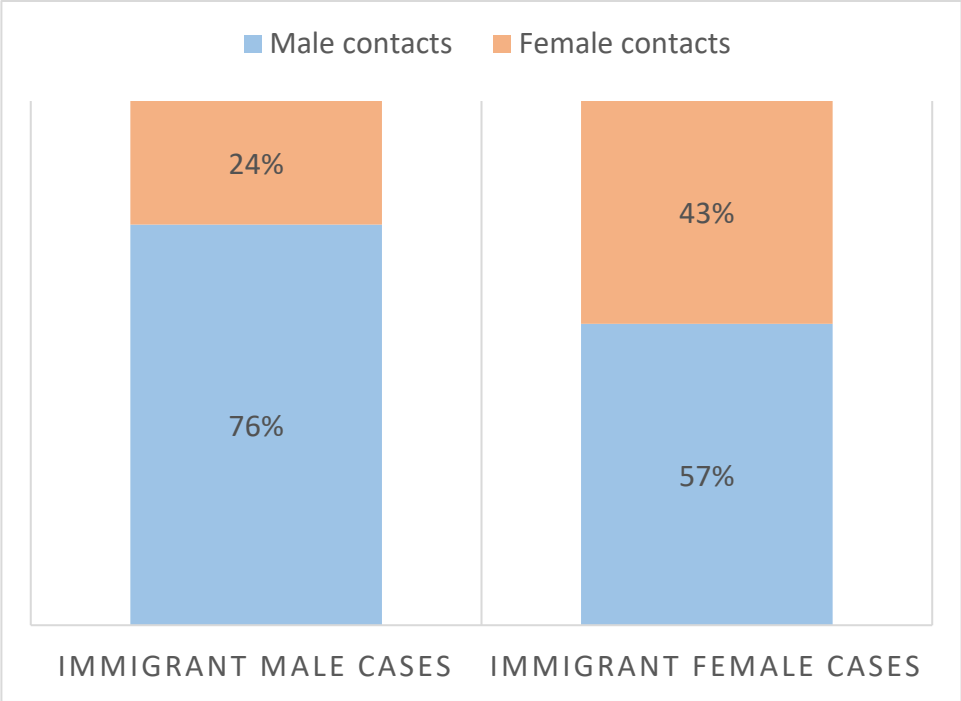

Figure 2.7: Gender relationship between immigrant TB cases (left: immigrant native causative agents; right: immigrant female causative agents) and their positive contacts (blue: infected male individuals; orange: female infected individuals).

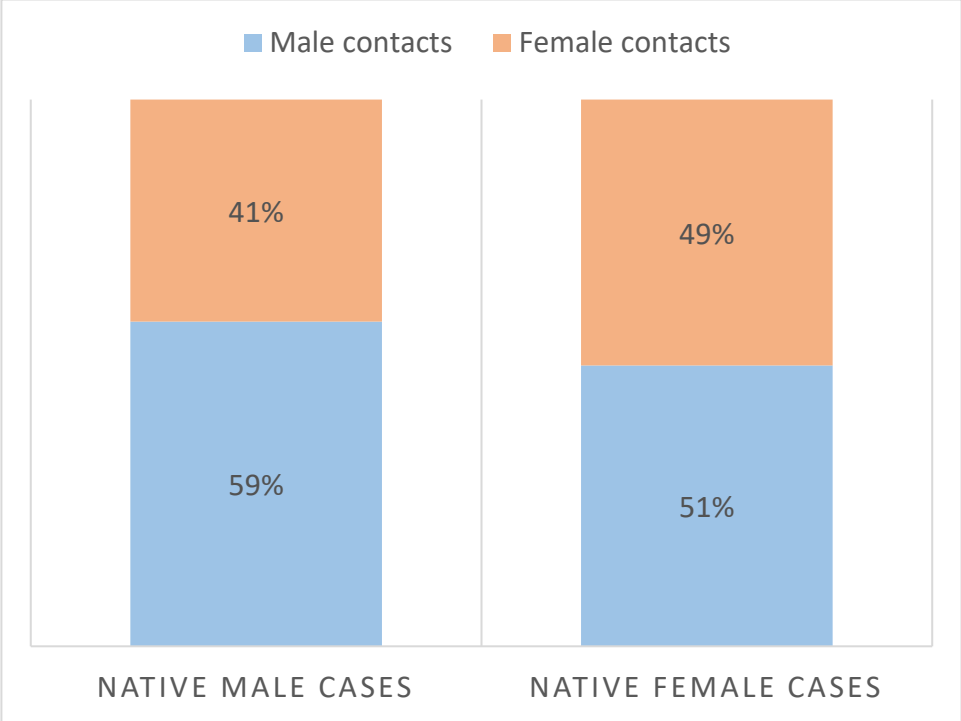

Figure 2.8: Gender relationship between native TB cases (left: native male causative agents; right: native female causative agents) and their positive contacts (blue: infected male individuals; orange: female infected individuals).

Further disaggregation of the plots above was done, separating the classes into age groups to check if age had an effect on the intensity of the male to male or immigrant to immigrant relationships. Data was inconclusive due to very few contacts for each subgroup and the plots can be found on the appendices section.

Resultant quantitative analysis

As an answer to question 3 from Table 1.2:

3. *How can the results be quantitatively evaluated to be included in the epidemiology model?*

After conducting a data analysis, the profile of the contact depending on the profile of the case will be quantitatively described through the following parameters. Table 2.1 summarizes the probabilities that can be calculated from the analysis detailed above, and that will be taken into account in the Individual-based model in Chapter 3.

Table 2.1 Quantitative description of the age relationship between TB cases and TB contacts

		Age of the cases			
		0-20	20-60 male	20-60 female	60-90
Age of the contacts	0-20	30%	5%	12%	5%
	20-60	65%	94%	85%	45%
	60-90	5%	1%	3%	50%

The gender and origin of the newly infected contact will also be related to the gender and origin of the infectious case, the relation is quantitively described following the probabilities shown in Table 2.2:

Table 2.2 Quantitative description of the origin and gender relationship between TB cases and TB contacts

		Gender and origin of the cases			
		Immigrant female	Immigrant male	Native female	Native male
Gender and origin of the contacts	Immigrant female	37%	21%	16%	13%
	Immigrant male	49%	65%	16%	19%
	Native female	6%	3%	33%	28%
	Native male	8%	11%	35%	40%

2.3.2 Sickening probability

This part of the study will attempt to answer question 2 from Table 1.2: *2. What is the probability of sickening for someone with latent TB depending on their profile?*
Data provided by the WHO shows the incidence and prevalence of the TB disease disaggregated by many factors like gender or age, among others. What we cannot deduce from the incidence data is to what extent the number of TB sick people is due to high infection rates, which could be mainly the consequence of social or behavioural factors, or due to a high risk of sickening, which would be mainly related to biological or physiological factors. Different collectives could have different probabilities of sickening or of getting infected, which would bias the results for TB sick people. For instance, it is globally known that there are more TB male cases than female cases. To what extent is this due to men being more likely to sicken and to what extent is it due to men being more likely to get infected?

Age

From all the contacts studied in Barcelona, only the ones testing positive for either latent or active TB where selected to carry out the following analysis. This should allow for the study of the sickening probability without the bias given by different infection patterns. The ensemble of active cases and latent infected cases detected during the contact tracing is denoted as positive contacts. From those, the distribution of active TB cases disaggregated by age is shown in Figure 2.9.
The x-axis on the plot below includes the age groups of the positive contacts in the study. The left-y-axis represents the percentage of positive contacts that were afterwards found to be sick, i.e. the percentage of sick contacts out of the infected + sick contacts. The right-y-axis shows the absolute number of cases found sick, so that data can be interpreted taking into consideration the noise that little data might create.
Figure 2.10 shows the same plot than Figure 2.9 but for the positive contacts in the neighbourhood of Ciutat Vella, together with the percentage and absolute number of sick cases among them.

A surprisingly coherent pattern can be observed for Ciutat Vella and for Barcelona. It seems clear that at a very young age (0-5 y.o), the probability of sickening once infected by TB increases up to around 50% of the cases. After the age of 15, according to the obtained results, the chance of sickening would remain constant at approximately 3%. A strange behaviour appears in the 75-85-year-old contacts in Ciutat Vella, but this is due to the noise created by very little data (only one sick case). Therefore, such surprising behaviour can be rejected. The explanation to this pattern is most likely the highly susceptible immune system of the new-borns compared to that of the grown-up adults, a hypothesis also supported by the findings of Marais et al., (2006) shown in Table 1.1 above.

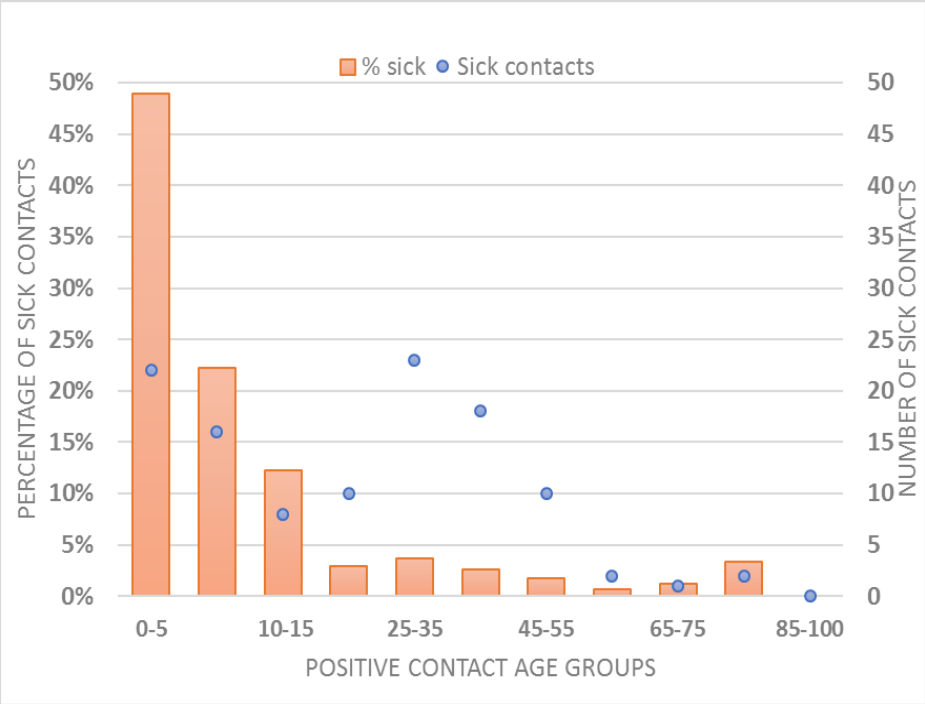

Figure 2.9 Percentage of sick contacts among positive contacts (infected + sick) disaggregated by age groups in Barcelona (bars), together with the absolute number of sick cases in each age group (dots). Both are calculated with data from 2010 to 2015.

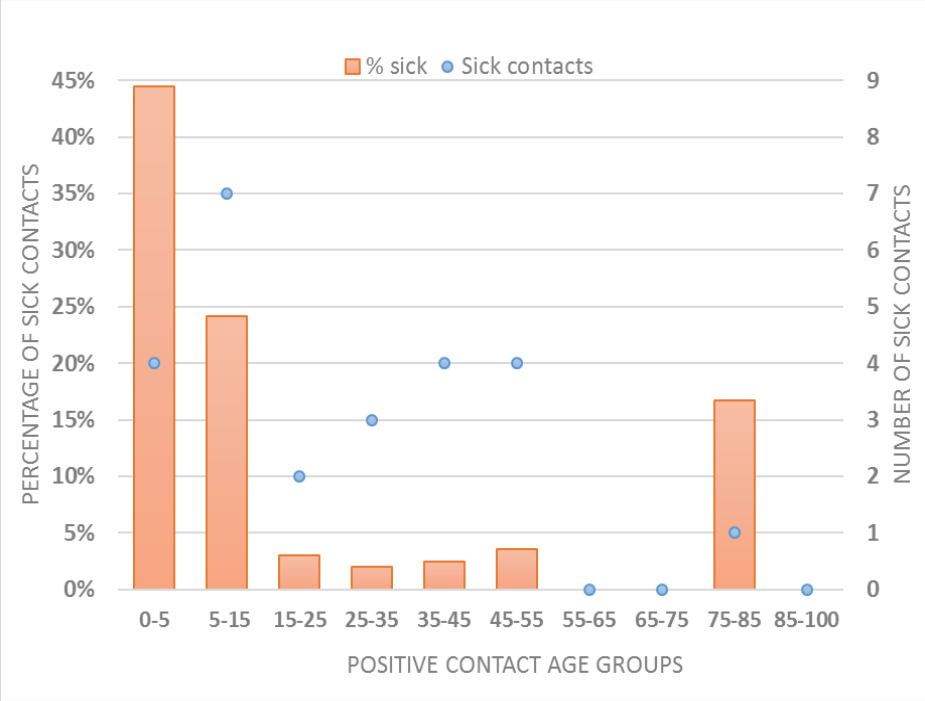

Figure 2.10 Percentage of sick contacts among positive contacts (infected + sick) disaggregated by age groups in Ciutat Vella (bars), together with the absolute number of sick cases in each age group (dots). Both are calculated with data from 2010 to 2015.

Gender

A question was raised before which wondered whether the reason for a higher TB incidence in male was due to men getting infected more of often or due to men having a higher risk of progression to disease. These two different explanations will be described as the behavioural hypothesis and the physiological hypothesis, respectively.
Narasimhan (2013) defends the behavioural hypothesis, which assumes there are more male cases because male get infected more often than female due to a more active social live.
Neyrolles (2009) thinks that the male bias in TB is due to male having a higher chance of sickening once infected: due to hormones, genetics and metabolism.
With the contact tracing study, we can see which hypothesis is supported by the data. To agree with the physiological hypothesis, a higher risk of sickening amongst men than women should be observed. Otherwise data would be supporting the behavioural hypothesis. Figures 2.11 and 2.12 show the probability of sickening disaggregated by gender for the city of Barcelona and for the neighbourhood of Ciutat Vella, respectively. This probability was assessed as the percentage of sick cases among positive cases, as before.

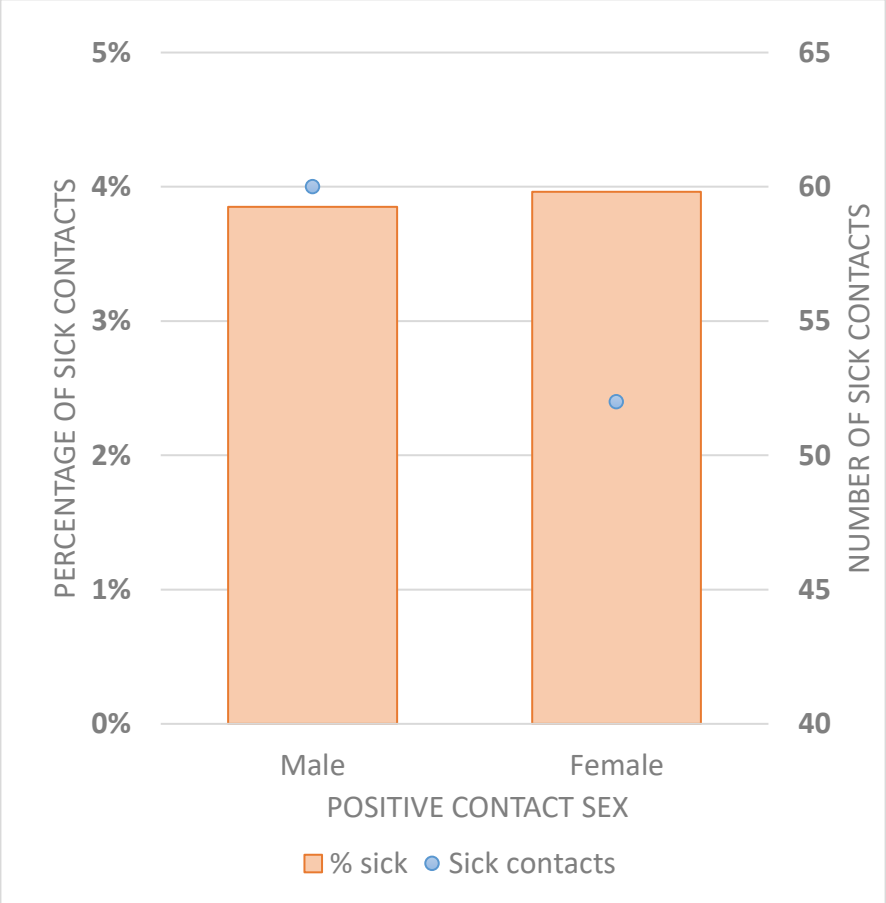

Figure 2.11 Percentage of sick contacts among positive contacts (infected + sick) disaggregated by gender (male/female) in Barcelona (bars), together with the absolute number of sick cases in each age group (dots). Both are calculated with data from 2010 to 2015.

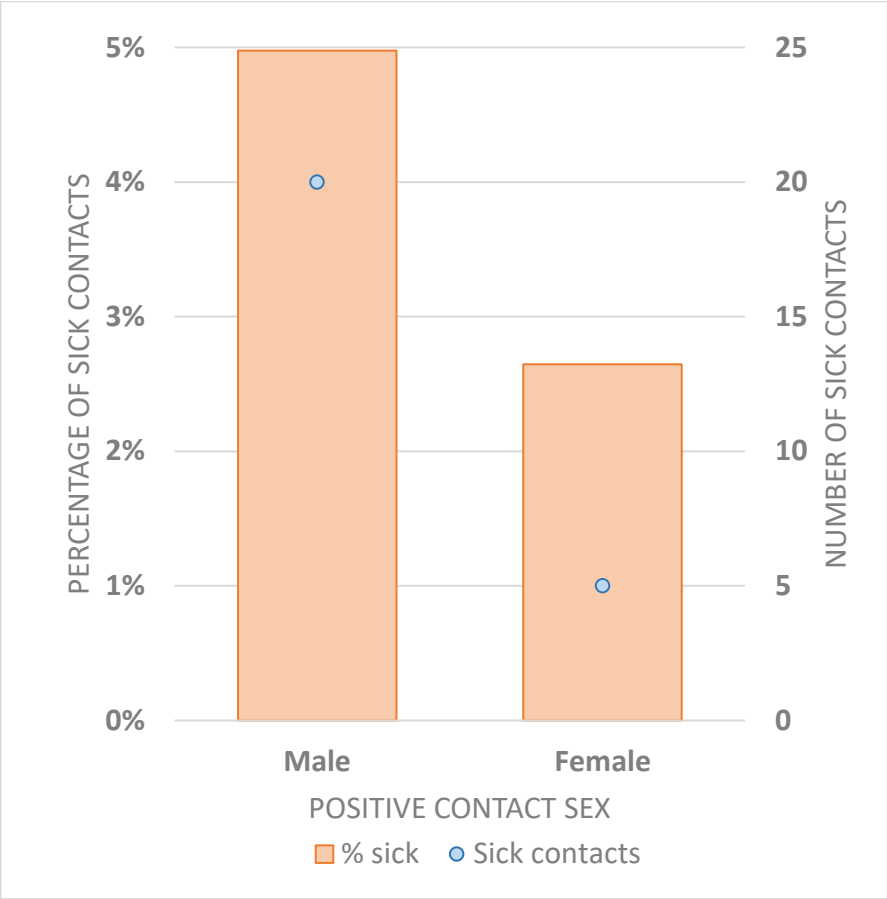

Figure 2.12 Percentage of sick contacts among positive contacts (infected + sick) disaggregated by gender (male/female) in Ciutat Vella (bars), together with the absolute number of sick cases in each age group (dots). Both are calculated with data from 2010 to 2015.

The plot for the city of Barcelona is slightly different to the one for Ciutat Vella. Since data for Ciutat Vella is very limited, it is not as statistically significant to take it into account as the one from Barcelona. Therefore, looking at the results for Barcelona, the sickening probability for both male and female would remain practically the same (3.85% for male and 3.96% for female).

This data is supporting the idea that male do not have more chances of sickening once infected than female. If there actually are more male TB cases, data suggests it is due to the fact male become infected more often than female. The data from Barcelona supports the behavioural theory presented above, and it does not support the physiological theory. Nevertheless, this could still be due to too little data to be statistically significant.

Origin

Two more plots were drawn to see if the risk of sickening was different depending on the origin of the tuberculosis patients. Again, this sickening probability was calculated as the percentage of sick cases among positive contacts. Some have argued that the physiology, metabolism and genetics of a human body could have an impact on the probability of sickening. This analysis should allow for stating if human bodies of different ethnics respond unalike to tuberculosis infection.

Below, Figure 2.12 for the city of Barcelona is shown along with Figure 2.13 for the population in Ciutat Vella. In both cases, the percentage of sick cases among positive contacts is disaggregated by origin, and evaluated for the 2010-2015 period. Since the amount of data is bigger for the city of Barcelona, the results obtained in the first figure are more consistent than the results obtained for Ciutat Vella, which are at the mercy of the little data noise effect.

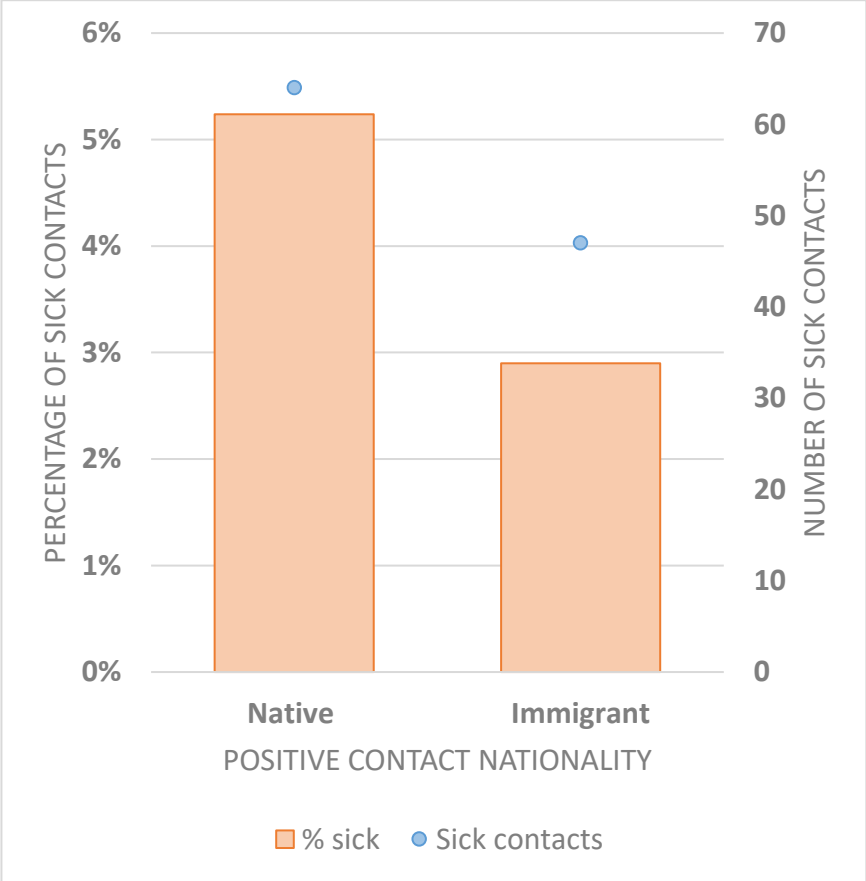

Figure 2.13 Percentage of sick contacts among positive contacts (infected + sick) disaggregated by origin (native/immigrant) in Barcelona (bars), together with the absolute number of sick cases in each age group (dots). Both are calculated with data from 2010 to 2015.

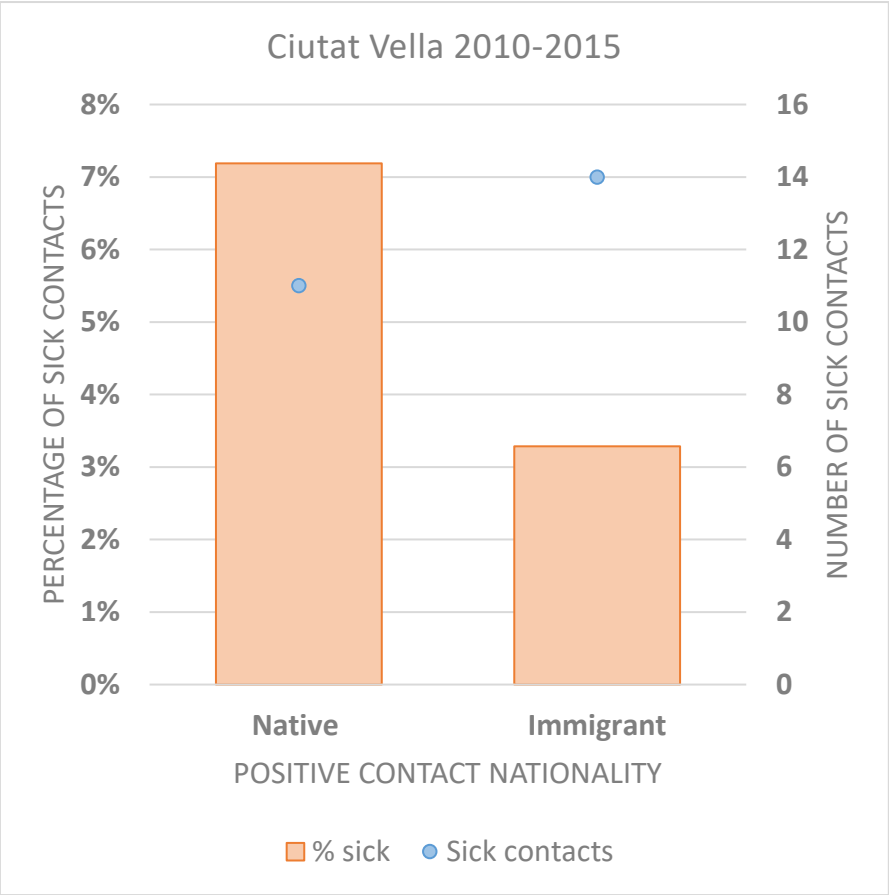

Figure 2.14 Percentage of sick contacts among positive contacts (infected + sick) disaggregated by origin (native/immigrant) in Ciutat Vella (bars), together with the absolute number of sick cases in each age group (dots). Both are calculated with data from 2010 to 2015.

Surprisingly, according to the results obtained, people who are from Spain are more susceptible to progress to the disease once infected than people coming from abroad. The reason this information should come as a surprise is due to the number of immigrant TB sick cases diagnosed in the past few years. According to the *Agència de Salut Pública de Barcelona,* throughout the years 2005-2015, from all the TB sick cases reported in Ciutat Vella, as much as 72% of them were immigrant people. If the distribution of immigrant people is so biased amongst the TB-sick community and it is not due to them having higher chances of falling sick, it has to be due to them becoming infected much more often than native people. Therefore, there are two main questions that arise from the plots above: Why do immigrant get infected more often than native? Why are immigrants less susceptible to the tuberculosis infection?

Resulting quantitative analysis

To conclude, where question 3 from Table 1.2 is: *3. How can the results be quantitatively evaluated to be included in the epidemiology model?*

Table 2.3 summarizes the sickening probabilities that can be calculated from the analysis detailed above, and that will be taken into account in the Individual-based model in Chapter 3.

Table 2.3 Quantitative description for the sickening probabilities by age, gender and origin.

BY AGE	**% sickening**
0-5	50%
5-15	15%
15+	3%
BY GENDER	
Female	4%
Male	4%
BY ORIGIN	
Native	6%
Immigrant	3%

Estimated probabilities of getting sick by the World Health Organization stand at 5% - 10% of the infected people (WHO Tuberculosis report 2015).
According to the data from *Agència de Salut Pública de Barcelona*, from the 2871 contacts surveyed in Barcelona who tested positive for the tuberculin test throughout 2010-2015, 3.90% had an active disease at the time, a value which is below the WHO's estimate. Let it be reminded that the contact tracing study only considers sick those who have been sick for a very little time, since they still did not know they had tuberculosis yet. The percentage of people who were found sick because of the contact tracing study will determine the experimental value for the probability of sickening immediately, probably for the first-year disease. It is then understandable that the value is lower than the WHO's estimate, since it is only considering the first year and sickening can occur for a long period of time. The remaining 6.10% chance of sickening will occur from the second year of infection onwards.

Although Table 2.3 presents the observed values from the epidemiological data, those have to be read carefully.

· The fact that there are no differences in the probability of sickening between male and female is doubtful. There are several studies which show clear evidence of increased TB susceptibility when male hormones are found (Neyrolles, 2009; Rhines, 2013; Holmes *et al*., 1997).

· The differences observed on the risk of progression to disease between native and immigrants have to be checked since the results are suspicious. Further bibliographic research has to be made to assess if the response to a tuberculosis infection differs greatly depending on the ethnicity of the patients.

· The increased chance of sickening by children seems excessive compared to the results found by Marais *et al*. (2006) shown in Table 1.1.

The previous doubts were brought up at a meeting with the *Epidemiology Department* of the *Agència de Salut Pública de Barcelona.* As it has been noted before, the scope of the contact studied carried out was limited, but several hypotheses were raised explaining how these surprising results could have come up.

· Apparently, it is likely for children to be over-diagnosed since it is common to label them as actively sick even if they haven't been tested, just as a preventive measure. That would explain the excessively high proportion of active TB amongst the infected.
· It is also likely that the immigrants found with latent TB had already been infected for a long time and were not infected by the source case. That would be due to very high TB incidences in their country of origin. Since the chance of sickening once infected decreases with time, the fact that there are many long-term infected immigrants compared to the long-term natives could have brought a lower proportion of active TB cases amongst the immigrants.

From Table 2.3, the increased chances of sickening for children (0-5 and 5-15) is the only parameter which is consistent with previous findings (Cruz and Starke, 2010). The other quantitative analysis have yet to be assessed.

In conclusion, the data provided by the *Agència de Salut Pública de Barcelona* has been the key to assess and identify different social patterns, comprehending better in which contexts the transmission of the disease occurs.

The comprehension of this patterns will allow us to refine and upgrade our individual-based model, which will be more accurate and precise when predicting the evolution of the tuberculosis disease in the neighbourhood of Ciutat Vella. This will lead us to take and informed decision when choosing the right control strategy for this particular neighbourhood.

3. EPIDEMIOLOGY MODEL

Chapter 2 has assessed the heterogeneity of the tuberculosis infected population in Ciutat Vella and the magnitude of the diversity has been quantitively evaluated with the available data. Transmission patterns and sickening probabilities have been defined according to the gender, age and origin of the individuals. Chapter 3 will use the quantitative analysis as parameters to be introduced into the model and it will evaluate how the introduction of these new parameters shapes the simulation responses. Conclusions will be drawn on whether the simulation results resemble the epidemiological distributions observed in Ciutat Vella. The final goal is to obtain, through the model, a similar distribution of ages, genders and origins amongst the TB sick to the distribution observed in real data. Chapter 3 will therefore, first describe the characteristics of the Individual-based Model bringing special attention to the factors that have been recently introduced, it will then show the results of the simulations and compare them to the epidemiological data and finally, conclusions will be drawn from the comparisons made.

3.1 DESCRIPTION OF THE IBM MODEL

Individual-based Modelling has been used in multiple fields, from simulation in social science to business, and also biology and epidemiology. As a consequence of this variety, IBM models have had almost as many description procedures as models have been developed. In order to deal with all the different description systems and standardize the description of IBM models the ODD (Overview, Design concepts, and Details) protocol was written (Grimm et al., 2010). In this section, the ODD protocol that was developed for the original model (Prats et al., 2016) will be updated and adjusted according to the modifications that have been made to the improved model. In the following section (3.2), the main changes between the previous model and the improved one are individually highlighted and detailed.

3.1.1 Overview

Purpose

The objective of this IBM is to analyse the evolution of pulmonary tuberculosis incidence in a community. It is fitted to the Ciutat Vella neighbourhood, considering the population to be constant. The adequacy of the simulation results will be checked and compared to the epidemiological data. The final purpose of this IBM, which could be met in a further project is to check through virtual experiments the possible effects of epidemiology control strategies and public health decisions.

Entities, state variables and scales

The fundamental entities in the model are persons. We consider that persons can go through five infection states: healthy, infected (i.e., with a latent TB infection), sick (i.e., with an active TB), under treatment, and recovered. Persons in four out of the five states, all but healthy, are simulated as individuals. We consider that the characteristics of a healthy population remain constant (e.g. native/immigrant distribution and HIV^+ percentage, among others). Moreover, a healthy collective is much larger than infected

or sick collectives. Therefore, it is not necessary to control healthy individuals one-by-one; they are considered as a property of space (i.e., the number of healthy people in a spatial cell). A healthy person will acquire individuality once he/she enters the infection cycle. This strategy is an important optimization for drastically reducing the computing time. It was previously tested to provide results comparable to those obtained considering healthy people as individuals (Montañola-Sales *et al.,* 2015).

The state variables of the individuals mainly refer to their status in the tuberculosis infection cycle as well as the time spent in such phases and individual diagnostic time when getting sick. Other individual state variables and parameters are age, native/immigrant origin, female/male gender, risk factors (e.g. smoking), diabetes, and possible immunosuppression (mainly HIV infection). Once a person gets infected, the presence (or not) of pulmonary cavitation is also considered. A state diagram of the model is presented in Figure 3.1. The population simulated is 105,123 people, which represents all the people of Ciutat Vella (2012).
The model is partially spatially explicit, i.e., space is considered but it does not mimic the real space of Ciutat Vella. Simulation occurs in a discrete area of 501 x 501 spatial cells. Each spatial cell represents a local abstract space where two persons can meet, and the bacilli can be spread in a day. The time step is set to 1 day, and the simulation may cover up to a period of 1 or more years.

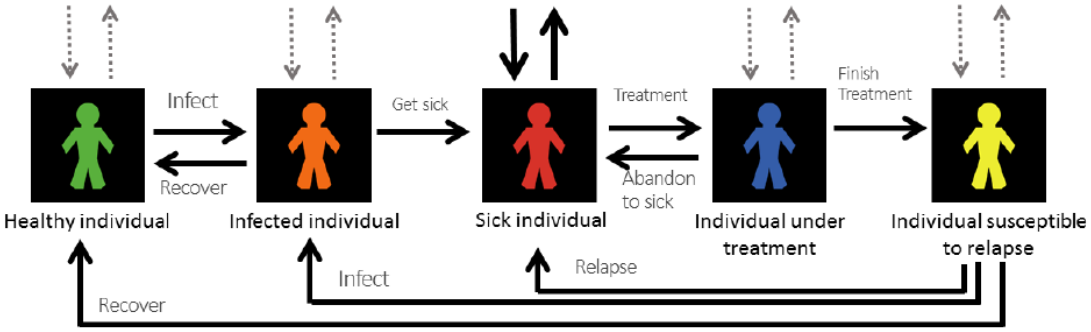

Figure 3.1. State diagram of the model, where the five states of individuals and possible transitions are shown. Output gray dotted arrows refer to deaths; input dotted arrows are the corresponding entrances of randomly selected individuals in order to keep population constant (Prats *et al.* 2016).

Process overview and scheduling
Our model was built in NetLogo (Tisue and Wilensky 2004), which is well suited for modelling a broad range of Individual-based systems in a user-friendly interface. The simulation starts with the set-up of the initial configuration, where the population is randomly generated according to the input distributions of parameters and randomly distributed in the 501 x 501 grid. The model assumes discrete time steps of 1 day, as mentioned. Each day, all individuals execute a series of actions, and their variables are updated immediately.

The individual actions may be: to age, to move, to get infected, to get sick, to be diagnosed and start a treatment, to abandon or finish the treatment, to recover, and to die. Some of the actions take place daily for all the individuals in the system (e.g., aging

and movement) and the other procedures are daily evaluated when necessary (e.g., the possibility of a sick individual to be diagnosed is daily assessed until it finally occurs). When an individual dies, a new healthy is generated adding 1 to the number of healthy people in a random spatial cell. At the end of each time step, global variables are updated.

3.1.2 Design Concepts

Basic principles: The model is based on general knowledge of the natural history of tuberculosis (Cardona, 2010). There are two essential characteristics of TB that must be taken into account in any epidemiological model. On the one hand, an infected individual does not necessarily develop an active disease; on average, only 10% of infected people become sick. Moreover, a person remains infected for an extended period and may develop active tuberculosis after several years, but the probability of developing the disease decreases with time (Ferebee, 1970; P-J Cardona and Ruiz-Manzano, 2004). Infected people are usually not diagnosed, except those detected in punctual screenings or in a contact tracing study. On the other hand, only TB sick can disseminate the infection. The infection rate increases if the patient has TB with cavitation. Once a TB sick is diagnosed, the pharmaceutical treatment takes 6 months (World Health Organization, 2010). Once the treatment is finished, the possibility of getting sick again because of a TB reactivation remains at 1% for 2 years. If an infective is detected, it may be treated with preventive drug therapy. This treatment is longer than the one given to persons with active TB. It lasts 9 months and is administered to infected individuals to prevent the development of an active disease once they have been detected during a screening process (World Health Organization, 2015). There is also a probability of relapse to the infected state that is calculated similarly to the first treatment.

Emergence: Emerging phenomena are mainly related to long-term dynamics of the infection at the population level. On the one hand, only non-treated people with active TB can spread the disease. Therefore, diagnosis time is an essential parameter for the prevalence of the disease. On the other hand, infected persons may develop active tuberculosis a few years after the infection. Therefore, global consequences of particular conditions at a precise moment may be detected some years later.

Interaction: Local interactions between healthy and ill individuals are explicitly modelled and crucial for the dynamics of the system. They refer to the meeting of two persons favored by the spatial proximity between them and the possibility that one of those individuals with an active TB may infect the other person. The interaction within or between some specific groups (i.e., among immigrant male adults) is of special interest in the context of Ciutat Vella, since it accounts for specific observed patterns of transmission and its consequences on the particular TB dynamics in this neighborhood.

Stochasticity: Randomness is introduced at all levels of the simulation. The initial distribution of individual properties is randomly executed according to input distributions. Movement is assumed to be random. Each action is associated with a certain probability and thus executed according to a stochastic number.

Collectives: Different collectives may be distinguished, according to the individuals' origin (native and immigrant), due to the individuals' gender (female and male) and due to the individuals' age (by age group). The difference between native and immigrant is the diagnosis time, and depending on the age and gender the probability of sickening will also differ. Due to the social patterns, it is considered that an individual of a specific collective (i.e. 5-year-old native female) will be more likely to infect another individual from specific characteristics (i.e. 35-year-old native female more likely than 60-year-old immigrant male).

Observation: Output data show the daily evolution of number (or prevalence) of healthy people, infected people, sick people, people under treatment, and persons already treated disaggregated by gender, age and origin. These data are exported to an external data file, and an annual report is shown to the user on the interface screen.

3.1.3 Details

Initialization

The user can change some initial conditions at the beginning of the simulation. For this particular study, most of the input parameters were taken from official reports. The initial population was fixed at 105,123 individuals. All percentages shown in Table 3.1 were used for calculating the configuration of initial population: rates sick, under treatment and recovered individuals per 100,000 inhabitants; mean diagnosis delay (MDD); mean treatment abandon rate; individuals with risk factors and with HIV infection. Other initial variables are assigned randomly: individual's age, gender and origin (following the percentages shown in Table 3.1), and time spent in the infection state assigned.

Table 3.1. Official data of Ciutat Vella used in simulations. Adapted from Prats *et al.* (2016) and extended with available data (Ajuntament de Barcelona, 2012; García de Olalla et., 2012; Bartoll et al., 2013; Orcau i Palau et al., 2013; Bartoll, 2014).

District of Ciutat Vella	**Value**	**Units**
Total population	105123	persons
For the infected population**:	-	-
Immigrant	73,57%	percentage
Male	68,02%	percentage
Age distribution:	-	-
0-4	2,20%	percentage
5-14	5,58%	percentage
15-24	12,01%	percentage
25-34	25,21%	percentage
35-44	27,75%	percentage
45-54	18,27%	percentage
55-64	5,75%	percentage
65-74	1,86%	percentage
75-84	1,18%	percentage
85+	0,17%	percentage

For the sick population*:	-	-
Immigrant	71,57%	percentage
Male	69,78%	percentage
Age distribution:	-	-
0-4	2,70%	percentage
5-14	3,15%	percentage
15-24	13,93%	percentage
25-34	30,00%	percentage
35-44	22,25%	percentage
45-54	11,69%	percentage
55-64	7,19%	percentage
65-74	3,82%	percentage
75-84	3,93%	percentage
85+	1,35%	percentage
Total annual mortality	0,83%	percentage
Detected cases of TB (immigrant)	53	persons
Detected cases of TB (native)	11	persons
Cavitation forms*	22%	percentage
Diagnosis delay (median)	39	days
Diagnosis delay native (median)	42	days
Diagnosis delay immigrants (median)	33	days
Treatment abandonment rate*	2,20%	percentage
Alive cases of HIV+	440	persons
Detected cases of TB/HIV+	32	persons
Risk factors*	24,1%	percentage
Diabetes cases	5,60%	percentage

(*) Percentages with respect to the total number of TB sick people. (**) Percentages with respect to the total number of TB infected people.

Submodels

Age: all individuals increase their age by 1 day each time step.

Move: all persons can move randomly through the surrounding local space, once a day.

Get infected: if there is a number of individuals susceptible to TB (healthy and treated) different from zero in the proximity of a sick individual, meaning one of the 4-neighbouring spatial cells, this sick person may infect one of them with a certain probability. The total of susceptible neighboring individuals is computed and then the infection process is repeated as many times as healthy and treated people have been found. The infection probability depends on the type of TB disease that the sick person has, either smear-positive or smear-negative. A smear-positive case is considered to double the infection probability. The value of the infection probability is closely linked to the spatial and temporal scales, i.e., the probability of infection is inseparable from the spatiotemporal scale. A change in any of these scales entails the revision of its value.

Therefore, it is not a real infection probability when a sick individual meets a healthy person, but an effective infection probability given the particular spatio-temporal constraints. In this case (501 x 501 spatial cells and 105123 individuals), the value of this probability was fixed at 49.7 %. Once a person is infected, a newly infected individual is created with the properties assigned according to the characteristics of the infectious. Whether the new person will be set to native or immigrant, male or female, and the age will depend on the characteristics of the infectious individual. Those probabilities are summarized in Table 3.2, according to the social behavior of these communities analyzed in Chapter 2. The infection time of the new individual is set at 0 and starts increasing with each time step.

Table 3.2. Distribution of the new-infected properties according to the characteristics of the infectious. Percentages describe the social patterns observed in the contact study carried out by the ASPB 2010-2015.

		Age of the cases			
		0-20	20-60 male	20-60 female	60-90
Age of the contacts	0-20	30%	5%	12%	5%
	20-60	65%	94%	85%	45%
	60-90	5%	1%	3%	50%

		Gender and origin of the cases			
		Immigrant female	Immigrant male	Native female	Native male
Gender and origin of the contacts	Immigrant female	37%	21%	16%	13%
	Immigrant male	49%	65%	16%	19%
	Native female	6%	3%	33%	28%
	Native male	8%	11%	35%	40%

Get sick: once infected, the individual may develop active TB according to a particular annual probability that decreases with infection time during the 7 years post-infection (Ferebee 1970; P-J Cardona and Ruiz-Manzano 2004). It is neglected for the subsequent years (t > 7 years). The probability of developing active TB will also depend on the age, gender and origin of the individual. For children aged 0-15, a factor multiplies the probability according to their increased chance of sickening described in Chapter 2. Since simulation time does not cover periods longer than 10 years, the approximation is good enough. For immunodeficient people, a certain factor multiplies this probability. The same happens if there are other risk factors (smoking, alcoholism) or if the patient has diabetes. The chance of becoming a TB sick individual is evaluated at each time step for all infected persons. Globally, the average of 10% of infected developing an active disease is satisfied. The possibility of relapse (getting sick again) for recovered patients is also evaluated daily according to the individual relapse probability (see below). Once a person

gets sick, the disease time counter starts running until the individual diagnostic time is reached.

Be diagnosed and start treatment: each individual has a particular diagnostic time that is randomly assigned when getting sick. These individual times are assumed to be distributed following a normal distribution centered around the mean diagnosis time shown in Table 3.1 and standard deviation 4 days. When the sick time counter reaches these values, the individual is diagnosed. Once diagnosed, medical treatment is assumed to start and TB to stop spreading. Individual time under treatment is initially fixed at 0 and then updated at each time step.

Abandon the treatment: there is a certain probability that an individual abandons the treatment before finishing it. This possibility is evaluated daily for each patient under treatment, according to the input abandonment probability. If a person leaves treatment during the initial 15 days post-diagnosis, he/she becomes ill again. If he/she abandons the treatment after 15 to 180 days post-diagnosis, the model will consider him/her to be recovered but with a certain probability of relapse during the following 2 years. This probability is assumed to decrease linearly from the 100% of a 15-day abandonment to the 1% of the 180-day treatment period.

Recover: when a sick individual is diagnosed and treated for 180 days, he/she becomes recovered and a relapse probability of 1% is assigned (the chance of getting sick again during the following 2 years). After 2 years, the individual is considered to be healthy.

Die: each individual has a certain probability of dying according to his/her age. These probabilities are fixed using demographic data from Ciutat Vella in 2012. Accordingly, the daily dying probabilities are considered to be 6.88×10^{-5} % for individuals under 10, 5.45×10^{-4} % for individuals between 10 and 65, and 1.22×10^{-2} % for individuals over 65, which is a simplification of the real mortality distribution. Furthermore, TB sick people have a distinct probability of dying from tuberculosis. This probability is evaluated daily for each sick individual, taking into account that 40% of non-treated TB sick may die in 5 years. Each time an individual dies, a new individual is introduced into the simulation world with the aim of maintaining a constant population. The individual's characteristics are fixed according to the distribution of the initial population.

3.2 INTRODUCTION OF NEW FACTORS INTO THE CODE

The improved model has been entirely described in Chapter 3.1. Nevertheless, with the aim of clarifying, further details on the specific modifications that were made with respect to the previous model are summarised in Table 3.3

Table 3.3 describes the general idea of the new variables and parameters introduced into the model. Nevertheless, further details of the programming specifics can be looked at on the source code which has been added to the appendices section. A screenshot of the commands used in the code during the INFECT submodel to assign the characteristics to the newly infected depending on the social patterns can be seen in Figure 3.2.

Table 3.3 Main conceptual differences between the model before the changes and after

Submodels	PREVIOUS MODEL (Prats *et al.*, 2016)	IMPROVED MODEL
SET-UP	For the initial sick, treated, under-treatment and infected population: · Gender was not taken into account. · The age distribution was considered to be equal to the general population distribution. · The percentage of immigrant was also inferred from the general population data in Ciutat Vella.	Different distributions are described for the infected population and for the sick, treated and under-treatment population: · Percentage of male / female, native / immigrant and age distributions for the infected population are drawn from the contact study carried out in Ciutat Vella by the ASPB during 2010-2015. · The distributions for the sick, treated and under-treatment population are drawn from the case study carried out in Ciutat Vella from 2005-2015.
INFECT	Once someone is sick and infects someone else new: · The new infected individual will be set its age randomly according to the percentages of the initial population (specified in Table 3.1) · If the infectious agent was immigrant, the new infected will have a 90% chance of also being immigrant · No gender taken into account	Once someone is sick and infects someone else new: · The new infected will be set an age according to the social patterns studied through the contact study. · The origin and gender of the new infected will also be set according to the social patterns observed. Depending on the age group, gender and origin of the infectious agent, the new infected will be set a specific age, gender and origin too. Those probabilities are described in Table 3.2.
GET SICK	· Probability of sickening depended on the time since first infection happened. · Individuals with diabetes, risk factors or immunodeficiency had a factor multiplying the probability.	· Probability of sickening depends on the time since first infection. · Individuals with diabetes, risk factors or immunodeficiency have a factor multiplying the probability. · Individuals younger than 15 also have a factor multiplying the probability.

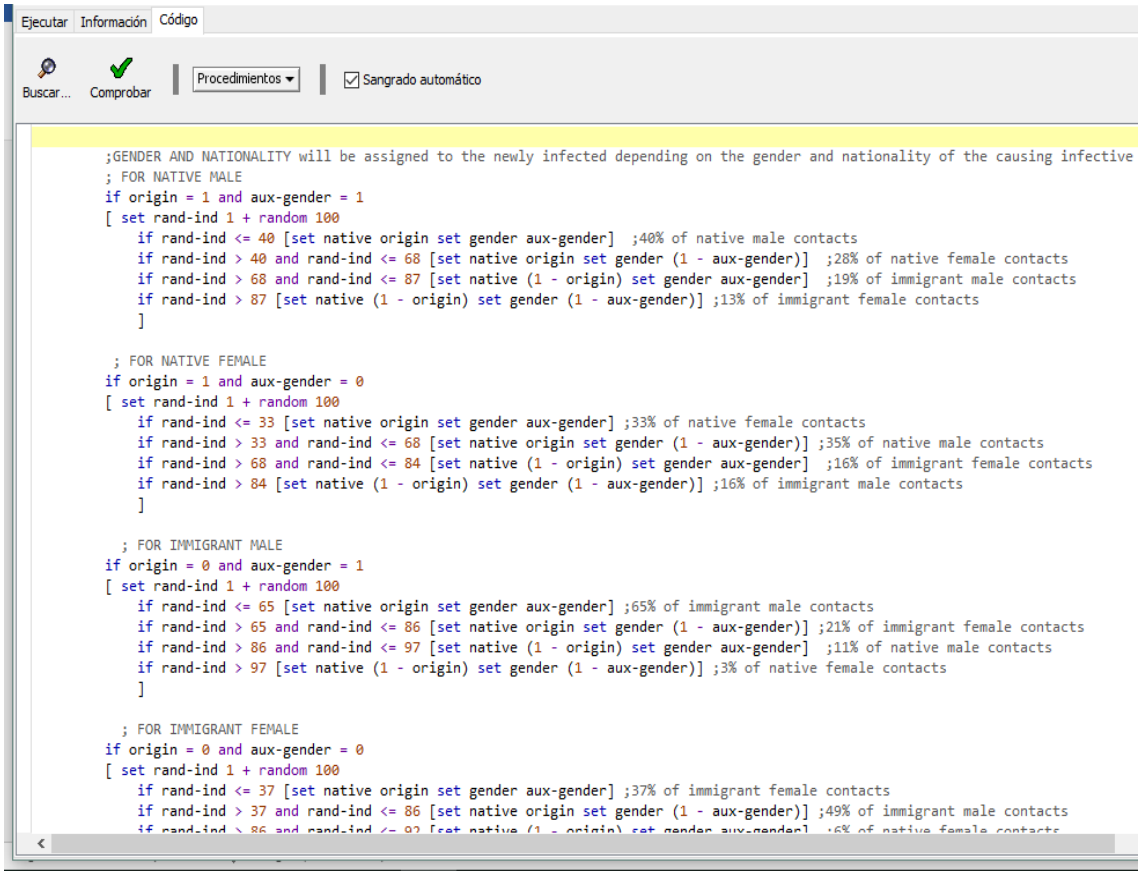

Figure 3.2. Screenshot of the source code of the model. Assignment of gender and origin to the new infected depending on the infectious individuals' characteristics.

3.3 SIMULATION RESULTS & DISCUSSION

3.3.1 Evolution of TB incidence during 10 years

To compare the suitability of the simulation results with the epidemiological data, the number of new TB cases will be used as a comparison parameter.

Epidemiological data

The evolution of the annual number of tuberculosis cases in Ciutat Vella from 2005 to 2015 can be observed in Figure 3.3.

Simulation results

The simulated evolution of the annual number of tuberculosis cases in Ciutat Vella during 10 years can be observed in Figure 3.4.

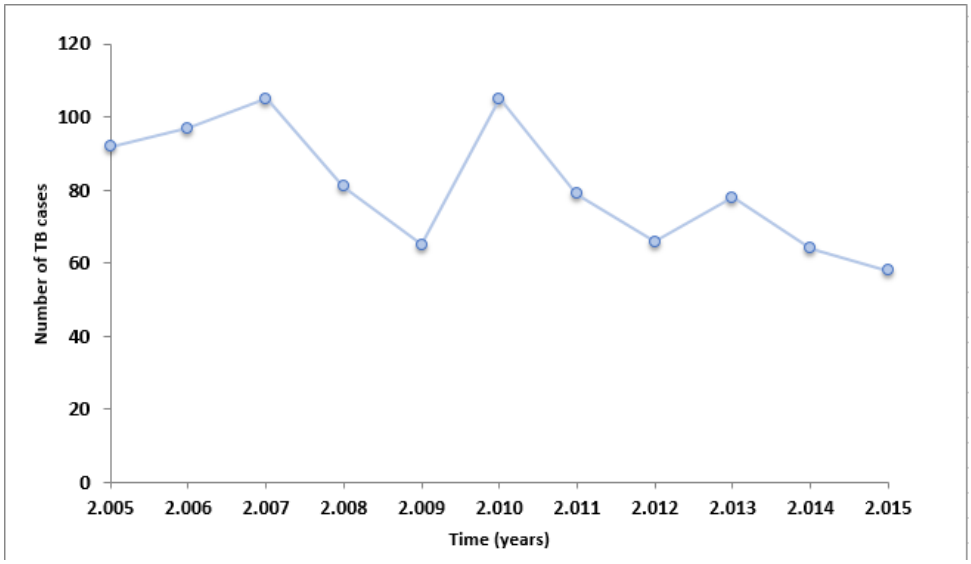

Figure 3.3 Evolution of the number of TB cases in Ciutat Vella from 2005 to 2015

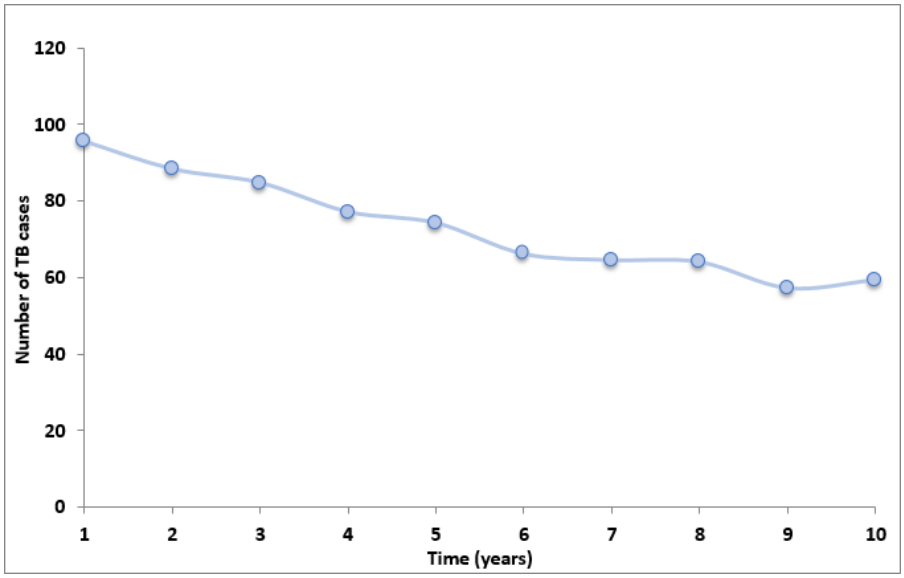

Figure 3.4 Simulated evolution of the number of TB cases in Ciutat Vella. Mean evolution of 10 different runs.

Comparison

Figure 3.3 shows the observed evolution of the TB incidence in Ciutat Vella. Figure 3.4 shows the 10-simulations mean evolution of TB incidence. It is difficult to draw a pattern from the epidemiological data (Fig. 3.3) since the oscillations are very wide due to the studied population size, but a general decreasing tendency from a value of around 100 TB cases per year to around 60 TB cases per year can be seen. The model faithfully represents this tendency. Oscillations cannot be seen in Figure 3.4 because the average values for each year have been computed from a number of 10 simulations, nevertheless if we look at each simulation individually, the variability between years can also be observed (see Figure 3.5 for the evolution of the TB incidence in each simulation individually).

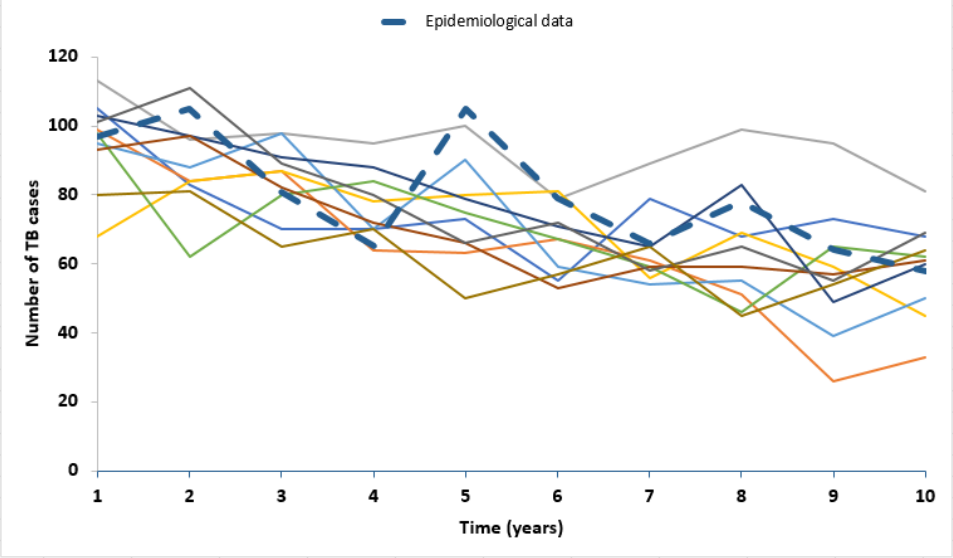

Figure 3.5 Simulated evolution of the number of TB cases in Ciutat Vella for all 10 different runs. Blue dotted line shows the epidemiological data evolution for comparison.

3.3.2 Mean pattern of TB cases according to age, gender and origin

To compare the suitability of the simulation results with the epidemiological data, the number of TB cases disaggregated by age, gender and origin will now assessed.

Epidemiological data

From the case study carried out in Ciutat Vella during 2005-2015 by the *Agència de Salut Pública de Barcelona*, Figures 3.6 and 3.7 were plotted.

From Figure 3.6, it can be clearly observed that there are more male TB cases in Ciutat Vella than female. A mountain-like pattern can be observed, which peaks at the age of 25-35 for both genders and fades down at the begging and at the end of life. The difference between male and female number of cases is very little during childhood and adolescence and it starts showing a great bias at the age of 15. By the age of 25-35 the bias rises to a value of 10 cases of difference.
The age and gender bias have already been assessed in Chapter 1, and it comes to no surprise to observe this tendency. There are clear differences between age groups and between genders and by disregarding those differences we could be drawing the wrong conclusions. Figure 3.6 is coherent with the hypothesis expounded before in this study.

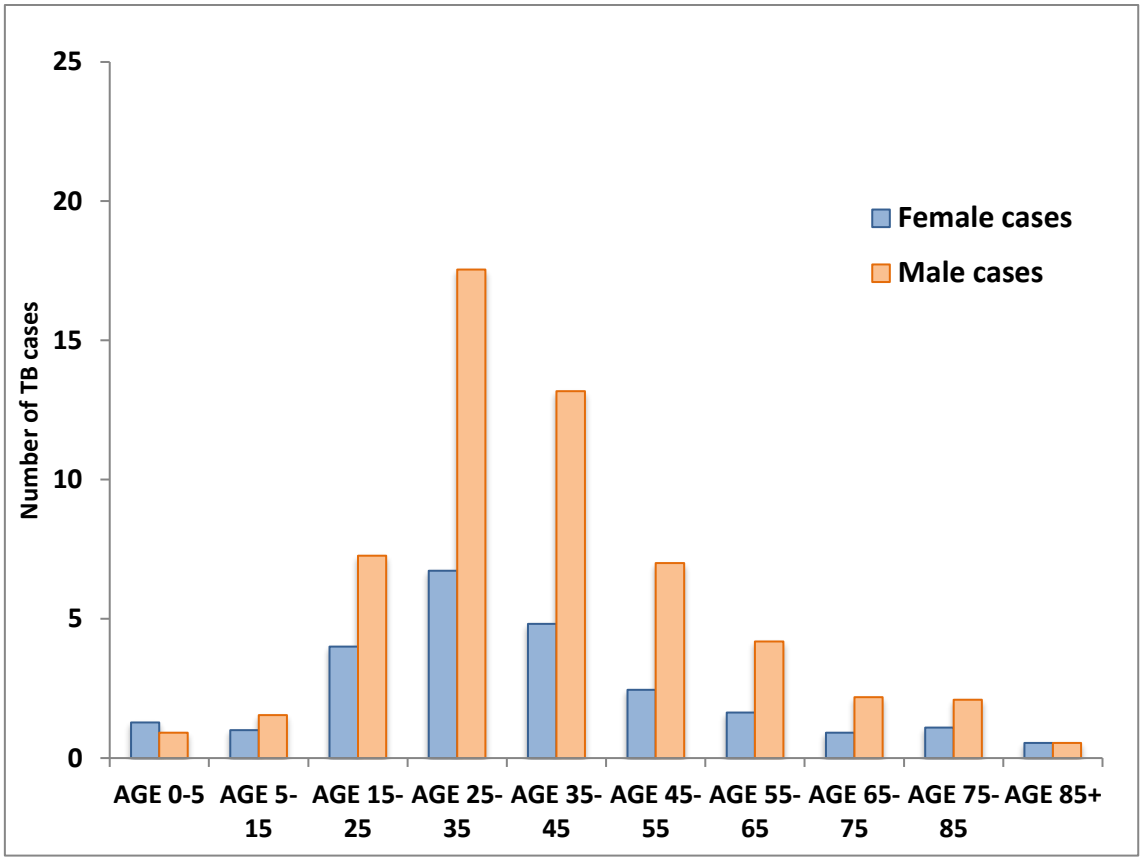

Figure 3.6 Mean annual number of TB cases (2005-2015) in Ciutat Vella by age groups and gender.

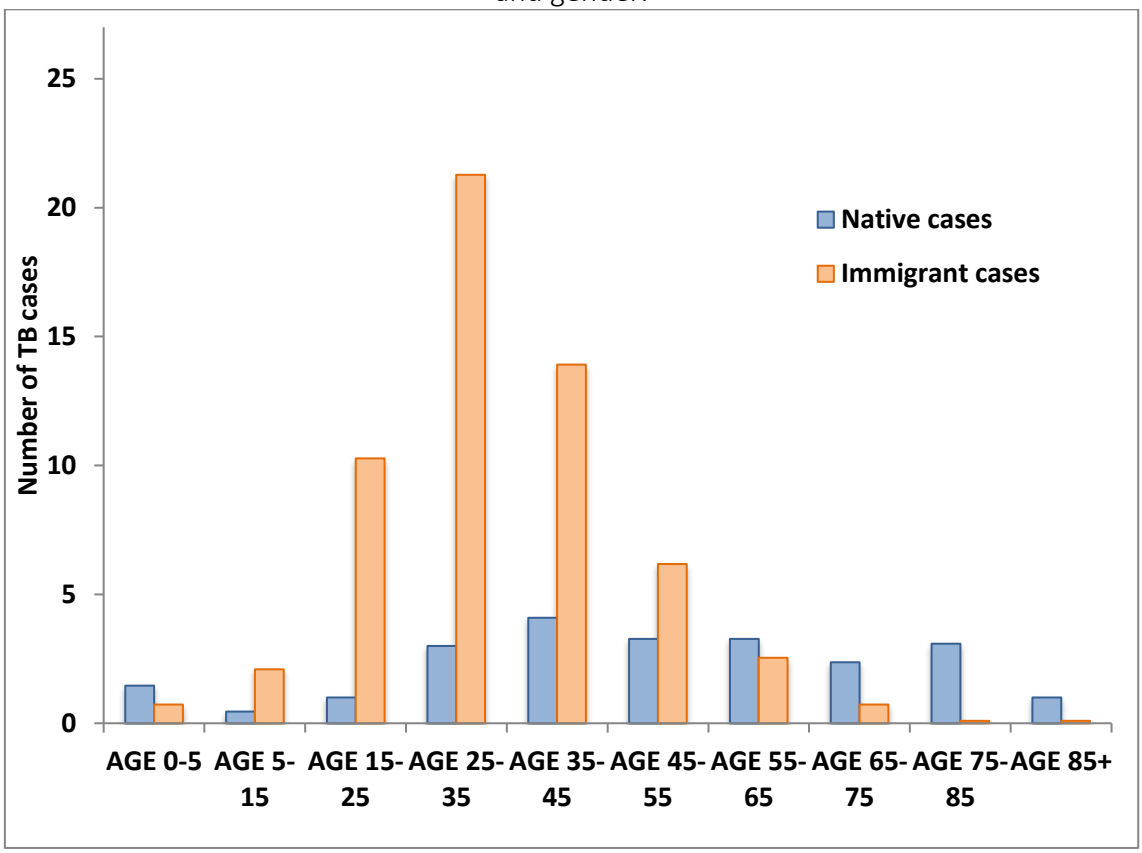

Figure 3.7 Mean annual number of TB cases (2005-2015) in Ciutat Vella by age groups and origin.

The percentage of registered cases from 2005 to 2015 in Ciutat Vella that were immigrant was around 70%. There is a very significant difference between the native TB incidence and the immigrant as it can be seen in Figure 3.6. Going back to Chapter 1, Figure 1.10 plotted the distribution of ages of the immigrant population in Ciutat Vella, and not surprisingly if Figure 3.7 is compared to Figure 1.10 a very similar shape can be observed. Hence, the distribution of ages of the TB sick population is greatly influenced by the distribution of ages of the immigrant population in this neighbourhood. In fact, when carrying out an epidemiology study for the population of TB sick in Ciutat Vella it will be essential to observe the immigrant population habits, characteristics and distributions rather than the general or the native population parameters.

Simulation results

Since the epidemiological data available scopes 10 years, all simulations were also run for 10 years. To obtain consistent results 10 different 10-year simulations were carried out and the mean was computed. The results obtained can be observed in Figure 3.8 and Figure 3.9.

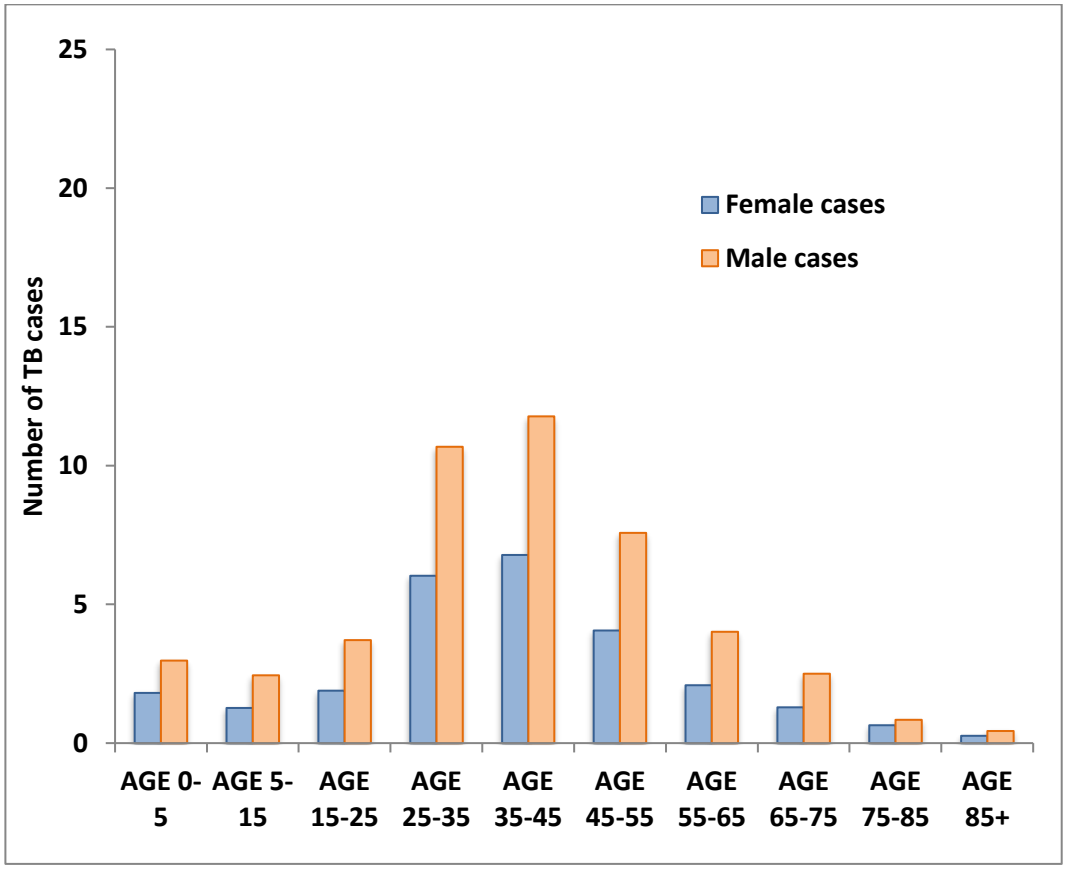

Figure 3.8 Mean annual number of TB cases (10 year simulations) in Ciutat Vella by age groups and gender. Results show the mean of 10 runs.

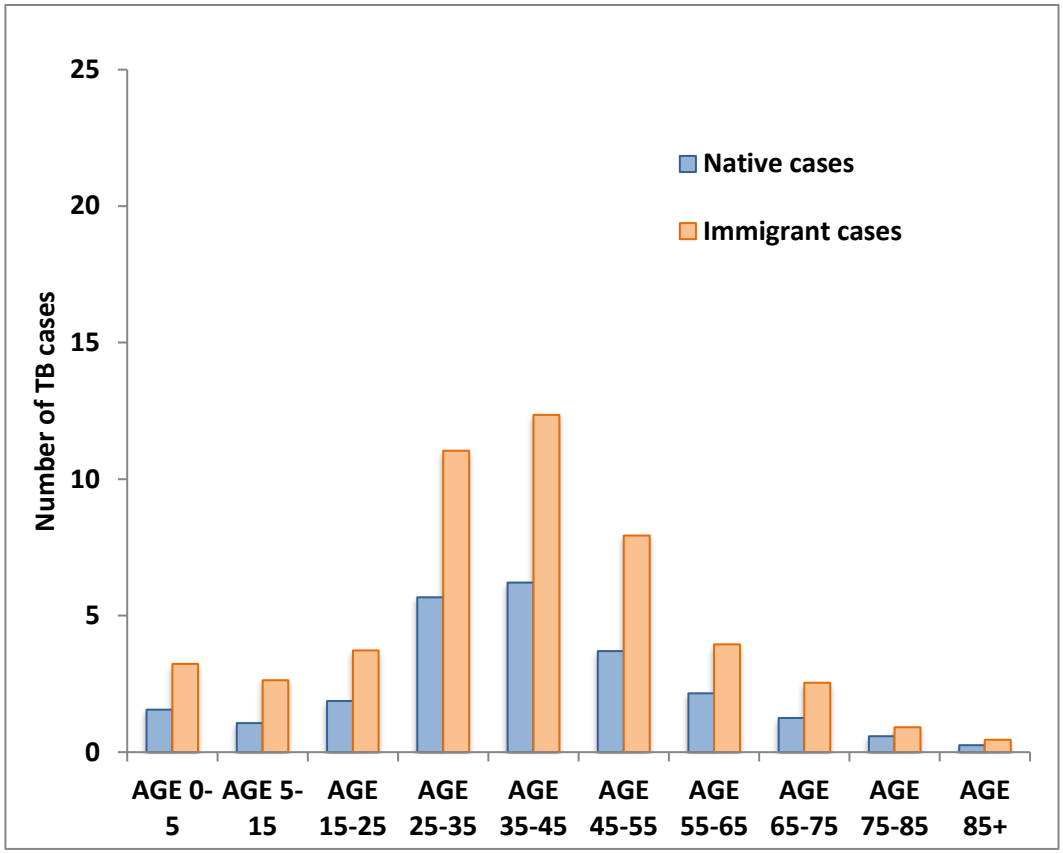

Figure 3.9 Mean annual number of TB cases (10 year simulations) in Ciutat Vella by age groups and origin. Results show the mean of 10 runs.

Comparison

Figures 3.6 and 3.8 both show the distribution of ages for the annual TB sick cases in Ciutat Vella disaggregated by male/female. Figure 3.6 shows the observed data for the past 10 years. Figure 3.8 shows the results obtained with the model, which attempts to simulate reality. A similar mountain-like pattern can be observed in both figures, with less cases during childhood and third age and more cases during the young adulthood. Males are clearly more affected by the disease than female. Nevertheless, some differences between the simulation results and the epidemiological data should be noted. The gender bias is greater in reality than the one simulated for the 25-45 age period. The simulated peak of the "mountain" appears at the age of 35-45 instead of the 25-35 observed peak in the epidemiological data.

Comparison between the simulations and the epidemiological data for the distribution of ages disaggregated by origin (native/immigrant) will now be assessed. Again, a similar distribution can be observed for the epidemiological data (Fig.3.7) and the simulation results (Fig. 3.9), but the differences here are notorious. The bias between immigrants and natives at the age of 25-35 has a magnitude of 15 TB cases in Figure 3.7, and only of approximately 5 in Figure 3.9. In general, simulation results should show less native cases for all age groups and more immigrant cases for the ages 15-25 and 25-35 for them to be more precise and close to reality.

3.3.3 Discussion

Simulation results for the evolution of tuberculosis are satisfactorily precise. The distribution of ages, gender and origin of the TB sick individuals is not very accurate in quantitative terms when comparing it to epidemiological data, although the initial qualitative agreement is promising.

Nevertheless, the differences observed between the simulated and the epidemiological data on profile distributions are insightful. Those differences are actually telling us that the distribution of TB infected that was used in the model (extracted from the available epidemiological data) is different from the real distribution. Hence, the model is stressing the need for further work to understand the distribution of the disease, specially the characteristics and profiles of the latent infected individuals.

It has been hypothesised that the differences observed between the epidemiological data and the simulations come from one specific source of error. The difficulty when inferring the distributions of the TB sick in the model comes from the distribution of the infected population. The infected population is a very ambiguous collective and little is known about them. Since most of the people who are infected, do not know they are, most of them do not even find out and they do not have any symptoms it is very difficult to characterize them and even more to keep track of them. In this case, we used the available data to infer the distribution of the infected population in Ciutat Vella. The contact study noted the characteristics of the friends and family of tuberculosis cases that turned out to have a TB infection. Therefore, the contact study gathered data from a significant number of TB infected people which was used by us to infer the characteristics of the whole TB infected population. Error is assured from this sampling, especially because this sample is biased. This sample is biased by the fact that all the studied sample was a relative of a TB case. For example, if the majority of found cases are immigrant, the majority of the contacts studied will also be immigrant, but this does not mean that there are not native people infected, it just means that it is not being studied. A non-oriented screening for detecting infected cases among general population and the profile of this subpopulation could provide interesting data to be incorporated that would improve the quality of simulation results. A better latent TB diagnosis will in turn give more accurate results on the model.

In conclusion, the results obtained by the simulations show a similar pattern to the epidemiological data and they can be used as a first approach to what the distribution of the individuals in the model should be like. Nevertheless, further research on what the distribution of the infected population should be done to obtain more precise epidemiological data on the latent TB population.

4. CONCLUSIONS

In addition of having developed an enhanced model, several conclusions can be drawn from the observed profile distributions, TB transmission patterns and the sickening probabilities study. Back in Chapter 1.6, the aim of the work was summarised in Table 1.2 and we will now to attempt to give an answer to every question raised at the beginning of the project.

Table 4.1. Answers to the questions raised at the beginning of the study

QUESTIONS AND ANSWERS	
1.	*What is the profile of the people infected by a TB case, depending on the profile of the case itself?*
	The profile of the people infected by a case depending on the profile of the case has been characterized and there are several specific features that should be noted: - There is a strong correlation of cases and contacts between the ages of 20 and 60 which seems to describe the working society. We can therefore conclude that cases in this age group (20-60) will most likely infect people who are also in this age group. - We can conclude that the elderly (60+) don't have contacts below the age of 50. Hence, an old TB sick person will only infect other older adults. - There is an observable transmission between children (0-10) and people in the parenting/teaching age (25-45) and vice versa. - Female relate, and therefore infect more often children and old people than male do. - Immigrants infect mostly (86%) other immigrants and native infect mostly but not that often (68%) other natives. - Male in Ciutat Vella infect mostly other male (73%), a result that is biased by the strong male-to-male correlation (76%) in the immigrant population compared to the male-to-male correlation (59%) in the native population.
2.	*What is the probability of sickening for someone with latent TB depending on their profile?*
	The probability of progressing to disease once infected from TB has also been assessed. The features that are worth noting are: - Children younger than 15 have an increased chance of sickening once infected compared to adults. - Adults from the age of 15 to 100 have all a similar risk of progressing to disease. - No conclusions could be drawn to whether there are or there are not differences on the risk of sickening between genders and between origins. Observed data was inconclusive and suspicious and further research needs to be carried out to determine these parameters.

3. *How can the results be quantitatively evaluated to be included in the epidemiology model?*

To be able to include the conclusions drawn into the model, they had to be assigned a value, they had to be parametrized. To do so:

- Percentages to quantitatively evaluate the intensity of transmission between different profiles were extracted from the plots that relate TB cases and TB contacts.
- Percentages on the probability of sickening disaggregated by age groups, by gender and by origin were also read from the plots drawn.

4. *Do the simulation results obtained faithfully represent the epidemiological results?*

Comparison between the simulation results and the epidemiological data from Ciutat Vella has been carried out and the following conclusions have been drawn:

- Satisfactory results have been obtained when comparing the evolution of the TB incidence in Ciutat Vella. Hence, the model faithfully represents the evolution of TB.
- The simulation results of the distributions of ages, gender and origin amongst the TB sick in Ciutat Vella are in qualitative agreement to the epidemiological distributions. The quantitative differences observed give us valuable information since they reveal there are hidden distributions of the TB infected population which remain unknown. The model has allowed us to see these differences, which stress the need for further work to study the TB infected individuals' characteristics.
- The simulations show a smaller bias between genders and between origins than the bias observed in the epidemiological data. The simulated male to female ratio and immigrant to native ratio are smaller than in reality. Further work is required when studying the infected population to infer more precisely the distribution of the sick and obtain more accurate results, closer to the epidemiological data observed.

5. *How will comprehending these patterns help us towards the goal of controlling and preventing the tuberculosis disease?*

In conclusion, a tuberculosis transmission pattern and different sickening probabilities depending on the profile of the individuals have been introduced into the simulation model that mimics the dynamics of the disease in Ciutat Vella. Introducing those parameters has allowed us to observe results which show a distribution of ages, gender and origin more similar to the epidemiological data.

This model can be used to make predictions on how the disease will evolve in a geographical area. Therefore, the impact different TB control strategies will have can also be assessed and quantified. Having a more accurate model which takes into account differences between male/female, native/immigrant and age groups will enable to make more precise simulations, hence more precise predictions on how the disease will evolve.

We have observed that the distribution of different profiles amongst the TB infected or sick population is very diverse. Considering the same proportion of males and females, natives and immigrants or children and adults when applying a control strategy can lead to making the wrong decision. Further disaggregated data should be available worldwide to be able to make an assessment on the diversity of profiles of the TB sick individuals.

When studying Ciutat Vella in particular, it can be observed that over 50% of the TB cases are immigrant male adults, and they mostly infect other immigrant male adults, hence there is a strong TB transmission channel in this specific collective. If the places where this collective usually gathers can be identified and tackled, it is likely that a significant decrease in the number of TB cases in Ciutat Vella will be observed.

It will be indispensable to take into account those factors when applying TB control strategies for the neighbourhood of Ciutat Vella. Knowing which are the most susceptible collectives and the transmission patterns will allow to apply optimized and more efficient measures for the control and eradication of the tuberculosis disease in Barcelona.

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APPENDICES

APPENDIX A. ADDITIONAL FIGURES OF CONTACT TRACING ANALYSIS

Figures A1 to A8: Gender and origin relationship between TB cases and contacts in Ciutat Vella disaggregated by age groups:

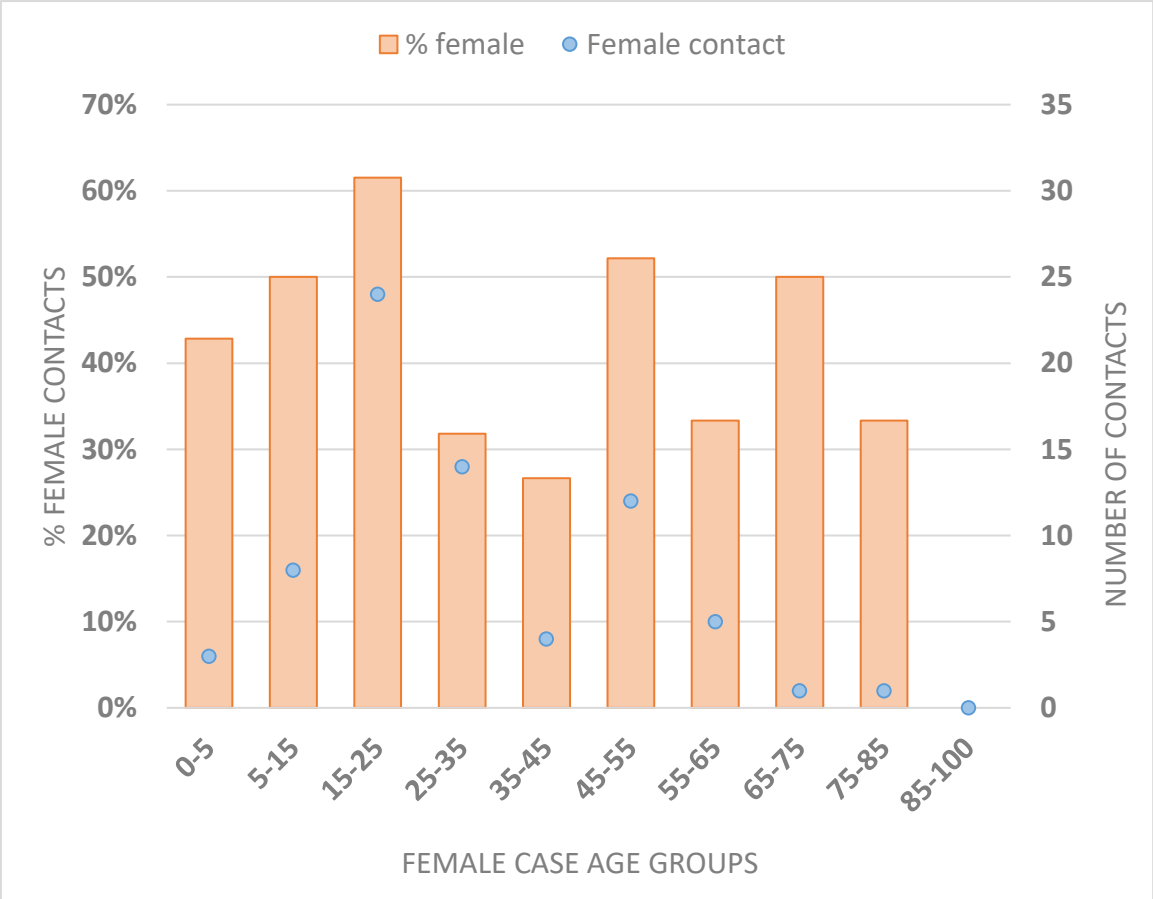

Figure A1: Percentage of female among positive contacts disaggregated by age groups in Ciutat Vella (bars), together with the absolute number of female contacts in each age group (dots).

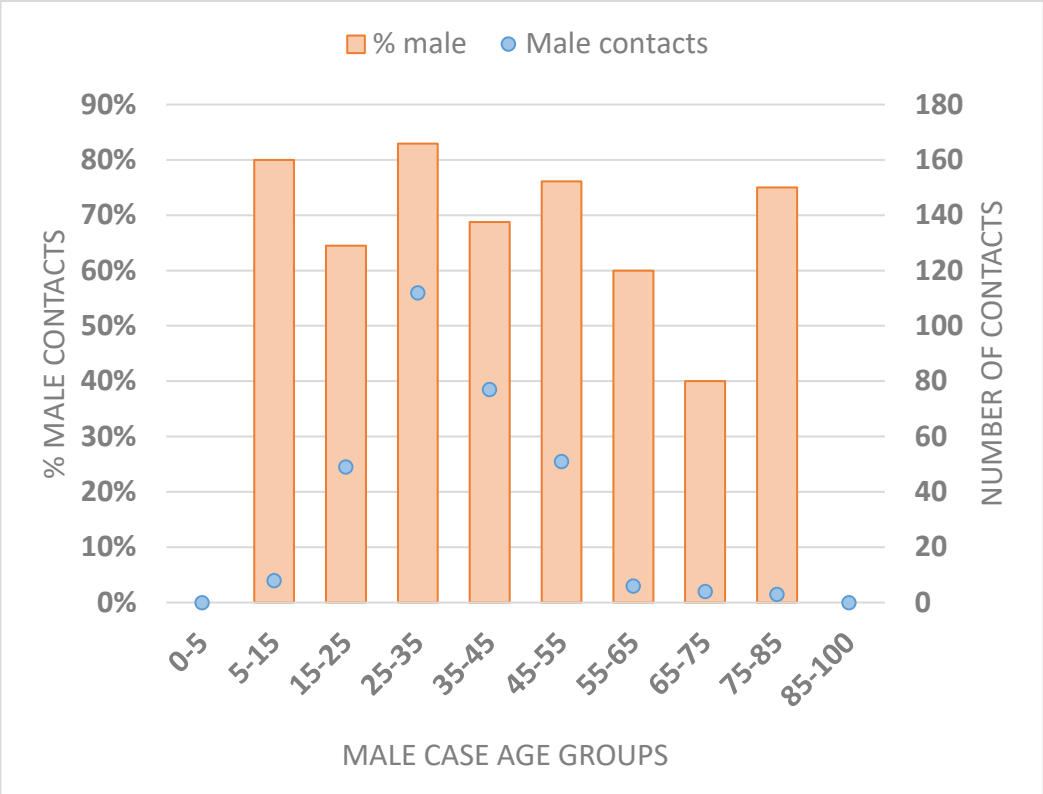

Figure A2: Percentage of male among positive contacts disaggregated by age groups in Ciutat Vella (bars), together with the absolute number of male contacts in each age group (dots).

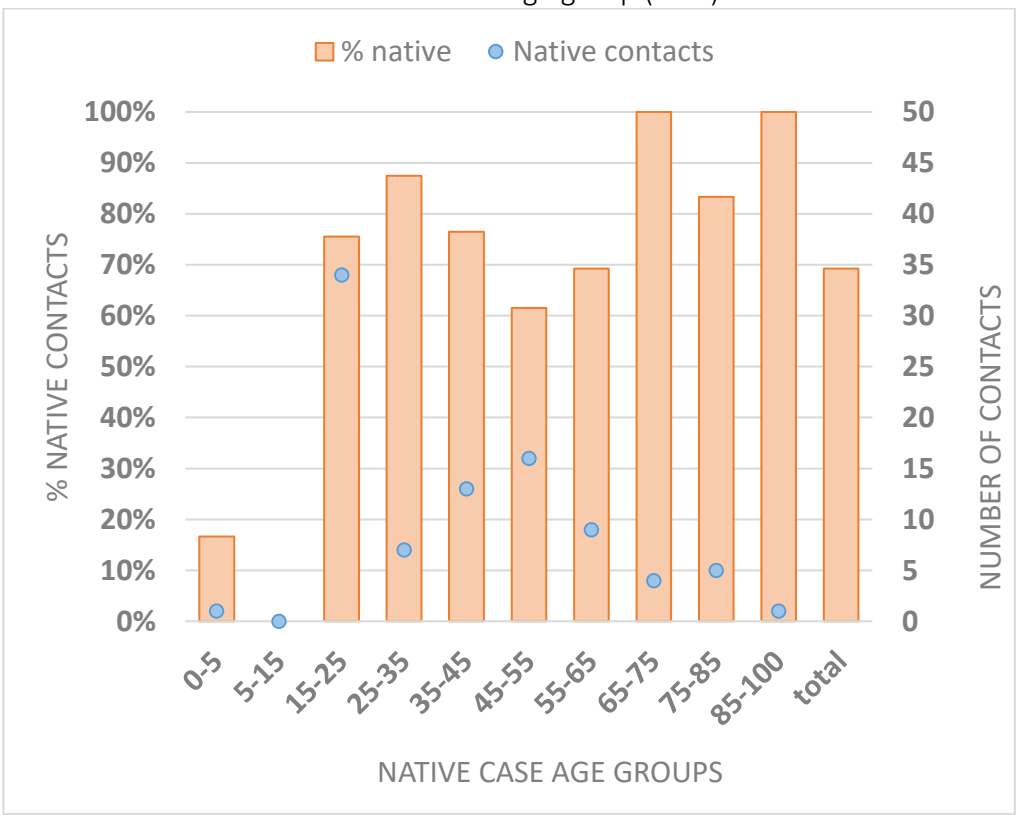

Figure A3: Percentage of native among positive contacts disaggregated by age groups in Ciutat Vella (bars), together with the absolute number of native contacts in each age group (dots).

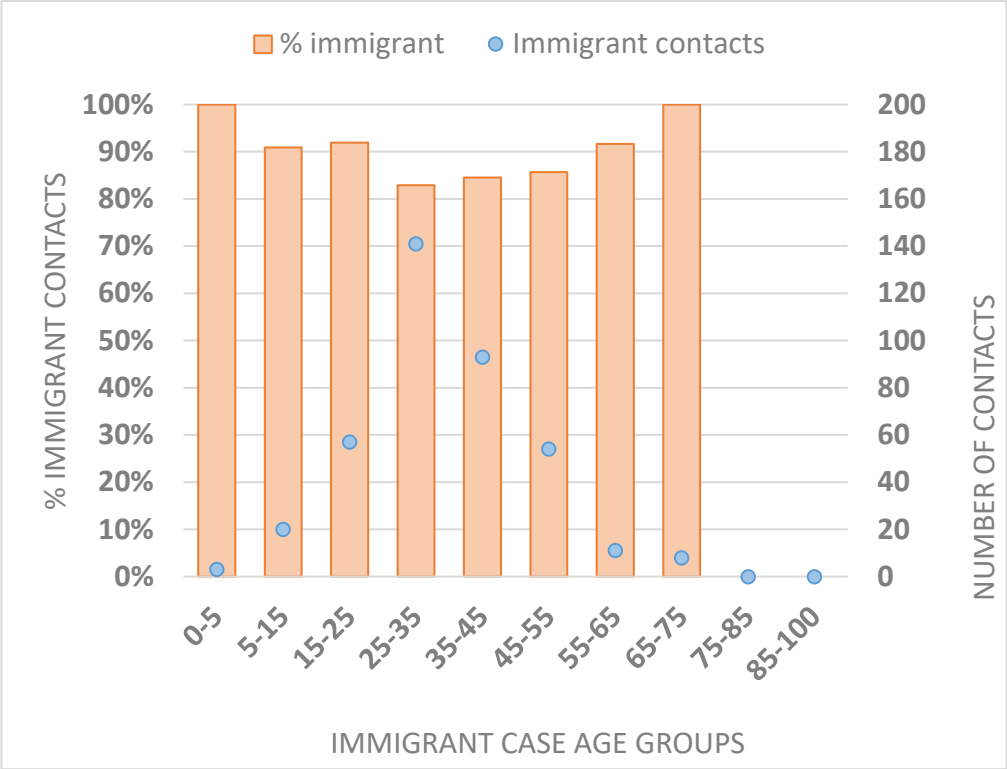

Figure A4: Percentage of immigrants among positive contacts disaggregated by age groups in Ciutat Vella (bars), together with the absolute number of immigrant contacts in each age group (dots).

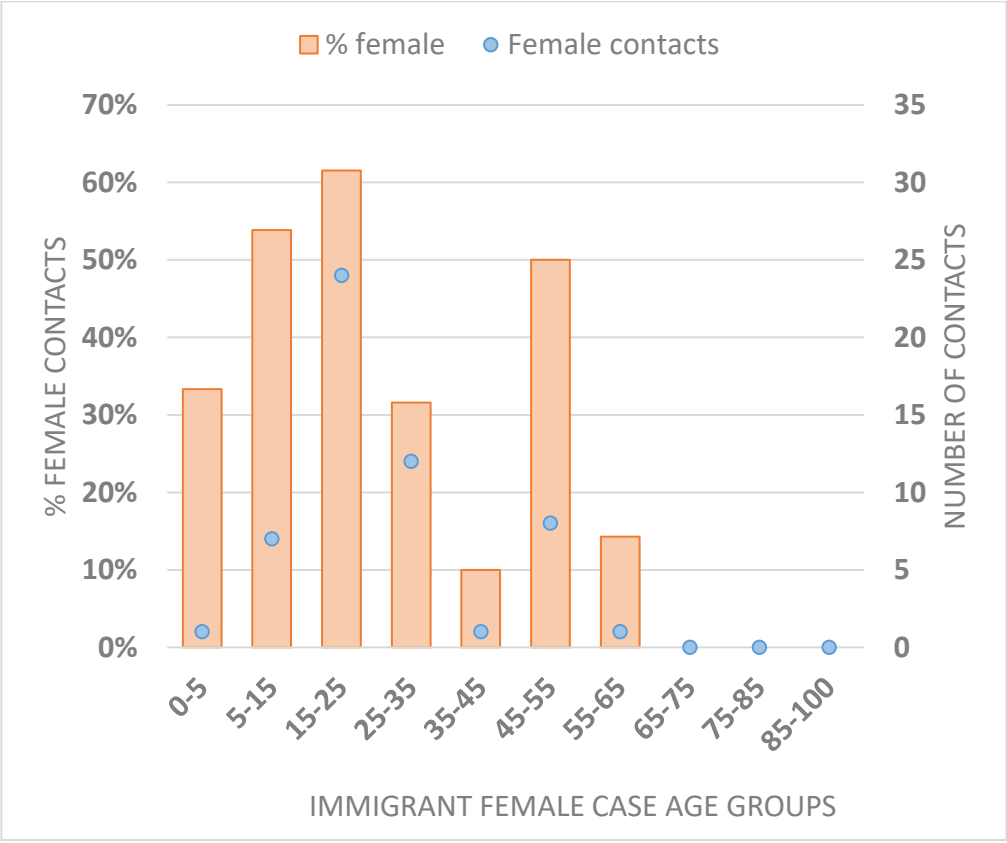

Figure A5: Percentage of immigrant female among positive contacts disaggregated by age groups in Ciutat Vella (bars), together with the absolute number of immigrant female contacts in each age group (dots).

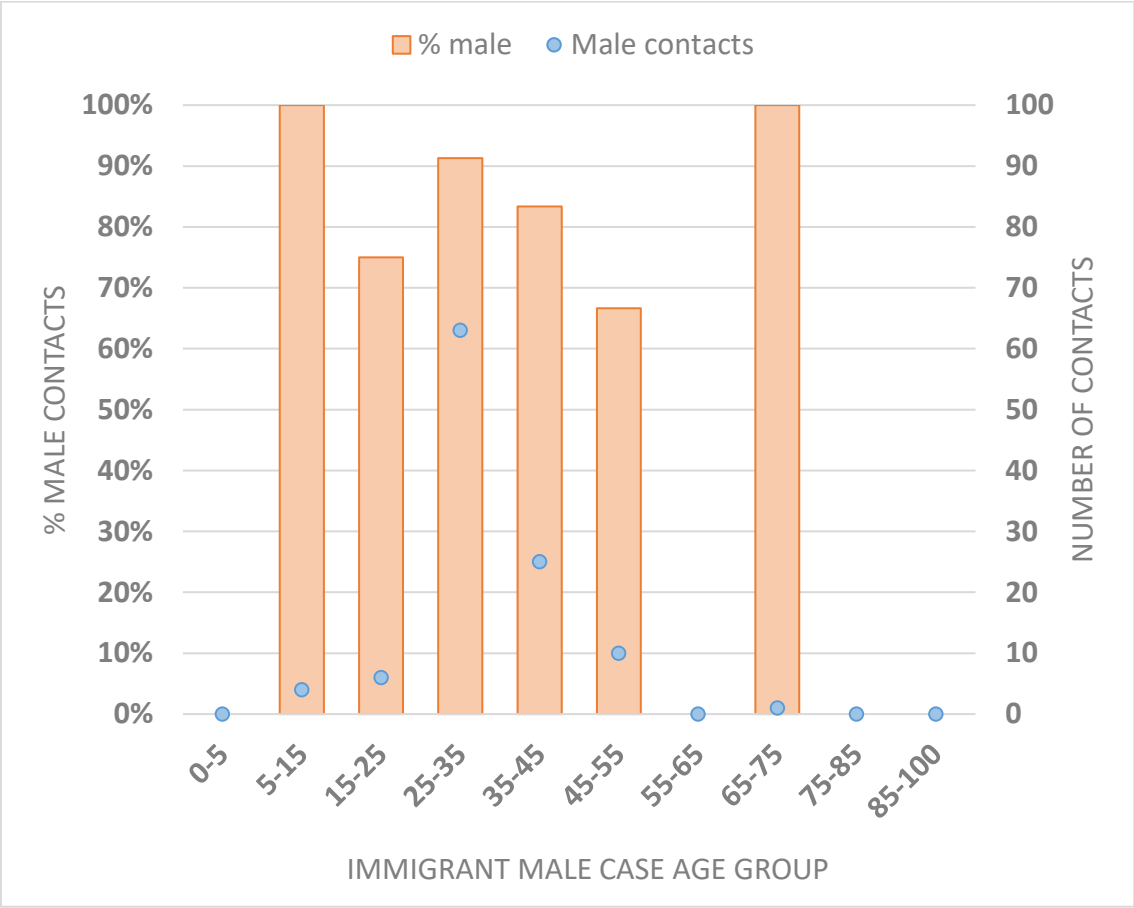

Figure A6: Percentage of immigrant male among positive contacts disaggregated by age groups in Ciutat Vella (bars), together with the absolute number of immigrant male contacts in each age group (dots).

APPENDIX B. SOURCE CODE OF THE MODEL

```
;; ************************************************************************
;; ** Simulation of the daily evolution of TB in Ciutat Vella (Barcelona) **
;; ************************************************************************


;; Declaration of global variables, subpopulations (breed) and features of
each subpopulation (note that "turtles" refer to all subpopulations).

globals
[
  death-index
  day-of-year
  day-total
  year-count
  rand-ind
  infection-rate
  get-sick-rate
  age-factor ;JULIAEDIT
  gender-factor ;JULIAEDIT
  nationality-factor ;JULIAEDIT
  timing

  initial-TB-sick-prevalence
  initial-TB-infected-prevalence
  initial-TB-treatment-prevalence
  initial-TB-treated-prevalence

  total-infected-people
  total-sick-people
  total-treatment-people
  total-treated-people
  total-native-sick
  total-foreign-sick

  total-healthy-to-infected
  total-treated-to-infected
  total-infected-to-sick
  total-treatment-to-sick
  total-treated-to-sick
  total-treatment-no-abandon
  total-treatment-abandon
  incidence-per-year ; JULIAEDIT


  total-create-infected
  total-create-sick
  total-create-treatment
  total-create-treated
  total-create-healthy


  total-sick-diabetes
  total-sick-risk
  total-sick-immunodep
  total-sick-smearpositive
  total-sick-women ;JULIAEDIT
  total-sick-men ; JULIAEDIT
  ;; Counters to evaluate de incidence disaggregated by age and gender and
origin. JULIAEDIT
  sick-men-0-5
  sick-men-5-15
  sick-men-15-25
  sick-men-25-35
  sick-men-35-45
  sick-men-45-55
```

```
sick-men-55-65
sick-men-65-75
sick-men-75-85
sick-men-85+
sick-women-0-5
sick-women-5-15
sick-women-15-25
sick-women-25-35
sick-women-35-45
sick-women-45-55
sick-women-55-65
sick-women-65-75
sick-women-75-85
sick-women-85+
sick-immigrant-0-5
sick-immigrant-5-15
sick-immigrant-15-25
sick-immigrant-25-35
sick-immigrant-35-45
sick-immigrant-45-55
sick-immigrant-55-65
sick-immigrant-65-75
sick-immigrant-75-85
sick-immigrant-85+
sick-native-0-5
sick-native-5-15
sick-native-15-25
sick-native-25-35
sick-native-35-45
sick-native-45-55
sick-native-55-65
sick-native-65-75
sick-native-75-85
sick-native-85+


total-treatment
total-healthy
total-abandon-treated
total-no-abandon-treated

from-treated-to-healthy
from-infected-to-healthy
total-death-people

second-inf-list
days-sick-list
mylist

aux-Mdd-rnd
aux-Mdd-val
aux-Mdd-var
aux-Mdd

aux-smearpositive
aux-days-treatment

aux-simulation-period
days-treatement-random

n-inf-1y
n-inf-2y
n-inf-3y
n-inf-4y
n-inf-5y
n-inf-6y
n-inf-7y
combined-prob
```

```
  state-simulation
]

breed [infected an-infected]
breed [sick a-sick]
breed [treatment a-treatment]
breed [treated a-treated]


patches-own [num-healthy]
turtles-own [age native immunodepression risk-factors diabetes smearpositive
gender] ;JULIAEDIT
infected-own [days-infected]
sick-own [days-sick days-diagnostic-delay second-infection]
treatment-own [days-treatment-ment]
treated-own [p-relapse days-start-treatment days-treatment-ed]


;; *************** SET-UP ***************
;; ** initial configuration of the world **
;; ***************************************

to set-up


  ;; clear all

  ca
  ;Total population 105121
  show "Initial time"
  show date-and-time
  ;random-seed 1024
  output-print "Running"
  set state-simulation "SET-UP"

  set-default-shape infected "person"
  set-default-shape sick "person"
  set-default-shape treatment "person"
  set-default-shape treated "person"


  ;set initial-TB-infected-prevalence initial-TB-infected-per-100000-
inhabitants / 1000
  set initial-TB-sick-prevalence initial-TB-sick-per-100000-inhabitants / 1000
  set initial-TB-treatment-prevalence initial-TB-treatment-per-100000-
inhabitants / 1000
  set initial-TB-treated-prevalence initial-TB-treated-per-100000-inhabitants
/ 1000


  ;; In Barcelona (1619337 inhabitants in 2010), there was 429 sick people. It
represents 0,0265 % of the total population (per year).
  ;; The exponential distribution of the sick people as function of the
diagnostic delay time shows that 66% of sick people goes to the medical
service before 44 days.
  set initial-TB-sick-prevalence initial-TB-sick-prevalence * (44 / 365)

    ;; It is considered an infected individual during 7 years.

  ;set initial-TB-infected-prevalence initial-TB-infected-prevalence  * 7

  ;; The treatment period lasts 180 days (0,5 year).

  set initial-TB-treatment-prevalence initial-TB-treatment-prevalence * (180 /
365)
```

```
  ;; It is considered a treated people during 2 years.

  set initial-TB-treated-prevalence initial-TB-treated-prevalence * 2


  ;; reset counters
  set total-infected-people 0
  set total-sick-people 0
  set total-native-sick 0
  set total-foreign-sick 0
  set total-treatment-people 0
  set total-treated-people 0
  set from-treated-to-healthy 0
  set from-infected-to-healthy 0

  set total-healthy-to-infected 0
  set total-treated-to-infected 0
  set total-infected-to-sick 0
  set total-treatment-to-sick 0
  set total-treated-to-sick 0
  set total-treatment-no-abandon 0
  set total-treatment-abandon 0
  set incidence-per-year 0

  set total-create-infected 0
  set total-create-sick 0
  set total-create-treatment 0
  set total-create-treated 0
  set total-create-healthy 0

  set total-sick-diabetes 0
  set total-sick-risk 0
  set total-sick-immunodep 0
  set total-sick-smearpositive 0
  set total-sick-women 0 ;JULIAEDIT
  set total-sick-men 0 ;JULIAEDIT
  ;; Counters to evaluate de incidence disaggregated by age and gender and
origin. JULIAEDIT
  set sick-men-0-5 0
  set sick-men-5-15 0
  set sick-men-15-25 0
  set sick-men-25-35 0
  set sick-men-35-45 0
  set sick-men-45-55 0
  set sick-men-55-65 0
  set sick-men-65-75 0
  set sick-men-75-85 0
  set sick-men-85+ 0
  set sick-women-0-5 0
  set sick-women-5-15 0
  set sick-women-15-25 0
  set sick-women-25-35 0
  set sick-women-35-45 0
  set sick-women-45-55 0
  set sick-women-55-65 0
  set sick-women-65-75 0
  set sick-women-75-85 0
  set sick-women-85+ 0
  set sick-immigrant-0-5 0
  set sick-immigrant-5-15 0
  set sick-immigrant-15-25 0
  set sick-immigrant-25-35 0
  set sick-immigrant-35-45 0
  set sick-immigrant-45-55 0
  set sick-immigrant-55-65 0
  set sick-immigrant-65-75 0
  set sick-immigrant-75-85 0
  set sick-immigrant-85+ 0
```

```
  set sick-native-0-5 0
  set sick-native-5-15 0
  set sick-native-15-25 0
  set sick-native-25-35 0
  set sick-native-35-45 0
  set sick-native-45-55 0
  set sick-native-55-65 0
  set sick-native-65-75 0
  set sick-native-75-85 0
  set sick-native-85+ 0

  set total-abandon-treated 0
  set total-no-abandon-treated 0
  set total-healthy 0

  set total-death-people 0


  ;; Creation of all subpopulations

  create-infected initial-TB-infected ;round (population * initial-TB-
infected-prevalence / 100)
  ask infected
  [
    set color orange
    set size 2
    set xcor random-pxcor
    set ycor random-pycor
  ]

  create-sick  round (population * initial-TB-sick-prevalence / 100)
  ask sick
  [
    set color red
    set size 2
    set xcor random-pxcor
    set ycor random-pycor
    set second-infection 0
  ]

  create-treatment round (population * initial-TB-treatment-prevalence  / 100)
  ask treatment
  [
    set color blue
    set size 2
    set xcor random-pxcor
    set ycor random-pycor
  ]

  create-treated round (population * initial-TB-treated-prevalence / 100)
  ask treated
  [
    set color yellow
    set size 2
    set xcor random-pxcor
    set ycor random-pycor
  ]

  set total-healthy (population - count sick - count treated - count treatment
- count infected)


  repeat total-healthy [ask one-of patches[ set num-healthy num-healthy + 1]]
  ;Li demana a un patch random que la seva variable num-helathy augmenti 1 de
valor. Aquesta demanda la fa tantes vegades com gent al mon hi ha (total
healthy).
  ;El resultat Ã©s distribuir aleatoriament tota la gent sana com a nÃºmeros
en els patches. La distribuciÃ³ Ã©s realment aleatÃ²ria? influeix?
```

```
   patch-colors

  ;; General features of populaton

  set population (count sick + count treated + count treatment)

  ;; Age is the number of days of life of people.
 ;; Age for the sick, treated and treatment (Age groups: 0-5,5-15,15-25,25-
35,35-45,45-55,55-65,65-75,75-85,85+). Data from the ASPB case study for
Ciutat Vella (mean 2005-2015) ; JULIAEDIT
;; Age distribution amongst the sick people (% of sick people in each age-
group)
ask turtles [set age 99999]

 let a round (population * 0.0270)
 let b round (population * 0.0315)
 let c round (population * 0.1393)
 let d round (population * 0.3000)
 let f round (population * 0.2225)
 let g round (population * 0.1169)
 let h round (population * 0.0719)
 let i round (population * 0.0382)
 let j round (population * 0.0393)
 let k round (population * 0.0135)

 ask n-of a turtles with [age = 99999][set age random 1825]; 0-5 y.o
 ask n-of b turtles with [age = 99999][set age (random 3650) + 1825] ; 5-15
y.o
 ask n-of c turtles with [age = 99999][set age (random 3650) + 5475] ; 15-25
y.o
 ask n-of d turtles with [age = 99999][set age (random 3650) + 9125] ; 25-35
y.o
 ask n-of f turtles with [age = 99999][set age (random 3650) + 12775] ; 35-45
y.o
 ask n-of g turtles with [age = 99999][set age (random 3650) + 16425] ; 45-55
y.o
 ask n-of h turtles with [age = 99999][set age (random 3650) + 20075] ; 55-65
y.o
 ask n-of i turtles with [age = 99999][set age (random 3650) + 23725] ; 65-75
y.o
 ask n-of j turtles with [age = 99999][set age (random 3650) + 27375] ; 75-85
y.o
 ask turtles with [age = 99999][set age (random 1825) + 31025] ; 85-90 y.o

 ;; Since the age distribution of infected is considered equal to the
population, data from Ajuntament de Barcelona (PadrÃ³ Municipal d'habitants
2015) for Ciutat Vella was used.
;; The age groups considered are (0-4, 5-14, 15-24, 25-34, 35-44, 45-54, 55-
64, 65-74, 75+).
;; The age distribution is determined following the Ciutat Vella contact study
ages ASPB 2010-2015
 ask infected [set age 99999]

 let l round (count infected * 0.0220)
 let m round (count infected * 0.0558)
 let n round (count infected * 0.1201)
 let o round (count infected * 0.2521)
 let p round (count infected * 0.2775)
 let q round (count infected * 0.1827)
 let r round (count infected * 0.0575)
 let s round (count infected * 0.0186)
 let t round (count infected * 0.0017)

 ask n-of l infected with [age = 99999][set age random 1825] ; 0-5 y.o
 ask n-of m infected with [age = 99999][set age (random 3650) + 1825] ; 5-15
y.o
```

```
 ask n-of n infected with [age = 99999][set age (random 3650) + 5475] ; 15-25
y.o
 ask n-of o infected with [age = 99999][set age (random 3650) + 9125] ;25-35
y.o
 ask n-of p infected with [age = 99999][set age (random 3650) + 12775] ; 35-45
y.o
 ask n-of q infected with [age = 99999][set age (random 3650) + 16425] ; 45-55
y.o
 ask n-of r infected with [age = 99999][set age (random 3650) + 20075] ; 55-65
y.o
 ask n-of s infected with [age = 99999][set age (random 3650) + 23725] ; 65-75
y.o
 ask infected with [age = 99999][set age (random 5475) + 27375] ; 75-90 y.o

  ;; In Ciutat Vella 56.83% of people are native and 43.17% are from others
countries (data corresponding to 2012).

  ;; JULIAEDIT 42.57% of people in CV are immigrant (data corresponding to
2015).
  ;; JULIAEDIT 71.57% of the sick cases in CV are immigrant (2005-2015 mean
case study ASPB)
  ;; JULIAEDIT 82.35% of the infected people in CV are immigrant
(extrapulmonary contact study ASPB 2010-2015)
  ;; JULIAEDIT 73.57% of the infected people in CV are immigrant (contact
study ASPB 2010-2015)

  ;; It will be assigned 1 to the variable native if the individual is from
here.
  ;; It will be assigned 0 to the variable native if the individual is from
others countries.

  ask turtles
  [
    set native 1
    set smearpositive 0
  ]

  ask n-of round (count treated * 0.7157) treated [ set native 0]
  ask n-of round (count treatment * 0.7157) treatment[ set native 0]
  ask n-of round (count sick * 0.7157) sick [ set native 0]
  ask n-of round (count infected * 0.7357) infected [set native 0]

  ;; It is assigned 1 to males and 0 to females following the gender
distribution
  ;; JULIAEDIT According to data for Ciutat Vella from Ajuntament de Barcelona
(2015) 52.6% are male in Ciutat Vella
  ;; JULIAEDIT 73.86% of the infected people in CV are male (extrapulmonary
contact study ASPB 2010-2015)
  ;; JULIAEDIT 68.02% of the infected people in CV are male (contact study
ASPB 2010-2015)

  ask infected [ifelse random-float 100 < 68.02 [set gender 1][set gender 0]]
  ;; For the sick, treated and treatment population 69.78% of them are male
according to the 2005-2015 mean case study ASPB conducted.
  ask sick [ifelse random-float 100 < 69.78 [set gender 1][set gender 0]]
  ask treated [ifelse random-float 100 < 69.78 [set gender 1][set gender 0]]
  ask treatment [ifelse random-float 100 < 69.78 [set gender 1][set gender 0]]

  ;; Percentage of population with AIDS and with other risk factors
  ask turtles
  [
    set immunodepression 1
    set risk-factors 1
    set diabetes 1
  ]

; set population (count turtles + sum [num-healthy] of patches)
```

```
  set population count turtles
  ask n-of (population * AIDS-rate / 100) turtles
  [
    set immunodepression Immunsupression-factor
  ]

  ask n-of (population * Other-risk-factors-rate / 100) turtles
  [
    set risk-factors Risk-factor  ;; Reduced from 2 to 1.5
  ]

  ask n-of (population * Diabetes-rate / 100) turtles
  [
    set diabetes Diabetes-factor
  ]
  ;; Particular features of some subpopulations


  ask sick
  [
    ;; The input data is Median-diagnostic-delay for authocton and foreign
people because it is different for both collectives.
    ;; The diagnostic delay time depends on the type of the individual (native
or not).
    ;; The diagnostic delay time for native individual is 45 days.
    ;; The diagnostic delay time for not native individual is 51.
    ;; It is considered a fixed value for native individual (45 days).
    ;; The increase (for not native individual) respect to the Median-delay-
time is parametrized with the variable aux-Mdd-var.

    ifelse native = 1
    [
      set aux-Mdd Mdd-authocton
    ]
    [
      set aux-Mdd Mdd-foreign
    ]

    set days-diagnostic-delay round random-normal aux-Mdd 4
    set days-sick random days-diagnostic-delay
  ]

  ask n-of (count sick * 0.22) sick [ set smearpositive 1]
  let n-inf 0

  ask infected
  [
    ;distribucio uniforme
    set days-infected 1 + random 365 * 7
    ;distribucio exponencial
    ;set days-infected (1 + item n-inf mylist)
    ;set n-inf n-inf + 1
  ]

  set n-inf-1y (count infected with [ days-infected <= 365 and days-infected >
0])
  set n-inf-2y (count infected with [ days-infected <= 730 and days-infected >
365])
  set n-inf-3y (count infected with [ days-infected <= 1095 and days-infected
> 730])
  set n-inf-4y (count infected with [ days-infected <= 1460 and days-infected
> 1095])
  set n-inf-5y (count infected with [ days-infected <= 1825 and days-infected
> 1460])
  set n-inf-6y (count infected with [ days-infected <= 2190 and days-infected
> 1825])
  set n-inf-7y (count infected with [ days-infected <= 2555 and days-infected
> 2190])
```

```
  ;show "nombre infectats"
  ;show initial-TB-infected
  ;show "nombre assignats a un any determinat"
  ;show (n-inf-1y + n-inf-2y + n-inf-3y + n-inf-4y + n-inf-5y + n-inf-6y + n-
inf-7y)
    ask treatment
  [
    set days-treatment-ment 1 + random 180
  ]

  ask treated
  [
    set p-relapse 1
    set days-treatment-ed 180

    ask n-of (count treated * abandon-rate / 100) treated
    [
      set days-treatment-ed 15 + 1 + random 164
    ]

    set days-start-treatment days-treatment-ed + random (731 - days-treatment-
ed)

    if days-treatment-ed < 180
    [
      set p-relapse 1 + 99 * (180 - days-treatment-ed) / 165
    ]
  ]

  ;; Initialization of global counters

  set year-count 0
  set day-of-year 0
  set day-total 0

  ;; Initialization of list of second infection indeces
  set second-inf-list []
  set days-sick-list []

  set total-healthy (sum [num-healthy] of patches)
  set population (count turtles + total-healthy)

  set population round population
  reset-ticks


  ;; Assignment of simulation period

  ifelse Simulation-period = "1 year"
  [
    set aux-simulation-period 365
  ]
  [
    ifelse Simulation-period = "2 years"
    [
      set aux-simulation-period 730
    ]
    [
      ifelse Simulation-period = "5 years"
      [
        set aux-simulation-period 1825
      ]
      [
        ifelse Simulation-period = "10 years"
        [
          set aux-simulation-period 3650
        ]
        [
```

```
          ifelse Simulation-period = "20 years"
          [
            set aux-simulation-period 7300
          ]
          [
            set aux-simulation-period 0
          ]
        ]
      ]
    ]
  ]



  set mylist []
  ask infected [
    set mylist lput days-infected mylist
  ]

  set combined-prob ( n-inf-1y * (0.0280 / 365) + n-inf-2y * ( 0.0220 / 365) +
n-inf-3y * (0.0168 / 365) + n-inf-4y * (0.0123 / 365) + n-inf-5y * (0.0085 /
365) + n-inf-6y * (0.0055 / 365) + n-inf-7y * (0.0032 / 365))
  ;show "Probabilitat combinada de la distribuciÃ³ de temps d'infecciÃ³ i
probabilitat d'emmalaltir"
  ;show combined-prob
  ;; Initialization values
  set day-total 1
  set day-of-year 1
  set timing 0

  set state-simulation "END OF SET-UP"
end



;; ******************** GO ******************
;; ** definition of the different processes **
;; ******************************************

to go


  ifelse aux-simulation-period = 0
  [
    if count infected = 0 and count sick = 0
    [
      set state-simulation "END OF SIMULATION"
      show date-and-time
      stop
    ]
  ]
  [
    if ticks > aux-simulation-period
    [
       ; set state-simulation "END OF SIMULATION"
        ;set-current-Æ’ "Histogram of number of second infections"
        ;set-plot-x-range 0 10
        ;set-plot-pen-mode 1
        ;set-histogram-num-bars 10
        ;histogram second-inf-list

;        print second-inf-list
        ;show "final-time"
        ;show date-and-time
        stop
    ]
  ]
```

```
  if day-total = 1
  [
    set state-simulation "SIMULATION"
    tick
  ]

  ;; This if-sentence is necessary to change de Median-diagnostic-delay in the
middle of the simulation.
  ;; You choose when you want to change this value. In the exemple, it is
chosen 2 years (730 days)

  ;; if day-total = 731
  ;; [
  ;;   set aux-Mdd-var 3
  ;; ]

  ;; Individuals increase their age in 1 day

  grow


  ;; Individuals move randomly

  move


  ;; Healthy and treated individuals may get infected if they meet a sick
person.

  infect

  ;; Infected individuals may get sick.

  get-sick

  ;; After the diagnosis period, sick people start to be treated.

  start-treatment


  ;; People under treatment may finish or abandon it.

 finish-treatment


  ;; To get sick again during the 2 years after initiating TB treatment (it
depends on the p-relapse (days of treatment)) or
  ;; to get healthy again after 2 years that the treatment started.

  relapse-or-recover


  ;; Individuals may die because of TB or for other reasons.

  death

  ;; Update patch colors

  patch-colors

  ;; Output files are updated.

 export-files


  ;; Update day's counters.

  refresh-day
```

```
  tick

end


;; ****************************
;; ** DETAILS OF EACH PROCESS **
;; ****************************

to patch-colors
  ask patches
  [
    set pcolor 60 + 1 * num-healthy
  ]

end

to grow

  ;; The age of each individual increases in 1 (one day) every day.

  ask turtles
  [
    set age age + 1
  ]

end


to move

  ;; Individuals move randomly to a neighbouring cells, one movement per day.

  ask turtles
  [
    rt random 360 fd 1
  ]

  ;; Same type of movement for healthy individuals

  ask patches [
    let loop-var num-healthy
    repeat loop-var
    [
      ask one-of neighbors
      [
        set num-healthy num-healthy + 1
      ]
      set num-healthy num-healthy - 1
    ]
  ]
end


to infect

  ;; If a healthy individual or a treated person meets a sick individual in
the own neighborhood, it gets sick with a certain probability.
  ;; This probability depends on the type of the sick individual
(smearpositive or smearnegative).
  ;; If the sick individual is smearpositive, the probability will be 30%.
  ;; If the sick individual isn't smearpositive, the probability will be 15%.
  ;; In Ciutat Vella there were, in 2010, 11 sick individual were
smearpositive.
  ;; The total of sick people was 104. This value corresponds to 10.58%.
```

```
  ;ask patches with [num-healthy > 0 and any? sick-on neighbors4]
  ask sick
  [
    let inf-produced 0
    let smear smearpositive
    set infection-rate 15 + 15 * smear
    let patchs nobody
    let origin native
    let aux-gender gender
    let aux-age age

;    ifelse  origin = 1 [
;      set patchs (patch-set neighbors4 patch-here)
;    ]
;    [
;      set patchs (patch-set neighbors patch-here)
;    ]
    ask (patch-set neighbors patch-here) with [num-healthy > 0]
    ;ask patches with [num-healthy > 0]
    [
    let loop-var num-healthy
    repeat loop-var
    [
    set rand-ind 1 + random 1000
    if rand-ind <= Infection-prob
    [
      set rand-ind 1 + random 100
      if rand-ind <= infection-rate ;
      [
        set num-healthy num-healthy - 1
        set inf-produced inf-produced + 1
        sprout-infected 1
        [
        set color orange
        set smearpositive 0
        set size 2

        ;GENDER AND NATIONALITY will be assigned to the newly infected
depending on the gender and nationality of the causing infective individual.
Data from the CONTACT STUDY
        ; FOR NATIVE MALE; JULIAEDDIT
        if origin = 1 and aux-gender = 1
        [ set rand-ind 1 + random 100
            if rand-ind <= 40 [set native origin set gender aux-gender]  ;40%
of native male contacts
            if rand-ind > 40 and rand-ind <= 68 [set native origin set gender
(1 - aux-gender)]  ;28% of native female contacts
            if rand-ind > 68 and rand-ind <= 87 [set native (1 - origin) set
gender aux-gender]  ;19% of immigrant male contacts
            if rand-ind > 87 [set native (1 - origin) set gender (1 - aux-
gender)] ;13% of immigrant female contacts
            ]

         ; FOR NATIVE FEMALE
        if origin = 1 and aux-gender = 0
        [ set rand-ind 1 + random 100
            if rand-ind <= 33 [set native origin set gender aux-gender] ;33%
of native female contacts
            if rand-ind > 33 and rand-ind <= 68 [set native origin set gender
(1 - aux-gender)] ;35% of native male contacts
            if rand-ind > 68 and rand-ind <= 84 [set native (1 - origin) set
gender aux-gender]  ;16% of immigrant female contacts
            if rand-ind > 84 [set native (1 - origin) set gender (1 - aux-
gender)] ;16% of immigrant male contacts
            ]

          ; FOR IMMIGRANT MALE
```

```
        if origin = 0 and aux-gender = 1
        [ set rand-ind 1 + random 100
            if rand-ind <= 65 [set native origin set gender aux-gender] ;65%
of immigrant male contacts
            if rand-ind > 65 and rand-ind <= 86 [set native origin set gender
(1 - aux-gender)] ;21% of immigrant female contacts
            if rand-ind > 86 and rand-ind <= 97 [set native (1 - origin) set
gender aux-gender]  ;11% of native male contacts
            if rand-ind > 97 [set native (1 - origin) set gender (1 - aux-
gender)] ;3% of native female contacts
            ]

          ; FOR IMMIGRANT FEMALE
        if origin = 0 and aux-gender = 0
        [ set rand-ind 1 + random 100
            if rand-ind <= 37 [set native origin set gender aux-gender] ;37%
of immigrant female contacts
            if rand-ind > 37 and rand-ind <= 86 [set native origin set gender
(1 - aux-gender)] ;49% of immigrant male contacts
            if rand-ind > 86 and rand-ind <= 92 [set native (1 - origin) set
gender aux-gender]  ;6% of native female contacts
            if rand-ind > 92 [set native (1 - origin) set gender (1 - aux-
gender)] ;8% of native male contacts
            ]

        ; AGE will be assigned to the newly infected depending on the age of
the sick person. Data from the CONTACT STUDY CV. JULIAEDIT

        if aux-age <= (20 * 365) [set rand-ind 1 + random 100 ;for a case
younger than 20.

            if rand-ind <= 30 ; 30% of 0-20 y.o contacts
            [set rand-ind 1 + random 100
             if rand-ind <= 20 [set age random (6 * 365)] ;0-5 yo
             if rand-ind > 20 and rand-ind <= 41 [set age (6 * 365) + random
(5 * 365)] ; 5-10 yo
             if rand-ind > 41 and rand-ind <= 70 [set age (11 * 365) + random
(5 * 365)] ; 10-15 yo
             if rand-ind > 70 [set age (16 * 365) + random (5 * 365)]] ; 15-20
y.o

            if rand-ind > 30 and rand-ind <= 95 ; 65% of 20-60 y.o contacts
            [set rand-ind 1 + random 100
             if rand-ind <= 26 [set age (21 * 365) + random (10 * 365)] ;20-30
yo
             if rand-ind > 26 and rand-ind <= 62 [set age (31 * 365) + random
(10 * 365)] ; 30-40 yo
             if rand-ind > 62 and rand-ind <= 86 [set age (41 * 365) + random
(10 * 365)] ; 40-50 yo
             if rand-ind > 86 [set age (51 * 365) + random (10 * 365)]] ; 50-
60 yo

            if rand-ind > 95 ; 5% of 60-90 y.o contacts
            [set rand-ind 1 + random 100
             if rand-ind <= 67 [set age (61 * 365) + random (10 * 365)] ;60-70
yo
             if rand-ind > 67 and rand-ind <= 88 [set age (71 * 365) + random
(10 * 365)];70-80 yo
             if rand-ind > 88 [set age (81 * 365) + random (10 * 365)]]] ;80-
90 yo


        if aux-age > (20 * 365) and aux-age <= (60 * 365) and aux-gender = 1
[set rand-ind 1 + random 100 ; for a male case between 20-60

            if rand-ind <= 5 ; 5% of 0-20 y.o contacts
            [set rand-ind 1 + random 100
             if rand-ind <= 20 [set age random (6 * 365)] ;0-5 yo
```

```
             if rand-ind > 20 and rand-ind <= 41 [set age (6 * 365) + random
(5 * 365)] ; 5-10 yo
             if rand-ind > 41 and rand-ind <= 70 [set age (11 * 365) + random
(5 * 365)] ; 10-15 yo
             if rand-ind > 70 [set age (16 * 365) + random (5 * 365)]] ; 15-20
y.o

            if rand-ind > 5 and rand-ind <= 99 ; 93% of 20-60 y.o contacts
            [set rand-ind 1 + random 100
             if rand-ind <= 26 [set age (21 * 365) + random (10 * 365)] ;20-30
yo
             if rand-ind > 26 and rand-ind <= 62 [set age (31 * 365) + random
(10 * 365)] ; 30-40 yo
             if rand-ind > 62 and rand-ind <= 86 [set age (41 * 365) + random
(10 * 365)] ; 40-50 yo
             if rand-ind > 86 [set age (51 * 365) + random (10 * 365)]] ; 50-
60 yo

            if rand-ind > 99 ; 1% of 60-90 y.o contacts
            [set rand-ind 1 + random 100
             if rand-ind <= 67 [set age (61 * 365) + random (10 * 365)] ;60-70
yo
             if rand-ind > 67 and rand-ind <= 88 [set age (71 * 365) + random
(10 * 365)];70-80 yo
             if rand-ind > 88 [set age (81 * 365) + random (10 * 365)]]] ;80-
90 yo

        if aux-age > (20 * 365) and aux-age <= (60 * 365) and aux-gender = 0
[set rand-ind 1 + random 100 ; for a female case between 20-60

            if rand-ind <= 12 ; 12% of 0-20 y.o contacts
            [set rand-ind 1 + random 100
             if rand-ind <= 20 [set age random (6 * 365)] ;0-5 yo
             if rand-ind > 20 and rand-ind <= 41 [set age (6 * 365) + random
(5 * 365)] ; 5-10 yo
             if rand-ind > 41 and rand-ind <= 70 [set age (11 * 365) + random
(5 * 365)] ; 10-15 yo
             if rand-ind > 70 [set age (16 * 365) + random (5 * 365)]] ; 15-20
y.o

            if rand-ind > 12 and rand-ind <= 97 ; 85% of 20-60 y.o contacts
            [set rand-ind 1 + random 100
             if rand-ind <= 26 [set age (21 * 365) + random (10 * 365)] ;20-30
yo
             if rand-ind > 26 and rand-ind <= 62 [set age (31 * 365) + random
(10 * 365)] ; 30-40 yo
             if rand-ind > 62 and rand-ind <= 86 [set age (41 * 365) + random
(10 * 365)] ; 40-50 yo
             if rand-ind > 86 [set age (51 * 365) + random (10 * 365)]] ; 50-
60 yo

            if rand-ind > 97  ;3% of 60-90 y.o contacts
            [set rand-ind 1 + random 100
             if rand-ind <= 67 [set age (61 * 365) + random (10 * 365)] ;60-70
yo
             if rand-ind > 67 and rand-ind <= 88 [set age (71 * 365) + random
(10 * 365)];70-80 yo
               if rand-ind > 88 [set age (81 * 365) + random (10 * 365)]]]
;80-90 yo


        if aux-age > (60 * 365) [set rand-ind 1 + random 100 ; for a case
older than 60

            if rand-ind <= 5  ;5% of 0-20 y.o contacts
            [set rand-ind 1 + random 100
             if rand-ind <= 20 [set age random (6 * 365)] ;0-5 yo
```

```
            if rand-ind > 20 and rand-ind <= 41 [set age (6 * 365) + random
(5 * 365)] ; 5-10 yo
            if rand-ind > 41 and rand-ind <= 70 [set age (11 * 365) + random
(5 * 365)] ; 10-15 yo
            if rand-ind > 70 [set age (16 * 365) + random (5 * 365)]] ; 15-20
y.o

           if rand-ind > 5 and rand-ind <= 50 ; 45% of 20-60 y.o contacts
           [set rand-ind 1 + random 100
            if rand-ind <= 26 [set age (21 * 365) + random (10 * 365)] ;20-30
yo
            if rand-ind > 26 and rand-ind <= 62 [set age (31 * 365) + random
(10 * 365)] ; 30-40 yo
            if rand-ind > 62 and rand-ind <= 86 [set age (41 * 365) + random
(10 * 365)] ; 40-50 yo
            if rand-ind > 86 [set age (51 * 365) + random (10 * 365)]] ; 50-
60 yo

           if rand-ind > 50 ; 50% of 60-90 y.o contacts
           [set rand-ind 1 + random 100
            if rand-ind <= 67 [set age (61 * 365) + random (10 * 365)] ;60-70
yo
            if rand-ind > 67 and rand-ind <= 88 [set age (71 * 365) + random
(10 * 365)];70-80 yo
            if rand-ind > 88 [set age (81 * 365) + random (10 * 365)]]] ;80-
90 yo

        set immunodepression 1

        ;if 1 + random 100 <= AIDS-rate
        if random-float 100 <= AIDS-rate
        [
          set immunodepression Immunsupression-factor
        ]


        set risk-factors 1

        if 1 + random 100 <= Other-risk-factors-rate
        [
          set risk-factors Risk-factor
        ]

        set diabetes 1

        if 1 + random 100 <= Diabetes-rate
        [
          set diabetes Diabetes-factor
        ]

        set days-infected 0
        ]

        set total-infected-people total-infected-people + 1

        set total-healthy-to-infected total-healthy-to-infected + 1
      ]
    ]
    ]
  ]
    ask treated-on (patch-set patch-here neighbors)  ;; PREGUNTAR. Els
treated-on ja tenen un sexe, age and nationality no?
    ;ask treated-on patchs
   [
    set rand-ind 1 + random 1000
    if rand-ind <= Infection-prob ;
    [
      set rand-ind 1 + random 100
```

```
      if rand-ind <= infection-rate ;
      [
        set inf-produced inf-produced + 1
        set breed infected
        set color orange

        set smearpositive 0
        set days-infected 0

        set total-infected-people total-infected-people + 1

        set total-treated-to-infected total-treated-to-infected + 1
      ]
    ]
  ]
   set second-infection second-infection + inf-produced
  ]
end

to get-sick

  ;; Estimated probabilities of getting sick (World Health Organization): 5% -
10% of the infected people. It is considered the maximum value (10%).
  ;; Then, 1st year: 2.80%; 2nd year: 2.20%; 3rd year: 1.68%; 4th year: 1.23%;
5th year: 0.85%; 6th year: 0.55%; 7th year: 0.32%
  ;; People with AIDS have a 10-fold increase in these probabilities, and
people with other risk factors increase them with a 1.5 factor.

  ask infected
  [
    set days-infected days-infected + 1

    if days-infected <= (365 * 1)
    [
      set get-sick-rate 0.0280 / 365
    ]

    if days-infected > (365 * 1) and days-infected <= (365 * 2)
    [
      set get-sick-rate 0.0220 / 365
    ]

    if days-infected > (365 * 2) and days-infected <= (365 * 3)
    [
      set get-sick-rate 0.0168 / 365
    ]

    if days-infected > (365 * 3) and days-infected <= (365 * 4)
    [
      set get-sick-rate 0.0123 / 365
    ]

    if days-infected > (365 * 4) and days-infected <= (365 * 5)
    [
      set get-sick-rate 0.0085 / 365
    ]

    if days-infected > (365 * 5) and days-infected <= (365 * 6)
    [
      set get-sick-rate 0.0055 / 365
    ]

    if days-infected > (365 * 6) and days-infected <= (365 * 7)
    [
      set get-sick-rate 0.0032 / 365
    ]

    if days-infected > (365 * 7)
```

```
    [

      ;; After 7 years of being infected, the individual is considered to be
healthy. (get-sick-rate = 0)

      set get-sick-rate 0
      set from-infected-to-healthy from-infected-to-healthy + 1
      ask patch-here [ set num-healthy num-healthy + 1]
      die
    ]


 ; Different sickening probabilities are assigned depending on the age of the
infected turtles. 50% of the 0-5 y.o infected will sicken, 15% for the 5-15
y.o and 3% for the 15 y.o plus.
 ; Data from the CONTACT STUDY

 if age <= (5 * 365) [set age-factor 10]
 if age > (5 * 365) and age <= (15 * 365) [set age-factor 3]
 if age > (15 * 365) [set age-factor 1]

 if gender = 1 [set gender-factor 1]
 if gender = 0 [set gender-factor 1]

 if native = 1 [set nationality-factor 1]
 if native = 0 [set nationality-factor 1]


    ;; Number of possibilities is equal (1/365) * 10 * 1,5 = 4,11E-2. This
number will be multiplied by 1E5 (= 4110)

    ;; It is necessary to use a correction factor. It depens on the type of
population (ex.: population density, population behaviour, ...)
    ;; This factor in Ciutat Vella will be 2.60

    set get-sick-rate get-sick-rate * Correction-factor
    set rand-ind 1 + random 1E5
    if rand-ind <= (get-sick-rate * immunodepression * risk-factors * diabetes
* 1E5 * age-factor * gender-factor * nationality-factor)
    [
      ifelse native = 1
      [
        set aux-Mdd Mdd-authocton
        set total-native-sick total-native-sick + 1
      ]
      [
        set aux-Mdd Mdd-foreign
        set total-foreign-sick total-foreign-sick + 1
      ]

      set breed sick
      set color red
      set days-sick 0
      set days-diagnostic-delay round random-normal aux-Mdd 4

      ifelse gender = 1 [set total-sick-men total-sick-men + 1][set total-
sick-women total-sick-women + 1]
      ;; Counters to evaluate de incidence disaggregated by age and gender and
origin. JULIAEDIT
      if gender = 1 [
        if age < (6 * 365) [set sick-men-0-5 sick-men-0-5 + 1]
        if age >= (6 * 365) and age < (16 * 365) [set sick-men-5-15 sick-men-
5-15 + 1]
        if age >= (16 * 365) and age < (26 * 365) [set sick-men-15-25 sick-
men-15-25 + 1]
        if age >= (26 * 365) and age < (36 * 365) [set sick-men-25-35 sick-
men-25-35 + 1]
```

```
        if age >= (36 * 365) and age < (46 * 365) [set sick-men-35-45 sick-
men-35-45 + 1]
        if age >= (46 * 365) and age < (56 * 365) [set sick-men-45-55 sick-
men-45-55 + 1]
        if age >= (56 * 365) and age < (66 * 365) [set sick-men-55-65 sick-
men-55-65 + 1]
        if age >= (66 * 365) and age < (76 * 365) [set sick-men-65-75 sick-
men-65-75 + 1]
        if age >= (76 * 365) and age < (86 * 365) [set sick-men-75-85 sick-
men-75-85 + 1]
        if age >= (86 * 365) [set sick-men-85+ sick-men-85+ + 1]
        ]
      if gender = 0 [
        if age < (6 * 365) [set sick-women-0-5 sick-women-0-5 + 1]
        if age >= (6 * 365) and age < (16 * 365) [set sick-women-5-15 sick-
women-5-15 + 1]
        if age >= (16 * 365) and age < (26 * 365) [set sick-women-15-25 sick-
women-15-25 + 1]
        if age >= (26 * 365) and age < (36 * 365) [set sick-women-25-35 sick-
women-25-35 + 1]
        if age >= (36 * 365) and age < (46 * 365) [set sick-women-35-45 sick-
women-35-45 + 1]
        if age >= (46 * 365) and age < (56 * 365) [set sick-women-45-55 sick-
women-45-55 + 1]
        if age >= (56 * 365) and age < (66 * 365) [set sick-women-55-65 sick-
women-55-65 + 1]
        if age >= (66 * 365) and age < (76 * 365) [set sick-women-65-75 sick-
women-65-75 + 1]
        if age >= (76 * 365) and age < (86 * 365) [set sick-women-75-85 sick-
women-75-85 + 1]
        if age >= (86 * 365) [set sick-women-85+ sick-women-85+ + 1]
        ]
      if native = 0 [
        if age < (6 * 365) [set sick-immigrant-0-5 sick-immigrant-0-5 + 1]
        if age >= (6 * 365) and age < (16 * 365) [set sick-immigrant-5-15
sick-immigrant-5-15 + 1]
        if age >= (16 * 365) and age < (26 * 365) [set sick-immigrant-15-25
sick-immigrant-15-25 + 1]
        if age >= (26 * 365) and age < (36 * 365) [set sick-immigrant-25-35
sick-immigrant-25-35 + 1]
        if age >= (36 * 365) and age < (46 * 365) [set sick-immigrant-35-45
sick-immigrant-35-45 + 1]
        if age >= (46 * 365) and age < (56 * 365) [set sick-immigrant-45-55
sick-immigrant-45-55 + 1]
        if age >= (56 * 365) and age < (66 * 365) [set sick-immigrant-55-65
sick-immigrant-55-65 + 1]
        if age >= (66 * 365) and age < (76 * 365) [set sick-immigrant-65-75
sick-immigrant-65-75 + 1]
        if age >= (76 * 365) and age < (86 * 365) [set sick-immigrant-75-85
sick-immigrant-75-85 + 1]
        if age >= (86 * 365) [set sick-immigrant-85+ sick-immigrant-85+ + 1]
        ]
      if native = 1 [
        if age < (6 * 365) [set sick-native-0-5 sick-native-0-5 + 1]
        if age >= (6 * 365) and age < (16 * 365) [set sick-native-5-15 sick-
native-5-15 + 1]
        if age >= (16 * 365) and age < (26 * 365) [set sick-native-15-25 sick-
native-15-25 + 1]
        if age >= (26 * 365) and age < (36 * 365) [set sick-native-25-35 sick-
native-25-35 + 1]
        if age >= (36 * 365) and age < (46 * 365) [set sick-native-35-45 sick-
native-35-45 + 1]
        if age >= (46 * 365) and age < (56 * 365) [set sick-native-45-55 sick-
native-45-55 + 1]
        if age >= (56 * 365) and age < (66 * 365) [set sick-native-55-65 sick-
native-55-65 + 1]
        if age >= (66 * 365) and age < (76 * 365) [set sick-native-65-75 sick-
native-65-75 + 1]
```

```
        if age >= (76 * 365) and age < (86 * 365) [set sick-native-75-85 sick-
native-75-85 + 1]
        if age >= (86 * 365) [set sick-native-85+ sick-native-85+ + 1]
        ]

      if diabetes > 1 [ set total-sick-diabetes total-sick-diabetes + 1]
      if risk-factors > 1 [ set total-sick-risk total-sick-risk + 1]
      if immunodepression > 1 [set total-sick-immunodep total-sick-immunodep +
1]

      if 1 + random 100 < 22.2 [
        set smearpositive 1
        set total-sick-smearpositive total-sick-smearpositive + 1
        ]
      set total-sick-people total-sick-people + 1

      set total-infected-to-sick total-infected-to-sick + 1

    ]
  ]

 ifelse ticks = 365 [set incidence-per-year total-infected-to-sick] ;JULIAEDIT
 [if ticks mod 365 = 0 [set incidence-per-year total-infected-to-sick -
incidence-per-year]] ;JULIAEDIT

end


to start-treatment

  ;; After the Median-diagnostic-delay, all sick individuals start being
treated.

  ask sick
  [
    set days-sick days-sick + 1
    let ds days-sick
    if days-diagnostic-delay <= days-sick
    [
      set aux-smearpositive smearpositive
      set second-inf-list lput second-infection second-inf-list
      set days-sick-list lput ds days-sick-list
      set breed treatment
      set color blue
      set days-treatment-ment 0
      set smearpositive aux-smearpositive

      set total-treatment-people total-treatment-people + 1
    ]
  ]

end


to finish-treatment

  ask treatment
  [
    set days-treatment-ment days-treatment-ment + 1

    ifelse days-treatment-ment >= 180
    [
      set aux-smearpositive smearpositive

      set breed treated
      set color yellow
      set smearpositive aux-smearpositive
      set days-treatment-ed 180
```

```
      set days-start-treatment 180
      set p-relapse 1

      set total-treated-people total-treated-people + 1

      set total-treatment-no-abandon total-treatment-no-abandon + 1
    ]
    [
      if ( 1 + random 1E5 ) <= ( abandon-rate / 0.18 ) ;
      [
        ifelse days-treatment-ment <= 15
        [

          ;; It is considered that people in treatment that abandon it in less
than 15 days will get sick again.
          ;; But, it is not considered as a new individual sick.

          set aux-smearpositive smearpositive

          ifelse native = 1
          [
            set aux-Mdd Mdd-authocton
            set total-native-sick total-native-sick + 1
          ]
          [
            set aux-Mdd Mdd-foreign
            set total-foreign-sick total-foreign-sick + 1
          ]
          set breed sick
          set color red
          set smearpositive aux-smearpositive
          set days-sick 0
          set days-diagnostic-delay round random-normal aux-Mdd 4

          ifelse gender = 1 [set total-sick-men total-sick-men + 1][set total-
sick-women total-sick-women + 1]
          ;; Counters to evaluate de incidence disaggregated by age and gender
and origin. JULIAEDIT
        if gender = 1 [
        if age < (6 * 365) [set sick-men-0-5 sick-men-0-5 + 1]
        if age >= (6 * 365) and age < (16 * 365) [set sick-men-5-15 sick-men-
5-15 + 1]
        if age >= (16 * 365) and age < (26 * 365) [set sick-men-15-25 sick-
men-15-25 + 1]
        if age >= (26 * 365) and age < (36 * 365) [set sick-men-25-35 sick-
men-25-35 + 1]
        if age >= (36 * 365) and age < (46 * 365) [set sick-men-35-45 sick-
men-35-45 + 1]
        if age >= (46 * 365) and age < (56 * 365) [set sick-men-45-55 sick-
men-45-55 + 1]
        if age >= (56 * 365) and age < (66 * 365) [set sick-men-55-65 sick-
men-55-65 + 1]
        if age >= (66 * 365) and age < (76 * 365) [set sick-men-65-75 sick-
men-65-75 + 1]
        if age >= (76 * 365) and age < (86 * 365) [set sick-men-75-85 sick-
men-75-85 + 1]
        if age >= (86 * 365) [set sick-men-85+ sick-men-85+ + 1]
        ]
      if gender = 0 [
        if age < (6 * 365) [set sick-women-0-5 sick-women-0-5 + 1]
        if age >= (6 * 365) and age < (16 * 365) [set sick-women-5-15 sick-
women-5-15 + 1]
        if age >= (16 * 365) and age < (26 * 365) [set sick-women-15-25 sick-
women-15-25 + 1]
        if age >= (26 * 365) and age < (36 * 365) [set sick-women-25-35 sick-
women-25-35 + 1]
        if age >= (36 * 365) and age < (46 * 365) [set sick-women-35-45 sick-
women-35-45 + 1]
```

```
        if age >= (46 * 365) and age < (56 * 365) [set sick-women-45-55 sick-
women-45-55 + 1]
        if age >= (56 * 365) and age < (66 * 365) [set sick-women-55-65 sick-
women-55-65 + 1]
        if age >= (66 * 365) and age < (76 * 365) [set sick-women-65-75 sick-
women-65-75 + 1]
        if age >= (76 * 365) and age < (86 * 365) [set sick-women-75-85 sick-
women-75-85 + 1]
        if age >= (86 * 365) [set sick-women-85+ sick-women-85+ + 1]
        ]
      if native = 0 [
        if age < (6 * 365) [set sick-immigrant-0-5 sick-immigrant-0-5 + 1]
        if age >= (6 * 365) and age < (16 * 365) [set sick-immigrant-5-15
sick-immigrant-5-15 + 1]
        if age >= (16 * 365) and age < (26 * 365) [set sick-immigrant-15-25
sick-immigrant-15-25 + 1]
        if age >= (26 * 365) and age < (36 * 365) [set sick-immigrant-25-35
sick-immigrant-25-35 + 1]
        if age >= (36 * 365) and age < (46 * 365) [set sick-immigrant-35-45
sick-immigrant-35-45 + 1]
        if age >= (46 * 365) and age < (56 * 365) [set sick-immigrant-45-55
sick-immigrant-45-55 + 1]
        if age >= (56 * 365) and age < (66 * 365) [set sick-immigrant-55-65
sick-immigrant-55-65 + 1]
        if age >= (66 * 365) and age < (76 * 365) [set sick-immigrant-65-75
sick-immigrant-65-75 + 1]
        if age >= (76 * 365) and age < (86 * 365) [set sick-immigrant-75-85
sick-immigrant-75-85 + 1]
        if age >= (86 * 365) [set sick-immigrant-85+ sick-immigrant-85+ + 1]
        ]
      if native = 1 [
        if age < (6 * 365) [set sick-native-0-5 sick-native-0-5 + 1]
        if age >= (6 * 365) and age < (16 * 365) [set sick-native-5-15 sick-
native-5-15 + 1]
        if age >= (16 * 365) and age < (26 * 365) [set sick-native-15-25 sick-
native-15-25 + 1]
        if age >= (26 * 365) and age < (36 * 365) [set sick-native-25-35 sick-
native-25-35 + 1]
        if age >= (36 * 365) and age < (46 * 365) [set sick-native-35-45 sick-
native-35-45 + 1]
        if age >= (46 * 365) and age < (56 * 365) [set sick-native-45-55 sick-
native-45-55 + 1]
        if age >= (56 * 365) and age < (66 * 365) [set sick-native-55-65 sick-
native-55-65 + 1]
        if age >= (66 * 365) and age < (76 * 365) [set sick-native-65-75 sick-
native-65-75 + 1]
        if age >= (76 * 365) and age < (86 * 365) [set sick-native-75-85 sick-
native-75-85 + 1]
        if age >= (86 * 365) [set sick-native-85+ sick-native-85+ + 1]
        ]
          if diabetes > 1 [ set total-sick-diabetes total-sick-diabetes + 1]
          if risk-factors > 1 [ set total-sick-risk total-sick-risk + 1]
          if immunodepression > 1 [set total-sick-immunodep total-sick-
immunodep]
          if aux-smearpositive = 1 [set total-sick-smearpositive total-sick-
smearpositive + 1]


          set total-treatment-to-sick total-treatment-to-sick + 1
          set total-sick-people total-sick-people + 1
        ]
        [
          set aux-days-treatment days-treatment-ment
          set aux-smearpositive smearpositive

          set breed treated
          set color yellow
          set smearpositive aux-smearpositive
```

```
          set days-treatment-ed aux-days-treatment
          set days-start-treatment days-treatment-ed
          set p-relapse ( 1 + 99 * ( 180 - days-treatment-ed ) / 165 )

          set total-treated-people total-treated-people + 1

          set total-treatment-abandon total-treatment-abandon + 1
        ]
      ]
    ]
  ]

end


to relapse-or-recover

   ask treated
  [
    set days-start-treatment days-start-treatment + 1

    ifelse days-start-treatment <= 730
    [
      set rand-ind ( 1 + random 1E6 )

      if rand-ind < ( p-relapse / 100 * 1E6 / ( 730 - days-treatment-ed ) ) ;
      [
        ifelse native = 1
          [
            set aux-Mdd Mdd-authocton
             set total-native-sick total-native-sick + 1
          ]
          [
            set aux-Mdd Mdd-foreign
            set total-foreign-sick total-foreign-sick + 1
          ]

        set aux-smearpositive smearpositive

        set breed sick
        set color red
        set smearpositive aux-smearpositive
        set days-sick 0
        set days-diagnostic-delay round random-normal aux-Mdd 4

        ifelse gender = 1 [set total-sick-men total-sick-men + 1][set total-
sick-women total-sick-women + 1]
        ;; Counters to evaluate de incidence disaggregated by age and gender
and origin. JULIAEDIT
        if gender = 1 [
        if age < (6 * 365) [set sick-men-0-5 sick-men-0-5 + 1]
        if age >= (6 * 365) and age < (16 * 365) [set sick-men-5-15 sick-men-
5-15 + 1]
        if age >= (16 * 365) and age < (26 * 365) [set sick-men-15-25 sick-
men-15-25 + 1]
        if age >= (26 * 365) and age < (36 * 365) [set sick-men-25-35 sick-
men-25-35 + 1]
        if age >= (36 * 365) and age < (46 * 365) [set sick-men-35-45 sick-
men-35-45 + 1]
        if age >= (46 * 365) and age < (56 * 365) [set sick-men-45-55 sick-
men-45-55 + 1]
        if age >= (56 * 365) and age < (66 * 365) [set sick-men-55-65 sick-
men-55-65 + 1]
        if age >= (66 * 365) and age < (76 * 365) [set sick-men-65-75 sick-
men-65-75 + 1]
        if age >= (76 * 365) and age < (86 * 365) [set sick-men-75-85 sick-
men-75-85 + 1]
        if age >= (86 * 365) [set sick-men-85+ sick-men-85+ + 1]
```

```
        ]
      if gender = 0 [
        if age < (6 * 365) [set sick-women-0-5 sick-women-0-5 + 1]
        if age >= (6 * 365) and age < (16 * 365) [set sick-women-5-15 sick-
women-5-15 + 1]
        if age >= (16 * 365) and age < (26 * 365) [set sick-women-15-25 sick-
women-15-25 + 1]
        if age >= (26 * 365) and age < (36 * 365) [set sick-women-25-35 sick-
women-25-35 + 1]
        if age >= (36 * 365) and age < (46 * 365) [set sick-women-35-45 sick-
women-35-45 + 1]
        if age >= (46 * 365) and age < (56 * 365) [set sick-women-45-55 sick-
women-45-55 + 1]
        if age >= (56 * 365) and age < (66 * 365) [set sick-women-55-65 sick-
women-55-65 + 1]
        if age >= (66 * 365) and age < (76 * 365) [set sick-women-65-75 sick-
women-65-75 + 1]
        if age >= (76 * 365) and age < (86 * 365) [set sick-women-75-85 sick-
women-75-85 + 1]
        if age >= (86 * 365) [set sick-women-85+ sick-women-85+ + 1]
        ]
      if native = 0 [
        if age < (6 * 365) [set sick-immigrant-0-5 sick-immigrant-0-5 + 1]
        if age >= (6 * 365) and age < (16 * 365) [set sick-immigrant-5-15
sick-immigrant-5-15 + 1]
        if age >= (16 * 365) and age < (26 * 365) [set sick-immigrant-15-25
sick-immigrant-15-25 + 1]
        if age >= (26 * 365) and age < (36 * 365) [set sick-immigrant-25-35
sick-immigrant-25-35 + 1]
        if age >= (36 * 365) and age < (46 * 365) [set sick-immigrant-35-45
sick-immigrant-35-45 + 1]
        if age >= (46 * 365) and age < (56 * 365) [set sick-immigrant-45-55
sick-immigrant-45-55 + 1]
        if age >= (56 * 365) and age < (66 * 365) [set sick-immigrant-55-65
sick-immigrant-55-65 + 1]
        if age >= (66 * 365) and age < (76 * 365) [set sick-immigrant-65-75
sick-immigrant-65-75 + 1]
        if age >= (76 * 365) and age < (86 * 365) [set sick-immigrant-75-85
sick-immigrant-75-85 + 1]
        if age >= (86 * 365) [set sick-immigrant-85+ sick-immigrant-85+ + 1]
        ]
      if native = 1 [
        if age < (6 * 365) [set sick-native-0-5 sick-native-0-5 + 1]
        if age >= (6 * 365) and age < (16 * 365) [set sick-native-5-15 sick-
native-5-15 + 1]
        if age >= (16 * 365) and age < (26 * 365) [set sick-native-15-25 sick-
native-15-25 + 1]
        if age >= (26 * 365) and age < (36 * 365) [set sick-native-25-35 sick-
native-25-35 + 1]
        if age >= (36 * 365) and age < (46 * 365) [set sick-native-35-45 sick-
native-35-45 + 1]
        if age >= (46 * 365) and age < (56 * 365) [set sick-native-45-55 sick-
native-45-55 + 1]
        if age >= (56 * 365) and age < (66 * 365) [set sick-native-55-65 sick-
native-55-65 + 1]
        if age >= (66 * 365) and age < (76 * 365) [set sick-native-65-75 sick-
native-65-75 + 1]
        if age >= (76 * 365) and age < (86 * 365) [set sick-native-75-85 sick-
native-75-85 + 1]
        if age >= (86 * 365) [set sick-native-85+ sick-native-85+ + 1]
        ]
        if diabetes > 1 [ set total-sick-diabetes total-sick-diabetes + 1]
        if risk-factors > 1 [ set total-sick-risk total-sick-risk + 1]
        if immunodepression > 1 [set total-sick-immunodep total-sick-
immunodep]
        if aux-smearpositive = 1 [set total-sick-smearpositive total-sick-
smearpositive + 1]
```

```
        set total-sick-people total-sick-people + 1

        set total-treated-to-sick total-treated-to-sick + 1
       ]
      ]
      [
       set from-treated-to-healthy from-treated-to-healthy + 1
       ask patch-here [set num-healthy num-healthy + 1]
       die
      ]
  ]
;
;  ;; The relapse occurs according to the individual probability assigned to
each individual after finishing or abandoning the treatment.
;  ;; After 2 years of the initial date of the treatment, an individual
doesn't relapse again.
;  ;; The probability to get sick again in one day is equal to (p-relapse /
100)Â·(1 / 714). The maximum value will be 1,401-3. This number will be
multiplied by 1E6.
;  ;; The maximum value will be 1401.

end


to death

  ;; Individuals may die because of TB (40 % of non-treated sick in 5 years,
0.0219 % daily)
  ;; In Ciutat Vella (105122 inhabitants), they died 847 people.
  ;; (2 children under 10 years old; 139 between 10 and 65 years old; 706 old
people over 65 years old).
  ;; That represents 2.51E-4%, 1.6999E-3% and 0.0456% death people per day,
respectively.
  ;; Age distribution: 7.57% under 10 years old, 77.71% between 10 and 65
years old and 14.72% over 65 years old.
  ;; That represents: 7963, 81769 and 15488, respectively.
  ;; The death index per day will be: 6.877E-5%, 4.65E-4% and 1.2249E-2%

  ask turtles
  [
        set death-index 5.454E-4
    ;set death-index 1.322E-3

    if age < 3650
    [
          ;set death-index 0
     set death-index 6.877E-5
    ]

    if age > 23725
    [
          ;set death-index 1.293E-2
      set death-index 1.2249E-2
    ]

    if breed = sick
    [
      set death-index 2.192E-2
    ]

    if (1 + random 1E7) < death-index * 1E5 ;
    [

     ;; A new individual is introduced whenever there is a death

     set total-death-people total-death-people + 1
     if breed = sick
     [
```

```
        set second-inf-list lput second-infection second-inf-list
        set days-sick-list lput days-sick days-sick-list
      ]
      create
      die
     ]
  ]

end


to create

   ;; Every time a death occurs, a new healthy individual is introduced to the
system in ordrer to keep a constant population.
   ask one-of patches[ set num-healthy num-healthy + 1]

end

to export-files
  ;; To export the counters that evaluate the incidence disaggregated by age,
gender and origin
  let spacer ","
  file-open ( word "TB_incidence_CV" behaviorspace-run-number ".csv" )
  file-print ( list   day-total ", " sick-men-0-5 ", " sick-men-5-15 "," sick-
men-15-25 "," sick-men-25-35 "," sick-men-35-45 "," sick-men-45-55 "," sick-
men-55-65 ","
    sick-men-65-75 "," sick-men-75-85 "," sick-men-85+ "," sick-women-0-5 ", "
sick-women-5-15 "," sick-women-15-25 "," sick-women-25-35 "," sick-women-35-45
"," sick-women-45-55 ","
    sick-women-55-65 "," sick-women-65-75 "," sick-women-75-85 "," sick-women-
85+ ", " sick-immigrant-0-5 ", " sick-immigrant-5-15 "," sick-immigrant-15-25
"," sick-immigrant-25-35 "," sick-immigrant-35-45 "," sick-immigrant-45-55 ","
sick-immigrant-55-65 ","
    sick-immigrant-65-75 "," sick-immigrant-75-85 "," sick-immigrant-85+ ","
sick-native-0-5 ", " sick-native-5-15 "," sick-native-15-25 "," sick-native-
25-35 "," sick-native-35-45 "," sick-native-45-55 ","
    sick-native-55-65 "," sick-native-65-75 "," sick-native-75-85 "," sick-
native-85+)
  file-close

end


to refresh-day

 ifelse day-of-year = 365
 [
   set year-count year-count + 1

   set day-of-year 1
 ]
 [
   set day-of-year day-of-year + 1
 ]

 set day-total day-total + 1

end
```