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Doctoral Thesis

Modelling infectious agent transmission using social mixing data

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The jury members were:

- Prof. Dr Philippe de Wals, President
- Prof. Dr Benoit Dervaux
- Prof. Dr Niel Hens
- Prof. Dr Yazdan Yazdanpanah
- Prof. Dr Joke Bilcke
- Prof. Dr Philippe Beutels

"I have not failed. I've just found 10000 ways that won't work."

Thomas A. Edison

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Abbreviations

°C	Celsius degree
°F	Fahrenheit degree
AIC	**A**kaike **I**nformation **C**riteria
ARCEP	**A**utorité de **R**égulation des **C**ommunications **E**lectroniques et des **P**ostes
BIC	**B**ayesian **I**nformation **C**riteria
CI	**C**onfidence **I**nterval
CMV	**C**yto**M**egalo**V**irus
Comes-F	**Co**ntact **M**atrix **E**stimation **F**rance
DNA	**D**eoxyribo**N**ucleic **A**cid
RNA	**R**ibo**N**ucleic **A**cid
ECDC	**E**uropean **C**entre for **D**isease prevention and **C**ontrol
ESEN	**E**uropean **S**ero-**E**pidemiology **N**etwork
GAM	**G**eneralized **A**dditive **M**odel
GEE	**G**eneralized **E**stimation **M**odel
GLM	**G**eneralized **L**inear **M**ixed
GLMM	**G**eneralized **L**inear **M**ixed **M**odel
HAV	**H**epatitis **A** **V**irus
HEV	**H**epatitis **E** **V**irus
HIV	**H**uman **I**mmunodeficiency **V**irus
HSV	**H**erpes **S**implex **V**irus
IQR	**I**nter **Q**uartile **R**ange
InVS	**I**nstitut **n**ational **V**eille **S**anitaire
INSEE	**I**nstitut **N**ational de la **S**tatistique et des **E**tudes **E**conomiques
kn	**kn**ot
LPS	**L**ipo**P**oly**S**accharides

mbar	**m**illibars
mi	**mi**les
MMR	**M**easles **M**umps **R**ubella
NbC	**N**um**b**er of **C**ontacts
NOAA	**N**ational **O**ceanic and **A**tmospheric **A**dministration
PAMP	**P**athogen-**A**ssociated **M**icrobial **P**attern recognition
RH	**R**elative **H**umidity
ROR	**R**ougeole **O**reillons **R**ubéole
RR	**R**ougeole **R**ubéole
RTC	**R**éseau **T**éléphonique **C**ommuté
SPC	**S**upplementary **P**rofessional **C**ontact
UK	**U**nited **K**ingdom
USA	**U**nited **S**tates of **A**merica
VSC	**V**lamms **S**upercomputer **C**entre
VZV	**V**aricella-**Z**oster **V**irus
WAIFW	**W**ho **A**cquires **I**nfection **F**rom **W**hom
WHO	**W**orld **H**ealth **O**rganisation

To my father

List of publications

Publications

- The French connection: The first large population contact survey in France and its implication for the spread of infectious diseases. **G. Béraud**, S. Kazmercziak, P. Beutels, D. Levy-Bruhl, X. Lenne, N. Mielcarek, Y. Yazdanpanah, PY. Boëlle, N.Hens, B. Dervaux. *PloS One*, 10(7):e0133203, 2015. ISSN 1932-6203. doi: 10.1371/journal.pone.0133203.

- On the role of weather conditions on social interactions relevant for the spread of infectious diseases. **G. Béraud**, L. Willem, P. Beutels, N. Hens, B. Dervaux. To be submitted.

- Resurgence risk for measles, mumps and rubella in France. **G. Béraud**, S. Abrams, D. Levy-Bruhl, D. Antona, P. Beutels, B. Dervaux, N. Hens. To be submitted.

Conferences

Oral communications:

- Intérêt des modèles mathématiques en pathologie infectieuse. **G. Béraud**. *Groupe d'Epidémiologie et Recherche en Infectiologie Clinique – Centre Ouest* 2014 (Nantes, FR).

- Social contact patterns in France. **G. Béraud**. *Simulation models of infectious diseases (SIMID)* 2013 (Antwerp, Belgium).

- Facteurs socio-démographiques influant la propagation d'une épidémie: Utilisation des données de contact. **G. Béraud**, S. Kazmierczak, D. Levy-Bruhl, Y.Yazdanpanah, P. Beutels, N. Hens, B. Dervaux. *Journée Nationales d'Infectiologie (JNI)* 2013 (Clermont-Ferrand, France).

Posters:

- Gender differences in infections: Not just physiology. **G. Béraud**, N. Hens, P. Beutels, B. Dervaux. ECCMID 2015 (Copenhagen, SWE).
- Mixing Patterns in France Vary According to Seasons: Implication for the Spread of Infectious Diseases. **G. Béraud**, S. Kazmierczak, D. Levy-Bruhl, X. Lenne, N. Mielcarek, Y. Yazdanpanah, D. Guillemot, PY. Boëlle, P. Beutels, N. Hens, B.Dervaux. *Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC)* 2013 (Denver, USA).
- On how the season shapes mixing patterns in France: social contact data relevant for the spread of infectious diseases **G. Béraud**, S. Kazmierczak, D. Levy-bruhl, X.Lenne, N. Mielcarek, Y. Yazdanpanah, D. Guillemot, PY Boëlle, P. Beutels, N.Hens, B. Dervaux. *European Society for Paediatric Infectious Diseases (ESPID)* 2013 (Milan, IT).

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- On the role of weather conditions on social interactions relevant for the spread of infectious diseases. G. Béraud, L. Willem, P. Beutels, N. Hens, B. Dervaux.

Chapter 1

General Introduction

1.1 Infectious diseases

Infectious diseases are illnesses affecting humans, animals or plants that share two unique characteristics among diseases. First and foremost, infectious diseases are transmissible diseases, that emerge from viruses, bacteria..., which requires understanding their "dynamics" before being able to control their spread within a population. Secondarily, these diseases result from an interaction between host and pathogen that usually is responsible for the symptoms, the severity and the prognosis of the infectious disease.

Being transmissible is a specificity of infectious diseases. There are different transmission routes for pathogens between two individuals, direct routes such as airborne, droplets, physical or sexual contact, orofecal (via contaminated food or water), but also indirect through contacts with an animal or an insect, known as vector-borne, or through fomites (objects). This thesis will focus on diseases transmitted via direct non-sexual contacts between individuals, such as airborne, droplet or physical contacts. Droplet transmission occurs when an infected individual, by coughing or sneezing, expels droplets that deposit on nasal or oral mucosa of a susceptible individual, while airborne transmission occurs via small expelled particles (sometimes called droplet nuclei), which remain suspended in the air as aerosols for extended periods of time (thereby allowing transmission even without direct concomitant contact between the 2 individuals) [Shaman and Kohn, 2009]. This thesis will focus on influenza, measles, mumps and rubella, even though these types of interactions also concerns varicella-zoster virus, parvovirus B19 or pertussis.

Host-pathogen interaction proceeds from the immune reaction from the host, with the production of antibodies specific to the pathogen (humoral immunity) and activation of cells dedicated to the destruction of the pathogen (cellular immunity). Once the

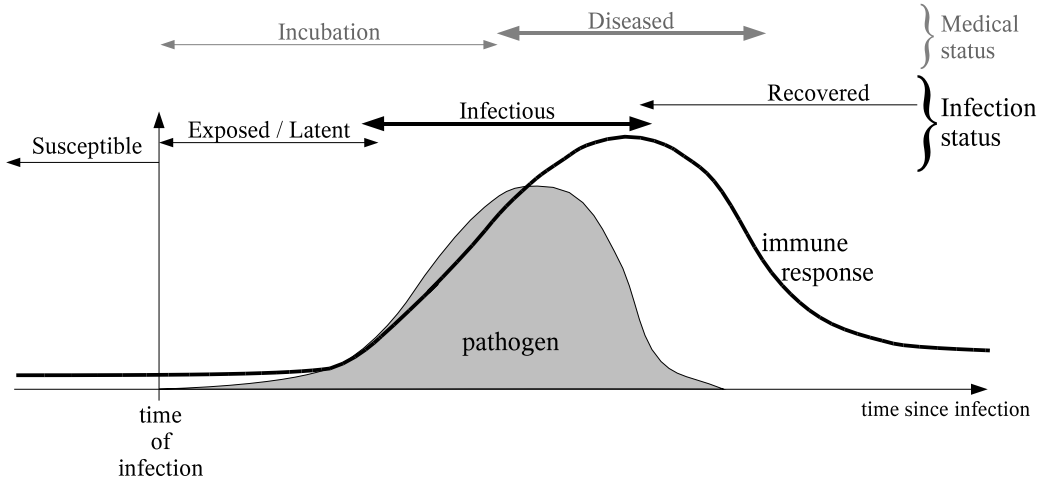


FIGURE 1.1: The different stages in infectious diseases, from the book "'Modelling infectious diseases"' by Keeling and Rohani, 2007

pathogen begins to replicate in the host, the latter is considered as *infected* but there is a period of variable length before the host is able to transmit the pathogen and thus *infectious*. Contacts made during the infectious period may get infected. Eventually, the host may *recover* and not be infectious any more. At this point, he may or may not be *immune* to another infection (Figure 1.1).

The immune system can use the cell-mediated immunity in which T-cells will destroy the cells that host the virus by detecting viral antigens on the cell surface. However, humoral immunity also plays a role by producing specific antibodies. Antibodies are proteins used by the immune system to recognize pathogens specifically. Once a pathogen is recognized via a specific fixation between the micro-organism and the antibody, an immediate destruction of the micro-organism could occur as well as an activation of other effector cells from the immune system, according the micro-organism and an eventual history of former encounter with this pathogen. Quickly after the onset of the infection, immunoglobulins M (IgM) are produced and will last only for a few weeks, their detection in blood signalling a recent infection. Immunoglobulin G (IgG) production is delayed compared to IgM, but it lasts longer and provides immunity for years, if not lifelong. It is to be noted that theses antibodies can be transferred from the pregnant mother to the fetus, granting him immunity against a particular pathogen for a few months. Vaccination aims to procure antibodies -similarly to an infection- in order to provide immunity. Therefore the presence of IgG with no history of immunization indicates a former infection.

From a modelling point of view, seropositivity is a marker of the fraction of a population having been in contact with the pathogen, which may be protected from it and is consequently no longer susceptible to infection. Infectious disease epidemiology will

use serological data to help identifying the proportion of individuals susceptible, infected, infectious and/or protected from a particular disease. Such proportions varying, mathematical modelling facilitates understanding of their evolution through time and at different time spans as well as the dynamic processes involved. Moreover, modelling proposes to estimate the impact of an action such as vaccination both on the disease and on the healthcare system by taking into account all of its effects, including herd immunity, age-shifting in disease onset, selective pressure... Managing infections at the individual level is not sufficient to control the spread of a pathogen within a population. To control an infectious disease at the population level, healthcare providers widely use modelling to guide their policies, particularly as regards vaccination guidelines.

1.2 Social contact studies

Models of disease transmission have demonstrated the importance of age-specific contact mixing patterns and population demography in the transmission of infectious diseases and the response to intervention [Wallinga et al., 2006]. Modelling an infectious disease can be summarized as modelling the transmission of a pathogen between groups of individuals. The cornerstone is to understand how individuals contact each other. A prerequisite for an "effective" contact -namely a contact in which infectious transmission occurred- is to have a contact between two individuals. The probability of having a contact between two individuals, resulting in a possibility for an effective contact and the transmission of the pathogen, can be represented by a contact rate. While a single number in the most basic models may suffice, different contact rates according to given individual's characteristics are necessary for precise models. Indeed, such contact mixing patterns pronouncedly vary according to age-class, among various factors. Arbitrary contact matrices containing age-dependent transmission rates were provided and widely used for years as a kind of standard [Anderson and May, 1991] and known as the "Who Acquires Infection From Whom" (WAIFW) matrix. The contact matrix had to be chosen among a set of matrices when it seemed to best fit a particular situation and according to prior knowledge (or assumptions) of social mixing behaviour. More recently, some authors have shown that the matrix structure was crucial, and that an arbitrary choice can lead to nonsensical results [Goeyvaerts et al., 2010]. Empirical contact matrices built from social data appeared to be much more informative [Wallinga et al., 2006], once the rates of contact are considered as proportional to transmission rates ("the social contact hypothesis"). This had motivated researchers to carry out population surveys aimed at determining contact matrices specific to countries. To date, large population surveys have been carried out for many countries (POLYMOD study: Belgium, Italy, Luxembourg, Germany, Finland, United Kingdom, The Netherlands, Poland [Mossong

et al., 2008] or Japan [Ibuka et al., 2015]) as well as household-based surveys (Vietnam, Peru, Taiwan, China ...) [Fu et al., 2012, Grijalva et al., 2015, Horby et al., 2011, Read et al., 2014], but not for France. Developing contact matrices for France remained extremely useful in order to model infectious disease transmission in France, and that is the subject of this thesis.

1.3 Outline of the thesis

We used the results of the first large contact survey conducted in France, which is described in Chapter 2. From this survey, we built and described the first contact matrix for France in Chapter 3. In addition to description of its specificity proper to the French study, we focused on the factors potentially influencing the number of contacts and the mixing patterns, without restricting our analysis to any pathogen.

In 2010-2011, a major measles outbreak occurred in France, which was allegedly favoured by insufficient vaccine coverage. Measles is one of the most contagious airborne-transmitted viral diseases and one of the most vaccine-preventable causes of infectious deaths. It is characterized by a red maculopapular rash occurring 3 to 5 days after fever and cough. Measles most marked complications are neurological. Consequently, estimating the potential for a resurgence of measles is crucial. A mumps outbreak recently occurred in the United Kingdom, and incidence of mumps is rising slowly in France for 2-3 years [Sentinelles, 2015]. Mumps is also a highly contagious viral disease characterized by fever and parotitis, which occurs two weeks after exposure and lasts for one week. Transmission occurs via droplets or direct contact. Rubella is usually less spectacular, and is characterized by a rash two weeks after exposure, which lasts for approximately for 3-5 days. Usually mild, this air-transmitted disease can be extremely severe during pregnancy with congenital rubella syndrome. For these three diseases, recovered individuals gain lifelong immunity after natural infection and vaccination is highly effective. Currently, vaccination is achieved with a trivalent vaccine. Therefore, it is important to estimate the resurgence for measles, mumps and rubella, and the effect of increasing the vaccine coverage. Chapter 4 provides a direct application of the French contact matrices to estimate the risk of emergence of measles, mumps and rubella in France.

In Chapter 5, we evaluated the impact of weather conditions on mixing patterns, which could contribute to the seasonality of infections such as influenza, which is a viral infection, expressed mainly with fever and respiratory symptoms. Symptoms usually start two days after the exposure and last for one week. Though influenza is frequently mild, its prognosis may nonetheless include respiratory complications. Seasonal influenza occurs on a yearly basis, in winter in the Northern Hemisphere. Less often, a pandemic

occurs, resulting from a major mutation of the virus. It is transmitted via droplets, airborne or through physical contacts whether directly with an infected person or via fomites; the precise importance of each route of transmission is still debated.

In Chapter 6 we investigated the role of gender on mixing patterns and transmission of infectious diseases. We first conducted a review on the mecanisms involved in gender differences in infectious diseases, with a systematic review concerning these differences in influenza, measles, mumps and rubella. Afterward, we used the French matrices to illustrate how contact patterns could participate to these differences.

Finally, in Chapter 7 the implications of the previous results are discussed, the perspectives and the future works are exposed.

1.4 Basic Concepts

In this paragraph, we will first define some basic concepts and terminology frequently used in mathematical modelling of infectious diseases. Then, we shall briefly describe some of the statistical tools used in the following chapters.

1.4.1 Modelling concepts

The first mathematical model was developed by Daniel Bernoulli in 1760 to estimate the benefits of inoculation in prevention of smallpox. It generated the family of deterministic models, which are still the most widely used nowadays. By attributing a condition to members of a population, it subdivides this population in compartments such as *Susceptible*, *Infected* or *Recovered*, hence the expression: "Compartmental models". Stochasticity is implicitly taken into account when the model is applied to large populations. However, for smaller populations, stochasticity has got to be modelled explicitly. In this thesis, we shall focus on deterministic models. The framework of infectious disease modelling was formally expressed by Sir Ronald Ross in *The Theory of Happenings* as an answer to the question "[During an outbreak] What will be the number of affected individuals, of new cases and the total number of population living at time t". Ross' happening element, now called the force of infection, is the per capita rate at which a susceptible individual becomes infected. Under the assumption of the mass action principle, it reflects the degree of contacts with infectious individuals in a population and depends on the transmission rate β. The transmission rate β is defined by the product of the contact rate between susceptible and infectious individuals and the probability of transmission given contacts occurred.

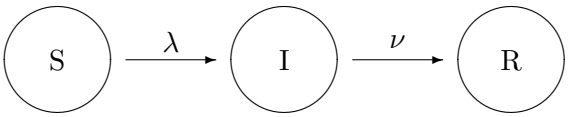


FIGURE 1.2: The basic SIR model

1.4.1.1 Basic deterministic model

The simplest compartmental model is the SIR model, first defined by Kermack and McKendrick in 1927 (Figure 1.2). In this model, the number of *susceptible* individuals S, of infected and *infectious* individuals I and *recovered* individuals R are summed up in a total population of constant size N. β is the transmission rate and ν is the recovery rate. With the mass action principle, the force of infection, which is the time-dependent rate at which susceptible individuals become infected and move from compartment S to compartment I, is defined as

$$\lambda(t) = \beta \frac{I(t)}{N}.$$

The SIR model can be formally expressed by the following equations:

$$\begin{aligned} \frac{dS(t)}{dt} &= -\beta S \frac{I}{N}, \\ \frac{dI(t)}{dt} &= \beta S \frac{I}{N} - \nu I, \\ \frac{dR(t)}{dt} &= \nu I, \end{aligned}$$

with $N = S + I + R$.

In this model, we have not taken into account the demography, notably mortality and the birth rate were not included, assuming the total population size is constant. This assumption is perfectly acceptable for an outbreak which won't last long and with little impact on population demography. As an example, seasonal influenza would meet this assumption, while Ebola won't. This model can easily be adapted to more complex situations. When one wishes to consider a disease with a newborn protected by maternal antibodies, a compartment (thus an equation) is added before the Susceptible compartment. To account for the fact that individuals may not be immediately infectious once infected, an extra compartment *Exposed* can be added between the *Susceptible* and *Infected* compartments. Moreover, some diseases, notably sexually transmitted diseases such as gonorrhea, do not provide protective immunity, and the compartment *Recovered* is consequently replaced by a return to the compartment *Susceptible* (SIS model). We provided here the simplest possible model, but many more exist...

1.4.1.2 Who Acquires Infection From Whom

To take into account contact rates varying according to age categories, assuming random but heterogeneous mixing and under the condition of a short mean infectious period, the force of infection $\lambda(a)$ can be approximated by:

$$\lambda(a) = \int_0^\infty \beta(a, a')I(a')da'$$

where $\beta(a, a')$ represents the transmission rate ("the per capita rate at which an individual of age a' makes effective contact with a person of age a per year" [Anderson and May, 1991]). The transmission rate is represented by a two-dimensional matrix also called the "Who Acquires Infection From Whom" (WAIFW) matrix. Anderson and May suggested constraining the structure of the WAIFW matrix according to prior knowledge of social mixing behaviour and restricted because of mathematical tractability, and then estimating the mixing parameters from serological data. Since then, some authors have shown that such constraint could lead to aberrant results and have proposed use of a social contact survey to estimate mixing patterns [Goeyvaerts et al., 2010]. This approach is based on the social contact hypothesis [Wallinga et al., 2006]:

$$\beta(a, a') = q \cdot c(a, a'),$$

with q a constant proportionality factor, and $c(a, a')$ the per capita rate at which an individual of age a' makes contact with a person of age a per year. With Y_{ij}, the number of contacts in age class j during one day as reported by a respondent in age class i $(i, j = 1, \ldots, J)$, one can calculate $m_{ij} = E(Y_{ij})$, the mean number of contacts in age class j during one day as reported by a respondent in age class i $(i, j = 1, \ldots, J)$. Then, the social contact matrix can be built with contact rates

$$c_{ij} = 365 \cdot \frac{m_{ji}}{w_i}$$

where w_i denotes the population size in age class i. At a later stage, the reciprocal nature of contacts can be taken into account

$$m_{ij}w_i = m_{ji}w_j$$

and smoothing can be applied. In this thesis, the contact surface smoothing was performed by applying a negative binomial model on the number of contact using a tensor product spline as a smooth interaction term. Smoothing was not systematically applied in this thesis, notably on location specific matrices.

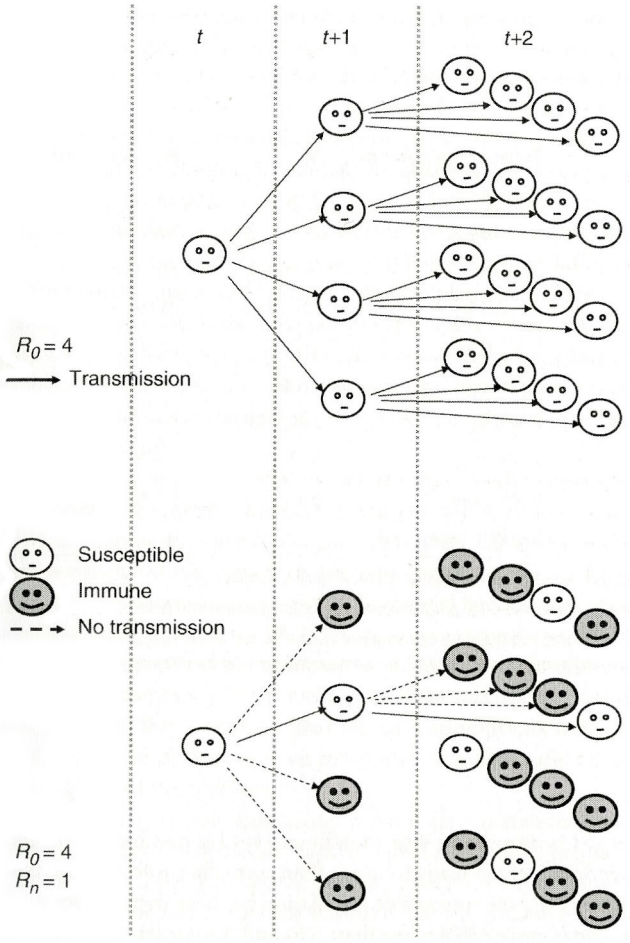


FIGURE 1.3: Illustration of the basic reproduction number, adapted from Fine 1993 and Vynnycky 2010

1.4.1.3 Basic reproduction number R_0

With the SIR model, it can be further demonstrated that if the number of S individuals is smaller than ν/β, then $dI(t)/dt < 0$ and the epidemic will die out. ν/β, called the relative removal rate, is inverse to the *basic reproduction number* R_0, a key parameter used to describe the ability of a pathogen to spread within a population. R_0 can be defined as the expected number of secondary infected individuals resulting from introducing one infected individual into an entirely susceptible population. Figure 1.3 illustrates the calculation of R_0. In the upper figure, one infected individual introduced at time t in an entirely susceptible population infects R_0=4 individuals at time $t+1$ who in turn infects R_0=4 individuals at time $t+2$. But if 75% of the population is immune (lower figure), then only 25% of the contacts infect individuals (the proportion of susceptible $s = 0.25$). Thereby, the effective reproduction number -namely, the expected number of secondary infected individuals resulting from introducing one infected individual into a partially immune population- is $R_e = R_0 \times s = R_0 \times 0.25 = 1$.

Therefore, an epidemic can occur only if $R_0 > 1$. An obvious implication is that a threshold value can be defined for vaccine coverage to reach a proportion of non-vaccinated individuals (the *Susceptible* compartment) less than the removal rate. The minimum coverage to achieve eradication should be $> 1 - 1/R_0$, defined as the *herd immunity threshold*. It clearly appears that the higher R_0, the higher the herd immunity threshold and consequently the efforts necessary to control the epidemic. Nonetheless, estimation of R_0 can be difficult, and is variable according to the type of data available and the methodology used. However, with R_0 being a summary of both the height of elements of the matrix -contact rates- and of it structure, it can be used to summarize the WAIFW matrix. When an *infectious* individual of age a' is introduced into an entirely susceptible population, the average number of individuals consequently infected can be expressed by the next generation operator, and R_0 is the dominant eigenvalue of the latter:

$$R_0 \ell(a') = \frac{ND}{L} \int_A^{+\infty} \ell(a) m(a) \beta(a, a') da,$$

where $\ell(a)$ denotes the leading right eigenfunction of the next generation operator [Diekmann et al., 1990], and with population size N stratified by age, mean duration of infectiousness D and life expectancy L. The relative incidence by age can then be calculated from the leading right eigenvector of the specific next generation matrix. However R_0 is rather theoretical as it is exceptional for all individuals of a population to be susceptible to an emerging infection. The effective reproduction number R_e then represents the actual average number of secondary cases.

Contact patterns can be compared graphically but also using the basic reproduction number R_0. The threshold value of R_0 is 1, as an epidemic will result from introduction of the infective agent when $R_0 > 1$, while the number of new infections per day will decline right after introduction when $R_0 \leq 1$. Although the graphical presentation of WAIFW can be very insightful, it is somewhat hard to compare two matrices, while it is much easier to compare two numbers. With this in mind, we have expressed the comparison with a ratio of R_0 instead of the values of R_0 to focus on the comparison, using the methodology of Hens et al. [2009a]. We then considered the ratio of R_0 estimated from different contact matrices. For comparison of 2 contact matrices C_1 and C_2, the ratio is calculated according to:

$$R_{0,1}/R_{0,2} = \frac{MaxEigenValue\left(\frac{N(a)D}{L} q \times C_1(a, a')\right)}{MaxEigenValue\left(\frac{N_(a)D}{L} q \times C_2(a, a')\right)},$$

with population size N stratified by age, mean duration of infectiousness D and life expectancy L, the proportionality factor q measuring among other things the disease-specific infectivity and susceptibility and $C_{1,2}$ the contact matrix. After cancelling the

normalizing constant, the ratio relates only to contact data. Under the null hypothesis of equal contact matrices and assuming q to be constant, this ratio is expected to equal 1. For each comparison, we assess the significance of any deviation from the null hypothesis by calculating 95% confidence intervals based on a nonparametric bootstrap. We also calculate the expected age-specific relative incidence in the population during the exponential phase, as given by the leading eigenvector of the next-generation matrix.

1.4.2 Statistical tools

The following paragraphs provide a brief description of the statistical tools used in this thesis.

1.4.2.1 Generalized Estimating Equations

The basic linear regression model requires observations to be independent, and independence is not achieved with repeated measures or longitudinal data. Two approaches have been derived from the Generalized Linear Model (GLM), the Generalized Linear Mixed Model (GLMM) and Generalized Estimating Equations (GEE) [Twisk, 2013]. GLMM enables to use random effects in addition to fixed effects and deals easily with non-normal data. GEE is an alternative to GLMM, which proposes to deal with correlated data, even when the correlation is unknown [Hardin and Hilbe, 2003]. GEEs are aimed at estimating population-averaged effects and are less sensitive to the variance structure than GLMM. We have used the GEE in Chapter 3 to assess the influence of various factors on the number of contacts. GEE and GLMM can deal both with repeated measures but where GLMM take it fully into account and model it, GEE treats correlation as a nuisance. Consequently, GEEs were chosen as we had no particular interest in studying the correlations. We also used a censored negative binomial model to reproduce the methodology used in Mossong et al. [2008]

1.4.2.2 Smoothing

When fitting a model to data, one tries to find a function that would fit the data correctly, in other words to minimize the difference between the observed response values and the response value that is predicted by our model. However, without constraints, a null difference can be obtained with a function that would interpolate all response values and thus overfit the data. Therefore, it is necessary to find a function that would render the difference small but smooth. Smoothing splines offer a trade-off using on the one hand a loss function compelling the model to fit the data well, and on the other hand a

penalty term that penalizes variability from the model [James et al., 2013]. Generalized Additive Models were initially developed to mix GLMs with additive models [Hastie and Tibshirani, 1990], but in this thesis they were used only for smoothing purpose [Wood, 2006].

1.4.2.3 Maximum-likelihood estimation

Modelling usually requires estimating the parameters included in the model. Among different methodologies, maximum likelihood aims at estimating the optimum parameters of a model. A likelihood is a function built on the parameters of a statistical model. The likelihood of a set of parameters, given an outcome, is the probability of having this outcome given these parameters. In other words, the likelihood is the probability that a model with a given set of parameters will be able to predict the given outcome accurately. Under the condition that a maximum exists and given a data set, the maximum of the likelihood function will correspond to the set of values for the parameters that will be optimum to predict the observed dataset. For convenience, the natural logarithm of the likelihood is widely used, and the maximum-likelihood estimation is based on the log-likelihood. Formally, the likelihood is expressed as follows:

$$\mathcal{L}(\theta; x_1 \dots x_n) = \prod_{i=1}^{n} f(x_i|\theta),$$

and the log likelihood as follows:

$$\log \mathcal{L}(\theta; x_1 \dots x_n) = \sum_{i=1}^{n} \log f(x_i|\theta),$$

where $x_1 \dots x_n$ are the observations and θ is the set of parameters. Several numerical techniques can solve the system of equations where there is a θ that can maximize (log-likelihood) such as Newton-Raphson, Fisher's scoring and EM algorithm.

1.4.2.4 Model selection

Modelling frequently requires making a choice between different potential models or different approaches. In a maximum-likelihood framework, model selection is performed by using the maximum log-likelihood and penalizing it according to the number of parameters. Akaike Information Criteria (AIC) [Akaike, 1973] and Bayesian Information Criteria (BIC) [Schwarz, 1978] are two ways to take the number of parameters into

account.

$$AIC = -2 \cdot \log \mathcal{L} + 2 \cdot k$$
$$BIC = -2 \cdot \log \mathcal{L} + \log(n) \cdot k$$

where n is the sample size and k the number of parameters. The "best" model will have the smallest AIC(BIC). It is to be noted that AIC tends to select the most complex model while BIC tends to choose the simplest model.

1.4.2.5 Bootstrap

Bootstrap is a technique developed by Efron in 1979 to provide standard error or bias estimates on parameters [Efron and Tibshirani, 1998]. It is based on the sampling with a replacement for a large number of iterations. In this thesis, we used non-parametric bootstrap, where samples are drawn from the data, and parametric bootstrap, where samples are drawn from the model. As resampling can be computationally expensive, the use of a supercomputer was frequently required for our analyses. In case of non-parametric bootstrap, we may wish to estimate the mean and variance of the outcome. We first select n observations from the dataset of size n to obtain a bootstrap dataset. The sampling is performed with replacement, which means that an observation can be drawn more than once in the bootstrap dataset. The mean of the outcome variable can be estimated from the bootstrap dataset. This procedure is repeated for B times, for a large value of B. The bootstrap estimation of the mean is

$$\hat{\mu}_* = \frac{1}{B} \sum_{b=1}^{B} \mu_b$$

and the bootstrap estimation of the variance is

$$\hat{\sigma}^2(\hat{\mu})_* = \frac{1}{B} \sum_{b=1}^{B} (\mu_b - \hat{\mu}_*)^2$$

Chapter 2

Datasets

2.1 France

2.1.1 The country

France is one of the largest countries of the European Union. With approximately 552 000 km^2, France is the third largest European country after Russia and Ukraine, but the second when including overseas territories. As a crossroads between many European countries, it shares frontiers with Belgium, Luxembourg, Germany, Switzerland, Italy, Monaco, Andorra and Spain. Its latitudes are comprised between 42°19′46″ N and 51°5′47″ N while its longitudes are comprised between 4°46′0″ W et 8°14′42″ E. A large portion of the French territory is overseas. With a continental part extending over 1000 km between its North and South, East and West boundaries, France presents substantial heterogeneity in geography as well as in climate. Its climate is temperate in the metropolitan part but with significant variations. The administrative territory of metropolitan France is mainly subdivided according to the three levels of municipality, department and region. Until 2015, there were in metropolitan France 22 regions, 96 departments and 36,681 municipalities. The median area for a department in metropolitan France is 5880 km^2. As a comparison, the median county size in England is 2.5 times smaller, and 3.5 times smaller in the USA. French population density is highly unbalanced, Paris urban area being 6 times more populated than the 2nd largest urban area (Lyon), and with low population density diagonally between Ardennes (North-East) and the Landes (South-West). In this thesis, we'll focus on metropolitan France.

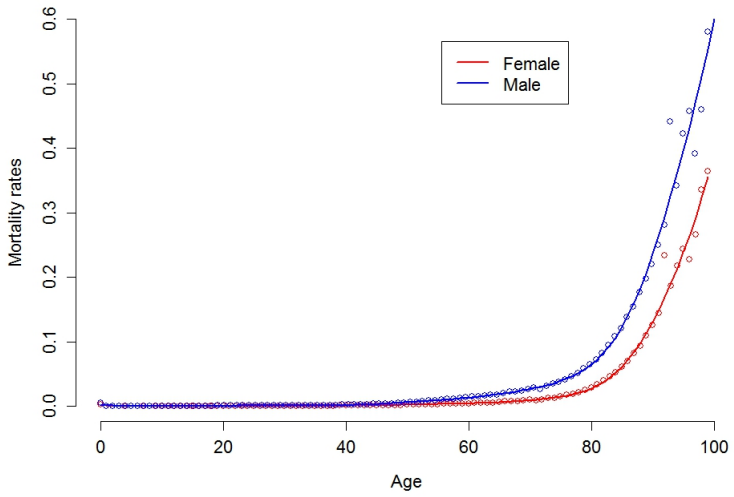


FIGURE 2.1: Mortality rate according to gender estimated from the population of France in 2012

Age category	Both genders, n (%)	Male, n (%)	Female, n (%)
$<$ 3 y	139,835 (18)	68,956 (18)	70,880 (19)
3 – 5 y	2,153,889 (93)	1,098,961 (93)	1,054,928 (93)
6 – 9 y	3,054,458 (99)	1,564,223 (99)	1,490,234 (99)
10 – 17 y	5,944,326 (98)	3,037,053 (98)	2,907,273 (98)
18 – 24 y	2,832,329 (52)	1,359,213 (49)	1,473,116 (55)
$\geq$ 25 y	651,492 (1)	292,943 (1)	358,549 (2)
Total	14,776,329 (24)	7,421,349 (25)	7,354,979 (23)

TABLE 2.1: School enrollment rate in France in 2012 (Eurostat).

2.1.2 The population

Demographic data were found on Eurostat, from the website `http://ec.europa.eu/eurostat/fr`(accessed on September 15, 2014). The French population in 2012 was constituted of 65,276,983 individuals, of whom 63,375,971 were living in metropolitan France. The population is aging ("papy boom") with approximately a quarter of the population over 60 years old. The male/female ratio revealed a higher proportion of women very mild from 25 years of age, and substantial after 65 years of age. The heightened imbalance can be explained by different mortality rates, which are significantly higher among men as early as 60 years of age (Figure 2.1).

School is mandatory from 6 to 16 years old. While kindergarten is not mandatory, 18% of two-year-old children and 93% the 3-to-5-year-old children attend kindergarten (Table 2.1).

Age category	Both genders, n (%)	Male, n (%)	Female, n (%)
15 – 24 y	2,079,000 (28.4)	1,145,000 (31.0)	934,000 (25.7)
25 – 49 y	16,426,000 (80.8)	8,540,000 (85.3)	7,886,000 (76.4)
50 – 54 y	3,386,000 (80.3)	1,748,000 (85.0)	1,638,000 (76.1)
55 – 64 y	3,635,000 (45.6)	1,851,000 (48.4)	1,784,000 (43.0)
≥ 65 y	238,000 (2.2)	139,000 (3.0)	99,000 (1.6)
Total	25,764,000	13,423,000 (55.4)	12,341,000 (47.6)

TABLE 2.2: Employment rate in France in 2012 (Eurostat).

Age category	hh=1	hh=2	hh=3	hh=4	hh=5	hh=6+	Total
0 – 4 y	0	118,395	901,919	1,075,500	482,819	266,143	2,844,778
5 – 9 y	0	164,380	563,576	1,509,062	855,015	427,001	3,519,034
10 – 14 y	26	167,431	573,713	1,348,001	879,338	490,092	3,458,600
15 – 19 y	76,025	283,737	784,479	1,174,566	700,288	440,892	3,459,987
20 - 24 y	631,062	817,884	764,765	679,091	343,633	245,283	3,481,716
25 - 34 y	1,231,531	2,068,749	1,798,666	1,290,101	442,574	230,417	7,062,039
35 - 44 y	965,060	1,091,370	1,618,942	2,603,913	1,122,981	419,764	7,822,030
45 - 64 y	2,405,431	5,941,298	3,102,590	2,106,185	794,534	377,522	14,727,561
≥ 65 y	3,143,165	5,338,499	612,071	163,674	73,393	62,301	9,393,102
Total	8,452,299	15,991,743	10,720,721	11,950,093	5,694,574	2,959,417	55,768,847

TABLE 2.3: French population according household size and age according INSEE 2009

The employment rate is higher for men compared to women. Unemployment was 10.6% in 2012, similar to the average rate in the European Union (Table 2.2).

Weighting of the participants was calculated with census data from INSEE 2009 [INSEE, 2009] (`http://www.recensement-2009.insee.fr/fichiersDetailTheme.action?codeTheme=INDCVI`, accessed on January, 10th 2013) which provided repartition of the population according to household size and age (Table 2.3).

2.2 The Comes-F study: Methodology of the survey

The Comes-F (**Co**ntact **M**atrix **Es**timation **F**rance) aimed at describing contacts made by participants over 2 consecutive days in metropolitan France. Participants had to report in a diary all the contacts made during that time, along with information about their household, professional and educational level. The survey was scheduled to take place from February 20th to March 17th, 2012 (first Design Period) and from April 16th to May 14th, 2012. Mailing incidents occurred as 350 diaries were lost when sent to the participants. An additional period was added to the first one from April 1st to 7th, 2012 to achieve a sufficient number of participants for the first period. Once a household was contacted and accepted to participate, the respondent was asked to enumerate the members of the household and their ages. The selection of the participants among the

household was done according to the Kish Selection Procedure [Kish, 1995], a method developed in 1949 to unsure that the person the most likely to answer the phone is not different form the general population. Briefly, the interviewer asked the person who answered on the phone to describe everyone in the household. All the eligible individuals are introduced in a selection grid (Kish grid) and a random selection is made according the place on the grid. Children between 15 and 17 years old were directly recruited while the recruitment for children under 15 years old was achieved through a parent. The diary was filled in by the participant for adults and children between 10 and 17 years old, and was filled in by a parent for children under 10, with help from the child, teachers, nanny...

The promoter of the survey was the Catholic University of Lille. It was realized by Ipsos, a global market research company, thanks to a grant from Glaxo-SmithKline. Ipsos did the random selection of participants, provided them explanations for filling the diaries and managed to send the diaries. In addition, it also managed the data capture and the preliminary cleaning of the database. The survey was preceded by a pilot study involving 5 participants -namely an 11-year-old girl, a student, a retired person, a teacher and a 1-year-old baby. They found the diary easy to fill in, and their comments concerned mainly the design of the diary and the explanations provided. Theses observations were taken into account to improve the survey diaries and the explanations given to the participants.

Participants were selected via random digit dialling. Since 1996, French subscribers have access to telephone providers different than France Telecom (Orange), which previously had the monopoly on telecommunications. Therefore, not all the French population owns a landline depending on France Telecom (Orange), and the phone book is consequently no longer in use. Besides, approximately 1% of the French population does not own a telephone, landline or mobile, and, is therefore excluded from a survey by phone. Random sampling made by telephone had to take into account that 6.4 million of French have a full unbundling and therefore without any remaining connection to France Telecom. However, 70% have kept their previous phone number, which is present in the sampling base. Therefore, 1.9 million French people do not have a geographical number (i.e. a number created by France Telecom) and 10% of the population only own a mobile phone. The sampling base was built with randomly generated numbers from geographical numbers and new numbers unrelated to France Telecom. To have a representative sample, notably in terms of age, 20% of the generated numbers had to be mobile phone. Therefore, two sampling bases were created. For the landline phone number base, 500 million numbers were randomly generated. Ninety percent of these numbers are not attributed or used by companies, so a cleaning of the base had to be

done, first using data on prefixes from ARCEP (Autorité de régulation des communications électroniques et des postes) to eliminate non-attributed numbers and using a communication tool to detect an RTC signal (Réseau Téléphonique Commuté) to know if the number is attributed. From this point, a reverse phone directory allowed to withdraw numbers assigned to companies, institutions or fax. Numbers to call were grouped, with an initial group of 15,000 numbers to be called first. Four groups of 1000 numbers were then used, to maintain set quotas. A sampling base for mobile phones was built, by randomly generated numbers according to the prefixes allowed by ARCEP and taking into account the weight of each provider. A call without response was repeated 15 times before being discarded. Finally, 24,250 persons responded out of the 263,000 contacted (9%), and 3977 accepted to participate in the study which represents 24% of eligible individuals. The recruitment of participants is representative of population distribution in France (Figure 2.2).

In order to limit refusal or withdrawal, a free hotline and an email address were available for participants requiring more information, and pollsters were trained for a minimum of half a day to be able to use a number of arguments to convince contacted persons to participate. The withdrawal rate (proportion of individuals who accepted to participate but finally failed to send their diary) was estimated at 23% (20 to 30%). Therefore, 1300 individuals were contacted to obtain 1000 participants per design period. In fact, only 51% of the participants sent their diary back for the first period, so adaptations had to be performed to obtain the required quotas for the second period among the 2033 final participants. The diary of 50 participants was lost or never arrived, although they claimed to have sent it back. During data cleaning by Ipsos, 63 participants filled out only one day. After having checked comments provided with the diaries, they were considered as valid and reported with 0 contacts for the other day. Thirty-eight participants sent back a diary without any contact reported and were discarded as non-valid. Some of them could indeed have had no contact for two days, but they could not be distinguished from individuals who found the diary too complex to fill in. Nor could they be counted, as were other participants who send back blank diaries, stating that they had had no contact to report. The diary had to follow three quotas, the age of the participant (which was mandatory), the day of the week and holidays. The objective and the actual quotas are presented in Tables 2.4 and 2.5.

2.3 Measles cases

Measles was a reportable disease up to 1986; from 1986 to 2004 its incidence was monitored via the national sentinel network of general practitioners. Reporting was made

	Period 1					Period 2					Periods 1 + 2				
Quotas	Obj.	Recruiting		Participants		Obj.	Recruiting		Participants		Obj.	Recruiting		Participants	
Age		Effect.	%	Effect.	%		Effect.	%	Effect.	%		Effect.	%	Effect.	%
		1300	100.0	729	100.0		2677	100.0	1304	100.0		3977	100.0	2033	100.0
<3y	10%	132	10.2	74	10.2	9%	245	9.2	113	8.7	10%	377	9.5	187	9.2
3-5y	10%	124	9.5	63	8.6	12%	251	9.4	106	8.1	10%	375	9.4	169	8.3
6-9y	10%	133	10.2	70	9.6	11%	281	10.5	141	10.8	10%	414	10.4	211	10.4
10-17y	10%	131	10.1	73	10.0	13%	350	13.1	155	11.9	10%	481	12.1	228	11.2
18-24y	10%	130	10.0	58	8.0	11%	336	12.6	119	9.1	10%	466	11.7	177	8.7
25-39y	10%	130	10.0	56	7.7	11%	300	11.2	115	8.8	10%	430	10.8	171	8.4
40-54y	10%	130	10.0	78	10.7	8%	227	8.5	129	9.9	10%	357	9.0	207	10.2
55-64y	10%	130	10.0	94	12.9	9%	237	8.9	170	13.0	10%	367	9.2	264	13.0
65y+	20%	260	20.0	163	22.4	17%	450	16.8	256	19.6	20%	710	17.9	419	20.6
Gender		Effect.	%	Effect.	%		Effect.	%	Effect.	%		Effect.	%	Effect.	%
Male	-	579	44.5	403	55.3	-	1217	45.5	530	40.6	-	1796	45.2	933	45.9
Female	-	721	55.5	326	44.7	-	1460	54.5	774	59.4	-	2181	54.8	1100	54.1

TABLE 2.4: Quota and effective for participant's age and gender

	Period 1					Period 2					Periods 1 + 2				
Quotas	Obj.	Recruiting		Participants		Obj.	Recruiting		Participants		Obj.	Recruiting		Participants	
Day		Effect.	%	Effect.	%		Effect.	%	Effect.	%		Effect.	%	Effect.	%
		1300	100.0	729	100.0		2677	100.0	1304	100.0		3977	100.0	2033	100.0
Mon-Tue	9.2%	119	9.2	65	8.9	9.2%	248	9.3	129	9.9	9.2%	367	9.2	194	9.5
Tue-Wed	16.7%	217	16.7	118	16.2	16.7%	459	17.1	236	18.1	16.7%	676	17.0	354	17.4
Wed-Thu	16.6%	216	16.6	125	17.1	16.6%	459	17.1	225	17.3	16.6%	675	17.0	350	17.2
Thu-Fri	9.2%	120	9.2	62	8.5	9.2%	248	9.3	139	10.7	9.2%	368	9.3	201	9.9
Fri-Sat	24.2%	314	24.2	158	21.7	24.2%	614	22.9	249	19.1	24.2%	928	23.3	407	20.0
Sun-Mon	24.2%	314	24.2	164	22.5	24.2%	649	24.2	284	21.8	24.2%	963	24.2	448	22.0
Other days	-			10	1.4	-			6	0.5	-			16	0.8
1 day	-			27	3.7	-			36	2.8	-			63	3.1
Holidays		Effect.	%	Effect.	%		Effect.	%	Effect.	%		Effect.	%	Effect.	%
≥25y	50.0%	650	50.0	391	53.6	50.0%	1215	45.4	670	51.4	50.0%	1865	46.9	1061	52.2
<25y&Reg. day	25.0%	379	29.2	168	23.0	25.0%	1035	38.7	306	23.5	25.0%	1414	35.6	474	23.3
<25y&Holiday	25.0%	271	20.8	170	23.3	25.0%	427	15.9	328	25.2	25.0%	698	17.5	498	24.5

TABLE 2.5: Quota and effective for day of the week and holidays

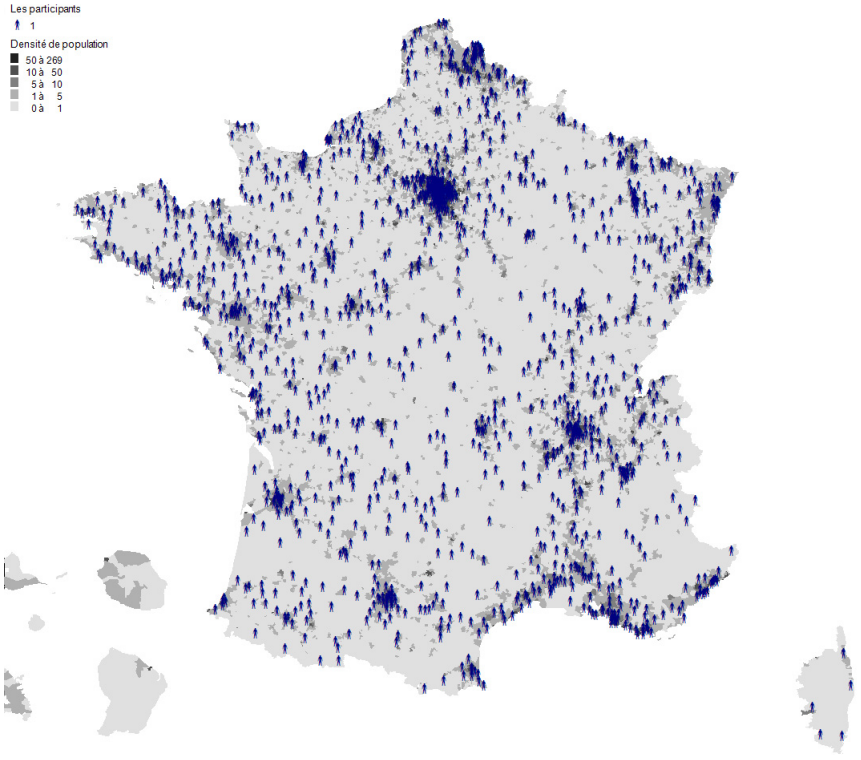


FIGURE 2.2: Participants in the study, in relation to population density in France

mandatory again in 2005. This dataset reports all the cases of measles reported from 01/01/2006 to 31/12/2013. It includes age, gender, department of declaration, department of residence, recent travel abroad, if yes in which country, and date of symptom onset. As shown in Figure 2.3, it reports the major outbreak that occurred in France between 2008 and 2011. The sex-ratio M/F was 1.04, and the median (Min; Max) age was 15 (0;88) years old. In 2006 and 2007, there were only 40 and 43 cases, respectively. But incidence increased with 604 cases in 2008, 1544 in 2009, 5090 in 2010 and 14,967 in 2011. The outbreaks subsequently died out with 861 cases in 2012 and 272 cases in 2013. Forty-four point three percent of the cases occurred during holidays. Two point three percent of patients reported recent travel abroad.

2.4 Seroprevalence survey for Measles-Mumps-Rubella

2.4.1 The Saturn-Inf study

The Saturn-Inf national study was designed to identify the national prevalence of saturnism (lead poisoning), the cadmium concentration and the seroprevalence of measles, mumps, rubella, varicella, toxoplasmosis, hepatitis A and herpes virus type 1 and 2) among children from 6 months to 6 years. The sampling base was built at two levels.

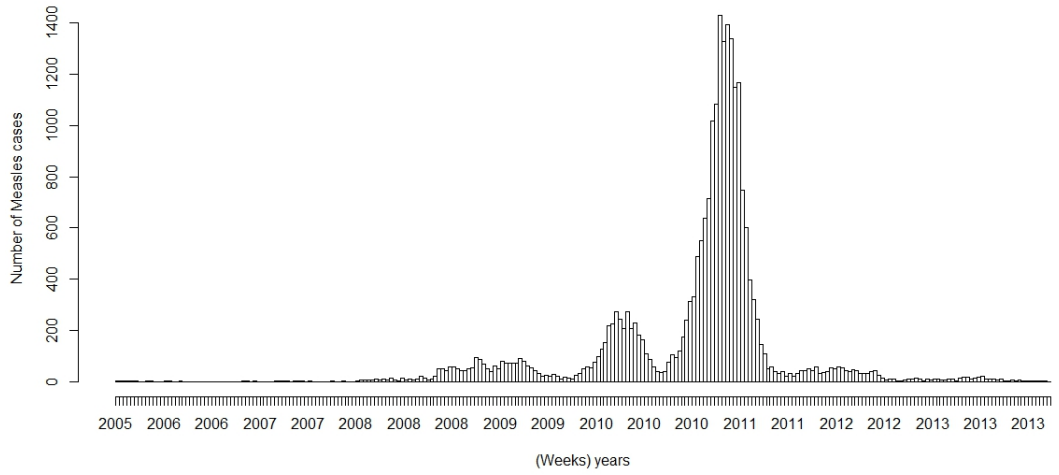


FIGURE 2.3: Measles cases reported fortnightly from 2006 to 2013.

First, hospitals were randomly selected, and then hospitalized children were randomly selected. The regions of Nord-Pas-de-Calais, Île-de-France, Haute-Normandie et Provence-Alpes-Côte d'Azur were overrepresented due to a known higher risk for saturnism. The inclusion criteria were an age comprised between 6 months and 6 years, being hospitalized, having a blood sample taken during hospitalization, living in France at the study time. Children hospitalized specifically for saturnism were excluded, as well as children with immunosuppression, chronic disease with influence on immunity, children having benefited from blood transfusion or gamma globulins during the previous 6 months or children with a life-threatening condition. The same laboratory carried out all the biological analyses. Finally, 1617 children were included from France including overseas territories, between September 2008 and February 2009. The variables reported included age and gender, department of residence, vaccination history (doses, date, brand...), qualitative and quantitative serology for measles, rubella, mumps, HAV, HEV, toxoplasmosis, VZV, HSV 1&2, CMV, childcare mode (home, kindergarten...), household size (adult and children), country of origin, parents' occupation and educational level.
The percentages of measles-, mumps- and rubella-susceptibility were 10%, 15% and 11% in the 1-6 years old (no children under one year were included), respectively [Lepoutre et al., 2013].

2.4.2 The Sero-Inf study

The Sero-Inf study aimed at completing the Saturn-Inf study. It focused on individuals from 6 to 49 years and estimated the seroprevalence for measles, rubella, mumps, HAV, VZV, Toxoplasmosis, Hepatitis E, HSV 1&2 for 6-19 years and CMV for 15-49 years.

It included 5300 participants from metropolitan France who went to a laboratory for a blood test. It started in April 2009 and included individuals for six months and excluded individuals with immunosuppression, with a history of transfusion or pregnant women who came for a follow-up for seronegativity to one of the diseases studied. The sampling was done at two levels, first the laboratory, with weighting according to their interregion, their global activity and their activity dedicated to <16 years children. One single laboratory did all the analyses. The variables reported included age and gender, ZIP code, country of origin, parents' occupation and educational level.
The percentages of measles-, mumps- and rubella-susceptibility were 8%, 14% and 8% for the 6-29 years old, and 1%, 6% and 5%for the 30-49 years old, respectively [Lepoutre et al., 2013].

The two previous datasets were merged for the analysis. Influence of the study was tested with a generalized additive model, including age. There was an effect of the study for measles (p=0.048) but not for mumps (p=0.428) or rubella (p=0.405). It could be a specific effect of the study as well as a "collateral" effect of the cut-off at six years, as the second dose could be administered until 2005 until six years old. We also searched for a potential interaction of the interregion with age, for the effect of age on serology. There was an interaction for measles (p=0.004) and rubella (p=0.0154) but not for mumps (p=0.288). Influence of the interregion, visible on Figure 2.4 for the particular case of measles, prompted us to include the localisation of the participants in the model used in Chapter 4.

2.4.3 The Sero-RR study

The Sero-RR study is a transversal study aiming at estimating the seroprevalence for measles and rubella using a population of blood donors, in France including overseas territories, during the second semester of 2013. The sampling was done at two levels, first the sites of blood sampling and then the individuals who were stratified for two age categories (18-25 years and 26-32 years). 4647 blood donors of 18 to 32 years were tested for measles and rubella and interviewed about their history regarding measles notably during the 2010-2011 outbreak. As most of the cases from the 2010-2011 measles outbreak were from the SouthEastern interregion, 4000 individuals from this interregion were interviewed on their measles recent history but without any blood sample drawn. A single laboratory did all the analyses. The variables reported included age and gender, department of residence, occupation (student, job...), educational level, vaccination against measles (if yes was it before or after Jan. 2009?), history of measles (if yes was it before or after Jan. 2009?, if yes medical was there a consultation?, if yes was there an hospitalization?).

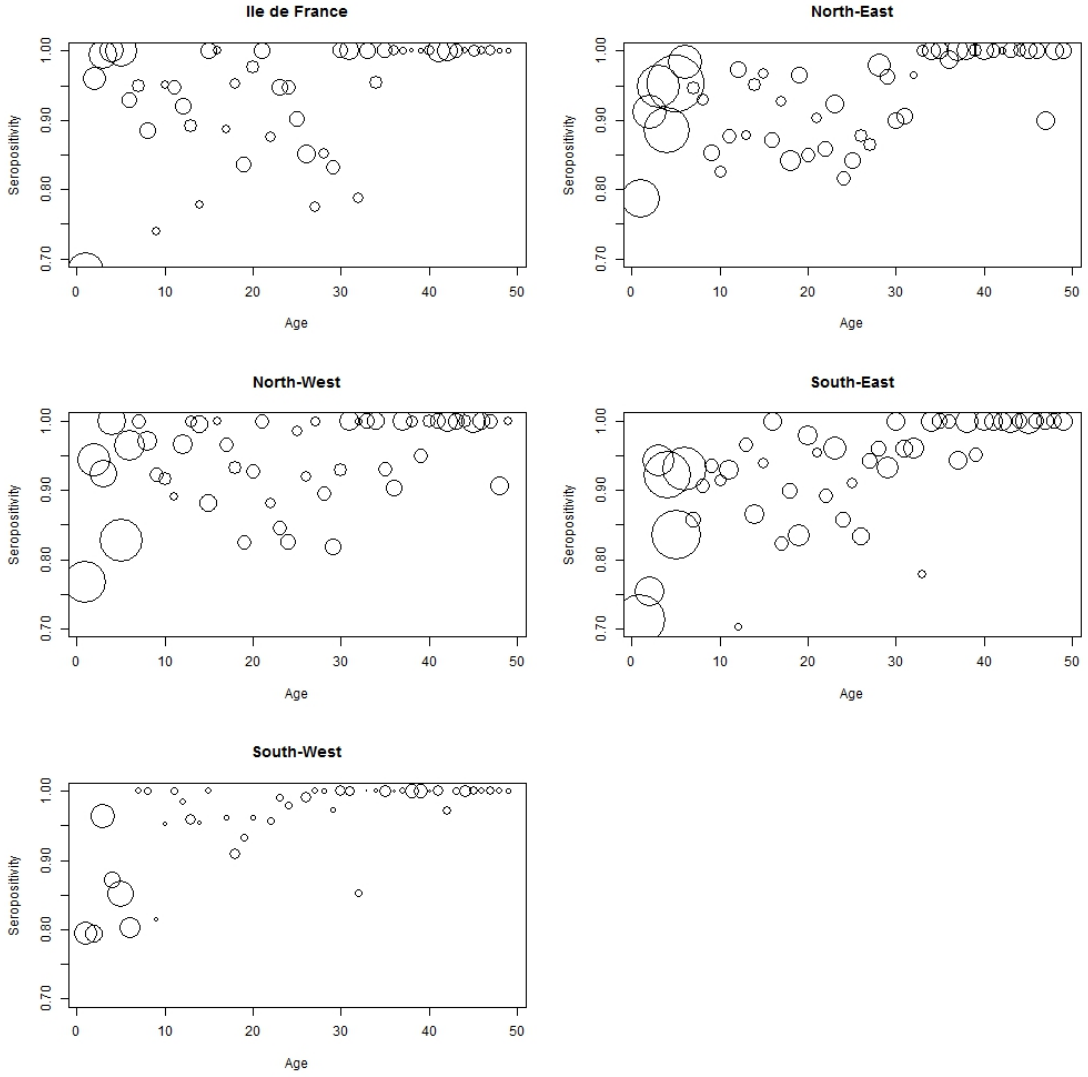


FIGURE 2.4: Effect of age on measles serology, according to the interregion.

2.5 Vaccine coverage

The vaccine coverage at 24 months was documented by departments, from 2004 to 2011. Report was supposed to be exhaustive, however some departments did not report their vaccine coverage. InVS made a quality assessment in order to identify irrelevant coverage reports. Coverage reports were considered irrelevant and discarded when (1) the coverage for the 2nd dose was exactly equal to the coverage for the first dose, (2) if the departmental coverage reported was more than 5 points lower than the departmental coverage reported the previous year, or (3) when the reported coverage for the 2nd dose was more than 5 points lower than the national mean. Finally, from 15 to 44 departmental coverages for the first MMR dose were missing or discarded, according to the year.

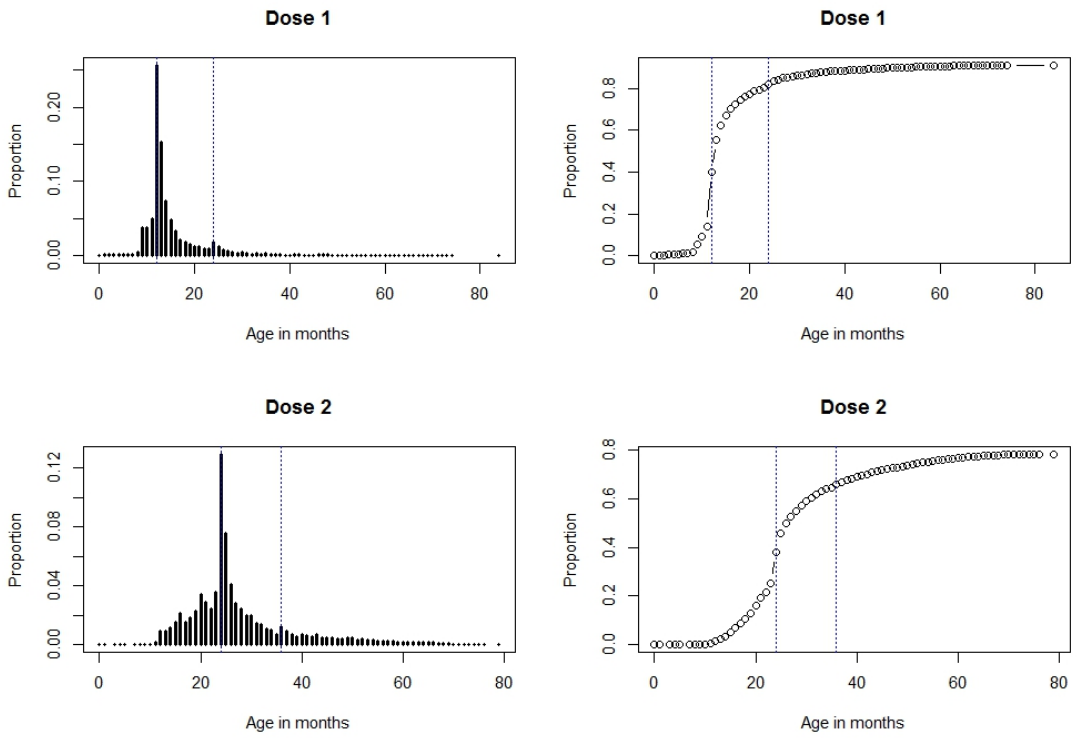


FIGURE 2.5: Distribution of the age of administration of MMR dose 1 and 2 for children of 5 years in 2012. Dashed lines indicate the age range at which the vaccination were recommended at that time.

We also used the result of surveys on the age of vaccination for MMR conducted at school. InVS carried out a study on the percentage of vaccine coverage by MMR vaccine among children in the great section of kindergarten (≈5 years old) in 2002-2003, 2005-2006 and 2012-2013. For the latter, the age of vaccination was one year for the first dose and two years for the second dose. But for the others, the second dose was recommended to be administered between three and six years old. In 2012-2013, information on dose 1 was missing for 1662 (8.9%) children among 18669 surveyed, and on 4118 (21.9%) of 18,804 children surveyed. The median of vaccination was 13 months for dose 1 and 25 months for dose 2 (Figure 2.5).

In 2005-2006, information was missing for dose 1 for 3017 (12.9%) of 23303 children surveyed, and on dose 2 for 13792 (59.0%) of 23365 children surveyed. The median of vaccination was 14 months for dose 1 and 55 months for dose 2 (Figure 2.6).

In 2002-2003, information was missing for dose 1 for 411 (8.7%) of 4723 children surveyed, and on dose 2 for 3539 (74.6%) of 4747 children surveyed. The median of vaccination was 15 months for dose 1 and 57 months for dose 2 (Figure 2.7).

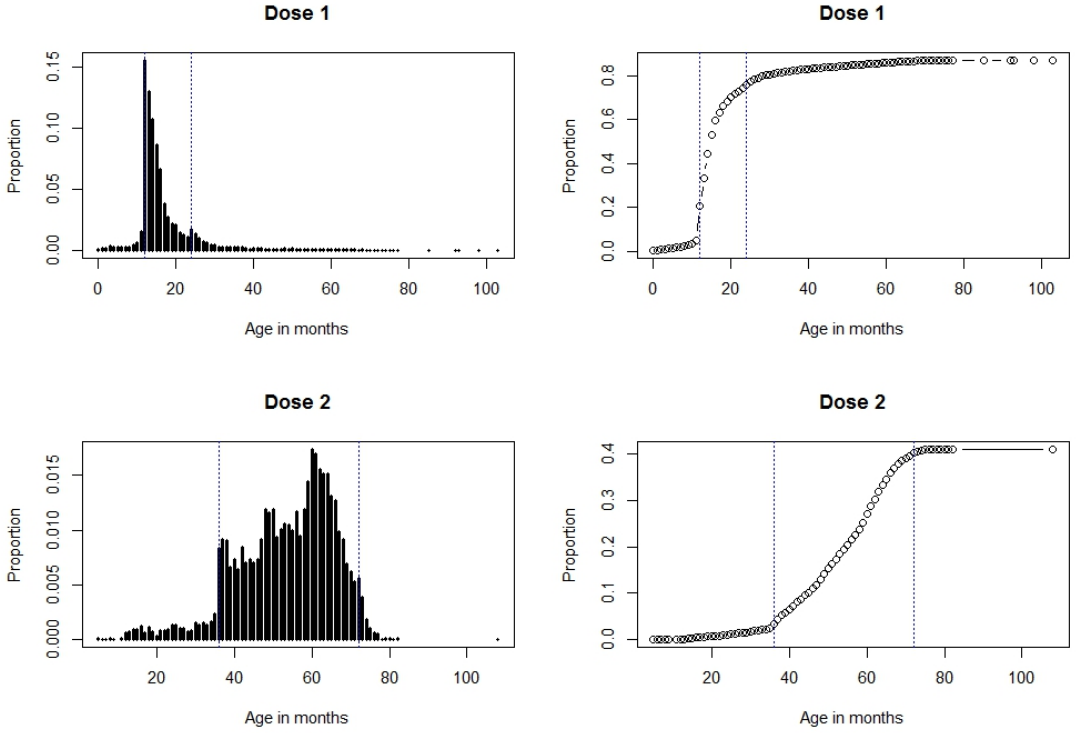


FIGURE 2.6: Distribution of the age of administration of MMR dose 1 and 2 for children of 5 years in 2005. Dashed lines indicate the age range at which the vaccination were recommended at that time.

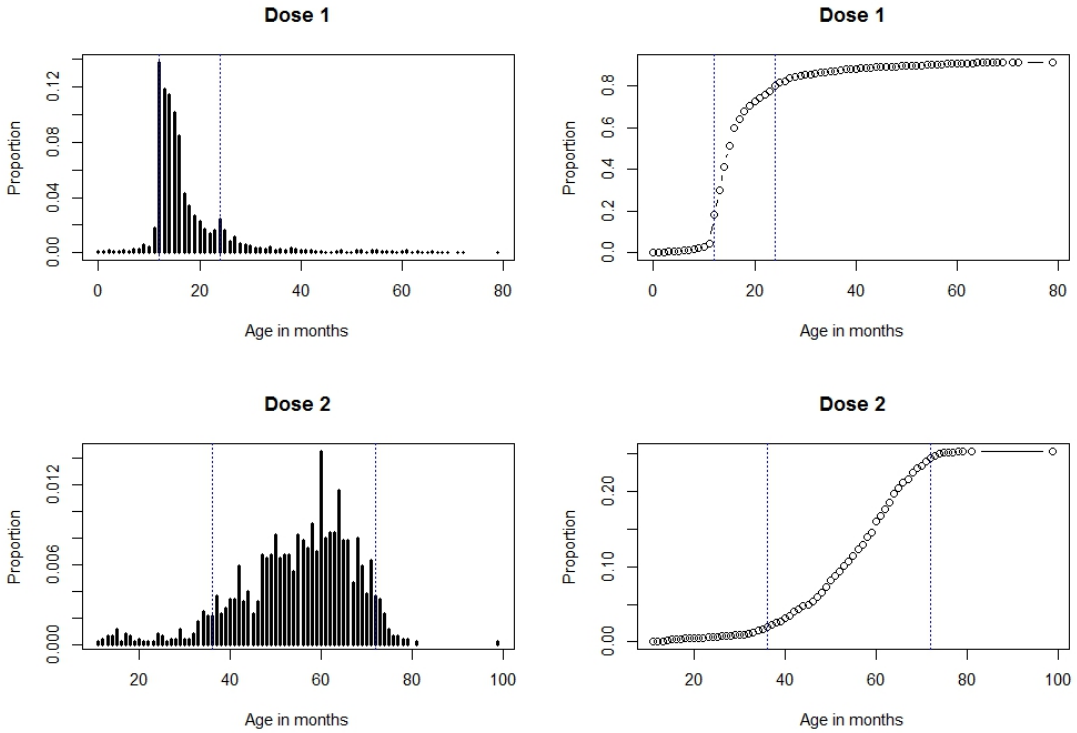


FIGURE 2.7: Distribution of the age of administration of MMR dose 1 and 2 for children of 5 years in 2002. Dashed lines indicate the age range at which the vaccination were recommended at that time.

2.6 Weather data

Data on weather conditions were obtained from the National Climatic Data Center website, part of National Oceanic and Atmospheric Administration (US Department of Commerce) at the following URL: http://www7.ncdc.noaa.gov/CDO/cdoselect.cmd?datasetabbv=GSOD&countryabbv=&georegionabbv= (accessed on February, 14th 2015). Two files were obtained at our request. The first file is a description of 936 weather stations, including the identification code, name, latitude, longitude, elevation and the available period when the station was active for weather observation. The second file reported weather data for the French stations from January, 1st 2012 to June, 1st 2012, which represented 28,676 observations. Data available were mean temperature, mean dew point, maximum temperature, minimum temperature in degrees Fahrenheit, mean sea level pressure and mean station pressure in millibars, mean visibility in miles, mean wind speed, maximum sustained wind speed and maximum wind gust in knots, precipitation amount and snow depth in inches. Moreover, there was an indicator for the occurrence of fog, rain or drizzle, snow or ice pellets, hail, thunder, tornado & funnel cloud. Of note, the daily extremes and totals for maximum wind gust, precipitation amount and snow depth were reported only if the station reported enough data to provide a valid value.

Chapter 3

French contact matrices

In this chapter, we built, described and analysed the matrices based on the results of the Comes-F study, before describing implications of these results. These findings have been published in Béraud et al. [2015], and are the basis for the analyses conducted in next chapters.

3.1 Introduction

Mathematical modelling of infectious diseases is invaluable to evaluate control and prevention strategies by comparing their (cost-)effectiveness and to inform public health decision makers. While most models make assumptions on transmission parameters, social contact data studies estimate the probability of contacts between individuals, and consequently of potential pathogen transmission. For instance, social contact data studies have shown better goodness-of-fit than mathematical and parsimonious models on seroprevalence data for varicella [Ogunjimi et al., 2009]. Contact diaries have several advantages in measuring the frequency and intensity of contacts between individuals. They are easy to use, capture social interaction in a wide range of settings and do not rely on peer-group participants [Read et al., 2012]. They successfully explained age-specific patterns of infection such as varicella-zoster virus, parvovirus B19 [Melegaro et al., 2011], mumps [Wallinga et al., 2006], influenza [Wallinga et al., 2006] and pertussis [Rohani et al., 2010]. Nonetheless, defining a contact suitable for infectious disease transmission remains difficult and varies according to pathogen [De Cao et al., 2014, Read et al., 2012]. A population-based contact survey provides the basic material allowing to build contact matrices with different levels of contact intimacy (e.g. physical or/and long-duration contacts versus conversational or/and short-duration contacts). Focusing on 8 European countries, POLYMOD was the first large-scale study to report on contacts

between individuals [Mossong et al., 2008]. To date, no such data existed for France. Fumanelli et al. [2012] estimated contact matrices by inferring the structure of social contacts from demographic data, but at the expense of substantial differences with the empirical contact matrices from the POLYMOD study. Time-Use surveys are widely available and provide a valuable alternative to estimate contact matrices, but they are often restricted to participants older than eight years [De Cao et al., 2014, Zagheni et al., 2008]. With regards to the pandemic influenza A/H1N1 virus, a French household-based survey reported meetings made by participants but with information restricted to the place and the age distribution of contacts [Lapidus et al., 2013]. Seasonality is a common feature in infectious diseases, usually attributed to environmental factors such as temperature or humidity [Lowen et al., 2007]. Term-time forcing for measles [Keeling and Rohani, 2011] and other childhood infections [Metcalf et al., 2009] suggests the importance of behavioural factors. But few studies have evaluated the change in the number of contacts for given persons over a period of time [DeStefano et al., 2011, Read et al., 2008]. None has compared the change in mixing patterns overtime. Hence, while contact matrices have been developed at the country-wide level, they lack in temporal information. In this paper, we describe the first large-scale population survey investigating contact patterns in France and their temporal variations. Taking advantage of the natural heterogeneity of France –one of the largest European countries– and using the largest sample size for a country-based population survey carried out to date, we have estimated French contact rates. We have reassessed the influence on mixing patterns of weekends and holidays as well as gender, children's contact patterns or class size. We have also explored the influence of people with high numbers of professional contacts on one or two consecutive days.

3.2 Methods

3.2.1 Study design

The study population was randomly sampled from all over France (excluding overseas territories) and planned over two time periods (February-March/April-May 2012) (Figure 3.1). An oversight leading to recruit fewer participants than originally planned during the February-March period (Actual Period 1), an additional period (Actual Period 2) was added in April to complete "Design Period 1". Recruitment during "Design Period 2" was completed according to plan (Actual Period 3). The Actual Period 2 being chronologically close to "Design Period 2", we presented data analyses according to (1) Design Periods 1 and 2, (2) the 3 Actual Periods 1, 2 and 3 and (3) to Actual Period 1 and a combination of Actual Periods 2 and 3.

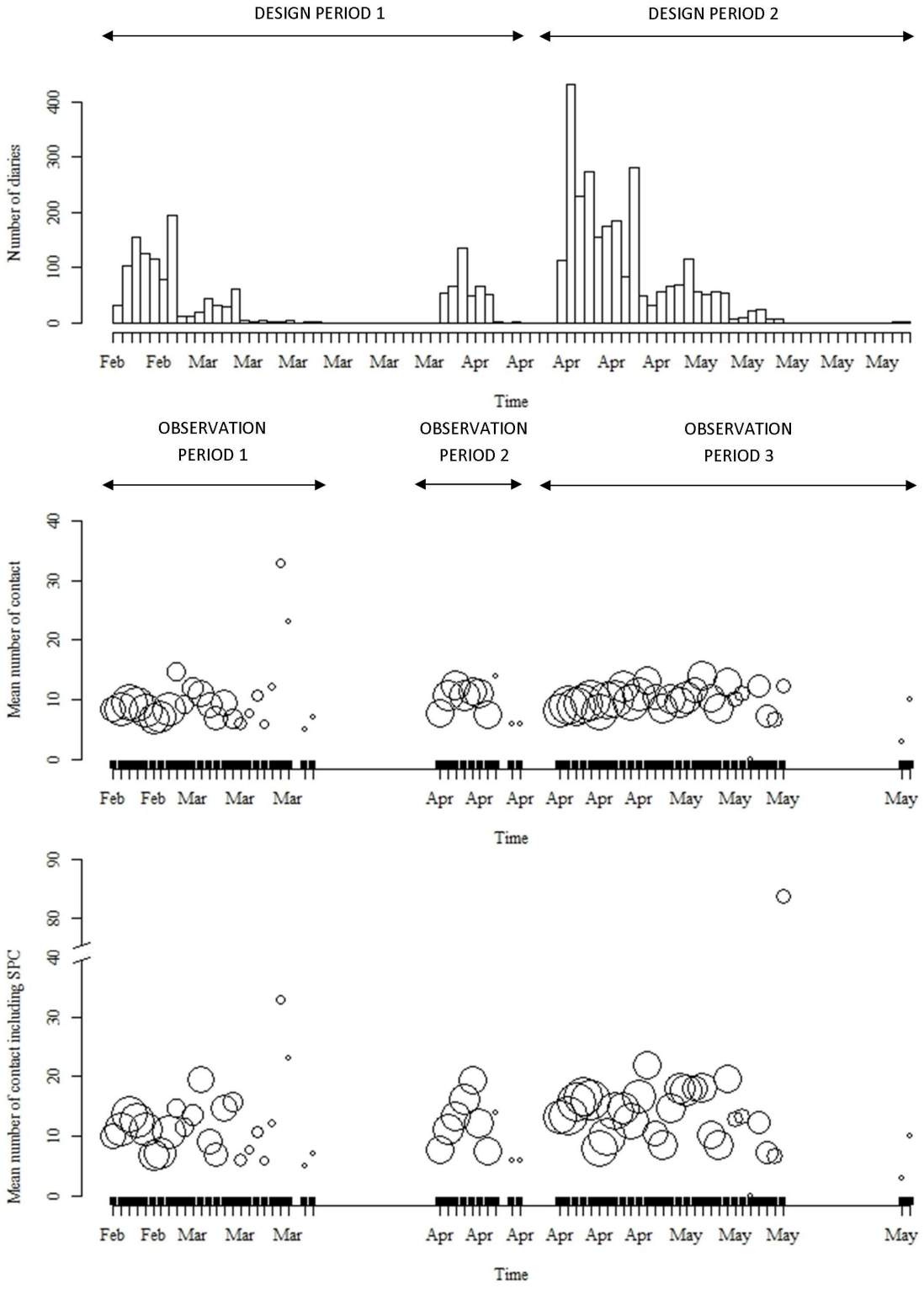


FIGURE 3.1: Timeline of the study, showing the distribution of participants and contacts over time. The dot size is proportional to the log of participant's number. (Design Period 1: 34 days; Design Period 2: 29 days).

Participants were recruited according to quotas for age, gender (sex-ratio=1), days of the week and school holidays from 24 250 persons contacted by random digit dialling (landlines and mobile numbers). Diaries (Appendix A) were sent to 3977 people who have accepted to participate, among whom 2033 actually participated (729 during Design Period 1; 1304 during Designed Period 2). Participants common to Design Periods 1 & 2 (n=278) represented respectively 38% and 21% of participants. Only one person per household could participate. Children and teenagers were oversampled to gain accuracy on age groups known to contribute largely to the spread of infections. Participants had to describe their environment (household, workplace, school...), their socio-professional background, and all their contacts for two consecutive days on a paper diary. A contact was defined as talking to someone within a distance of less than 2 meters, or skin-to-skin touching. Each contact had to be described with age (or estimated age category), gender, location, frequency, type (skin contact or not) and duration of the contact. A contact was to be reported only once daily in the diary. The diary was derived from the POLYMOD study but had some additional features. The daily number of potentially recorded contacts was limited to 40 (versus 29 to 90 in POLYMOD [Mossong et al., 2008]). A specific diary for children 0-15 years old (27.9% of all the diaries) was designed with instructions for caregivers to help complete it. This diary had specific questions about childcare, school and location of contacts (school and day care centre). Participants were coached by phone and could seek information to complete the diary through a hotline and an email address. They were contacted up to 3 times if the diary was not returned. Participants who returned the diary were offered 5€for themselves or donation. Participants provided verbal consent when they accepted to participate in the study, as they were contacted by phone. Moreover, they confirmed their consent by returning the diary. Thus, returning the diary was considered as a written consent. For children younger than 15 years, their consent and the consent of a parent or legal caregiver had to be obtained, in a similar ways (first by phone, then by returning the diary). Children between 15 and 17 years were considered as adults; thus, their consent was obtained without requiring an adult.

3.2.2 Data analysis

Data analysis was done using the statistical programming language R 3.1.0 [Team, 2012]. Sampling weights were calculated according to participants' age, household size (Table 2.3), weekdays and weekends, regular and holiday periods. Continuous variables are expressed as weighted median (first quartile-third quartile).

3.2.3 Number of contacts

Regarding the number of contacts, the variable selection was done using random forests [Breiman, 2001] (R package randomForest). Age was transformed into five-year age categories and days of the week were transformed into weekday/weekend for data sparseness and model interpretability. Generalized Estimation Equation (GEE)(R package geepack) [Yan, 2005] with a negative binomial distribution were used to regress the number of contacts and the selected variables. Variables influencing the number of contacts were compared with the percentage of change and 95% confidence interval (95% CI) based on the estimates from GEE. The GEE approach can handle correlations between repeated observations from the same participants. The degree distribution of the number of contacts was modelled using Generalized Additive Models (GAM) with spline smoothing (R package mgcv [Wood, 2006]) stratified according to age, gender, weekdays and weekend, regular and holiday periods.

3.2.4 Who mixes with whom?

Contact matrices were obtained using GAM assuming a negative binomial distribution, using a one-year age interval and a tensor product spline as smooth interaction term between contact age and participant age. Different matrices were calculated: a base-case matrix without supplementary professional contacts, a matrix with physical contacts only, a matrix with supplementary professional contact information and matrices according to the 3 actual periods of the study. To assess the influence of gender, 2-by-2 matrices were built according to gender and age ($\leqslant$18 years; >18 years) of both participants and contacts. To assess the influence of the place of contact, location-based matrices were built using six age categories and no smoothing. Data sparseness prompted us to use different methods to obtain the matrices as described above. The reciprocal nature of contacts was taken into account by a 'smooth-then-constrain' approach [Hens et al., 2009b], except for location matrices where no reciprocity was imposed. We also built duration specific matrices, to which we imposed reciprocity. Comparing the impact of different mixing patterns on the spread of infectious diseases, we calculated the relative change in the basic reproduction number R_0 for a generic epidemic by calculating the ratio of dominant eigenvalues of the respective next generation matrices [Diekmann et al., 1990, Hens et al., 2009a] (Section 1.4.1.3). Similarly, we used the leading right eigenvector of the specific next generation matrices to calculate relative incidence by age. For the location matrices, we used the eigenvalue of the contact rate matrices as there was no population size by location, warranting a somewhat different interpretation, and

did not impose reciprocity. Resampling was done to estimate 95% CI of leading eigenvalues and eigenvectors. Changes in R_0 and contact rate were compared with a ratio and 95% CI based on a non-parametric bootstrap.

3.2.5 Professional contacts

Participants with more than 20 daily professional contacts were asked not to report them but rather to provide their total number and age distribution (0-3 years; 3-10 years; 11-17 years; 18-64 years; 64+ years) (referred as "supplementary professional contacts" or "SPC" in the remainder of the paper). Other contact characteristics were imputed by resampling the characteristics of professional contacts from participants who had between 10 and 20 professional contacts. A threshold value was set at 20 per day for contacts made at work, to reduce reporting bias for individuals with a high number of professional contacts such as for example a bus driver. If participants had more than 20 professional contacts, they were asked not to report them individually but to indicate the number of these supplementary professional contacts and their age distribution (0-3 years, 3-10 years, 11-17 years, 18-64 years, 64+ years). Secondarily, these supplementary professional contacts were imputed according to the methodology used by Hens et al. [2009b]. Supplementary professional contacts were defined when participant i reported having n_i^w (>20) contacts at work made in a specific set of age-categories I_i^a. We used the age, gender, duration of contact and whether the contact involved skin-to-skin touching of the reported contacts at work when $10 < n_i^w < 20$ as a basis for imputation. This set of contacts was resampled with probabilities according to the reported age distribution, taking into account the French population age structure in 2012 (INSEE) and implemented into the data set when the day of study was a weekday. We also developed a model where censoring was applied to the supplementary professional contacts, considering they followed a negative binomial distribution, to retain 95% of the SPC. This 95% boundary results in censoring at a maximum of 134 SPC per participant and per day. Finally, we also developed a non-linear model similar to Mossong et al. [2008] with censoring at 29 contacts per day. As these were imputed contacts and not fully described contacts, analyses were done with and without these supplementary professional contacts.

We repeated our analyses including the SPC and applied censoring, once at 134 contacts (the 95% percentile) (Table 3.1) to limit the impact of outliers, and once modelling censor at 29 contacts (Table 3.2), similarly to what had been done in the POLYMOD study [Mossong et al., 2008]. Unless mentioned otherwise, results concerned the model without SPC.

3.3 Results

Participants' age (weighted median (first quartile-third quartile)) was 37 (19-59) years old, with 46 (2%) <1 year and 795 (39%) <18 years. Women represented 1136 (56%) of participants. Participation day was a weekend day for 890 (44%) participants, always associated with a weekday, and neither weekend nor holiday for 552 (27%) participants. Participants were on average significantly older than the originally recruited people who didn't send in their diaries (37.1(27.0) years vs. 30.9(25.4) years; p<0.001). Non-participants were mostly aged 18-39 years and 3-9 years (whose diaries were filled by an adult, usually aged 18-39 years). Results have to be interpreted within that context. We checked 200 diaries to find and quantify errors in data capture. Among the 200 diaries checked (≈290 variables per diary), we found 59 coding errors in 37 diaries (such as age of newborn coded 1 instead of 0; 0.1%) and 200 missing values in 72 diaries (such as indication of skin contact or duration of contact; 0.4%).

3.3.1 Number of Contacts

Participants reported 38 881 contacts (8(5-14) per day; Figure 3.2), with +9% [1%;18%] more contacts in Design Period 2 but without significant differences between Actual Periods 1, 2 or 3 (Table 3.1)(Figure 3.3), or between the combination of Actual Periods 2 & 3 vs. Actual Period 1 (+4%[-4%;13%]).

Factors influencing the number of contacts are summarized in Table 3.1. The region of residence did not influence the number of contacts.

The relative number of contacts rapidly increased with age to reach a plateau at around 20 years old. Among children, babies (<1 year) had slightly fewer contacts than toddlers (1-3 years) (Figure 3.4).

Women had 8% [1%;14%] more contacts than men, mainly due to differences for adult women (Figure 3.5).

During weekends and holidays the number of all contacts decreased respectively by 21% [14%;27%] and 21% [16%;26%] (Table 3.1), and by 16% [8%;23%] and 19% [13%;25%] for physical contacts The impact was different between children and adults (Figure 3.6).

Duration was associated with the frequency of contacts, as daily contacts lasted longer than less frequent contacts (Figure 3.7A&C). Physical contacts were associated with longer duration (Figure 3.7B&D) and more frequent contacts (Figure 3.7E). Physical contacts occurred more often at home or in private places than at work or study place, and rarely during transport (Figure 3.7D&F).

Covariate		Number of participants	Mean (SD) of Number of Reported Contacts	Relative Number of Reported Contacts (95% CI)	Relative Number with SPC (95% CI)	Relative Number with censored SPC (95% CI)
Age (y)	0-4	305	8.64(7.23)	1	1	1
	5-9	262	10.50(8.07)	1.31(1.17-1.47)	1.26(1.09-1.45)	1.30(1.15-1.48)
	10-14	160	12.92(10.44)	1.67(1.45-1.93)	1.46(1.22-1.76)	1.54(1.33-1.80)
	15-19	131	12.96(9.55)	1.62(1.41-1.87)	1.48(1.24-1.77)	1.54(1.32-1.79)
	20-24	114	11.14(8.91)	1.74(1.44-2.11)	1.82(1.45-2.30)	1.75(1.42-2.15)
	25-34	108	9.95(6.70)	1.77(1.36-2.30)	1.70(0.86-3.38)	1.37(0.92-2.03)
	35-44	108	9.93(7.10)	1.61(1.24-2.10)	1.42(0.91-2.21)	1.51(1.04-2.17)
	45-64	426	9.24(7.23)	1.86(1.45-2.40)	1.22(0.80-1.85)	1.29(0.92-1.82)
	65+	419	7.01(5.73)	1.71(1.32-2.22)	1.27(0.78-2.06)	1.23(0.87-1.74)
Gender	Female	1136	9.78(8.04)	1	1	1
	Male	897	9.29(7.52)	0.92(0.86-0.99)	0.80(0.63-1.02)	0.84(0.73-0.96)
Household size	1	323	7.88(6.60)	1	1	1
	2	668	8.14(6.60)	1.04(0.94-1.16)	1.03(0.79-1.33)	0.95(0.76-1.18)
	3	321	10.49(8.50)	1.27(1.12-1.45)	1.11(0.86-1.43)	1.12(0.87-1.43)
	4	468	10.99(8.62)	1.42(1.25-1.62)	1.28(0.88-1.86)	1.14(0.89-1.47)
	5+	253	11.66(8.61)	1.39(1.19-1.62)	1.78(0.92-3.42)	1.37(0.98-1.93)
Day of the week	Week Day	1584	9.90(8.13)	1	1	1
	Week End	449	8.37(6.50)	0.79(0.73-0.86)	0.44(0.37-0.52)	0.48(0.42-0.54)
Participating day	First	1016	9.87(7.92)	1	1	1
	Second	1016	9.26(7.72)	0.94(0.89-0.98)	0.94(0.87-1.03)	0.96(0.91-1.02)
Holiday	Regular Day	972	11.05(9.05)	1	1	1
	Holiday	1061	8.20(6.20)	0.79(0.74-0.84)	0.85(0.66-1.10)	0.85(0.74-0.99)
Occupation	Under education	909	10.82(8.80)	1	1	1
	Employed	435	10.67(7.46)	0.85(0.68-1.07)	2.64(1.83-3.80)	2.31(1.72-3.10)
	Unemployed	685	7.20(5.89)	0.63(0.50-0.79)	0.79(0.56-1.10)	0.76(0.57-1.02)
Period	Period 1	517	8.74(7.06)	1	1	1
	Period 2	212	10.27(8.42)	0.94(0.82-1.07)	0.93(0.68-1.27)	0.97(0.75-1.25)
	Period 3	1304	9.77(7.98)	1.06(0.98-1.16)	1.22(1.03-1.45)	1.15(0.99-1.33)

TABLE 3.1: Factors influencing the number of contacts, modelled with Generalized Esimation Equations. SPC: Supplementary Professional Contacts)

Covariate		Relative Number of Reported Contacts (95% CI) without SPC, censored at 29	Relative Number of Reported Contacts (95% CI) with SPC, censored at 29
Age (y)	0-4	1	1
	5-9	1.29(1.13-1.48)	1.29(1.13-1.48)
	10-14	1.61(1.40-1.86)	1.61(1.40-1.86)
	15-19	1.58(1.38-1.82)	1.58(1.38-1.82)
	20-24	1.74(1.41-2.02)	1.74(1.50-2.03)
	25-34	1.61(1.31-1.97)	1.59(1.30-1.95)
	35-44	1.81(1.48-2.22)	1.80(1.46-2.20)
	45-64	1.60(1.31-1.95)	1.59(1.30-1.94)
	65+	1.50(1.22-1.85)	1.49(1.21-1.83)
Gender	Female	1	1
	Male	0.93(0.88-0.98)	0.93(0.88-0.98)
Household size	1	1	1
	2	1.06(0.98-1.14)	1.06(0.98-1.14)
	3	1.22(1.12-1.34)	1.22(1.12-1.34)
	4	1.36(1.24-1.50)	1.36(1.24-1.50)
	5+	1.45(1.30-1.61)	1.45(1.30-1.61)
Day of the week	Week Day	1	1
	Week End	0.65(0.61-0.69)	0.65(0.61-0.69)
Participating day	First	1	1
	Second	0.94(0.90-0.99)	0.94(0.90-0.99)
Holiday	Regular Day	1	1
	Holiday	0.82(0.78-0.87)	0.82(0.78-0.87)
Occupation	Under education	1	1
	Employed	1.45(1.24-1.71)	1.47(1.25-1.73)
	Unemployed	0.69(0.58-0.81)	0.69(0.59-0.82)
Period	Period 1	1	1
	Period 2	0.97(0.89-1.05)	0.97(0.89-1.05)
	Period 3	1.10(1.03-1.17)	1.10(1.03-1.17)

TABLE 3.2: Factors influencing the number of contacts, with a censor at 29 contacts per day based on a non-linear model similarly to Mossong et al 2008. SPC: Supplementary Professional Contacts)

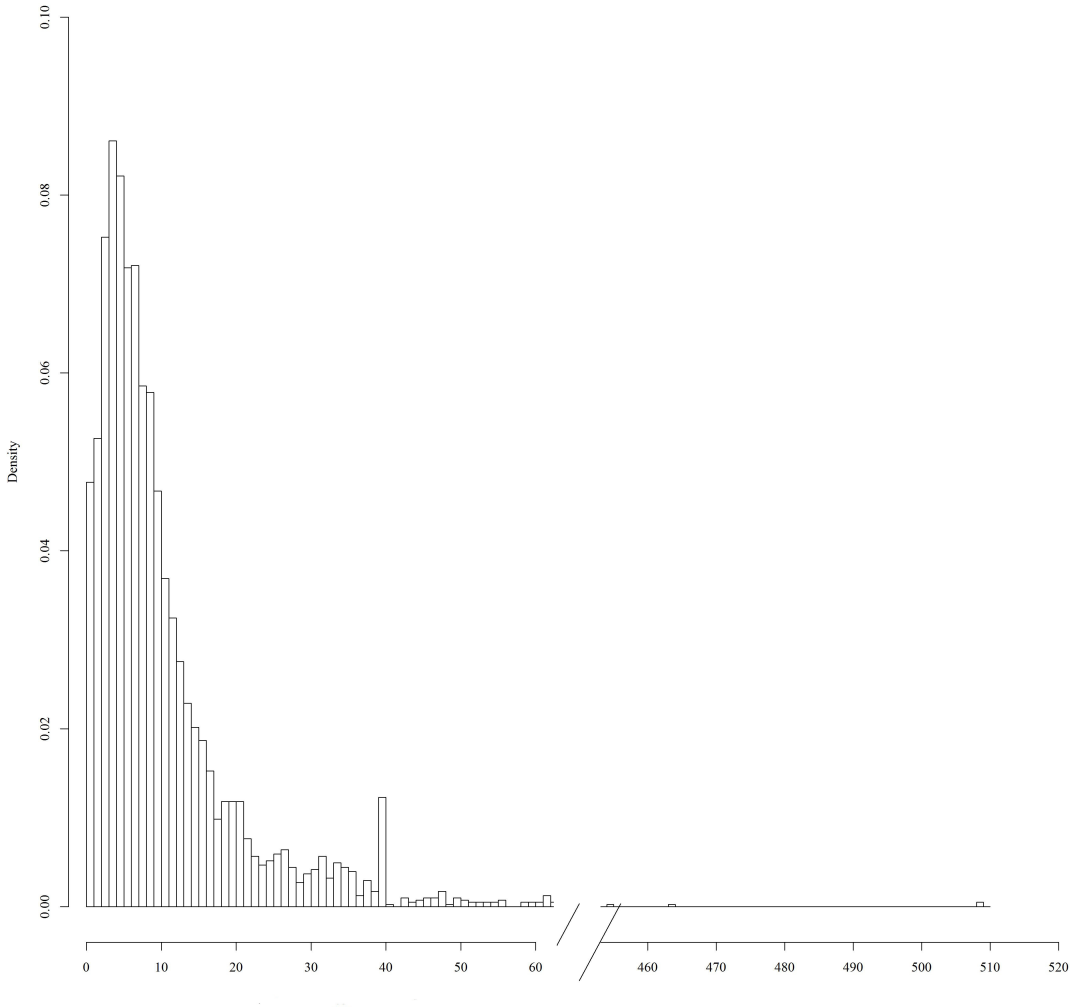


FIGURE 3.2: Contact number density: Histogram of the contact number, including SPC. Limitation at 40 contacts per day explains the peak at 40 contacts.

Transportation modes did not significantly influence the number of contacts, despite a trend for a higher number of contacts with public transport (+36%[-20%;+131%]). For a subanalysis of contacts made by participants common to Design Periods 1 & 2, trends were similar as observed in the full data analysis, though only age, household size, regular or holiday period and occupation remained significant. No association was found between the size of classroom or childcare centre and the total number of contacts or those specifically at kindergarten (4.8[0.0;9.0]), at school (5.0[0.0;16.0]) or study place (6.0[0.0;16.0]). Participants reported 6%[1%;10%] fewer contacts on the 2nd day of the study. The more contacts they reported on the first day, the larger the proportional decrease in contacts on the second day.

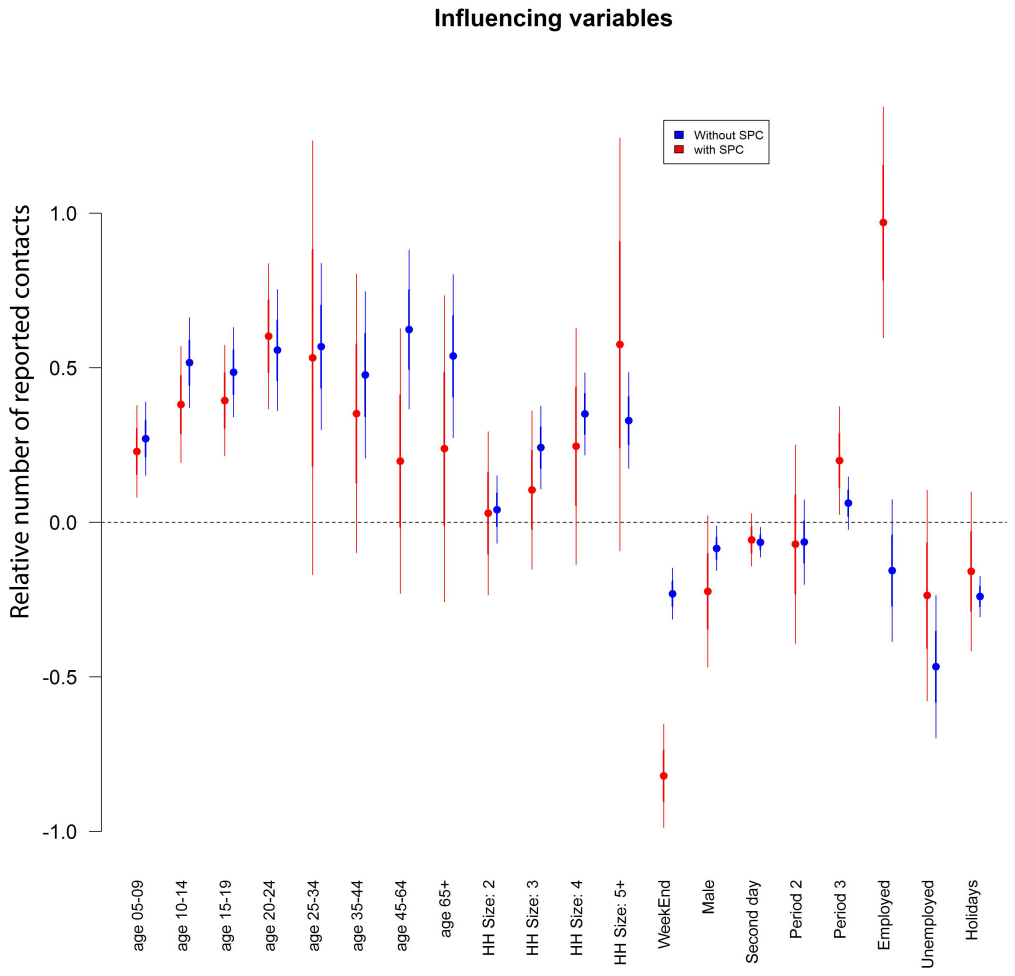


FIGURE 3.3: Variables influencing the number of contacts, with and without SPC

3.3.2 Who mixes with whom?

The R_0 of an epidemic occurring during Design Period 2 was 12%[1%;23%] higher than during Design Period 1, but lost significance when comparing 2 out of 3 Actual Periods (P1 vs P2: +13%[-9%;46%]; P1 vs P3: 11%[-4%;26%]). Mixing patterns (Figures 3.8, 3.9, 3.10)(Appendix B) also showed an important contribution during the initial phase of an epidemic for the 10-20 year olds (predominantly for Actuals Periods 2 and 3), and for the 35-50 year olds (predominantly for Actual Period 1). The central diagonal on Figures 3.8, 3.9, 3.10, 3.11 shows that contact patterns were highly assortative with age (i.e. participants tend to mix with people of similar age). The 2 secondary parallel diagonals for people with age differences of about 30 years exhibited a high contact rate: children mixing with adults aged 30-39 years and adults mixing with older contacts (>60 years). These diagonal bands were found only in the home matrix (Figure 3.11), and mostly represent contacts between (grand)parents and their (grand)children. These mixing patterns were maintained for physical contacts and over the different periods.

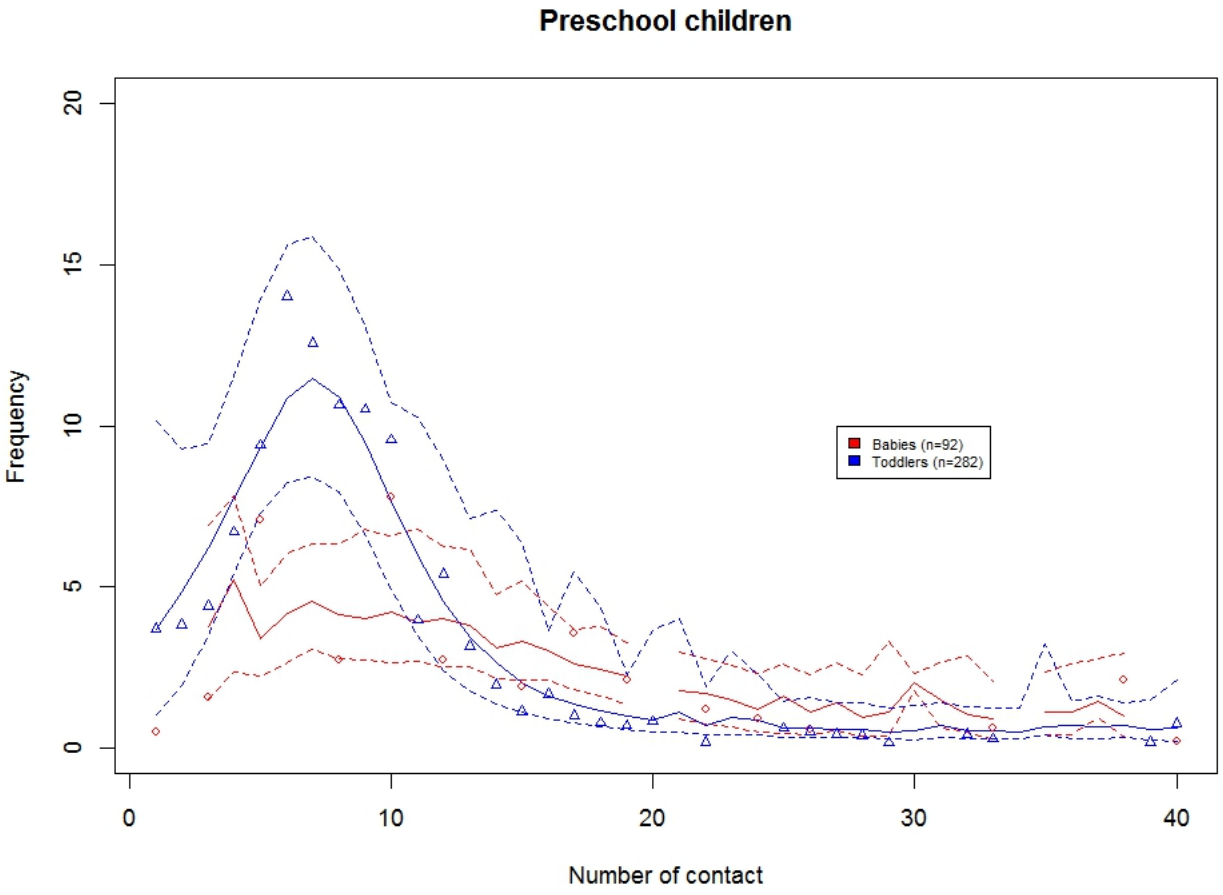


FIGURE 3.4: Degree distribution of children <4y, comparing number of contacts between <1y to 1-3y. Blue triangles and red circles represent the data points on which the curve is smoothed with a gam function. Dashed lines represent the 95% bootstrap confidence intervals.

Men reported significantly fewer contacts with children than women, whatever the contact gender. Men reported significantly fewer contacts with women, whatever the participant or contact age. And boys reported significantly fewer contacts with girls than with boys (Table 3.3).

The impact of school closures on an epidemic was estimated by the relative change in R_0 on the weekend compared to a weekday and on holidays compared to a regular day. R_0 decreased during weekend and holidays by 28%[10%;44%] and 33%[25%;41%], respectively.

3.3.3 Where do people mix?

Contact patterns were different according to location (Figure 3.11), with most contacts made at school and home and fewer contacts during transport and in public places.

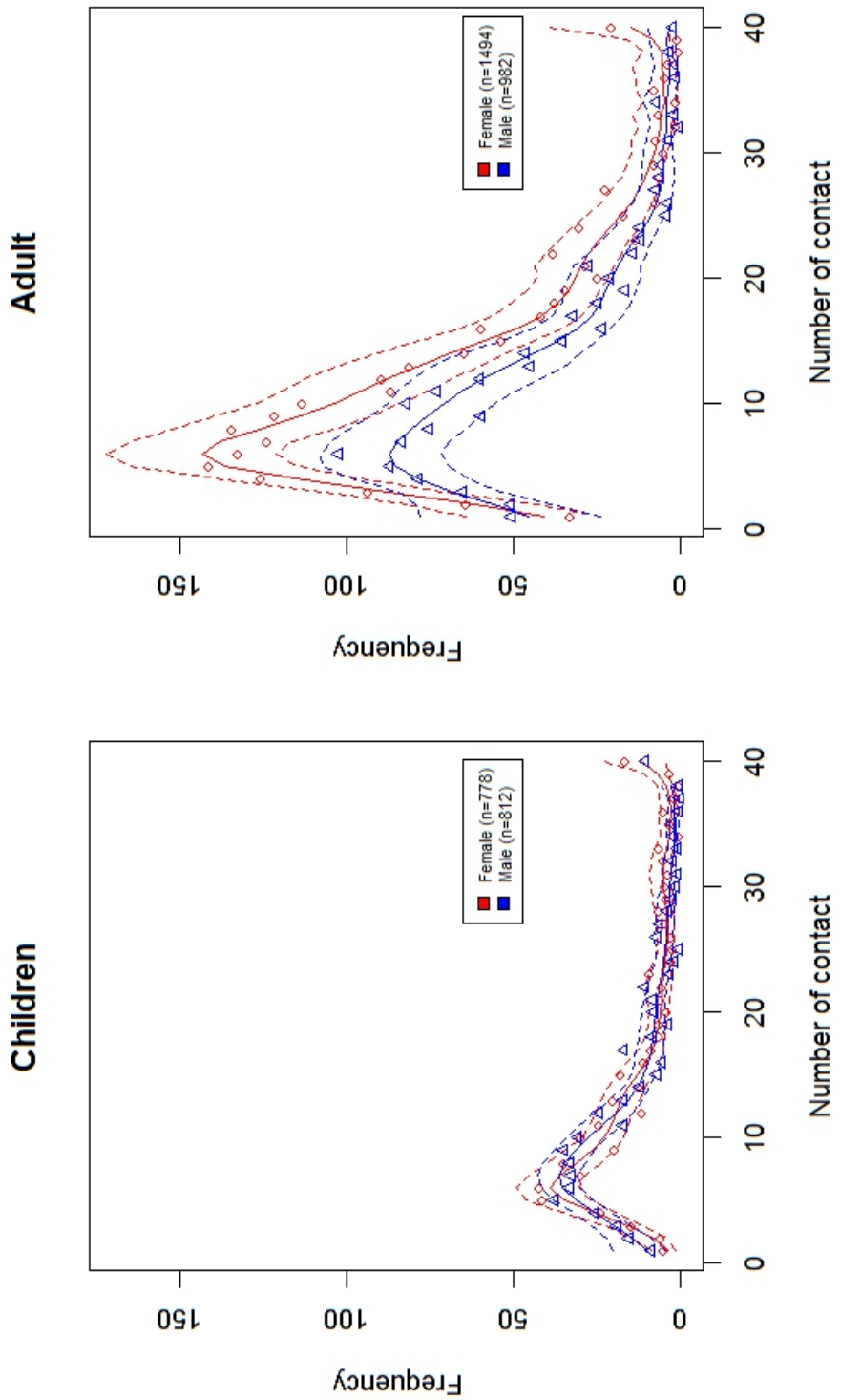


FIGURE 3.5: Degree distribution comparing number of contacts according to gender in <18y and >18y. Blue triangles and red circles represent the data points on which the curve is smoothed with a gam function. Dashed lines represent the 95% bootstrap confidence intervals.

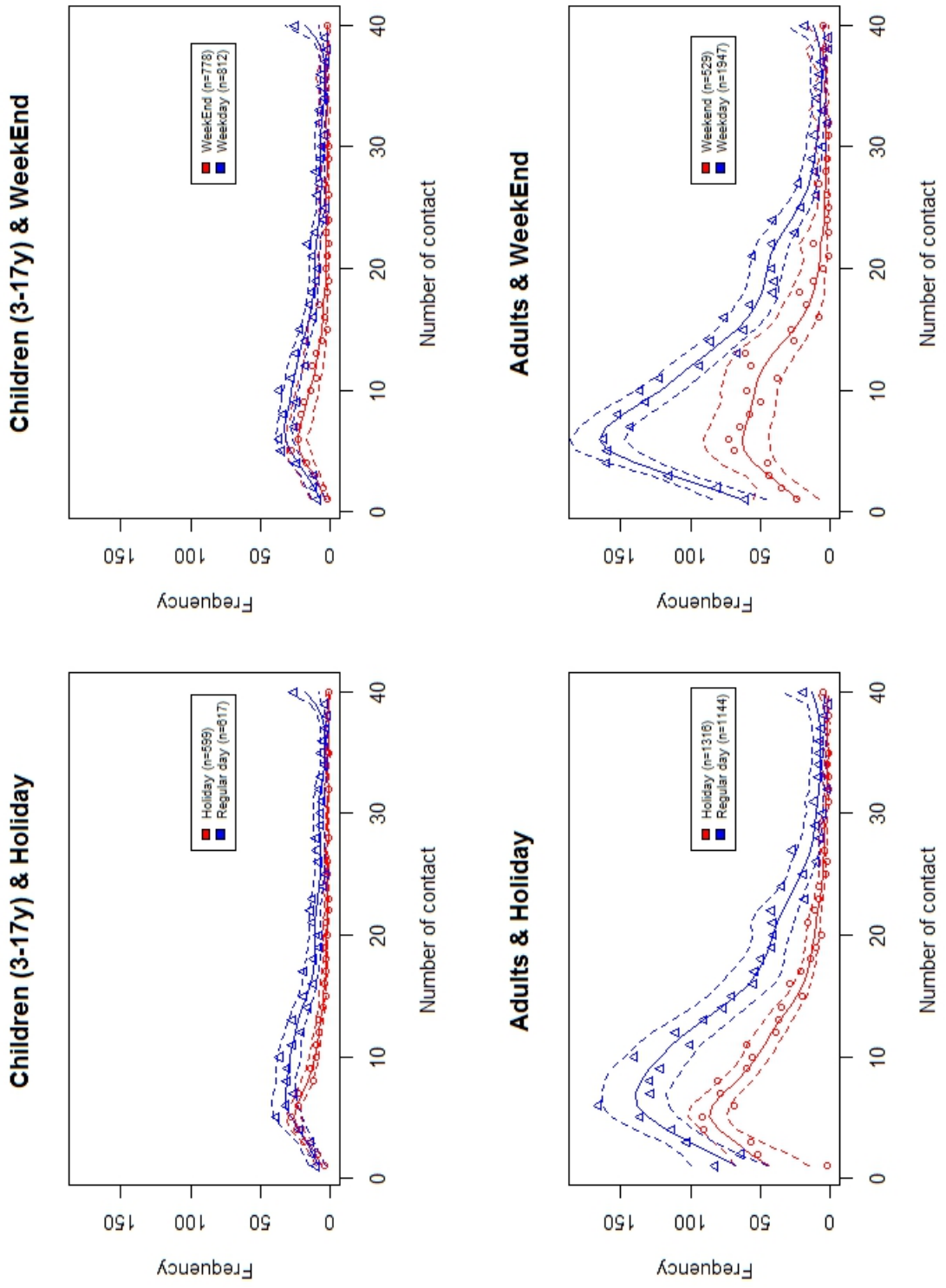


FIGURE 3.6: Degree distribution comparing number of contacts according to weekends and holidays in children (3-18y) and adults. Blue triangles and red circles represent the data points on which the curve is smoothed with a gam function. Dashed lines represent the 95% bootstrap confidence intervals.

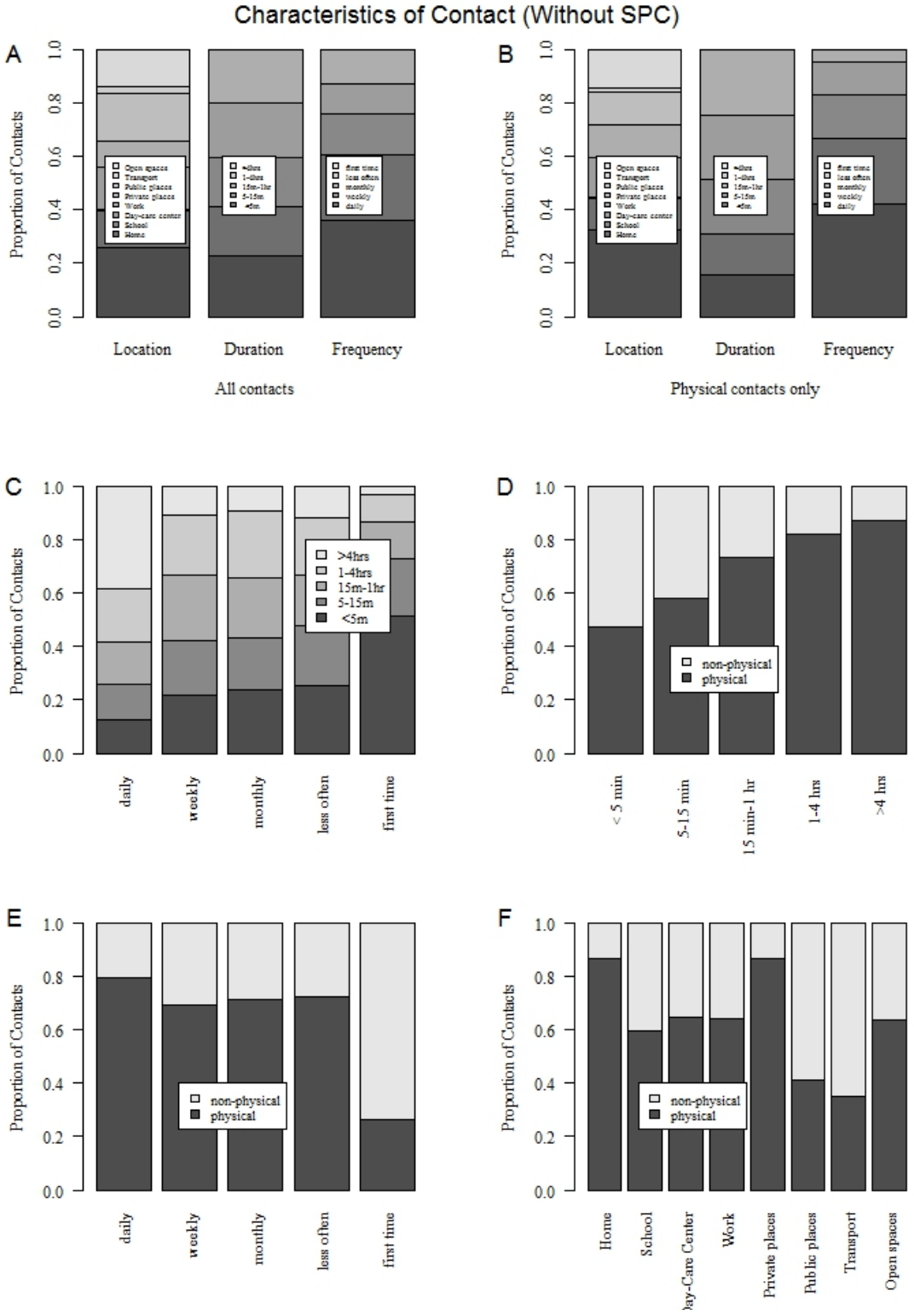


FIGURE 3.7: Characteristics of contacts (without SPC). Distribution of location, duration and frequency for all contacts (A) and physical contacts (B). Duration of contact according to frequency (C). Proportion of physical contacts according to duration (D), frequency (E) and location (F).

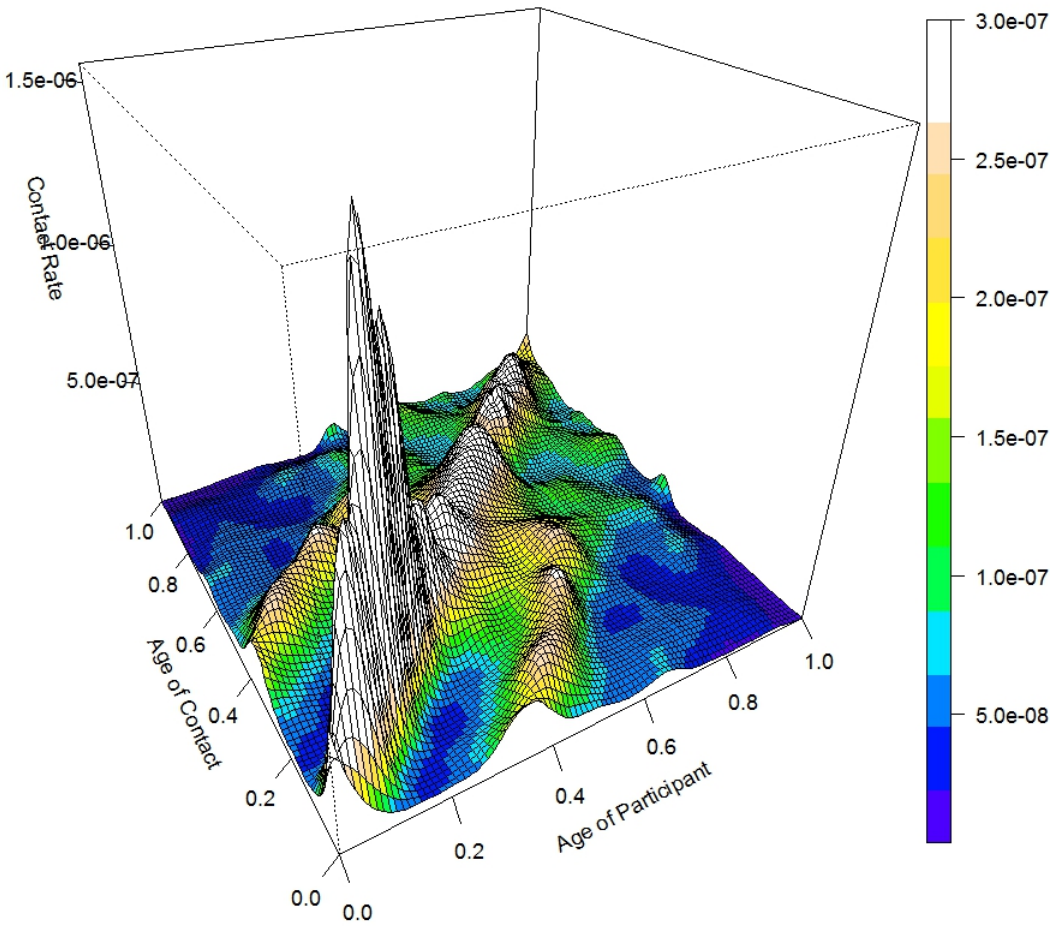


FIGURE 3.8: 3D representation of the base-case matrix without SPC.

		Contact (Male & female)	
Participant	Age	≤18y	>18y
Male	≤18 years	0.88[0.73;1.06]	0.85[0.75;0.96]
	>18 years	0.63[0.48;0.82]	0.95[0.86;1.05]
		Contact (Male)	
Participant	Age	≤18y	>18y
Male	≤18 years	1.42[1.15;1.74]	0.99[0.83;1.18]
	>18 years	0.71[0.52;0.97]	1.15[1.01;1.31]
		Contact (Female)	
Participant	Age	≤18y	>18y
Male	≤18 years	0.51[0.42;0.62]	0.75[0.67;0.84]
	>18 years	0.55[0.39;0.78]	0.79[0.71;0.87]

TABLE 3.3: Gender of participant and contact, without SPC: Ratio of contact for male participants compared to female, not taking into account the gender of contact and taking into account the gender of contact.

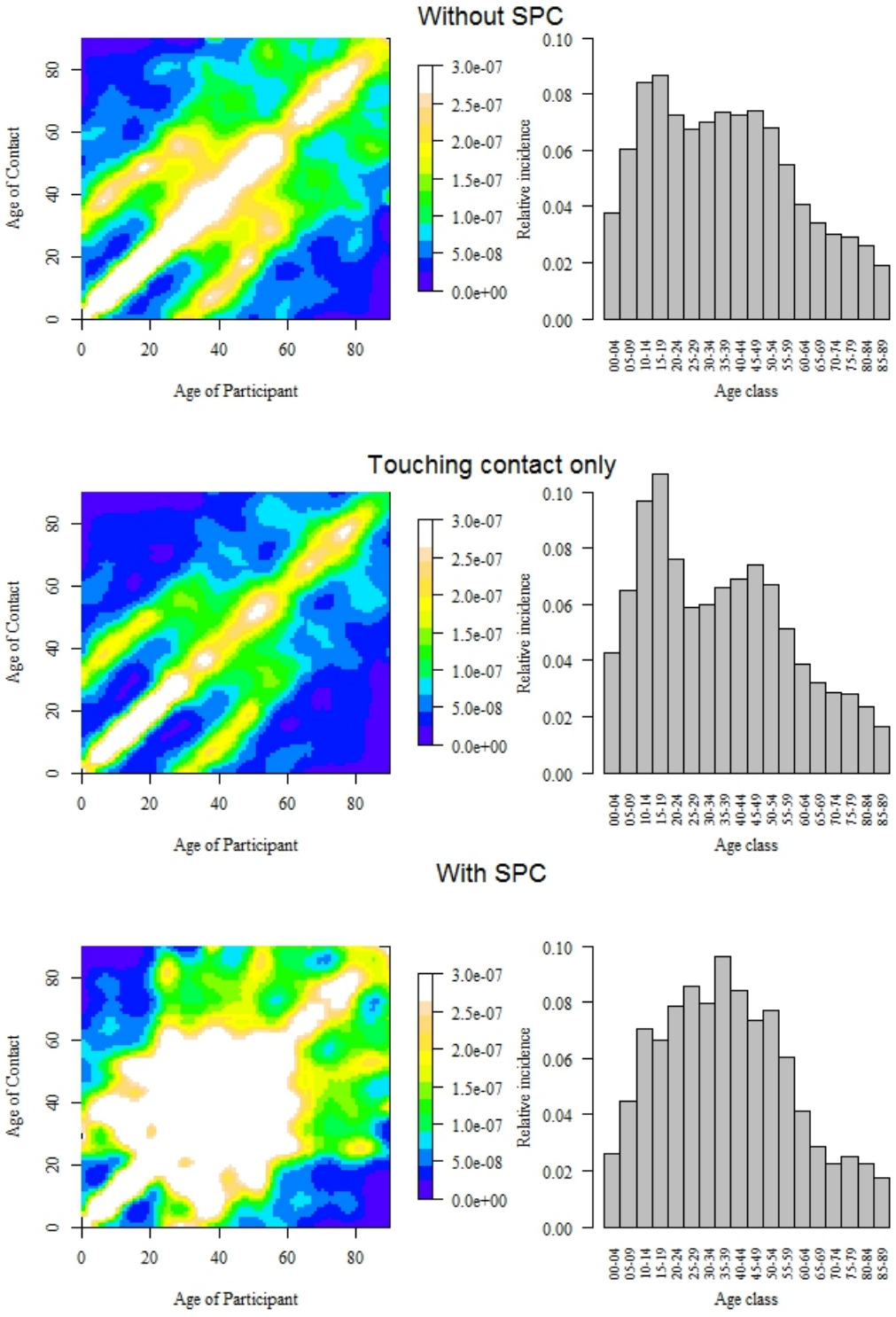


FIGURE 3.9: Smoothed contact matrices without SPC, for physical contacts only and with SPC (right). Relative incidence of a new emerging infection in a completely susceptible population estimated from the matrix in regard (left).

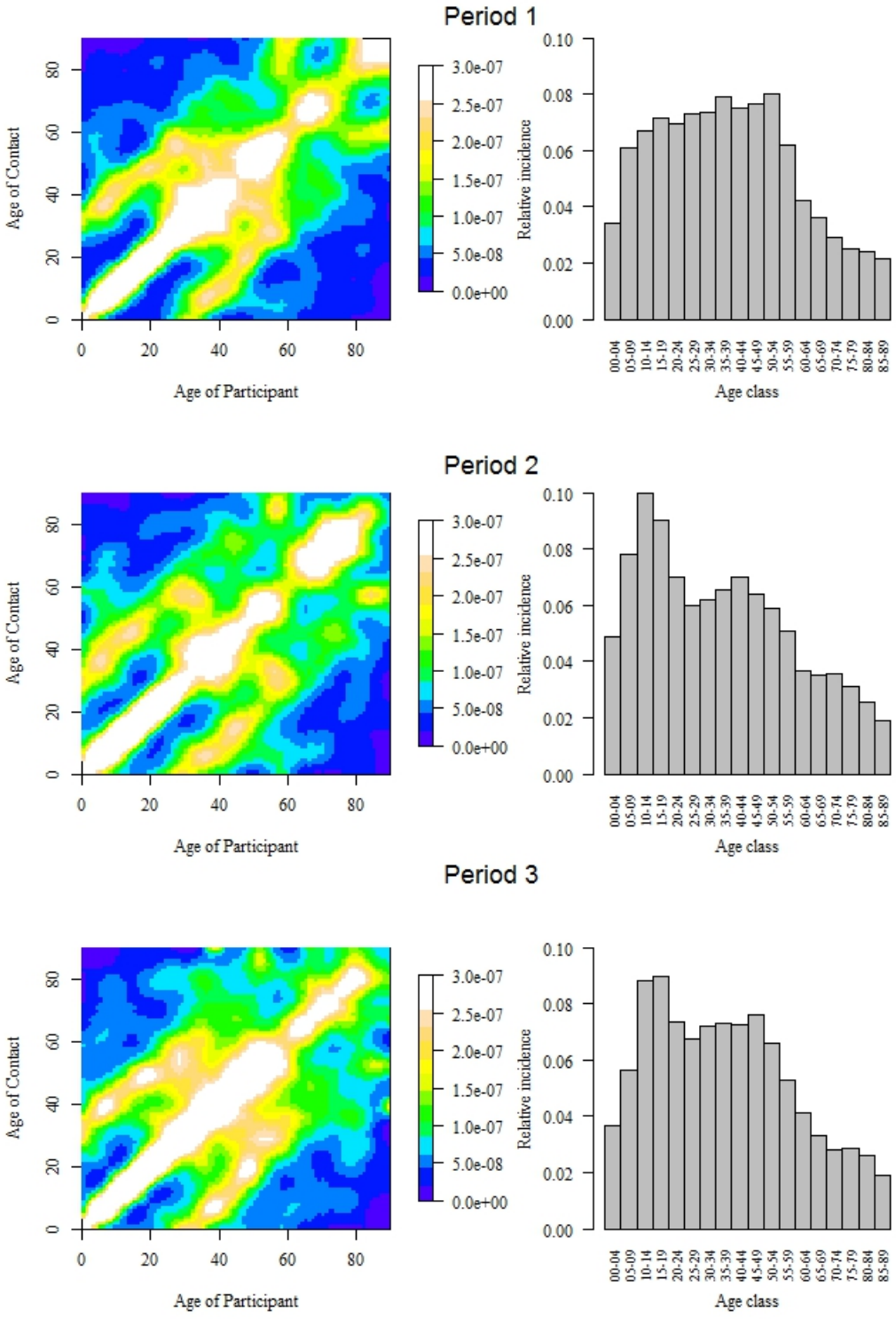


FIGURE 3.10: Smoothed contact matrices according to Actual Periods (right). Relative incidence of a new emerging infection in a completely susceptible population estimated from the matrix in regard (left).

Contact patterns were found to be assortative with age at all locations, and transgenerational mixing occurred mainly at home. With home as a baseline (=1), the contact ratio was higher at school (1.55 [1.25-1.91]), but lower at work (0.56 [0.43-0.72]), in private places (0.42 [0.35-0.50]), in public places (0.59 [0.49-0.69]), in transportation (0.23 [0.15-0.40]), and not different in open spaces (0.85 [0.68-1.04]).

3.3.4 How long do people mix?

Contact patterns were also different according to the duration of contact (Figure 3.12). The central diagonal showed that patterns were assortative with age for every kind of duration of contact but were very exclusive for long duration contacts. The 2 secondary parallel diagonals were distinctive mainly for long duration contacts (>1 h). On the contrary, short duration contacts (notably when shorter than 5 min.) were less assortative with age, showing a wide plateau of important contact rates extending through age of both contacts and participants, notably between 20 and 65 years. Relative incidence by age was also different according to duration, with a plateau for an incidence concerning preferentially individuals between 20 and 60 years. Relative incidence for individuals over 20 years never exceeded 10%, whatever the contact duration. For contact >1 h, the relative incidence of individuals between 5 years and 20 years old could exceed 15%. As the duration increased, a peak for a high incidence emerged for the <20 years old. The R_0 values were estimated for each duration matrix and presented as a ratio compared to the R_0 value for contacts of duration <5 min. Indeed, the highest ratio were for contacts <5 min. (1) and >4 h (0.91). One should note that disentangling the contact matrix by duration was made for an illustrative purpose. Similarly, the estimation of relative incidence and R_0 ratio was also illustrative to highlights the relative and different importance of the different type of contacts (long vs. short).

3.3.5 Professional contacts

The total number of contacts with SPC was 54 378 (9(5-17)) contacts per day), and was 52,042 contacts (9(5-17)) with SPC censored at 134. Hence the reduction of 4% of the total number of contacts involved 22 (1%) participants. Censored participants were similar in gender, age and household size to other participants. SPC increased the variance and attenuated the effect of all variables, except for age <25y, gender, weekend, occupation when employed and the period (Table 3.1,3.4 , Figure 3.13).

SPC increased the number of contacts during the last period (Design and Actual), and R_0 for Actual Period 2 and 3 up to 9%[-27%;111%] and 46%[8%;100%] with full SPC, and to 6%[-26%;84%] and 33%[1%;72%] with censored SPC. With SPC, the contact matrix

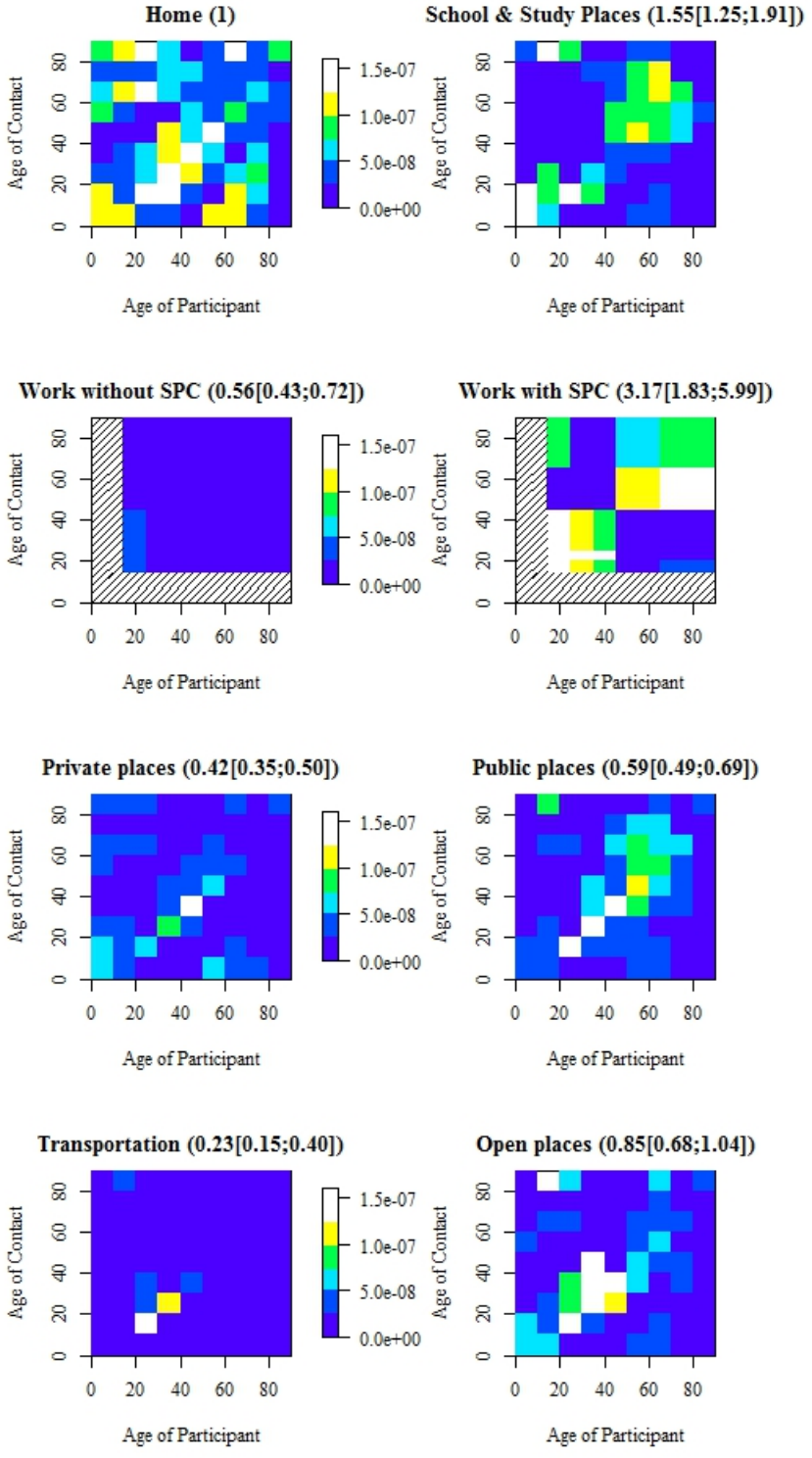


FIGURE 3.11: Contact matrices according to location. Numbers are the ratios of contact rate made at the corresponding location with contact rate at home (95%CI). No smoothing or reciprocity was applied (particular location wouldn't be the same for a participant and a contact (e.g., at home vs. not at home), the matrices were kept asymmetric).

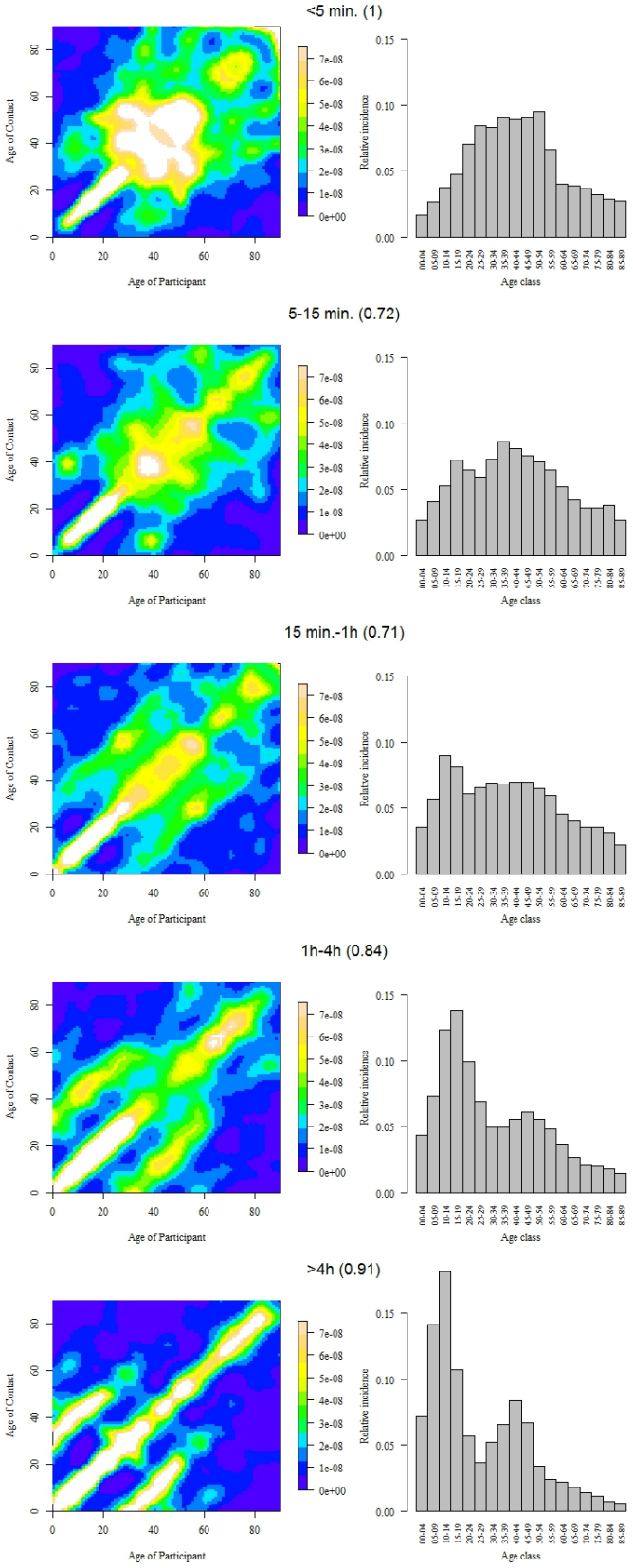


FIGURE 3.12: Contact matrices and relative incidence by age according to duration of contact

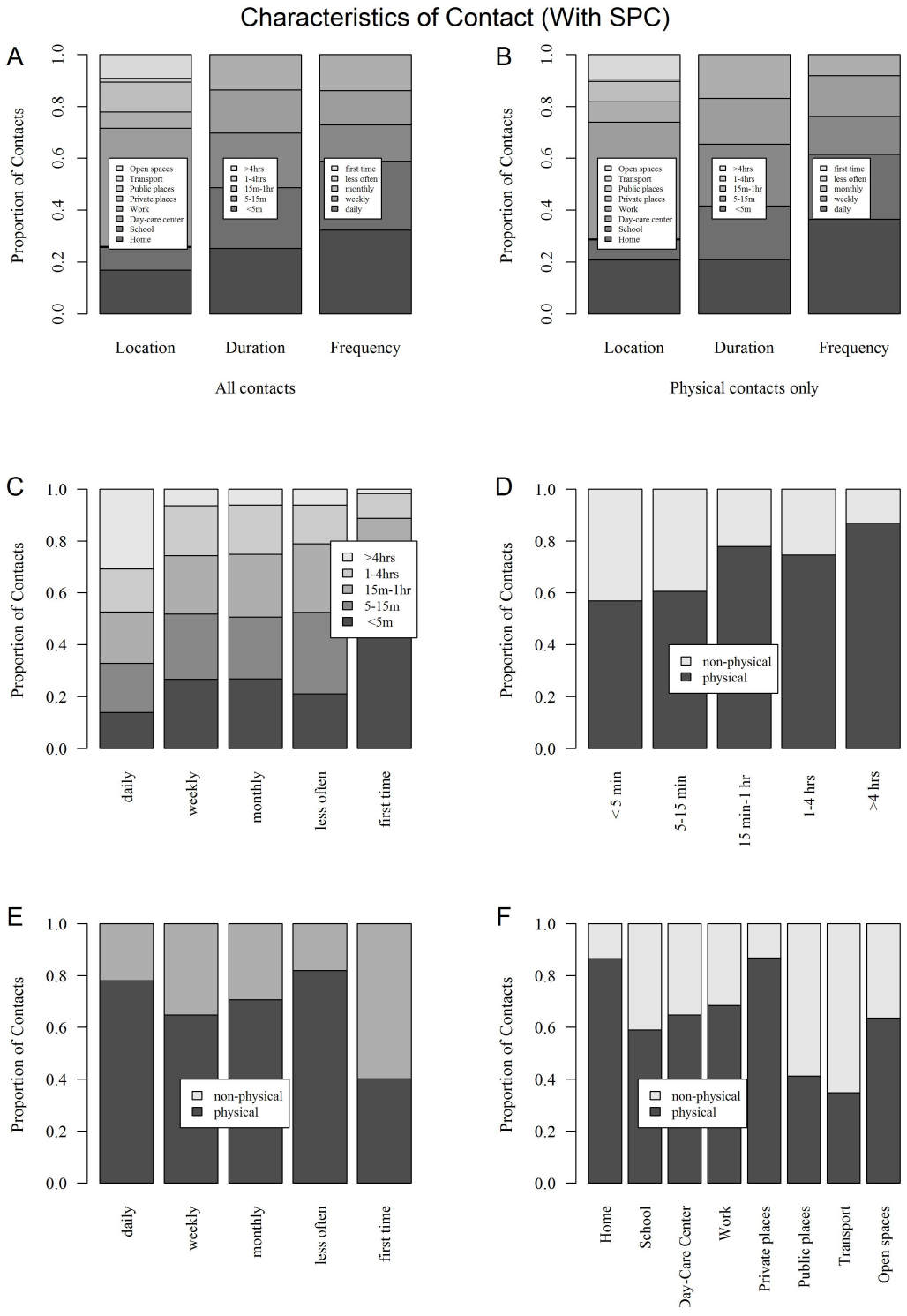


FIGURE 3.13: Characteristics of contact (with SPC). Distribution of location, duration and frequency for all contacts (A) and physical contacts (B). Duration of contact according to frequency (C). Proportion of physical contacts according to duration (D), frequency (E) and location (F).

		Contact (Male & female)	
Participant	Age	≤18y	>18y
Male	≤18 years	0.88[0.73;1.06]	0.85[0.75;0.96]
	>18 years	0.54[0.17;1.72]	0.79[0.62;1.01]
		Contact (Male)	
Participant	Age	≤18y	>18y
Male	≤18 years	1.42[1.15;1.74]	0.99[0.83;1.18]
	>18 years	0.57[0.18;1.8]	0.90[0.69;1.16]
		Contact (Female)	
Participant	Age	≤18y	>18y
Male	≤18 years	0.51[0.42;0.62]	0.75[0.67;0.84]
	>18 years	0.51[0.16;1.66]	0.70[0.55;0.89]

TABLE 3.4: Gender of participant and contact, with SPC: Ratio of contact for male participants compared to female, not taking into account the gender of contact and taking into account the gender of contact.

(Figure 3.9) showed a wider contact "plateau", corresponding to less assortative mixing for ages 20-65 years. It resulted in a ratio of contact at work higher than anywhere, at 3.17[1.83;5.99], and a mixing pattern at the workplace mildly assortative by age, but showing a cut-off at 45 years (Figure 3.11). The specific number of contact made at work was 3[0;10] and 20[6;38] with SPC. With SPC, R_0 decreased during weekends and holidays by 63%[53%;70%] and 20%[-1%;22%], and public transport increased the number of contacts by 96%[28%;198%]). For participants common to Design Periods 1 and 2, SPC led to similar results except that weekends became significantly associated with fewer contacts.

3.4 Discussion

Comes-F is the first study on temporal variation of social contact patterns to use a contact diary approach. The trend toward more contacts in April-May was significant for design periods but only with SPC for actual periods. The period did not influence the number of contacts among participants common to Design Periods 1 and 2. Hence, actual/design periods in this study showed little influence on the number of contacts compared to age, household size, gender, holidays and weekends. Weather may help to explain these minor differences between the periods. Willem et al. [2012] showed that weather conditions could influence the number of contacts and mixing patterns. DeStefano suggested similar trends, although without information on the statistical significance or mixing patterns [DeStefano et al., 2011]. Besides temporal variation, spatial variation such as place of residence, albeit non-significant, could be a confounding effect as weather varies according to both season and primarily latitude, which could influence

mixing patterns. As in POLYMOD, we found that contacts were mostly influenced by age. Contact patterns were likewise highly assortative with age, with a high contact rate for children and adolescents, and a strong child-parent component (Figures 3.8, 3.9, 3.10). Mixing with both contacts of similar age and with their parents explains the strong participation of children and adolescents in an epidemic [Wallinga et al., 2006] (Figures 3.9, 3.10). Their high number of contacts favours an important influence of these age groups at the beginning of an epidemic. Additional contacts with other age groups (such as adults aged 35-50 years) lead to a rapid spread among other age groups.

Our most original result was the difference in gender, with men having fewer contacts than women and mixing assortative with age and gender. The POLYMOD study [Mossong et al., 2008] found a similar trend, but could not establish its statistical significance. With a different methodology, DeStefano et al. [2011] found that women had 13% more speaking interactions per day. Nonetheless, to the best of our knowledge, no previous study has ever presented contact matrices according to gender. So far, gender differences in infectious diseases epidemiology have been attributed only to hormonal differences [Klein et al., 2012] or to differences in risk assessment [Gustafson, 1998] leading to incomplete reporting [Barbara et al., 2012]. We suggest that the higher participation of women in infectious diseases such as influenza [World Health Organization, 2010] or pertussis [Haslam et al., 2014] could also be attributed to behaviour. Data from Japan [Eshima et al., 2012] showed that several infections were more frequent among males during childhood and females at an older age. The authors' hypothesis was that mothers were more likely to stay at home with a sick child and consequently more likely to be exposed to infection. More contact should result in accelerated circulation of pathogens among women. Women should consequently get infected sooner than men, and present a shorter serial interval (time between symptoms onset of a case and its infector). Indeed, in a study on pertussis transmission in Dutch households, the mean serial interval was 20 days when the mother was the infector vs. 28 days when it was the father or a sibling [te Beest et al., 2014]. In a study on household transmission of 2009 influenza in New York City, the secondary attack rate among females was almost twice the rate among males [France et al., 2010]. And in a prospective cohort study, female gender was associated with increased influenza transmission [McCaw et al., 2012]. These differences according to age and gender of both participants and contacts could result from the higher involvement of women in childcare as well as gender differences in professional contacts. In our study gender preference occurred evenly among children, in agreement with a study carried out in a school using wearable sensors [Stehlé et al., 2013]. For strong interaction, gender preference increased with grade while for low interaction it decreased for girls and increased for boys. Therefore, different trends on gender preference according to countries in POLYMOD [Mossong et al., 2008] could have led to an

average non-significant trend.

In accordance with previous work [Melegaro et al., 2011], most contacts occurred at home and school and far fewer in other locations such as transportation. Whatever the location, contacts were assortative with age but less assortative in places where the contact rate was the highest (home, school or workplace with SPC). The diagonals on the home matrix demonstrated that parent-children contact occurred primarily at home, in accordance with findings from Lapidus et al. [2013]. This finding confirms the importance of home and school in the spread of infectious diseases, both because contact rates are high, and because contacts are not limited to a specific age category, thereby allowing the pathogen to spread across age categories. Therefore, home quarantine or school closures would have a higher impact than transport-related measures on the contact rate and the spread of infections. Most of the studies on school closures have relied on strong assumptions about contact patterns [Ferguson et al., 2006, Germann et al., 2006, Glass et al., 2006], or were based on a specific context (multiple non-pharmaceutical measures taken simultaneously, school closures among others), such as 1918 pandemic [Markel et al., 2007], 2009 H1N1 pandemic in Mexico [Chowell et al., 2011] or SARS in Beijing [Cowling et al., 2008]. Like Hens et al. [2009a], we used social contact data to quantify the impact of school closure, not relying on data specific to a particular pathogen. Based on our analysis and in Hens et al. [2009a], school closure would have more impact on disease transmission in France than in other European countries, as the R_0 of an epidemic decreased by 28% and 33% during weekends and holidays, compared to 21% and 17% in the European countries where a significant decrease was found [Hens et al., 2009a]. This difference should be taken into account when estimating the benefits of school closure, which may nonetheless be counterbalanced by a macroeconomic cost that would render such strategies questionable [Keogh-Brown et al., 2010]. Unlike Hens et al. [2009b], we found no influence of day-care centre or classroom size on the number of contacts. This could be a methodological issue, resulting from different definitions of the variable, as well as undeniable differences between Belgium and France. Hence, if the size of day-care centre or classroom influences the number of contacts, it is neither strong nor linear in our setting.

Duration of contact is supposed to play a role in infectious transmission as long duration contact is part of the definition of intimate contacts which were shown to be the most susceptible to transmit infection such VZV and parvovirus B19 [Melegaro et al., 2011]. However long duration contacts (>1h) were in itself significantly associated with infectious transmission. An alternative explanation could be that long duration contact are the best and most completely reported compared to short duration contact [Smieszek et al., 2012], therefore minimizing the importance of short duration contacts. Our findings confirmed that long duration contacts are important for infectious diseases

transmission notably because they considerably increased the transmission for individuals under 20 years. However, we also showed that shorter duration contacts could play a role, similarly to SPC contacts, by favouring contacts between different age categories, notably between 20 years and 65 years. Contrary to location matrices that have practical implications (school closures, quarantine ...), nobody has published any modelling studies in which favouring contacts of a particular duration was explored as a strategy. However, such matrices could be used to estimate a strategy in time of epidemics, in which people would be requested to minimize social contacts out of their family or household. This strategy would result in a decrease in the shortest contacts and may have an impact on the spread of the pathogen within the population.

The inclusion of SPC pronouncedly modified the number of contacts and influencing variables. Partly this effect resulted from our methodology: SPC were included only for weekdays, hence the strong effect of weekends. But it also influenced mixing patterns, as an adult could make contact outside his or her own age category outside the home, notably in the workplace, which could facilitate the spread of a pathogen among different age categories. This observation raises the question of the possible role of the workplace, as well as public transport in pathogen transmission. Gender difference enhanced by SPC could reflect gender difference in the rate of employment. In contrast, the influence of SPC on the period is less clear, even though a higher number of contacts increases the power of the analysis and could render a trend significant. One difficulty is that professional contacts -notably when numerous- are unlikely to have the same importance as others regarding infectious disease transmission (e.g. bus driver). Of note, report of professional contacts was limited at 10 in 4 of 8 countries in POLYMOD (20 in Belgium). Issued from a parametric approach, our results are sensitive to extreme values (e.g. participants with a high number of professional contacts). Hence, limiting the maximum number of contacts to 40 a day and modelling the SPC separately may effectively help to limit the effect of these outliers. That said, while limiting the number of reported contacts facilitates completion of the diary, it inevitably leads to artificial boundaries (Figure 3.2). Therefore, separate modelling of SPC (see [Hens et al., 2009b]) may represent an optimal trade-off between relevance and feasibility.

The reporting of contacts for two consecutive days offered a large amount of data resulting in the largest contact survey for a country. But this positive factor is counteracted by fatigue in reporting, with fewer reported contacts during the second day. Smieszek et al. [2012] showed higher underreporting for highly connected individuals than for isolated individuals. As the proportion of short and non-intense contacts increased with the total number of contact partners, underreporting of contacts was correlated with contact duration. The fact that participants were slightly older than non-participants could be related to their being less active and employed, with more time to participate.

Therefore, there is a limit to the amount of information we could request in view of achieving optimal accuracy.

We have presented the first large population contact survey in France, and the largest contact survey of its kind. It improves our understanding on the spread of infectious diseases, on the role of some age categories and the impact of school closures in France. It raises more fundamental questions on the optimal design of those surveys, on the role of professional contacts and locations, and on the gender difference in the epidemiology of infectious diseases. Finally, it provides some basic material to be used in applied model-based analyses.

Chapter 4

Measles, Mumps and Rubella

This chapter exposes the first practical application of the French matrices described in Chapter 3. Contact matrices being developed in view of modelling transmission of pathogens, we first apply them to measles, mumps and rubella. These three diseases have in common to be air transmitted, highly contagious and for which the protection is provided by the same trivalent vaccine. The findings exposed in this chapter are soon to be submitted for publication.

4.1 Introduction

France experienced a massive measles outbreak in 2010-2011, with more than half of the 30,000 cases reported in Europe in 2010-2011 [Antona et al., 2013]. Its occurrence was mostly attributed to suboptimal vaccination coverage, both for the first and the second dose of the Measles-Mumps-Rubella vaccine. Large measles and mumps outbreaks occurred more recently in Europe notably in the Netherlands [Knol et al., 2013] and UK [Pegorie et al., 2014], as well as in the USA [McCarthy, 2015]. Although insufficient coverage is usually considered as the primary factor enabling the occurrence of large-scale outbreaks, a significant proportion of individuals affected by these outbreaks had been fully vaccinated [Antona et al., 2013, Eriksen et al., 2013], which questions both lifelong persistence of vaccine-induced immunity and the optimality of the vaccination schedule. The currently used vaccine is common to measles, mumps and rubella, therefore a risk for measles due to incomplete coverage may be associated with a risk for mumps and rubella. The first dose of the MMR vaccine has been administered in France at one year of age since 1986. From 1996 to 2005 a second dose was administered between three and six years old, then at two years old since 2005. Measles vaccination coverage in France is one of the lowest in Europe (ECDC/WHO report) and the ongoing measles outbreak

in neighbouring Germany may overflow in France, thereby potentially catalysing a new European outbreak. Moreover, WHO/Europe targeted measles and rubella elimination in Europe by 2015 [WHO/Europe, 2013], but recent measles outbreaks hamper the achievement of these goals. The risk of resurgence of measles and mumps was recently assessed in Belgium, in a highly vaccinated population in which no recent large outbreaks have occurred, with an original methodology combining serological data and vaccination coverage information [Abrams et al., 2014, Hens et al., 2015]. Therefore, using a cross-sectional serological survey completed in 2013, we aimed at evaluating the risk of a novel measles outbreak in 2016 in France. Using serological surveys from 2009 and 2013, we also aimed at validating our methodology and assessing the risk of an outbreak of mumps and rubella in France in 2016.

4.2 Methods

The multi-cohort model was originally developed for Belgian data [Abrams et al., 2014, Hens et al., 2015], aiming at combining serological information and vaccination coverage to quantify the risk for a future mumps outbreak. This multi-cohort model was adapted and refined to model the French data. We notably had to take into account multiple datasets, the different and changing over time guidelines for immunisation age, the different spatial resolution of data (department instead of region for vaccine coverage information, department instead of municipality for seroprevalence information) and the use of gender-specific modelling. Briefly, a model predicting the serology of measles, mumps and rubella is determined first for the year of data collection (2009 or 2013); then age-dependent susceptibility by department is derived for the year of interest (2010 or 2016), and, finally, department-specific effective reproduction numbers and age-dependent relative incidences of a potential outbreak are estimated using social contact data.

4.2.1 Cohorts

The multiple datasets used and combined are presented in detail in Chapter 2. A specific anti-measles vaccine was introduced in 1983 for toddlers (1-3 years), as part of the immunisation schedule, then the combined MMR vaccine has been used since 1986, at 1-year-old. The second MMR dose was added to the vaccination schedule in 1996. Up to 2004, the first dose had to be administered at 1 year of age and the second dose at 3-6 years. The catch-up program consisted in one single MMR dose for unvaccinated children of 6-13 years. Since 2005, the second dose has been administered at 2 years of age. Therefore, the age shift for the second dose had to be taken into account when the

modelling. Two catch-up doses were recommended for unvaccinated persons born after 1991 and 1 dose when born between 1980 and 1991. Although a school-based survey indicated a global proportion of vaccinated children of 11 years old in 2008, no coverage information about the administration of the catch-up dose was available by department, and after 2008. The Lexis diagram in Figure 4.1 graphically depicts the available data.

The serological survey from 2013 was conducted for individuals from 18 to 32 years old. These persons will be between 21 and 35 years old in 2016. For this age span, individuals benefited from a single-dose vaccination. We do not have serological information for individuals from 36 years and older, and we cannot use vaccination coverage data as they have not been vaccinated. Nonetheless, upon the presence of some existing humoral immunity, one can assume that some of those individuals have experienced natural infection. Such natural immunity is assumed to persist for life. Thus, for the analyses based on the 2013 data, we split the population according to the following age categories:

- $<$ 1 year: Maternal immunity
- 1 year $\longrightarrow$ 21 years: Vaccination coverage
  - For individuals of age below 14 years:
    - 1 year $\longrightarrow$ 2 years: 1 dose
    - 2 year $\longrightarrow$ 21 years: 2 doses
  - For individuals of age from 14 up to 21 years:
    - 1 year $\longrightarrow$ 4 years: 1 dose
    - 4 year $\longrightarrow$ 21 years: 2 doses
- 22 years $\longrightarrow$ 36 years: Serology, resulting from a mix between vaccination and natural infection.
- >36 years: Natural immunity, but no data

Using the dataset from 2009, serological information is available for individuals from 6 months (but in practice one year) up to 49 years old. Hence, from a 2016 perspective, we can use serology for individuals aged 8 up to 56 years old. Hence, we split the population according to the following age categories:

- $<$ 1 year: Maternal immunity
- 1 year $\longrightarrow$ 8 years: Vaccination coverage
  - 1 year $\longrightarrow$ 2 years: 1 dose

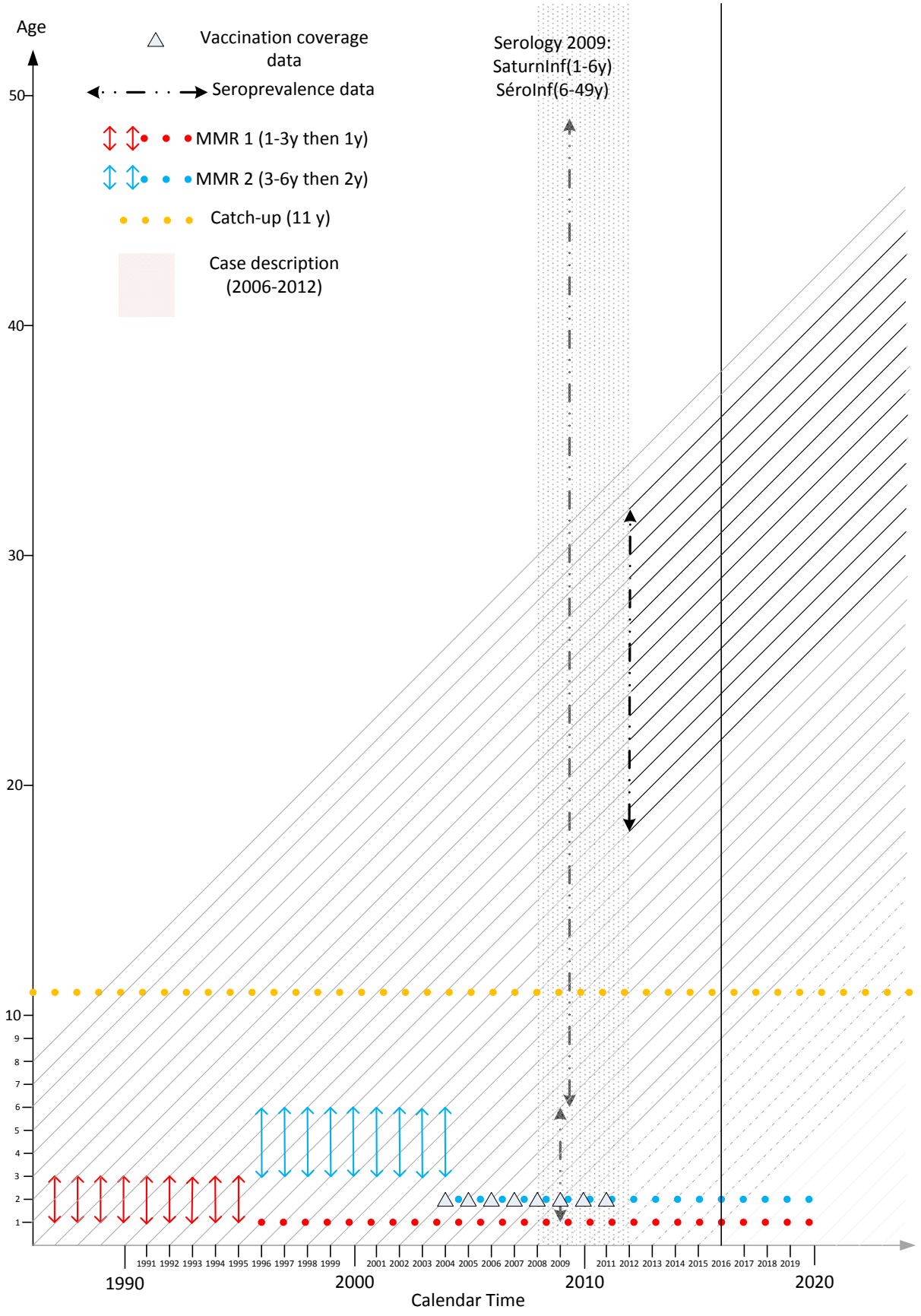


FIGURE 4.1: Lexis diagram, illustrating the aging of yearly cohorts (1996-2023), with the period of reported cases for measles, collection time for seroprevalence survey (2009 and 2013), vaccination coverage information and age of vaccination.

  - 2 year $\longrightarrow$ 8 years: 2 doses

- 9 years $\longrightarrow$ 56 years: Serology, resulting from a mix between vaccination and natural infection.

- >57 years: Natural immunity, but no data

Vaccination coverage at 24 months was documented by department from 2004 to 2011. As this vaccination coverage was supposed to be exhaustive, no confidence intervals were provided nor available. Using a finite population correction factor and the average number of 7000 births by department per year, we found a variation from 3 up to 5% according to the coverage proportion. Therefore, the confidence intervals were estimated with ±5%, as a conservative approach. The conservative approach is meant here as a choice to not minimize the confidence intervals of the findings, in order to not overestimate their validity. Newborns may be protected by maternal antibodies, but quickly lose their protection after 3 months for children born from vaccinated women and 5 months for children born from naturally immune women on average [Leuridan et al., 2010, Waaijenborg et al., 2013]. Therefore, we assumed that maternal antibodies decay exponentially at a rate of 3.87 $year^{-1}$ (i.e. the mean duration of maternal protection is 3.1 months) to account for both children born from vaccinated and naturally immune mothers [Abrams et al., 2014].

4.2.2 Modelling the serology for the year of data collection

We first explored for potential interactions with interregions, using a general additive model of seropositivity as a function of age and interregion:

- Measles serological dataset from 2009: There was an interaction with an effect of the interregion on the relation between age and seropositivity. Therefore, we took into account models with an interaction.

- Measles serological dataset from 2013: There was an interaction between age and the interregion. Hence, age had an influence on the probability of seropositivity but this influence was variable according the interregion. The effect of age on seropositivity seemed very different in Ile de France compared to other Interegion (Figure 2.4). Hence, that suggests the importance of taking into account the spatial dimension.

- Mumps serological dataset from 2009: There was no interaction found between the interregion and age for mumps seropositivity.

- Rubella serological dataset from 2009: There is a clear interaction by most of the interregions (again, Ile de France seemed very different from other Interegions) with age for rubella seropositivity.
- Rubella serological dataset from 2013: There is a non-significant trend to an interaction by the south-east interregion with age for rubella seropositivity.

We used a generalised additive model with complementary log-log link function to model the observed seroprevalence as a function of age a, gender g and spatial location (x, y):

$$\text{cloglog}(\pi(a, g, x, y)) = f(a, g, x, y)$$

where $\pi(a, g, x, y)$ is the proportion of seropositives of age a and gender g with spatial coordinates (x, y) and f is a smooth function. We considered several submodels of the previous model using different smoothing functions such as splines (noted s) or tensor product based smooths (noted te), and with or without gender or interactions with the interregion (noted IntR) in Tables 4.1, 4.2, 4.3, 4.4, 4.5. In the specific case of smoothing spatial coordinates, it should be noted that a spline generates a two-dimensional smooth similar in both directions while a tensor product allows for differential smoothing along the two directions. The best model is chosen based on the Akaike Information Criterion (AIC), by retaining the model with the smallest AIC-value. Next to AIC, we mentioned the Bayesian Information Criteria (BIC). BIC tending to choose the most parsimonious model, we wanted to see if it selected the same models than AIC, which tends to choose the most complex model. Modelling the 2009 seroprevalence data in view of estimating risk in 2016 was restricted to individuals older than two years, as the 2nd MMR dose administered at two years would have affected estimates of the seroprevalence. Indeed, modelling susceptibility including individuals under 2 years who would have received only 1 dose would result in overestimating the proportion of susceptible individuals, thus the risk of an outbreak. This restriction was not relevant for the 2013 dataset as only individuals older than 18 years old were included. According to AIC, we selected the following model for measles and rubella:

$$\text{cloglog}(\pi(a, g, x, y)) = te(x, y, a, by = g) + te(x, y, a, by = 1 - g)$$

and a simpler model for mumps:

$$\text{cloglog}(\pi) = s(x, y) + s(a)$$

Models	AIC	BIC
s(a)	2785.15	**2843.77**
s(a) + InterRegion	2789.32	2875.41
s(a) + s(a, by=InterRegion)	2794.79	2956.38
s(x,y) + s(a)	2785.90	2865.58
s(a,by=g) + s(a,by=1-g)	2769.79	2869.12
te(x,y,a)	2771.88	3085.49
te(x,y) + s(a)	2782.47	2893.73
te(x,y,a,by=g) + te(x,y,a,by=1-g)	**2761.43**	3142.27

TABLE 4.1: Models for measles 2009. Age is represented by a, gender by g (0/1 for Male/Female), (x, y) are spatial coordinates, Interregion is used as cofactor or as an interaction. Smoothing functions are splines (s) or tensor product splines (te).

Models	AIC	BIC
s(a)	2668.67	**2688.83**
s(a) + InterRegion	2670.06	2716.05
s(a) + s(a, by=InterRegion)	2654.74	2804.82
s(x,y) + s(a)	2562.59	2689.50
s(a,by=g) + s(a,by=1-g)	2669.26	2702.55
te(x,y,a)	2539.60	2908.00
te(x,y) + s(a)	2566.81	2663.24
te(x,y,a,by=g) + te(x,y,a,by=1-g)	**2538.30**	2975.08

TABLE 4.2: Models for measles 2013. Age is represented by a, gender by g (0/1 for Male/Female), (x, y) are spatial coordinates, Interregion is used as cofactor or as an interaction. Smoothing functions are splines (s) or tensor product splines (te).

Models	AIC	BIC
s(a)	4319.54	**4383.35**
s(a,by=g) + s(a,by=1-g)	4319.33	4433.99
s(x,y) + s(a)	**4293.18**	4483.93
te(x,y,a)	4325.83	4495.60
te(x,y) + s(a)	4296.93	4465.38
te(x,y,a,by=g) + te(x,y,a,by=1-g)	4316.10	4638.40

TABLE 4.3: Models for mumps 2009. Age is represented by a, gender by g (0/1 for Male/Female), (x, y) are spatial coordinates. Smoothing functions are splines (s) or tensor product splines (te).

Models	AIC	BIC
s(a)	3356.40	**3409.94**
s(a) + InterRegion	3353.25	3434.01
s(a) + s(a, by=InterRegion)	3326.76	3495.77
s(x,y) + s(a)	3349.88	3518.91
s(a,by=g) + s(a,by=1-g)	3320.48	3421.03
te(x,y,a)	3350.41	3617.36
te(x,y) + s(a)	3350.96	3435.85
te(x,y,a,by=g) + te(x,y,a,by=1-g)	**3312.81**	3673.45

TABLE 4.4: Models for rubella 2009. Age is represented by a, gender by g (0/1 for Male/Female), (x, y) are spatial coordinates, Interregion is used as cofactor or as an interaction. Smoothing functions are splines (s) or tensor product splines (te).

Models	AIC	BIC
s(a)	1749.86	1805.22
s(a,by=g) + s(a,by=1-g)	1689.98	**1787.64**
s(x,y) + s(a)	1615.50	1832.00
te(x,y,a)	1642.13	1933.80
te(x,y) + s(a)	1616.39	1803.89
te(x,y,a,by=g) + te(x,y,a,by=1-g)	**1555.84**	1970.06

TABLE 4.5: Models for rubella 2013. Age is represented by a, gender by g (0/1 for Male/Female), (x, y) are spatial coordinates. Smoothing functions are splines (s) or tensor product splines (te).

4.2.3 Deriving age-dependent susceptibility by department to the year of interest

The proportion of susceptible individuals in the year of interest, $s_b(a)$, is modelled with the following set of equations:

$$1 - s_b(a) = \begin{cases} e^{(-\eta \times a)} \times (1 - s_b(0)), & if\ 0 \leq a < 1, \\ e^{(-\gamma_1 \times (a-1))} \times \rho\nu_1, & if\ 1 \leq a < 2, \\ e^{(-\gamma_2 \times (a-2))} \times \rho\nu_2, & if\ 2 \leq a \end{cases}$$

where a is the age of individuals, b their birth year, ρ the seroconversion rate, γ_1 and γ_2 the decay rates of vaccine-induced immunity after one dose and two vaccine doses respectively, $s_b(0)$ is the proportion of susceptible newborns (related to the proportion of susceptible women of childbearing age) and η the decay rate of maternal antibodies. For the youngest individuals for whom susceptibility could not be estimated because the model was restricted (e.g., individuals under 2 years in 2009 who were under 9 years in 2016) or because data were not available (2013 dataset), we used vaccination coverage information and took into account the waning of vaccine-induced immunity by multiplying the proportion of vaccinated individuals by $e^{(-\gamma_2 \times (a-a_0))}$ where a_0 is the age at the time of the data collection (2009 or 2013). For older ages where natural immunity would provide lifelong protection, we set the proportion of susceptibles equal to the proportion of susceptibles of the penultimate age determined by seroprevalence data, as no data were available. Therefore, the 2009 dataset provided seroprevalence from 1 up to 49 years old, which concerned individuals from 8 to 56 years from a 2016 perspective. The 2013 dataset provided seroprevalence between 18 and 32 years, which corresponds to individuals from 21 up to 35 years from a 2016 perspective. Figure 4.1 illustrates the use of the different datasets with the multicohort model. Then, our approach can be described as follows:

For individuals aged from 14 years up to 21 years, we took into account that their 2nd dose was administered on average at four years old instead of 2 years.

We also combined the two datasets for rubella modelling. The dataset from 2009 was used to model the susceptibility in 2016 for individuals aged 20 years and less, and 36 years and more, while susceptibility profiles obtained from both datasets were averaged for individuals of age comprised between 21 and 35. In that way, we were able to use all the available information.

Primary and secondary vaccine failure rates were estimated from the literature (Tables 4.6 and 4.7) and summarized in Table 4.8. Different published estimates were combined with a random-effects meta-analysis approach to calculate overall estimates for seroconversion (primary vaccine failure) and waning rates (secondary vaccine failure) for mumps and measles according to the approach undertaken by Abrams et al. [2014] and Hens et al. [2015]. We have reproduced in Tables 4.6 and 4.7 what has been done in the previously cited articles.

For the particular case of rubella, the random-effects meta-analysis for waning was not relevant due to extreme heterogeneity in the very few published studies and resulted in extremely large confidence intervals. Therefore, we estimated a waning rate using the ESEN 2006 study, focusing on the Belgian population aged between 13 years and 20 years. This age interval was selected to have individuals vaccinated by 2 doses (vaccination for MMR was introduced in 1981 in Belgium and the second dose was recommended at 10-12 years since 1995). The logarithm of antibody levels from individuals seropositive for rubella were linearly modelled as a function of age, consequently the slope equalled the rate of exponential waning. The coefficient [standard error] (-0.00328 [0.01258]) was not significantly different from 0 (p-value=0.79). However, we used this rate to model a possible waning. We estimated Wald-confidence interval to be used in our modelling (Table 4.7). This confidence interval included negative and positive values, but we used only the range of values from 0 to -0.028 in our modelling, under the assumption that antibodies would not increase (thence, would decrease (waning) or not(no waning)). Nonetheless, as a sensitivity analysis, we also studied 2 alternate scenarios, one without waning (0[0-0])(as the coefficient was not significantly different from 0) and one estimated from literature with a fixed-effect meta-analysis (after 1 dose: 0.015(0.013-0.018); after 2 doses: 0.016(0.014-0.018); common rate: 0.016(0.014-0.018) where waning rates may be overestimated, and compared the results. We chose a conservative approach (in the sense that it will minimize the outbreak risk) in which infection is believed to confer lifelong immunity [Plotkin et al., 2013]. We considered seronegative individuals as fully susceptible, thus not taking into account possible cellular immunity, which is very difficult to estimate [Plotkin, 2013].

4.2.4 Estimating the effective reproduction number and age-dependent relative incidence

We aimed at estimating the effective reproduction number R_e, the expected number of secondary cases generated by one single infectious case during his/her entire infectious period when introduced in a partially immune population. Combining the proportion of susceptible individuals in the French population with the French social contact matrix determines the next generation operator. Effective reproduction numbers and the age-dependent relative incidence can be estimated through the dominant eigenvalue and eigenvector of this next generation operator, respectively. R_e lower than one implies that the outbreak will fade out, while outbreaks are able to spread in case R_e is larger than one. It should be noted that the contact matrices were not spatially determined. Among the refinements brought to Abrams methodology is that these quantities were determined by department, and the use of gender-specific contact matrices for measles and rubella. Indeed, modelling the serology showed that gender was included in the best model for measles and rubella but not for mumps. Therefore, the R_e accommodates both the gender differences in susceptibility and those in mixing patterns. For that reason, we expressed the age-dependent relative incidence separately for males and females when necessary. We used a parametric bootstrap with 2000 bootstrap samples to account for uncertainty and we provided 95% bootstrap-percentile CIs associated with our estimates. For each sample, an interpolating spline was fitted to the susceptibility curve thereby merging estimates based on the observed seroprevalence and those based on vaccination coverage information. We compared the R_e using a contact matrix for holidays and regular days, simulating the occurrence of an outbreak during regular days or school holidays. We based our calculations upon D, the mean infectious period and the basic reproduction number R_0 that expresses a similar quantity as R_e in a fully susceptible population. Selected measles, mumps and rubella estimates of R_0 were 12, 10 and 8 respectively, and D at 6 days/365, 6 days/365 and 7 days/365 respectively [Anderson and May, 1991, Farrington, 2009], this is a conservative approach, as it tends to minimize the risk of outbreak, but we also provided a sensitivity analysis with higher R_0.

4.2.5 Escape probability

Estimating R_e is a way to express a risk. When $R_e > 1$, or more precisely, when the upper limit of the confidence interval is above 1, a risk exists that an outbreak happens. The escape probability is another way to express this risk, in terms of the probability that a beginning outbreak fades out spontaneously. We calculated the escape probability according to a simplification of the methodology published in Flasche et al.

Study	Measles	Mumps	Rubella
Author [year]	$\hat{\rho}$ 95% CI	$\hat{\rho}$ 95% CI	$\hat{\rho}$ 95% CI
Bhargava et al. [1995]			0.989 (0.939;1.000)
Böttiger et al. [1987]	0.917 (0.873;0.950)	0.867 (0.821;0.905)	0.998 (0.987;1.000)
Christenson et al. [1983]			0.992 (0.958;1.000)
Crovari et al. [2000]	0.993 (0.983;0.998)	0.970 (0.951;0.983)	1.000 (0.995;1.000)
dos Santos et al. [2006]	0.992 (0.959;1.000)	0.793 (0.666;0.888)	0.913 (0.868;0.947)
Ehrenkranz et al. [1975]	0.986 (0.925;1.000)	0.944 (0.863;0.985)	
Feiterna-Sperling et al. [2005]		0.912 (0.883;0.936)	
Forleo-Neto et al. [1997]			0.990 (0.947;1.000)
Gatchalian et al. [1999]	0.992 (0.954;1.000)	0.927 (0.870;0.964)	1.000 (0.976;1.000)
Gothefors et al. [2001]	0.941 (0.713;0.999)	0.971 (0.899;0.996)	
Khalil et al. [1999]	1.000 (0.961;1.000)	0.929 (0.805;0.985)	1.000 (0.916;1.000)
Klinge et al. [2000]	0.932 (0.870;0.970)	0.949 (0.893;0.981)	0.975 (0.927;0.995)
Lee et al. [2002]	1.000 (0.927;1.000)	0.945 (0.904;0.972)	1.000 (0.982;1.000)
Lee et al. [2011]	0.989 (0.942;1.000)	0.876 (0.794;0.934)	1.000 (0.960;1.000)
Lim et al. [2007]	1.000 (0.965;1.000)	0.981 (0.945;0.998)	0.966 (0.916;0.991)
Mitchell et al. [1998]	0.810 (0.730;0.874)	0.766 (0.683;0.836)	0.935 (0.877;0.972)
Nolan et al. [2002]	0.972 (0.903;0.997)	0.966 (0.916;0.991)	1.000 (0.950;1.000)
Peltola et al. [2008]	0.991 (0.975;0.998)		
Rager-Zisman et al. [2004]	0.956 (0.891;0.988)	0.947 (0.871;0.985)	0.933 (0.851;0.978)
Redd et al. [2004]	0.940 (0.924;0.954)	0.916 (0.897;0.933)	0.944 (0.927;0.957)
Robertson et al. [1988]			0.991 (0.966;0.999)
Samoilovich et al. [2000]			0.960 (0.932;0.978)
Schwarzer et al. [1998]	0.997 (0.982;1.000)	0.965 (0.920;0.989)	0.988 (0.968;0.997)
Stück et al. [2002]	0.948 (0.900;0.977)	0.949 (0.885;0.983)	0.994 (0.964;1.000)
Tischer and Gerike [2000]	0.997 (0.984;1.000)	0.974 (0.940;0.991)	0.981 (0.963;0.992)
Usonis et al. [1998]	0.992 (0.972;0.999)	0.936 (0.898;0.962)	1.000 (0.984;1.000)
Vesikari et al. [1984]		0.961 (0.865;0.995)	1.000 (0.979 1.000)

TABLE 4.6: Estimated seroconversion rates and associated 95% Clopper-Pearson confidence intervals based on the studies mentioned. Taken from Abrams et al. [2014] for mumps, from Hens et al. [2015] for measles, and calculated similarly for rubella [Kourkouni, 2014]

[2011]. This estimate represents the probability that a single initial infected individual will not transmit the disease sufficiently to generate an outbreak. If we consider that the effective reproduction number is negatively binomially distributed, with a mean m and a variance to the mean ratio v, therefore the extinction probability q of an outbreak (here considered as a Poisson process) given one infected individual can be calculated by solving the following equation:

$$0 = \sqrt{\frac{m}{(m-v)\,q + v}\frac{-2m}{m-v}} - q$$

We selected the ratio of the variance to the mean v= 1, 5 or 25, similar to Flasche et al. [2011]. A variance to the mean ratio equal to 1 (having the variance equal to the

Study	Measles		Mumps		Rubella	
Author [year]	$\hat{\rho}$ (95% CI)	dose	$\hat{\rho}$ (95% CI)	dose	$\hat{\rho}$ (95% CI)	dose
Boulianne et al. [1995]	0.023 (0.016;0.033)	1	0.029 (0.020;0.039)	1	0.006 (0.002;0.010)	1
Broliden et al. [1998]	0.001 (0.000;0.003)	1	0.031 (0.023;0.039)	1		
Davidkin et al. [1995]			0.054 (0.034;0.075)	1		
			0.027 (0.009;0.044)	2		
Davidkin et al. [2008]	0.003 (0.001;0.008)	2	0.020 (0.012;0.028)	2	0.000 (0.000;0.000)	2
	0.005 (0.003;0.007)	2				
Kremer et al. [2006]	0.007 (0.002;0.011)	1				
	0.018 (0.005;0.031)	2				
LeBaron et al. [2007]	0.002 (0.000;0.006)	1				
	0.006 (0.003;0.010)	1				
	0.009 (0.004;0.017)	2				
LeBaron et al. [2009]			0.013 (0.010;0.016)	2	0.016 (0.013;0.020)	2
			0.013 (0.010;0.016)	2	0.040 (0.030;0.047)	2
Miller et al. [1995]	0.009 (0.003;0.018)	1	0.053 (0.036;0.070)	1	0.001 (0.000;0.004)	1
Poethko-Müller and Mankertz [2012]	0.018 (0.015;0.022)	1	0.057 (0.049;0.063)	1	0.017 (0.014;0.020)	1
	0.014 (0.012;0.016)	2	0.022 (0.019;0.025)	2	0.008 (0.006;0.010)	2

TABLE 4.7: Estimated exponential waning rates and associated 95% Clopper-Pearson confidence intervals based on the studies mentioned. Taken from Abrams et al. [2014] for mumps, from Hens et al. [2015] for measles, and calculated similarly for rubella [Kourkouni, 2014]

	Measles	Mumps	Rubella
Seroconversion rates	$\hat{\rho}$ 95% CI	$\hat{\rho}$ 95% CI	$\hat{\rho}$ 95% CI
	0.977 (0.959;0.990)	0.934 (0.910;0.954)	0.984 (0.974;0.992)
Exponential waning rates	$\hat{\rho}$ 95% CI	$\hat{\rho}$ 95% CI	$\hat{\rho}$ 95% CI
After 1 dose	0.007 (0.003;0.018)	0.043 (0.029;0.065)	
After 2 doses	0.008 (0.004;0.020)	0.024 (0.015;0.042)	
Common waning rate	0.008 (0.005;0.014)	0.030 (0.021;0.043)	0.003(-0.023;0.028)

TABLE 4.8: Estimated seroconversion rates and exponential waning rates used in the model. For rubella, 3 models were used, one according to the waning rates estimated from ESEN 2006, one without waning and one with a fixed-effects approach.

mean results in a Poisson distribution) could be interpreted as a low proportion of super spreading events while a ratio of 25 would assume that super spreading events would represent an important proportion of the infectious transmission. Although applied to influenza by Flasche et al. [2011], the choice of these numbers was originally inspired by a study on SARS from Lipsitch et al. [2003]. If super spreading events represent an important part of the transmission, it will result in a high probability of extinction of the outbreak. A low number of secondary infections will also increase that probability (an $R_e < 1$ results in 100% of the outbreaks that dies out).

Calculations were made with R 3.1.0 and with the R packages mgcv, splines, spdep, RColorBrewer, classInt, maptools, meta and metafor.

4.3 Results

We first analysed the risk of measles emergence in 2010 based on the data from 2009, to compare model predictions with data related to the large-scale 2010-2011 measles outbreak in France. Then, we investigated the risk for an emergence in 2016 based on the data from 2013 for measles, from 2009 for mumps, and from both for rubella. We summarized the susceptibility and the risk for measles, mumps and rubella at the country level in Figure 4.2.

Maps (Figures 4.3, 4.7, 4.10, 4.13, 4.15, 4.16) showed which departments have the highest risk of a future outbreak. Curves showed the susceptibility profile and the age-dependent relative incidence of the department with the highest and the lowest R_e estimates together with those for Paris. For measles and rubella, curves showed gender-specific differences. Moreover, there is a substantial variation in susceptibility between departments, and therefore in the outbreak risk and the age-dependent relative incidence of a potential outbreak between different departments. It is to be noted that data sparseness with regard to the seroprofiles for some departments (notably Corsica) resulted in huge confidence intervals.

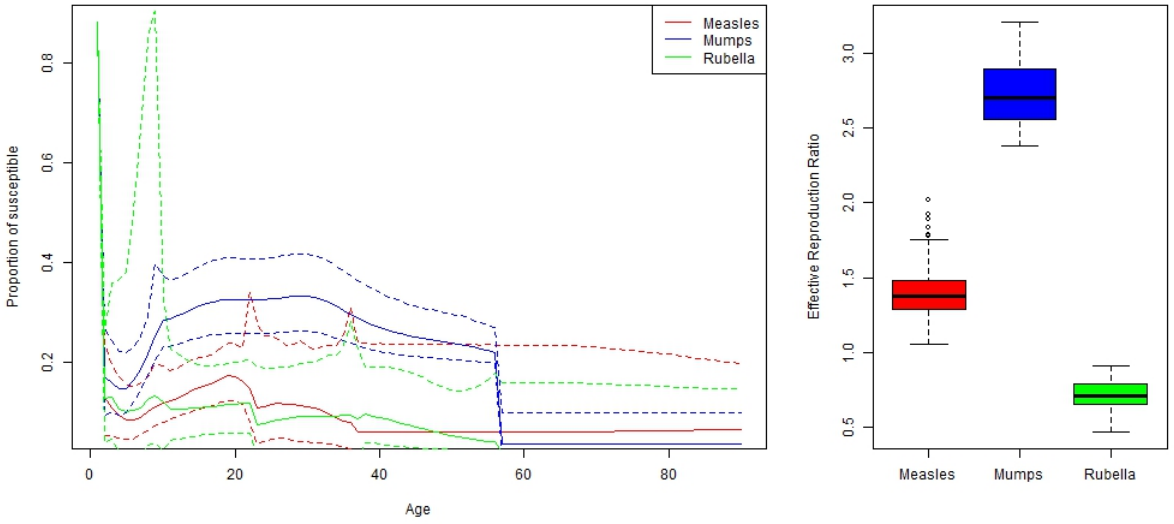


FIGURE 4.2: Measles, mumps and rubella predicted for France in 2016. Left panel:Susceptibility curves indicating the mean proportion (solid line) of susceptible individuals in every age cohort with 95% CI (dashed lines). Right panel: Boxplot of R_e among the French departments for measles, mumps and rubella

4.3.1 Measles risk in 2010 based on data from 2009

We first assessed our methodology to estimate the risk for measles outbreaks in 2010, based on the 2009 dataset and compared it to the 2010-2011 outbreak. The median (min-max) effective reproduction number was 0.856 (0.651;1.203). R_e was higher than one in 16 departments out of 96. The upper limit of the 95 %CI was always higher than one irrespective of the department considered (median(min-max) was 1.921 (1.386;10.83)). The predicted age-dependent relative incidence in the two departments (Haut-Rhin & Savoie) with the highest number of reported measles cases is graphically shown in Figure 4.4 along with the observed incidence of reported cases during the outbreak. Our approach seems to provide predictions with relatively good concordance with the observed incidence.

4.3.2 The French measles outbreak

As illustrated in Figure 2.3, the overall incidence of measles from 2008 to 2011 can be divided in 3 periods (2008-2009, January-August 2010 and the main period September 2010 to August 2011). The spatial distribution of cases is showed in Figure 4.5. The map highlights the fact that most cases occurred in Southeast France, but a significant number of cases occurred in the rest of the territory. Indeed, Vendée, one of the 2 departments with the highest number of cases during the first period was one of the

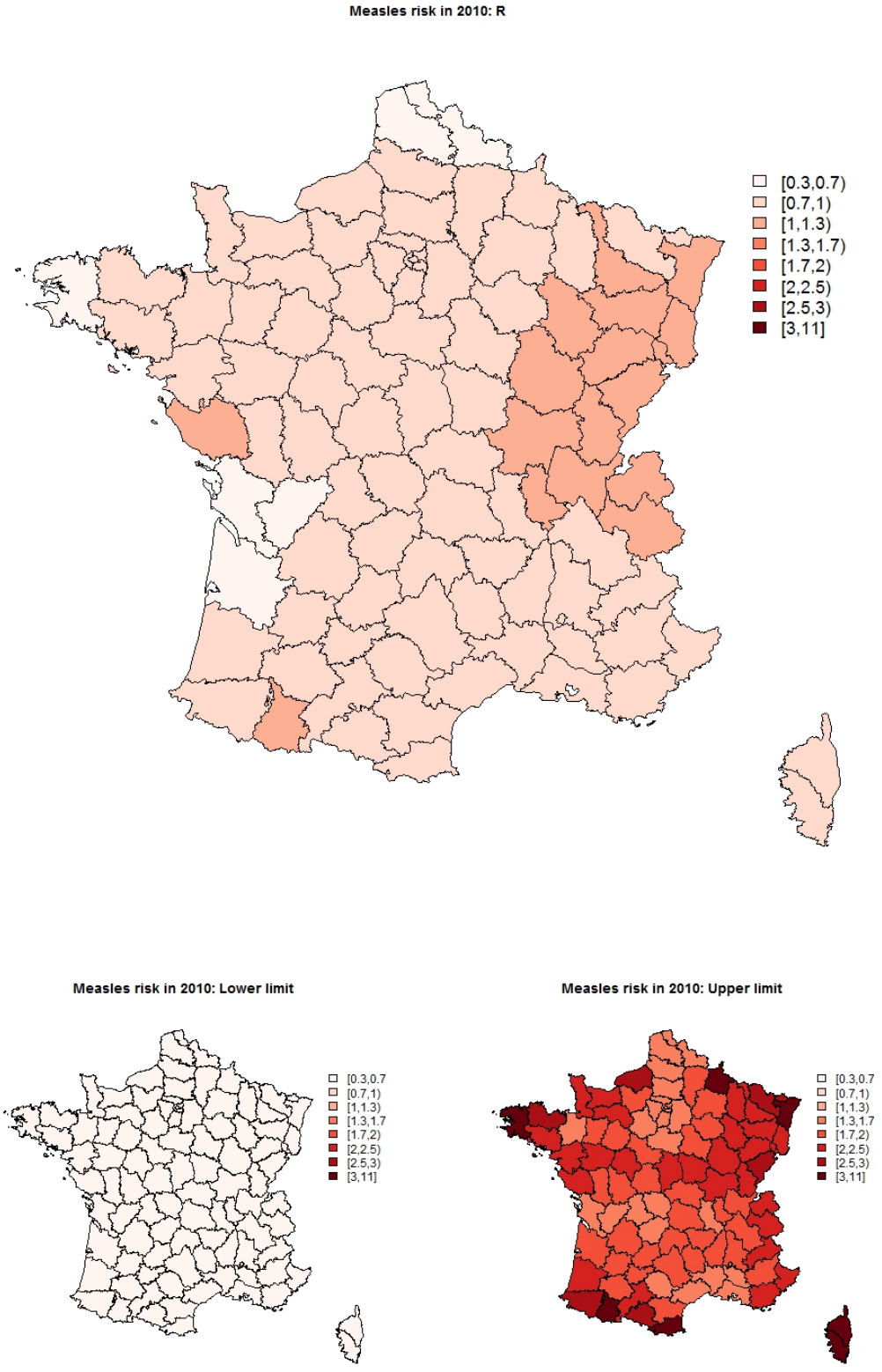


FIGURE 4.3: Measles risk map in 2010 based on 2009 data, illustrating the estimation of the effective reproduction numbers R_e for each department (upper central), with lower (lower left) and upper (lower right) 95% confidence limits.

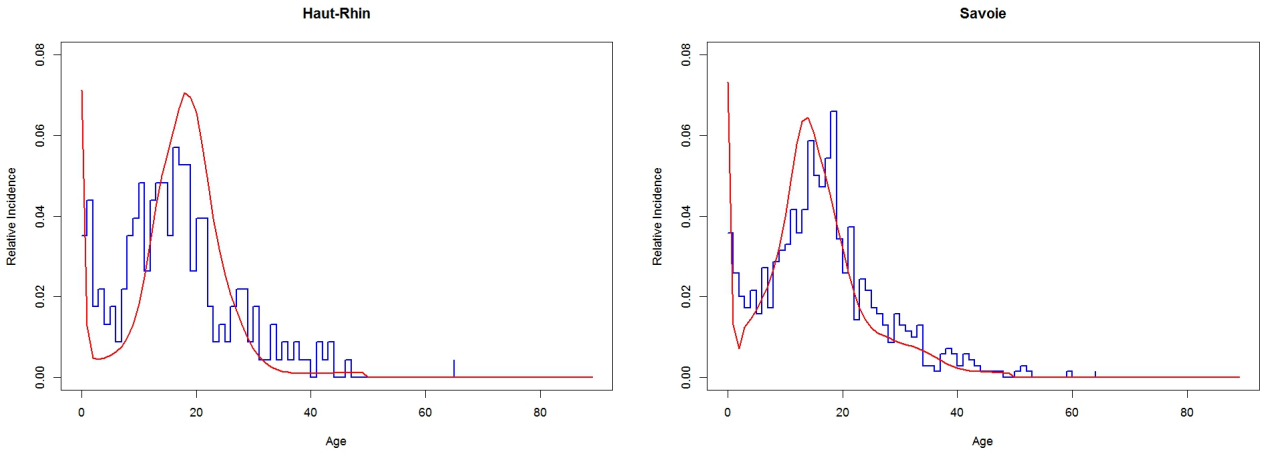


FIGURE 4.4: Predicted incidence (red) for measles in 2010 based on 2009 serology and vaccination coverage and cases (blue) reported between 2009-2012, in Haut-Rhin (Left) and Savoie (Right)

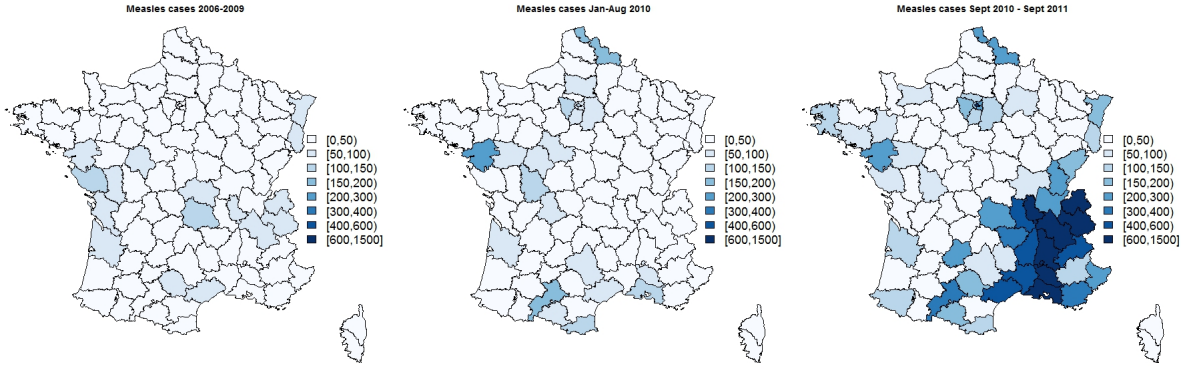


FIGURE 4.5: Spatial distribution of cases for measles in 2006–2009 (left); Jan–August 2010 (center); September 2010–September 2011

department with the highest risk. Moreover, some of the departments with the highest number of cases during the third period -Haute-Savoie, Savoie, Ain, Jura- were also some of the departments the most at risk according our model. There were no differences in incidence between men and women, whatever the age category or the period during the outbreak.

4.3.3 Measles risk in 2016 based on data from 2013

The risk for measles resurgence in 2016 was evaluated based on the serological survey from 2013. Because of the outbreak in 2010-2011, we could not rely on the serological data from 2009. R_e values and their confidence intervals are presented in Figure 4.6, ordered from the smallest to the largest R_e, and on a map of France in Figure 4.7. Figure 4.8 illustrate the susceptibility and the age relative incidence of an outbreak in

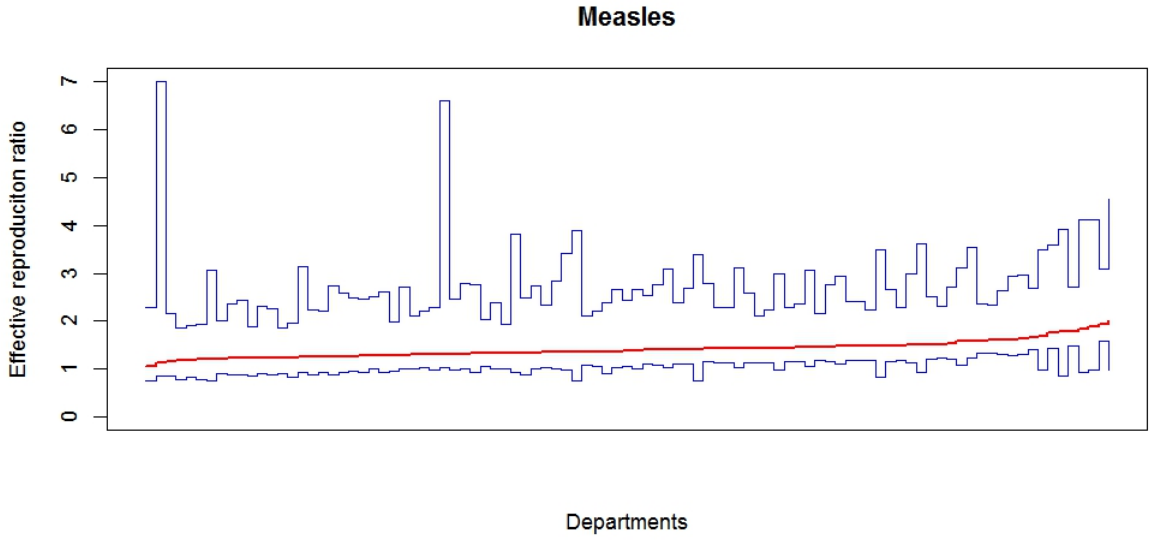


FIGURE 4.6: R_e (red) for measles and their confidence interval (blue), by department, ordered from the smallest to the largest R_e.

3 departments. The highest effective reproduction R_e was estimated 2.02 [0.99; 4.55] in Haute-Marne, the lowest value was obtained in Bas-Rhin, namely 1.06 [0.76; 2.30], while its value for Paris was 1.18 [0.79; 1.86].

4.3.4 Mumps

Taking into account the dataset from 2009, we estimated outbreak risk in 2016. R_e values and their confidence intervals are presented in Figure 4.9, ordered from the smallest to the largest R_e, and on a map of France in Figure 4.10. Figure 4.11 illustrates the susceptibility and the age-relative incidence of an outbreak in 3 departments. The highest R_e is estimated for Cantal, namely 3.21 [2.71; 3.86], the lowest one is estimated for Marne with R_e equal to 2.38 [2.03; 2.75] while the estimate for Paris equals 2.48 [2.23; 2.76]. All the R_e values were higher than 2, and most of the lower limits were above 2, except for 3 departments, of which 2 are part of Corsica, entailing wider CIs with lower limits below but still close to 2.

4.3.5 Rubella risk in 2016 based on data from 2009 and 2013

A first analysis was conducted modelling the 2 dataset separately. Although the curves and the estimates of R_e differed somewhat, the confidence intervals overlapped. However, the comparison between the 2 modelling was difficult because of a very different age span covered by the serology. The dataset from 2013 only covered 14 years, which is barely a

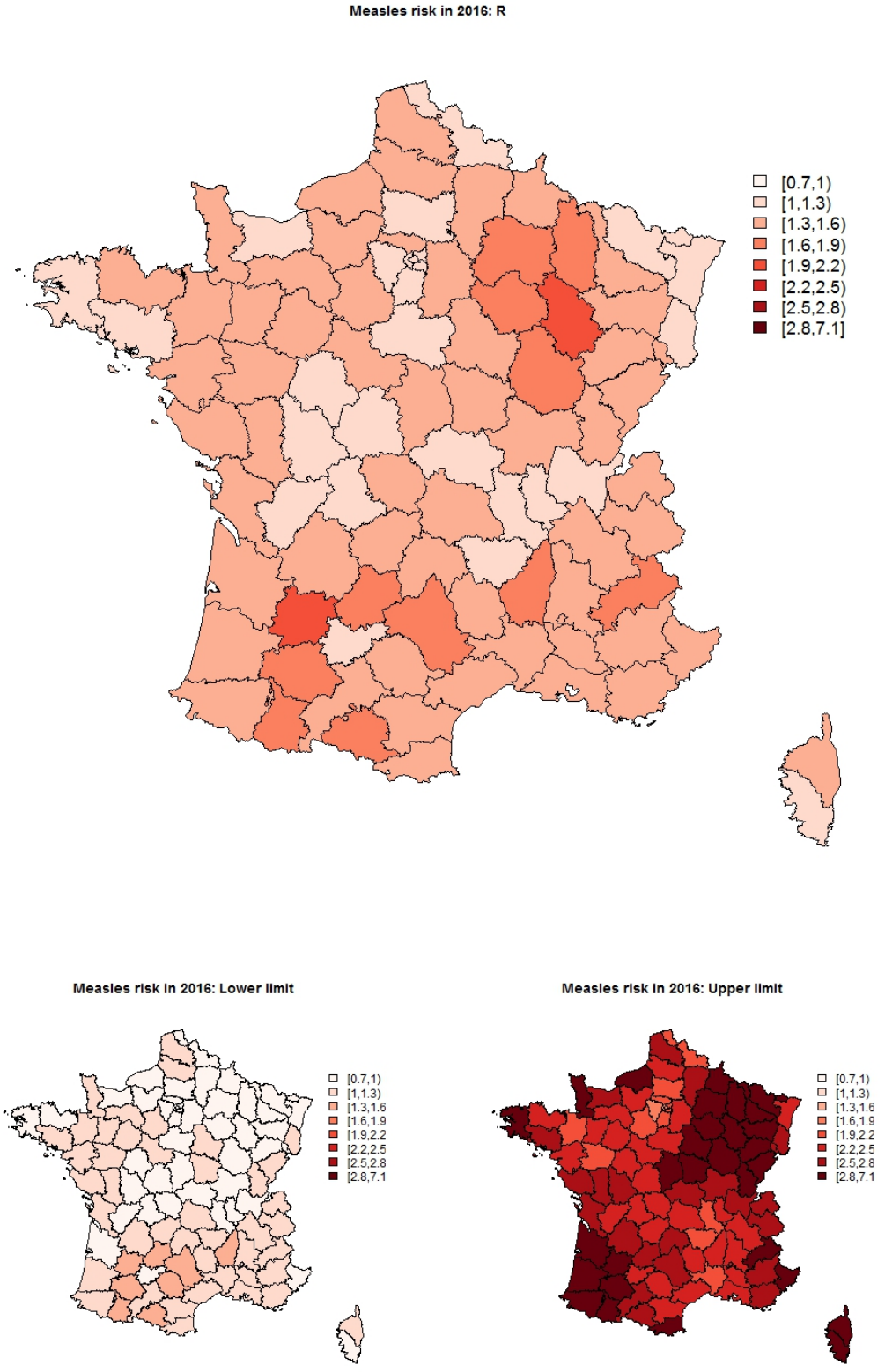


FIGURE 4.7: Measles risk map in 2016 based on 2013 data, illustrating the estimation of the effective reproduction numbers R_e for each department (upper central), with lower (lower left) and upper (lower right) 95% confidence limits.

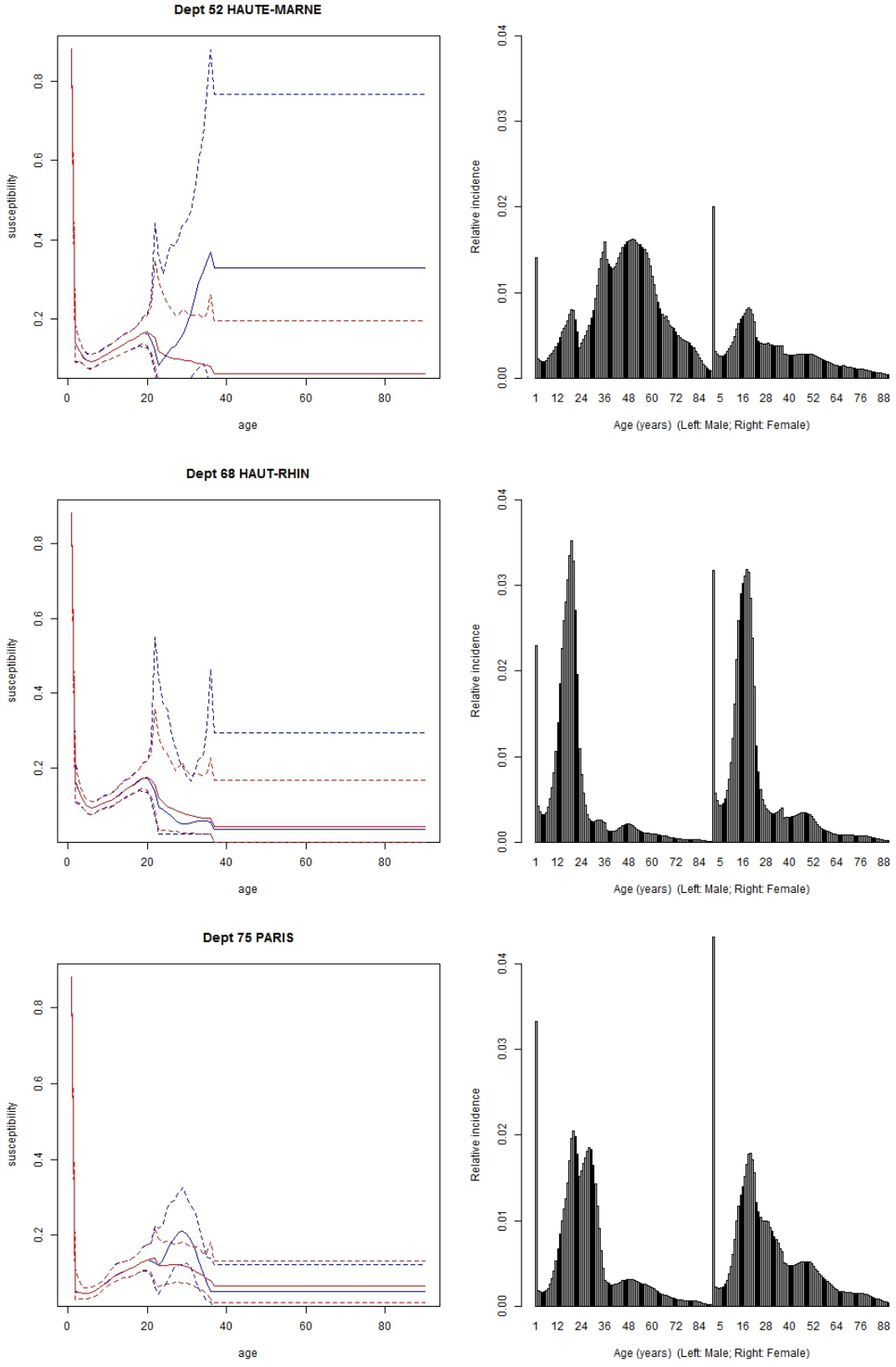


FIGURE 4.8: Measles estimate of susceptible proportion (upper panel) and potential incidence according age (lower panel) in 3 departments (left: highest risk, centre: Lowest risk, right: Paris) in 2016 based on 2013 serology for males (blue lines) and females (red lines). Age-dependent relative incidence is represented for males (left part) and females (right part) separately.

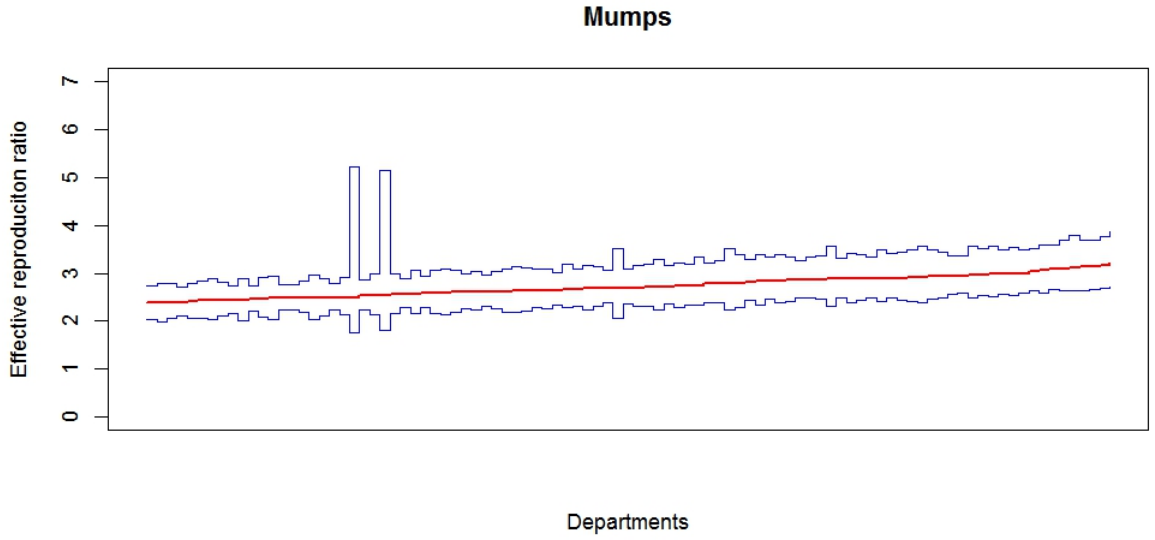


FIGURE 4.9: R_e (red) for mumps and their confidence interval (blue), by department, ordered from the smallest to the largest R_e

third of the 47 years covered by the dataset from 2009. Therefore, the modelling with the dataset from 2013 was mostly based on the vaccine coverage while the modelling with the dataset from 2009 was mostly based on the serology. Combining the 2 datasets gave us the opportunity to use all the data available without making an arbitrary choice on the dataset to choose. Thereby, the risk of rubella resurgence in 2016 was evaluated by averaging the susceptibility profiles derived from both datasets from 2009 and 2013 for ages between 21 and 35 years, otherwise using the dataset from 2009. We used the waning rate estimated from ESEN 2006. R_e are and their confidence interval are presented in Figure 4.12, ordered from the smallest to the largest, and on a map of France in Figure 4.13. Figure 4.14 illustrates the susceptibility and the age-relative incidence of an outbreak in 3 departments. The highest R_e is estimated for Puy-de-Dôme, namely at 1.06 [0.67; 1.76], the lowest one is estimated for Les Landes with R_e equal to 0.64 [0.38; 1.57] while the estimate for Paris' equals 0.82 [0.50; 1.33] as shown in Figure 4.14.

Waning rates estimated from ESEN being non-significantly different from 0, we also estimated R_e with a null waning rate (Figure 4.12 (dashed line), 4.15).

We also estimated R_e using the rates estimated from the meta-analysis with a fixed effect, and presented the result in (Figure 4.12 (dotted line), 4.16).

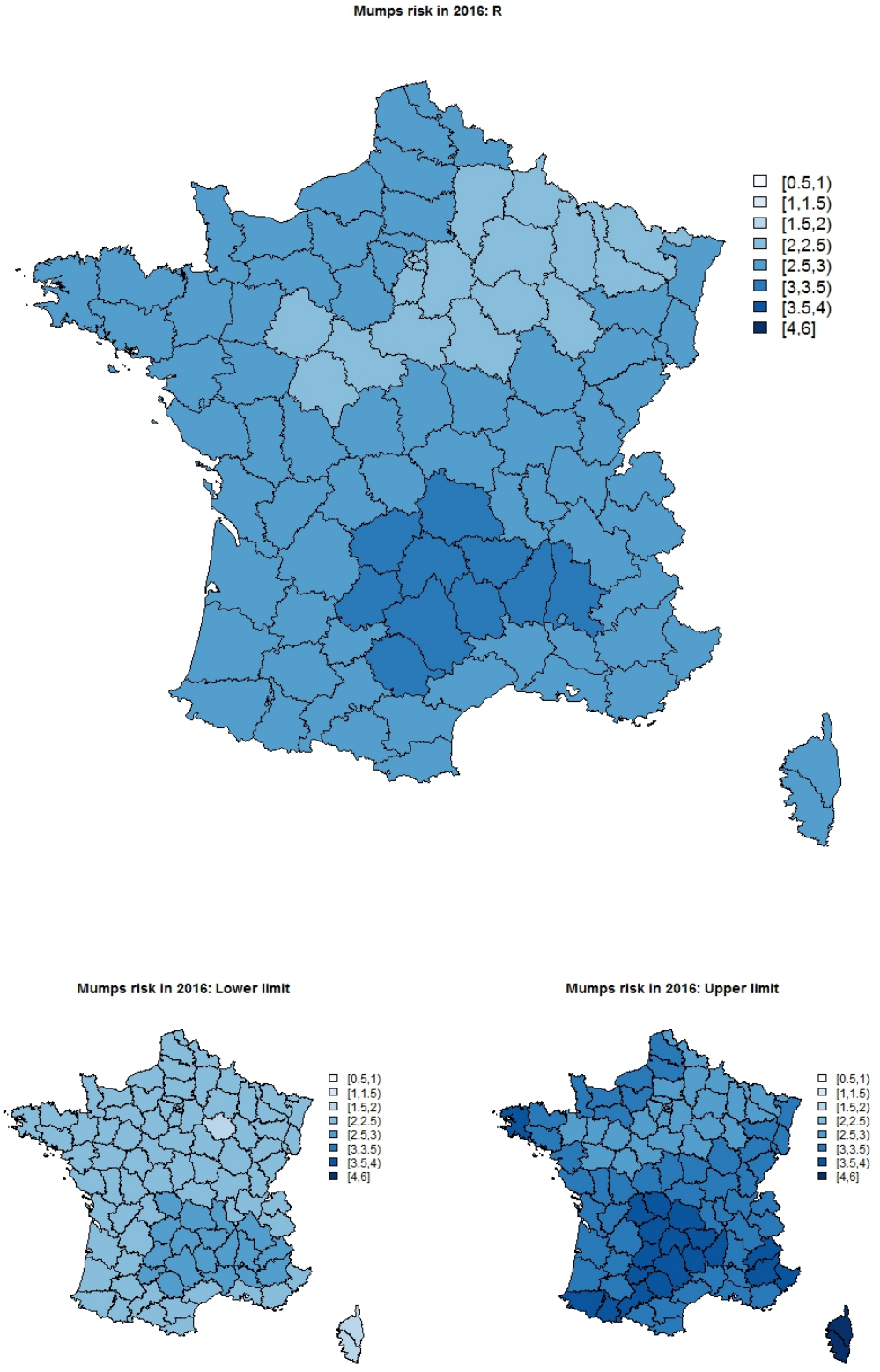


FIGURE 4.10: Mumps risk map in 2016 based on 2009 data, illustrating the estimation of the effective reproduction numbers R_e for each department (upper central), with lower (lower left) and upper (lower right) 95% confidence limits.

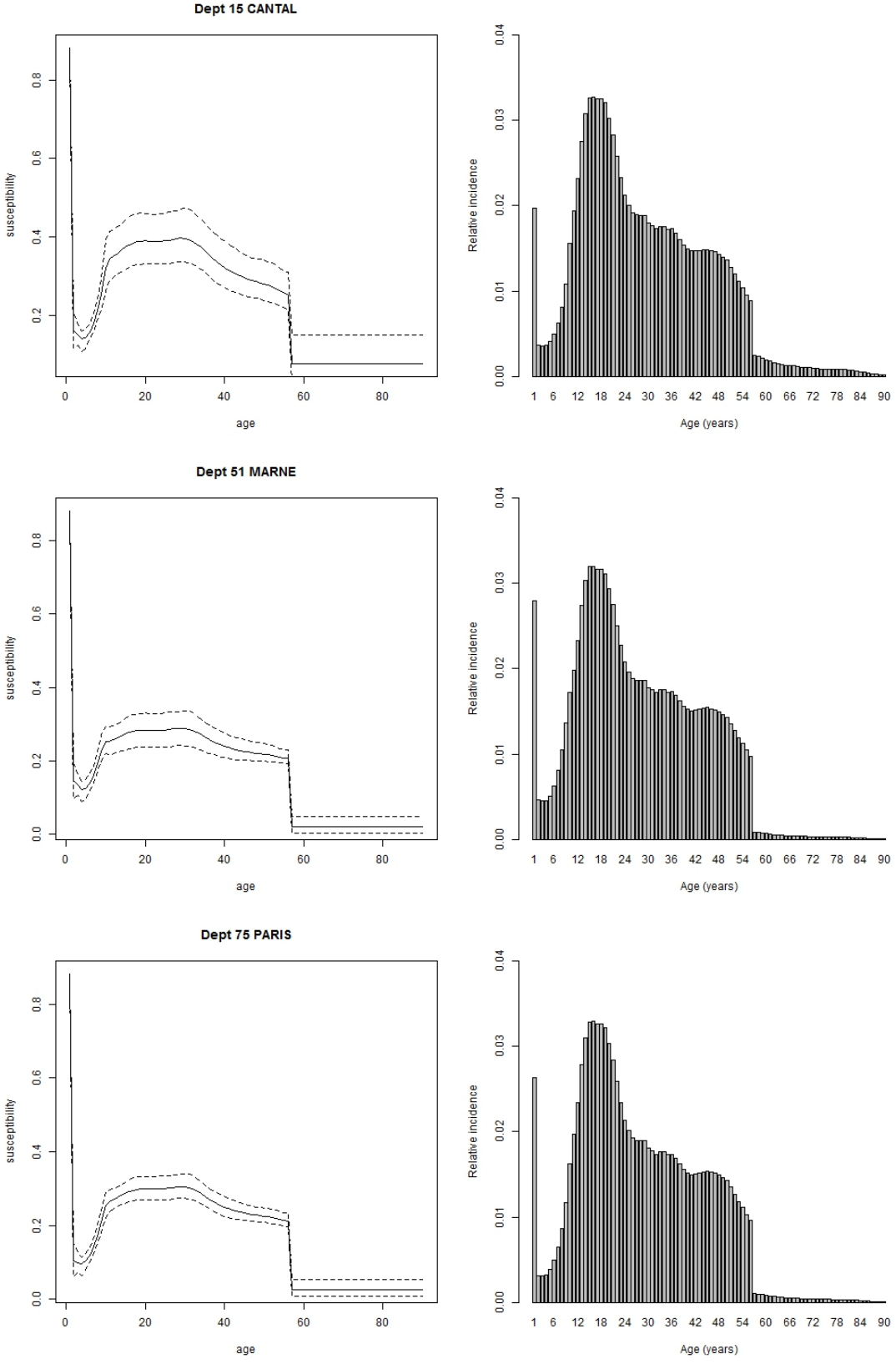


FIGURE 4.11: Mumps estimate of susceptible proportion (upper panel) and potential incidence according age (lower panel) in 3 departments (left: highest risk, centre: Lowest risk, right: Paris) in 2016 based on 2009 serology

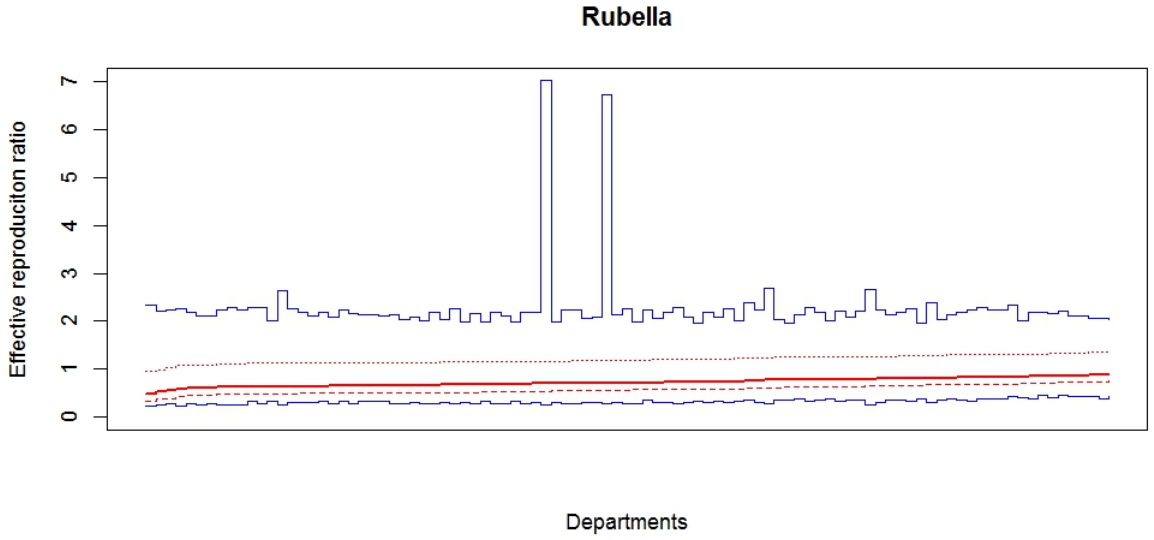


FIGURE 4.12: R_e (red) for rubella and their confidence intervals (blue), by department, ordered from the smallest to the largest R_e. Results from ESEN-estimated waning rate are presented with solid lines, from null waning with dashed lines, and from fixed Effect with dotted lines. For clarity, confidence intervals are not represented for null waning and fixed effect waning, but were smaller than the CI calculated with ESEN 2006.

4.3.6 Holidays, Age of onset, Escape probability and sensitivity analysis

Comparing R_e estimates during regular days with those in holiday periods showed an average reduction in R_e of 37.2%, 29.5%, 33.4% for measles, mumps and rubella respectively. A sensitivity analysis increasing R_0 by four points (thus, 16, 14, 12 for measles, mumps and rubella respectively) showed an increase in the outbreak risk of:

- 27% on average of R_e for measles, with the lower limit of the confidence interval and the R_e for each department systematically above 1.
- 40% on average of R_e for mumps, with the lower limit of the confidence interval and the R_e for each department systematically above 2.
- 50% on average of R_e for rubella, with none of the lower limits of the confidence intervals above 1, and all the upper limits above 1.99.

The measles outbreak in 2010-2011 generated cases almost everywhere in France, which can explain the scattered aspect of the risk map for measles compared to mumps and rubella. Beyond the differences among departments, some similarities arise. Infants under 1 age would be seriously implicated in a future outbreak, due to the rapid waning of the maternal antibodies. But the highest overall contribution in the caseload would

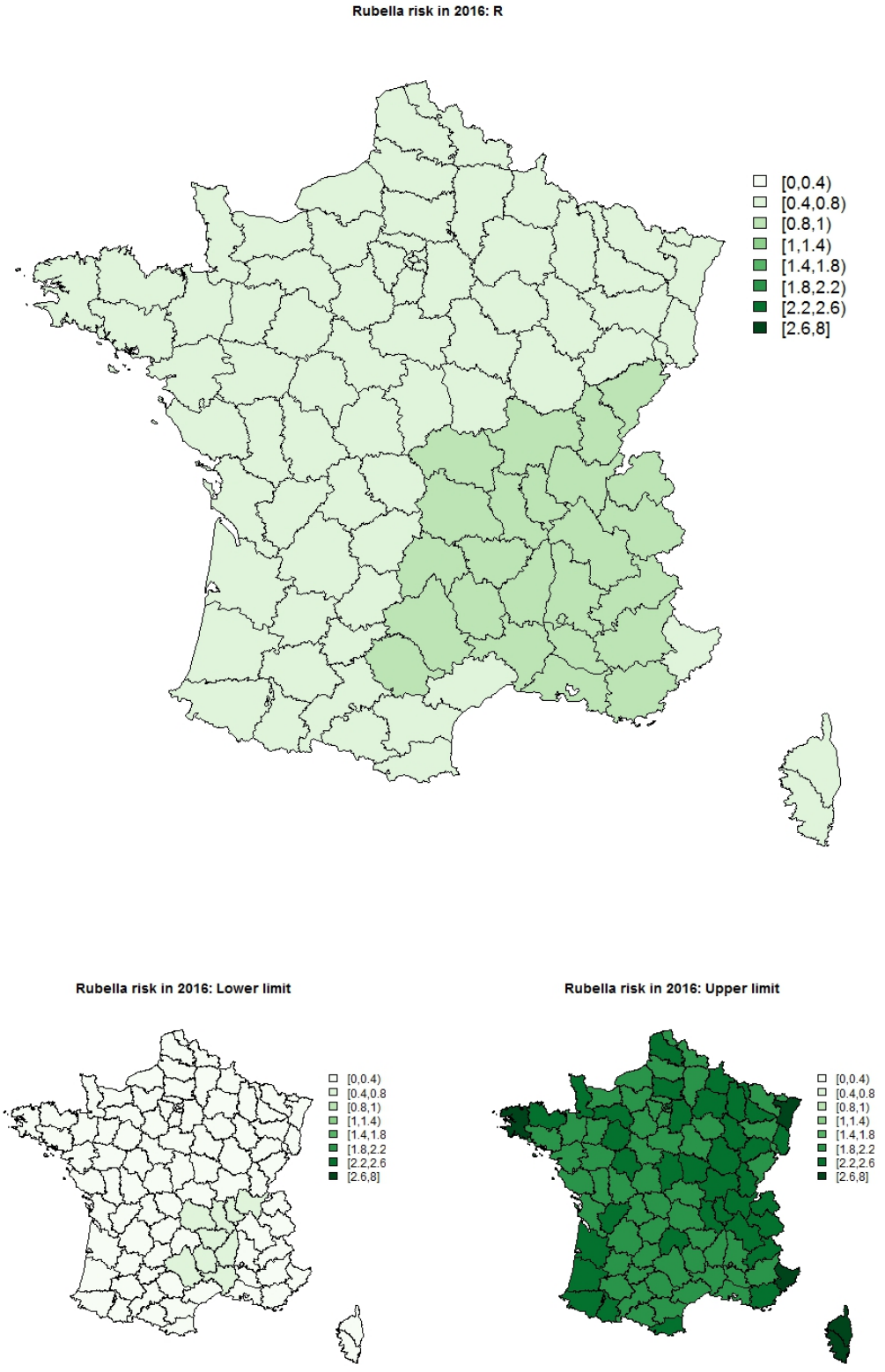


FIGURE 4.13: Rubella risk map in 2016, illustrating the estimation of the effective reproduction numbers R_e for each department (upper central), with lower (lower left) and upper (lower right) 95% confidence limits, with ESEN-estimated waning rate.

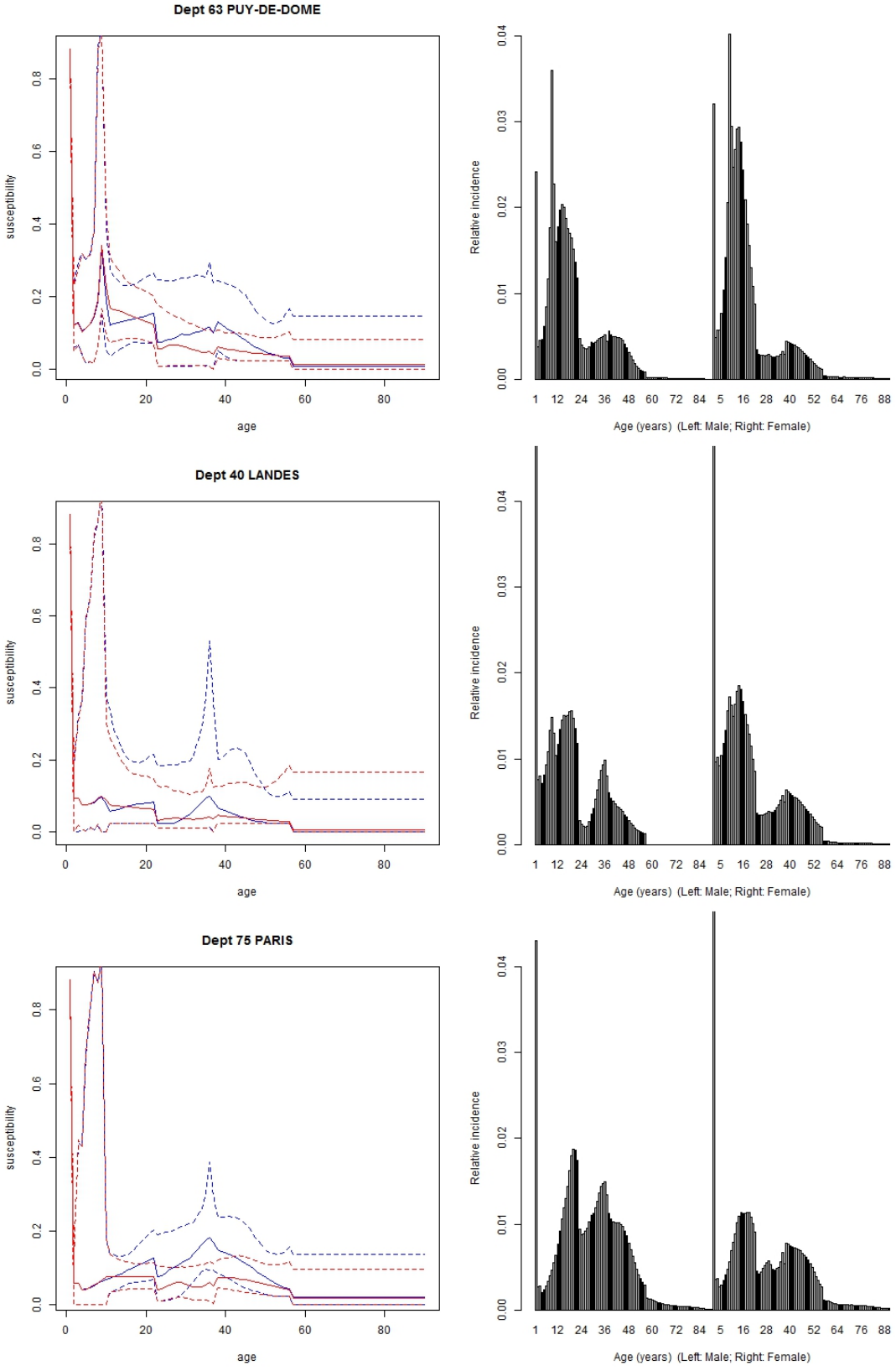


FIGURE 4.14: Rubella estimate of susceptible proportion (upper panel) and potential incidence according age (lower panel) in 3 departments (left: highest risk, centre: Lowest risk, right: Paris) in 2016, with ESEN-estimated waning rate for males (blue lines) and females (red lines). Age-dependent relative incidence is represented for males (left part) and females (right part) separately.

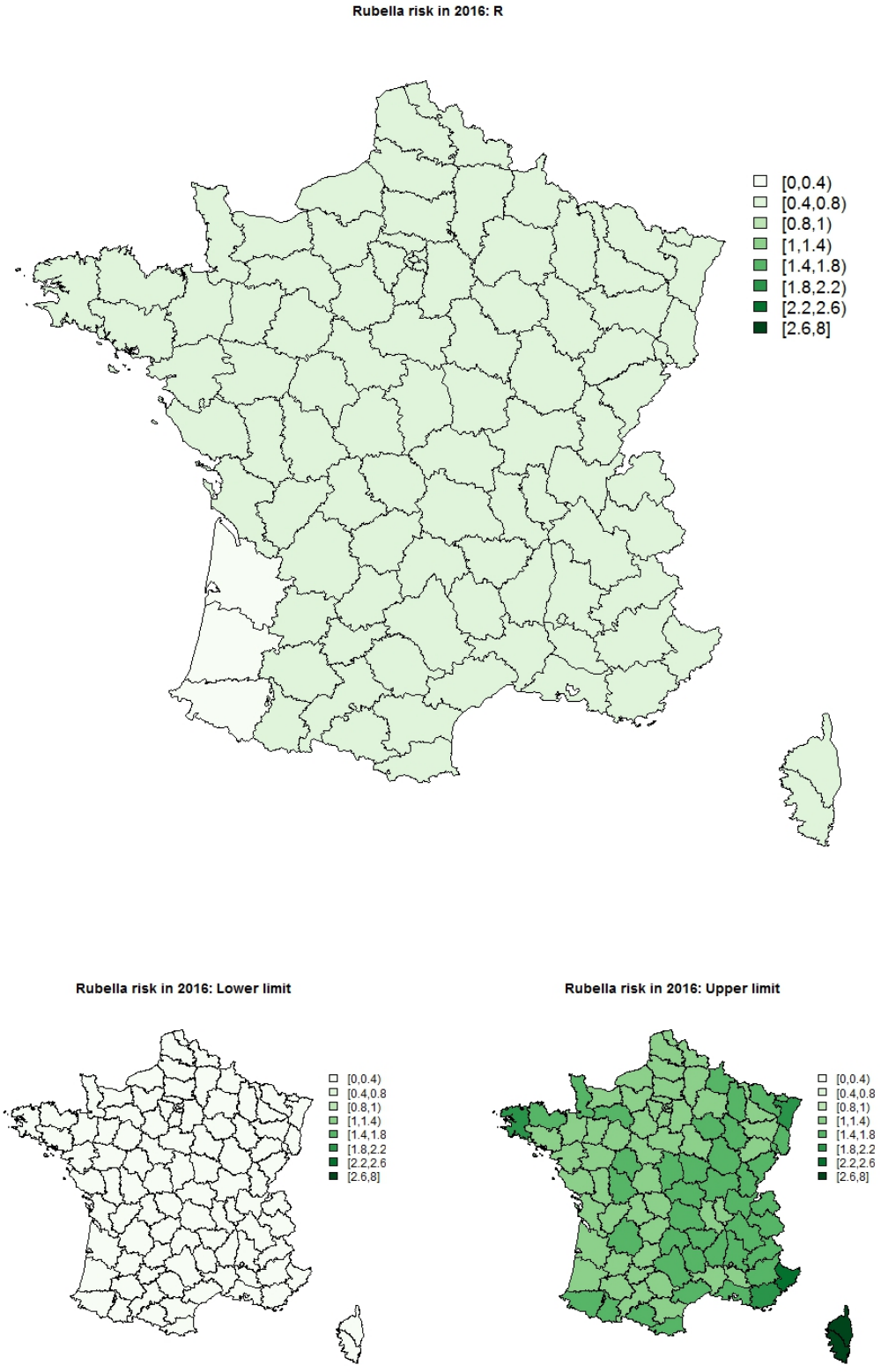


FIGURE 4.15: Rubella risk map in 2016 with a null waning rate, illustrating the estimation of the effective reproduction numbers R_e for each department (upper central), with lower (lower left) and upper (lower right) 95% confidence limits.

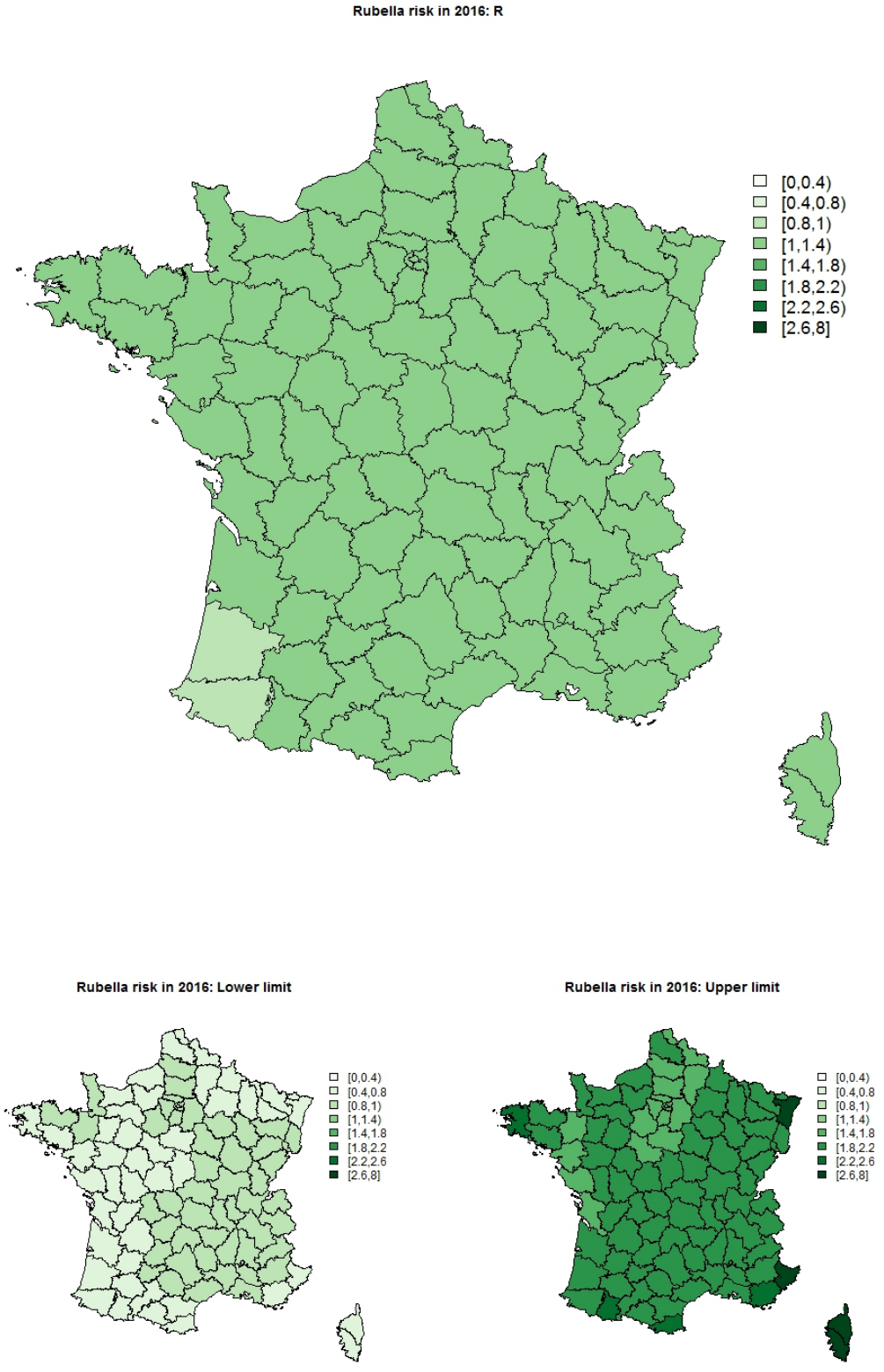


FIGURE 4.16: Rubella risk map in 2016 with a rate estimated with a fixed effect meta analysis, illustrating the estimation of the effective reproduction numbers R_e for each department (upper central), with lower (lower left) and upper (lower right) 95% confidence limits.

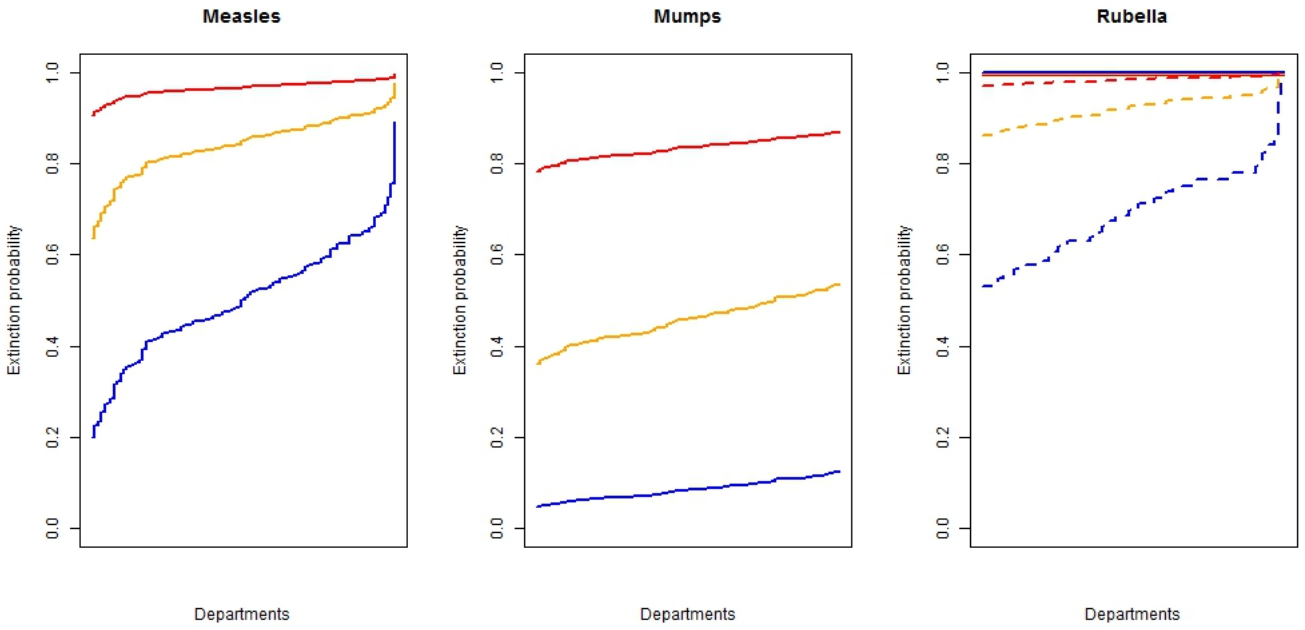


FIGURE 4.17: Escape probability for measles (left), mumps (center) and rubella (rigth), with a ratio of the variance to the mean at 1 (blue, rare super spreading events), 5 (orange, medium proportion of super spreading events) and 25 (red, numerous super spreading events). For rubella, ESEN based rates and null waning resulted in probability of extinction of 1, while with Fixed effect rates (dashed lines), outbreaks are possible with high escape probabilities nonetheless.

come from teenagers and young adults (10 to 25 years old) albeit with variation according to gender, pathogens and departments. We estimated the average age of disease onset to be :

- For measles: 22.1 years for men and 24.1 years for women.
- For mumps: 27.0 years.
- For rubella: 23.9 years for men and 22.6 years for women.

We also calculated the escape probability for each department and for each pathogen, and summarized the results in Figure 4.17. For rubella, with ESEN rates and null waning, departments have R_e estimates below 1 resulting in the escape probabilities equal to 1. Alternatively, for fixed effect estimated waning rates, escape probabilities are generally very high, underlining the very low risk of rubella re-emergence. On the contrary, escape probabilities for mumps are low, notably under the scenario of variance to the mean ratio low or medium, showing the high risk of a mumps outbreak. Escape probabilities for measles showed substantial heterogeneity between departments (from 19.8% to 89.1% in the scenario of a variance to mean ratio equal to 1).

4.4 Discussion

By combining information on vaccination coverage with available serological survey data, we were able to estimate the risk of re-emergence for measles, mumps and rubella, while accounting for gender and spatial differences in susceptibility and hence outbreak risk. We first showed that the 2010-2011 outbreak was predictable based on the information available at that time. One should note that a model predicts a risk for an outbreak, not the occurrence of an outbreak. Since all the departments had an upper limit of the confidence interval above 1, an outbreak could have occurred anywhere. Still, estimating the amplitude of the risk is useful, as it helps identifying the departments where more efforts have to be done to achieve an efficient protection.

Secondly, we showed that there remains a risk of a new measles outbreak in the French population, even if the susceptibility has decreased due to the recent measles outbreak. Indeed, to date, several new cases have been reported in the East of France, more precisely in Alsace. From the 199 cases reported in France during the first six months of 2015, 151 cases were observed in Haut-Rhin in mid-April, these individuals having contracted the virus during a school trip to Berlin, where the measles virus was circulating. Among the 146 cases with a known vaccination status, 136 were not vaccinated, and 9 had received only one dose. This recent, currently contained outbreak illustrates the current measles outbreak risk. The fact that this small-scale measles outbreak occurred in a department previously identified as having a small outbreak risk (Figure 4.7) could explain the rather limited expansion and containment of the epidemic. However, close to Haut-Rhin, the Haute-Marne and its neighbouring departments are much more at risk for a measles epidemic.

In addition, there is a risk for mumps and rubella outbreaks, with a clear predominance of mumps compared to the two others. The high risk of a mumps outbreak results from a less effective vaccine compared to measles and rubella, from the absence of a recent outbreak that would have increased the proportion of seropositive individuals in the population and, obviously, from high infectiousness reflected through higher values of the basic reproduction number R_0. On the contrary, the risk for rubella is relatively low, probably due to a lower level of infectiousness and a very effective vaccine. Concerning measles, even if the recent outbreak has increased the proportion of seropositives, the considerable infectiousness led to a persistent risk of re-emergence. Figure 4.17 showed that the predominant risk or resurgence mainly concerns mumps, is not negligible for measles, and is minimal for rubella.

Besides, one should keep in mind that the escape probabilities represent the risk for an outbreak to die out in case of one single infected subject. Introduction of more than one infected subject will decrease such probabilities. As an example, introduction of 10 measles-infected individuals in Haut-Rhin would result in an escape probability of 28.8%

(0.883^{10}) instead of 88.3% with one single individual (and a variance to mean ratio at 5).

The location of the department the most at risk for mumps and rubella overlaps as it concerned the south-east/south-centre of France, which can be explained by some of the lowest vaccination coverage, notably for the second dose. Departments at risk for measles are more scattered, probably due to the recent outbreak. That may appear as limiting the risk since the departments at risk will not be spatially clustered. However, the current sizeable flow of long-distance travelling individuals makes spatial proximity relative.

We showed a large risk for infants under one year of age, but also for teenagers and young adults, for the three diseases. This finding is of paramount importance, as complications are more frequent and more severe in these age groups. Indeed, the common knowledge about measles, mumps and rubella, considered as benign diseases, dates back to the pre-vaccine era, where the mean age of onset was 5-6 years, an age at which complication risk is substantially lower compared to risk at higher ages. However, the average age of onset has increased nowadays as observed during the last French measles outbreak [Antona et al., 2013] where the median age rose from 12 years to 16 years. It is consistent with our results on the mean age of onset in case of a future outbreak. Current reports of congenital rubella syndrome showed a mean age of 24 years, with almost 2/3 of the cases before 25 years, while the mean age for pregnancy in France was 30 years in 2010 (INSEE).

Our results suggest that an outbreak occurring during school holidays would have less chance to spread compared to regular days. This has already been observed, notably in the United Kingdom during the influenza A(H1N1)v pandemic [Flasche et al., 2011]. However, considering holidays as a proxy for school closures [Hens et al., 2009a] is also a way to estimate the impact of the latter on a potential future outbreak. However, school closures had to be timely set to be efficient [Davis et al., 2015] but that might be at a cost that would make them questionable [Keogh-Brown et al., 2010].

Therefore, the most efficient intervention to limit the risk of an outbreak would be to improve vaccination coverage notably for the second dose. Susceptibility was usually higher among males compared to females, which could be partially related to the initial use of monovalent rubella vaccine and then to MMR vaccine specifically among girls to protect them from rubella. Gender-specific differences in susceptibility highlight the interest to consider gender-specific vaccination strategies. Improving vaccination coverage among girls could be preferred as they have more contacts (Chapter 6) and may consequently be more likely to spread the virus, but increasing coverage among boys could be easier as it is the lowest. Moreover, the theoretical benefit of gender-specific vaccination strategies may nonetheless be counterbalanced by suboptimal acceptability by the general population or a negative effect on vaccination coverage. A recent study conducted

in a French school indeed suggests higher coverage for MMR vaccine among girls [InVS, 2007]. Girls received significantly more often the second dose than boys in 2001-2002 for 10-year-old children (measles: 58.9 vs. 54.7%; mumps: 54.6 vs. 49.7%: rubella: 58.8 vs. 54.4%). Vaccination was usually performed with a MMR vaccine (95.9%). However, there were no significant differences according to gender for 5-year-old and 14-15 year old teenagers in 2002-2003 (but numbers were not provided)[InVS, 2007]. The coverage at 24 months for the first dose, among children born in 2010, was 90,2% (F: 90,37% & M: 90,01%) and (71,32%) two doses (F: 71,75% & M: 70,96%).

Our findings also highlight the need for collecting better serological data, as data sparseness explains the wide confidence intervals. Moreover, interpretation of serology as a proxy for protection, as well as seronegativity as a proxy for susceptibility has been questioned. Indeed, mumps antibody levels among students before a mumps outbreak in Kansas University revealed that cases had lower titres than exposed subjects who did not develop mumps. But titres overlapped and statistically determined cut-off values did not separate all cases from the non-cases [Cortese et al., 2011]. Additionally, a recent study reported 2 physicians fully vaccinated who got infected by patients with measles, developed an atypical and mild form of measles diagnosed a posteriori, and did not transmit the disease despite providing care to more than 100 patients [Rota et al., 2011]. Therefore, it is possible that the probability of getting infected after a contact, and the probability of transmitting the disease could be correlated not only to the fact of being above or below a threshold, but also to the level of antibodies.

In our study, it is to be noted that we only considered seropositivity when titres were above the defined threshold, and patients with a positive serology (i.e. detection of antibodies) but with titres below threshold were considered as seronegative. An improvement to our approach could be to use a probability distribution of getting infected and/or transmitting the disease as a function of antibody level. However, it would require data which are currently unavailable. This highlights the difficulty of identifying a proxy for immunity based on antibody levels (and a dichotomization thereof).

Our study presents some limitations, notably as the age span for which seroprevalence was available was limited and narrower than in the Belgium studies. This underlines the need for better serological data with a wider age span in the cross-sectional sample. Vaccination coverage has an influence on the final result, hence, as the coverage information is already smoothed in a certain way, it can artificially influence the result, depending on the time span during which the coverage is used. A seroprevalence survey including individuals with a large age span would require vaccination coverage information for a very limited number of age categories and would thereby limit the influence of the vaccination coverage information on the result of the modelling.

Moreover, French guidelines about MMR vaccination also recommend a catch-up dose with MMR for unvaccinated children between 6 years and 13 years. Although it is

known to be poorly applied, we do not have precise information on the coverage of this catch-up dose. Therefore, we could not take it into account in our model, even though this catch-up could lower the risk of an outbreak.

AIC tends to choose the most complex model, contrary to BIC. We chose to select our model with AIC, first to be homogeneous with the choice made with the Belgian analysis but also because the French data are sparse, given the size of France relative to Belgium. In fact, BIC always chose the simplest model, which did not include geographical coordinates. Therefore, our data might be insufficient to fully satisfy the complexity of our model. In other words, it may be possible that we cannot see a large spatial effect given our data, thereby BIC will not select a model with a spatial effect. Our results should be interpreted in that context. In Belgian studies, the selected model usually used splines for smoothing instead of a tensor product. Spline smooths in a symmetrical way while tensor product smooths differently according to the direction. One could think that splines would be more logical for smoothing coordinates, but the tensor product frequently outperforms the spline fit in our modelling approach.

In addition to the known complications due to measles, a recent study showed that measles induced an immunomodulation predisposing to opportunistic infection for as long as 2-3 years [Mina et al., 2015]. Therefore, measles influence on mortality and morbidity goes beyond the direct mortality and morbidity usually attributed to measles. The notion of measles, mumps and rubella as benign diseases should be emended, and public health policy makers may use our findings to advocate for a better vaccination coverage to avoid future outbreak.

Chapter 5

Weather impact on mixing patterns

Besides modelling infectious diseases transmission, the study of contact matrices structure and the factors influencing it provides insights on elements driving infectious transmission. The findings presented in this chapter are to be submitted soon.

5.1 Introduction

Benefiting from one of the largest social contact surveys of its kind, the Comes-F social contact study was based on the reporting of contacts at different periods of the year. Mild variations in mixing patterns between the different study periods were shown. More precisely, participants tended to have more contacts during the last period (April-May) compared to the first period (February-March) (relative change:1.06[0.98-1.16]) though not significant. When including Supplementary Professional Contacts (SPC), the relative change was found to be significantly different from 1 (1.22[1.03-1.45]). Such variations may have resulted from seasonal differences, as the last period of the survey took place during Spring, while the first period took place during Winter. But it also could have come from the length of day [Witham et al., 2014](for which seasons may be a proxy), public holidays being more frequent during May than February-March or meteorological conditions (which may be a proxy for seasons). Recently, some authors have shown an association between meteorological conditions and mixing patterns [Chan et al., 2015, Willem et al., 2012]. Willem et al. [2012] used social data collected in Belgium in Winter in which variations of meteorological conditions may have been limited. But data sparseness limited the analysis to regular weekdays and median temperature, precipitation, and absolute humidity. Chan et al. [2015] used a similar approach to

explore the influence of tropical weather conditions on mixing patterns, which is also a climate with extreme conditions compared to temperate climate, with limited variations. We aimed to analyse the influence of meteorological conditions on mixing patterns described in the Comes-F study, during regular weekdays, but also during holiday weekdays and weekends (whether holidays or regular days), taking advantage of having a social contact study carried out over 2 different seasons, under a temperate climate. This analysis uses the methodology by Willem et al. [2012] to explain the influence of meteorological conditions on social contacts. The French contact survey having been conducted during 2 different seasons, we might expect a wider variation of meteorological conditions. Moreover, meteorological conditions being a proxy for seasons, we might get an insight on the potential influence of the season.

5.2 Methodology

We collected daily meteorological data from the National Oceanic and Atmospheric Administration (NOAA, http://www.noaa.gov/)(Section 2.6), according to 329 weather stations situated in metropolitan France, reporting mean daily values for temperature, dew point, sea and station level pressure, visibility, wind speed, maximum wind speed, minimum and maximum temperature, total precipitation, rain and fog. Participants and weather stations were mapped respectively by their postal code of residence and their spatial coordinates after conversion to Cartesian coordinates based on datum Lambert 93.

5.2.1 Matching weather data

Spatial coordinates of French municipalities were expressed according to the Lambert 93 projection with Cartesian coordinates. However, spatial coordinates of weather stations were expressed as a latitude and a longitude according to the datum WGS84. We transformed geographic coordinates (latitude and longitude) into spatial coordinates according to Lambert conformal conic projection, also known as the datum Lambert 93. Briefly, the isometric latitude L according to the latitude φ on an ellipsoid of first excentricity e was calculated as follows:

$$L = \ln\left(\tan\left(\frac{\pi}{4} + \frac{\varphi}{2}\right) \cdot \left(\frac{1 - e \cdot \sin\varphi}{1 + e \cdot \sin\varphi}\right)^{\frac{e}{2}}\right),$$

with e=0.08181919106 then, coordinates were calculated with the following formula:

$$X = X_s + c \cdot e^{-n \cdot L} \cdot \sin\left(n\left(\lambda - \lambda_c\right)\right),$$

$$Y = Y_s - c \cdot e^{-n \cdot L} \cdot \cos\left(n\left(\lambda - \lambda_c\right)\right),$$

with

λ : longitude with regard to the original meridian.

φ : latitude.

n : exponent of the projection (0.7279292).

c : constant of the projection (7064264).

λ_c : longitude of the origin with regard to the original meridian (0.05235988).

Xs, Ys : Pole coordinates for the projection (700 000, 12636341).

The R code for this conversion is available in Appendix C.

Selection of stations from metropolitan France (without overseas territories and buoys) with data available from 20 February 2012 to 30 May 2012 resulted in a subset of 211 stations. Each participant was matched with meteorological data from the weather station closest to his/her residence (Figure 5.1). The shortest distance between a residence as determined by the postal code and a station was determined by the Pythagorean theorem. The median (min; max) distance of a participant to closest station was 15540 (351; 75860) meters.

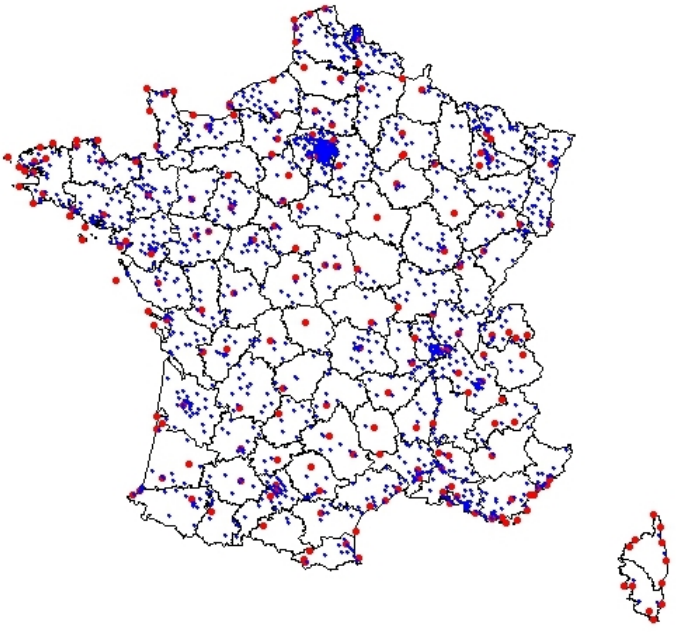


FIGURE 5.1: Stations (red dot) and participants (blue dot) repartition.

5.2.2 Preparing weather data

Fahrenheit degrees were converted into Celsius degrees ($Celsius = (Fahrenheit - 32) \times 5/9$). Among the various possible measures of absolute humidity, we chose vapor pressure, which was calculated from the mean air and dew point temperature according to Wallace et al. [2006]. The average relative humidity in France over a year being 68.5% (and >50%), relative humidity (RH) was calculated according to $RH = 100 - 5 \times (T - T_d)$ (under the condition RH>50%) with T the air temperature and T_d the dew point temperature. Then, saturation vapor pressure was derived from the temperature with the Clausius-Clapeyron relation $e_s(T) = e_s(T_0) \times e^{\frac{L}{R_v} \cdot \left(\frac{1}{T_0} - \frac{1}{T}\right)}$ with $e_s(T)$ saturation vapor pressure at temperature T, $e_s(T_0)$ saturation vapor pressure at the reference temperature (6.11 mbar), T_0 the reference temperature (273.13 K), L the latent heat of evaporation for water (2260 kJ/kg) and R_v the gas constant for water vapor (461.5 J/kg*Kelvin). Finally, absolute humidity (AH $\Leftrightarrow$ vapor pressure) was calculated with $AH = e(T) = e_s(T) \times \left(\frac{RH}{100}\right)$. Precipitations, expressed in inches, were transformed in centimeters ($centimeter = inches \times 2.54$).

5.2.3 Number of contacts and mixing patterns

The population of the study was split according to the day (regular weekday, holiday weekday or weekend) and the weather at the day the diary was filled in for. Diary weights for each sample were calculated according to the age of the participant, household size, weekend/weekday and regular vs. holiday period, using the French population in 2012 as reference (Eurostat). The mean number of contacts was calculated for all contacts, physical contacts only and for contacts at a specific location (home, school (for participants <18y), work and at other places) and of a specific duration (<15 min, >15 min, >1h, >4h). The potential for transmission was summarized by the basic reproduction number R_0 [Diekmann et al., 1990, Hens et al., 2009a]. The mean number of contacts and the R_0 were calculated for each sub-population in relation to a particular meteorological condition, and expressed as a ratio i.e. the relative change in the mean number of contacts and in R_0 associated with this particular meteorological condition. For consistency, we systematically divided the values of mean number of contacts and R_0 related to the sub-population with the highest values from the meteorological condition of interest by the lowest ones (e.g., mean number of contacts associated with high temperatures divided by mean number of contacts associated with low temperatures). The reciprocal nature of contacts was assumed for all situations with the exception of contacts at a specific location. A non-parametric bootstrap was done re-sampling participants 2000 times to calculate the 95% confidence intervals. The precise methodology is described in

Chapter 3. We looked at temperature, absolute humidity, and rain (absence/presence). Significance levels were corrected for multiple testing using a Bonferroni adjustement [Dunn, 1961]. We also looked at other weather variables such as sea level pressure, visibility, wind speed, maximum wind speed, maximum and minimum temperature and fog. In addition to variation around the median, we also looked at the variations around the first quartile and the third quartile. Thereby, quartiles (0.25,0.5,0.75) were used as thresholds for weather data to differentiate very low (< first quartile), low (below median), high (above median), very high (> third quartile). Contacts made at place number 3 (Appendix A) for children represented summer camps or residential schools, but was usually associated with results similar to "other" places, and was then merged with "other" places. In this analysis, supplementary professional contacts were not taken into account, for consistency with Willem et al. [2012]. They were modelled contacts, might have represented contacts of a lesser importance for the transmission of infectious diseases and added a considerable weight to workplaces, which would have been difficult to interpret. Considering there were only 115 adults over 18 years under education, and only two over 25 years, school contacts in the following analysis concerned only children. Contacts made at school by adults were included in the "other" places category for the analysis concerning regular weekdays, but not for holiday weekdays and weekends.

5.3 Results

The general description of the weather observed at the time of the study is described in Table 5.1. Taking the latitude (6,702,040 m) of Tours as a boundary, Table 5.2 describes the weather differences between North and South, while Table 5.3 describes the weather according to the Design and Actual periods where participants reported their contacts. Fog was reported for 377 days over 4066 reporting days, rain for 2183 days, snow for 42 days, hail for 76 days, thunder for 146 days and no days of tornado were reported. Thus, we did not analyse the effect of snow, hail, thunder or tornado. There was a significant relationship between holidays and weather variables ($p<0.001$ for temperature, absolute humidity or rain and holidays, and for temperature and weekends)(Student t-test or Chi-square test). Due to this interaction, we had to analyse the effect of weather by separating our data set according to holidays and weekend, thereby eliminating a confounding effect. We initially considered the impact of the weather condition on the number of contacts and the mixing pattern during regular weekdays, and then during holiday weekdays and weekend (whether regular or holidays). Due to data sparseness, we did not split the weekends according to holidays or regular days.

Variable	Min.	1st Quart.	Median	Mean	3rd Quart.	Max.	Missing values
Temperature (°C)	-2.17	7.39	9.06	9.11	11.10	23.83	266
Max. temperature (°C)	0.39	11.61	13.50	14.06	16.22	30.22	266
Min. temperature (°C)	-9.00	2.78	5.22	4.74	7.28	17.89	266
Absolute humidity (mbar)	1.87	7.27	8.54	8.44	9.69	16.36	295
Mean wind speed (kn)	0.5	4.4	6.7	7.5	9.8	55.5	273
Max. sustained wind speed (kn)	1.9	8.9	13.0	13.7	18.1	64.9	273
Mean sea level pressure (mbar)	985.0	1001.0	1008.0	1009.0	1016.0	1037.0	2105
Mean station pressure (mbar)	827.0	980.9	991.9	990.0	1003.0	1035.0	2074
Mean visibility (mi)	0.2	6.8	8.2	9.5	11.3	43.5	535

TABLE 5.1: Description of the weather during the time of the study. Values were rounded to 2 decimals except when provided with only one decimal in the original dataset from NOAA.

Variable: median (IQR)	North	South
Temperature (°C)	8.33(2.89)	9.89(4.10)
Max. temperature (°C)	12.72(3.61)	14.72(5.11)
Min. temperature (°C)	4.89(4.06)	5.78(5.11)
Rain (%)	61.9	53.0
Absolute humidity (mbar)	8.45(1.98)	8.69(2.74)
Fog (%)	11.0	8.8
Mean wind speed (kn)	7.0(5.0)	6.5(5.7)
Max. sustained wind speed (kn)	12.0(8.0)	14.0(9.2)
Mean sea level pressure (mbar)	1005.8(18.7)	1008.8(10.2)
Mean station pressure (mbar)	993.7(21.6)	990.0(27.7)
Mean visibility (mi)	8.2(4.6)	8.3(4.7)
Snow (%)	1.1	1.1
Hail (%)	2.8	1.2
Thunder (%)	3.8	3.9

TABLE 5.2: Weather differences between North and South at the time of the study. Values were rounded to 2 decimals except when provided with only one decimal in the original dataset from NOAA.

5.3.1 Influence of temperature, absolute humidity and rain

REGULAR WEEKDAYS:

Influence of temperature, absolute humidity and rain during regular weekdays are graphically represented in Figure 5.2.

Temperature: Temperature did not significantly influence number of contacts or R_0, but there was a trend for more contacts at home and in other places, more contacts of long duration and a higher R_0 at home for high temperatures.

Absolute humidity: High absolute humidity was associated with a higher mean number of contacts at home (1.172[1.009;1.359]), a similar trend in other places, and higher R_0 at home (1.181 [1.006; 1.381].

Variable: median (IQR)	Design Period 1	Design Period 2	Actual Period 1	Actual Period 2	Actual Period 3
Temperature (°C)	7.89(4.83)	9.50(3.94)	6.44(5.35)	9.78(3.17)	9.50(3.94)
Max. temperature (°C)	12.10(4.50)	14.10(4.50)	11.00(3.78)	15.20(4.72)	14.10(4.50)
Min. temperature (°C)	3.00(6.61)	5.78(3.89)	1.83(7.72)	4.89(4.97)	5.78(3.89)
Rain (%)	31.9	71.6	27.0	42.9	71.6
Abs. humidity (mbar)	7.57(3.34)	8.75(1.73)	7.11(3.73)	8.14(2.69)	8.75(1.73)
Fog (%)	19.3	4.8	24.5	7.3	4.8
Mean wind speed (kn)	4.6(3.6)	8.1(5)	4.2(3.7)	5.5(3.3)	8.1(5.0)
Max. Wd speed (kn)	8.9(5)	15.9(7.9)	8(5.1)	11.1(5.1)	15.9(7.9)
Mean SLP (mbar)	1025.0(19.3)	1005.0(12.7)	1028.0(5.7)	1008.0(3.8)	1005.0(12.7)
Mean STP (mbar)	1006.0(24.1)	988.0(19.8)	1016.0(17.5)	995.0(22.9)	988.0(19.8)
Mean visibility (mi)	6.7(3.2)	9.2(4.7)	6.5(3.2)	7.4(3.9)	9.2(4.7)
Snow (%)	0.2	1.6	0.3	0.0	1.6
Hail (%)	0.1	3.0	0.1	0.2	3.0
Thunder (%)	1.4	5.2	0.0	4.6	5.2

TABLE 5.3: Weather statistics according to design and actual periods. Values were rounded to 2 decimals except when provided with only one decimal in the original dataset from NOAA. SLP: Sea Level Pressure, STP: Station Level Pressure, Max. Wd speed: Maximum Sustained Wind Speed.

Rain: Mean number of long duration contacts tended to increase with rain. R_0 increased with rain for all contacts (1.248[1.040; 1.468]), long-duration contacts (>15 min: 1.391[1.815; 1.110] ; >1h: 1.563[2.237; 1.122]), with a trend for physical contacts and contacts at school and other places.

WEEKENDS:

Temperature: Low temperature was significantly associated with more contacts (1.206[1.026; 1.444]) and higher R_0 (1.222[1.011; 1.477]) at home and a trend toward more contacts of longer duration.

Absolute humidity: Low absolute humidity was associated with more physical contacts (1.180[1.007; 1.360]), and with a trend for more contacts and higher R_0 for all types of contacts.

Rain: Mean number of contacts tended to increase with rain for all types of contacts, and significantly for all contacts (1.153 [1.005; 1.323]), short contacts <15 min (1.305 [1.001; 1.686]) and contacts in other places (1.302 [1.056; 1.610]. R_0 also tended to increase with rain for all types of contacts (all contacts: 1.176 [0.995; 1.397]) but significantly for contacts in other places (1.389 [1.030; 1.821]).

HOLIDAYS WEEKDAYS: Temperature, absolute humidity and rain were not significantly associated with changes in number of contacts and R_0. The mean trend estimates appear

to be half way between the mean trend estimates for regular weekdays and for weekends.

Influence of weather conditions on the mean number of contacts and R_0, uncorrected for multiple analyses, for variation around Q1 and Q3 in addition to the median, and for other meteorological variables (sea level pressure, visibility, wind speed, maximum wind speed, maximum and minimum temperature and fog) are presented in Appendix E.

5.3.2 Impact of weather on the number of contacts with regard to other variables

The analysis in Chapter 3 showed the influence of age, household size, gender, weekend, holidays, and occupation with generalized estimation equations. We used this basic model to which we added and tested each weather variable one by one to assess their influence in comparison to known influencing variables. In addition to the influence of the level of the variable on the number of contacts (very low, low, high ...), we wanted to assess the influence of medium values compared to extreme values. Each weather variable has been discretized as a qualitative variable with 3 levels (< first quartile / within the inter-quartile range / > third quartile) and with 2 levels (within the inter-quartile range / out of the inter-quartile range). No weather variable was found significant when introduced in the GEE, although there was a trend for more contacts with p=0.07 for sea level pressure within the IQR, and p=0.09 for rain (Figure 5.5). The results were similar when applied to the sub-group of common participants for Periods 1 & 2 of the Comes-F study. To assess the effect of each weather variable, we represented their influence on the residuals of the basic model (Figure 5.6). The impact of the weather variable was smoothed with a loess smoother [Cleveland et al., 1992]. None of the variables were associated with a clear increase as shown by the flatness of the loess curve. However, heterogeneity seemed more important when the weather variable was within the inter-quartile range.

5.4 Discussion

The main result of our study is that there is a differential effect of weather on social mixing according to the type of day, notably weekdays and weekends, which was already suggested by Chan et al. [2015]. Differences with Willem et al. [2012] should be interpreted with caution considering that their dataset was analysed only for regular weekdays. In Willem et al. [2012], weather had no effect on total number of contacts

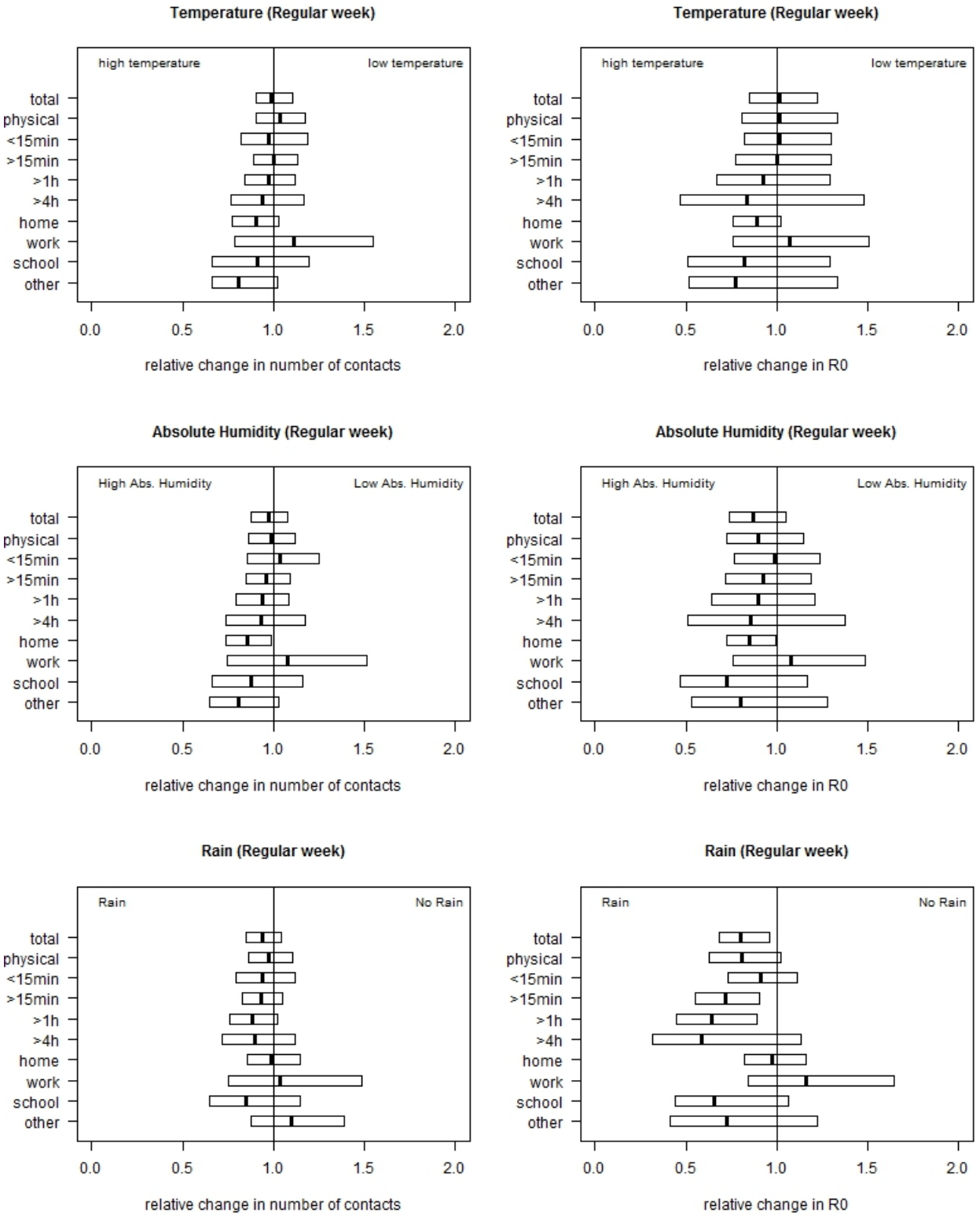


FIGURE 5.2: Influence of temperature, absolute humidity and rain on the number of contacts and R_0 during regular weekdays.

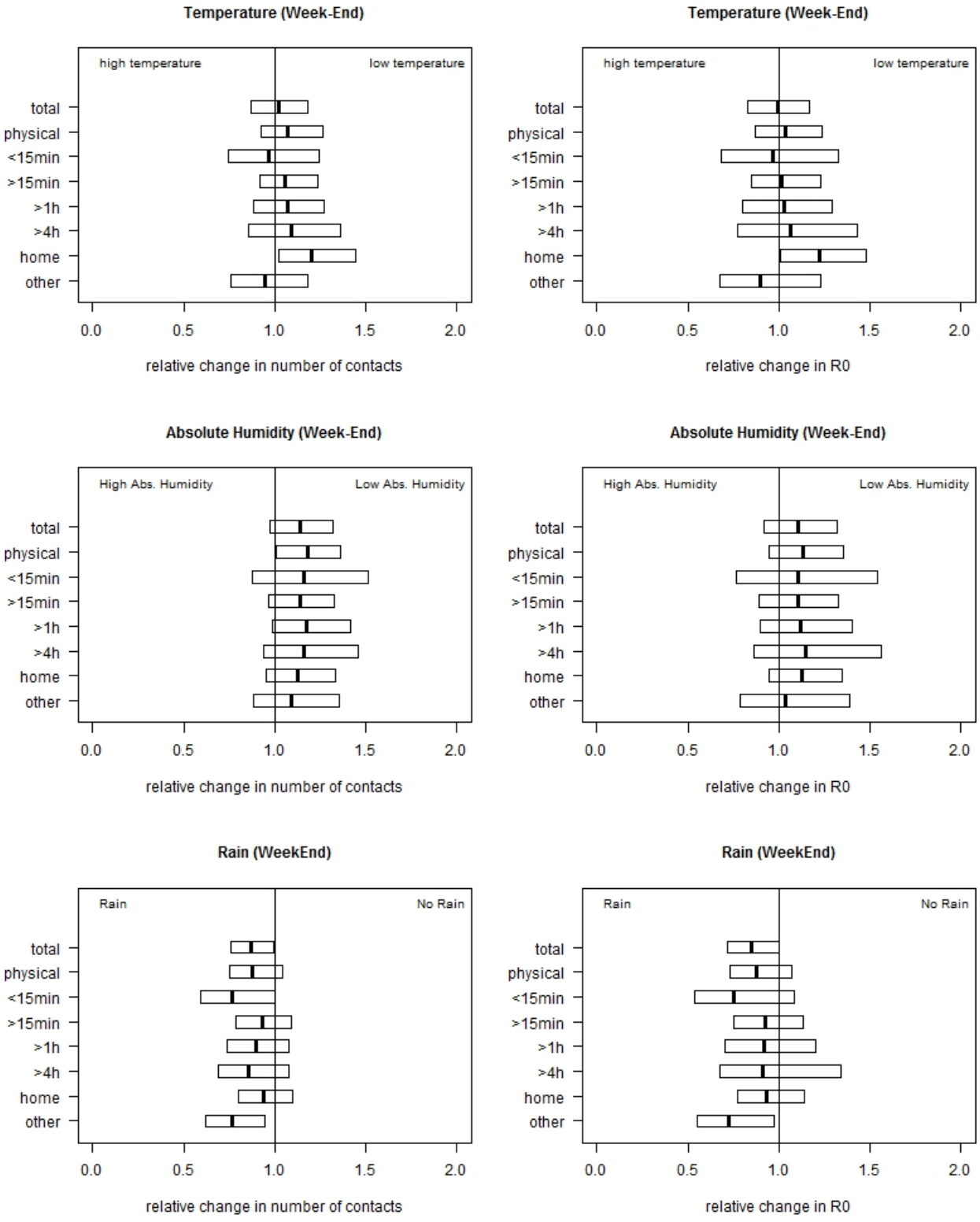


FIGURE 5.3: Influence of temperature, absolute humidity and rain on the number of contacts and R_0 during weekends.

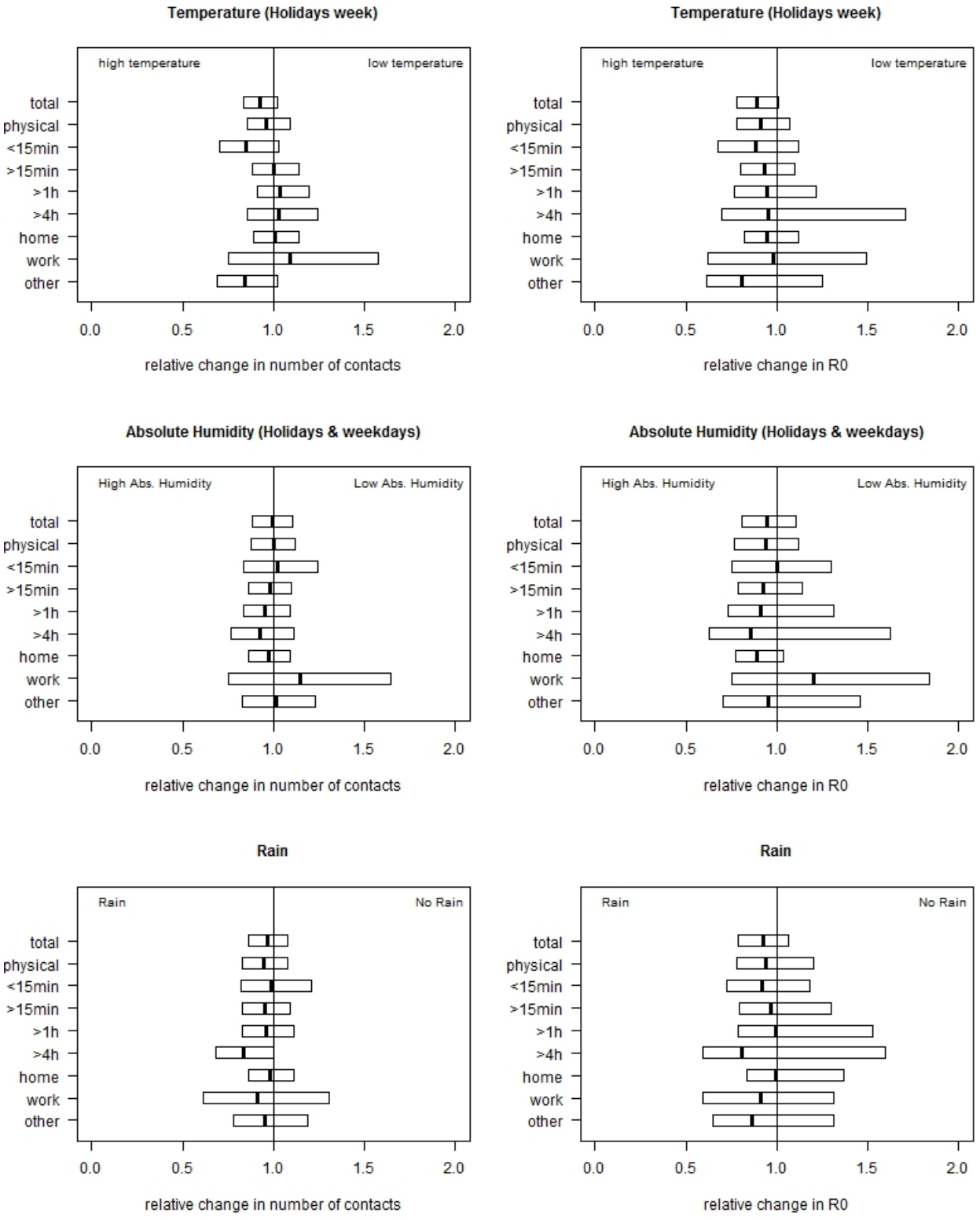


FIGURE 5.4: Influence of temperature, absolute humidity and rain on the number of contacts and R_0 during regular holidays.

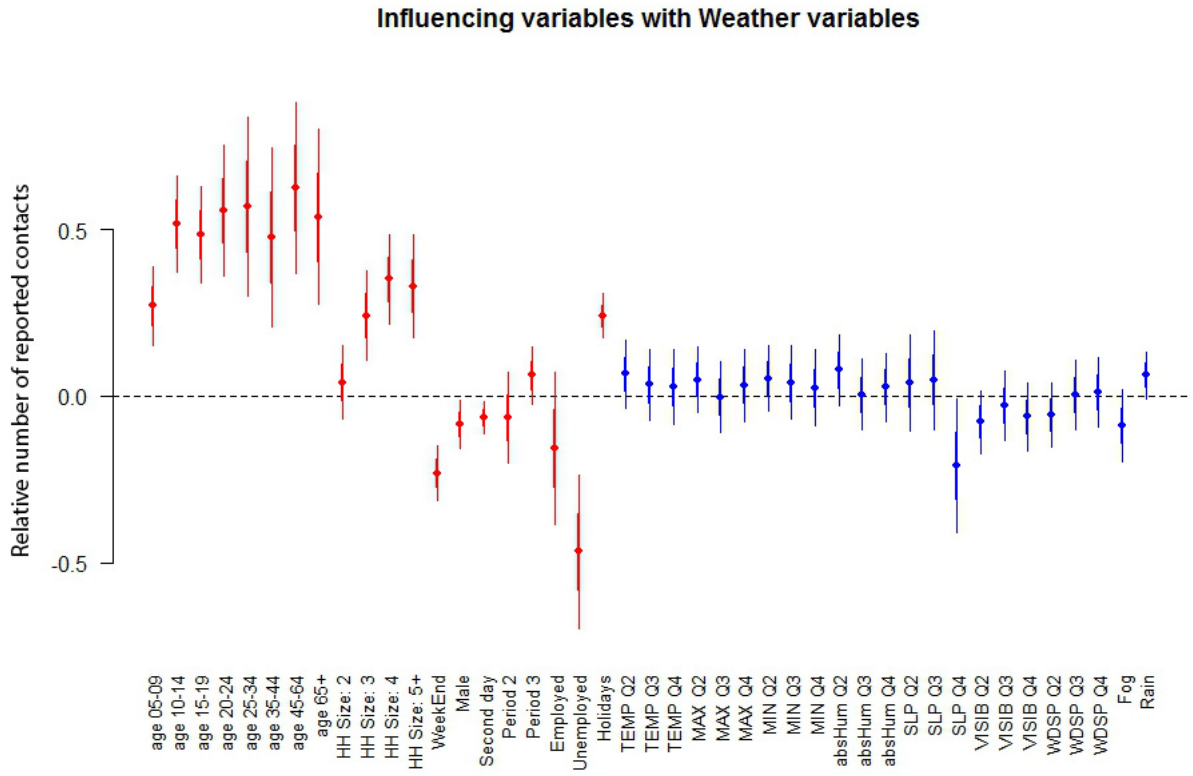


FIGURE 5.5: Influence of weather variables in comparison with variables from the basic model.

but on contact duration; low temperature was associated with more long-duration contacts and less contacts in other places. In our study, low temperature was associated with less long-duration contacts and contacts at home during regular weekdays, but more of them during weekends. Likewise, low absolute humidity was associated with less contacts in other places in Willem et al. [2012]. However, in our study, low absolute humidity was associated with less contacts, in particular at home and in other places during regular weekdays but more contacts of all types, notably physical contacts, during weekends. Low precipitation was associated with more long-duration contacts and contacts at school in Willem et al. [2012]. On the contrary, in our study, absence of rain was associated with a trend toward less contacts in both weekdays and weekends, but significantly for short contacts and contacts in other places only during weekends, and long-duration contacts only during regular weekdays. Our results present some similarities with Chan et al. [2015], as they also showed some differences between weekdays and weekends, as well as a trend toward less contacts in other places with low temperature during weekdays (similarly to Willem et al. [2012]), and a trend toward more contacts (during holidays) with high temperature and absolute humidity. However, none of these 2 studies corrected for multiple testing, therefore limiting the comparison. Other meteorological variables (Appendix E) also tended to have a differential effect according

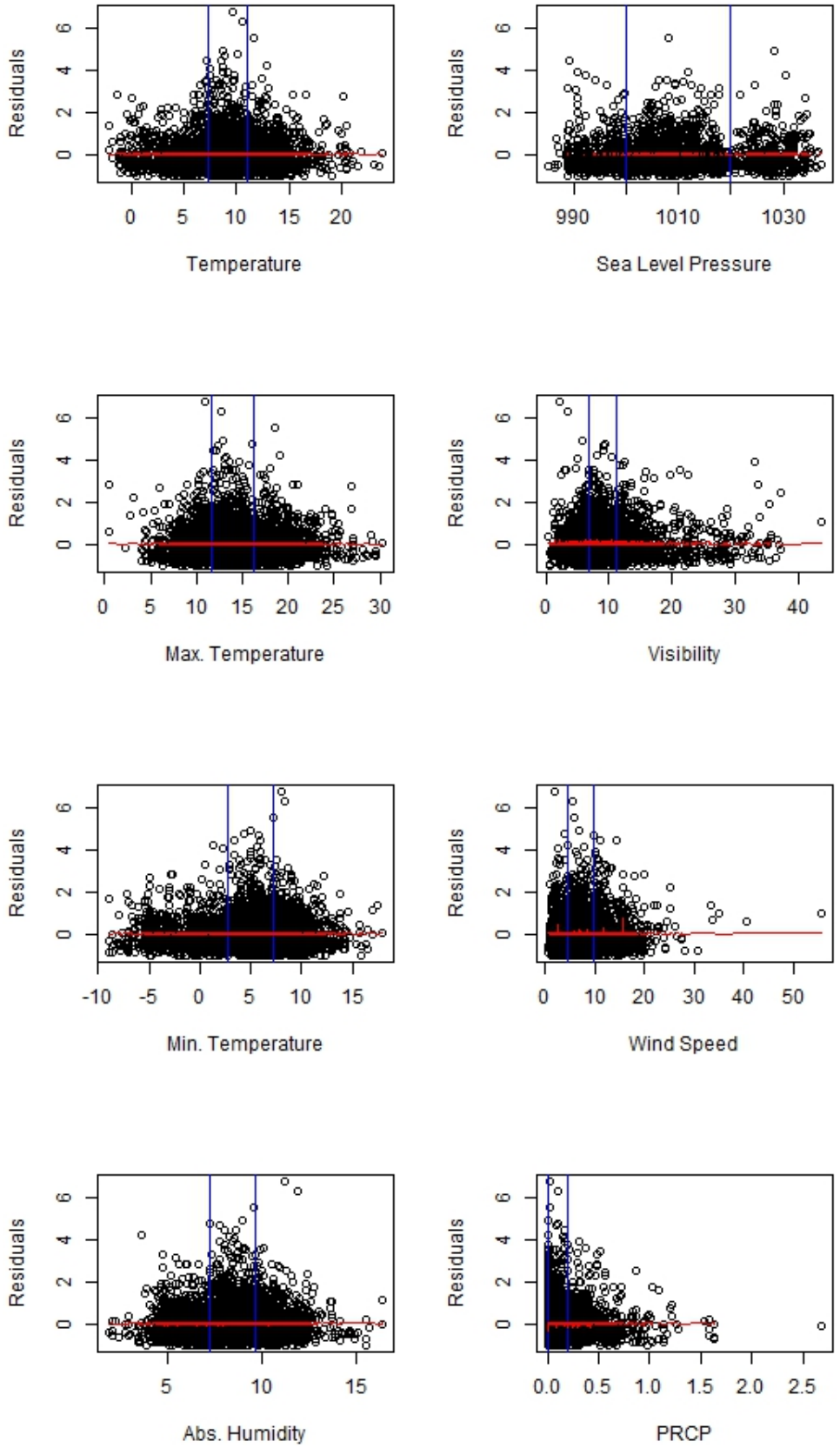


FIGURE 5.6: Influence of weather variable on the residuals of the basic model. The red line represents the loess curve.

to weekdays and weekends. Indeed, high wind speed, low sea level pressure and high visibility were associated with more long duration contacts during weekdays (regular & holidays) and short-duration contacts during weekends. Besides, a decrease for contacts of all types was found associated with fog during weekdays but not weekends, but an increase with high wind speed during weekends but not weekdays, and with high visibility only during holidays and weekends. Low sea level pressure was associated with an increase in the number of contacts at school and R_0 in other places only during regular weekdays. In general, holiday weekdays showed an effect similar to regular weekdays, or intermediary between regular weekdays and weekends.

Weather conditions have been widely advocated to explain the seasonality of some infectious diseases, notably influenza. Indeed, aside from transmission through direct physical contacts with infected individuals and transmission via fomites, influenza is supposed to be transmitted via droplets expelled from infected individuals by coughing before reaching a susceptible person or via airborne transmission via expelled small particles, referred to as droplet nuclei, which remain suspended in air for extended periods of time and allow influenza transmission without contacts between infected and susceptible individuals. Dry air enabling a partial evaporation of the droplets would facilitate their conversion into droplet nuclei and their likelihood to stay airborne, thereby increasing the potential for transmission to a susceptible individual [Shaman and Kohn, 2009]. Moreover, cold and dry air is a favourable condition to the lipid envelope of the virus and increases its stability for airborne transmission [Lowen et al., 2007]. Therefore, weather conditions would explain that seasonal influenza occurs in wintertime in temperate regions. However, it does not explain the fact that influenza occurs throughout the year in tropical (hence with warm air with elevated absolute humidity) regions, although its incidence may increase during a rainy season, which contrasts with influenza dynamics in temperate regions [Viboud et al., 2006]. Therefore, the impact of weather conditions on mixing patterns has been suggested to explain influenza seasonality, in addition to variations on virus survival and host immunity [Tamerius et al., 2011]. Individuals spending on average two more hours per day indoors during cold days may increase their contact rates, which would suggest indoor crowding during winter as a key factor [Graham and McCurdy, 2004]. A significant decline in the number of contacts among school children during rainy days could also play a role [Mikolajczyk et al., 2008]. Through various mechanisms such as indoor crowding during wintertime, decreased ambient temperature, indoor heating, air travel, bulk aerosol transport, social interactions are then supposed to produce oscillations in influenza incidence [Lofgren et al., 2007]. However, the first study to systematically analyse the influence of weather conditions on mixing patterns was Willem et al. [2012], soon followed by Chan et al. [2015]. Considering that meteorological conditions are probably a proxy for seasons, it may be difficult

to distinguish a respective and separate role of weather and season (or more generally temporality). An aspect to consider for further study would be the length of day as it has proved to influence the social life of elders [Witham et al., 2014], it is correlated only to seasons and not with weather and therefore an influence of the length of day significantly more important than meteorological conditions may help to distinguish the influence of weather and temporality.

But we also found that the impact of weather on social mixing was mild, if not negligible, compared with other variables such as age, household size, gender, weekend, holidays, and occupation. Moreover, beyond some similarities with the results from Willem et al. [2012] and Chan et al. [2015], many differences appear. An obvious explanation would be that Belgium in winter and tropical weather in Taiwan are very different from the temperate climate of France in winter and spring. Indeed, Chan et al. [2015] reported a mean average daily temperature of 26.3°C while Willem et al. [2012] reported a median daily temperature of 6.83°C, respectively higher than our maximum value and lower than our first quartile. Moreover, mean number of contacts being superior in Belgium and in Taiwan could express an ontological difference in social mixing patterns as well as the consequence of methodological differences in the estimation of mixing patterns (Chapter 3). Nonetheless, the statistically significant results emerging from the three studies should not hide the considerable heterogeneity of the results within and between each study. We cannot exclude the possibility the weather does not really impact mixing patterns, notably as neither Willem et al. [2012] nor Chan et al. [2015] adjusted the significance level for multiple testing. In that sense, our study was the first to take into account multiple analyses. Moreover, the remaining results after correction for multiple testing as well as the differences with Willem et al. [2012] and Chan et al. [2015] highlight the fact that the most important result of our study is the differential effect of weekdays and weekends more than the particular effect of a particular weather condition on a particular type of contact. Moreover, it is also possible that individuals do not modify their behaviour according to day to day changes in weather conditions, but rather according to general trends on a weekly or monthly basis or even according to the general climate of the location. In other words, individuals from the Mediterranean part of France are supposed to have frequent outdoor social activities in the evening, known as part of the Mediterranean culture, which contrast with individuals from the northern part of France who would favor more indoor social life. What is considered as part of the local culture could simply reflect an adaptation to the local climate. Therefore, the impact of the weather on mixing patterns would depend not on the daily weather but more on the general trend. However, in that case, it seems extremely difficult to link highly precise data such as the daily number of contacts and the mixing pattern according to location and duration with aggregated data such as meteorological trends

for a region, a department or a town. Our results also showed that considering the variation around the 25th percentile and the 75th percentile could be more informative than just considering the variation around the median as did Willem et al. [2012] and Chan et al. [2015]. Trends toward "medium" values appeared, as opposed to extreme values lower than first quartile and higher than third quartile. This would support the idea that weather variables would be a proxy for some "comfort" zone were contacts would more frequent and/or of longer duration. But, it would be extremely difficult to study how various weather variables would represent comfort or discomfort. Advanced statistical techniques such as quantile regression may be able to identify such an effect, but would also probably require larger sample sizes, which might not be the case in our study. However, we presented in Figure E.24 (Appendix E) some preliminary results illustrating the fact that weather variables such as temperature, but also variables such as weekend had an effect on the number of contacts different according to the average number of contacts made by a participant. As an example, an housewife having contacts almost only within her household will barely decrease her average number of contacts according to temperature or weekend, while an employed individual with a high average number of contacts will certainly decrease his number of contacts, notably during weekend. Nonetheless, several studies have suggested that human behaviour could vary according to the comfort coming from the environment. With mobile phone use data, a recent study highlighted the influence of (presumably) uncomfortable weather conditions (very cold/warm ...) as individuals tend to communicate with fewer social ties, favouring strong ties [Phithakkitnukoon et al., 2012]. Moreover, when temperature fell or air pressure increased, the likelihood of longer calls increased. In addition, gender differences were reported in the perception of thermal comfort, females being more sensitive to temperature, and less sensitive to humidity [Karjalainen, 2007, Lan et al., 2008]. Our study presents some limitations, however. Among possible biases, differences in the absolute number of contacts could have a role as the average number of contacts per participant was higher in Belgium and Taiwan than in France. It could possibly result from a difference in the methodology of the studies (e.g. household-based survey for Chan et al. [2015]) or from a real difference in the behaviour between those countries. Another limitation is that, despite being one of the largest population surveys of its kind, our data may be considered as scarce with regard to the size of France. Furthermore, we may simply have not chosen the most relevant meteorological variables to explore. It may be of interest to explore other variables such as the length of day [Witham et al., 2014], daily range of the previously explored variables Chan et al. [2015], solar radiation [Hervás et al., 2015, Tamerius et al., 2011].

In conclusion, we suggest that weather may have an influence on mixing patterns, but in a limited way, compared to the requirements of the everyday life (e.g. work for adults and

school for children). The difference between weekdays and weekends could represent the lesser requirements during the weekend. More probably, it suggests that weather simply boosts the natural difference of behaviour between weekdays and weekend. Therefore, it highlights the importance of taking into account weekends and holidays in social contact studies and in mathematical epidemiology.

Chapter 6

Gender differences

Epidemiological studies have reported gender differences in morbidity and mortality for many infectious diseases, usually suggesting gender differences in immunity as a mechanism. Gender being identified as a factor influencing the number of contacts in the Comes-F study, we hypothesize that differences in the social mixing patterns could partly explain gender differences in morbidity and mortality. We briefly describe the role of the immune system in gender differences, and then, other mechanisms not related to the immune system as well as behaviour and bias. After which, we conducted a systematic review about gender differences specifically in influenza, measles, mumps and rubella, with regard to the subject of this thesis on directly transmitted infectious diseases, focusing on what could have an impact on the transmission of infectious diseases and their epidemiology. We will not develop the aspect of gender differences in pharmacokinetics or therapeutics, neither for other kind of infectious diseases such as HIV or tuberculosis. This review aimed at identifying epidemiological differences in morbidity and mortality according to gender, and which mechanisms were identified to explain such differences. Finally, we provided an exploration of the impact of gender on mixing patterns, and eventually the potential implication for modelling.

6.1 A literature review

Differences in epidemiology and the response to infection between males and females have been reported for many diseases [Klein and Roberts, 2015]. Women appear more resistant and less susceptible to infections, notably between puberty and menopause, but the price to be paid is they are more likely to develop autoimmune diseases during the same period [Bouman et al., 2005, Gleicher and Barad, 2007, Klein, 2000]. Therefore, a difference in immunity between males and females seems an obvious mechanism

to explain differences in the response to infection, and has been the main explanation proposed so far, while differences in behaviour and bias had been frequently discussed but much less studied. Conducting a search in Pubmed with the MESH term "Influenza" + "Sex" resulted in only one study, while "Measles", "Mumps" or "Rubella" + "Sex" resulted respectively in 2, 2 and 4 very old studies, totally irrelevant to our topic of interest. Consequently, we decided to conduct a review of all studies dedicated to Influenza [*("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields])*], Measles [*("measles"[MeSH Terms] OR "measles"[All Fields])*], Mumps [*("mumps"[MeSH Terms] OR "mumps"[All Fields])*] or Rubella [*("rubella"[MeSH Terms] OR "rubella"[All Fields])*] with the filters for clinical studies dedicated to human of all ages written in English [*("humans"[MeSH Terms] AND English[lang] AND ("female"[MeSH Terms] OR "male"[MeSH Terms]) AND jsubsetaim[text] AND (("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms]) OR "adult"[MeSH Terms] OR "infant"[MeSH Terms] OR "adult"[MeSH Terms:noexp] OR "aged"[MeSH Terms]))*], without restriction of time for the search. In addition we also included in our review numerous references provided by the book "Sex and gender differences in infection and treatments for infectious diseases" by Sabra L. Klein and Craig W. Roberts ([Klein and Roberts, 2015]), the third supplement of the Journal of Infectious Diseases (Volume 209 suppl 3 July 15, 2014) "Sex Differences in the Manifestations of Infectious Diseases" and the WHO report "Sex, gender and influenza" ([World Health Organization, 2010]). The articles were screened by title and abstract in order to identify studies reporting incidence of influenza, measles, mumps or rubella according to gender. Then, full text were obtained to select articles reporting age-stratified gender or at least one age category. We present the flow chart of our systematic literature review in Figure 6.1.

6.1.1 Gender differences in immune response

Briefly, an efficient immune response initially requires a detection of the pathogen, mediated by the recognition of pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs), among which the Toll-like receptors are most often described. After this mandatory stage for triggering immune response, the first line of defence to protect the host from a pathogen is the innate immune system, which provides non-specific protection. Monocytes and neutrophils can phagocytize pathogens directly, but innate immune cells are also able to "digest" pathogens and to present some antigens to naive T lymphocytes to generate an adaptive immune response. Adaptive immunity comprises humoral and cellular immunity, involving T and B lymphocytes,

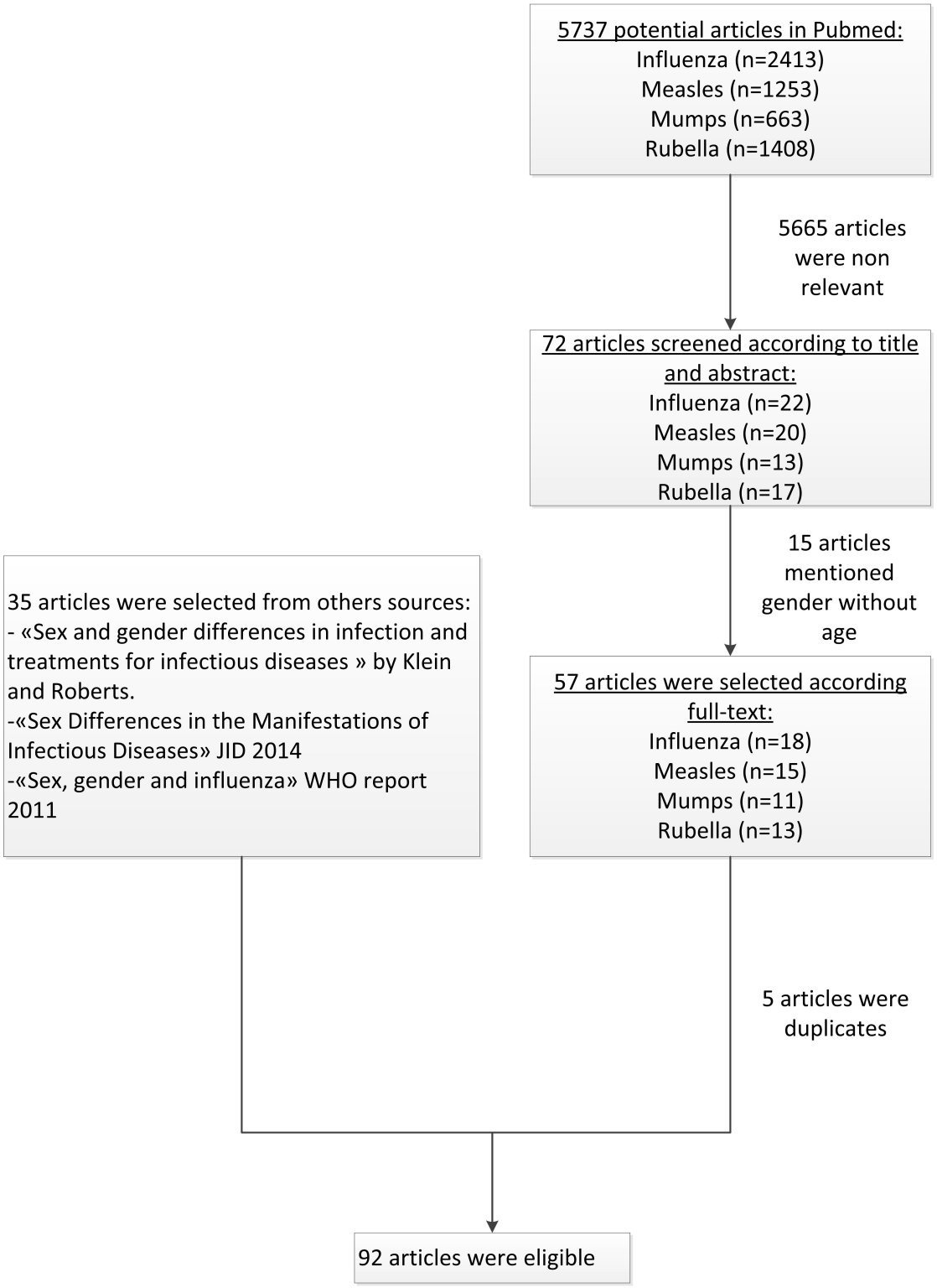


FIGURE 6.1: Systematic review on the influence of gender on the incidence of influenza, measles, mumps and rubella.

and provides a specific immune response, notably through the production of antibodies, but also enhances the bactericidal activity of innate immunity. The production of antibodies is mainly devoted to B lymphocytes, while T lymphocytes, through the production of cytokines, orchestrate immune response. It can be roughly divided into a Th1 and Th2 response. Th1 is the pro-inflammatory response, mainly mediated by interferon gamma. To counteract a potential excessive pro-inflammatory response, the Th2 response modulates the Th1-mediated microbicidal action.

Gender differences have been observed in pathogen recognition. The best known example concerns HIV-1 [Meier et al., 2009], as females express more pathogen-associated microbial pattern recognition (PAMP) receptors, such as Toll-like receptors, which would favor females to trigger an immune response to specific pathogens.

Moreover, immune response is stronger for females compared to males [Bouman et al., 2005]. Innate immunity presents different profiles according to gender. Males present higher monocyte count in circulation compared to females [Bouman et al., 2004], but a lower natural killer T lymphocyte count [Kee et al., 2012]. In addition to absolute counts, the response of innate immune cells to LPS stimulation is higher for males, as shown for monocytes and IL-1β, TNF-α, IL-12 [Bouman et al., 2004]. Moreover, the hyperresponsiveness of neutrophils from males to LPS may be a mechanism helping to explain the higher susceptibility of males to sepsis compared to females [Aomatsu et al., 2013].

Gender-differences are less well studied in adaptive immunity. However, some findings suggest that females have higher levels of circulating CD3 lymphocytes and CD4+ T lymphocytes and a higher CD4/CD8 ratio [Amadori et al., 1995, Das et al., 2008]. In addition, activated peripheral blood CD4+ T lymphocytes from females produce higher levels of Th1 cytokine IFN-γ [Zhang et al., 2012]. More generally, activated CD4 and CD8 T lymphocytes express differential patterns according to gender [Hewagama et al., 2009]. There is no convincing evidence of gender differences in B lymphocytes.

Among the potential aetiologies for these differences, not only hormones but also chromosome composition and microbiome have been advocated.

Hormones offer the most obvious potential explanation for gender differences in the immune response. Indeed, 17-βestradiol influences surface receptor expression, which allows viral entry into cells. It has been described notably for HIV receptor [Mo et al., 2005] as well as for an integrin [Woodward et al., 2001] allowing cell entry for adenovirus [Wickham et al., 1993], coxsackievirus A9 [Roivainen et al., 1994] and hantavirus [Gavrilovskaya et al., 1998]. As an example, 17-βestradiol in mice has been protective for *Coxiella burnetii* [Leone et al., 2004] and *Mycobacterium avium* [Tsuyuguchi et al., 2001]. Oestrogens bind to the oestrogen receptor, and the resulting complex goes into

the nucleus to bind DNA. The oestrogen receptors are naturally expressed in the female reproductive tract but also in immune cells such as B and T lymphocytes, neutrophils, macrophages, natural killer T lymphocytes or thymic stromal cells [Bouman et al., 2005]. Many studies have highlighted a particular effect of oestrogens in human or animals, in vivo or in vitro, but have rarely depicted a global mechanism. An additional difficulty is to link a specific isolated effect with the physiological variations induced by the menstrual cycle. Thereby, scientific literature about effects of oestrogens on the innate immune response may appear variable if not conflicting . 17-βestradiol may reduce the number of monocytes [Ben-Hur et al., 1995] but increase phagocytose [Chao et al., 1994] and NK cell cytotoxicity. More importantly, plasmacytoid dendritic cells, which play a crucial role in antiviral response [Gilliet et al., 2008], produce more interferon α in response to activation by TLR7 in females compared to males. This effect is mediated by oestrogens [Seillet et al., 2012].

With regard to the adaptive immune response, oestrogens decrease IL-2 production by T cells, with a greater effect on females [Moulton et al., 2012]. Moreover, oestrogens exert immunomodulation on CD4+, with Th1 and Th2 response being dose-dependent on the levels of oestrogens, and they might increase the B cell pool.

Progesterone modulates immune response, notably by driving Th2 response [Szekeres-Bartho et al., 2001] and decreasing B lymphocyte antibody production [Lü et al., 2002]. Testosterone may also decrease antibody production, via androgen receptors in B lymphocytes [Sader et al., 2005]. This could explain why males with high levels of testosterone have a low antibody response to influenza vaccine compared to females or to males with low testosterone levels [Furman et al., 2014].

Nonetheless, gender differences in immune response in prepubertal boys and girls, and in postmenauposal women and elderly men suggests that hormones are not the only driving factor [Lefèvre et al., 2012]. Many genes located on the X chromosomes are involved in immune system regulation. Therefore, male cells expressing only one X chromosome, male are more susceptible to X-linked mutation. Moreover, specific male genes situated on the Y chromosome could play a role in the regulation of the immune system [Case et al., 2013]. Finally, microRNAs are small non-coding RNA involved in the regulation of many cellular processes. Only two microRNAs are situated on the Y chromosome while 7-10% of all microRNAs in the genome are coded on the X chromosome. A recent study showed that some X chromosome-specific microRNAs are involved in the regulation of immune response and could help to explain gender differences in immune response [Pinheiro et al., 2011].

It is now well-demonstrated that the microbiome has a crucial influence on immunity [Cho and Blaser, 2012]. However, a major sex bias after puberty was shown between twins of opposite sexes, compared to twins of the same sex [Yatsunenko et al., 2012]. Bacteria metabolising sex steroids, alteration or modification of the bacteria from the

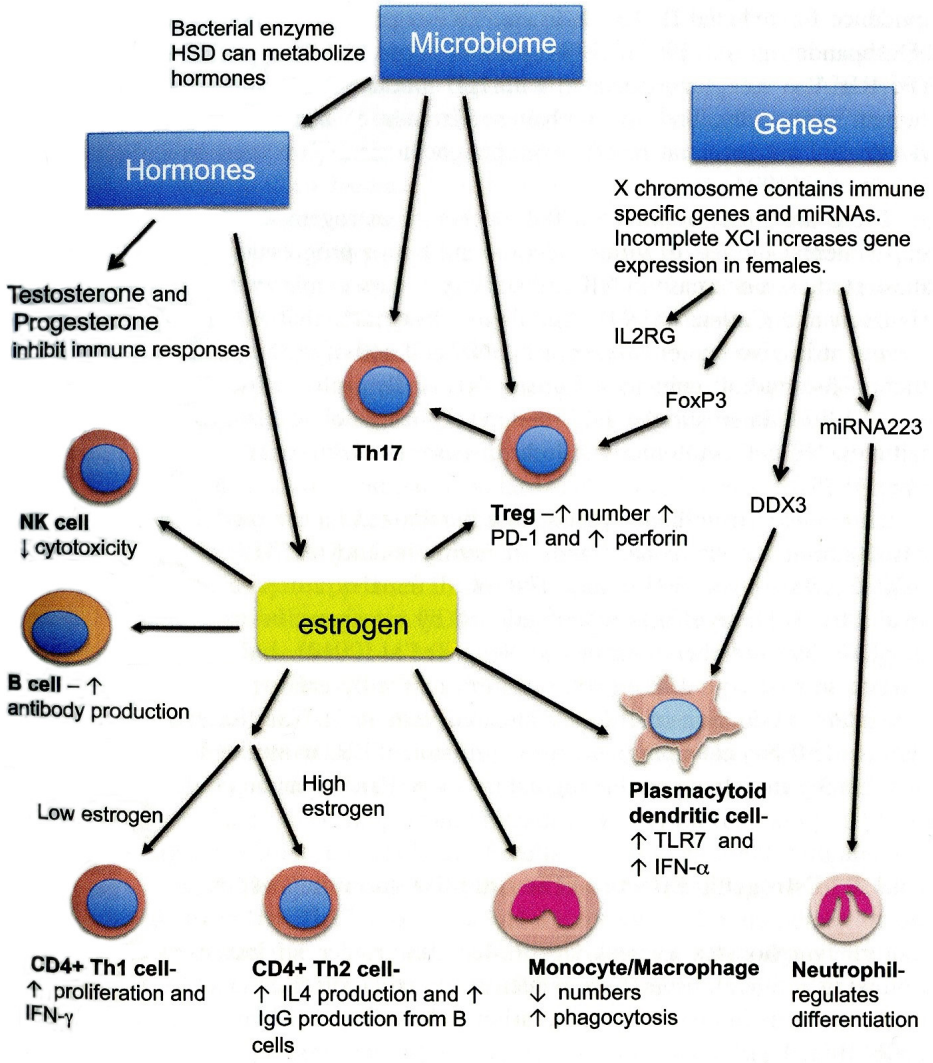


FIGURE 6.2: Mechanisms involved in gender specific immune response, from the book [Klein and Roberts, 2015]

gut will influence the metabolism of sex hormones, and consequently their activity on the immune system [Markle et al., 2013].
Mechanisms for gender-specific immune response are summarized in figure 6.2 extracted from [Klein and Roberts, 2015].

6.1.2 Gender differences in behaviour

As early as 1995, a demographic study aimed at assessing the differences in mortality between genders showed that it could be explained at least partially by differences in behaviour, such as discrimination toward girls or differences in immunisation rates [Hill and Upchurch, 1995]. Few studies had interest in behaviour to explain differences in infectious diseases. Nonetheless, studies on tuberculosis highlighted the fact that tuberculosis

notification reported more male cases than female cases. Several studies identified gender differences in health-seeking behaviour that could explain differences in case findings [Boeree et al., 2000]. This phenomenon is particularly notable in low-income countries [Cambanis et al., 2005], because of stigma and discrimination. To date, only one study has aimed at assess the respective roles of physiology and behaviour, focusing on diseases for which age-gender data permitted to estimate biases such as those generated by leishmaniasis, schistosomiasis, pulmonary tuberculosis, leptospirosis, meningococcal meningitis, hepatitis A, severe dengue, typhoid fever and leprosy [Guerra-Silveira and Abad-Franch, 2013]. Behavioural factors were predominant for leishmaniases, schistosomiasis, tuberculosis and leptospirosis. No assessment of the possible role of behaviour has been conducted for influenza or MMR. Although the demonstration was not formal, Peter Aaby et al. were some of the first to suggest, in addition to having demonstrated the importance of non-specific effects of vaccines, the potential impact of behaviour on the transmission of infectious diseases such as measles. With data from Guinea-Bissau, they notably pointed out that females spent more time at home than their male counterparts, which could decrease their exposure to pathogens [Aaby, 2007].

6.1.3 Gender differences in influenza

Most cases of seasonal influenza are not reported; therefore data on the differences between males and females are limited. Reports on seasonal influenza usually do not take into account gender, or when they do, they do not mention age, which clearly interacts with gender. The few available studies on influenza with hospitalization come from Canada and report higher hospitalisation rates or higher severity among prepubertal (Male OR: 1.9, 95%CI: 1.0-3.7) and elderly (1393 per 100,000 males and 969 per 100,000 females) males compared to age-matched females [Crighton et al., 2004, 2008, Quach et al., 2003]. A Danish study shows that the difference between males and females shifted at puberty, males being more likely to have severe seasonal influenza illness before puberty (Relative risk for hospitalisation for males: 1.64, 95%CI:1.29-2.08), while females were more likely to have severe seasonal influenza illness after puberty and before menopause (RR for hospitalisation for males: 0.61,95%CI:0.45-0.81) [Jensen-Fangel et al., 2004]. A few studies did not stratify gender by age but focussed on a subpopulation of children or adults, which resulted in similar finding. In 3 studies conducted in pediatric populations, males were predominant for seasonal influenza hospitalisation (55-60% in [Dawood et al., 2010] and 57% in [Dalziel et al., 2013]) as well as death (53% in [Wong et al., 2013]. In a study carried out among adults (18 years to >75 years), hospitalizations predominate among women (56-58.3%)[Dao et al., 2010].

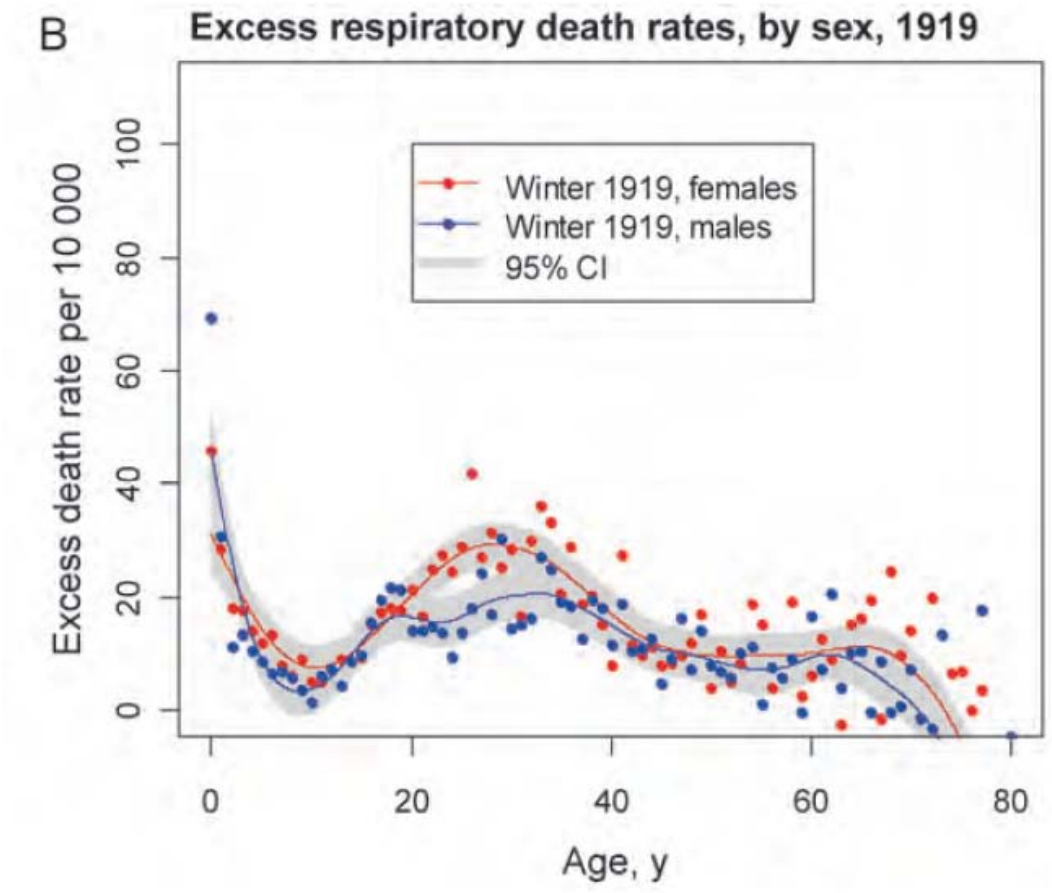


FIGURE 6.3: Sex-specific differences during winter 1919 pandemic wave (blue, males; red, females), from Viboud et al. [2013].

On the contrary, pandemic influenza cases were widely reported as early as the start of the 20th century. Indeed, Viboud et al analysed death certificates from Kentucky during 1918-1919 influenza pandemic and showed higher death rates among females between 18 years and 40 years old (Figure 6.3)[Viboud et al., 2013].

Gender differences were observed in pandemic influenza but rarely explained. The 1918 H1N1 influenza pandemic proved particularly fatal in young adult males (20-40 years old), but was further worsened by co-infection with tuberculosis, whose incidence was higher among males [Noymer and Garenne, 2000, Sawchuk, 2009]. Fatality during the 1957 H2N2 pandemic was not associated with concomitant bacterial infection but rather with underlying cardiac or pulmonary conditions. Such conditions may have been more frequent and severe among females, which could explain the higher fatality rates among females compared to males ($<$ 50 years old) [Kilbourne, 2006]. Reported cases from the 2009 H1N1 pandemic showed that female gender was a risk factor for higher incidence (53.2% vs. 46.8% in the USA), greater severity and mortality, but also had an interaction with age. Among individuals under 19 years old, incidence and severity were

higher among males, while the ratio was reversed in adults of 19-64 years, with a higher risk of hospitalization and death for females [Jacobs et al., 2012]. Among individuals over 75 years old, the risk of hospitalization was higher for males, but the risk of death prevailed for females. Although not stratified by age, a study on the influenza A(H1N1) pandemic in 10 states from USA identify a switch in gender for the incidence as males predominates among children (58% <18 years) compared to adults (42% > 18 years)[Cox et al., 2012]. Male incidence in incidence of influenza A(H1N1) predominate in California when only children were considered (59%)[Louie et al., 2010]. But even when there was a predominance of male in children with influenza A(H1N1), female were at higher risk of death [Randolph et al., 2011]. In Japan, data from 2009 H1N1 pandemic and 2005 seasonal influenza showed higher incidence among males for individuals under 20 years old and above 80 years old, and higher incidence for females, during reproductive years (20-49 years) [Eshima et al., 2012]. Description from H1N1 cases located in Canada showed similar trends, with an incidence higher in males at 10-19 years, higher in females at 20-39 years and equivalent after 40 years of age. A suggested explanation was that many cases involved underlying conditions such as chronic pulmonary diseases, known to be more severe among males before puberty and females after puberty [Ontario, 2009]. Male-female differences for 2009 H1N1 pandemic have been extensively reported in Canada, but Canada was the only country to require incidence data to be stratified by both sex and age-group. Among those aged 10–19 years, more cases were confirmed in males than in females (Figure 6.4). Besides, a report from Brazil showed a higher proportion of females between 20 and 40, but more importantly the difference was predominant during the first phase of the epidemic (containment phase) compared to the second phase when much more individuals were infected (mitigation phase) [Pires Neto et al., 2013]. Albeit sample size were small, this could be in favour of shorter mean serial interval for women, which has been already suggested by te Beest et al. [2014].

Avian H5N1 is mainly transmitted from poultry to humans and rarely from human to human. From 2003 to 2015 (latest update available: July 2015) 449 out of the 844 reported cases died [WHO, 2015a]. Global incidence, severity and mortality of H5N1 infections were higher among females between 10 to 39 years of age compared to males [WHO, 2013]. No statistically significant male-female differences were found for the cases reported from China and Vietnam between 2004 and 2006 [Hien et al., 2009, Liem et al., 2009, Yu et al., 2008], but samples were small (n=29, 67, 29, respectively). On the contrary, case fatality rates were significantly higher for females compared with males (90% vs. 67%) in Indonesia (2005-2006) [Sedyaningsih et al., 2007], as well as in Egypt (2009-2010) [Kayali et al., 2011] for females >10 years old (60% of H5N1 cases, 90% fatality rate). However, incidence was higher for males among individuals < 10 years old [Dudley, 2009, Kayali et al., 2011]. Such variations in the gender differences according

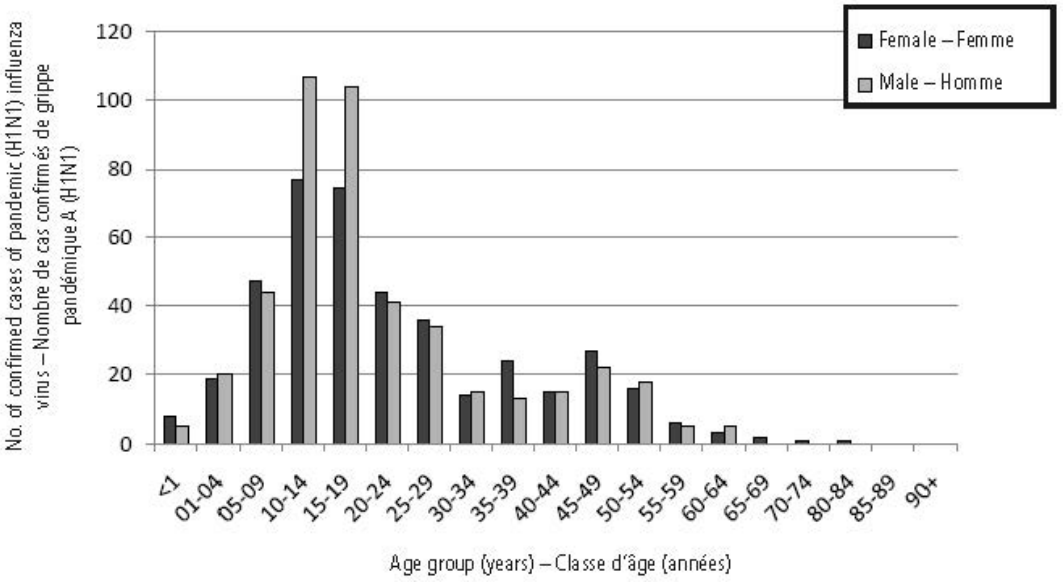


FIGURE 6.4: Distribution by age group and sex of laboratory-confirmed cases of the pandemic influenza A (H1N1) 2009 virus in Ontario, from Ontario [2009]

to countries or periods may suggest factors other than purely hormonal and genetic ones, which are supposed to be somehow similar between individuals. Gender-related occupational differences could be a factor. A study reporting cases of H5N1 from Egypt showed most cases concerned women of 20-39 years old and that exposure to poultry was the primary risk factor. Although men managed poultry slaughter, women were more exposed, as they fed and cared for the backyard poultry, boiled and purchased it in markets [Fasina et al., 2010]. Significant differences in the contact pattern with poultry between men and women has been also shown in Asian countries, which may impact H5N1 influenza transmission [Van Kerkhove et al., 2008].

Avian H7N9 influenza virus comes from poultry and migratory birds and is not transmissible from human to human. An outbreak has been ongoing since 2013 mostly in China (568 cases out of 571) [WHO, 2015b]. Old males (>50 years) were most at risk for getting infected, and presented the highest case fatality rates compared to age-matched females or young (<50 years) males and females [Dudley, 2009]. No studies provided a definite explanation for the gender difference. However, [Yang et al., 2014] showed high levels of H7N9 antibodies in most of the non-fatal cases but rarely in fatal cases, suggesting that a reduced humoral immune response could explain the outcome. Indeed, many studies found that aging and male gender were independent risk factors for reduced humoral immune response.

Comparative epidemiology between influenza A(H7N9) and A(H5N1) supports the importance of differences in exposure to explain differences in incidence [Cowling et al., 2010]. Cases were much more common in males for A(H7N9) and A(H5N1) in urban

area, while in rural area, males predominated for A(H7N9) but females were more frequent for A(H5N1). And most of cases of A(H7N9) occurred among persons of more than 60 years old while A(H5N1) cases were predominantly young adults. Such findings are more consistent with gender differences in exposure rather than in immunity. Indeed, males cases predominated notably in Shanghai, the Chinese city were men are known to be the most involved in retail exposures to live poultry compared to women. And in rural area, the higher risk for females is may result from their greater involvement in rearing, slaughtering and cooking backyard poultry.

Trends switch at puberty and probably at menopause obviously suggest an hormonal role. However, behaviours, notably those related with occupation or responsibilities at home, change after puberty and consequently could impact the exposition to infected poultry or individuals. Moreover, the switch at the time of menopause is less obvious and may be occur as early as 40 years old [World Health Organization, 2010], which could also correspond to changes in professional occupation. Unfortunately, reports of age-stratified gender incidence proportion were rare even for pandemic influenza, at the notable exception of Canada. Individuals with an occupation associated with close contact with infected individuals (healthcare, contacts with young children) are obviously with an higher risk to get infected. Indeed, a common aspect of most countries around the world is that nurses, teachers and day-care workers are females, resulting in a gender-specific occupational risk for getting infected with influenza or other directly transmitted infections. Caregiving children or family members at home is also usually achieved by women and is an important risk factor to get infected as suggested by the Tecumseh study, which followed approximately 1000 individuals through years and documented acute respiratory illnesses [Monto, 1974]. It showed that incidence was higher among young boys up to 3 years, when incidence decreased and predominated among females. Between 20 and 29 years old, incidence started to increase and the difference between males and females was the greatest. Authors suggested that it could coincide to the exposure of family members to young children with infection as women who worked out of the home had a lower rate of illnesses than women who did not work out of home, but still a higher rates than males [Monto and Sullivan, 1993].

Mice models have been widely used to study male-female differences for influenza. Most studies have shown that male mice are more resistant to influenza viruses than female mice. However, a potential flaw is that mice are not naturally susceptible to human influenza viruses; therefore, viruses must be adapted for the purpose of experimental studies.

Studies on acceptance via questionnaires showed that the intention of receiving pandemic or avian influenza vaccine is 2-3 times lower for females, even among healthcare providers

[Chor et al., 2009, Opstelten et al., 2008]. Seasonal influenza vaccine uptake is lower among females compared to age-equivalent males [Bean-Mayberry et al., 2009, Endrich et al., 2009, Jiménez-García et al., 2010], which was also the case for the monovalent vaccine during the 2009 H1N1 pandemic [Furman et al., 2014].

As previously detailed, females produce higher antibody titres than males after seasonal trivalent vaccination, whatever the age group [Engler et al., 2008, Furman et al., 2014]. A similar reaction was observed with 2009 H1N1 vaccine, but the avidity of those antibodies was significantly lower for females. Avidity being considered as a marker of efficacy, these findings suggest that the quality of antibody response may be better among males [Khurana et al., 2012].

Adverse reactions to vaccine, local (muscle pain, redness) as well as systemic (fever, headache ...) are more frequent among females, whatever the age category or vaccine type [Cook, 2009, Nichol et al., 1996].

Among patients with influenza A treated with oseltamivir (but not with zanamivir), males showed shorter time of alleviation of symptoms and higher virological response [Blanchon et al., 2013], which could have an effect on transmission potential.

Another aspect of the differences between males and females is that pregnancy is a female-specific risk factor for severe influenza [Cox et al., 2006, Jamieson et al., 2009]. There is 3 to 10 times more risk for a pregnant women to be hospitalized, notably in ICU, compared to the general population and non-pregnant women. Seasonal influenza as well as pandemic are both concerned. This factor can be explained by the immunological changes observed during pregnancy. Vaccine efficacy is the same as for non-pregnant women.

6.1.4 Gender differences in measles, mumps and rubella

The long-known higher morbidity and mortality for male infants has recently been confirmed in developing as well as developed countries [Sawyer, 2012]. It has been hypothesized that the excessively elevated male morbidity could depend on the symptomatic to asymptomatic ratio. Diseases with a high ratio (i.e. few asymptomatic individuals), such as measles, would appear equally in males and females, while diseases with a large number of asymptomatic individuals would be expressed more frequently among males [Green, 1992]. However, reporting gender without stratification by age does not permit to assess gender-differences correctly. We synthesized the findings of the rare studies

providing results for gender differences stratified by age, or at least focusing on a particular age category in Table 6.1 for measles, Table 6.2 for mumps and Table 6.3 for rubella.

Measles:

Studies on measles showed more male children hospitalized compared to females, significantly in Korea (58.5% for Measles from 1989 to 2001)[Lee et al., 2007], but also non significantly during an outbreak in Korea in 2007 (52%)[Choi et al., 2011], or in Ireland in 2000 (53%)[McBrien et al., 2003]. Measles incidence is usually reported higher among male children than among their female counterparts [Green, 1992].

On the contrary, measles mortality rate among children was nearly 70% greater in girls than in boys [Morris et al., 2013] in India (2001-2003). According to a national data registry statistics published by the WHO, female mortality for measles was found to be significantly and systematically superior to male mortality in all regions of the world, with the notable exceptions of the Philippines and Thailand [Garenne, 1994]. In this study, higher female mortality for measles was observed from birth to 50 years. The difference in comparison with male mortality was mild at age 0-4 (+4.2%) and increased at age 5-14 (+10.9%) and age 15-44 (+42.6%). However, subacute sclerosing panencephalitis -an exceptional but fatal complication of measles occurring on average six years after measles infection- may be more frequent and more severe among males. But many bias, such as different vaccination rates according to gender, may skew this result [Gutierrez et al., 2010].

One of the few studies to report age-stratified gender in a measles outbreak in Vietnam clearly showed a predominance for male children (1-4 years: 54.9% 95%CI:52.5-57.3 for the whole country; 5-9 years: 56.3 95%: 51.3-61.1 for the South region) but with a significantly greater proportion of females among young adults in South and Central regions ((58.3%; 95% CI, 53.4–63.1) and (63.1%; 95% CI, 51.9–73.4) for 20–24 year age groups)((63.4%; 95% CI,55.8–70.6) and (71.4%; 95% CI, 55.4–84.2) for the 25–29 year age groups). Authors suggested the implication of mother in childcare as a potential explanation [Sniadack et al., 2011].

Opportunely, the oldest report we found on measles described an outbreak in rural Germany in 1861 [Aaby et al., 1992]. It was able to show that girls were likely to be the index cases and young boys the secondary cases. In addition to a higher proportion of cases among boys, the case-fatality ratio was higher among boys among the secondary cases, but not among the index cases. And cross-sex transmission from girls tended to increase the case-fatality ratio. These findings permitted to the authors to conclude that "transmission patterns may partly explain popular beliefs about the stronger sex being the weaker one" in a study published 23 years ago based on data from an outbreak that occurred one century and half ago. The same author conducted a prospective study in

Measure	Gender difference	Study population	Country	Reference
Hospitalisation	1989-1990 (n=116) M:F ratio 69:47(1.5:1) 1993-1994 (n=127) M:F ratio 79:48(1.6:1) 2000-2001 (n=277) M:F ratio 156:121(1.3:1)	Children during 3 periods (1987-2001)(0-15y)(half were <1y)	Korea	[Lee et al., 2007]
Hospitalisation	1999-2000 (n=111) 53% of male	Children (5m-10y)	Ireland	[McBrien et al., 2003]
Incidence	Origin of data unclear, infant <1y had a M:F ratio at 1.6	Infant <1y	Israel	[Green, 1992]
Incidence	Male predominance for children, female for young adults: Nationally: Male 1-4y: 926 [54.9%] of 1688; 95%CI, 52.5-57.3. South region: -Male 1-4y: 423 [55.8%] of 758; 95%CI, 52.1-59.4. -Male 5-9y: 233 [56.3%] of 414; 95%CI, 51.3-61.1. -Female 20-24y: 242 [58.3%] of 415; 95%CI, 53.4-63.1. -Female 25-29y: 111 [63.4%] of 175; 95%CI, 55.8-70.6. Central region: -Female 20-24y: 53 [63.1%] of 84; 95%CI, 51.9-73.4. -Female 25-29y: 30 [71.4%] ; 95%CI, 55.4-84.2.	Children and young adult (0-29y)	Vietnam	[Sniadack et al., 2011]
Mortality rates	Excess female mortality: 0-4y: +4.2% 5-14y: +10.9% 15-44: +42.6%	World population (0-44y)	Worldwide (except Philippines & Thailand)	[Garenne, 1994]
Mortality rates	Girls: 4.3 (99%CI: 3.0-6.2) Boys: 2.5 (99%CI 1.7-3.9) Estimation for 2005 based on 2001-2003)	Children 1 month to 15 years	India	[Morris et al., 2013]
Mortality rates	Girls: 7.3% (53/722) Boys: 5.8% (45/778). (secondary cases infected by a child of opposite sex had a 2.44(1.48-4.02) times higher risk)(risk of cross-sex transmission greater for females (1.26[1.09-1.47])	Children <10y (1983-1986)	Senegal	[Aaby, 1992]
Mortality rates	Girls: 2.0% (2/83) Boys: 11.0% (10/94) (differences only among secondary cases)(no difference among index cases)	Children <15 years from one village, 1861	Germany	[Aaby et al., 1992]

TABLE 6.1: Gender differences for measles when age stratification was provided.

Measure	Gender difference	Study population	Country	Reference
Incidence	Male/Female ratio: 0y: 1.32 (1.24–1.42) 1y: 1.28 (1.25–1.31) 2y: 1.15 (1.14–1.17) 3y: 1.13 (1.11–1.14) 4y: 1.10 (1.09–1.12) 5y: 1.13 (1.12–1.14) 6y: 1.10 (1.08–1.11) 7y: 1.07 (1.05–1.09) 8y: 1.05 (1.03–1.08) 9y: 1.07 (1.04–1.09) 10-14y: 1.06 (1.04–1.08) 15-19y: 0.81 (0.75–0.86) ≥20y 0.54 (0.52–0.56)	Report from pediatric sentinel point, 2000-2009	Japan	[Eshima et al., 2012]
Incidence	Male/Female ratio: <1y: 13/9 (1.44) 1-4y: 25/38 (0.66) 5-9y: 138/108 (1.28) 10-14y: 378/240 (1.58) 15-19y : 1398/834 (1.68) 20-29y : 871/383 (2.27) >30y : 432/352 (1.23)	National report of all cases in 2009-2011 (n=5219)	Bosnia-Herzegovina	[Hukic et al., 2011]
Incidence	Male/Female ratio: ≤6y: 2/0 7-9y: 5/0 10-14y: 6/4 15-19y: 66/29 20-29y: 112/69 30-39: 29/6 ≥40: 5/2	Reported cases in Serbia 2012 (n=335)	Serbia	[Nedeljković et al., 2015]

TABLE 6.2: Gender differences for mumps when age stratification was provided.

Measure	Gender difference	Study population	Country	Reference
Incidence	% of cases in this age category for males (n=10,985) and females (n=3,372): <1y 1% vs. 1% 1-4y 2% vs. 4% 5-9y 1% vs. 3% 10-14y 2% vs. 3% 15-19y 4% vs. 11% 20-29y 24% vs. 40% 30-39y 34% vs. 16% 40-49y 23% vs. 9% >50y 9% vs. 13%	Outbreak: Reported cases 2012-2013	Japan	National Institute of Infectious diseases [NIID, 2013]
Incidence	Numbers not provided but presented in Figure 6.8	Reported cases 2003-2008	Poland	[Zimmerman et al., 2011]
Incidence	RR (95%CI) Male vs. Female rates (total number of cases(rate per 100,000 persons)): 0-4: 0.97(0.63;1.47); 87(12.6) 5-9: 0.85(0.61;1.17); 144(20.3) 10-14: 1.17(0.87;1.57);181(25.9) 15-19:8.61(5.87;12.64);292(40.5) 20-24:8.74(5.68;13.44);234(29.6) 25-29:6.19(3.52;10.86);104(13.1) 30-34: 4.94(2.59;9.45);66(8.0) 35-39:1.45(0.90;2.33);71(9.0) 40-44:1.19(0.70;2.00);57(7.5) 45-49:0.47(0.22;1.00);31(4.7) >50y:0.78(0.43;1.39);47(1.7) Total:2.48(2.20;2.80);1314(12.8)	Reported cases 1990-1996	South Australia	[Cheffins et al., 1998]
Incidence	Numbers not provided but presented in Figure 6.9	Reported cases in 1985	Sweden	[Böttiger et al., 1987]

TABLE 6.3: Gender differences for mumps when age stratification was provided.

rural Senegal, and showed (1) a higher case fatality ratio among girls and (2) a higher risk of death for child infected by a child from opposite sex than by a child from the same sex, and a risk of cross-sex transmission greater for female secondary cases than for males [Aaby, 1992]. The combination of these two findings would explain the difference in the risk of death from measles between boys and girls. A similar study was conducted in Guinea-Bissau on the risk of death from infectious diseases, with similar results, whether measles was included or not in the cause of death [Aaby and Mølbak, 1990]. Differences in mixing patterns appears a more plausible than purely genetic differences. A difference in the intimacy of contact could result in a difference in the "viral load" transmitted, which could result in return in a difference in the prognosis.
Immunosuppression associated with measles was studied among 272 children hospitalized in Zambia and showed higher total lymphocyte counts in males, but higher CD4/CD8 ratio and more severe and prolonged lymphopenia during recovery in females [Ryon et al., 2002]. Among 11-22 year individuals, female response to the MMR vaccine was higher for TNF-α, IL-6 and INF-γ than among males [Umlauf et al., 2012].

All vaccines generated a differential antibody response according to gender. However, the gender-specific response is variable and potentially modulated by factors such as age, vaccine type, nutritive state and country. Indeed, age group modulates the gender effect on the antibody response. Measles vaccination resulted in higher antibody response in male infants at nine months [Semba et al., 1995], and in females when vaccinated as adults [Green et al., 1994]. Vaccination in Guinea-Bissau with the Edmonston-Zagreb strain at nine months resulted in higher response for females, but not with the Schwarz strain [Martins et al., 2013]. When vitamin A was given simultaneously to measles vaccination, the antibody response was higher among males. However, among infants who did not receive vitamin A, antibody titres was higher among females [Benn et al., 1997]. In accordance with Semba et al. [1995], five-year-old females in Pakistan had lower anti-measles antibody titres than males [Hussain et al., 2013]. However, Tanzanian females under five years old had higher anti-measles antibody titres than males [Lyamuya et al., 1999]. When the focus is on non-vaccinated infants, pre-vaccination anti-measles antibody titres at 4.5 months were lower in females than in males, but non-vaccinated females were more likely to have protective antibodies levels at 9 months, in Guinea-Bissau [Martins et al., 2009], suggesting that females were more likely to have had a subclinical measles infection before 9 months, maybe favoured by their initial lower antibody levels. This is in accordance with the Pakistani study where non-vaccinated female infants had higher seropositivity rates and serum titres than male infants, at nine months of age [Hussain et al., 2013].

Few studies have investigated gender differences in vaccine-induced cellular immunity, and even fewer for measles. However, no differences were found whether in the IFN-γ

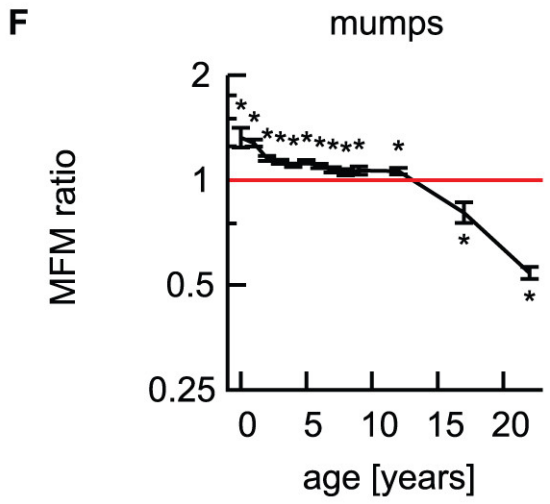


FIGURE 6.5: Male/Female ratio for mumps in Japan, from Eshima et al. [2012]

response nor the immunosuppression after vaccination for children [Dhiman et al., 2005, Hussey et al., 1996]. Vaccine-related adverse effects are known to be more important among females, but there might be an interaction with age as adverse effects overall are usually reported more frequently for male infants [Ribeiro-Vaz et al., 2013]. More fever and rash occurred after MMR vaccine in an Israeli study [Shohat et al., 2000] but not in a Finnish study [Virtanen et al., 2000]. Some studies have shown that higher rate of adverse effect in male infants may switch after puberty toward more adverse effects in females.

Non-specific effects of vaccine comprise the general effects on the immune system modifying the susceptibility to non-vaccine-related infections and therefore modifying morbidity and mortality. Interestingly, the "nonspecific effects" of vaccine, now called "heterologous effects", were initially described with measles vaccine. Measles vaccination in low-income countries have reduced overall morbidity and mortality to an extent exceeding morbidity and mortality caused by measles [Aaby et al., 1995]. Moreover, females are more susceptible to these heterologous effects than males [Aaby et al., 1995, Flanagan et al., 2013]. In addition to gender, the order in which vaccines are given will affect the heterologous effects [Aaby et al., 2010].

Mumps:

A previously cited Japanese registry showed that mumps was predominant among males during infancy, but that the ratio reversed toward a higher morbidity among females during adolescence (Figure 6.5)[Eshima et al., 2012]. It is one of the few studies providing age-stratified gender proportions in mumps hitherto.

Two outbreaks were also described in Bosnia-Herzagovina 2009-2011 (Figure 6.6) and Serbia 2012 (Figure 6.7), which showed a different pattern with male predominance

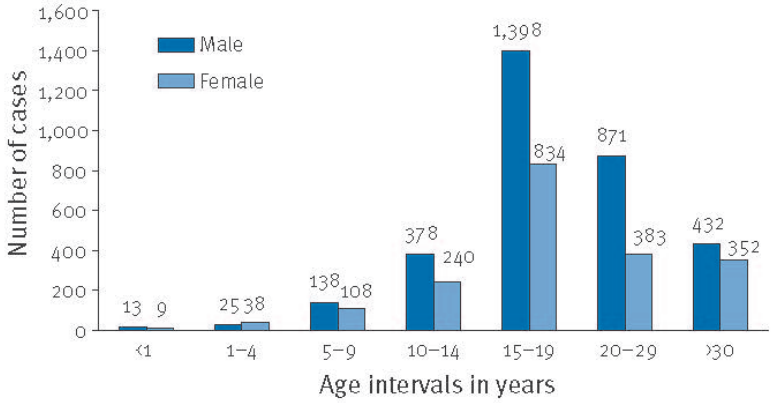


FIGURE 6.6: Number of cases in relation to age and sex, mumps outbreak, Federation of Bosnia and Herzegovina, Bosnia and Herzegovina, Dec. 2009–Jul. 2011 (n=5,219), from Hukic et al. [2011]

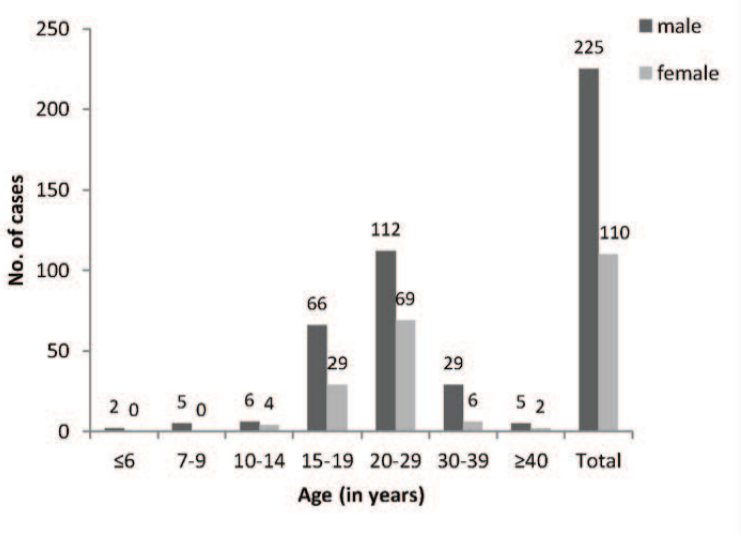


FIGURE 6.7: Number of mumps cases reported in Vojvodina between January and June 2012 according to age group and gender from Nedeljković et al. [2015]

even after the puberty, which may due to a vaccination coverage [Hukic et al., 2011, Nedeljković et al., 2015] very different from Japan.

Complications may also predominate among males, contrary to measles, (15-30% of orchitis for males, 5% of oophoritis for females) [Hviid et al., 2008] although this could be due to a reporting bias, as no studies clearly assessed gender differences in mumps, and such complications are gender-specific by definition.

A follow-up on 20 years of the persistence of mumps antibodies showed that antibody levels were higher among females, after the second dose, 8 years ($p<0.05$) and 15 years ($p=0.05$) [Davidkin et al., 2008]. The proportion of vaccinees becoming seronegative was the highest for mumps, compared to measles and rubella, but results were not stratified by gender. A serological survey conducted in 1989 among 1547 US Army recruits (18-24

years) revealed that females were less susceptible to measles, mumps and rubella than their male counterparts [Kelley et al., 1991]. Combined serological surveys in the USA between 1999-2004 showed a lower prevalence of mumps seropositivity among males compared to females (89.0% [95% CI, 87.5%–90.4%] vs 90.9% [95% CI, 89.6%–92.1%]; $p<0.05$) [Kutty et al., 2010], which may be a consequence of the targeted vaccination of women with MMR vaccine in order to prevent rubella. But, ages stratified by gender were not provided.

Despite lower seropositivity among males, incidence was higher among females (64% of the cases) during the large 2006 mumps outbreak in the USA (13.5 cases per 100,000 population vs. 7.7 cases per 100,000 population among males)[Dayan et al., 2008]. There were no difference in coverage, and presumably in age although age-relative incidence stratified by gender was not provided (highest incidence was 14-24 years). Authors suggested that this difference in incidence could reflect the difference in the proportions of women in colleges. Complications were more frequent among men, which is usually attributed to the fact that orchitis is clinically more spectacular than oophoritis. This higher incidence of mumps among women has already been already reported in previous outbreaks [Cheek et al., 1995, Wharton et al., 1988], but again without age-relative incidence by gender.
A case-control study focusing on cases from Kansas University also showed higher prevalence among women and <22 year students, despite similar and high coverage (≈99.0%). The higher prevalence among women being notable for dormitory residents, authors speculated that it could result from differences in social behaviour [Huang et al., 2009]. The difference in social contact was also supposed to be the cause of higher incidence among the youngest students as they attend much larger and more crowded classes than older students. On the contrary, no gender difference was reported in mumps outbreaks in the University of Illinois, but only univariate analysis and un-stratified data were available [Sosin et al., 1989].
Three surveys of mumps incidence in USA (1929, 1942, 1967) reported that 54% of the 43000 reported cases were males, with a predominance in every age category [Witte and Karchmer, 1968]. Similarly, a predominance of males was found for mumps encephalitis (≈70%).

Rubella:
Gender differences in rubella may be obvious, notably because girls were preferentially vaccinated or even exposed to prevent congenital rubella syndrome, before MMR became mandatory. However, studies reporting potential differences in incidence or mortality according to gender are scarce.

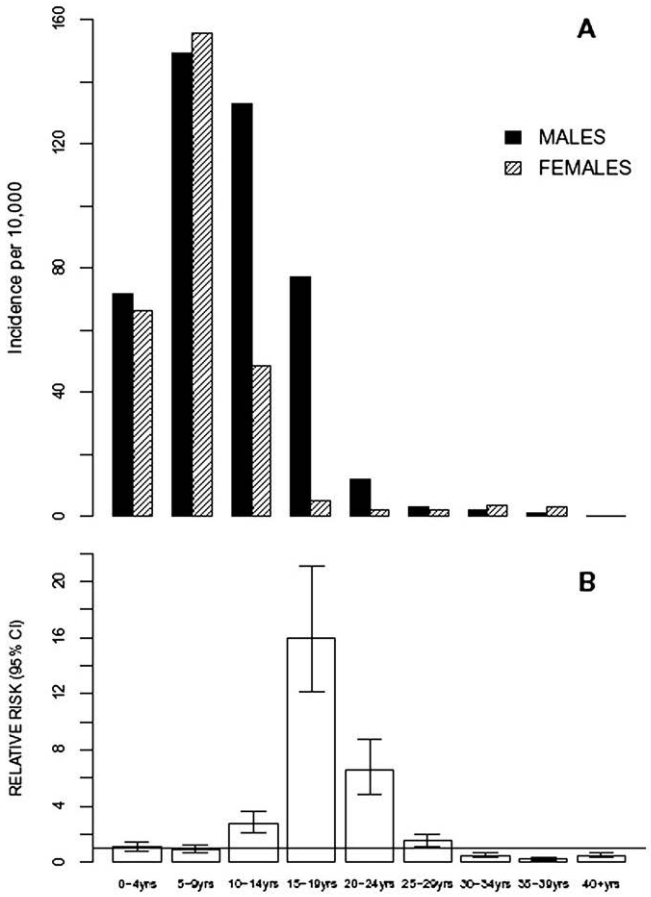


FIGURE 6.8: Incidence per 10000 individual and relative risk of rubella, males versus females, by age group, in Poland 2003-2008 from Zimmerman et al. [2011]

The 2012-2013 rubella outbreak in Japan resulted in 15,000 cases, mainly among men of 35-51 years, and men and women of 24-34 years. The authors suggested that the former did not receive vaccines, as in their generation only schoolgirls were vaccinated for their generation, and the latter benefited from a low vaccine coverage [Ujiie et al., 2014].
Poland reported rubella incidence between 1966 and 2008, with a 4-6 year inter-epidemic cycle. Monovalent rubella vaccine was given for 13-year-old girls from 1989 to 2005, thereafter, one dose of MMR vaccine for babies of 13-15 months since 2003 and a second MMR dose at 10 years since 2005. Overall, 64% of reported cases between 2003 and 2008 were males. Figure 6.8 illustrates the fact that incidence was the highest for 5-9 year-old male and female children but remained high for males up to 19 years. The risk of rubella was predominant among males between 10 and 24 years, but among females after 30 years [Zimmerman et al., 2011]. The higher risk for males during adolescence can be explained by the fact that the initial vaccine campaign was dedicated to girls. However, females are at higher risk among individuals over 30 years, which cannot be due to vaccination bias.

The largest outbreak of rubella in the USA occurred in 1999 among workers at a meatpacking plant, who were almost all of Latin American origin [Danovaro-Holliday et al., 2000]. The eighty-three cases occurred among unvaccinated individuals. The cases related to the meatpacking plant and the community were predominantly Hispanic foreign-born young males (median age 26 years), while the cases related to the day care center were US-born non-Hispanic and predominantly females (14 children of 5-17 months and 2 parents 34 & 35 years).
Notifications of cases in Australia between 1990 to 1996 showed rubella occurred predominantly and significantly among males for individuals between 15-34 years (RR of males compared to females ranging between 8.61 to 4.94). Females were significantly more affected than males after 45 years [Cheffins et al., 1998].
Similarly, an outbreak in Sweden in 1985 affected primarily males between 15 and 24 years, reflecting the fact that between 1974 and 1982, only girls were vaccinated, as illustrated by the Figure 6.9 [Böttiger et al., 1987].

Taking into account the discrimination against girls in India (boys have vaccination rates 16% higher than girls in Bombay), British authors aimed at assessing the gender differences in vaccination rates among immigrants from South Asia in Newcastle. Gender differences in vaccination coverage existed only for MMR vaccine among non-Moslem South Asians with a lower rates among girls (IC95% 0-13%) [Martineau et al., 1997]. On the contrary, gender did not affect consent for vaccination in Liverpool [Pearson et al., 1993].
A serological survey conducted in England during 1986-1987 showed that susceptibility to rubella was higher for males among individuals aged 10 to 30 years ($p<0.01$). This may reflect the selective vaccination of girls. Susceptibility increased after 31 years, as rubella vaccination was not offered to this generation, but was different for males [Morgan-Capner et al., 1988]. Serological surveys among recent immigrants in Montreal, Canada found females more susceptible to at least 1 condition (measles, mumps or rubella) (38% (35-41) compared to males 31% (27-35)) [Greenaway et al., 2007]. Trends were similar among individuals under 35 years and over 35 years, but no precise stratification was provided. The oldest publication we found on a serological survey on rubella was conducted in Canada in 1963 and 1966 showing that boys were more susceptible than girls among individuals under 11 years, although the sample size was small. Older individuals were mostly pregnant women, which makes the comparison between genders irrelevant [Chagnon and Pavilanis, 1970].

Mechanisms of gender differences in immunity have been presented previously. No studies have investigated the consequences of differences in immunity specifically for MMR. However, sex differences in breastfeeding have been explored. Indeed, in addition to optimal nutrition, breastfeeding provides maternal antibodies, modulates innate immune

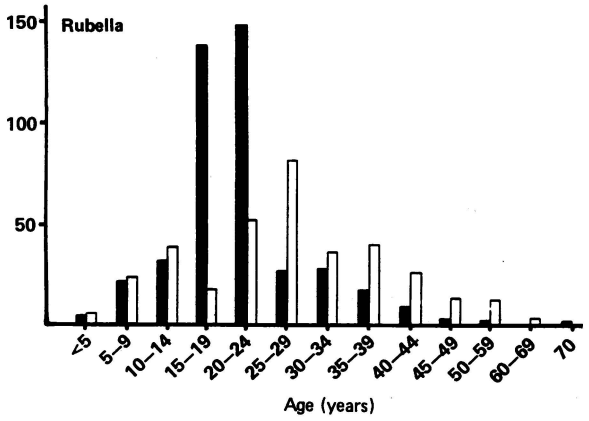


FIGURE 6.9: Age and sex distribution of rubella in Sweden during 1985, from Böttiger et al. [1987]

response, and protects neonates through their first months of life [Lamberti et al., 2013]. Therefore, variation in breastfeeding according to child gender could have an impact on children's susceptibility to infections. In urban India, female infants were more likely to have early weaning [Nath and Goswami, 1997]. A common theory in evolutionary biology (the Trivers-Willard effect) suggests that parents in good socio-economic conditions will favour their investment toward males, while parents in poor socio-economic conditions will favour females, in order to optimize their chance for a higher number of descendants in the next generation. This theory was confirmed by studies showing that sons were breastfed longer than daughters in highly educated families [Gaulin and Robbins, 1991, Koziel and Ulijaszek, 2001]. Similarly, a Kenyan study showed that the richest mothers delivered richer milk in term of fat concentration for sons while the poorest mothers produced the richest milk for daughters [Fujita et al., 2012]. Moreover, the protection provided by breast milk may vary according to gender, and benefit preferentially to female infants rather than males. Breastfeeding protected females but not males from respiratory tract infections [Klein et al., 2008, Sinha et al., 2003]. No gender difference was found in a Swiss study in maternally transferred measles antibodies [Nicoara et al., 1999], but decay was faster for females infant compared to males [Martins et al., 2009], resulting in higher susceptibility among female infants during their first months of life.

As a conclusion, this literature review underscores the fact that even if gender differences was not unnoticed, their full extent has been minored by the aggregation by age, making difficult to understand the precise role of immunity, behaviour and other risk factors. Therefore, we recommend that studies on infectious diseases should systematically take gender into account, with an age stratification. Not doing so may leads to confounding bias and erroneous results, as illustrated by a study where a herpes vaccine was efficient on women but not on men, with no efficiency when analysed ignoring gender [Stanberry et al., 2002].

In addition, gender differences presents many similarities but also discrepancies according to the pathogen, the country and the span of the age category considered. Consequently, even if immunological differences between males and females are obvious, they may not be the only source of observed differences in morbidity and mortality between genders. We suggest that behaviour, notably mixing patterns, may participate to such differences and explain discrepancies between studies.

6.2 Gender differences and contact matrices

6.2.1 Descriptive analysis according to gender

The differences in the number of contacts can be described with a degree distribution taking into account the gender of both the participant and the contact. Figure 6.10 represents these degree distributions and clearly show that the most important difference comes from males (<18 years & >18 years) having a different distribution of contacts according the gender of the contact. Males tend to shift their degree distribution and the peak toward the right for their contact with females, and toward the left for their contact with males. On the contrary, there is no clear shift among the females according the gender of the contact. This findings may appear counter-intuitive with regards to our previous findings, one should take into consideration that these graphs represent a distribution of contact degree and not a mean number of contacts. Thereby, a mean number of contact cannot resume efficiently the differences in mixing patterns between genders.

6.2.2 Contact matrices according to gender

The first approach consisted in unravelling the French contact matrices according to participant's and/or contact's gender. Contact patterns are different according to the gender participants, as illustrated in Figure 6.11. Contact gender not being taken into account, reciprocity was not imposed. The most noticeable aspect are parallel diagonals, usually attributed to parent-child or parent-grandparent contacts, which are more important in female contact patterns, expressing a higher contact rate among women with children and elders (supposedly their children and their parents), compared to their male counterparts.

When gender is taken into account for participants and for contacts (then, we made the matrices reciprocal), as illustrated in Figure 6.12, it first confirms the greater implication from females with children and parents. Those matrices also shows that assortativeness by age is higher for contact with opposite gender, as the main diagonal is thinner, while

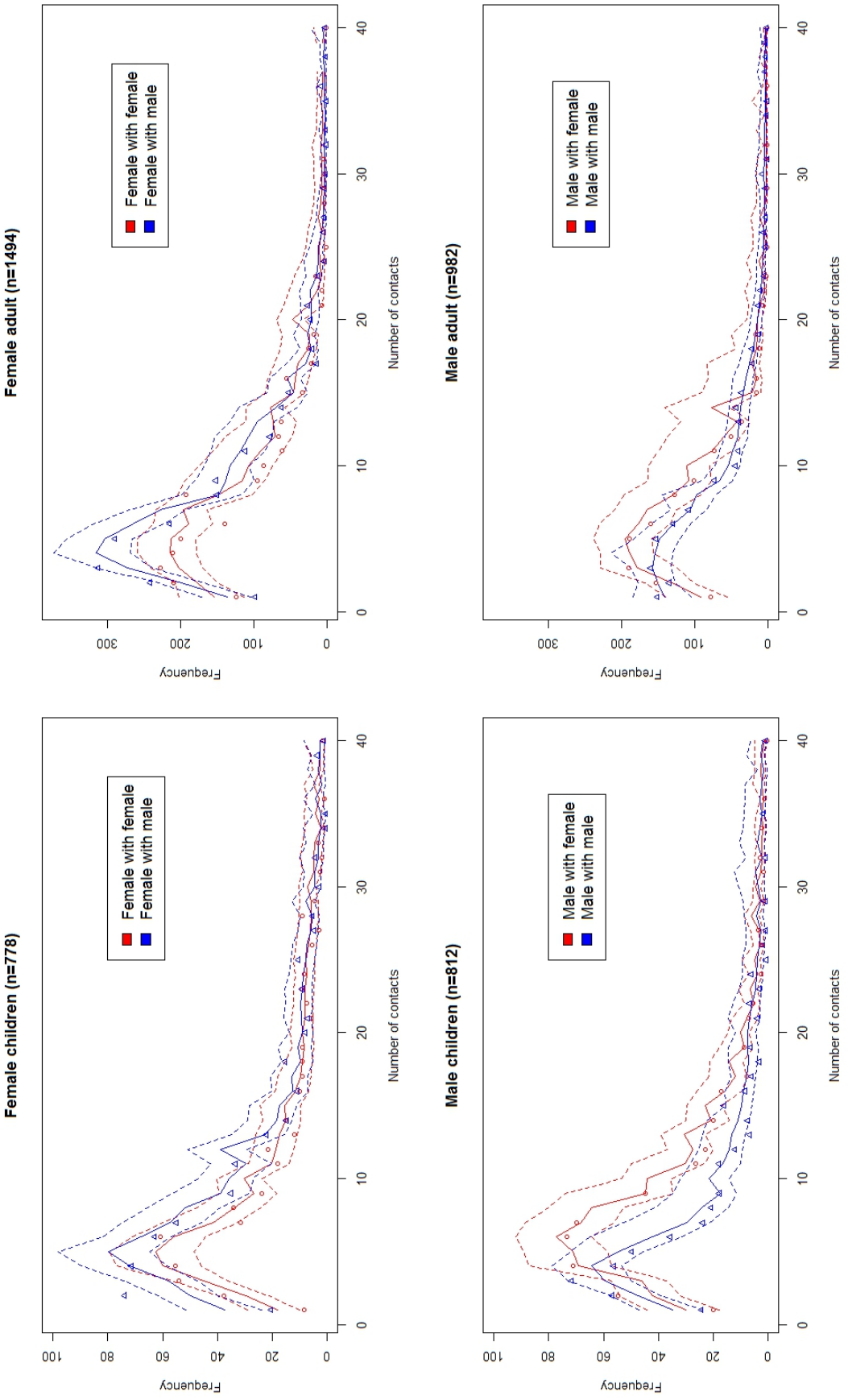


FIGURE 6.10: Degree distribution according to gender of both participant and contact. Blue triangles and red circles represent the data points on which the curve is smoothed with a gam function. Dashed lines represent the 95% bootstrap confidence intervals. Children are individuals < 18 years, adult are individuals ≥ 18 years.

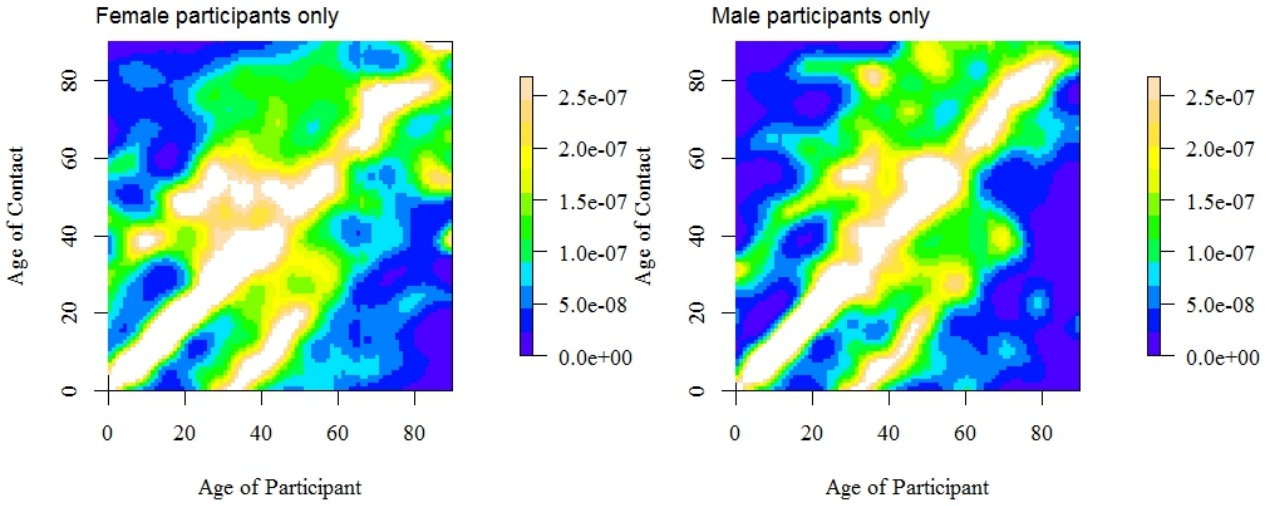


FIGURE 6.11: Contact matrices according to participant gender, without reciprocity

this diagonal widens to almost a "plateau" between 20 years and 60 years old for contacts with the same gender. Moreover, this plateau, expressing contacts not limited to the same age of the participant, seems larger for female participants, suggesting a trend for less assortativeness by age among females with their contact.

Graphical comparison being nonetheless subjective, we aimed to provide numerical values characterizing each contact matrices [Hens et al., 2009a]. Indeed, these contact patterns can be summarized by their maximum eigen value, which is an estimate of their R_0, as detailed in Chapter 1. However, we chose to not focus on a particular disease, in order to not specify a particular disease duration D or proportionality factor q, therefore one should consider the maximum eigen value as a quantity proportional to R_0. We used a non-parametric bootstrap, as described in Chapter 3 to provide confidence intervals for the gender-specific matrices. When considering all contacts, the maximum eigen value for the basecase matrix (no specific period or gender) was 10.89[10.35,11.44], and 11.30[10.59,12.07] for female participant specific matrix and 10.53[9.64,11.54] for male participant specific matrix. Moreover, the maximum eigen value was 6.34[5.89,6.88] for female participants with female contact only matrix and 4.96[4.59,5.36] for female participants with male contact only matrix. The maximum eigen value was 4.56[4.18,5.09] for male participants with female contact only matrix and 6.14[5.49,7.04] for male participants with male contact only matrix. Another way to summarize contact patterns is to use the relative incidence of a newly emerging infection in a fully susceptible population, estimated by the leading right eigen vector of the matrix of interest. Figure 6.13 illustrates the relative incidence calculated from the gender-specific matrices in Figure 6.12. Not only the peak incidence for teenagers and young adults is higher for contacts within the same gender, but it is in fact absent for contacts between male participants and female contacts.

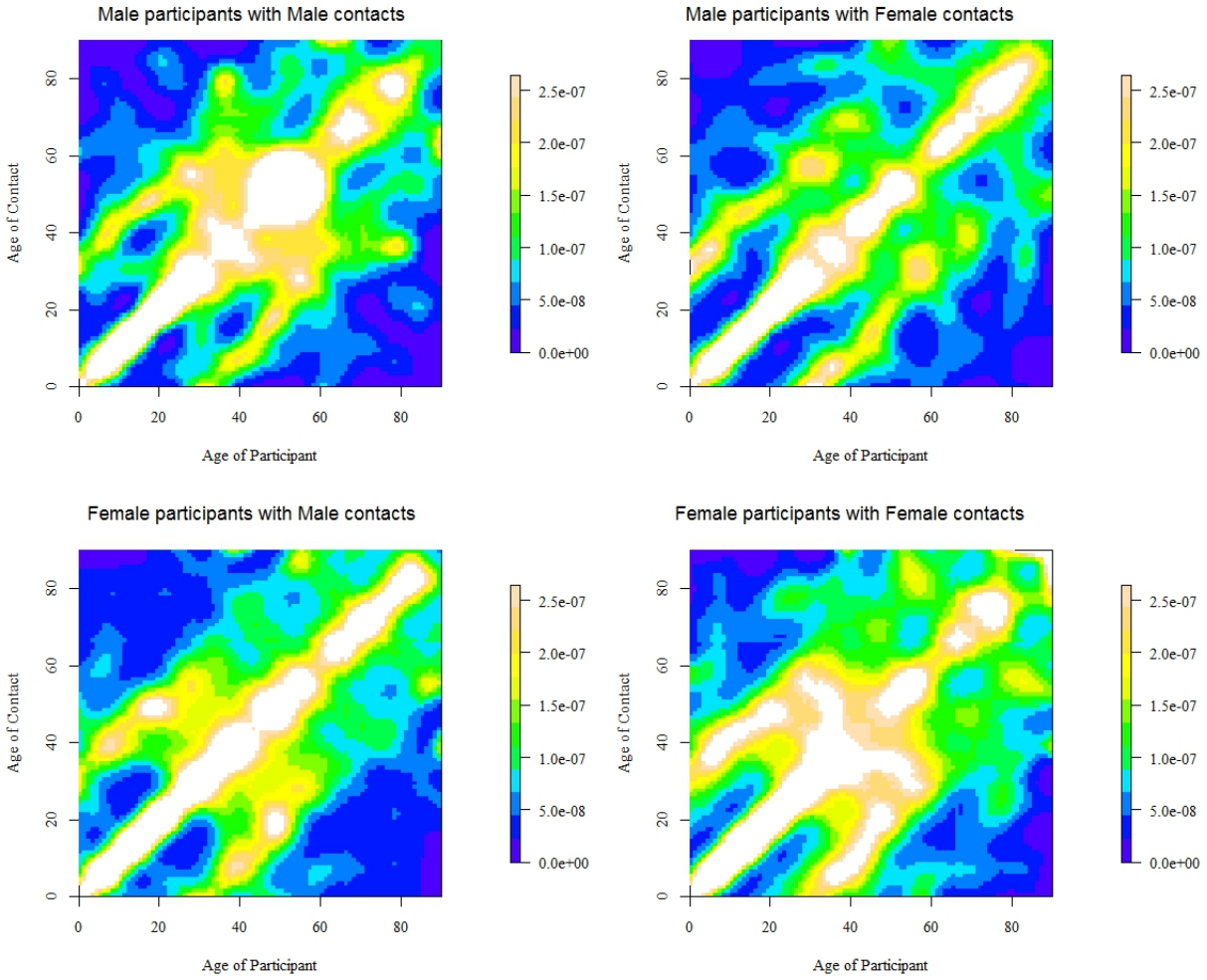


FIGURE 6.12: Contact matrices according to both participant and contact gender, with reciprocity

Similar trends were found for matrices representing physical contact only (Appendix D). R_0 for physical contact basecase matrix was 7.27[6.83,7.79], 7.22[6.67,7.90] for female participant physical matrix and 7.57[6.81,8.62] for male participant physical matrix. Moreover, R_0 was 4.10[3.70,4.68] for female participants with female physical contact only matrix and 3.24[2.95,3.65] for female participants with male contact only matrix. R_0 was 3.03[2.74,3.55] for male participants with female contact only matrix and 4.70[4.09,5.68] for male participants with male contact only matrix.

We hypothesized that the difference in contact patterns between genders could also be visible in the duration of contact (Figure 6.14) and in the location (Figure 6.15). We notably focused on contacts at home and school as known locations for infectious transmission, and at work as differences among gender could result from differences in employment. Concerning duration, the main difference is that female contacts are usually less assortative than male, for contacts of equivalent duration. Concerning the

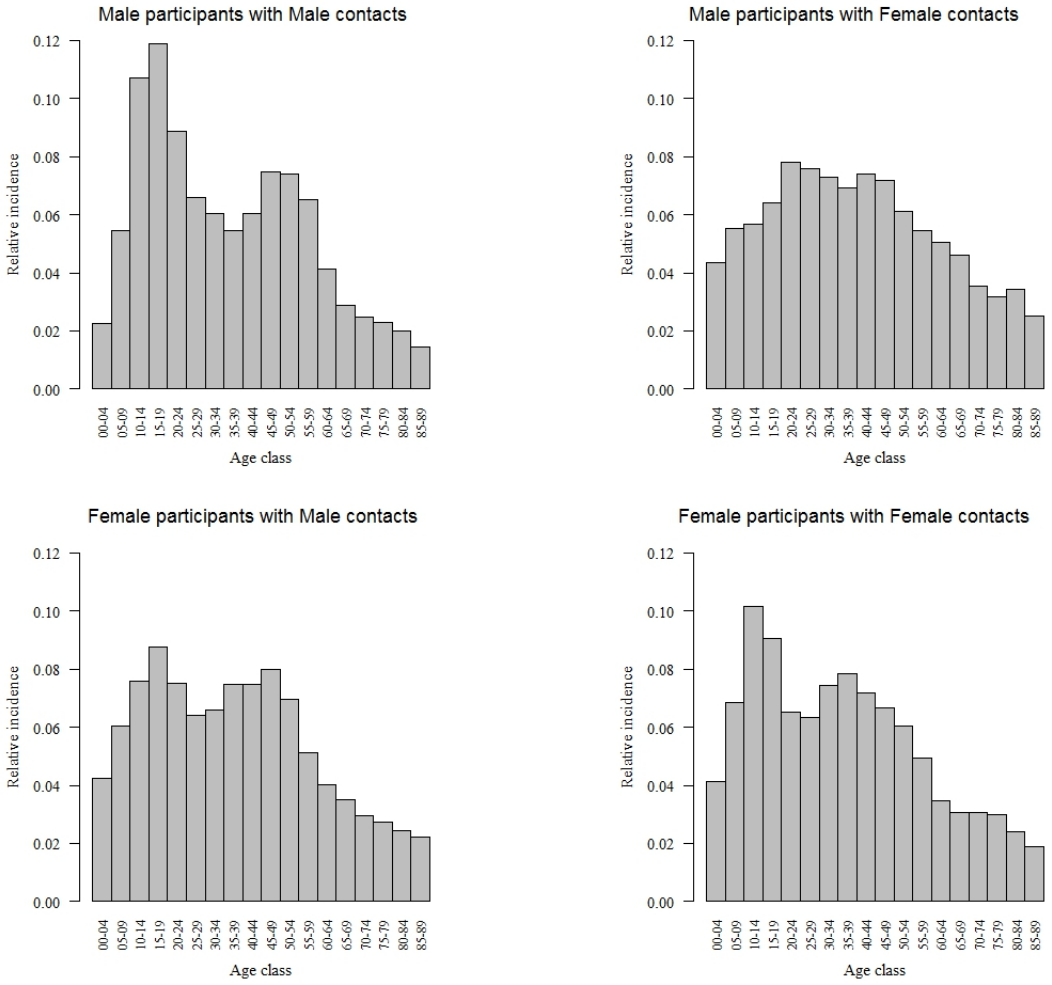


FIGURE 6.13: Relative incidence calculated from gender specific matrices

location, the main difference concerns contacts made at work, when taking into account SPC. Contacts (with SPC) at work were notably much higher for participants before 45 years old, which was not compensated by the slightly higher rates among females after 45 years, as expressed by a maximum eigen value for male 1.5 times the value for females (while the difference was minimal for other locations).

6.2.3 Difference in ratio for France and POLYMOD

We applied to the POLYMOD data the same approach we used with the Comes-F data to estimate ratio of contacts with 2 x 2 matrices (Table 3.3), although no differences in gender were originally described in the publications related to the POLYMOD study. When we compared the findings for France and for the other countries of POLYMOD, we found similar trends between all the countries, albeit with different amplitudes (Table 6.4). Therefore, we can conclude that the gender differences we found in the Comes-F

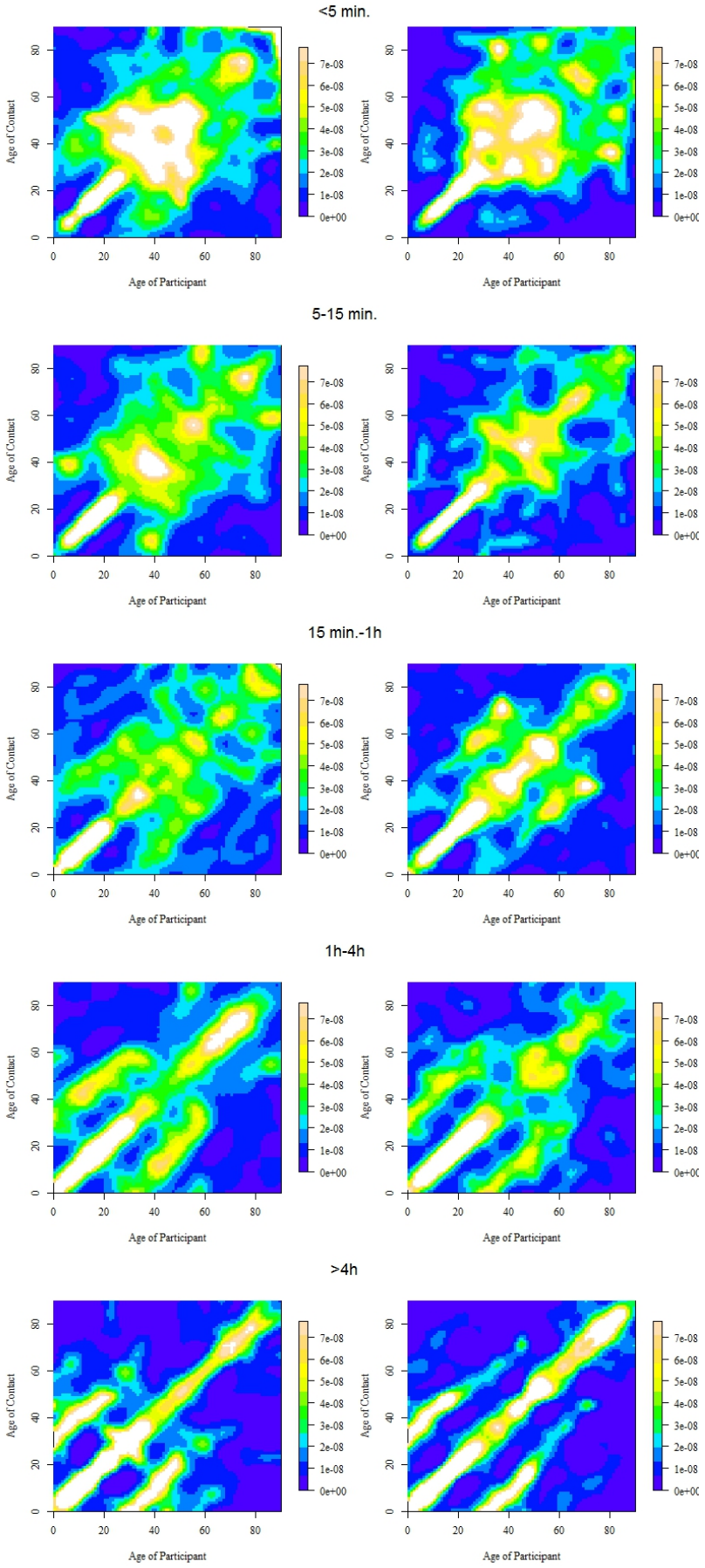


FIGURE 6.14: Duration matrices for female participants (on the left) and male participants (on the right).

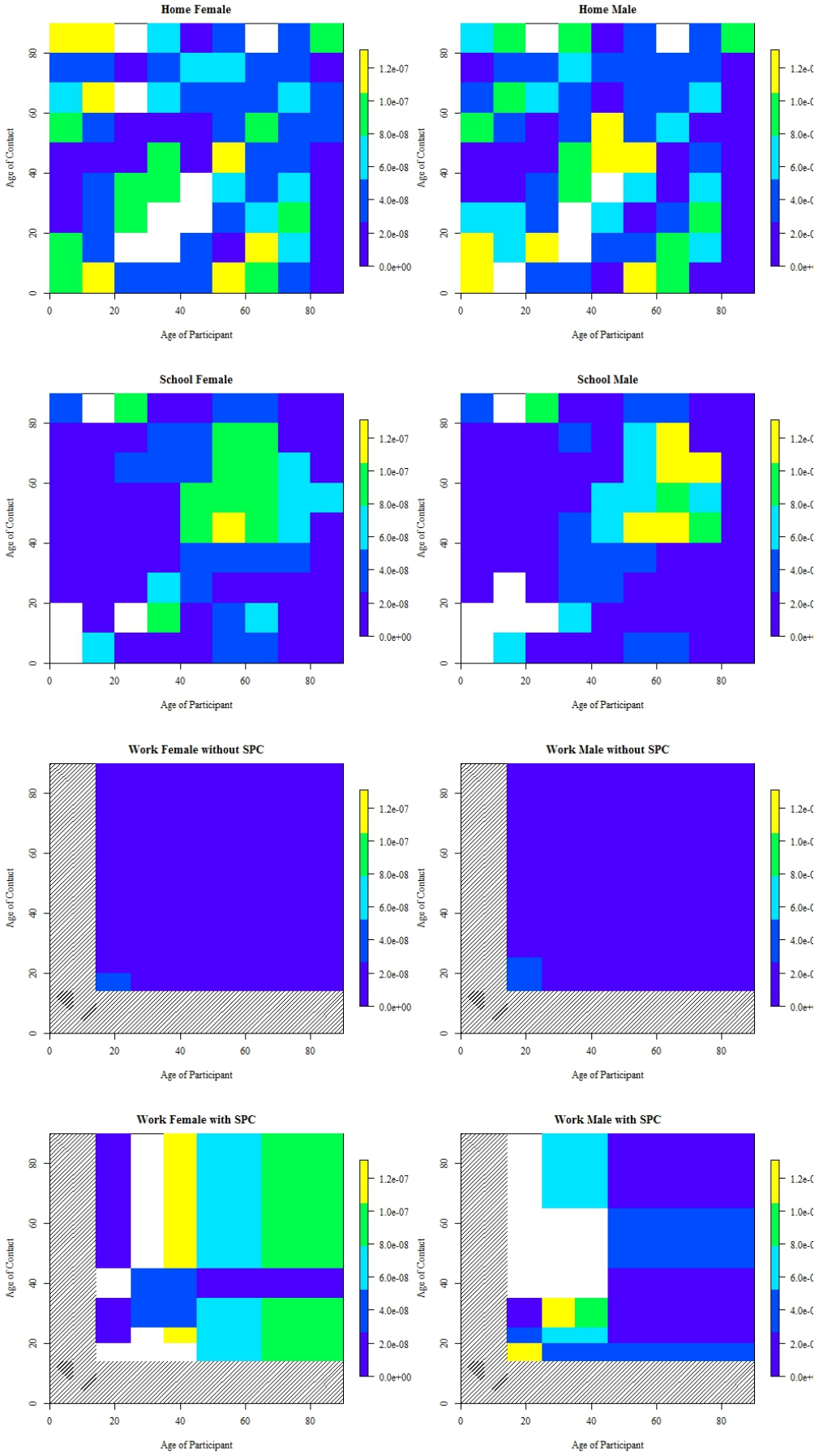


FIGURE 6.15: Location matrices for female participants (on the left) and male participants (on the right).

study are neither the result of chance, neither a French specificity. Males had less contacts than females, notably adults males with children in general, and males have usually less contacts with females than with males, compared to females.

6.3 Taking gender into account

In Chapter 4, we estimated the risk of an outbreak for measles and rubella, taking gender into account when modelling the susceptibility and using the contact matrices to estimate the effective reproduction number. Figure 6.16 illustrates how the next generation operator is obtained, which is the basis to extrapolate the effective reproduction ratio or the age-relative incidence of a potential outbreak. Figure 6.17 shows the same process when gender is taking into account. We aimed to assess how the gender differences in susceptibility profiles (estimated from seroprevalence survey and coverage data) and contact matrices could influence the results (Figure 6.18). To do so, we used "uniform" (i.e. not gender-related) as well as gender-related susceptibility, with "uniform" and gender-related contact matrices. To use uniform matrices with gender-related susceptibility, we duplicated the uniform contact matrices four times. Similarly, we duplicated the susceptibility profile when uniform susceptibility was used with gender-related matrices. We used this approach for measles and rubella, but also for mumps. As susceptibility for mumps was not influenced by gender according our initial modelling analysis (Table 4.3), we hypothesized that it would permit to highlight the influence of gender in contact matrices. Tables 6.5, 6.6, 6.7 summarize the influence of gender in susceptibility and contact matrices on the R_e for measles (dataset from 2013), mumps and rubella, respectively. Taking into account gender for susceptibility reduced InterQuartile Range (IQR) for measles and rubella, but not for mumps. Using gender-related matrices had little influence on IQR. Taking into account gender for susceptibility systematically lower median and mean of R_e for each pathogens (although minimally for mumps), but gender-related matrices had minimal and heterogeneous effect (increasing for measles, decreasing for mumps and rubella). Taking gender into account for susceptibility and matrices systematically decreases median and mean compared to the "uniform" approach. Figures 6.19, 6.20, 6.21 illustrate the influence of gender in susceptibility and contact matrices on the age-dependent relative incidence. We present in the same figure age-dependent relative incidence using Uniform matrix & Uniform susceptibility (black), Gender-related matrix & Uniform susceptibility (blue), Uniform matrix & Gender-related susceptibility (red) and Gender-related matrix & Gender-related susceptibility (green). Differences were seen mainly for 15-25 year old and 35-50 year old individuals. For measles and mumps, the differences in relative incidence for 35-50 years individuals resulted almost exclusively from the fact of taking into account gender-related matrices. Of note, we

France		Contact (Male & female)		Contact (Male)		Contact (Female)	
Participant		≤18y	>18y	≤18y	>18y	≤18y	>18y
Male	≤18 years	0.88[0.73;1.06]	0.85[0.75;0.96]	1.42[1.15;1.74]	0.99[0.83;1.18]	0.51[0.42;0.62]	0.75[0.67;0.84]
	>18 years	0.63[0.48;0.82]	0.95[0.86;1.05]	0.71[0.52;0.97]	1.15[1.01;1.31]	0.55[0.39;0.78]	0.79[0.71;0.87]
Belgium		Contact (Male & female)		Contact (Male)		Contact (Female)	
Participant		≤18y	>18y	≤18y	>18y	≤18y	>18y
Male	≤18 years	0.85[0.61;1.19]	0.83[0.68;1.01]	1.28[0.91;1.79]	0.87[0.66;1.15]	0.55[0.37;0.80]	0.79[0.66;0.95]
	>18 years	0.78[0.52;1.15]	0.97[0.82;1.14]	0.78[0.50;1.21]	1.21[1.00;1.47]	0.77[0.43;1.37]	0.79[0.67;0.95]
Finland		Contact (Male & female)		Contact (Male)		Contact (Female)	
Participant		≤18y	>18y	≤18y	>18y	≤18y	>18y
Male	≤18 years	1.02[0.83;1.26]	0.97[0.86;1.10]	1.69[1.33;2.14]	1.12[0.96;1.32]	0.60[0.47;0.77]	0.88[0.76;1.02]
	>18 years	0.85[0.66;1.10]	0.85[0.73;0.96]	0.78[0.57;1.08]	1.30[1.10;1.54]	0.80[0.58;1.09]	0.62[0.53;0.72]
Germany		Contact (Male & female)		Contact (Male)		Contact (Female)	
Participant		≤18y	>18y	≤18y	>18y	≤18y	>18y
Male	≤18 years	1.08[0.87;1.33]	0.96[0.77;1.21]	1.80[1.34;2.42]	1.17[0.84;1.63]	0.65[0.50;0.85]	0.87[0.72;1.05]
	>18 years	0.78[0.48;1.27]	1.18[1.05;1.33]	0.71[0.44;1.12]	1.50[1.29;1.74]	0.86[0.49;1.52]	0.93[0.82;1.05]
Italy		Contact (Male & female)		Contact (Male)		Contact (Female)	
Participant		≤18y	>18y	≤18y	>18y	≤18y	>18y
Male	≤18 years	1.05[0.87;1.26]	0.99[0.85;1.15]	1.51[1.23;1.86]	1.04[0.83;1.30]	0.72[0.58;0.89]	0.95[0.81;1.11]
	>18 years	0.51[0.35;0.74]	1.19[1.05;1.36]	0.65[0.42;1.01]	1.62[1.38;1.91]	0.38[0.24;0.61]	0.88[0.76;1.02]
Luxembourg		Contact (Male & female)		Contact (Male)		Contact (Female)	
Participant		≤18y	>18y	≤18y	>18y	≤18y	>18y
Male	≤18 years	1.03[0.85;1.25]	1.05[0.92;1.21]	1.38[1.11;1.73]	0.70[0.49;1.01]	0.75[0.62;0.92]	0.96[0.83;1.11]
	>18 years	0.58[0.42;0.81]	1.12[0.97;1.29]	1.18[1.00;1.40]	1.45[1.22;1.72]	0.46[0.32;0.65]	0.86[0.74;0.99]
The Netherlands		Contact (Male & female)		Contact (Male)		Contact (Female)	
Participant		≤18y	>18y	≤18y	>18y	≤18y	>18y
Male	≤18 years	0.81[0.57;1.16]	0.77[0.58;1.01]	1.12[0.72;1.75]	0.75[0.50;1.12]	0.62[0.40;0.95]	0.79[0.61;1.02]
	>18 years	0.51[0.23;1.11]	1.27[0.95;1.69]	0.51[0.19;1.33]	2.21[1.61;3.05]	0.48[0.23;1.02]	0.89[0.67;1.19]
Poland		Contact (Male & female)		Contact (Male)		Contact (Female)	
Participant		≤18y	>18y	≤18y	>18y	≤18y	>18y
Male	≤18 years	1.04[0.84;1.28]	0.93[0.77;1.14]	1.51[1.18;1.93]	0.99[0.78;1.27]	0.71[0.57;0.88]	0.90[0.74;1.10]
	>18 years	0.84[0.64;1.11]	1.11[0.98;1.27]	1.05[0.74;1.49]	1.60[1.38;1.86]	0.67[0.50;0.89]	0.78[0.68;0.90]
United Kingdom		Contact (Male & female)		Contact (Male)		Contact (Female)	
Participant		≤18y	>18y	≤18y	>18y	≤18y	>18y
Male	≤18 years	0.90[0.75;1.08]	0.91[0.81;1.03]	1.50[1.22;1.84]	1.13[0.95;1.34]	0.54[0.44;0.68]	0.79[0.68;0.90]
	>18 years	0.65[0.51;0.82]	1.02[0.89;1.17]	0.79[0.60;1.03]	1.38[1.18;1.62]	0.53[0.40;0.71]	0.78[0.68;0.91]

TABLE 6.4: Ratio of contacts for male compared to female participants, for France and for the POLYMOD countries.

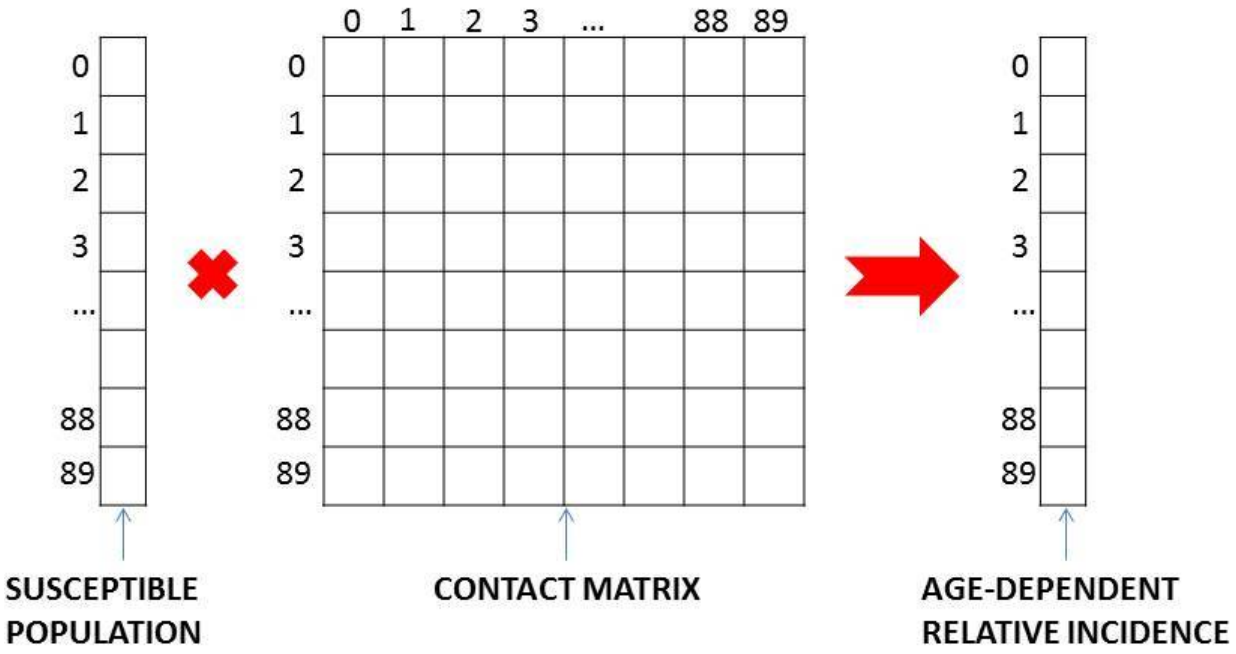


FIGURE 6.16: Combining susceptibility with contact patterns to obtain the next generation

	Uniform susceptibility	Gender-related susceptibility
Uniform matrix	Min. Q1 Median Mean Q3 Max. 1.034 1.285 1.400 1.446 1.518 2.423 IQR: 0.233	Min. Q1 Median Mean Q3 Max. 1.030 1.273 1.373 1.395 1.466 2.034 IQR: 0.193
Gender-related matrix	Min. Q1 Median Mean Q3 Max. 1.056 1.296 1.421 1.457 1.529 2.384 IQR: 0.232	Min. Q1 Median Mean Q3 Max. 1.059 1.293 1.382 1.412 1.481 2.019 IQR: 0.188

TABLE 6.5: Respective role of gender differences on susceptibility and contact matrices, for measles (dataset 2013).

used matrices without SPC, but SPC could have accentuated the differences for this age category. Besides, differences within this age category were more important for males than females in the case of measles and mumps. Albeit the pathogen and the time for data collection are completely different, we cannot help but to compare those curves where there is a difference among young adults between male and female and the curve provided by Viboud et al. [2013] on influenza (Figure 6.3). Consequently, combining our contact matrices with data on influenza could be insightful.

As a conclusion, we showed in the literature review that gender differences in behaviour may help to elucidate gender differences in epidemiology of infectious diseases. Therefore, reports for outbreaks or seroprevalence survey should systematically be presented according age-stratified gender. Albeit mild, the influence of gender in our modelling did exist and may help for a better understanding of the transmission of infectious diseases.

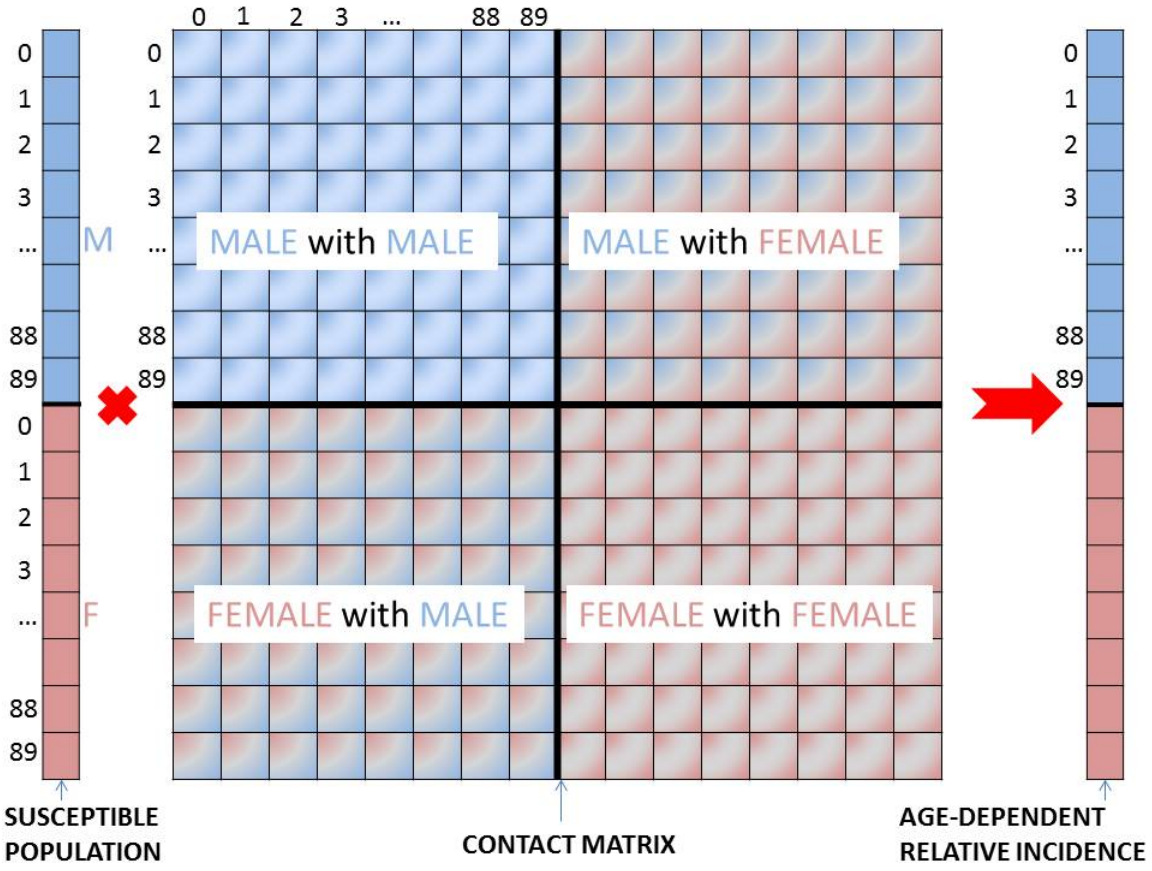


FIGURE 6.17: Combining susceptibility with contact patterns taking gender into account

	Uniform susceptibility	Gender-related susceptibility
Uniform matrix	Min. Q1 Median Mean Q3 Max. 2.330 2.549 2.683 2.714 2.882 3.191 IQR: 0.334	Min. Q1 Median Mean Q3 Max. 2.294 2.540 2.660 2.698 2.888 3.129 IQR: 0.348
Gender-related matrix	Min. Q1 Median Mean Q3 Max. 2.311 2.530 2.665 2.695 2.861 3.172 IQR: 0.331	Min. Q1 Median Mean Q3 Max. 2.240 2.529 2.647 2.682 2.869 3.111 IQR: 0.340

TABLE 6.6: Respective role of gender differences on susceptibility and contact matrices, for mumps.

	Uniform susceptibility	Gender-related susceptibility
Uniform matrix	Min. Q1 Median Mean Q3 Max. 0.400 0.677 0.740 0.753 0.841 1.011 IQR: 0.163	Min. Q1 Median Mean Q3 Max. 0.477 0.671 0.714 0.731 0.805 0.918 IQR: 0.134
Gender-related matrix	Min. Q1 Median Mean Q3 Max. 0.387 0.668 0.737 0.748 0.836 1.013 IQR: 0.168	Min. Q1 Median Mean Q3 Max. 0.467 0.656 0.711 0.724 0.793 0.911 IQR: 0.137

TABLE 6.7: Respective role of gender differences on susceptibility and contact matrices, for rubella.

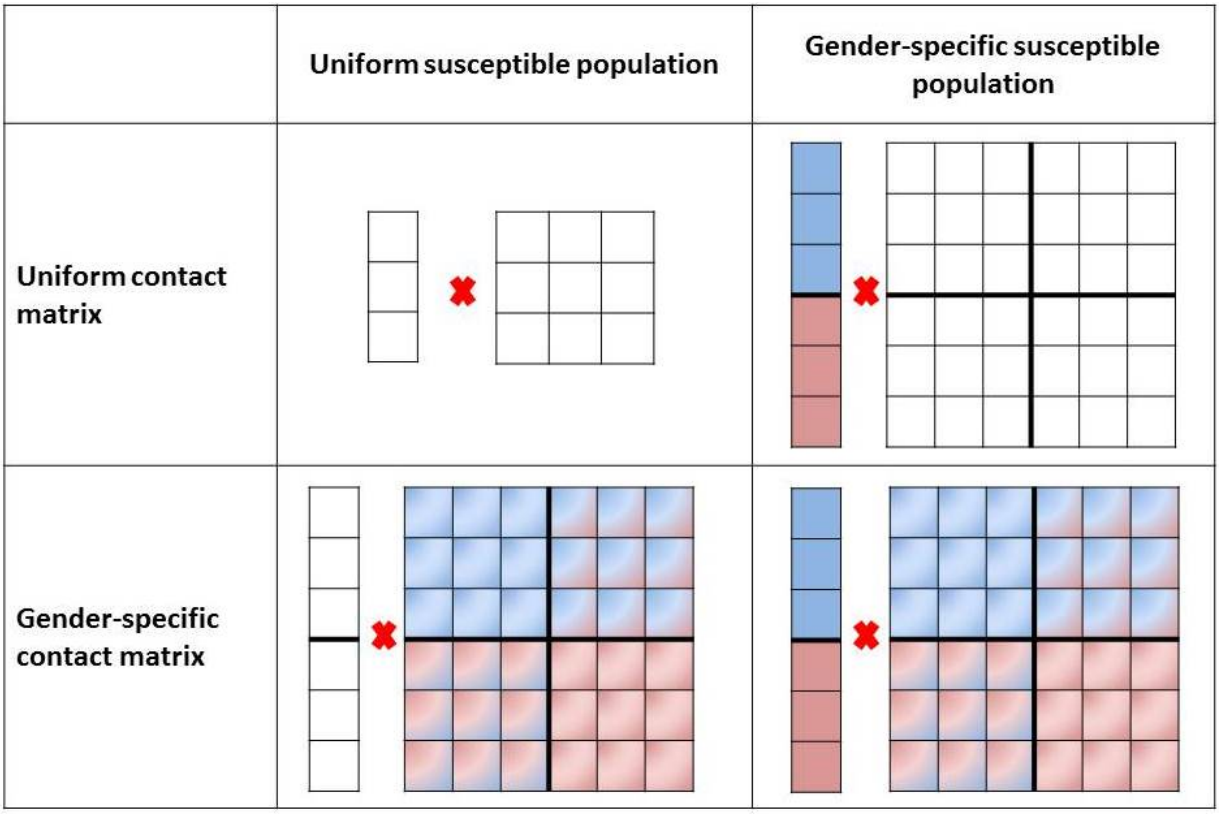


FIGURE 6.18: Different combination of susceptibility and contact patterns: Uniform vs. Gender-specific

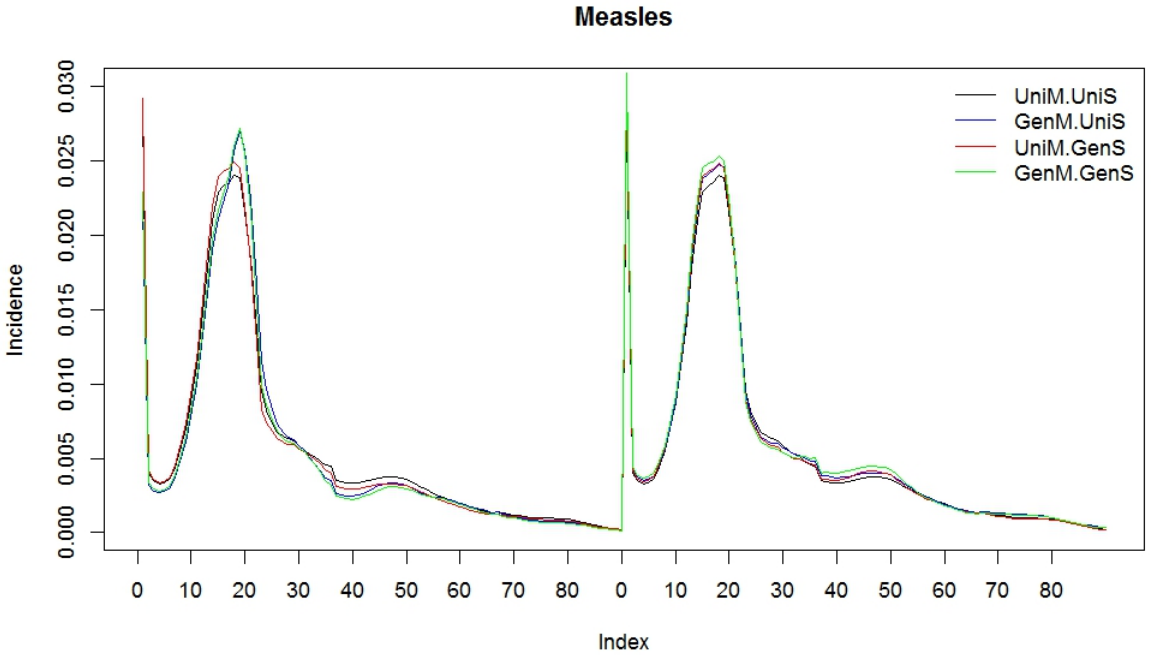


FIGURE 6.19: Age relative incidence for measles (Left: Males; Right: Females), using gender-related susceptibility (GenS) or uniform susceptibility (UniS), and gender-related matrix (GenM) or uniform matrix (UniM)

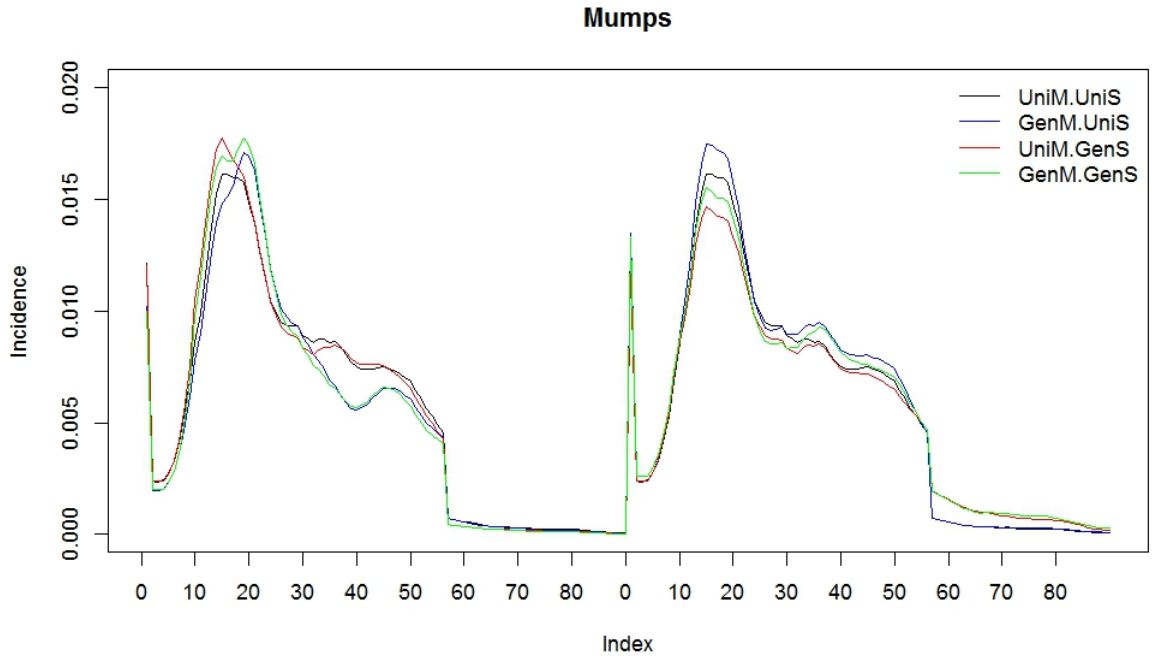


FIGURE 6.20: Age relative incidence for mumps (Left: Males; Right: Females), using gender-related susceptibility (GenS) or uniform susceptibility (UniS), and gender-related matrix (GenM) or uniform matrix (UniM)

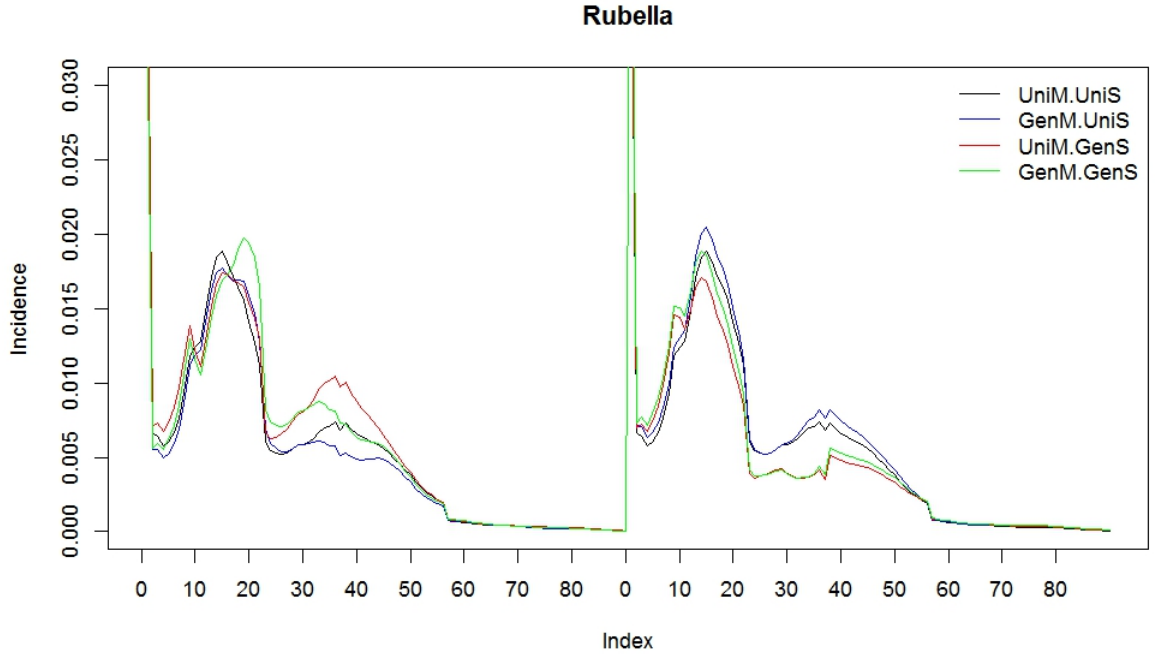


FIGURE 6.21: Age relative incidence for rubella (Left: Males; Right: Females), using gender-related susceptibility (GenS) or uniform susceptibility (UniS), and gender-related matrix (GenM) or uniform matrix (UniM)

Chapter 7

General discussion

In this thesis, we used original data collected in 2012 in France to build contact matrices with the methodology developed for POLYMOD. Afterwards, we used these newly provided matrices to assess the risk of re-emergence of measles, mumps and rubella in France, and then to explore the influence of weather on social behaviour. Finally, we reviewed the impact of gender in several infectious diseases and explored the influence of gender in modelling with contact matrices.

7.1 Summary of our findings

This work resulted in the first French contact matrices estimated from a large population survey, described in Chapter 3. Moreover, it is the first to assess temporal variations of mixing patterns with the methodology of contact diaries. Despite a trend towards more contact in April/May compared to February/March, temporal variation was barely significant, and very mild with regards to other influencing variables such as age, household size, gender, holidays and weekends. Otherwise, the French contact matrices shared many similarities with the matrices provided by the POLYMOD studies, with mixing patterns highly assortative with age, a large contact rate for individuals under 20 years, and a substantial assortativity between children and parents. However, our study also presented some specificities.

It notably highlighted the gender differences in the number of contacts and in mixing patterns. Gender differences in infection and epidemiology have been known for a long time but is incompletely understood and usually attributed to gender differences in immunity. However, some authors have suggested that different social behaviour between boys and girls could impact infectious disease epidemiology [Aaby, 2007]. Although we were the first to present an impact of gender on mixing patterns, this effect is not

specific to France (Table 6.4). While gender was not significantly associated with the number of contacts in the POLYMOD study, this was mainly because the analysis was done merging the datasets from the 8 countries. Reanalysing the POLYMOD data for each country separately, building 2x2 matrices, we were able to show a similar effect in each country from the POLYMOD study, thereby confirming that gender differences in mixing patterns is neither a French specificity nor a statistical chance.

We also showed the importance of the so-called supplementary professional contacts (SPC), which were sometimes taken into account in the publications related to the POLYMOD study [Hens et al., 2009b], but not systematically. First of all, inclusion of the SPC highlighted the importance of the youngest individuals as well as gender, weekends and occupations on the number of contacts and the mixing patterns. The model with the SPC was also the only one to show a significant difference according to the period of the study. Although work places and professional contacts are usually considered of lesser importance compared to home and school for infectious transmission, consideration of SPC illustrates the potential of professional contacts to facilitate infectious transmission from an infected individual beyond his/her age category and his/her infants/parents age category. In that way, professional contacts have a "bridge" function as they facilitate transmission outside of the home. Such a function echoes partly what does school contacts as children get infected at school and then bring back the infection at home. But professional contacts are often situated geographically at a further distance from home than school, then may be more influential for the spatial spread of an epidemic. Moreover, the enlargement of gender differences by the addition of SPC suggests that they result not only from different implication in childcare between men and women but also from differences in employment. Nonetheless, inclusion of SPC raises the problem of the impact of individuals with a very high number of contacts (e.g. bus driver). Such individuals would have a substantial effect on the final results, even though all their contacts may not be relevant for modelling infectious transmission. Truncating the maximum number of contacts at 95% was a simple way though ad hoc to limit the effect of outliers.

The importance of physical contacts or place of contacts has been well-established, but duration of contact has rarely been put upfront except for contacts lasting more than 15 min. as a proxy for intimate contacts. Unravelling the contact matrix according to duration of contacts illustrates that contacts of different duration may have different importance in the definition of the optimal contact suitable for infectious transmission, extending the findings by De Cao et al. [2014]. While we acknowledge that contacts of long duration are of paramount importance for infectious transmission, short-duration contacts may have a role to play in infectious disease transmission, notably favouring transmission across different age categories. Moreover, duration of contact is highly correlated with location of contact (as demonstrated with association rules in Hens et al.

[2009b]), and to a lesser extent with gender of both participants and contacts. Figure 6.14 illustrates the association between participant gender and duration of contact. In addition to the illustrative purpose, duration-specific matrices may be regarded as a result of a recommendation to reduce the duration of contacts during an epidemic or to have contacts restricted to the family. Such recommendations would affect the proportion of contacts of long and short duration and their efficiency could be evaluated with these duration-specific matrices.

The primary incentive for building these contact matrices was the lack of any contact matrix to precisely model infectious disease transmission in France. Besides, we took the opportunity to provide a renewed assessment on the methodology of social contact studies, such as the role of professional contacts, of weekends and holidays, taking advantage of one of the largest population surveys carried out in one of the largest European countries. But estimation of the risk or re-emergence of measles, mumps and rubella in France, or the influence of weather on mixing patterns showed that a larger survey has to be considered with respect to the scale of the country. Once it was placed into perspective with the size of a large country such as France, our survey was finally not that large compared to other POLYMOD surveys. The same problem arose with regard to serological surveys. French serological surveys had twice more samples than the Belgian ones, but the fact that the French population is 6 times Belgium's and the area of metropolitan France is 18 times Belgium's should be taken into account. Therefore, given the size of France, our datasets are no less scarce than those from other European countries. Besides modelling problems, it may have resulted in wide confidence intervals and non-significant trends.
The first "application" of our contact matrices illustrates this point. We combined serological data from 2 surveys, coverage information and the French contact matrices to estimate the risk of resurgence of measles, mumps and rubella. The fact that the BIC always chose a model without spatial coordinates may result from the fact that our dataset is insufficient to take advantage of the complexity of a model with spatial coordinates. It is particularly spectacular for the estimation of the risk in Corsica where the scarceness of data resulted in a confidence interval so wide that the estimation is almost non-informative.

Nonetheless, we were able to show that the reemergence of measles, mumps and rubella was possible in France, the highest risk of an outbreak concerning mumps, with a moderate risk for measles and a very mild, if not non-existent risk for rubella. We also showed that the risk for mumps or rubella outbreaks mainly concerned southeastern and south-central France, primarily because of lower vaccine coverage, notably for the second dose, while the risk for measles is more scattered over the country, probably as

a result of the 2010 outbreak. The fact that "pockets" of susceptibility are scattered instead of being grouped in a particular region may have an influence on the global risk of an outbreak.
However, our model does not really take into account the spatial dimension -apart from the smoothing of positive serology- as it is essentially a juxtaposition of independent modelling for each department. Therefore, it would be of interest to compare our results with those from a spatial modelling of the outbreak risk.
Gender influence on rubella susceptibility was anticipated, as an anti-rubella vaccine has been used specifically for girls to provide protection from rubella and Congenital Rubella Syndrome. However, the influence of gender on measles susceptibility was unexpected. It could result from the use of MMR vaccine instead of a monovalent anti-rubella vaccine to provide protection against rubella to girls. But it may have resulted in an influence of gender on mumps susceptibility as well. Therefore, differences in infectious transmission according to gender may be involved, which we explored in Chapter 6.

In Chapter 5, we tried to explain the mild temporal variations of mixing patterns by the influence of meteorological conditions. Our most striking result was the differential effect of the weather according to weekdays and weekends, that was present in most of the meteorological conditions and for most of the types of contact, even after correction for multiple testing. Our findings are inconsistently comparable to previous studies. That can be explained by the fact that correction for multiple comparisons was not conducted in the other studies, which in addition were carried out in different and very specific settings (Belgium in winter ([Willem et al., 2012]) and tropical Taiwan ([Chan et al., 2015]) compared to our study, which was conducted during 2 seasons throughout metropolitan France), and did not include weekends ([Willem et al., 2012]) or holidays ([Chan et al., 2015, Willem et al., 2012]). Indeed, heterogeneity in our results underlines the difficulty of linking mixing patterns to meteorological conditions, and calls into question the relevance of our approach. As a matter of fact, we did not explore the influence of the spatial component on the results, even though it could be a confounding effect, the weather varying significantly according to the place of residency in a large country such as France, could consequently influence mixing patterns. Moreover, cultural background and social behaviour could also vary considerably according to different latitudes or different urban environments, and spatial components are now recognized as decisive features in infectious disease modelling [Riley, 2007]. But, beyond the choice of the most relevant methodology, our findings call into question the choice of relevant data, as collecting contact data over 2 periods vaguely related to 2 seasons may be insufficient. But to ask a higher number of individuals to report their contacts over 4 seasons might be difficult in terms of logistics as well as the fatigue of participating in such a long study.

One of our most striking results was the influence of gender on mixing patterns, which we explored in Chapter 6. Epidemiological studies have long since demonstrated the influence of gender on morbidity and mortality, but it is usually explained by ontological differences in immunity, or alternatively through reporting bias. There are undoubtedly differences in the immune system that contribute to the epidemiological differences between males and females, but they may explain only a part of the differences between genders. Although differences in social contacts and more generally in behaviour had been cited, they have never been thoroughly studied as an explanation for epidemiological differences and as a possible opportunity to provide gender-specific recommendations. Indeed, our literature review underlines the fact that studies have almost never provided age-stratified gender proportions when reporting epidemics, while only a few studies ([Viboud et al., 2013, Zimmerman et al., 2011]) have shown that gender-specific risk is different between children and adults. Therefore, we recommend that gender-specific incidence always be reported with age stratification.
Besides, we took gender-specific susceptibility and contact matrix into account so as to study the respective influence of each component. Finally, we showed that using gender-specific matrices had a substantial influence, albeit non-crucial, on the results. Therefore, we recommend the use of gender-specific contact matrices, including the gender of both the participant and the contact, whenever relevant.

Among studies on mixing patterns, our findings are congruent with others. We notably confirmed the crucial role of children in the spread of pathogens the general population, having oversampled the children. One should note that we included in our study a substantial number of infants under 1 year old (n=46). To date, only one study has thoroughly described the mixing patterns of the very young [van Hoek et al., 2013], but it focused on 115 infants alone, without exploring the mixing patterns of the rest of the population. It showed that infants had 29% (95%CI: 9% - 49%) fewer contacts with males than with females, with an even greater difference for physical contacts. When physical contacts > 5 minutes were considered within the household, the mother had significantly more contact than the father or the siblings. This difference according to the gender of the contact existed for all the age categories of the contact. Of course, contacts were not assortative with age
Our findings also highlight the potential role of workplace and professional contact in the spread of a pathogen. Although workplaces are usually considered of lesser importance compared to home and school, a social contact study focusing on dynamic social networks [Read et al., 2008] showed the large role of workplace in the spread of casual contact infections such as influenza and measles, which do not require very close contact to transmit.
A large study on contact patterns in Japan was recently published, with 3146 individuals

reporting their contacts [Ibuka et al., 2015]. Besides assortativity by age and influence of weekend, they found different gender-specific mixing patterns according to different age groups. As an example, among participants aged 20-59 years, women had more contact than men with children younger than 15 years, but men had more contact than women with adults aged 20-59 years.
The use of degree distribution is more common in social network studies than in mixing patterns studies, and for sexually transmitted diseases than for close contact infections. However, degree distribution was explicitly shown in a few studies focusing on dynamic social network for modelling the spread of non-sexually transmitted infections [Read et al., 2008], or simply illustrating an household contact-survey [Read et al., 2014]. By using gender-specific degree distribution, we implicitly referred to the networks used for sexually transmitted diseases. Albeit conceptually different, we think it would be of interest to generate contact networks from contact matrices. We are currently reviewing the methodological difficulties we could face with such an approach.

7.2 Perspectives

Contact matrices' usefulness is now well-acknowledged in the modelling of infectious disease transmission. Having provided the first contact matrices for France, we are planning to use them to model the spread of pathogens such as pertussis or influenza under the condition to benefit from sufficiently precise data, and also to explore the influence of the matrix structure on the modelling result. In particular, our findings support the need for larger seroprevalence surveys, as even very precise contact matrices will not compensate for the lack of information on population seroprofiles.
The preliminary results obtained with a quantile regression suggested an effect of temperature and weekend on the number of contacts different according to the average number of contacts made by an individual. This approach may describe more thoroughly the influence of weather variables, and consequently may improve our understanding of seasonality. It could be also of interest to re-explore in such ways the data from Belgium as well as to consider other variables such as radiation and length of day. Indeed, radiation and length of day are directly correlated to seasons, with probably little potential confounding variables contrary to the meteorological variables we explored. For this reason, we have contacted the Meteo-France service from InVS to obtain these data. Moreover, we are planning to re-analyse our dataset with a quantile regression in order to evaluate the variation of the effect according to the quantile of the number of contacts.
We intend to use the data from GrippeNet and InfluenzaNet in combination with gender-specific matrices to estimate in which proportion gender differences in mixing patterns may explain gender differences in epidemiology. An obvious approach would be to

estimate a gender-specific q [Goeyvaerts et al., 2010], which may summarize the infectiousness , thereby, which part of the transmission is due to immune differences, or in other word, which part is not due to the contact characteristics. On the contrary, a q similar between male and female would suggest that most of the differences between male and female result from differences in contact and not from intrinsic differences in infectiousness between male and female. Afterwards, a cost-effective analysis of gender-specific vaccination strategy should be evaluated.

We have shown that measles outbreak from 2010-2011 was predictable, but we'll explore thoroughly the cases report to understand to which extent the spatial repartition of cases was predictable. Moreover, we estimated rubella waning rate using Belgian data from ESEN. We are planning to estimate theses rates combining data from other countries from ESEN. Although difficult, we may also try to evaluate the meaning of seropositivity in terms of protection for getting infected, by trying to estimate a probability distribution of getting infected as a function of antibody level. We may use the fact of benefiting of seroprevalence survey for measles before and after an epidemic, of which we have a description. However, we may be limited by insufficiently precise data.

Besides, with a large proportion of children in our survey, and a substantial number of infants under 1 year old, we may provide a thorough analysis of mixing patterns among children. We may use the description of the household to reassess the findings of van Hoek et al. [2013] and to confirm the importance of the mother-child relation in the mixing pattern.

Appendix A

Contact diaries

This appendix present the diary for children and for adult.

UNIVERSITÉ CATHOLIQUE DE LILLE 1875

E ☐☐☐☐☐☐☐☐☐☐ V2

Ipsos

ÉTUDE CONTACTS - CoMEs-F

Quelques données personnelles sur l'enfant qui participe à l'enquête

1. Indiquez son âge : ☐☐ ans

2. Indiquez son sexe :

- Fille ☐1
- Garçon ☐2

3. Quel est votre lien avec l'enfant ?
(une seule réponse possible)

- Mère ☐1
- Père ☐2
- Ni son père, ni sa mère, mais son responsable légal ☐3

4. Quand votre enfant se déplace, quels sont ses **modes de déplacement** privilégiés (avec ou sans vous) ?
Vous pouvez cocher plusieurs réponses pour la semaine et plusieurs réponses pour le week-end / vacances

	La semaine	Le week-end et en vacances
Voiture particulière ou deux roues	☐1	☐1
Transport collectif (bus, métro, train…)	☐2	☐2
À pied	☐3	☐3

Quelques données personnelles sur vous-même

5. Indiquez le code postal de votre résidence principale :

☐☐☐☐☐

6. Vous êtes :

- Une femme ☐1
- Un homme ☐2

7. Indiquez l'âge de **toutes les personnes résidant dans votre foyer** :
- En commençant par vous
- Puis par l'enfant sélectionné pour l'enquête
- Et en poursuivant par les autres personnes : de la plus âgée à la plus jeune.

	Âge		Âge
Vous-même	☐☐ ans	6ème personne	☐☐ ans
Enfant sélectionné	☐☐ ans	7ème personne	☐☐ ans
3ème personne	☐☐ ans	8ème personne	☐☐ ans
4ème personne	☐☐ ans	9ème personne	☐☐ ans
5ème personne	☐☐ ans	10ème personne	☐☐ ans

8. Quel est le diplôme le plus élevé que vous ayez obtenu ?
(une seule réponse possible)

- Aucun diplôme / Certificat d'étude primaires ☐1
- BEPC, brevet ☐2
- CAP, brevet de compagnon, BEP ☐3
- Baccalauréat (général, technique ou professionnel) ☐4
- BTS et diplôme de l'enseignement supérieur du 1er cycle (jusqu'au BAC+3) ☐5
- Diplôme de l'enseignement supérieur du 2ème ou du 3ème cycle, diplômés des grandes écoles… ☐6

9. Quelle est votre **situation professionnelle actuelle** ?
(une seule réponse possible)

- Agriculteur ☐01
- Artisan, commerçant, chef d'entreprise ☐02
- Cadre, profession intellectuelle supérieure ☐03
- Profession intermédiaire ☐04
- Employé ☐05
- Ouvrier ☐06

Passez à **10.**

- Retraité ☐07
- À la recherche d'un emploi ☐08
- Élève ou étudiant ☐09
- Autre sans activité (personne au foyer…) ☐10

Passez à **11.**

(Si vous exercez actuellement une profession)

10. Dans quel **secteur d'activité** travaillez-vous ?
(une seule réponse possible)

- Agriculture, sylviculture, pêche ☐01
- Industrie agricole et alimentaire ☐02
- Autre industrie ☐03
- Énergie ☐04
- Construction ☐05
- Commerce ☐06
- Activités financières et immobilières ☐07
- Services aux entreprises ☐08
- Services aux personnes ☐09
- Éducation, santé, action social ☐10
- Administration ☐11

Quelques informations sur les activités de l'enfant qui participe à l'enquête

11. L'enfant est-t-il scolarisé ?

- Oui ..... ☐1
- Non ..... ☐2

*Si votre enfant n'est **pas scolarisé**, répondez aux **questions 12 à 15***
*Si votre enfant est **scolarisé**, passez **directement à la question 16**.*

➔ **Votre enfant n'est pas encore scolarisé :**

12. Votre enfant est-il habituellement gardé **à la maison ou dans la famille** ?

- Oui..... ☐1
- Non..... ☐2

13. Votre enfant est-il habituellement gardé **au domicile d'une assistante maternelle** ?

- Oui..... ☐1 ➔ *Passez à* **13a** et **13b.**
- Non..... ☐2 ➔ *Passez à* **14.**

13a. En moyenne et sans compter votre enfant, combien d'enfants y a-t-il chez l'assistante maternelle :

|___| enfant(s)

13b. L'assistante maternelle accueille-t-elle l'après midi ou le soir des enfants scolarisés ?

- Oui..... ☐1
- Non..... ☐2

14. Votre enfant est-il habituellement gardé **en crèche** ?

- Oui..... ☐1 ➔ *Passez à* **14a.**
- Non..... ☐2 ➔ *Passez à* **15.**

14a. Dans la crèche :
il y a en moyenne combien d'enfants ?

- Moins de 20 enfants ..... ☐1
- Entre 20 et 50 enfants..... ☐2
- Plus de 50 enfants..... ☐3

15. Si votre enfant n'est pas gardé en crèche :
à quelle fréquence votre enfant va-t-il en halte-garderie ?

- Plus d'une fois par semaine..... ☐1
- Une fois par semaine ..... ☐2
- Très rarement ..... ☐3
- Jamais..... ☐4

Allez directement en question 18.

➔ **Votre enfant est scolarisé :**

16. Combien y-a-t'il d'enfants dans sa classe ?

- il y a moins de 20 enfants dans la classe ..... ☐1
- entre 20 et 30 enfants dans la classe..... ☐2
- plus de 30 enfants dans la classe ..... ☐3

17. Lorsqu'il va à l'école, votre enfant …?
(une seule réponse possible)

- ne mange jamais à la cantine..... ☐1
- mange occasionnellement à la cantine ..... ☐2
- est demi-pensionnaire ..... ☐3
- est interne ..... ☐4

➔ **Les loisirs de votre enfant (qu'il soit ou non scolarisé) :**

18. Votre enfant a -t-il des activités dans un centre aéré ou un centre de loisirs ?

- Oui..... ☐1 ➔ *Passez à* **18a** et **18b.**
- Non..... ☐2 ➔ *Passez à la page suivante*

18a. Le mercredi ou la samedi, durant les périodes scolaires, votre enfant a -t-il des activités dans un centre aéré ou un centre de loisirs… ?

- Toutes les semaines ..... ☐1
- Occasionnellement..... ☐2
- Jamais..... ☐3

18b. Durant les vacances, votre enfant a -t-il des activités dans un centre aéré ou un centre de loisirs … ?

- Plus de 5 semaines par an..... ☐1
- Entre 5 et 2 semaines par an..... ☐2
- Moins de 2 semaines par an ..... ☐3
- Jamais..... ☐4

Guide de remplissage du carnet

Nous vous prions d'indiquer dans ce journal toutes les personnes avec qui l'enfant a un **contact direct** et qu'il a rencontrées durant **les deux journées retenues**.

① **L'enquête concerne les contacts directs**

Qu'est ce qu'un contact direct ?

- Un contact veut dire que l'enfant a **parlé avec quelqu'un en sa présence physique et à une distance inférieure de 2 mètres**.
  - Les contacts par téléphone ou internet sont exclus,
  - les contacts ayant donné à une discussion non rapprochée (plus de 2 mètres) ne doivent pas être pris en compte.
- Un contact peut aussi être physique: **toucher la peau** de l'autre personne (se donner ou se serrer la main, s'embrasser, se donner l'accolade…).

  On ne retient pas les contacts avec des animaux.

② **Une ligne par personne contactée**

Il faut utiliser une seule ligne par personne contactée.

Si l'enfant a rencontré la même personne plusieurs fois dans la même journée, ne remplissez qu'une seule ligne en estimant au total combien de temps il a passé avec cette personne dans la journée.

Exemple 1 : Ce matin, vous avez accompagné votre fille à l'école en prenant le bus. Sa maîtresse était dans le bus et votre fille lui a dit bonjour en s'approchant d'elle. En fin de journée, en partant de l'école, votre fille a un peu discuté avec sa maîtresse. Sa maîtresse vous a expliqué qu'à la récréation elle a mis un pansement au genou de votre fille. Vous connaissez l'âge exact de la maîtresse qui a 26 ans

***Ce qu'il faut noter dans le carnet :** il faut indiquer sur une même ligne l'ensemble des contacts que votre enfant a eu avec sa maîtresse. Ne pas oublier de consigner **tous les lieux** où ont eu lieu les contacts : transport en commun (bus) et école. Additionner la durée totale des contacts : 20 minutes.*

③ **Conseils généraux sur le remplissage du questionnaire**

La réponse au questionnaire sera plus facile si vous (ou votre enfant / ou la personne qui sera avec lui) prenez des notes au fur et à mesure au cours de la journée (toutes les 2 heures ou après les repas par exemple). Vous pouvez aussi vous appuyer sur son rythme habituel.

Vous pouvez décrire ses contacts directs **par ordre chronologique**, en commençant par la personne qu'il a rencontrée en premier lors de la journée et en continuant avec toutes les autres personnes dont vous pouvez ou dont il peut se souvenir en fonction des activités de la journée.

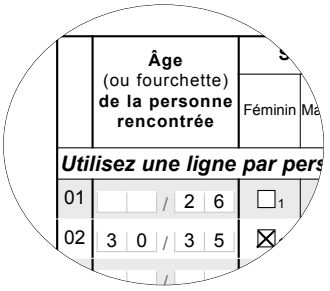
④ **Les difficultés possibles**

Je ne connais pas l'âge de la personne avec qui l'enfant a eu un contact direct ?

Donnez **une estimation de l'âge de la personne** avec qui il a eu un contact.

Exemple 2 : Avec votre fils, vous êtes allés faire des courses. La vendeuse qui avait une trentaine d'années lui a touché la main en lui tendant un produit. Vous allez rarement dans ce magasin.

***Ce qu'il faut noter dans le carnet :** une fourchette pour l'âge de la vendeuse (30-35) et son sexe, le lieu (autre lieu clos), la fréquence des rencontres (la première fois), la vendeuse a touché la peau de votre fils, le contact a duré moins de 5 minutes.*



Que dois-je faire si l'enfant à eu plusieurs contacts directs avec la même personne pendant la journée ?

Utilisez une seule ligne et estimez le temps total qu'il a passé avec cette personne lors de la journée attribuée.

Dans l'exemple 1 : Tous les contacts avec la maîtresse (dans la même journée) sont notés sur une seule ligne (bonjour du matin, pansement, et discussion du soir soit 20 minutes de contact au total)

A noter que la durée totale des contacts est inférieure au temps que votre enfant a passé avec sa maîtresse : environ 6h mais au fond de la classe donc pas en situation de contact.

⑤ **Une fois le questionnaire rempli**

Quand vous avez décrit le dernier contact direct de l'enfant, nous vous conseillons de réfléchir encore une fois afin de vérifier avec lui que vous n'avez pas oublié une activité ou un contact.
Son agenda pourra être utile.

N'oubliez pas de décrire les contacts que vous avez avec l'enfant.

Au moment de remplir les grilles, n'hésitez pas à vous référez au document 'Aide au remplissage' - tous les exemples sont illustrés et les consignes rappelées - nous espérons que cela vous aidera.

Jour 1 : ☐☐ ☐☐

Carnet des contacts de l'enfant désigné pour participer à l'enquête

	Âge (ou fourchette) **de la personne rencontrée par l'enfant**	**Sexe**		**Lieu(x) de contacts** noter tous les lieux où la personne a été en contact avec votre enfant							**À quelle fréquence votre enfant rencontre-il cette personne ?**					**A-t-elle touché sa peau ?**		**Durée totale passée avec la personne**				
		Féminin	Masculin	Domicile, véhicule ou autres lieux privatifs	Crèche, école, collège	Centre scolaire ou de loisirs avec hébergement (Colonie, internat, …)	Chez des proches en lieux clos	Autre lieux clos (restaurant, commerce, …)	Transport collectif	Lieux ouverts (parc, rue…)	(presque) chaque jour	Quelques fois par semaine	Quelques fois par mois	Quelques fois par an ou moins souvent	1ère fois	Oui	Non	Moins de 5 min	5 -15 min	15 min - 1 h	1-4 h	4H ou plus
Utilisez une ligne par personne rencontrée et avec laquelle votre enfant a eu au moins un 'contact'																						
01	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
02	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
03	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
04	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
05	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
06	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
07	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
08	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
09	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
10	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
11	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
12	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
13	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
14	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
15	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
16	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
17	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
18	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
19	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
20	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5

Jour 1 *(suite…)*

	Âge (ou fourchette) **de la personne rencontrée par l'enfant**	**Sexe**		**Lieu(x) de contacts** noter tous les lieux où la personne a été en contact avec votre enfant							**À quelle fréquence votre enfant rencontre-il cette personne ?**					**A-t-elle touché sa peau ?**		**Durée totale passée avec la personne**				
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21	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
22	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
23	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
24	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
25	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
26	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
27	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
28	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
29	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
30	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
31	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
32	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
33	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
34	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
35	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
36	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
37	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
38	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
39	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
40	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5

Jour 2 : ☐☐ ☐☐

Carnet des contacts de l'enfant désigné pour participer à l'enquête

	Âge (ou fourchette) **de la personne rencontrée par l'enfant**	**Sexe**		**Lieu(x) de contacts** noter tous les lieux où la personne a été en contact avec votre enfant							**À quelle fréquence votre enfant rencontre-il cette personne ?**					**A-t-elle touché sa peau ?**		**Durée totale passée avec la personne**				
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Utilisez une ligne par personne rencontrée et avec laquelle votre enfant a eu au moins un 'contact'																						
01	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
02	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
03	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
04	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
05	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
06	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
07	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
08	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
09	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
10	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
11	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
12	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
13	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
14	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
15	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
16	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
17	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
18	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
19	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
20	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5

Jour 2 *(suite…)*

	Âge (ou fourchette) **de la personne rencontrée par l'enfant**	**Sexe**		**Lieu(x) de contacts** noter tous les lieux où la personne a été en contact avec votre enfant							**À quelle fréquence votre enfant rencontre-il cette personne ?**					**A-t-elle touché sa peau ?**		**Durée totale passée avec la personne**				
		Féminin	Masculin	Domicile, véhicule ou autres lieux privatifs	Crèche, école, collège	Centre scolaire ou de loisirs avec hébergement (Colonie, internat, …)	Chez des proches en lieux clos	Autre lieux clos (restaurant, commerce, …)	Transport collectif	Lieux ouverts (parc, rue…)	(presque) chaque jour	Quelques fois par semaine	Quelques fois par mois	Quelques fois par an ou moins souvent	1ère fois	Oui	Non	Moins de 5 min	5 -15 min	15 min - 1 h	1-4 h	4H ou plus
21	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
22	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
23	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
24	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
25	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
26	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
27	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
28	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
29	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
30	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
31	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
32	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
33	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
34	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
35	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
36	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
37	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
38	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
39	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
40	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5

Notes

Un événement particulier s'est déroulé pendant les jours d'enquête, vous vous êtes posé des questions lors du remplissage, vous souhaitez nous apporter des précisions… merci d'écrire vos commentaires ci-dessous…

Pour vous aider

N'hésitez pas à relire **les explications qui se trouvent en page 3 de votre carnet**, ou à vous reporter **aux exemples qui figurent sur la feuille 'Aide au remplissage'**.

Un N° de téléphone est à votre disposition : vous pouvez nous contacter aux heures de bureau si vous avez des questions ou des informations à nous communiquer.

Pour de plus amples informations, vous pouvez aussi nous téléphoner ou nous écrire.

Email : **enquete.contacts@ipsos.com**

Tél : **08 00 97 07 32**

MERCI

d'avoir participé à cette enquête, aux noms d'Ipsos et de l'équipe de recherche en charge de ce projet.

UNIVERSITÉ CATHOLIQUE DE LILLE 1875

V2

Ipsos

A

ÉTUDE CONTACTS - CoMEs-F

Quelques données personnelles sur vous-même

1. Indiquez le code postal de votre résidence principale :

2. Vous êtes… :

- une femme ☐1
- un homme ☐2

3. Indiquez votre âge et l'âge des autres personnes **résidant dans votre logement** : en commençant par vous puis en poursuivant par la personne la plus âgée.

Faites figurer dans ce tableau toutes les personnes résidant dans votre logement.

	Âge		Âge
Vous-même	ans	6ème personne	ans
2ème personne	ans	7ème personne	ans
3ème personne	ans	8ème personne	ans
4ème personne	ans	9ème personne	ans
5ème personne	ans	10ème personne	ans

4. Quel est le diplôme le plus élevé que vous ayez obtenu ? *(une seule réponse possible)*

- Aucun diplôme / Certificat d'étude primaires ☐1
- BEPC, brevet ☐2
- CAP, brevet de compagnon, BEP ☐3
- Baccalauréat (général, technique ou professionnel) ☐4
- BTS et diplôme de l'enseignement supérieur du 1er cycle (jusqu'au BAC+3) ☐5
- Diplôme de l'enseignement supérieur du 2ème ou du 3ème cycle, diplômés des grandes écoles… ☐6

5. Indiquez vos **modes de déplacements** privilégiés

Vous pouvez cocher plusieurs réponses pour la semaine et plusieurs réponses pour le week-end / vacances

	La semaine	Le week-end et en vacances
Voiture particulière ou deux roues	☐1	☐1
Transport collectif (bus, métro, train…)	☐2	☐2
À pied	☐3	☐3

6. Quelle est votre **situation professionnelle actuelle** ? *(une seule réponse possible)*

- Agriculteur ☐01
- Artisan, commerçant, chef d'entreprise ☐02
- Cadre, profession intellectuelle supérieure ☐03
- Profession intermédiaire ☐04
- Employé ☐05
- Ouvrier ☐06

Passez à **7.**

- Élève ou étudiant ☐07 → *Passez à* **9.**

- Retraité ☐08
- À la recherche d'un emploi ☐09
- Autre sans activité (personne au foyer…) ☐10

Passez à la page **3.**

➔ **Vous exercez actuellement une profession :**

(Si vous exercez actuellement une profession)

7. Dans quel **secteur d'activité** travaillez-vous ?
(une seule réponse possible)

- Agriculture, sylviculture, pêche ☐01
- Industrie agricole et alimentaire ☐02
- Autre industrie ☐03
- Énergie ☐04
- Construction ☐05
- Commerce ☐06
- Activités financières et immobilières ☐07
- Services aux entreprises ☐08
- Services aux personnes ☐09
- Éducation, santé, action social ☐10
- Administration ☐11

8. Exercez-vous une profession qui entraîne beaucoup de contacts *(clients pour les commerciaux, les coiffeurs…, patients pour les personnels soignants, élèves ou étudiants pour les professeurs…)* ?

- Oui ☐1 ➔ *Passez à* **8a** et **suivantes**
- Non ☐2 ➔ *Allez directement en page 3*

8a. À combien estimez-vous en moyenne le nombre de ces personnes (clients, patients, élèves,...) que vous rencontrez par jour :

|_____| personnes

8b. Ces contacts professionnels se situent plutôt dans les groupes suivants :
(plusieurs réponses possibles)

- 0-3 ans ☐1
- 3-10 ans ☐2
- 11-17 ans ☐3
- 18-64 ans ☐4
- plus de 64 ans ☐5

8c. Si vous estimez le nombre de ces contacts à plus de 20, nous vous prions de ne pas énumérer vos contacts professionnels dans votre journal, et de seulement indiquer les autres contacts.

- J'ai plus de 20 contacts professionnels ☐1
- J'ai moins de 20 contacts professionnels ☐2

➔ **Vous êtes élève ou étudiant :**

9. Combien y a-t-il d'élèves / étudiants dans votre classe ?
(une seule réponse possible)

- il y a moins de 20 élèves/étudiants dans la classe... ☐1
- entre 20 et 30 élèves/étudiants dans la classe ☐2
- plus de 30 élèves/étudiants dans la classe ☐3

10. Lorsque vous êtes en cours, vous …?
(une seule réponse possible)

- ne mangez jamais à la cantine / au restaurant universitaire ☐1
- mangez occasionnellement à la cantine / au restaurant universitaire ☐2
- êtes demi-pensionnaire ☐3
- êtes interne ☐4

Guide de remplissage du carnet

Nous vous prions d'indiquer dans ce journal toutes les personnes avec lesquelles vous avez été en **contact direct** et que vous avez rencontrées durant **les deux journées retenues**.

① **L'enquête concerne les contacts directs**

Qu'est ce qu'un contact direct ?

- Un contact veut dire que vous avez **parlé avec quelqu'un en sa présence physique et à une distance inférieure de 2 mètres.**
  - Les contacts par téléphone ou internet sont exclus,
  - les contacts ayant donné à une discussion non rapprochée (plus de 2 mètres) ne doivent pas être pris en compte.
- Un contact peut aussi être physique : **toucher la peau** de l'autre personne (se donner ou se serrer la main, s'embrasser, se donner l'accolade…).

  On ne retient pas les contacts avec des animaux.

② **Une ligne par personne contactée**

Il faut utiliser une seule ligne par personne contactée.

Si vous avez rencontré la même personne plusieurs fois dans la même journée, ne remplissez qu'une seule ligne en estimant au total combien de temps vous avez passé avec cette personne dans la journée, comme cela est donné en exemple.

Exemple 1 : Vous avez parlé 10 minutes à votre fils de 9 ans en le conduisant à l'école le matin. Le soir, vous l'avez accompagné pendant ses devoirs, vous avez joué ensemble et discuté ensemble pendant le repas entre 18 et 20 heures (pendant 2 heures) et vous l'avez embrassé avant d'aller au lit.

③ **Conseils généraux sur le remplissage du questionnaire**

La réponse au questionnaire sera plus facile si vous prenez des notes au fur et à mesure au cours de la journée (toutes les 2 heures ou après les repas par exemple). Vous pouvez aussi vous appuyer sur **votre agenda**.

Vous pouvez décrire vos contacts directs **par ordre chronologique**, en commençant par la personne que vous avez rencontrée en premier lors de la journée et en continuant avec toutes les autres personnes dont vous vous souvenez en fonction des activités de la journée.

④ **J'ai plus de 20 contacts professionnels dans la journée**

J'ai une profession qui m'amène à rencontrer de nombreuses personnes. Dois-je limiter le nombre de contacts décrits ?

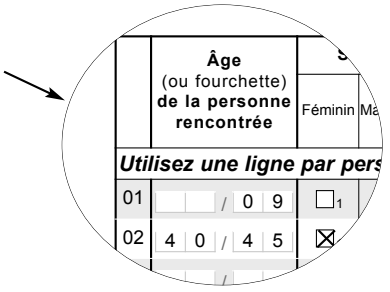
Si vous avez estimé le nombre de ces contacts professionnels à plus de 20, nous vous prions de ne pas énumérer vos contacts professionnels dans votre journal, et de seulement indiquer les autres contacts.
Si vous êtes dans cette situation, n'oubliez pas de le préciser dans le questionnaire dans le point 12c.

⑤ **Les difficultés possibles**

Je ne connais pas l'âge de la personne avec qui j'ai eu un contact direct ?

Donnez **une estimation de l'âge de la personne** avec qui vous avez eu un contact

Exemple 2 : Vous avez parlé à une vendeuse âgée d'une quarantaine d'années dans votre magasin de chaussures préféré, où vous allez plusieurs fois par an.



Que dois-je faire si j'ai eu plusieurs contacts directs avec la même personne pendant la journée ?

Utilisez une seule ligne et estimez le temps total que vous avez passé ensemble lors de la journée attribuée.

Dans l'exemple 1 : Vous avez parlé 10 minutes à votre fils le matin. Le soir, entre le temps passé aux devoirs, à jouer et discuter et à manger, vous avez passé plus de 2 heures 'en contact' avec lui ➔ ***la durée des contacts (avec votre fils) à indiquer pour cette journée sera '1-4h'***

⑥ **Une fois le questionnaire rempli**

Quand vous avez décrit votre dernier contact direct, nous vous conseillons de réfléchir encore une fois afin de vérifier que vous n'avez pas oublié une activité où un contact. Votre agenda pourra être utile à cet effet.

Au moment de remplir les grilles, n'hésitez pas à vous référez au document 'Aide au remplissage' - tous les exemples sont illustrés et les consignes rappelées - nous espérons que cela vous aidera.

Jour 1 : ☐☐ ☐☐

Carnet des contacts

	Âge (ou fourchette) **de la personne rencontrée**	**Sexe**		**Lieu(x) de contacts** noter tous les lieux où la personne a été en contact avec vous							**À quelle fréquence rencontrez-vous cette personne ?**					**A-t-elle touché votre peau ?**		**Durée totale des contacts avec une même personne**				
		Féminin	Masculin	Domicile, véhicule ou autres lieux privatifs	École, collège, lycée ou tout autre lieu d'études	Lieux de travail clos (bureau, atelier)	Chez des proches en lieux clos	Autre lieux clos (restaurant, commerce, …)	Transport collectif	Lieux ouverts (parc, rue) y compris pour le travail (chantier, voie publique…)	(presque) chaque jour	Quelques fois par semaine	Quelques fois par mois	Quelques fois par an ou moins souvent	1ère fois	Oui	Non	Moins de 5 min	5 -15 min	15 min - 1 h	1-4 h	4H ou plus
Utilisez une ligne par personne rencontrée et avec laquelle vous avez eu au moins un 'contact'																						
01	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
02	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
03	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
04	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
05	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
06	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
07	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
08	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
09	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
10	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
11	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
12	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
13	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
14	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
15	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
16	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
17	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
18	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
19	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
20	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5

Jour 1 *(suite…)*

	Âge (ou fourchette) **de la personne rencontrée**	**Sexe**		**Lieu(x) de contacts** noter tous les lieux où la personne a été en contact avec vous							**À quelle fréquence rencontrez-vous cette personne ?**					**A-t-elle touché votre peau ?**		**Durée totale des contacts avec une même personne**				
		Féminin	Masculin	Domicile, véhicule ou autres lieux privatifs	École, collège, lycée ou tout autre lieu d'études	Lieux de travail clos (bureau, atelier)	Chez des proches en lieux clos	Autre lieux clos (restaurant, commerce, …)	Transport collectif	Lieux ouverts (parc, rue) y compris pour le travail (chantier, voie publique…)	(presque) chaque jour	Quelques fois par semaine	Quelques fois par mois	Quelques fois par an ou moins souvent	1ère fois	Oui	Non	Moins de 5 min	5 -15 min	15 min - 1 h	1-4 h	4H ou plus
21	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
22	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
23	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
24	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
25	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
26	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
27	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
28	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
29	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
30	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
31	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
32	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
33	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
34	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
35	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
36	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
37	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
38	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
39	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
40	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5

Jour 2 : ☐☐ ☐☐

Carnet des contacts

	Âge (ou fourchette) **de la personne rencontrée**	**Sexe**		**Lieu(x) de contacts** noter tous les lieux où la personne a été en contact avec vous							**À quelle fréquence rencontrez-vous cette personne ?**					**A-t-elle touché votre peau ?**		**Durée totale des contacts avec une même personne**				
		Féminin	Masculin	Domicile, véhicule ou autres lieux privatifs	École, collège, lycée ou tout autre lieu d'études	Lieux de travail clos (bureau, atelier)	Chez des proches en lieux clos	Autre lieux clos (restaurant, commerce, …)	Transport collectif	Lieux ouverts (parc, rue) y compris pour le travail (chantier, voie publique…)	(presque) chaque jour	Quelques fois par semaine	Quelques fois par mois	Quelques fois par an ou moins souvent	1ère fois	Oui	Non	Moins de 5 min	5 -15 min	15 min - 1 h	1-4 h	4H ou plus
Utilisez une ligne par personne rencontrée et avec laquelle vous avez eu au moins un 'contact'																						
01	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
02	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
03	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
04	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
05	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
06	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
07	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
08	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
09	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
10	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
11	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
12	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
13	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
14	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
15	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
16	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
17	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
18	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
19	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
20	☐☐ / ☐☐	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5

Jour 2 *(suite…)*

	Âge (ou fourchette) **de la personne rencontrée**	**Sexe**		**Lieu(x) de contacts** noter tous les lieux où la personne a été en contact avec vous							**À quelle fréquence rencontrez-vous cette personne ?**					**A-t-elle touché votre peau ?**		**Durée totale des contacts avec une même personne**				
		Féminin	Masculin	Domicile, véhicule ou autres lieux privatifs	École, collège, lycée ou tout autre lieu d'études	Lieux de travail clos (bureau, atelier)	Chez des proches en lieux clos	Autre lieux clos (restaurant, commerce, …)	Transport collectif	Lieux ouverts (parc, rue) y compris pour le travail (chantier, voie publique…)	(presque) chaque jour	Quelques fois par semaine	Quelques fois par mois	Quelques fois par an ou moins souvent	1ère fois	Oui	Non	Moins de 5 min	5 -15 min	15 min - 1 h	1-4 h	4H ou plus
21	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
22	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
23	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
24	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
25	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
26	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
27	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
28	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
29	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
30	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
31	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
32	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
33	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
34	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
35	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
36	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
37	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
38	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
39	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5
40	/	☐1	☐2	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐1	☐2	☐3	☐4	☐5	☐1	☐2	☐1	☐2	☐3	☐4	☐5

Notes

Un événement particulier s'est déroulé pendant les jours d'enquête, vous vous êtes posé des questions lors du remplissage, vous souhaitez nous apporter des précisions… merci d'écrire vos commentaires ci-dessous…

Pour vous aider

N'hésitez pas à relire **les explications qui se trouvent en page 3 de votre carnet**, ou à vous reporter **aux exemples qui figurent sur la feuille 'Aide au remplissage'**.

Un N° de téléphone est à votre disposition : vous pouvez nous contacter aux heures de bureau si vous avez des questions ou des informations à nous communiquer.

Pour de plus amples informations, vous pouvez aussi nous téléphoner ou nous écrire.

Email : **enquete.contacts@ipsos.com**

Tél : **08 00 97 07 32**

MERCI

d'avoir participé à cette enquête, aux noms d'Ipsos et de l'équipe de recherche en charge de ce projet.

Appendix B

Matrices

The following tables are the contact matrices for all contact without SPC, and for touching contact only, respectively.

	0-4y	5-9y	10-14y	15-19y	20-24y	25-29y	30-34y	35-39y	40-44y	45-49y	50-54y	55-59y	60-64y	65-69y	70y+
0-4y	4.42e-07	3.40e-07	1.21e-07	5.53e-08	4.39e-08	9.27e-08	2.06e-07	1.75e-07	1.10e-07	8.05e-08	5.01e-08	6.02e-08	6.76e-08	4.43e-08	2.52e-08
5-9y	3.40e-07	8.25e-07	5.71e-07	1.58e-07	5.03e-08	5.67e-08	1.11e-07	1.75e-07	2.11e-07	1.62e-07	6.37e-08	4.60e-08	5.56e-08	6.85e-08	3.43e-08
10-14y	1.21e-07	5.71e-07	1.63e-06	9.87e-07	1.46e-07	5.63e-08	5.65e-08	9.46e-08	2.29e-07	1.96e-07	9.69e-08	5.17e-08	3.53e-08	4.94e-08	4.80e-08
15-19y	5.53e-08	1.58e-07	9.87e-07	1.28e-06	8.56e-07	2.35e-07	8.02e-08	7.58e-08	1.35e-07	2.11e-07	1.82e-07	1.08e-07	5.50e-08	4.44e-08	3.71e-08
20-24y	4.39e-08	5.03e-08	1.46e-07	8.56e-07	7.13e-07	4.96e-07	2.23e-07	1.49e-07	1.22e-07	1.76e-07	1.73e-07	1.64e-07	1.17e-07	4.99e-08	4.58e-08
25-29y	9.27e-08	5.67e-08	5.63e-08	2.35e-07	4.96e-07	5.16e-07	4.22e-07	2.63e-07	1.79e-07	2.02e-07	1.76e-07	2.08e-07	1.65e-07	7.26e-08	5.79e-08
30-34y	2.06e-07	1.11e-07	5.65e-08	8.02e-08	2.23e-07	4.22e-07	3.46e-07	3.43e-07	2.45e-07	2.38e-07	1.98e-07	1.94e-07	2.11e-07	1.30e-07	7.38e-08
35-39y	1.75e-07	1.75e-07	9.46e-08	7.58e-08	1.49e-07	2.63e-07	3.43e-07	3.70e-07	3.26e-07	2.32e-07	1.77e-07	1.59e-07	1.56e-07	1.45e-07	1.35e-07
40-44y	1.10e-07	2.11e-07	2.29e-07	1.35e-07	1.22e-07	1.79e-07	2.45e-07	3.26e-07	3.11e-07	2.94e-07	2.31e-07	1.86e-07	1.45e-07	1.22e-07	9.07e-08
45-49y	8.05e-08	1.62e-07	1.96e-07	2.11e-07	1.76e-07	2.02e-07	2.38e-07	2.32e-07	2.94e-07	3.24e-07	3.05e-07	2.53e-07	1.97e-07	1.33e-07	7.50e-08
50-54y	5.01e-08	6.37e-08	6.69e-08	1.73e-07	1.64e-07	2.08e-07	1.94e-07	1.59e-07	1.86e-07	2.53e-07	3.13e-07	3.29e-07	2.52e-07	1.45e-07	9.38e-08
55-59y	6.02e-08	4.60e-08	5.17e-08	1.08e-07	1.64e-07	2.08e-07	1.94e-07	1.59e-07	1.86e-07	2.53e-07	3.13e-07	3.29e-07	2.52e-07	1.45e-07	9.38e-08
60-64y	6.76e-08	5.56e-08	3.53e-08	5.50e-08	1.17e-07	1.65e-07	2.11e-07	1.56e-07	1.45e-07	1.97e-07	2.15e-07	2.52e-07	2.36e-07	2.28e-07	1.69e-07
65-69y	4.43e-08	6.85e-08	4.94e-08	4.44e-08	4.99e-08	7.26e-08	1.30e-07	1.45e-07	1.22e-07	1.33e-07	1.19e-07	1.45e-07	2.28e-07	3.60e-07	2.49e-07
70y+	2.52e-08	3.43e-08	4.80e-08	3.71e-08	4.58e-08	5.79e-08	7.38e-08	1.35e-07	9.07e-08	7.50e-08	8.92e-08	9.38e-08	1.69e-07	2.49e-07	2.13e-07

TABLE B.1: Base case matrix

	0-4y	5-9y	10-14y	15-19y	20-24y	25-29y	30-34y	35-39y	40-44y	45-49y	50-54y	55-59y	60-64y	65-69y	70y+
0-4y	2.53e-07	2.13e-07	8.80e-08	4.65e-08	3.55e-08	7.02e-08	1.70e-07	1.47e-07	7.84e-08	5.74e-08	3.70e-08	4.80e-08	5.84e-08	3.51e-08	2.09e-08
5-9y	2.13e-07	4.68e-07	3.58e-07	1.14e-07	3.53e-08	3.95e-08	8.13e-08	1.36e-07	1.63e-07	1.20e-07	4.80e-08	2.94e-08	3.69e-08	5.76e-08	2.61e-08
10-14y	8.80e-08	3.58e-07	1.03e-06	6.43e-07	9.91e-08	3.10e-08	2.68e-08	5.70e-08	1.76e-07	1.46e-07	7.13e-08	3.60e-08	2.31e-08	3.37e-08	3.36e-08
15-19y	4.65e-08	1.14e-07	6.43e-07	9.94e-07	6.58e-07	1.62e-07	3.36e-08	3.51e-08	9.31e-08	1.49e-07	1.33e-07	9.05e-08	3.07e-08	2.53e-08	2.63e-08
20-24y	3.55e-08	3.53e-08	9.91e-08	6.57e-07	5.27e-07	3.64e-07	1.21e-07	7.41e-08	6.38e-08	8.84e-08	1.15e-07	1.18e-07	6.15e-08	2.91e-08	2.80e-08
25-29y	7.02e-08	3.95e-08	3.10e-08	1.62e-07	3.64e-07	3.68e-07	2.82e-07	1.61e-07	8.82e-08	8.30e-08	1.02e-07	1.32e-07	9.85e-08	4.50e-08	2.37e-08
30-34y	1.70e-07	8.13e-08	2.68e-08	3.36e-08	1.21e-07	2.82e-07	2.29e-07	2.12e-07	1.49e-07	1.25e-07	1.21e-07	1.25e-07	1.17e-07	7.21e-08	3.24e-08
35-39y	1.47e-07	1.36e-07	5.70e-08	3.51e-08	7.41e-08	1.61e-07	2.12e-07	2.35e-07	2.06e-07	1.38e-07	1.10e-07	9.26e-08	8.86e-08	8.60e-08	6.50e-08
40-44y	7.84e-08	1.63e-07	1.75e-07	9.31e-08	6.38e-08	8.82e-08	1.49e-07	2.06e-07	2.15e-07	1.87e-07	1.45e-07	1.17e-07	8.92e-08	7.84e-08	5.06e-08
45-49y	5.74e-08	1.20e-07	1.46e-07	1.49e-07	8.84e-08	8.30e-08	1.25e-07	1.38e-07	1.87e-07	2.20e-07	2.17e-07	1.74e-07	1.19e-07	7.99e-08	4.22e-08
50-54y	3.70e-08	4.80e-08	7.13e-08	1.33e-07	1.15e-07	1.02e-07	1.26e-07	1.10e-07	1.45e-07	2.17e-07	2.29e-07	2.23e-07	1.44e-07	7.36e-08	4.98e-08
55-59y	4.79e-08	2.94e-08	3.60e-08	9.05e-08	1.18e-07	1.32e-07	1.25e-07	9.26e-08	1.17e-07	1.74e-07	2.23e-07	2.43e-07	1.79e-07	1.05e-07	6.31e-08
60-64y	5.84e-08	3.69e-08	2.31e-08	3.07e-08	6.15e-08	9.85e-08	1.17e-07	8.86e-08	8.92e-08	1.19e-07	1.44e-07	1.79e-07	1.98e-07	1.83e-07	1.22e-07
65-69y	3.51e-08	5.76e-08	3.37e-08	2.53e-08	2.91e-08	4.50e-08	7.21e-08	8.59e-08	7.84e-08	7.99e-08	7.36e-08	1.05e-07	1.83e-07	2.66e-07	1.88e-07
70y+	2.09e-08	2.61e-08	3.36e-08	2.63e-08	2.80e-08	2.37e-08	3.24e-08	6.50e-08	5.06e-08	4.22e-08	4.98e-08	6.31e-08	1.22e-07	1.88e-07	1.64e-07

TABLE B.2: Physical contact matrix

Appendix C

R code

R code for converting latitude and longitude into geographic coordinate according Lambert 73.

```
# function for conversion
latlong2xy<-function(latitude,longitude){
  phi=(latitude*pi)/180 # conversion en radians
  l=(longitude*pi)/180
  # Variables:
  a=6378137            # half great axis of the ellipsoid (m)
  e=0.08181919106      # first excentricity of the ellipsoid
  l0=lc=(3*pi)/180     # To convert degree in radian: /pi and * 180
  phi0=(46.5*pi)/180   # latitude of origin in radian
  phi1=(44*pi)/180     # first standard parallel (FR: automecoique)
  phi2=(49*pi)/180     # second standard parallele

  x0=700000            # coordinates at the origin
  y0=6600000           # coordinates at the origin

  ##calcul des grandes normales
  gN1=a/sqrt(1-e*e*sin(phi1)*sin(phi1));
  gN2=a/sqrt(1-e*e*sin(phi2)*sin(phi2));

  #calculs des latitudes isometriques
  gl1=log(tan(pi/4+phi1/2)*((1-e*sin(phi1))/(1+e*sin(phi1)))^e/2)
  gl2=log(tan(pi/4+phi2/2)*((1-e*sin(phi2))/(1+e*sin(phi2)))^e/2)
  gl0=log(tan(pi/4+phi0/2)*((1-e*sin(phi0))/(1+e*sin(phi0)))^e/2)
  gl=log(tan(pi/4+phi/2)*((1-e*sin(phi))/(1+e*sin(phi)))^e/2)
```

```
  #calcul de l'exposant de la projection
  n=(log((gN2*cos(phi2))/(gN1*cos(phi1))))/(gl1-gl2)#ok

  #calcul de la constante de projection
  c=((gN1*cos(phi1))/n)*exp(n*gl1)#ok

  #calcul des coordonnees
  ys=y0+c*exp(-1*n*gl0)

  x93=x0+c*exp(-1*n*gl)*sin(n*(l-lc))
  y93=ys-c*exp(-1*n*gl)*cos(n*(l-lc))

  return (c(x93,y93))
}
```

Appendix D

Gender Matrixes

Matrices representing physical contact only showed similar trends that matrices for all contacts (Figures D.1 and D.2).

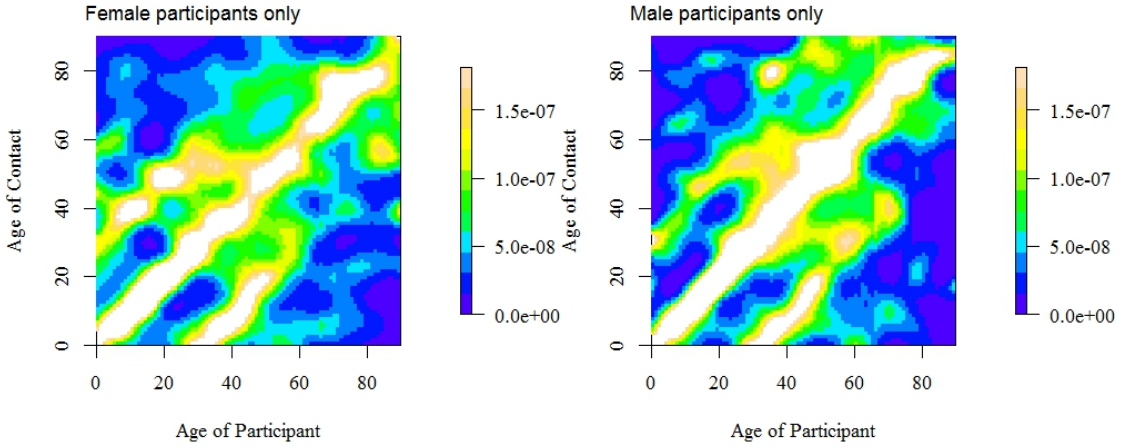


FIGURE D.1: Physical contact matrices according participant gender, without reciprocity

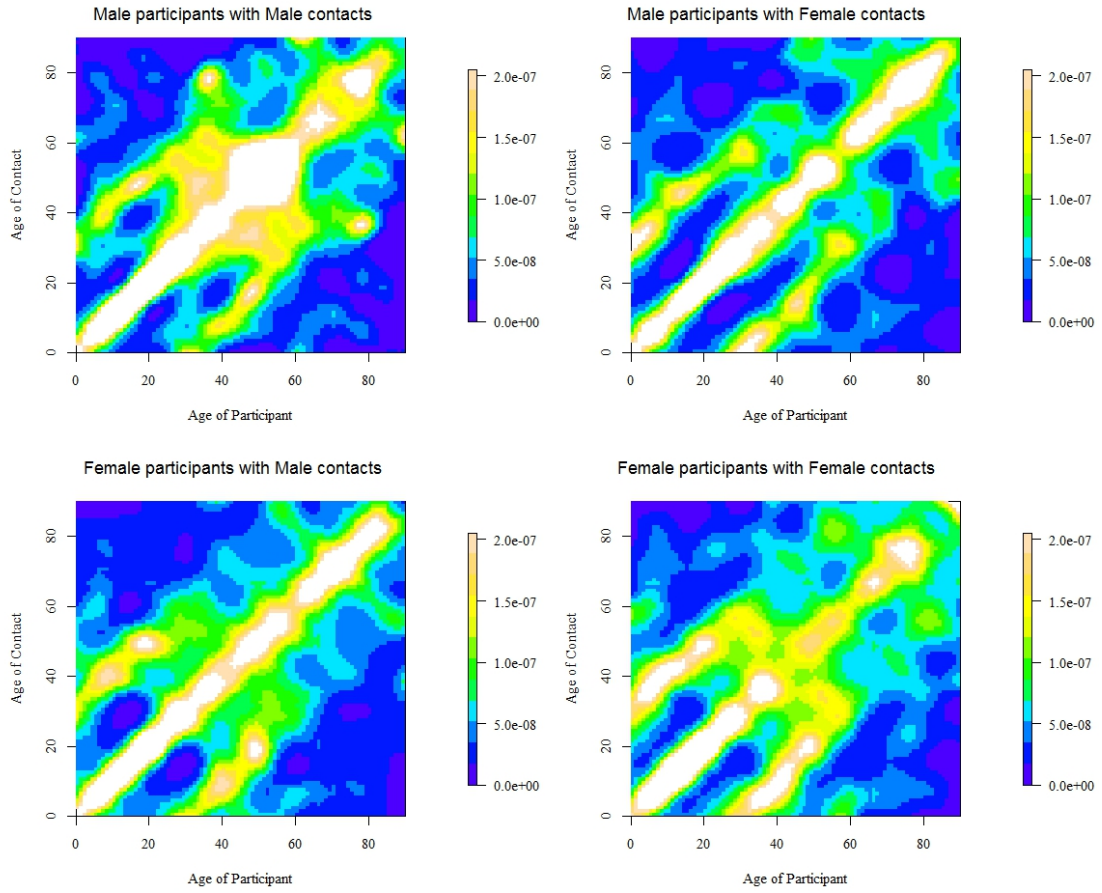


FIGURE D.2: Physical contact matrices according both participant and contact gender, with reciprocity

Appendix E

Weather analysis

E.1 Analysis by weather variable

E.1.1 Temperature

On regular weekdays, temperature (average, minimum or maximum) had no significant effect on the total or physical number of contacts, but participant tended to have a maximum number of contacts toward "medium" temperatures (i.e. for temperature within the InterQuartile range). Likewise, the transmission potential represented by R_0, for total contacts, decreased for low minimum temperature (below median 0.869[0.763;1.003], <Q1 0.836[0.713;0.968]) and increased for low maximum temperature (below median: 1.200[1.023;1.410]). Similarly, during holiday weekdays, total number of contacts decreased with temperature (average temperature <Q1 0.905[0.820,0.995]), as well as R_0 for total contacts (average temperature below median 0.889[0.797,0.996]; minimum temperature below median 0.877[0.781,0.979], <Q1 0.876[0.773,1.000]). On the contrary, temperature had no influence during weekend in total or physical contacts.
On regular weekdays, low temperature decreased the number of long duration contacts (maximum temperature <Q1: >15min 0.894[0.802;0.989]; >1h 0.862[0.749;0.974]; >4h 0.755[0.618;0.901]), but without any influence on R_0, while it decreased short duration (<15 min) contacts during holiday weekdays (average temperature below median 0.851[0.723,0.995]; maximum temperature below median 0.852[0.728,0.998]). On the contrary, during weekend, low temperature increased very long (>4h) contacts (average temperature <Q1 NbC: 1.166[0.959;1.391], R_0: 1.249[0.991,1.596]) while short contacts (<15 min) decreased (maximum temperature <Q1: NbC 0.740[0.570,0.931] and R_0 0.727[0.535,0.974]; minimum temperature <Q1: NbC 0.766[0.580,0.994]).
Low temperature decreased number of contacts at home (average temperature <Q1 (0.846[0.735;0.981]), maximum temperature <Q1 (0.874[0.766;0.989])) as well as R_0

(average temperature below median (0.891[0.787;1.000]), <Q1 (0.757[0.622;0.888]); and maximum temperature <Q1 (0.858[0.731;0.989])). But it increased contacts during weekend (average temperature below median NbC:1.206[1.051,1.395] and R_0:1.222[1.046,1.417]; minimum temperature below median NbC:1.158[1.010,1.340], <Q3 1.152[1.000,1.318]).
School contacts decreased for low minimum temperatures (NbC: below median 0.746[0.593;0.915], <Q3 0.761[0.599;0.948]; R_0: below median 0.915[0.410;0.820]) during regular weekdays.
Contacts at work increased for "medium" temperature, notably when lower than 3rd quartile (average temperature <Q3: 1.509[1.071;2.244], maximum temperature <Q3: 1.438[1.051;2.074], minimum temperature <Q3: 1.467[1.057;2.173]), with similar trend for R_0 (average temperature <Q3: 1.395[0.988;2.018], minimum temperature <Q3: 1.394[0.977;2.133]) during regular weekdays.
Number of contacts in "other" places decreased with temperature (average temperature below median 0.808[0.686;0.975], <Q3: 0.774[0.628;0.957])(maximum temperature <Q3 0.796[0.653;0.992])(minimum temperature <Q1: 0.843[0.690;1.007]) with similar trends for R_0 (minimum temperature <Q1 0.730[0.512;0.998]) during regular weekdays. Similarly during holiday weekdays, low temperature decreased number of contacts in other places (average temperature below median 0.840[0.722,0.990], <Q1 0.833[0.701,0.985]; maximum temperature below median 0.816[0.698,0.958]; minimum temperature <Q1 0.840[0.712,0.995]).

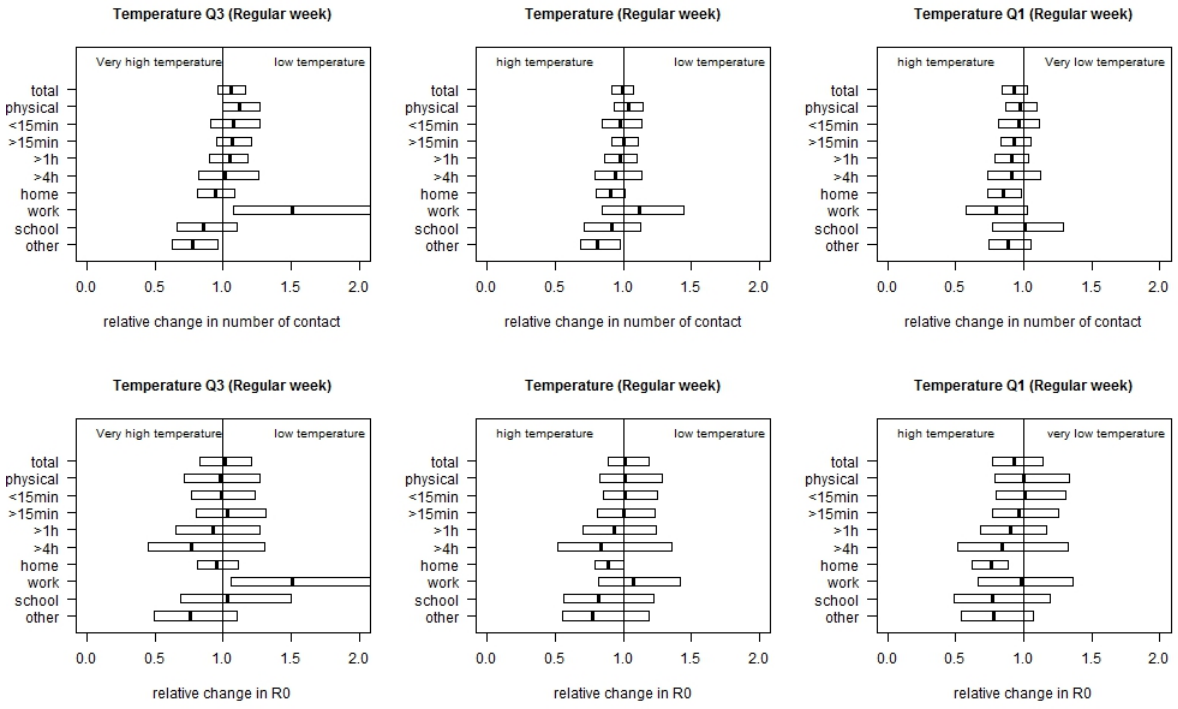


FIGURE E.1: Influence of the temperature on the number of contacts and R_0 during regular weekdays

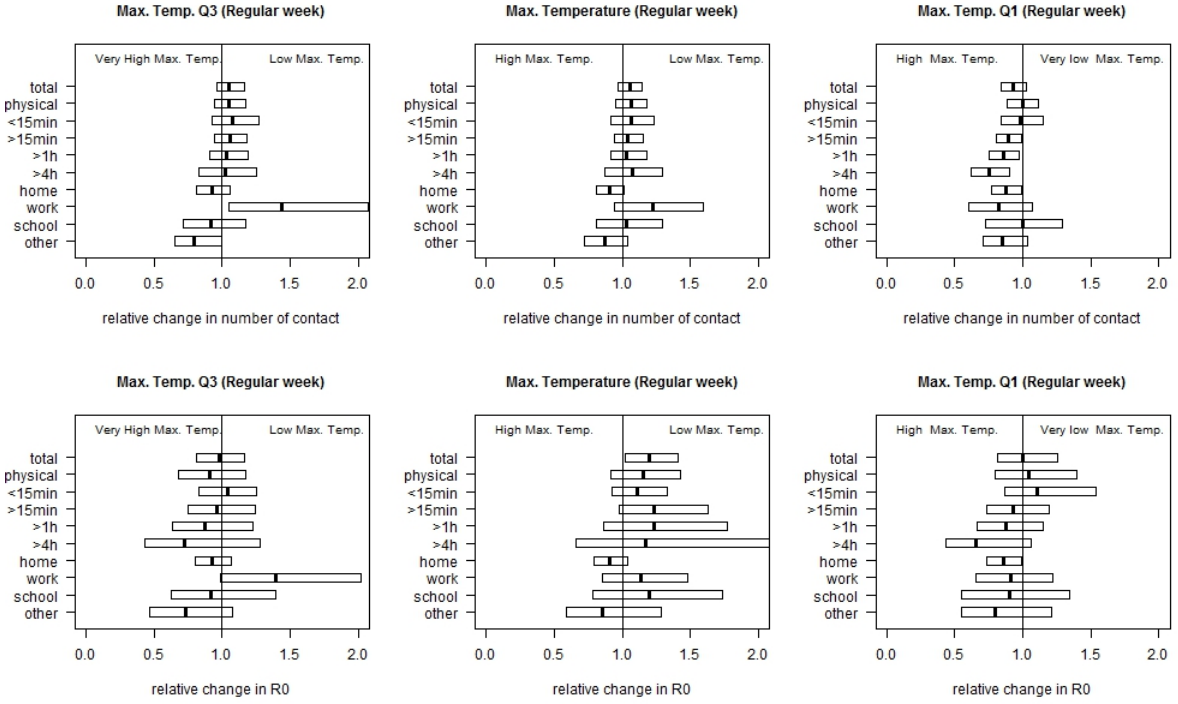


FIGURE E.2: Influence of the maximum temperature on the number of contacts and R_0 during regular weekdays

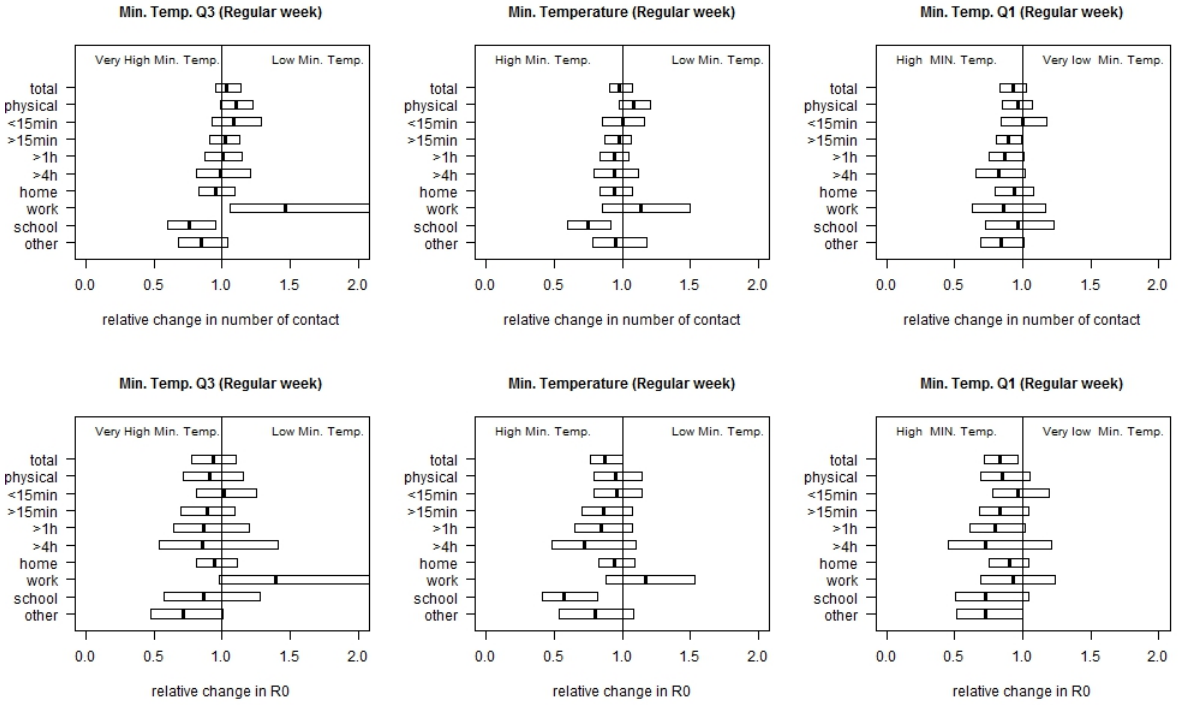


FIGURE E.3: Influence of the minimum temperature on the number of contacts and R_0 during regular weekdays

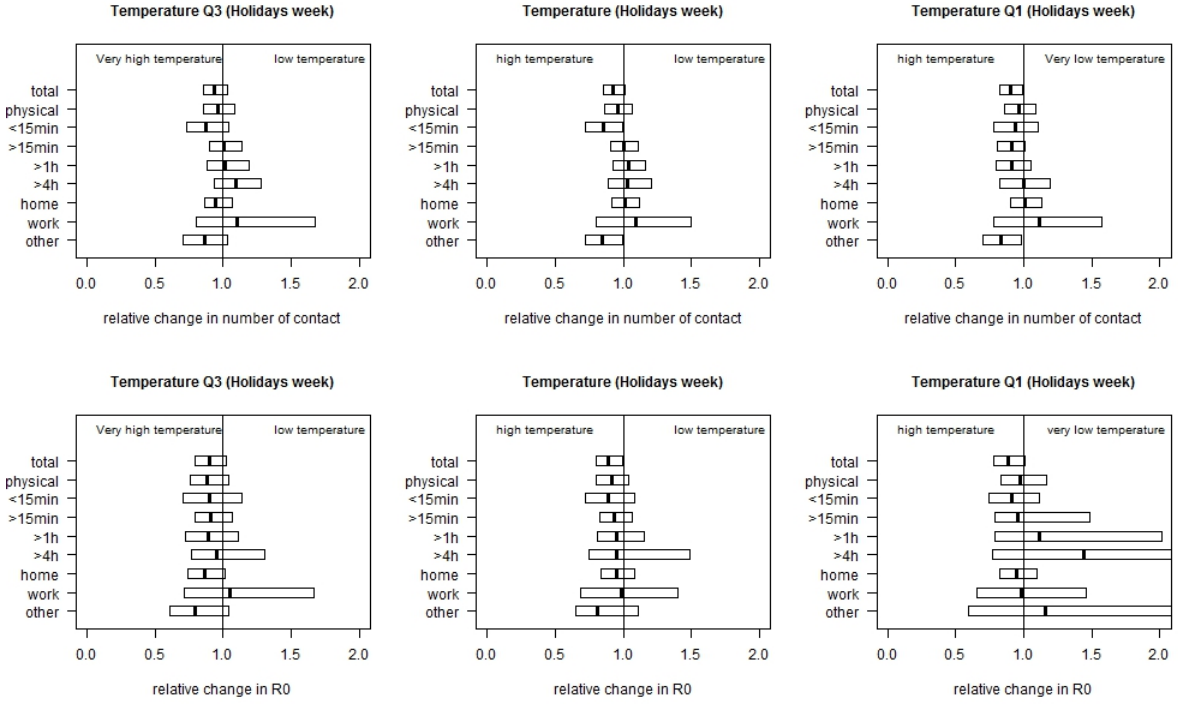


FIGURE E.4: Influence of the temperature on the number of contacts and R_0 during holiday weekdays

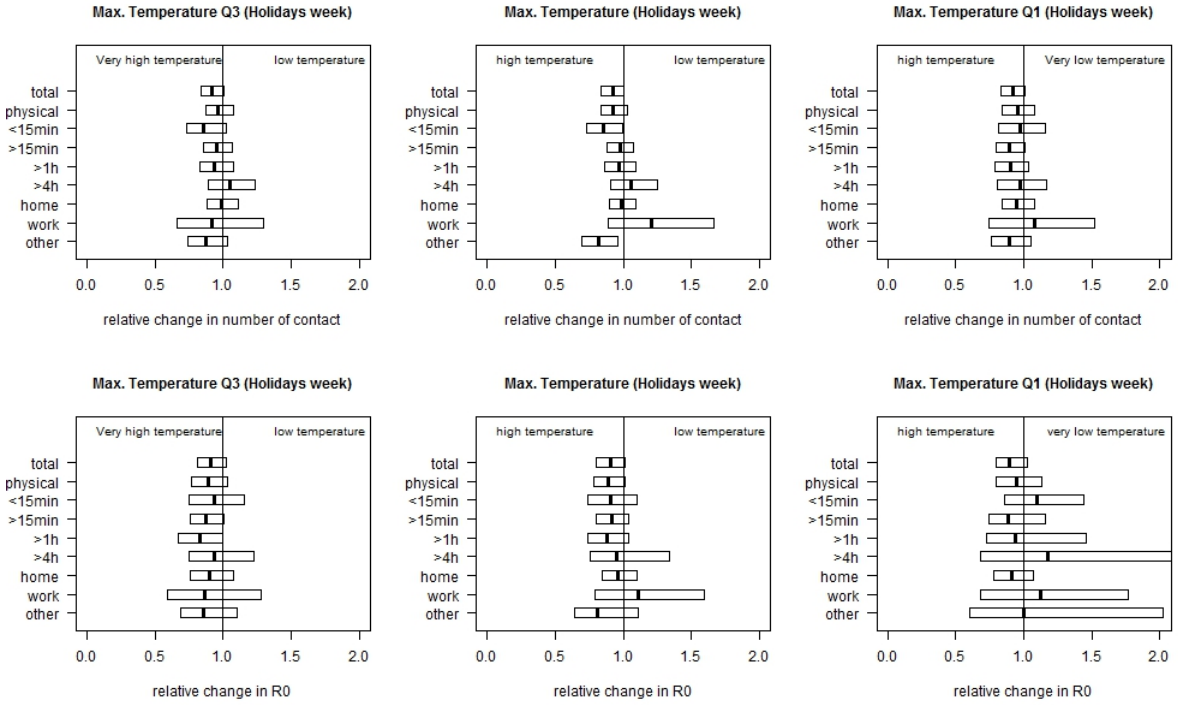


FIGURE E.5: Influence of the maximum temperature on the number of contacts and R_0 during holiday weekdays

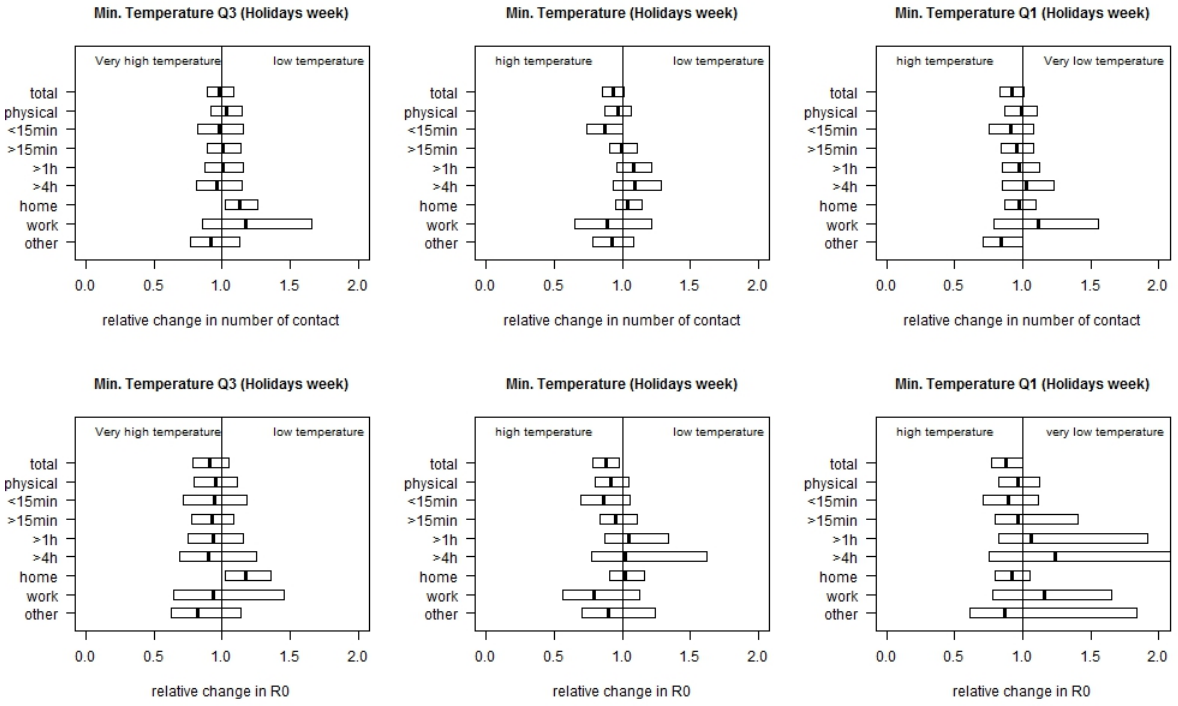


FIGURE E.6: Influence of the minimum temperature on the number of contacts and R_0 during holiday weekdays

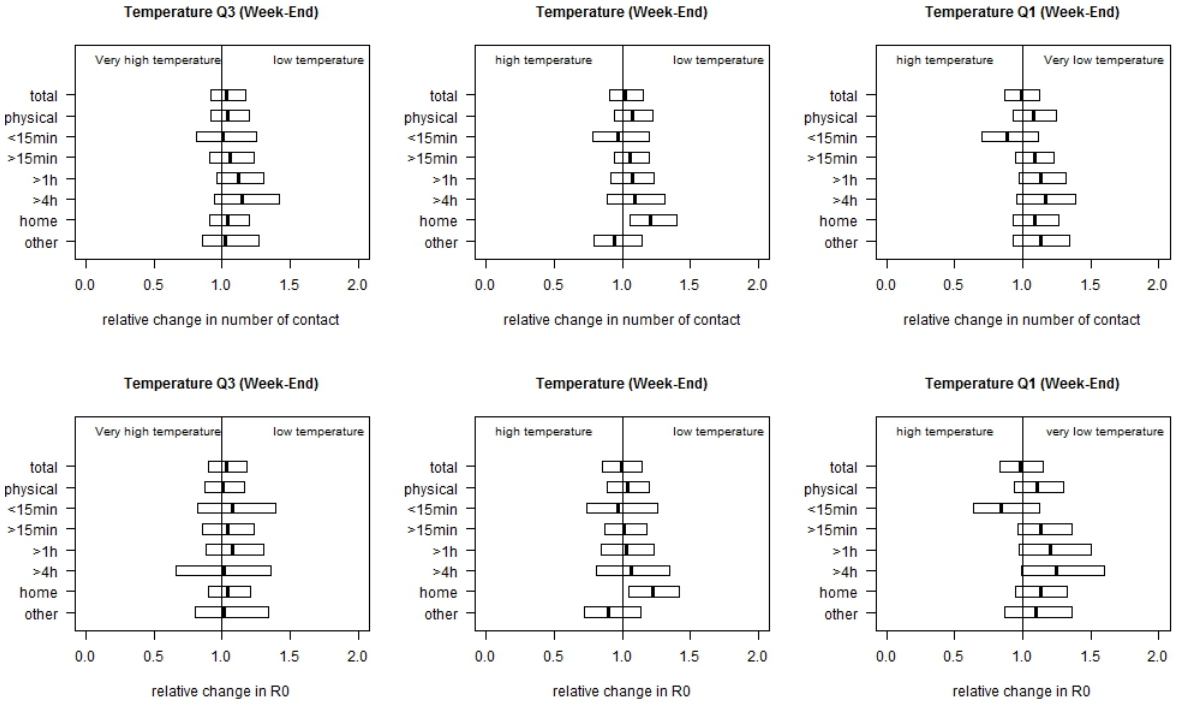


FIGURE E.7: Influence of the temperature on the number of contacts and R_0 during week-end

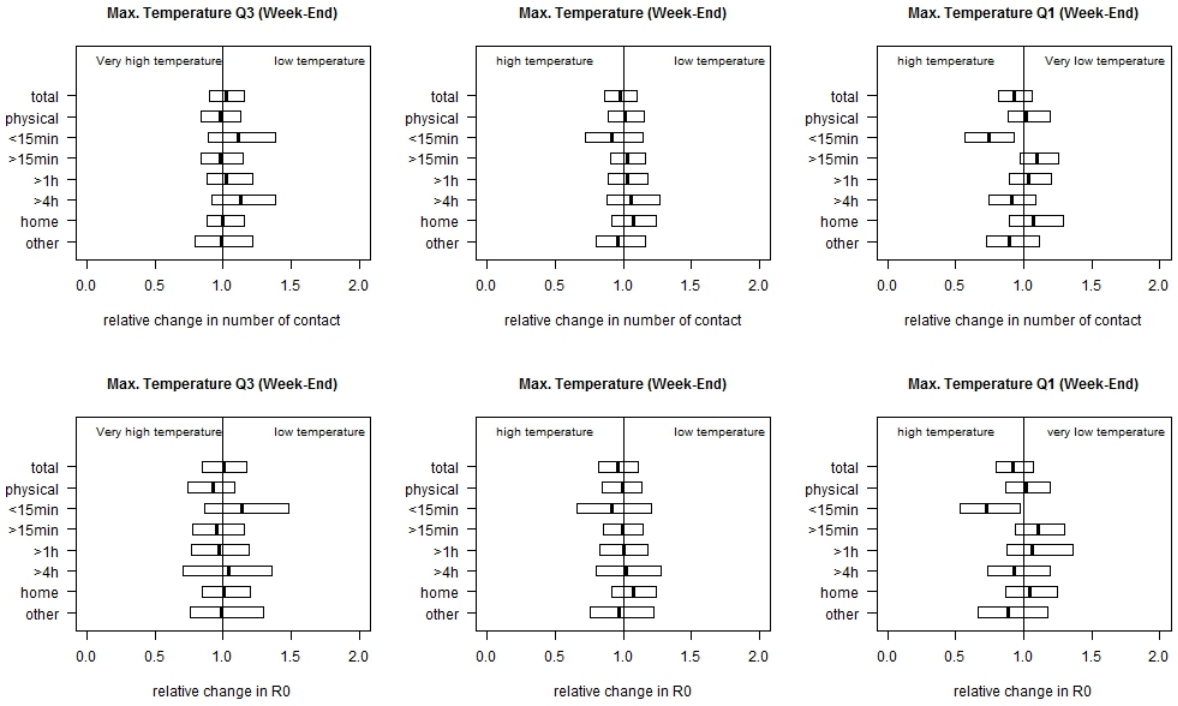


FIGURE E.8: Influence of the maximum temperature on the number of contacts and R_0 during week-end

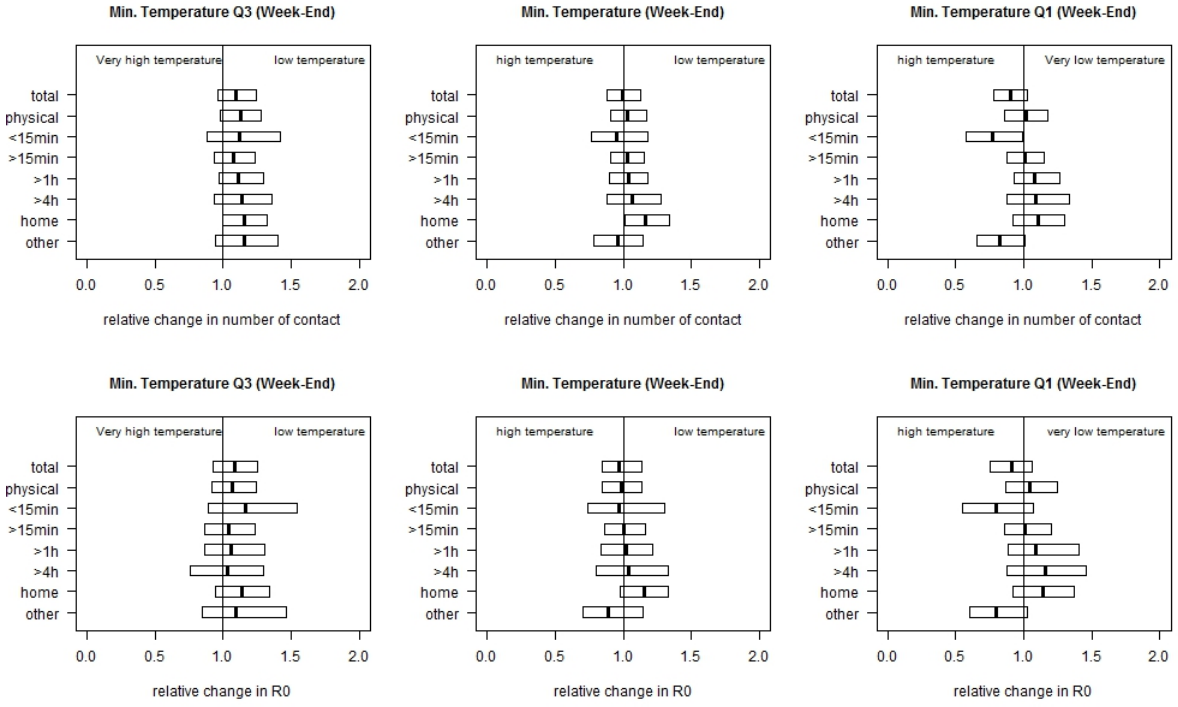


FIGURE E.9: Influence of the minimum temperature on the number of contacts and R_0 during week-end

E.1.2 Absolute Humidity

During regular weekdays, Absolute Humidity had no effect on the total number of all or physical contacts but low absolute humidity decreased the R_0 for all contacts (below median 0.873[0.756;1.009], <Q1 0.935[0.855;1.024], <Q3 0.785[0.642;0.967]) and physical contacts (below median 0.898[0.747;1.095], <Q1 0.970[0.868;1.078], <Q3 0.750[0.574;0.982]).
Very low absolute humidity (<Q1) had a similar effect during holiday weekdays on total contacts (number of contacts 0.893[0.803;0.985] and R_0 0.851[0.746;0.973], but low absolute humidity had an opposite effect during weekends as it increased number of all contacts (below median 1.140[1.011;1.299], <Q3 1.231[1.100;1.387]) and physical contacts (below median 1.180[1.034;1.332], <Q3 1.149[1.006;1.326]), with an impact on R_0 limited to all contacts(<Q3 1.237[1.086;1.420]).
Absolute Humidity had little effect on contacts of specific duration, but decreased R_0 on long contacts (>15 min)(<Q3 0.744[0.538;0.999]) during regular weekdays, increased number of long duration contacts (>1h) during weekend (above median 1.176[1.015;1.357]) and short duration contacts during weekends (<Q3 NbC: 1.495[1.211;1.886]; R_0 1.496[1.156;1.946]).
Low absolute humidity decreased contacts (0.853[0.755;0.966]) and R_0 (0.847[0.745;0.971]) at home and for other places (below median NbC 0.811[0.678;0.977], <Q3 0.730[0.590;0.932]) during regular weekdays, but with an opposite trend during weekend (<Q3: other places: Number of contacts 1.406[1.165;1.747] and R_0 1.382[1.052;1.851]).

E.1.3 Rain

Precipitation coded as binary & Rain showed similar trends. Precipitation considered according to the 3rd quartile (Very high precipitation vs. not very high precipitation) also showed a similar trend. The only significant difference was that contacts at the workplace are more important when precipitation is lower than the 3rd quartile. Hence, we'll focus on the variable Rain.

Absence of Rain decreased number of contacts and R_0 for all contacts (0.938[0.867,1.020] and 0.801[0.695,0.926]) and physical contacts (0.973[0.882,1.081] and 0.807[0.668,0.978]) during regular weekdays as well as week-end (respectively 0.867[0.776,0.969], 0.850[0.740,0.978], 0.879[0.774,1.000], 0.874[0.755,1.033]), but not significantly during holidays.
Absence of Rain decreased the number of short duration contacts (<15 min) only during weekend 0.766[0.617,0.954] and correspondent R_0 0.750[0.566,1.002], while it decreased long duration contacts during regular weekdays (>1h) 0.886[0.787,1.006] >4h 0.896[0.745,1.086] and correspondent R_0 0.640[0.475,0.847] and 0.585[0.361,1.001].

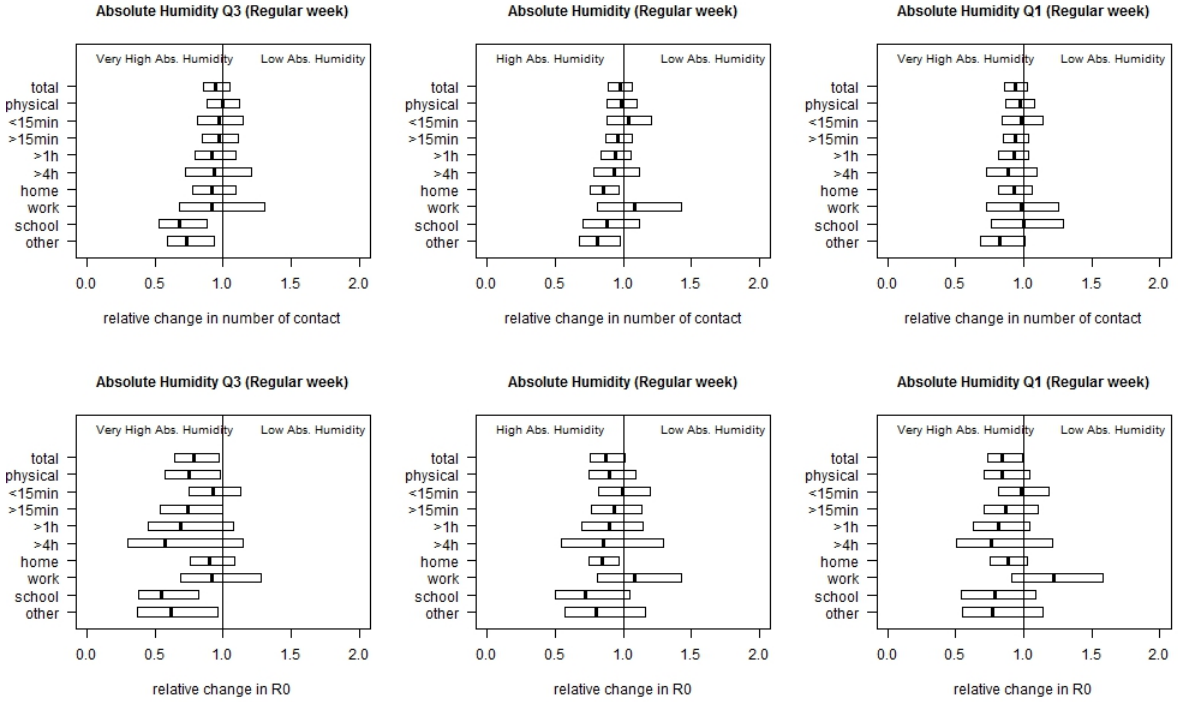


FIGURE E.10: Influence of the absolute humidity on the number of contacts and R_0 during regular weekdays

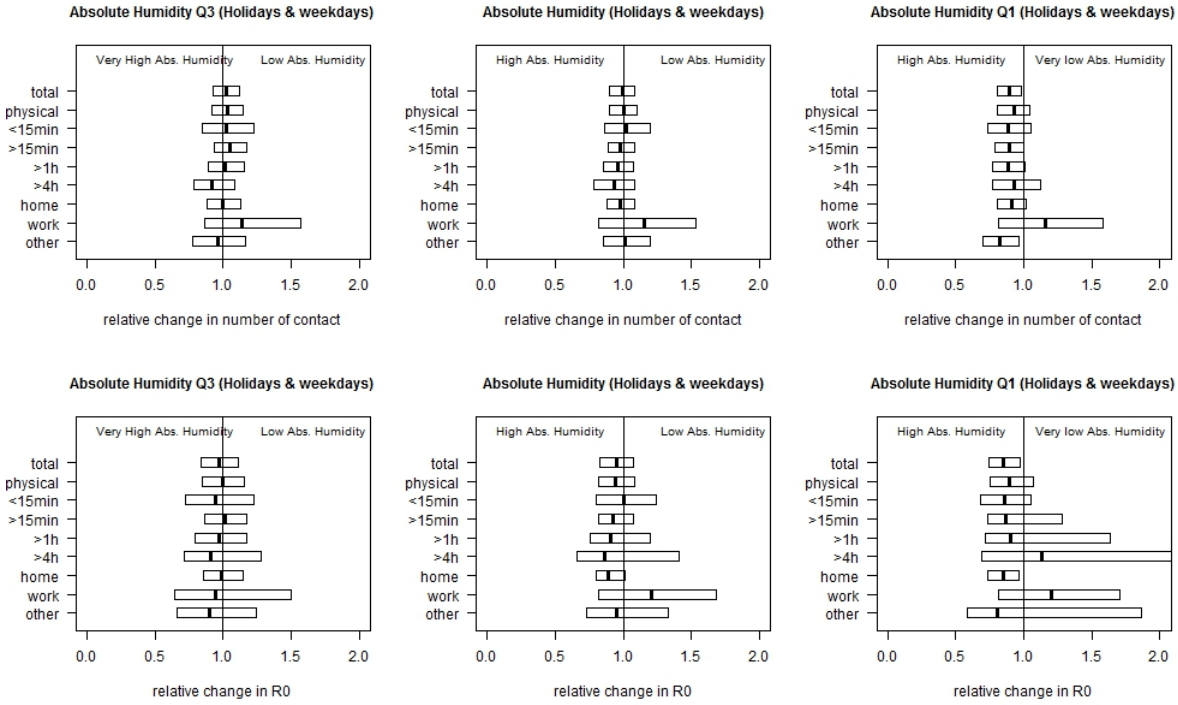


FIGURE E.11: Influence of the absolute humidity on the number of contacts and R_0 during holiday weekdays

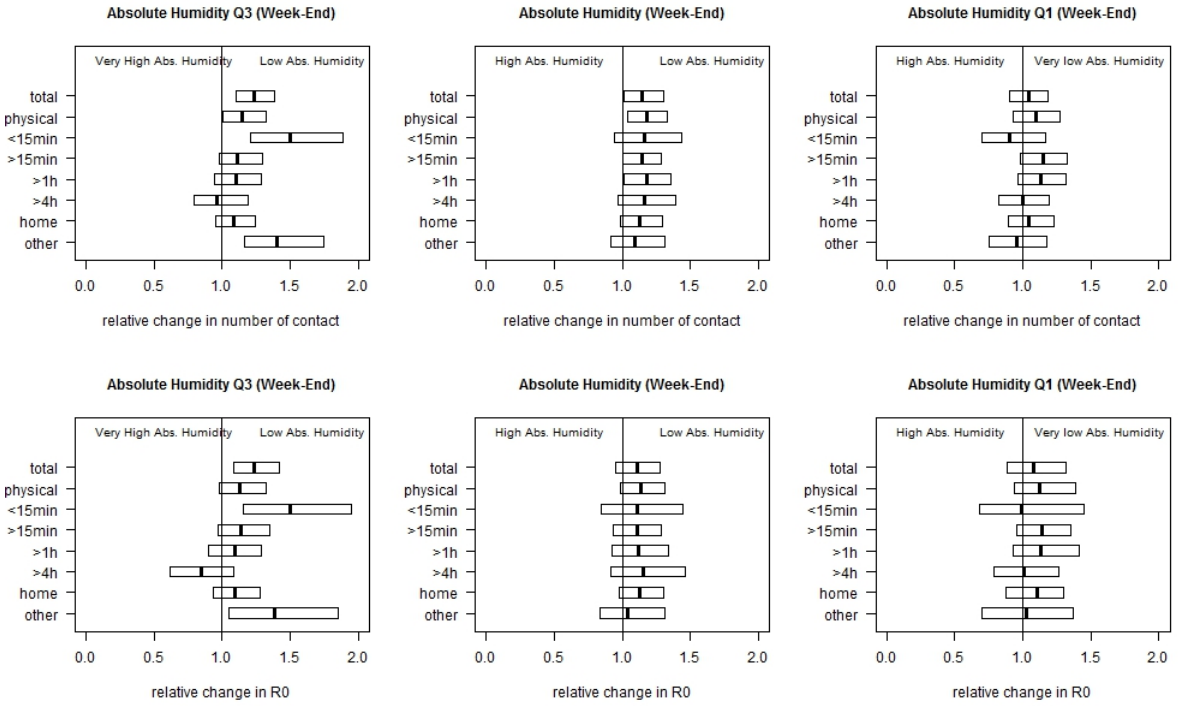


FIGURE E.12: Influence of the absolute humidity on the number of contacts and R_0 during week-end

Absence of Rain decreased the number of contacts 0.768[0.646,0.916] and R_0 0.722[0.577,0.920] in other places only during weekend.

E.1.4 Fog

During regular weekdays, Fog decreased all and physical contacts (respectively 0.817[0.712;0.922] and 0.868[0.757;0.998], contacts at work 0.440[0.275;0.629] and contacts of short and long duration (<15 min: 0.714[0.552;0.921] & >15 min 0.854[0.733;0.994]) without impact on R_0. On the contrary, Fog had no influence during holiday or weekend, but simply decreased number of contacts at work (0.528[0.288;0.829]) and increased R_0 for contacts at home during holidays (1.211[1.013,1.396].

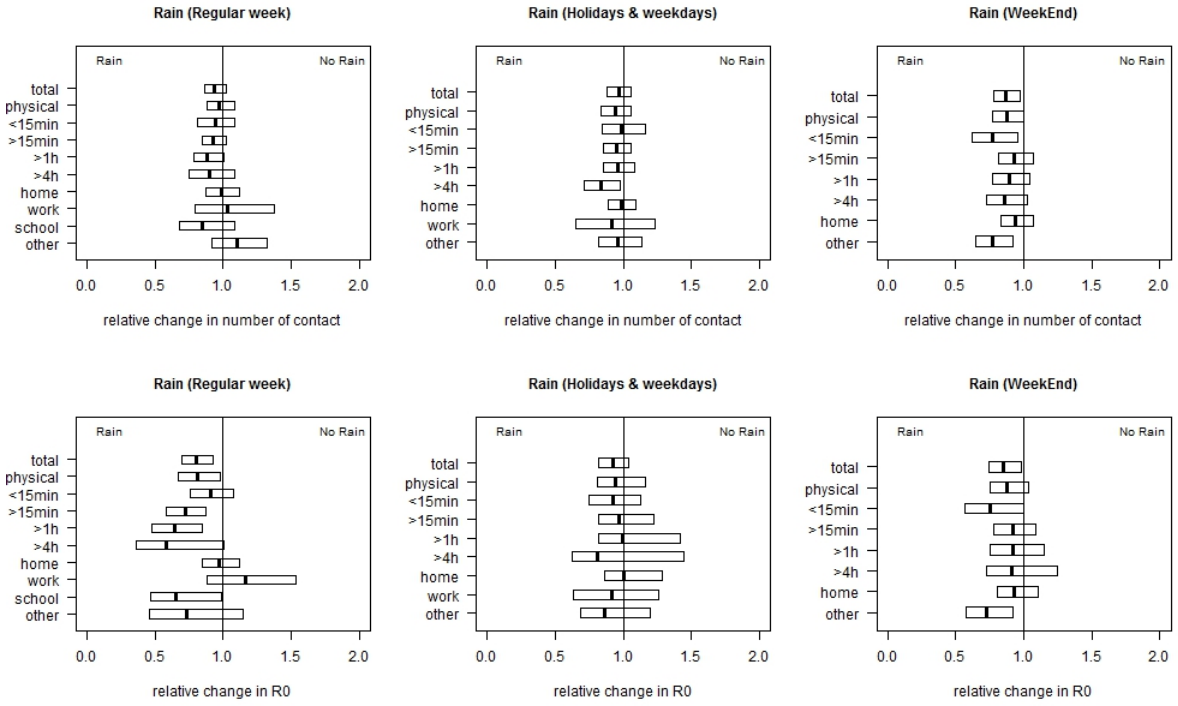


FIGURE E.13: Influence of the rain on the number of contacts and R_0 during regular and holiday weekdays, and weekend

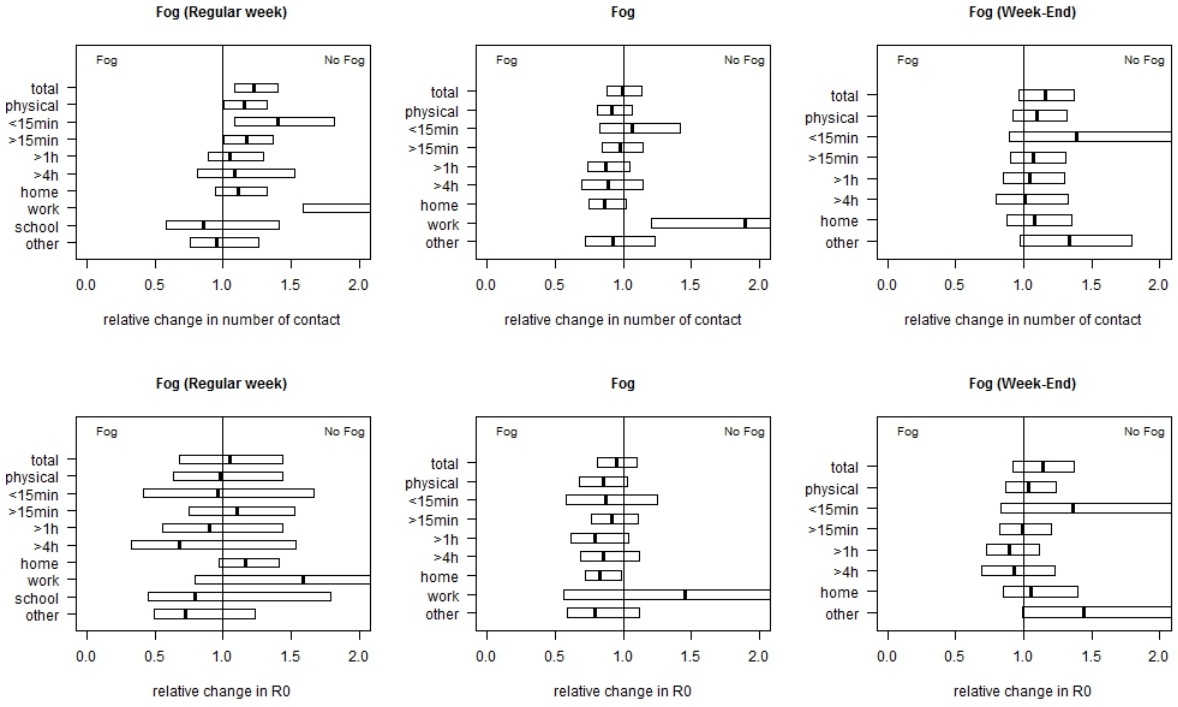


FIGURE E.14: Influence of the fog on the number of contacts and R_0 during regular and holiday weekdays, and weekend

E.1.5 Wind speed

Wind speed had no effect on the number of all contacts and touching contacts neither on the corresponding mixing patterns during weekdays but number of all contacts (below median 0.850[0.757;0.953], <Q3 0.845[0.726;0.981]) and R_0 (below median 0.830[0.723;0.954], <Q3 0.836[0.687;1.001]) decreased for low wind speed during weekend, as well as physical contacts (<Q3 0.854[0.734;0.994] and 0.818[0.569;0.992]). Low wind speed decreased long duration contacts (>15 min) during regular weekdays (below median 0.902[0.817;0.992]) and holiday weekdays (>4h)(below median NbC 0.813[0.694;0.948], R_0 0.698[0.578;0.846)(<Q3 NbC 0.766[0.650;0.905], R_0 0.628[0.455;0.796]), but on the contrary decreased short duration contacts during weekend (< 15 min) (below median NbC 0.749[0.609;0.916], R_0 0.699[0.539;0.893])(<Q3 NbC 0.794[0.619;0.997]. Low wind speed decreased number of contacts and R_0 only at work (below median 0.714[0.539;0.941], 0.703[0.540;0.901]) Maximum wind speed showed similar trends.

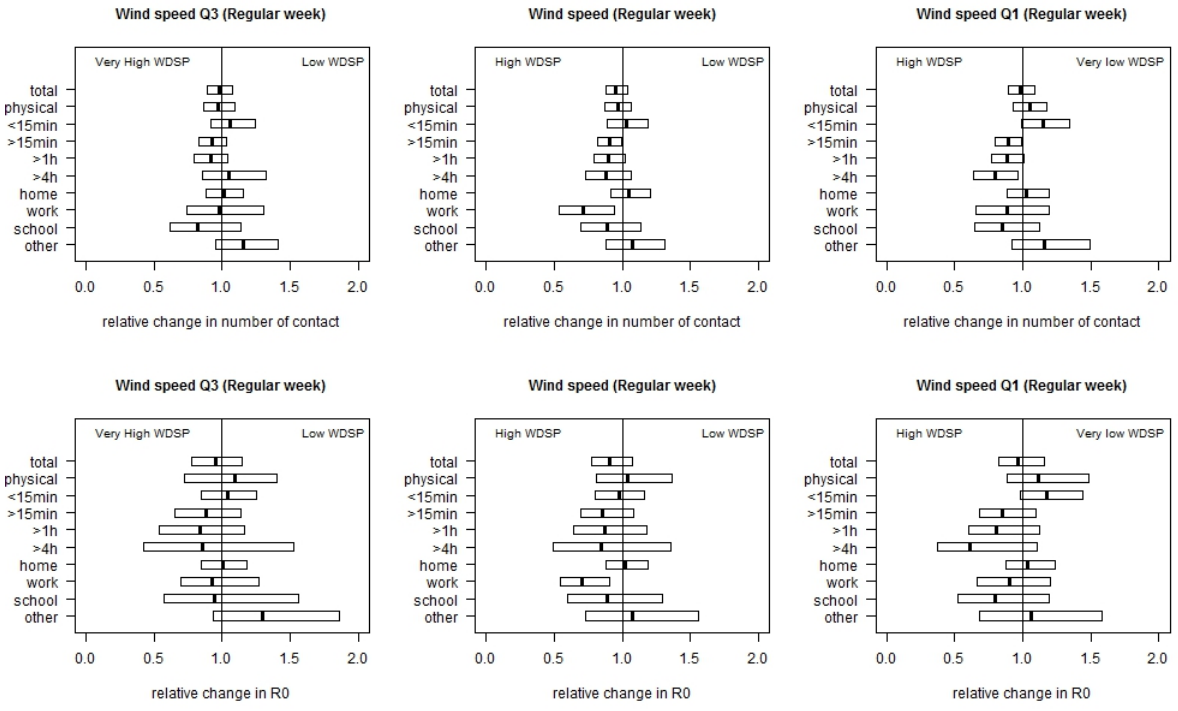


FIGURE E.15: Influence of the wind speed on the number of contacts and R_0 during regular weekdays

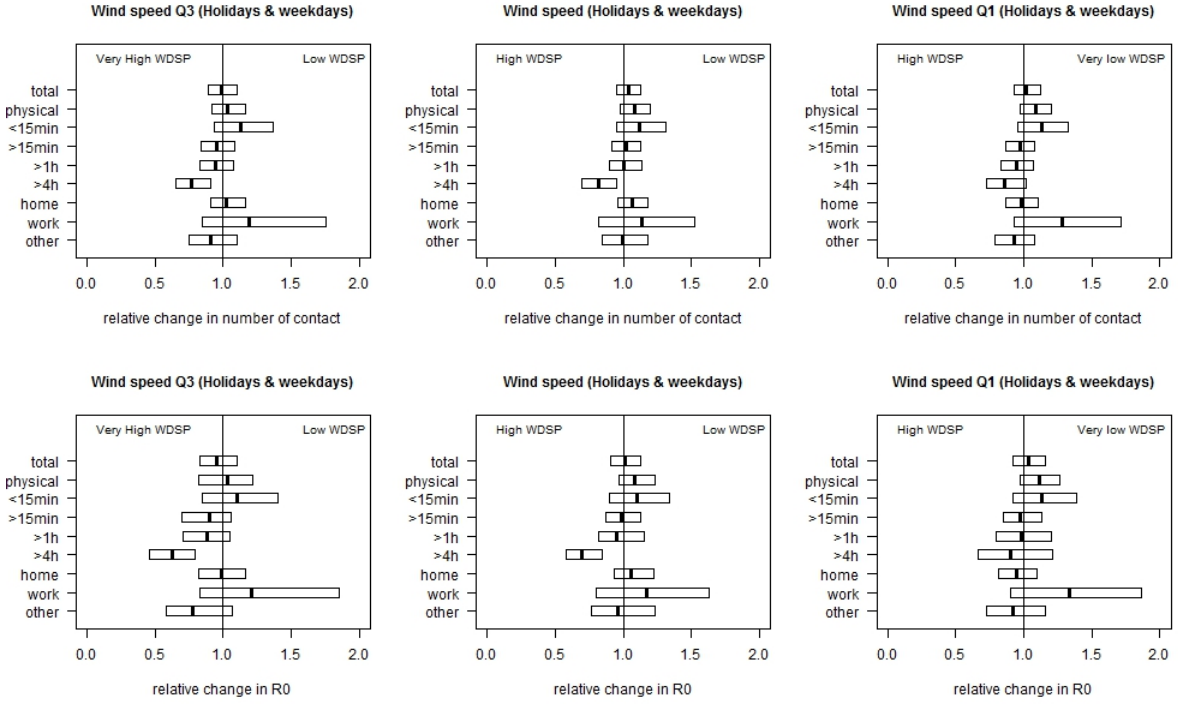


FIGURE E.16: Influence of the wind speed on the number of contacts and R_0 during holiday weekdays

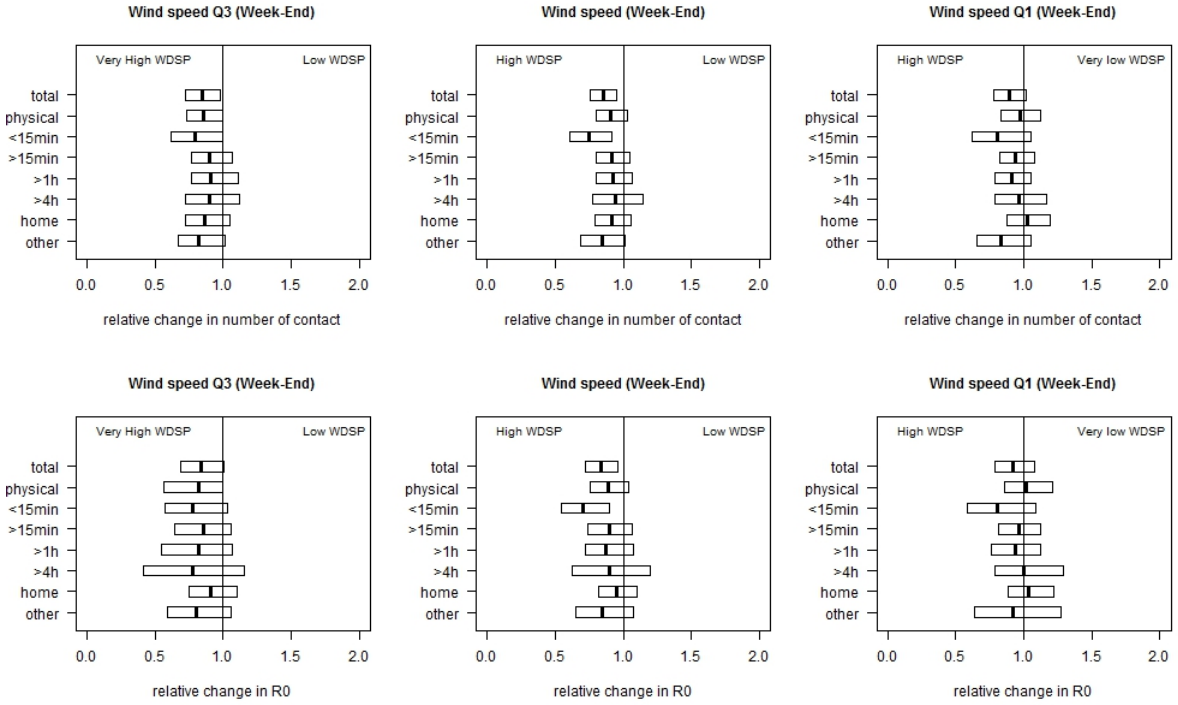


FIGURE E.17: Influence of the wind speed on the number of contacts and R_0 during week-end

E.1.6 Atmospheric pressure

The sea level pressure for locations that are not situated at the sea level (almost all locations) is the station level pressure corrected for the altitude. For that reason, we analyzed the dataset taking into account the sea level pressure, as it is the most comparable measure, whatever are locations and altitudes.

Sea level pressure had no influence on the number of all and physical contacts during regular weekdays, but low sea level pressure decreased the number of physical contacts during holiday weekdays (<Q1 0.850[0.745;0.989]) and increased R_0 of all contacts during regular weekdays (below median 1.267[1.006;1.572], <Q1 1.455[1.201;1.745], <Q3 1.343[1.073;1.636]). Low sea level pressure increased the number of long duration contacts during holiday weekdays (below median >4h 1.271[1.021;1.565], >1h 1.184[1.009;1.384], <Q3 >15 min 1.169[1.001;1.377] >4h 1.312[1.055;1.693]) and the R_0 for long duration contacts during regular weekdays (<Q1 >15 min 1.507[1.144;1.980]; <Q3 >15 min 1.445[1.137;1.856], >4h 1.903[1.186;3.307]) and holiday weekdays (below median >1h 1.254[1.021;1.544], >4h 1.438[1.100;1.918]; <Q1 >1h 1.380[1.056;1.864], >4h 1.783[1.095;3.013]; <Q3 >15 min 1.195[1.006;1.440]), but not during weekends. On the contrary, during weekend, low sea level pressure increased the number of short duration contacts (<Q3 <15 min 1.424[1.049;1.937]) Low sea level pressure decreased for the number of contacts at school (<Q1 0.511[0.273;0.866]) but increased the R_0 in other place (<Q3 1.534[1.087;2.362]) during regular weekdays, without any effect during holidays or weekend.

E.1.7 Visibility

Visibility had no effect on the number of all contacts or physical contacts neither on contacts of specific location during regular weekdays. On the contrary, high visibility increased the number of all contacts and physical contacts during holiday weekdays (NbC, above Q1, all contacts: 1.111[1.229;1.004] and physical contacts 1.126[1.264;1.002]) and weekend (All contacts, NbC, above median 1.163[1.310;1.021], R_0 1.174[1.344;1.025].). High visibility increased the number of contacts of very long duration (>4h)(above median 1.240[1.030;1.501]) during regular weekdays, and R_0 (above Q3 1.382[1.763;1.055]) during holiday weekdays, but contacts of short duration during weekends for number of contacts (<15 min, above median: 1.270[0.999;1.594], above Q1: 1.411[1.053;1.950]) and long duration for number of contacts (>1h, above median: 1.155[1.001;1.344]) and R_0 (>15min, above median: 1.178[1.003;1.392].

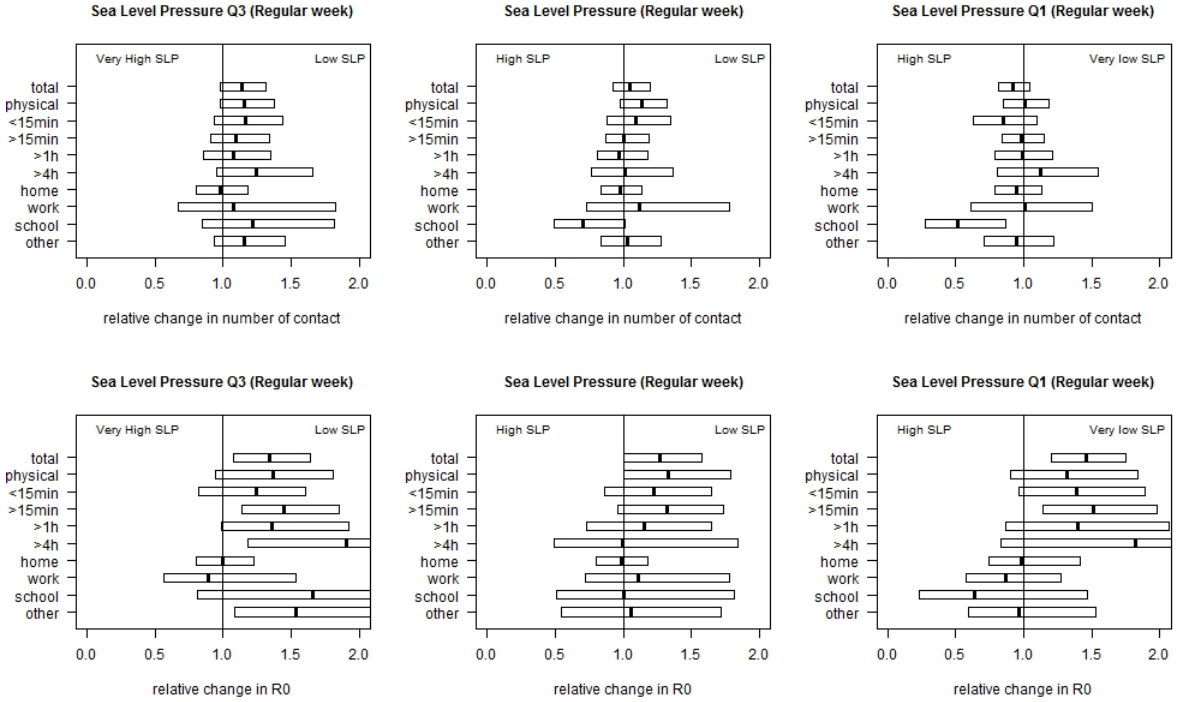


FIGURE E.18: Influence of the sea level pressure on the number of contacts and R_0 during regular weekdays

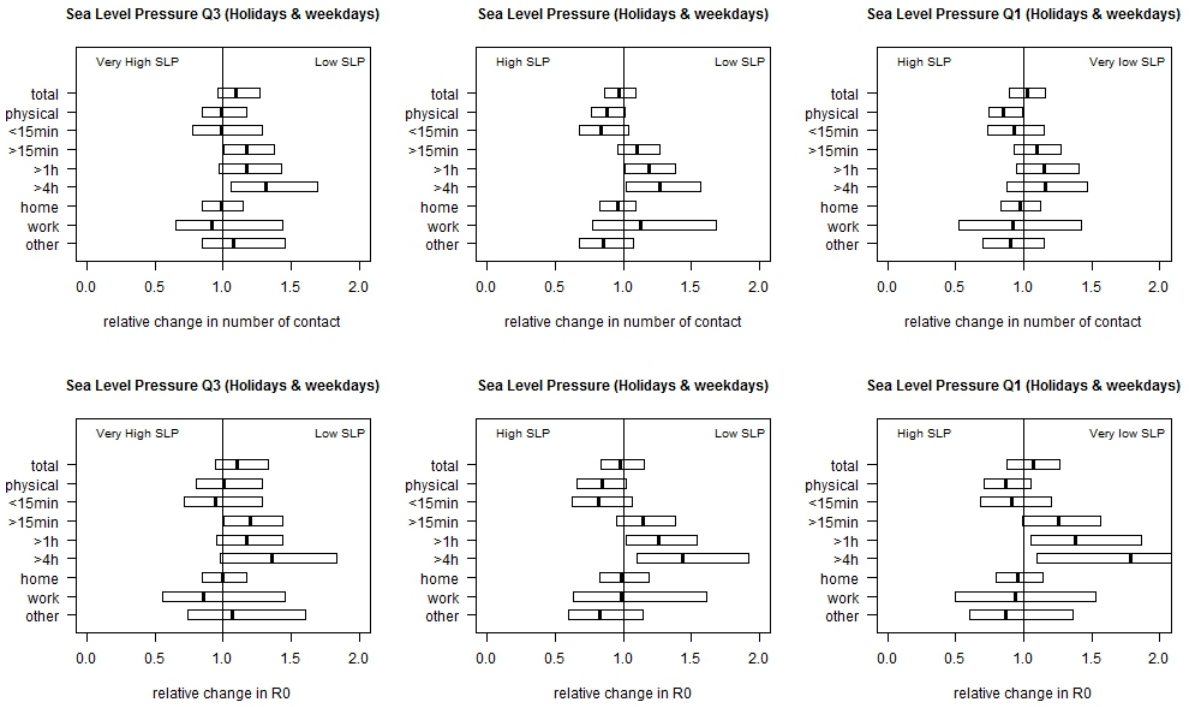


FIGURE E.19: Influence of the sea level pressure on the number of contacts and R_0 during holiday weekdays

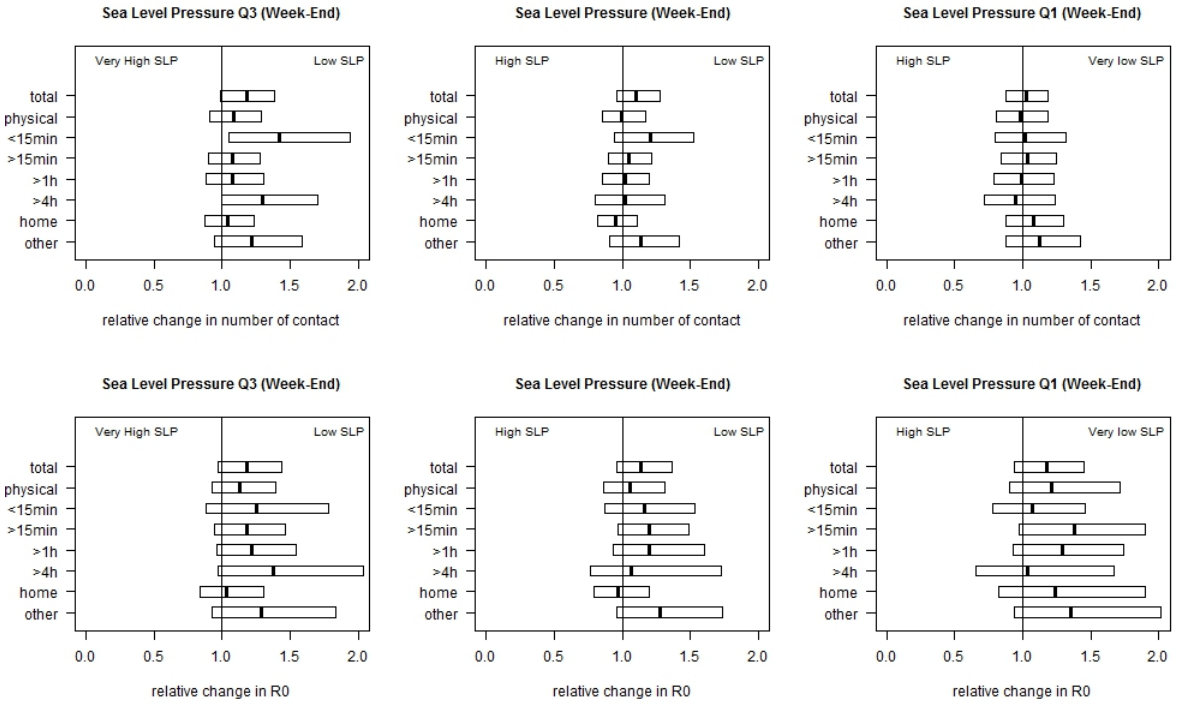


FIGURE E.20: Influence of the sea level pressure on the number of contacts and R_0 during week-end

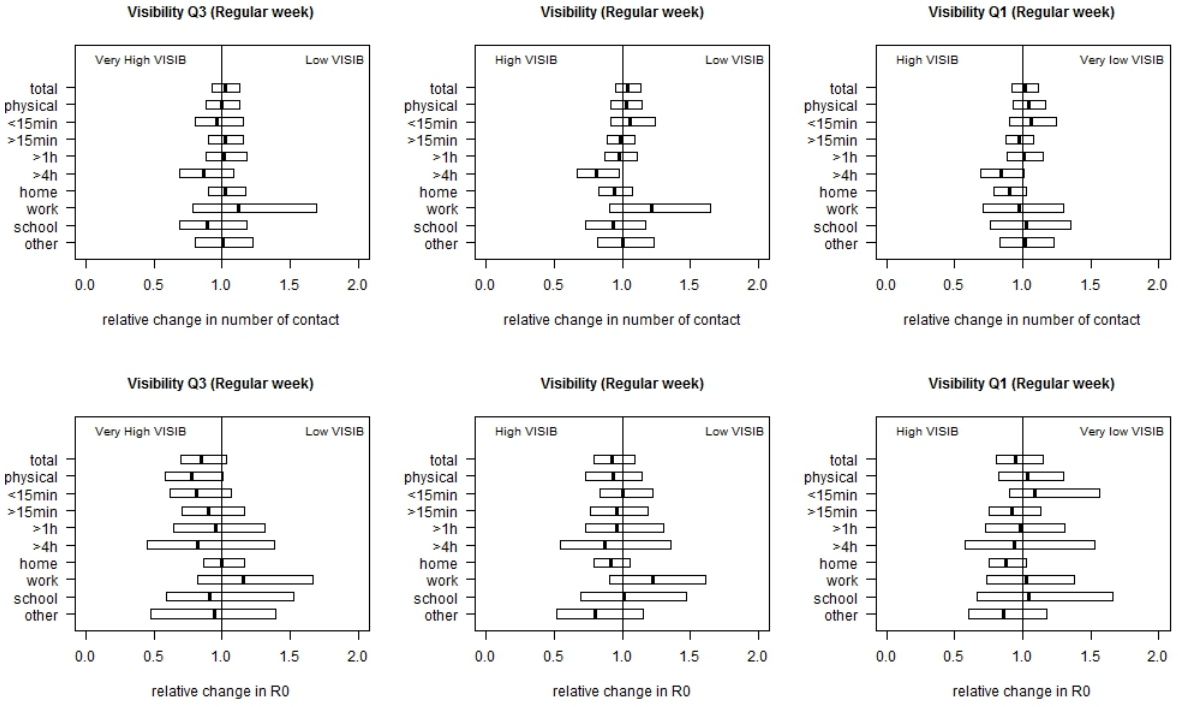


FIGURE E.21: Influence of visibility on the number of contacts and R_0 during regular weekdays

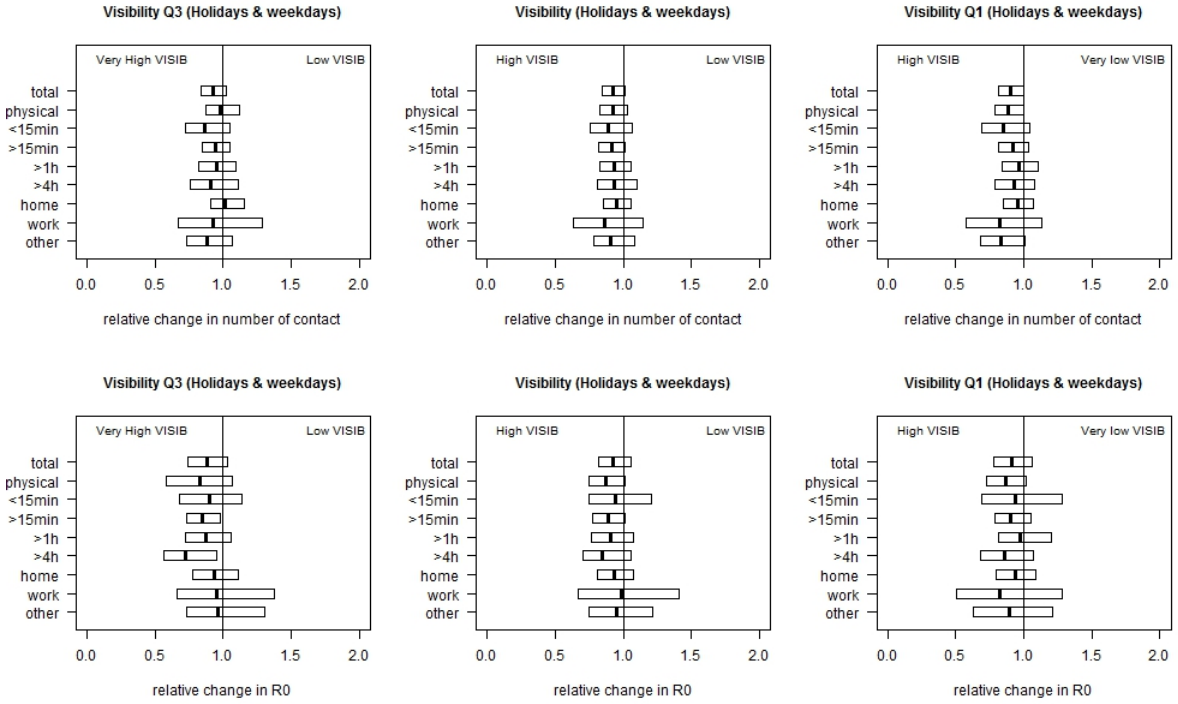


FIGURE E.22: Influence of visibility on the number of contacts and R_0 during holiday weekdays

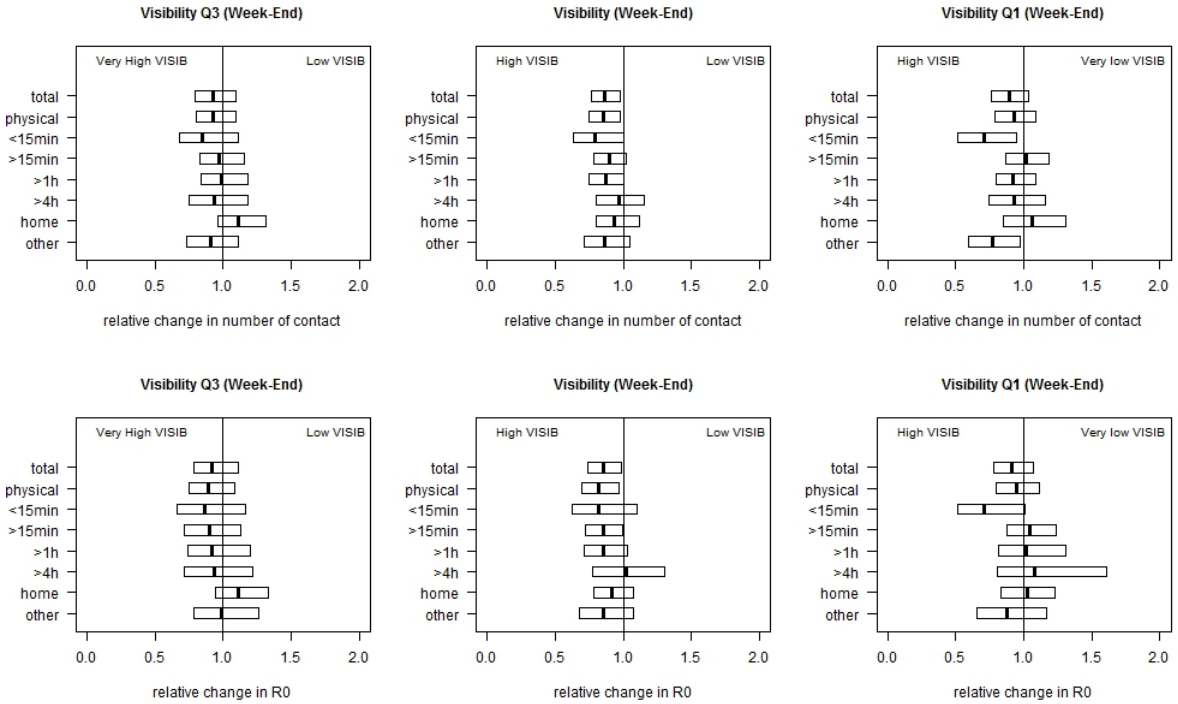


FIGURE E.23: Influence of visibility on the number of contacts and R_0 during week-end

E.2 Impact of weather according to the type and place of contacts

Total contacts: The total number of contacts only decreased with fog during regular weekdays but decreased with low temperature (<Q1) and low absolute humidity (<Q1) during holiday weekdays. During weekend, they decreased with low absolute humidity (< median & Q3) but increased with rain, wind speed (> median & Q3) and visibility. R_0 increased with low maximum temperature and high minimum temperature, with high absolute humidity and rain, low sea level pressure during regular weekdays, and with high average and minimum temperature, with high absolute humidity during holiday weekdays, but decreased with high absolute humidity and increased with rain, wind speed and high visibility during weekend.

Physical contacts: Physical contacts only decreased with fog during regular weekdays but increased with high sea level pressure and visibility during holiday weekdays, and with low absolute humidity, very high wind speed and high visibility during weekend. R_0 increased with high absolute humidity, low sea level pressure and rain during regular weekdays, but only with high visibility during weekends.

Home contacts: Home contacts increased for high temperature (NbC & R_0) and high absolute humidity (NbC & R_0) during regular weekdays, while NbC & R_0 decreased for high minimum temperature (<Q3) during holiday weekdays, and for high temperature during weekend. R_0 also increased with high absolute humidity and fog during holiday weekdays.

Work contacts Work contacts increased for temperature (average, min. and max.)(<Q3)(NbC & R_0) and high wind speed during regular weekdays. The number of contacts at work decreased with fog during regular and holiday weekdays, and no variables influenced R_0 during holiday weekdays. Contacts at work were not considered during weekend.

School contacts: School contacts for children increased for high minimum temperature (NbC and R_0)(and very high min temperature (>Q3) for NbC), very high absolute humidity (NbC and R_0), rain (R_0), high sea level pressure (>Q1) for NbC during regular weekdays. Contacts at school were not considered during holidays nor weekend.

Contacts in Other places: the number of contacts and R_0 in other places increased with high temperature, high absolute humidity during regular weekdays, but only number of contacts without influence on mixing patterns during holiday weekdays, while NbC and R_0 decreased with high absolute humidity and increased with rain during weekends. R_0 increased with low SLP during regular weekdays and NbC increased for visibility >Q1.

Long and short duration contacts Long duration contacts (>15 min, >1h, >4h) increased for max temp and min temp >Q1 (NbC) during regular weekdays, and holiday weekdays for max temp >Q3 (R_0). Short duration contacts (<15min) increased for max temp (NbC & R_0) and min temp (NbC) >Q1 during weekends and for high temperature and max. temperature during holiday weekdays (NbC). Low absolute humidity decreased R_0 for long duration contacts during regular weekdays, had no effect during holiday weekdays and increased short and long duration contacts during weekend. Rain increased long duration contacts during regular and holiday weekdays, and short duration contacts during weekend. Fog decreased the number of long and particularly short durations contacts. High wind speed increased long duration contacts during regular and holiday weekdays, but short duration contacts during weekends. Low sea level pressure increased long duration contacts (NbC & R_0) during regular and holiday weekdays, but short duration contacts during weekend. High visibility increased long duration contacts during regular and holiday weekdays, and both during weekends.

E.3 Quantile regression

We present here some preliminary results obtained with a quantile regression. It shows how the effects of temperature and week-end are variable according to the number of contacts made by a participant. Here, temperature and above all weekend have no effect on the number of contact for participants with a low number of contact, a moderate effect for participants with an average number of contacts and a sizeable effect (notably weekend) for participants with many contacts.

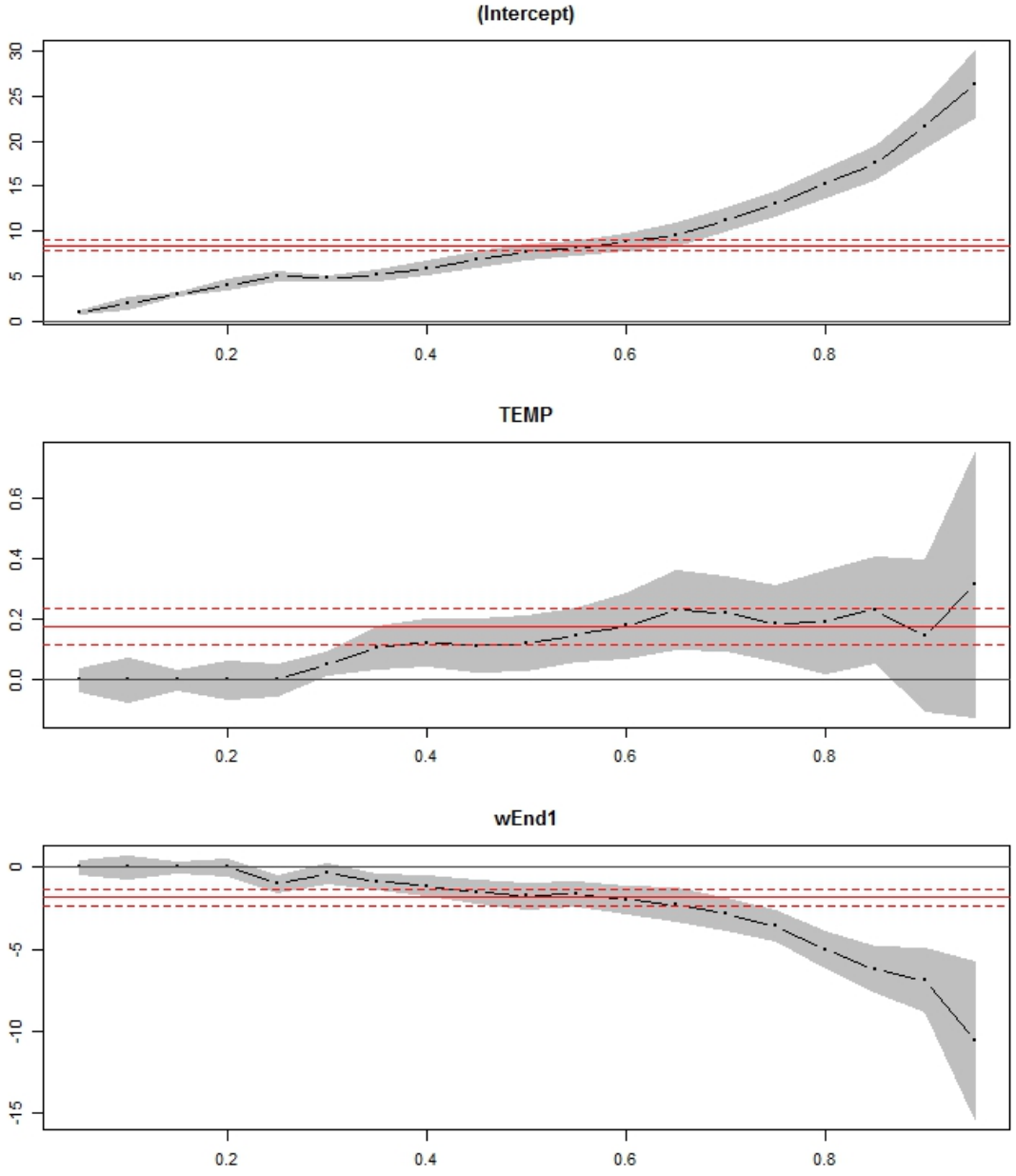


FIGURE E.24: Result of a quantile regression when the number of contacts is modelled according to temperature, weekend and an interaction of both.

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UNIVERSITE LILLE 2 - HASSELT UNIVERSITY

Abstract

Modelling infectious agent transmission using social mixing data

by Dr Guillaume Béraud

Keywords: Mixing patterns; infection transmission; Mathematical modelling; gender differences

English abstract:

Introduction

The economic evaluation of new vaccines requires the modelling of infectious disease transmission within a population, which in turn requires making assumptions about specific mixing patterns in the population. In the European POLYMOD project, matrices generated from social contact studies were determined for 8 European countries. To date, no such data exist for France. The Comes-F study (Contact Matrix Estimation – France) aimed to fill this gap.

Methodology

Contact matrices: The survey was carried out over 3 different periods (Feb-Mar, Apr, Apr-May) with 278 participants common to the first and the last periods. Participants had to list all their contacts for 2 consecutive days in a diary, with age, sex, location, frequency, type and duration of the contact, from which we estimated French contact matrices.

Outbreak risk: Combining cross-sectional serological surveys from 2009 and 2013 and vaccine coverage information, we determined an optimal model for the seroprevalence of measles, mumps and rubella for the year of the data collection; age-dependent susceptibility by department was then derived for the year of interest (2016), and effective reproduction number and age-dependent relative incidence of a potential outbreak were estimated using the French contact matrices.

Meteorological conditions and mixing patterns: We analysed the influence of meteorological conditions on the temporal variations in mixing patterns. The study population was split according to day and weather at the time the diary was filled in. The mean number of contacts and the potential for transmission summarized by R_0 were calculated for type and location of contact under different weather conditions.

Gender and mixing patterns: We conducted a systematic review on gender differences in infection, focusing on influenza, measles, mumps and rubella. Finally, we provided an exploration of the impact of gender on mixing patterns, and eventually the potential implications for modelling.

Results

The 2033 participants reported 38,881 contacts (median [first quartile-third quartile]: 8[5–14] per day), and 54,378 contacts with supplementary professional contacts (9[5–17]). Contrary to age, gender, household size, holidays, weekend and occupation, the period of the year as available in this study had little influence on either the number of contacts or the mixing patterns. Contact patterns were highly assortative with age, irrespective of the location of the contact, and gender, with women having 8% more contacts than men. Although most contacts occurred at home and school, the inclusion of professional contacts modified the structure of the mixing patterns. Holidays and weekends reduced the number of contacts dramatically, and as proxies for school closure, reduced R_0 by 33% and 28%, respectively. The outbreak risk for mumps and rubella mainly concerned southeastern and south central France, while the risk for measles was more scattered over the country. Risk differed by gender for measles and rubella. Besides infants under 1 year of age, incidence was estimated highest for teenagers and young adults. The weather had a different effect on social mixing according to the type of day, notably weekdays and weekend. But correcting for multiple testing made some results no more significant, although the trend for a differential effect between weekdays and weekend remained. Gender differences in social mixing might explain some gender differences in infectious disease epidemiology. Using gender-specific susceptibility and gender-specific contact matrices had a significant impact on the result of the modelling.

Conclusion

French contact matrices shared many common aspects with and were qualitatively similar to those of other European countries, despite differences in design and conduct of the survey. Notably, school closures were likely to have a substantial impact on the spread of close contact infections in France. While the risk of a new measles outbreak persists, it predominates for mumps. The effect of weather on social mixing was mild, if not negligible. Gender differences in modelling should be emphasized.

UNIVERSITE LILLE 2 - HASSELT UNIVERSITY

Abstract

Modelling infectious agent transmission using social mixing data

by Dr Guillaume Béraud

Keywords: Schémas de contact; transmission infectieuse; modélisation mathématique; différences selon le genre

French abstract:

Introduction

L'évaluation économique de nouveaux vaccins exige de modéliser la transmission infectieuse au sein de la population, et donc des hypothèses sur la structure et la répartition des contacts. Les matrices de contact obtenues à partir d'enquête de population ont été déterminées pour 8 pays européens. Mais aucune donnée de ce type n'existe à ce jour pour la France. L'étude ComesF (Contact Matrix Estimation – France) vise à combler cette lacune.

Méthodologie

Matrices de contact: L'enquête s'est effectuée sur 3 périodes (Février-Mars, Avril, Mai-Avril) avec 278 participants communs à la première et dernière période. Les participants devaient rapporter tous leurs contacts au cours de 2 jours consécutifs dans un journal, avec l'âge, le sexe, l'endroit, la fréquence, le type et la durée du contact.

Risque épidémique: En combinant des enquêtes sérologiques de 2009 et 2013 et les données de couverture vaccinales, nous avons modélisé la séroprévalence de la rougeole, des oreillons et de la rubéole; puis extrapolé la susceptibilité selon l'âge par département à l'année d'intérêt (2016) ; enfin le potentiel épidémique et l'incidence relative selon l'âge d'une future épidémie ont été estimés.

Conditions météorologiques et schémas de contact: Nous avons analysé l'influence de conditions météorologiques sur les variations temporelles des matrices de contact. La population de l'étude a été analysée selon le jour et la météorologie pour estimer le nombre moyen de contacts et le potentiel de transmission estimée avec le R_0.

Genre et schémas de contact: Nous avons effectué une revue systématique de la littérature sur les différences selon le genre pour la grippe, la rougeole, les oreillons et la rubéole, puis exploré l'impact du genre sur les matrices de contact et la modélisation des maladies infectieuses.

Résultats

2033 participants ont rapporté 38881 contacts (médiane pondérée [premier quartile-troisième quartile] : 8 [5–14] par jour) et 54378 contacts avec les contacts professionnels

supplémentaires (9 [5–17]). Contrairement à l'âge, le genre, la taille du foyer, les vacances scolaires, le week-end et l'activité professionnelle, la période de l'année influait peu le nombre de contacts ou les schémas de contact. Les schémas de contact étaient influencés par l'âge indépendamment du lieu de contact, et par le genre, les femmes ayant 8 % plus de contacts que les hommes. La plupart des contacts avaient lieu à la maison et à l'école, mais l'ajout des contacts professionnels modifiait la structure des schémas de contact. Les vacances scolaires et les week-ends réduisaient le nombre de contacts, et le R_0 de 33 % et de 28 %, respectivement. Le risque pour les Oreillons et la Rubéole concerne surtout le Sud Est et le Centre de la France, alors que le risque pour la rougeole est plus dispersé. Le risque varie avec le genre pour la Rougeole et la Rubéole. Outre les bébés < 1 an, l'épidémie toucherait surtout les adolescents et les jeunes adultes. Les conditions météorologiques influençaient les schémas de contact différemment entre les jours de semaine ou les weekends. La correction pour analyses répétées limitait le nombre de résultats significatif, mais la tendance pour un effet de la météorologie variant entre les jours de semaine et le week-end restait. Les différences de genre dans le schéma de contact pourraient expliquer en partie les différences de genre dans l'épidémiologie des maladies infectieuses. L'utilisation de données spécifiques par genre avait un impact significatif sur le résultat de la modélisation du risque d'une épidémie.

Conclusion

Les matrices de contact françaises partageaient de nombreux points communs avec les autres matrices européennes, notamment avec un impact substantiel des fermetures d'école en cas d'épidémie sur la progression de l'épidémie. Le risque d'une nouvelle épidémie de rougeole persiste, mais prédomine pour les oreillons. L'effet des conditions climatiques sur les schémas de contact était modeste, voire négligeable. L'utilisation des données spécifiques par genre est à considérer en modélisation des maladies infectieuses.

UNIVERSITE LILLE 2 - HASSELT UNIVERSITY

Abstract

Modelling infectious agent transmission using social mixing data

by Dr Guillaume Béraud

Trefwoorden: Het mengen van patronen; infectie transmissie; Wiskundige modellen; sekseverschillen

Dutch abstract:

Introductie

De economische evaluatie van nieuwe vaccins vereist het modelleren van de verspreiding van infectieziekten in een populatie. Zulke verspreidingsmodellen worden sterk geïnformeerd door contactpatronen die de intensiteit van contacten tussen mensen weergeven. In het kader van de Europese POLYMOD studie werden reeds contactstudies uitgevoerd in en vervolgens contactpatronen bepaald voor acht verschillende Europese landen. Tot voor kort werd er nog geen dergelijke studie uitgevoerd in Frankrijk. De Comes-F studie (Contact Matrix Estimation-France) werd opgezetom deze leemte in te vullen. Gebaseerd op de resultaten van deze contactstudie werd nagegaan wat het uitbraakrisico is voor pathogenen waarvoor de overdracht in kaart gebracht kan worden met behulp van deze contactpatronen, en wat de invloed is van, respectievelijk, meteorologische omstandigheden en geslacht op de structuur van deze contactpatronen.

Methodologie

Contactstudie: De enquête werd uitgevoerd over 3 verschillende periodes (februari-maart, april, april-mei) met 278 deelnemers die hun contactgedrag zowel in de eerste als in de laatste periode rapporteerden. Deelnemers moesten een lijst van al hun contacten in 2 opeenvolgende dagen invullen in een dagboek, met desbetreffende informatie over leeftijd, geslacht, locatie, frequentie, type en duur van de gerapporteerde contacten. Gebaseerd op deze informatie hebben we Franse contactpatronen geschat.

Uitbraakrisico: Op basis van de combinatie van cross-sectionele serologische gegevens uit 2009 en 2013, en informatie over de vaccinatiegraad in de Franse populatie hebben we de seroprevalentie van mazelen, bof en rubella in het jaar van gegevensverzameling bepaald. Vervolgens werd de leeftijdsafhankelijke vatbaarheid berekend voor de daaropvolgende jaren. Tenslotte werd het uitbraakrisico voor deze virale ziekten ingeschat gebruikmakend van de Franse contactpatronen. Geografische informatie werd waar mogelijk meegenomen in deze analyse.

Meteorologische omstandigheden en contactpatronen: We analyseerden de invloed van de meteorologische omstandigheden op de temporele variaties in contactpatronen. De

onderzoekspopulatie werd opgesplitst naar dag waarop het dagboek werd ingevuld en de bijbehorende weersomstandigheden op dit tijdstip. Het gemiddeld aantal contacten en de structuur van contactpatronen, uitgedrukt door gebruik te maken van het basaal reproductiegetal R_0, werden berekend voor verschillende locaties en onder verschillende weersomstandigheden.

Geslacht-specifieke contactpatronen: We voerden een systematische review uit naar geslachtsverschillen in prevalentie en incidentie van griep, mazelen, bof en rubella. Dit motiveerde ons om geslachtsverschillen in contactpatronen te bestuderen en te exploreren hoe deze verschillen zich vertalen in verspreidingsmodellen.

Resultaten

De 2033 deelnemers rapporteerden in totaal 38 881 contacten (mediaan waarde [eerste kwartiel-derde kwartiel] = 8 [5-14] per dag), en 54 378 contacten wanneer aangevuld met beschikbare informatie over professionele contacten (9 [5-17]). In tegenstelling tot leeftijd, geslacht, huishoudensgrootte, vakantie, weekend en beroep, had de periode van het jaar zoals geobserveerd in deze studie weinig invloed op het aantal contacten en de contactpatronen. Contactpatronen vertoonden een grotere contactintensiteit tussen mensen van eenzelfde leeftijd, ongeacht de plaats van het contact, en van eenzelfde geslacht, waarbij vrouwen 8% meer contacten rapporteerden dan mannen. Hoewel de meeste contacten thuis en op school plaatsvonden, had het in rekening brengen van de professionele contacten een grote impact op de structuur van de contactpatronen. Vakantie en weekend verminderden het aantal contacten dramatisch, en kunnen een indicatie geven van de impact van schoolsluiting op de verspreiding van pathogenen; R_0 verminderde met maar liefst 33% en 28% respectievelijk in een vakantieperiode en gedurende het weekend. Het grootste risico op bof en rubella uitbraken werd teruggevonden in Zuidoost en Zuid-Centraal Frankrijk, terwijl het risico voor mazelen meer verspreid was over het hele land. Het uitbraakrisico verschilde tussen mannen en vrouwen voor mazelen en rubella. Naast zuigelingen jonger dan één jaar, is de verwachtte incidentie bij een toekomstige uitbraak het grootste voor tieners en adolescenten. Het weer had een verschillend effect op contactpatronen afhankelijk van de dag. De correctie voor meervoudig testen gaf echter aan dat dit effect statistisch niet-significant was. Het significante verschil voor week- en weekenddagen bleef echter behouden. De analyse van verspreidingsmodellen waarin rekening gehouden werd met geslacht-specifieke contactpatronen maakte duidelijk dat geslacht-specifieke contactpatronen kunnen leiden tot geslachtsverschillen in prevalentie en incidentie.

Conclusie

Ondanks verschillen in studieopzet en uitvoering, leidde de Franse contactstudie tot kwalitatief gelijkaardige resultaten als de Europese POLYMOD studie. Gebaseerd op onze risicoanalyse is er een duidelijk uitbraakrisico voor mazelen en in een nog grotere

mate voor bof in Frankrijk. De invloed van meteorologische omstandigheden op contactpatronen was beperkt doch is er een potentieel belangrijke rol weggelegd voor geslachtspecifieke verschillen in contactpatronen met betrekking tot de verspreiding van pathogenen.

UNIVERSITE LILLE 2 - HASSELT UNIVERSITY

Abstract

Modelling infectious agent transmission using social mixing data

by Dr Guillaume Béraud

Substantial French abstract:

La modélisation mathématique des maladies infectieuses est inestimable pour évaluer les stratégies de contrôle et de prévention en comparant leur (coût) efficacité et pour informer les décideurs en santé publique. Alors que la plupart des modèles font des hypothèses sur les paramètres de transmission, des études de données de contacts sociaux estiment la probabilité de contacts entre les individus, et par conséquent de transmission d'agents pathogènes potentiels. Par exemple, les études sur les schémas de contacts sociaux ont montré de meilleurs résultats que les modèles mathématiques parcimonieux sur les données de séroprévalence pour la varicelle.

Les carnets de recueil de contact ont plusieurs avantages notamment en ce qui concerne la mesure de la fréquence et de l'intensité des contacts entre individus. Ils sont faciles à utiliser, recueillent les interactions sociales avec un large éventail de paramètres et ne reposent pas sur la participation à des groupes de pairs. Ils ont ainsi pu expliquer avec succès les schémas de transmission de l'infection selon l'âge pour le VZV, le parvovirus B19, les oreillons, la grippe et la coqueluche.

Néanmoins, définir un contact à risque de transmission de maladie infectieuse reste difficile et varie en fonction de l'agent pathogène. Une enquête en population sur les schémas de contact peut fournir les données permettant de construire des matrices de contact avec différents niveaux d'intimité de contact (par exemple, des contacts physiques et/ou de longue durée vs. de simple conversation et/ou des contacts de courte durée).

Impliquant 8 pays européens, POLYMOD a été la première étude à grande échelle à rapporter et décrire les contacts entre individus. À ce jour, ces données n'existent pas pour la France. Fumanelli et al. ont estimé des matrices de contact en inférant la structure de contacts sociaux à partir des données démographiques, mais au détriment de la précision et au prix de différences substantielles avec les matrices de contact empiriques de l'étude POLYMOD. Les enquêtes de type emploi du temps sont largement disponibles et offrent une alternative intéressante pour estimer les matrices de contact, mais ils sont souvent limités aux participants âgés de plus de huit ans. A l'occasion de la pandémie de grippe A/H1N1, une enquête auprès des ménages français rapportait les réunions à laquelle participaient les participants, mais les informations fournies étaient limitées en ce qui concernait le lieu et la répartition par âge de contacts.

La saisonnalité est une caractéristique fréquente et propre aux maladies infectieuses, que l'on attribue le plus souvent à des facteurs environnementaux tels que la température ou l'humidité. Pourtant l'épidémiologie de la rougeole et d'autres maladies infantiles varie avec les périodes scolaires, ce qui souligne l'importance des facteurs comportementaux. Néanmoins, peu d'études ont évalué les variations du nombre de contacts d'une personne donnée dans le temps. Aucune n'a comparé les modifications des schémas de contact dans le temps. Ainsi, alors que des matrices de contact ont été déterminées à l'échelle de pays, elles ne bénéficient pas d'information temporelle. Nous décrivons la première enquête de population à grande échelle sur les schémas de contact en France et leurs variations temporelles. Grâce à l'hétérogénéité naturelle de la France -un des plus grands pays d'Europe- et au plus grand échantillon utilisé pour une enquête en population pour un pays à ce jour, nous avons estimé les taux de contact français. Nous avons également réévalué l'influence sur les schémas de contact des week-ends et des vacances scolaires aussi bien que du genre, des schémas de contact des enfants ou de la taille des classes. Nous avons également exploré l'influence des individus avec un nombre élevé de contacts professionnels (contacts professionnels supplémentaires) sur un ou deux jours consécutifs.

L'inclusion des participants s'est faite par téléphone afin d'obtenir des quotas d'âge prédéfinis, dont 1/3 de sujet d'âge <18 ans. Les participants devaient remplir un carnet décrivant tous leurs contacts pendant 2 jours. L'âge des contacts, le sexe, le lieu, la durée, la fréquence et la nature du contact (cutané ou pas) était recueilli. Les participants ont été recrutés en 2 vagues (Hiver/Printemps).

Parmi les 24250 personnes en contact avec un numéro de téléphone généré aléatoirement, 3977 ont été recrutés, 2033 ont effectivement participé et 278 participants étaient communs aux 2 périodes. Les participants étaient significativement plus âgés que les non-participants (30,9 (25,4) vs 37,1 (27,0); p <0,001). 39,1% de tous les participants avaient moins de 18 ans. Après vérification de 10% des carnets, les erreurs de codage et les données manquantes représentaient 0.17% et 0.4% de l'ensemble des données, respectivement.

Les participants ont notifié 38881 contacts sur 2 jours, permettant d'estimer le nombre moyen de contacts à 9.56 par jour. Des différences significatives dans le nombre de contacts apparaissent selon la saison, le jour de la semaine, les vacances, l'âge des participants et la taille du foyer. L'âge des participants a influencé de façon significative le nombre moyen (SD) de contact, avec un minimum lorsque l'âge des participants étaient < 4 ans [8,64 (7,23)] et > 65 ans [7,01 (5,73)], et un maximum à 15-19 ans [12,96 (9,55)] (p <0,001). Le nombre de contacts augmentait avec la taille du foyer et diminuait lorsque les participants étaient des hommes [9,29 (7,52) vs 9,78 (8,04), p = 0,025]. Les participants avaient moins de contact pendant le week-end [8,37 (6,50) vs 9,90 (8,13) (p <0,001)] et les vacances scolaires [8,20 (6,20) vs 11,05 (9,05), p <0,001]. Les variations

entre les périodes de l'étude étaient plus modestes et n'étaient significatives qu'après prise en compte des contacts professionnels supplémentaires. Les matrices de contact montraient que les participants privilégiaient les contacts d'âge similaires, ainsi que les contacts ayant une trentaine d'années de différence d'âge (Figure E.26). La prise en compte des contacts professionnels supplémentaires modifiait considérablement la structure de la matrice.
L'étude de ces matrices de contact françaises permet donc d'améliorer notre compréhension de la propagation des maladies infectieuses, sur le rôle de certaines catégories d'âge et de l'impact de la fermeture des écoles en France. Cela soulève également des questions plus fondamentales sur la conception optimale de ces enquêtes, sur le rôle des contacts et lieux professionnels, et sur la différence entre les sexes dans l'épidémiologie des maladies infectieuses. Enfin, il fournit des données fondamentales pouvant être directement utilisées dans la modélisation de la transmission infectieuse.

La France a connu une épidémie de rougeole importante en 2010-2011, avec plus de la moitié des 30.000 cas rapportés en Europe en 2010-2011. Ceci a été principalement attribué à une couverture vaccinale sous optimale, pour la première et surtout la deuxième dose du vaccin contre la rougeole-oreillons-rubéole. Des foyers épidémiques de rougeole et d'oreillons sont apparus récemment en Europe notamment aux Pays-Bas et au Royaume-Uni, ainsi qu'aux Etats-Unis. Pourtant, bien que la couverture vaccinale insuffisante soit généralement considérée comme le principal facteur à l'origine de l'épidémie, une proportion importante des personnes touchées était correctement vacciné, ce qui amène à s'interroger sur la persistance à long terme de l'immunité vaccinale et l'adéquation du calendrier vaccinal. Le vaccin actuellement utilisé étant commun à la rougeole, aux oreillons et à la rubéole, un risque de résurgence pour la rougeole en raison d'une couverture incomplète peut être associé à un risque pour la rubéole et les oreillons.
La première dose du vaccin ROR a été administrée en France à l'âge d'un an depuis 1986. De 1996 à 2005, une deuxième dose a été administrée entre l'âge de trois et six ans, puis à deux ans depuis 2005. La couverture vaccinale de la rougeole en France est une des plus basse en Europe (ECDC/OMS) et l'épidémie de rougeole en cours en Allemagne voisine pourrait « déborder » en France, et catalyser ainsi une nouvelle épidémie européenne. En outre, l'OMS/Europe visait à l'éradication de la rougeole et la rubéole en Europe d'ici à 2015, mais les récentes épidémies de rougeole laissent supposer que cet objectif ne sera pas atteint.
Le risque de résurgence de la rougeole et des oreillons a été récemment évalué en Belgique, dans une population présentant un fort taux de vaccination sans épidémie récente,

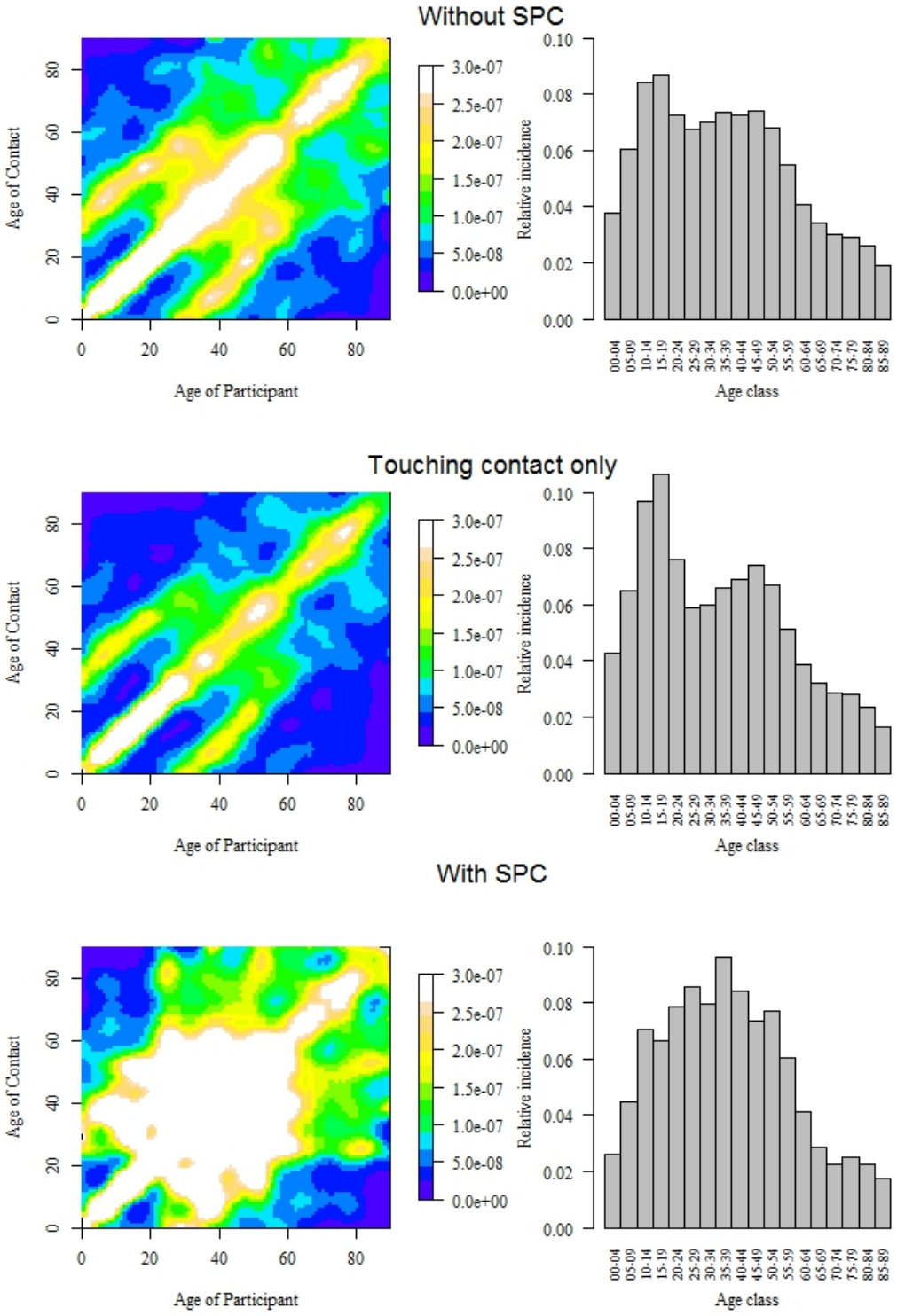

FIGURE E.25: Matrices de contact sans SPC, restreinte aux contacts physiques et avec SPC, avec l'incidence relative en regard.

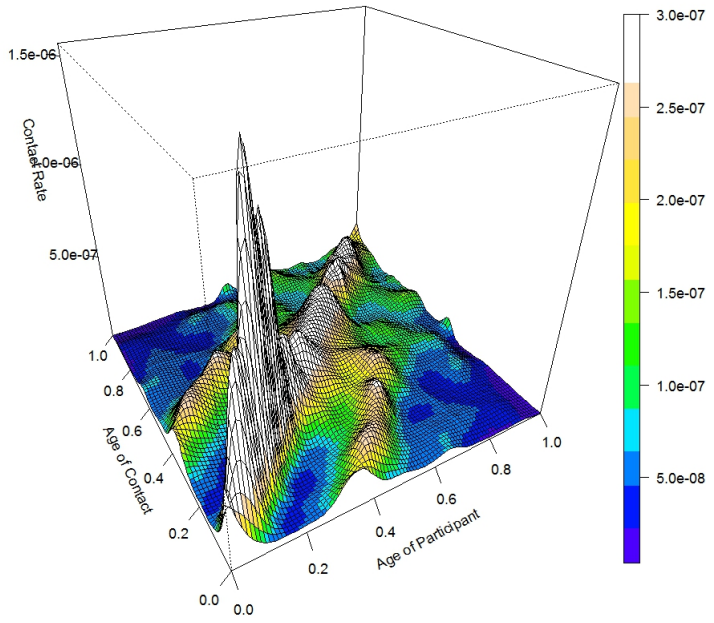

FIGURE E.26: Representation en 3D de la matrice de contact, sans SPC.

avec une méthodologie originale combinant les données sérologiques et la couverture vaccinale. Par conséquent, en utilisant des enquêtes sérologiques réalisées en 2009 et 2013, nous avons cherché à estimer et cartographier le risque de résurgence de la rougeole, les oreillons et la rubéole en France en 2016.

Nous avons utilisé un modèle multi-cohorte, combinant des données sérologiques et la couverture vaccinale, dans laquelle (1) la sérologie de la rougeole, des oreillons et de la rubéole est modélisée afin de prédire la susceptibilité à ces infections dans l'année de collecte de données (2009 ou 2013); (2) la susceptibilité en fonction de l'âge par département (n = 96) est dérivée pour l'année d'intérêt (2016); (3) le potentiel épidémique représenté par le nombre de reproduction effectif propre à chaque département et l'incidence selon l'âge en cas de nouvelle épidémie sont estimés en utilisant les données de contact sociaux de l'étude Comes-F. Ce modèle initialement créé pour la Belgique a été adapté afin de tenir compte des changements de calendrier vaccinal, d'une résolution spatiale par département et la prise en compte du genre dans la modélisation.

Le risque global pour une épidémie de rougeole, oreillons ou la rubéole en France en 2016 est le plus élevé pour les oreillons, modéré pour la rougeole et négligeable pour la rubéole. Il y avait une hétérogénéité dans le risque d'épidémie entre les départements, dont le plus à risque pour la rougeole, les oreillons et la rubéole étaient respectivement

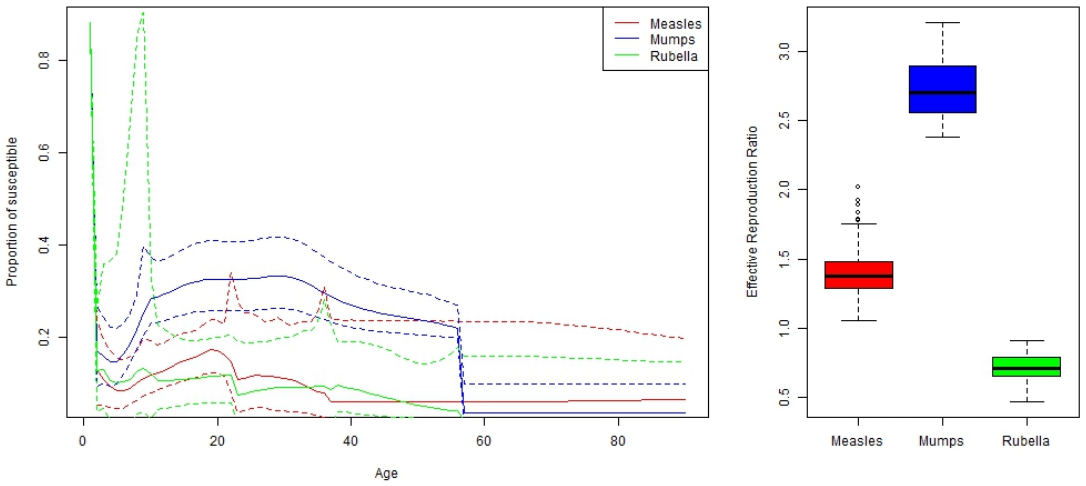

FIGURE E.27: Courbes de susceptibilité moyenne et R_e pour la rougeole, les oreillons et la rubéole estimé pour la France en 2016.

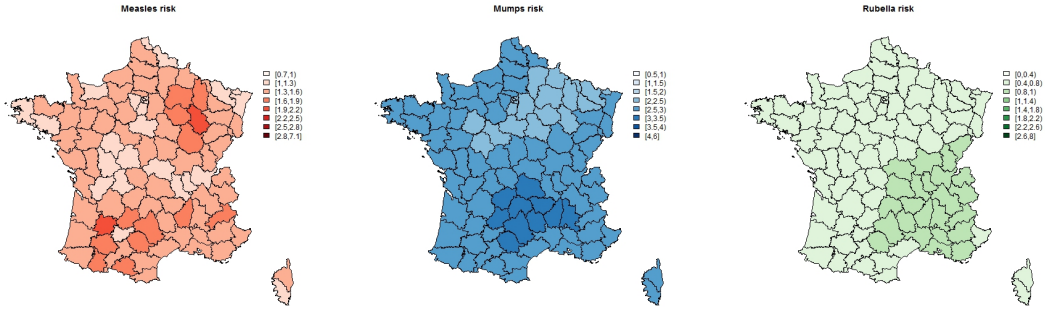

FIGURE E.28: Risque d'émergence de rougeole (gauche), d'oreillons (centre) et de rubéole (droite) en France, 2016

la Haute-Marne, le Cantal et le Puy-de-Dôme. Les départements partagent des risques communs pour les oreillons (Figure: Centre) et la rubéole (Figure: Droite) (au sud-est / sud-centre de la France), tandis que les départements à risque sont plus dispersés pour la rougeole (Figure: Gauche) comme représenté sur la Figure.

Les nourrissons de moins de 1 an d'âge seraient gravement impliqués dans une future épidémie, mais la contribution la plus élevée serait payée par les adolescents et les jeunes adultes (âgés de 10 à 25 ans). Les vacances (qui permettent d'estimer l'impact des fermetures d'écoles) permettraient de réduire le nombre de reproduction effectif en moyenne respectivement de 37,2%, 29,5%, et 33,4% pour la rougeole, oreillons et rubéole. Pour rougeole et la rubéole, la susceptibilité – et donc, le risque de résurgence - diffère selon le genre, les hommes étant plus fréquemment susceptibles que les femmes. Cela n'est pas le cas pour les oreillons.

L'âge moyen de survenue serait pour la rougeole de 22.1 ans pour les hommes et de 24.1 ans pour les femmes, pour les oreillons de 27 ans, pour la rubéole de 23.9 ans pour les hommes et de 22.6 ans pour les femmes. Nous avons également calculé la probabilité d'échappement pour chaque département et pour chaque agent pathogène. Pour la rubéole, les probabilités d'échappement sont très élevées et souvent égales à 1 ce qui souligne le très faible risque de réémergence de la rubéole. Au contraire, les probabilités d'échappement pour les oreillons sont faibles, montrant le risque élevé d'une épidémie d'oreillons. Enfin, les probabilités d'échappement pour la rougeole sont très hétérogène entre les départements.
En utilisant des enquêtes sérologiques et des données de couverture vaccinale, nous avons pu estimer le risque de résurgence de la rougeole, les oreillons et la rubéole dans une population largement vaccinée. Malgré l'épidémie de rougeole récente, le risque d'une nouvelle épidémie persiste en France, mais prédomine surtout pour les oreillons. Le risque élevé pour les adolescents et les jeunes adultes est préoccupante en raison de la vulnérabilité de ces âges à des formes graves de rougeole, d'oreillons et de rubéole. Les différences de susceptibilité liées au genre soulèvent la question de campagne de vaccination tenant compte du genre pour réduire le risque futur de l'épidémie.

Les participants de l'étude Comes-F avaient tendance à avoir plus de contacts au cours de la dernière période (Avril-Mai) que lors de la première période (Février-Mars) (changement relatif: 1,06 [0,98 à 1,16]) bien que non significativement. En incluant les contacts professionnels supplémentaires, cette tendance s'avérait significative (1,22 [1,03 à 1,45]). Ces variations peuvent être la conséquence de la différence de saison, la dernière période de l'enquête ayant eu lieu au cours du printemps, alors que la première a eu lieu pendant l'hiver. Cela pourrait également être une conséquence de la longueur du jour, des jours fériés plus fréquents en Mai ou des conditions météorologiques (qui dépendent en partie de la saison).
Récemment, certains auteurs ont montré une association entre les conditions météorologiques et les schémas de contact. La première étude a eu lieu en Belgique pendant l'hiver au cours duquel les variations des conditions météorologiques peuvent avoir été limitées. Mais les données disponibles limitaient l'analyse aux jours de semaine hors vacances et à la médiane des températures, des précipitations et de l'humidité absolue. L'autre étude a exploré l'influence des conditions météorologiques tropicales de Taïwan sur les schémas de contact, là aussi dans le cadre d'un climat avec des conditions très éloignées de celles d'un climat tempéré, et avec des variations limitées. Les conditions météorologiques sont connues pour influencer la transmission de maladies infectieuses, pour des raisons biophysiques, mais aussi par des changements de comportement humain. Nous avons donc émis l'hypothèse que les variations des conditions météorologiques pouvaient être

corrélées avec les schémas de contact, et donc influencent la transmission des pathogènes respiratoires.

Les données météorologiques quotidiennes, le nombre moyen de contacts et le potentiel de transmission (R_0) ont été calculés pour des contacts directs, les contacts physiques, les contacts spécifiques à certains lieux (maison, école - pour les participants <18y-, lieu de travail et les autres lieux) et les contacts de durées spécifiques ($<$ 15 min, $>$ 15 min, $>$ 1h, $>$ 4h). Les comparaisons ont été exprimées sous forme d'un changement relatif dans le nombre moyen de contacts et dans le R_0 associées à la température et / ou humidité absolue et / ou la pluie.

Pendant les jours de semaine hors vacances scolaires, on observait une tendance à plus de contacts à la maison et dans les lieux «autres», plus de contacts de longue durée et un R_0 supérieur à la maison lors des températures élevées. Une humidité absolue élevée était associée à un plus grand nombre de contacts (nombre de contacts pour une humidité absolue haute, divisé par le nombre de contact pour une humidité absolue faible: 1,2 [1,0; 1,4]) et à un plus grand R_0 (1,2 [1,0; 1,4] à la maison), et à une tendance similaire pour les autres lieux. Le nombre de contacts de longue durée tendait à augmenter avec la pluie, et le R_0 augmentait avec la pluie pour tous les contacts (1,2 [1,0; 1,5]), les contacts de longue durée ($>$ 15 min: 1.4 [1.1; 1,8];$>$ 1h: 1,6 [1,1; 2,2]), et avec une tendance similaire pour tous les contacts, les contacts physiques à l'école et dans les autres lieux.

Pendant le week-end, une température basse était significativement associée à plus de contacts (1,2 [1,0; 1,4]) et à un R_0 supérieur (1,2 [1,0; 1,5]) à la maison et une tendance vers plus de contacts de plus longue durée. Un faible taux d'humidité absolue était associé à plus de contacts physiques (1,2 [1,0; 1,4]), et à une tendance pour plus de contacts et un R_0 plus élevé pour tous les types de contacts. Le nombre moyen de contacts tendait à augmenter avec la pluie en général, et de manière significative pour tous l'ensemble des contacts (1,23 [1,0; 1,3]), les contacts courts <15 min (1,3 [1,0; 1,7]) et les contacts dans d'autres lieux (1,3 [1,1; 1,6]). R_0 tendait également à augmenter avec la pluie pour tous les types de contacts (l'ensemble des contacts: 1,2 [1,0; 1,4]) mais significativement pour les contacts dans les autres lieux (1,4 [1,0; 1,8]).

Cependant, une fois l'âge, la taille du foyer, le genre, le week-end, les jours fériés et l'occupation ont été prises en compte, l'association entre les conditions météorologiques et le nombre moyen de contacts devenait négligeable.

Il y a un effet donc différent de la météo sur les schémas de contact selon les jours de semaine et week-ends. Bien que discret, les conditions météorologiques sont corrélés avec les schémas de contact et peuvent contribuer par ce biais à la transmission de la grippe saisonnière, en plus de l'impact sur la survie du virus et sur l'immunité de l'hôte.

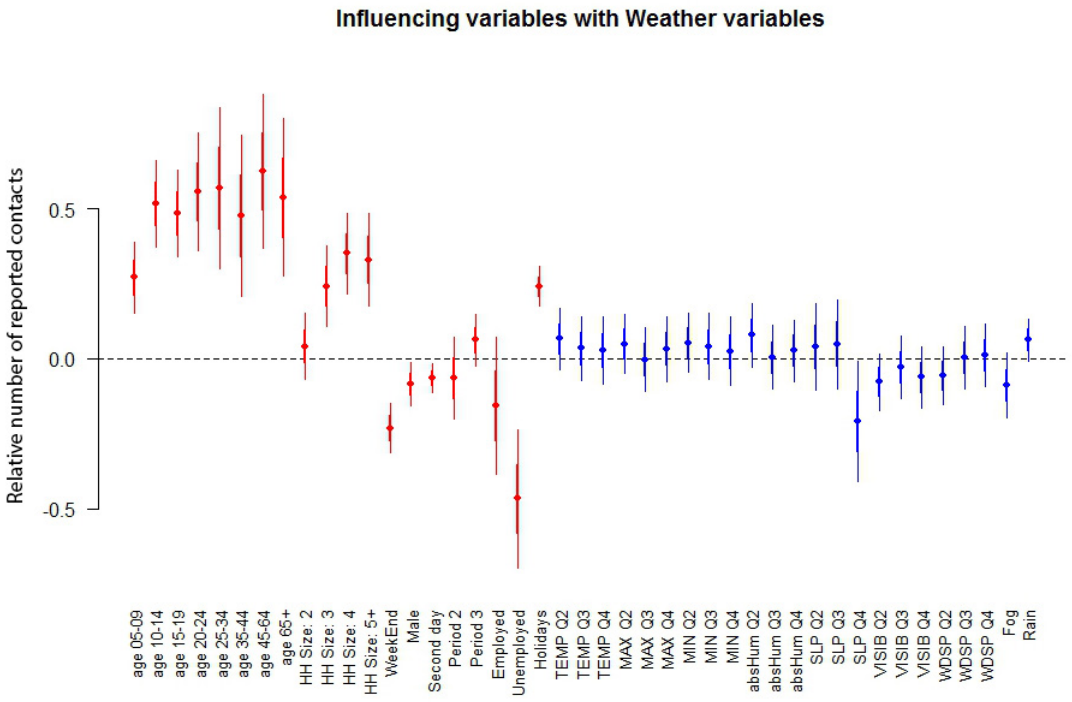

FIGURE E.29: Comparison de variables météorologiques avec les variables du modèle initial.

Des études épidémiologiques ont rapporté des différences de morbidité et de mortalité selon le genre pour de nombreuses maladies infectieuses, ce qui est habituellement attribué à des différences liées au genre au niveau du système immunitaire.

Le genre étant identifié comme un facteur influençant le nombre de contacts dans l'étude Comes-F, nous émettons l'hypothèse que les différences dans les schémas de contact pourraient expliquer en partie les différences entre les genres dans la morbidité et la mortalité.

Les différences liées au genre en ce qui concerne l'immunité ont été largement explorées mais laissent pourtant de la place pour d'autres mécanismes. De nombreux biais dans la notification du genre ont été décrits dans la littérature, la notification du genre sans stratification par âge ne permet notamment pas d'évaluer ces différences correctement. De fait notre revue de la littérature souligne le fait que, même si les différences selon le genre étaient reconnues, leur impact a été minoré par l'agrégation par âge, ce qui rend donc difficile la compréhension du rôle précis de l'immunité, du comportement et des autres facteurs de risque. Nous recommandons donc que les études sur les maladies infectieuses prennent systématiquement en compte le genre, avec une stratification par âge.

Les différences selon le genre présentent de nombreuses similitudes, mais aussi des différences selon l'agent pathogène, le pays et la durée de la catégorie d'âge considéré. Par conséquent, même si des différences immunologiques entre hommes et femmes sont

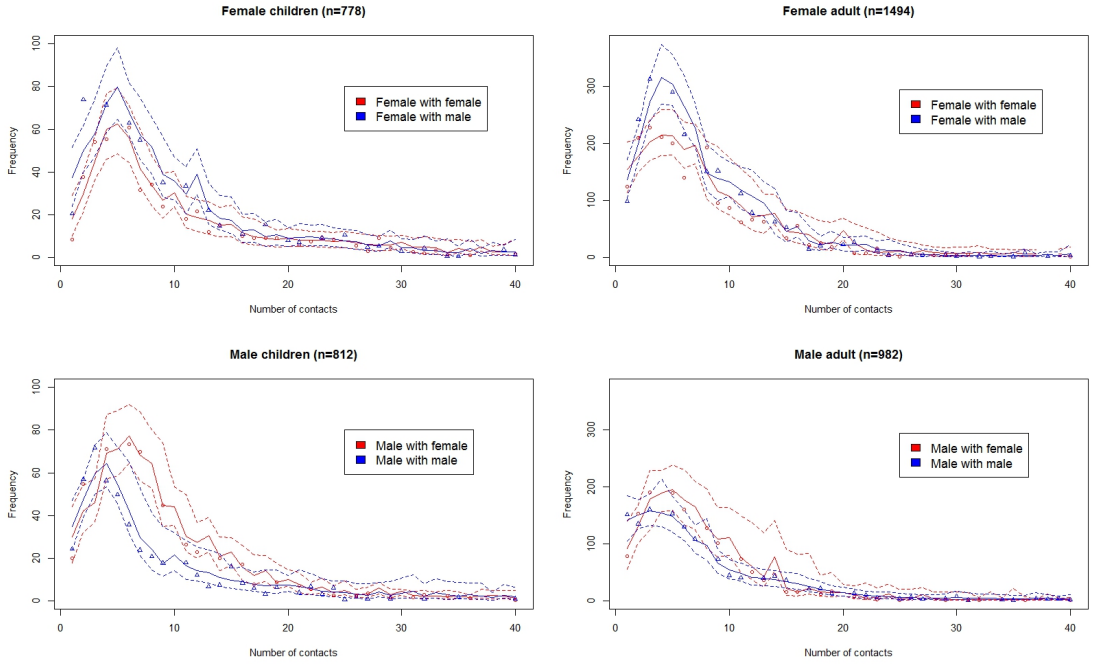

FIGURE E.30: Distribution des degrés de contact selon le genre du participant et du contact.

évidents, ils ne peuvent pas être la seule source de différences observées dans la morbidité et la mortalité. Nous suggérons que le comportement, notamment les schémas de contact, pourraient participer à de telles différences et expliquer les discordances entre les études.

Les différences dans le nombre de contacts peuvent être décrites avec une distribution des degrés de contact en tenant compte du genre du participant et à la fois le contact. De fait, le nombre moyen de contact ne peut pas représenter efficacement les différences dans les schémas de contact entre les genres.

Les graphiques des matrices de contact illustrent les différences en fonction du genre des participants et des contacts. L'aspect le plus notable sont les diagonales parallèles, généralement attribuées aux contacts parent-enfant, qui sont plus importantes chez les femmes, exprimant un taux de contact plus élevé chez les femmes avec leurs enfants et leurs séniors, comparé à leurs homologues masculins.

Lorsque genre est prise en compte pour les participants comme pour les contacts, cela confirme d'abord la plus grande implication des femmes avec les enfants et les parents. Ces matrices montre également que l'assortativité par âge (i.e. le fait d'avoir des contacts essentiellement avec des contacts du même âge que le participant) est plus élevée pour le contact avec le sexe opposé, puisque la diagonale principale est plus mince, alors que cette diagonale s'élargit presque en un "plateau" entre 20 ans et 60 ans pour les

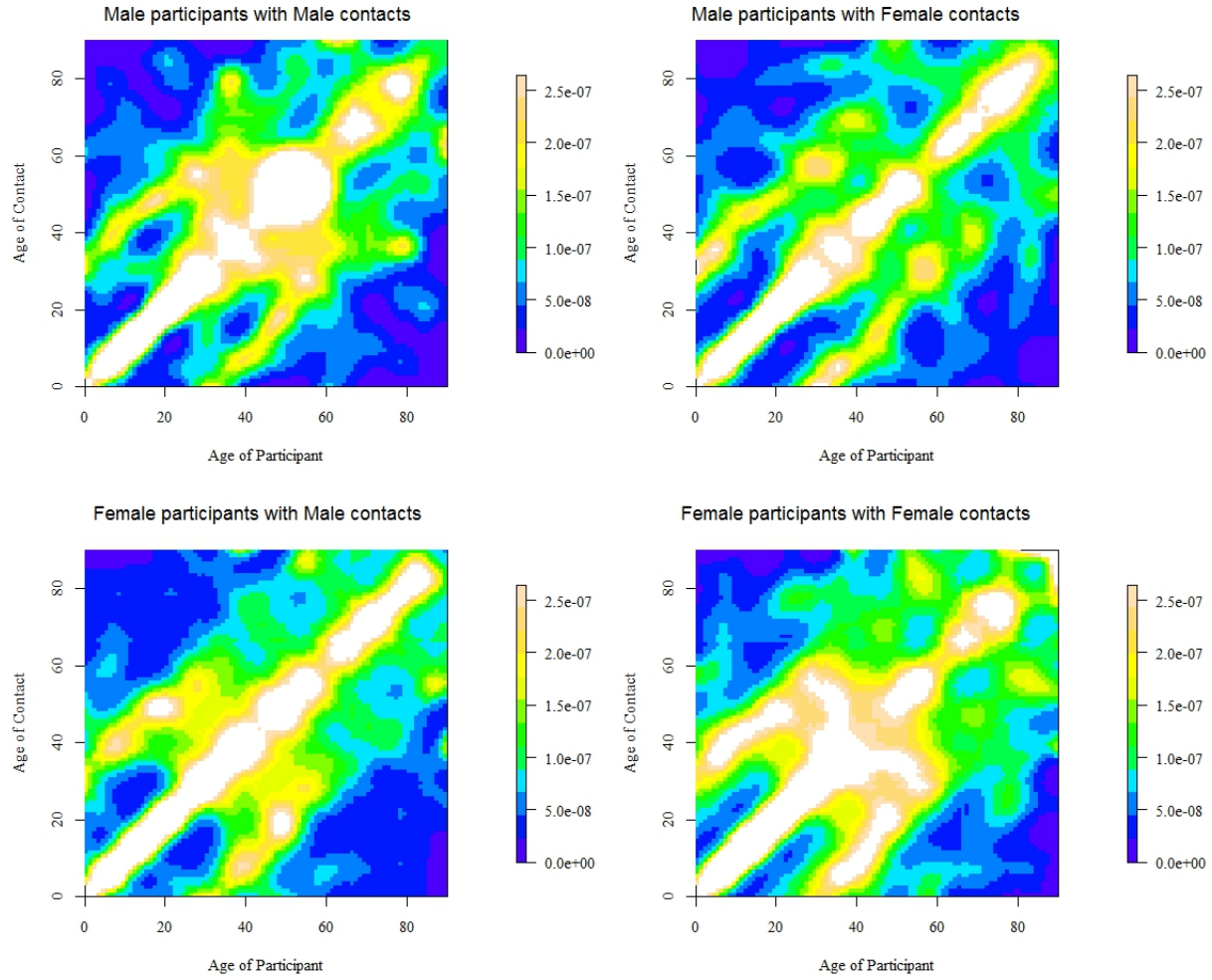

FIGURE E.31: Matrices de contact selon le genre du participant et du contact.

contacts avec le même genre. En outre, ce plateau, qui représente des contacts d'âge ne se limitant pas à celui du participant, semble plus grand pour les femmes, ce qui suggère une assortativité moindre chez les femmes.

Bien les publications liées à POLYMOD n'aient pas identifié d'influence du genre sur le nombre de contacts, nous avons ré-analysé les données de POLYMOD en réalisant des matrices de contact simplifiées 2x2 comme pour Comes-F. Lorsque nous avons comparé les résultats pour la France et les autres pays de Polymod, nous avons constaté des tendances similaires entre tous les pays, mais avec des amplitudes différentes. Par conséquent, nous pouvons conclure que les différences selon le genre que nous avons identifié dans Comes-F ne sont ni le fruit du hasard, ni une spécificité française. Les hommes avaient moins de contacts que les femmes, notamment les hommes adultes avec des enfants en général, et les hommes ont généralement moins de contacts avec les femmes qu'avec les hommes, comparativement aux femmes.

En conclusion, notre revue de la littérature montrait que les différences de comportement entre les genres peuvent participer aux différences de genre dans l'épidémiologie des maladies infectieuses. Par conséquent, les études d'incidence et les enquêtes de séroprévalence devraient systématiquement être présentées avec le genre stratifié par âge. Quoique modeste, l'influence du genre dans la modélisation basée sur les schémas de contact existe et peut permettre une meilleure compréhension de la transmission des maladies infectieuses.