Measles dynamics and vaccination diffusion : a model and an application to the French case

Coudeville Laurent
CRESGE- LABORES, Catholic University of Lille
*

July 2002

Abstract

A lot of mathemical models focused on measles dynamics have been proposed in the literature. Yet, the modelling effort in this area is essentially concentrated on the mechanismes of measles propagation. If present, vaccination diffusion is treated as an exogenous factor despite the clear interactions between these two phenomenons. Here, we propose a model representing the joint evolution of measles incidence and vaccination coverage in France since the diffusion of the vaccine. Estimation of the parameters of this model has been achieved through an original method based on an E-M algorithm. This model gives indications on the way measles propagation and vaccination diffusion interact. It also allow to discuss the ability to eliminate this disease in the next future in France.

1. Introduction

Since the first mathemical models focused on infectious disease dynamics, measles has always been one of the disease whom dynamics has been the most studied [1]. The availability of an effective vaccine and the implementation of vaccination programs all over the world has besides renewed the interest of this kind of models during the last decades. Their use is in fact essential to treat the questions related to the ability to eliminate or even eradicate measles through vaccination. Yet, if a large diversity of models can be found in the literature, the modelling effort is essentially concentrated on the way the virus spread out in the population (age heterogeneity[2], spatial heteregoneity[3], duration of the infectious period[4]...). On the contrary, if present, the evolution of vaccination coverage is treated as an exogenous factor which affect measles dynamics but which is not affected by it.

This kind of interactions has nevertheless been studied on a theoretical viewpoint through the use of economic models focused on individual behaviours regarding vaccination[5]. These analysis show that a key point in the difficulties

*60 Boulevard Vauban BP109 59016 Lille cedex. e-mail : l.coudeville@cresge.fupl.asso.fr

raised by the eradication of a vaccine-preventable disease is the fact that the decrease of the risk to contract the disease induced by an increase of the vaccination coverage make non-vaccinated individuals less likeky to vaccinate. These analysis then underline the need to take into consideration interactions betweeen measles propagation and vaccination diffusion in both ways.

We present here a model reproducing the evolution of measles in France in which individual behavior as regards vaccination is modelled on the basis on a related theoretical work based on vaccination diffusion[6]. For this purpose, we also propose an original method for estimating simultaneously transmission parameters and parameters related to vaccination diffusion from observed data. The model used is presented §2 and the estimation procedure in §3. After having described data used in §4, we present the results obtained in §5. We then conclude (§6) by a discussion of the results obtained and the possible extensions of the analysis performed.

2. Model Presentation

Most of the models used to assess the impact of vaccination on measles incidence at a country level are of Realistic Age Structured (RAS) type [7][8][9]. As stated by Bolker & Grenfell[10], these models, by taking into account the impact of age heterogeneity and seasonal effects on the propensity to contract and to transmit the disease, include the minimum level of complexity allowing to represent measles dynamics. The only difference between RAS models and the one used in this analysis relies on the inclusion of a modelling for the evolution of vaccination coverage. It can be described by the following set of differential equations :

$$\left\{\begin{array}{lcc} \frac{dS(a,t)}{dt} & = & (m(a)+\lambda(a,t)-v(a,t))\,S(a,t) \\ \frac{dE(a,t)}{dt} & = & \lambda(a,t)\,(S(a,t)+V^s(a,t))-(m(a)+\delta)\,E(a,t) \\ \frac{dI(a,t)}{dt} & = & \delta E(a,t)-(m(a)+\rho)\,I(a,t) \\ \frac{dR(a,t)}{dt} & = & \rho I(a,t)-m(a)R(a,t) \\ \frac{dV^P(a,t)}{dt} & = & e(a)v(a,t)S(a,t)-m(a)V^P(a,t) \\ \frac{dV^s(a,t)}{dt} & = & (1-e(a))\,v(a,t)S(a,t)-(m(a)+\lambda(a,t))\,V^s(a,t) \end{array}\right. \tag{2.1}$$

Measles propagation is represented by the evolution of 6 categories of states variables representing the status of individuals of age a at date t : $S(a,t)$ for individuals susceptible to contract measles, $E(a,t)$ for individuals exposed to the virus but not yet infectious, $I(a,t)$ for infectious individuals, $R(a,t)$ for individuals having recovered from measles, $V^P(a,t)$ for individuals protected by an effective vaccination and $V^S(a,t)$ for vaccinated individuals remaining susceptible to contract the disease. $m(a)$ and $e(a)$ defines respectively mortality rate and vaccine's efficacy at age a, δ and ρ the constant transition rates from exposed, to infectious and recovered states. The age limit in the model (L) is fixed to 100

years. To limit the number of state variables of the model for simulation constraints, the population in this model is divided in cohorts of age with a unique date of birth by year (1st September). So, globally there is 600 state variables in this model. (2.1) is solved using a 4th order runge kutta algorithm programmed in Fortran 95 language with a step fixed to 1 day (year is the unit of time). To simplify calculations, we have assumed a constant duration for each month (31 days).

It has to be noted that sometimes protection by maternal antibodies is taken into account in this kind of model through a specific category of state variable. Regarding the method of estimation used, we haven't added this category of state variable. The impact of the protection by maternal, which concerns exclusively infants, is captured here through a lower values of the parameters related to the propensity to contract the disease for children under one year of age.

The two most important parameters, or more precisely functions of parameters, are the force of infection ($\lambda(a,t)$), and the vaccination rate ($v(a,t)$) which determines respectively the number of individuals of age a who who contract measles at date t and receive vaccination against measles. $\lambda(a,t)$ is given by the following expression :

$$\lambda(a,t) = \int \beta(a,a',t) I(a',t) da' + \lambda_0 \tag{2.2}$$

$\beta(a,a',t)$ represent the propensity of infectious individuals of age a' to transmit the disease to individuals of age a. λ_0 defines immigration of infectives from an external reservoir. Excluding seasonal effects and considering that transmission rates remain constant in a given age group leads to the traditional WAIFW matrix (Who Acquires Infection From Whom) for RAS models. If a belongs to age class i, $\lambda(a,t)$ can then be reexpressed as follows:

$$\lambda(a,t) = \sum_j \beta_{ij} \int \beta I_j(t) + \lambda_0 \tag{2.3}$$

β_{ij} are here the coefficients and $I_j(t)$ the number of the infectious in the age class j at date t.We will analyze 2 different configurations for WAIFW matrix described in Appendix A.

Seasonal effects are captured by considering that the propensity to contract and transmit measles within children aged from 3 to 9 years changes each month of the year. Multiplying coefficients $\{s_k, k = 1, 11\}$[1] are then used to complete parameters of the WAIFW matrix related to 3 to 9 years old age group (β_4 in WAIFW matrix n°1, $\beta_6, \beta_7, \beta_8, \beta_9, \beta_{10}$ in WAIFW matrix n°2). 3 to 9 years old children are the age group in which the force of infection is the highest and correspond to the age for infant schools and primary schools in France. Seasonal effects are

[1]Month n°12 (August) is consider as the month of reference for the assessment of the impact of seasonnality. Implicitely, s_{12} is then fixed to 1.

in fact often related to the increase of contacts within school terms. That's why seasonal effects are usually taken into account this way in RAS models. Following Ferguson et al.[1], it has nevertheless to be noted that using an unique birth date for an entire cohort create also a baseline seasonnality. Then, adding explicitly seasonality leads to complete and, eventually correct, this baseline seasonality.

The vaccination rate $v(a,t)$ is given by the following expression:

$$v(a,t) = \frac{f_v(a,t)}{1 - F_v(a,t)} \tag{2.4}$$

$F_v(a,t)$ refers to the proportion of individuals born at date t-a who consider that vaccination is the best choice at date t. It has to be noted that $F_v(a,t)$ doesn't indicate the proportion of effectively vacccinated individuals : some of the individuals who would have been ready for vaccination at date t have contracted measles previously or even are dead. $F_v(a,t)$ is defined as follows :

$$F_v(a,t) = \max_a \left[\min \left\{ \begin{array}{c} G\left[a;\alpha_1,\alpha_2\right]; \\ G\left[\frac{(\alpha_5+\alpha_6\overline{I}(t))}{(1+\overline{I}(t))}\frac{(\overline{R}(t)+\alpha_7)}{(1+\alpha_7)};\alpha_3;\alpha_4\right] \end{array} \right\} \right] \tag{2.5}$$

$G[]$ refer here to Gamma cumulative distribution functions with α_1 and α_3 as shape parameters and α_2 and α_4 as scale parameters. $\overline{R}(t)$ indicates the perception by individuals of their risk to contract measles if they are not vaccinated at date t, and $\overline{I}(t)$ the information given on vaccination by previously vaccinated individuals. $F_v(a,t)$ has been defined in reference to an analysis of vaccination diffusion mechanisms based on an Bayesian approach[6] and take into account of several elements:

- The first one is related to the age at which vaccination occurs : even if the parents of a child concerned by vaccination are favorable to vaccination, they may consider that their child must reach a given age before being vaccinated. This effect can also be related to official recommendations as regards the age of vaccination. $G\left[a;\alpha_1,\alpha_2\right]$ express then the fact that as the age increases, the proportion of a given cohort ready for vaccination is also increasing.

- The second element is related to the perception of the value of vaccination. This perception is updated after each piece of information on vaccination received. This updating procedure modelled through a Bayesian approach leads to the expression in the second bracket : at the beginning of vaccination the proportion of individual favorable to vaccination is based on α_5 and as $\overline{I}(t)$ increases this proportion becomes progressively entirely determined

by α_6. $\overline{I}(t)$ is defined as follows:

$$\overline{I}(t) = \int_{t_V}^{t} \int_{0}^{L} z \left[V^P(a,t') + V^S(a,t') \right] dadt' \tag{2.6}$$

$\overline{I}(t)$ corresponds to the traditional word-of-mouth effects in diffusion models[11]: By their experience, previously vaccinated individuals or their relatives can give indications to those who have not already made their decision regarding vaccination. More generally, $\overline{I}(t)$ can be considered as a proxy variable of the amount of information on vaccination circulating in the population. For example, physicians who plays an important role for motivating the parents of a child in age to be vaccinated become also more aware of the consequences of vaccination as the number of vaccination they have achieved increases. The constant z in $\overline{I}(t)$ is used for normalization ($z = 10^{-8}$).

- The third element is related to the perceived risk to contract the disease. As indicated above, the decrease of this risk for not vaccinated individuals when the vaccination coverage increases appears as a key element in the difficulties raised by eradication. In $F_v(a,t)$ the role played by this perception is directly related to the value of α_7. If α_7 is close to 0, the evolution of $\overline{R}(t)$ has a great impact on $F_v(a,t)$ On the contrary is α_7 has an high value, the role of $\overline{R}(t)$ is limited. $\overline{R}(t)$ is defined as follows:

$$\overline{R}(t) = \int_{t}^{t-D} \int_{0}^{L} \frac{R_{NV}}{D} \left[\lambda(a',t') \left(S(a',t') + V^s(a',t') \right) \right] da'dt' \tag{2.7}$$

$\overline{R}(t)$ is based on the number of measles cases observed on a period ranging from t to $t-D$. In fact, the effective risk to contract measles at date t for a individual who hasn't already chosen vaccination is not directly related to measles incidence observed previously, but what is important here is not the effective risk but the risk as it is perceived. Secondly, the only available information at date t on this risk is based on the consequences associated to measles in the past.$\frac{R_{NV}}{D}$ is a constant used for normalization. R_{NV} refers to the mean annual incidence of measles before the introduction of vaccination (in fact the annual incidence associated to the equilibrium state without seasonality). So, using $\frac{R_{NV}}{D}$ ensures that $\overline{R}(t)$ will remain essentially lower than 1.
Several values of D ranging from 4 years to 16 years will be tested during estimation. In order to simplify calculations, we will also consider that individuals update their perceptions of $\overline{R}(t)$ only once a year corresponding to the date a new cohort is introduced into the model (1st september).

- The decision to delay vaccination because of age is not independant from the perception of the value of vaccination. Here we consider that those who

are the least favorable to vaccination are also those who fix the highest the limit of age for vaccination. Then the proportion of the population ready for vaccination at each age a corresponds to the minimum of the proportion ready for vaccination regarding age and regarding the perceived value of vaccination.

- Vaccination is an irreversible decision. That's why $F_v(a,t)$ has been defined here as a non decreasing function remaining as the highest value achieved since the birth of the cohort, even if the decrease of the perceived risk to contract measles made vaccination less attractive after this maximum has been achieved.

3. Estimation method

Traditionally, the method used to estimate transmission parameter in RAS model is based on data observed before vaccination introduction[12]. For this method, the first step is to estimate the force of infection corresponding to the age distribution of measles cases observed before vaccination. The second step is to determine transmission coefficients by identification using the equilibrium state in absence of vaccination associated to a RAS model without seasonality. This method cannot be implemented with data observed after the diffusion of the vaccine and is inappropriate to estimate parameters related to vaccination diffusion. We then propose here an original method based on an Expectation-Method algorithm[2] allowing to estimate simultaneously transmission parameters and parameters related to vaccination diffusion using data observed after the diffusion of the vaccine.

The method employed here uses longitudinal data about measles incidence and evolution of the vaccination coverage in different age cohorts. The difficulty raised by the use of this kind of data is that there's no simple way to express the quantities in a RAS model corresponding to these data, notably because of the interactions between vaccination diffusion and measles propagation processes. To overcome this difficulty, we calculate the evolution of the number of susceptibles which would have been observed if there were no interactions between vaccination diffusion and measles propagation processes. More specifically, for a given cohort born at date t_0, we calculate the two following expressions :

$$S^P_{t_c}(a) = \exp\left(-\int_0^a \lambda_{t_c}(a')da'\right) \tag{3.1}$$

$$S^V_{t_c}(a) = \exp\left(-\int_0^a v_{t_c}(a')da'\right) \tag{3.2}$$

[2] See [13] for a general presentation of EM algorithms

$S^P_{t_c}(a)$ defines the number of susceptibles in the cohort born at date t_c who would have been observed at age a if the process of virus propagation were independent from vaccination diffusion and mortality (the only way to leave the state of susceptible is to contract measles). Similarly $S^V_{t_c}(a)$ defines the number of susceptibles who would have been observed at age a in the t_c cohort if the process of vaccination diffusion were not affected by virus propagation and mortality. $\lambda_{t_c}(a')$ and $v_{t_c}(a')$ refer respectively to the force of infection and vaccination diffusion rate corresponding to the number of measles cases and vaccinations observed at age a' in the cohort born at date t_c. Calculating $\lambda_{t_c}(a')$ and $v_{t_c}(a')$ is a key element in this estimation procedure and we will discuss it more extensively below (§4).

$S^P_{t_c}(a)$ and $S^V_{t_c}(a)$ give in fact an indirect information on measles incidence and vaccination coverage allowing to proceed to estimations based on the Maximum Likelihood method for interval-censored data[3]. For this, the following Log-likelihood functions can be used :

$$L_P = \sum_{c=1}^{P} \sum_{i=1}^{N_c^P} \left[\begin{array}{c} \left(S^P_{t_c}(a_{i-1}) - S^P_{t_c}(a_i)\right) \ln\left(1 - \exp\left(-\int_{a_i}^{a_{i+1}} \lambda(a', t_c + a')da'\right)\right) \\ -S^P_{t_c}(a_i) \int_{a_i}^{a_{i+1}} \lambda(a', t_c + a')da' \end{array} \right] \tag{3.3}$$

$$L_V = \sum_{c=1}^{V} \sum_{i=1}^{N_c^V} \left[\begin{array}{c} \left(S^V_{t_c}(a_{i-1}) - S^V_{t_c}(a_i)\right) \ln\left(F_v(a_i, t_c + a_i) - F_v(a_{i-1}, t_c + a_{i-1})\right) \\ +S^V_{t_c}(a_i) \ln\left(1 - F_v(a_i, t_c + a_i)\right) \\ -S^V_{t_c}(a_{i-1}) \ln\left(1 - F_v(a_{i-1}, t_c + a_{i-1})\right) \end{array} \right] \tag{3.4}$$

P and V defines the number of cohorts on which data are available, N_c^P and N_c^V the number of intervals for which information are available in the cohort c. Whatever the cohort considered a_0 is set to 0.

To proceed to the estimations, we not only need to calculate $S^P_{t_c}(a)$ and $S^V_{t_c}(a)$, but also the values of regressors determining the value taken by the $\lambda(a', t_c + a')$ and $F_v(a_i, t_c + a_i)$ (i.e.: $\overline{R}(t), I_j(t)$ and $\overline{I}(t)$). All these calculation can be achieved along with the resolution of (2.1).

As vaccination diffusion and virus propagation are not really independent processes and that the value of regressors depends on the initial value chosen for the parameters to be estimated, the only maximization of L_P, L_V doesn't lead to the correct value for $\alpha_i, \beta_{i,j}, s_k$ parameters. Nevertheless, the deterministic version of the RAS model used in this analysis defines the expectation of the global process we want to estimate. So, the calculations and estimations described above defines the expectation and maximization step of an EM algorithm which

[3]For a presentation of Maximum Likelihood estimation of interval-censored data, see for example[14].

will converges to the correct value of $\alpha_i, \beta_{i,j}, s_k$ after a set of iterations. This one can then be defined as follows :

- E-step : Calculation of $S^P_{t_c}(a), S^V_{t_c}(a), \overline{R}(t), I_j(t)$ and $\overline{I}(t)$ along with the resolution of the set of differential equations (2.1) defining the model.
- M-step: Estimation of the $\alpha_i, \beta_{i,j}, s_k$ parameters by maximizing separately the log-likelihoods L_P and L_V.

After each iteration the estimate values of $\alpha_i, \beta_{i,j}, s_k$ are used as initial values for the next iteration. Convergence is considered as obtained if the difference between the values of any parameter doesn't exceed 1% in absolute value. The convergence criterion, assuming that no parameter has a zero value, can then be then defined as follows :

$$\forall i,j,k \quad \left|\frac{\widehat{\alpha}_i^l - \widehat{\alpha}_i^{l-1}}{\widehat{\alpha}_i^{l-1}}\right| < 0.01, \left|\frac{\widehat{\beta}_i^l - \widehat{\beta}_{i-1}^{l-1}}{\widehat{\beta}_{i-1}^{l-1}}\right| < 0.01, \left|\frac{\widehat{s}_i^l - \widehat{s}_{i-1}^{l-1}}{\widehat{s}_{i-1}^{l-1}}\right| < 0.01 \tag{3.5}$$

$\widehat{\alpha}_i^l, \widehat{\beta}_i^l, \widehat{s}_i^l$ defines the adjusted value $\alpha_i, \beta_{i,j}, s_k$ obtained at iteration l.

If we have insisted on the fact that this EM algorithm allows to perform estimation despite the complexity of the process on which this model is based, one of his interest is also to make possible estimation even if only incomplete information is available on measles incidence and vaccination diffusion, which is the case here (Cf. §4). This incompleteness doesn't modify the estimation procedure. It nevertheless implies to determine initial values for the E-step of the first iteration. For the transmission parameters, these initial values can be obtained from previous works using RAS models. We have used here the evolution of force of infection according to age considered by Levy-bruhl et al. [7] in an analysis also focused on measles propagation in France. We then have carried out the usual identification method to determine transmission parameters from these data. For parameters related to vaccination diffusion in the absence of available initial values for parameters, we have build a complete set of data for the period considered in the analysis using extrapolation from observed data.

Another problem raised by available data is that is difficult to determine the exact size of the population on which each measles incidence data is based (measles transmission) or that data came from different sources differing as regards methodology and exhaustiveness (vaccination coverage). We have then made the choice here to give a similar weight to each cohort of age fixed to 1. This make difficult to assess the global accuracy of the estimation carried out. We then use the 95% confidence interval associated to each parameter to assess the quality of adjustment. This 95% confidence interval is calculated through naive bootstrapping using 1000 simulations. We also consider pseudo-R2 ratios

to obtain information on the quality of adjustment (Cf. Appendix B for the calculation of this pseudo-R^2).

It also has to be noted that if this estimation procedure has been developed to allow the estimation of vaccination diffusion, it presents some advantages for the estimation of transmission parameters as compared to the usual method :

- It allows to use data on measles incidence observed after the introduction of the vaccine. That is to say the most recent data available on measles incidence As the modifications of the social environment over time (the decrease of the mean age at the beginning of scolarization for example) has an impact on the propensity to transmit and to contract the disease, this is an important element. Moreover, there's no reliable data on measles incidence in France before the introduction of the vaccine.

- The identification step in the usual method implies the use of specific configurations for the WAIFW matrix (a number of transmission coefficients having a different value equivalent to the rank of the WAIFW matrix. This is not the case with the method used here. It then allows to assess the accuracy of usual configurations of WAIFW matrix.

- The parameters related to seasonality are usually estimated separately using a least squares method and a few number of parameters (see for example[10]). Here parameters related to seasonality are estimated simultaneously with the transmission coefficients of the WAIFW matrix.

4. Data

We present successively below the data used for measles incidence and evolution of vaccination coverage in France and conclude this section by a brief presentation of the other data used in this analysis. Considering data available, the period of reference in this analysis goes from September 1969 (diffusion of measles vaccine) to April 2001 (latest data on measles incidence).

4.1. Measles incidence

The main source of information about measles incidence in France is the surveillance achieved by the Sentinel Network[4]. Sentinel network collect information about measles incidence since November 1984 with the help of around 500 general practitioners volunteer for this surveillance[5]. Based on the cases on which data are collected (7331 cases for the period considered in this analysis), sentinel

[4]See[15] for a brief presentation of the sentinel network. Extensive information are also available on the following website : http://www.b3e.jussieu.fr/sentiweb/

[5]The number of these General Practitionners vary over time and goes from 442 in 1998 to 614 in 1994.

network is able to give information on the age distribution of measles and cases and to extrapolate the monthly number of measles cases in France, which is the information used here. These data are depicted Figure 1.

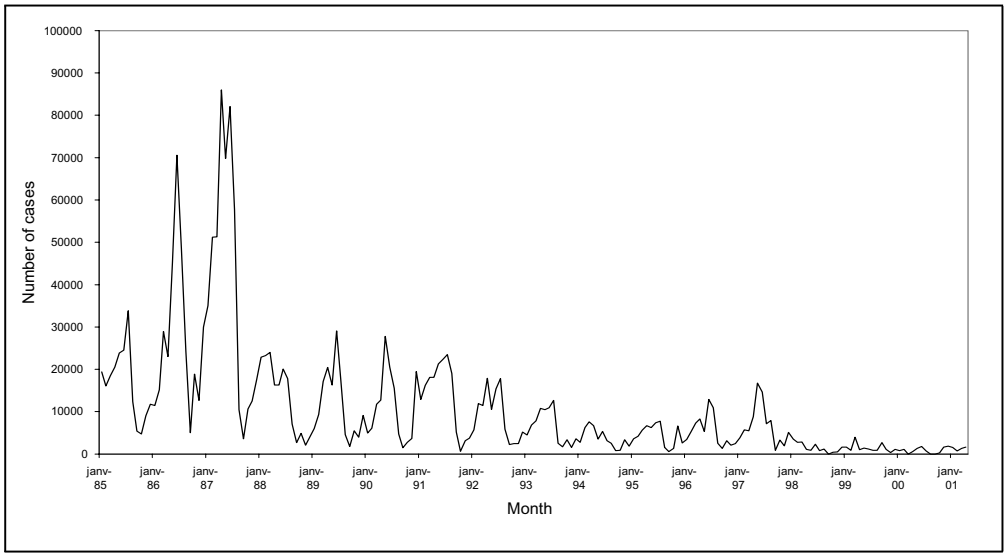

Figure 3.1 Monthly number of measles cases based on Sentinel Network surveillance From November 1984 to April 2001

Data collected by the Sentinel network make possible to characterize each month the proportion of measles case at each age. Nevertheless, if the representativeness is correct for low ages because of a higher force of infection, this is not the case for older ages : the proportion of adult cases is around 4%. We have then used 13 classes for the age distribution of monthly number of measles cases : a specific class for each age lower than 10, and 3 classes for respectively teenagers of 10 to 14 years, 15 to 19 years and adults of 20 years and over.

To include measles incidence data into the model, we have determined for each age class and month the constant forces of infection corresponding to the number of cases derived form sentinel network surveillance (the $\lambda_{t_c}(a')$ cited above, §2). this has been done by using a least squares minimization based on a standard algorithm (Levenberg-Marquard). The error level associated to this calculation is very low and never exceed 10^{-5}. For periods for which no data is available, the evolution of measles incidence is determined by using the value of transmission parameters at the current iteration.

It has to be noted that using as data the monthly number of measles cases in France required that the size of the population considered in the model is similar to the one of the French population. The size of each cohort at birth has then be determined using data of the French Agency of statistics INSEE. Age mortality rates are also based on INSEE data and we have used a specific rate for each age.

4.2. Vaccination coverage

In France, measles vaccination is not mandatory but is strongly recommended by health authorities. Since 1997, the recommended scheme for measles vaccination includes two vaccinations : the first one to be given before 2 years of age and the second one between 3 to 6 years of age[6]. Our analysis is yet focused here only on the first vaccination notably because data used are related to generations not concerned by this new recommendation. Gathering information from the different sources existing on this point in France leads to 54 points of observation related to 23 generations born between 1969 and 1997 (see. Table 4.1).

GENERATION	AGE						
	9 months	1year	1 year 3 months	1 year 6 months	2 years	4 years	6 years
1969					0.04		
1971					0.08		
1973					0.11		
1975					0.13		
1977					0.15		
1979	0.008	0.037	0.091		0.189		0.261
1981	0.005	0.03	0.1	0.173	0.22	0.371	0.412
1982					0.29		
1983	0.01	0.055	0.187	0.312	0.35	0.553	0.588
1984					0.394		
1985	0.012	0.045	0.106		0.456		0.72
1986					0.515		
1987		0.049		0.408	0.588		0.815
1988					0.67		
1989					0.735	0.816	
1990					0.755	0.84	
1991					0.778	0.852	0.9
1992					0.803	0.88	
1993					0.826	0.886	
1994					0.838	0.908	
1995					0.833	0.912	
1996					0.825		
1997					0.827		

Table 3.1 Evolution of vaccination coverage against measles in France (generations 1969-1997)

Data presented Table 3.1 came from four different sources : Surveys carried out by physicians working for the public education system on the vaccinal status at 4 years old (1989 to 1995 generations) and 6 years of age (1979, 1981, 1983,

[6]Information about official recommandations in France concerning measles vaccination are available on the website of the Institut de Veille Sanitaire (http://www.invs.sante.fr/).

1985, 1987, 1991 generations), systematic report achieved in the context of the mandatory medical consultation at 2 years old (1984 to 1997 generation) and finally data collected from the main vaccine's manufacturer for a study used to establish the new recommendation (1969, 1971, 1973, 1975, 1977 generations, see [7]). A detailed presentation on data available on vaccination coverage in France can be found in a technical report of INVS[16].

These information don't allow to assess directly the monthly progression of vaccination coverage. Regarding the evolution observed, using a constant rate between two ages for which data is available is not a good approximation. Such as for measles incidence, we have then assumed that $v_{t_c}(a')$ remain constant only on a monthly interval. To rebuild the monthly progression of vaccination coverage, we have used linear approximation for the first iteration. For the following iterations, this monthly progression is based on estimation of $F_v(a,t)$ at the current iteration. Given this information , the constant $v_{t_c}(a')$ has been determined through least squares minimization. Such as the $\lambda_{t_c}(a')$, the error level associated to this calculation never exceed 10^{-5}.

For generations for which no data is available and beyond the age for which data are available for generations mentioned in Table 4.1, linear approximation for the first iteration and estimation of $F_v(a,t)$ for the following iterations have also been used to determine the progression of vaccination coverage.

4.3. Duration of Measles

For the duration of an episode of measles, data used are similar to those of Anderson and May[2] : 7 days for the mean duration of the period during which an individual is exposed but not infectious which leads to $1/\delta = 7/365$ and 7 days for the mean duration of the infectious period which leads to $1/\rho : 7/365$.

4.4. Vaccine's efficacy

Data on vaccine's efficacy are similar to those by Levy-bruhl et al.[7]: 92.5% until 18 months of age, 95% beyond.

5. Results

5.1. Measles transmission

As discussed when presenting the method of estimation, it is possible to define WAIFW matrix different from the usual ones (a number of coefficient having a different value equivalent to the rank of the matrix). We have nevertheless made the choice to limit our investigation to these configurations. Reasons for this choice are twofold. The first one is that the aim of this analysis is to add vaccination diffusion in an usual measles dynamics model not to build a model for measles dynamics different from the usual ones. The second reason is that the kind

of model used can lead to chaotic evolution when the WAIFW matrix has a general form (See [1] for an analysis of this point). Yet, observed evolution for measles incidence at a country level is of cyclic form (either biennal or triennal). Moreover, chaotic evolution make convergence difficult to achieve. Results associated to 4 different models are presented here :

- Model W7-S : Use of WAIFW n°1 with 7 age classes completed by parameters related to seasonality.
- Model W13-S : Use of WAIFW n°2 with 13 age classes completed by parameters related to seasonality.
- Model W13-NS : Use of WAIFW n°2 with 13 age classes without parameters related to seasonality.
- Model W13-NI : Use of WAIFW n°2 with 13 age classes with parameters related to seasonality but without parameters related to measles transmission due to immigration of infectives (λ_0).

To prevent the impact of interactions between estimations of measles propagation and vaccination diffusion, we have used for each of these models the same configuation regarding vaccination diffusion, the one considered in the R16 model defined below.

	Model W7-S		Model W13-S		Model W13-NS		Model W13-NI	
β_0*10^6	**2.58**	*(1.29-4.56)*	**1.47**	*(0.23-3.36)*	**1.38**	*(0.24-3.2)*	**1.71**	*(0.59-3.56)*
β_1*10^6			**8.42**	*(7.13-9.97)*	**8.26**	*(6.94-9.74)*	**8.79**	*(7.41-10.48)*
β_2*10^6			**12.35**	*(10.08-15.51)*	**12.22**	*(9.98-15.27)*	**13.23**	*(10.61-16.3)*
$\beta_{1-2}*10^6$	**11.79**	*(10.39-13.28)*						
β_3*10^6			**13.34**	*(8.51-18.97)*	**23.6**	*(20.45-27.2)*	**13.94**	*(8.47-19.87)*
β_4*10^6			**19.54**	*(12.18-28.33)*	**35.09**	*(30.27-40.33)*	**20.35**	*(12.17-30.28)*
$\beta_{3-4}*10^6$	**30.87**	*(28.11-33.71)*						
β_5*10^6			**30.86**	*(18.77-45.37)*	**56.34**	*(46.37-66.15)*	**31.88**	*(18.79-48.18)*
β_6*10^6			**62.57**	*(34.86-98.57)*	**113.3**	*(81.17-144.41)*	**64.89**	*(35.99-102.01)*
β_7*10^6			**20.65**	*(10.14-34.06)*	**38.73**	*(23.34-56.25)*	**21.77**	*(10.51-34.73)*
β_8*10^6			**15.13**	*(7.49-24.95)*	**25.84**	*(13.59-38.29)*	**16.19**	*(8.11-25.87)*
β_9*10^6			**9.27**	*(4.65-15.04)*	**16.53**	*(9.01-24.97)*	**10.75**	*(5.05-17.95)*
$\beta_{5-9}*10^6$	**17.63**	*(9.32-29.24)*						
$\beta_{10+}*10^6$	**6.74**	*(4.14-9.47)*	**14.56**	*(12.96-16.31)*	**15.44**	*(13.75-17.1)*	**16.28**	*(14.7-17.85)*
$\beta_{15+}*10^6$	**2.62**	*(1.51-3.99)*	**9.27**	*(7.47-11.13)*	**10.29**	*(8.59-12.36)*	**11.4**	*(9.52-13.27)*
$\beta_{20+}*10^6$	**0.19**	*(0.05-0.36)*	**8.47**	*(6.68-10.54)*	**9.94**	*(7.9-12.26)*	**14.84**	*(11.73-17.96)*
λ_0*10^6	**131.13**	*(73.27-199.51)*	**147.09**	*(49.33-247.63)*	**127.32**	*(36.01-226.22)*		
s_1	**0.64**	*(0.13-1.44)*	**0.34**	*(0.05-0.79)*			**0.41**	*(0.12-0.93)*
s_2	**2.72**	*(1.39-5.19)*	**2.13**	*(1.37-3.47)*			**2.26**	*(1.5-3.83)*
s_3	**2.34**	*(1.17-4.57)*	**1.95**	*(1.28-3.36)*			**2.03**	*(1.28-3.39)*
s_4	**2.97**	*(1.72-5.5)*	**2.21**	*(1.55-3.54)*			**2.2**	*(1.51-3.62)*
s_5	**2.03**	*(1.2-3.93)*	**1.55**	*(1.03-2.6)*			**1.58**	*(1.02-2.72)*
s_6	**3.02**	*(1.84-5.48)*	**1.86**	*(1.31-2.95)*			**1.83**	*(1.25-3.01)*
s_7	**2.61**	*(1.55-4.84)*	**1.85**	*(1.28-3.06)*			**1.81**	*(1.25-3.03)*
s_8	**2.82**	*(1.67-5.1)*	**1.88**	*(1.31-3.02)*			**1.82**	*(1.26-3.03)*
s_9	**2.74**	*(1.61-5.01)*	**1.88**	*(1.32-3.01)*			**1.83**	*(1.26-2.98)*
s_{10}	**2.86**	*(1.74-5.1)*	**1.97**	*(1.4-3.14)*			**1.92**	*(1.33-3.21)*
s_{11}	**2.3**	*(1.32-4.35)*	**1.71**	*(1.17-2.83)*			**1.66**	*(1.15-2.78)*
Log-likelihood	**-37.14**		**-36.78**		**-36.77**		**-36.72**	
PR^2_I	**0.688**		**0.661**		**0.653**		**0.659**	
PR^2_{II}	**0.712**		**0.723**		**0.711**		**0.722**	

Table 5.1 Results of the estimation of transmission parameters

The results presented Table 2 underline the good quality of the adjustement performed. Whatever the model consider, each of the parameter has the expected sign and is significatevely different from 0 and the pseudo-R^2 measures are around 70%. In fact, the quality of adjustment is rather good if one considers the overall measles incidence but is poorer when considering specifically age groups for which measles incidence is low (see Figure 4.1, Figure 4.2). This result can be at first related to the quality of the data used in this analysis. It has been pointed out notably that this quality becomes questionable for a low level of measles incidence[17].

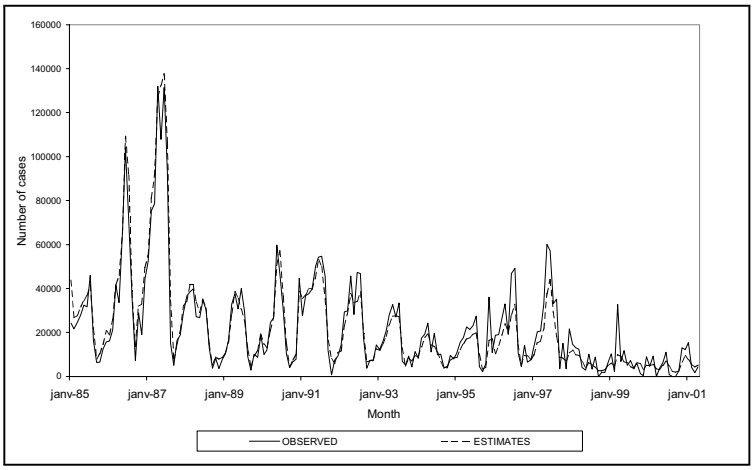

Figure 4.1 Observed and Estimated monthly measles incidence (All age classes – Model W13-S).

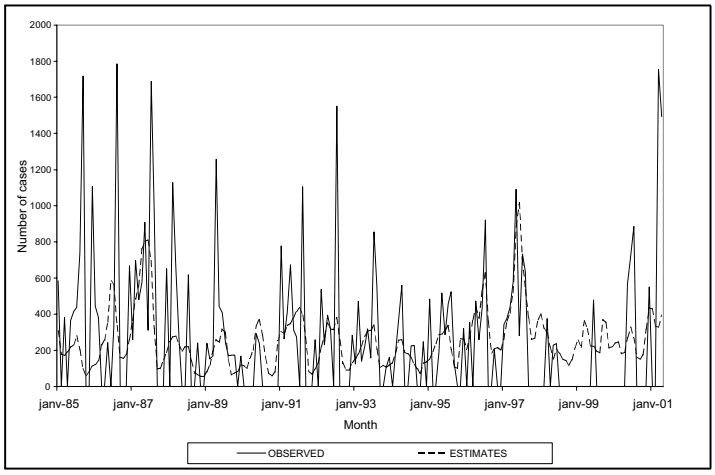

Figure 5.2 Observed and estimated monthly measles incidence (20 years and over adults only - Model W13-S)

The second element which can be noted is that the increase of the number of parameters of the WAIFW matrix, such as the introduction of seasonality, induces only a slight change of the quality of adjustement : Pseudo-R^2 of type I (based on log-likelihood) go from 67.1% to 68.0% and Pseudo-R2 od type II go from 71.1% to 72.2%. RAS models ability to describe measles can be put forward for explaining this result. This ability becomes less good as the level of vaccination coverage increases notably because of possible spatial decorrelation (see [3] for a discussion of vaccination on measles dynamics). Refining WAIFW matrix then only leads to slight improvements of the adjustement, not to a modification of the overall ability of the RAS model to describe measles dynamics.

According to the values associated to s_1-s_{11}, measles transmission seems lower in September (s_1) and August (month of reference). These results can at first be

related to the usual explanation for seasonal effects in measles transmission : this one is higher at the beginning of school year and lower during summer holidays. The value associated to s_1 can also be related to the fact that in the model all infants in a cohort are considered as having the same birth date. As indicated §2, this creates a baseline seasonality that the low value associated to s_1 contributes to attenuate.

The quality of the adjustment performed can also be assessed by comparing results obtained with the ones associated to the usual method. Here initial values for transmission parameters are those of an analysis also focused on measles transmission in France [7] and have been determined through the usual method. So, they can be used for this comparison. These initial values lead to pseudo-R^2 of around 55% (55.7% for PR^2_I, 55.5% for PR^2_{II}) for the Model W13-S. This gives an indication that the method employed here outperforms the usual one.

5.2. Vaccination diffusion

Such as for the estimation of transmission parameters, several specifications have been tested for the estimation of vaccination diffusion. 5 specifications which differs according to the duration of the period considered to assess the perceived risk to contract measles have been in fact analyzed :

- Model R16 : Perceived risk to contract measles based on the number of measles occurred during the 16 last years
- Model R12 : Perceived risk to contract measles based on the number of measles occurred during the 12 last years
- Model R8 : Perceived risk to contract measles based on the number of measles occurred during the 8 last years
- Model R4 : Perceived risk to contract measles based on the number of measles occurred during the 4 last years
- Model NR : Perceived risk to contract measles not included in the specification of $F_V(a,t)$

For these 5 models, we have considered the same configuration for the transmission parameters, the one corresponding to the model W13-S defined above.

	Model R4	Model R8	Model R12	Model R16	Model NR
α_1	**18.32**	**18.34**	**16.65**	**18.54**	**18.3**
	(15.66-21.5)	(15.65-21.15)	(14.73-20.62)	(15.54-21.36)	(15.62-21.27)
α_2	**11.22**	**11.23**	**10.29**	**11.33**	**11.21**
	(9.64-13.03)	(9.7-12.84)	(9.15-12.53)	(9.64-12.98)	(9.71-12.93)
α_3	**2.51**	**2.87**	**3.34**	**6.7**	**2.48**
	(1.65-6.26)	(1.62-7.94)	(1.58-8.43)	(1.65-12.54)	(1.52-6.07)
α_4	**501.69**	**114.77**	**10.29**	**21.08**	**23.14**
	(455.15-646.22)	(37.48-213.29)	(1.8-24.93)	(1.21-34.21)	(19.12-29.64)
α_5	**0.001**	**0.01**	**0.1**	**0.16**	**0.03**
	(0.001-0.01)	(0-0.03)	(0.03-0.41)	(0.03-0.39)	(0.01-0.13)
α_6	**0.02**	**0.1**	**1.47**	**1.16**	**0.42**
	(0.01-0.04)	(0.06-0.23)	(0.63-4.85)	(0.39-6.19)	(0.3-0.74)
α_7	**162.9**	**11.6**	**3.01**	**2.32**	
	(2.44-1276.98)	(2.33-825.77)	(1.65-345.99)	(1.55-248.87)	
Log-likelihood	**-16.993**	**-16.993**	**-17.031**	**-16.987**	**-16.993**
$\mathbf{PR^2_I}$	**0.944**	**0.9439**	**0.9387**	**0.9447**	**0.944**
$\mathbf{PR^2_{II}}$	**0.9709**	**0.9708**	**0.9691**	**0.9713**	**0.9709**

Table 5.2. Results of the estimation of parameters related to vaccination diffusion

As previously, the estimation performed leads to a good quality of adjustment. This one is even excellent if one considers the values associated to the pseudo-R^2 measures : pseudo-R^2 of type I are all higher than 93% and pseudo-R^2 of type II are all higher than 96%. This result can also be illustrated graphically by comparing the observed and estimated vaccination coverage rates at 2 years, 4 years and 6 years (Cf. Figure 5.3).

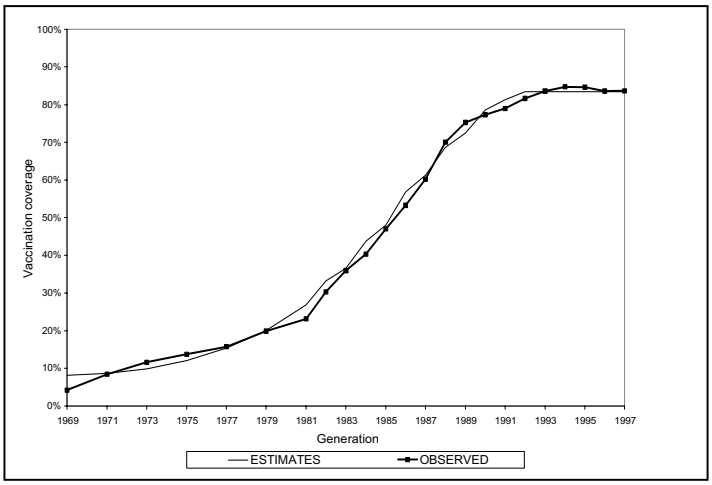

Figure 5.3 Observed and estimated vaccination coverage at 2 years old (Model R16)

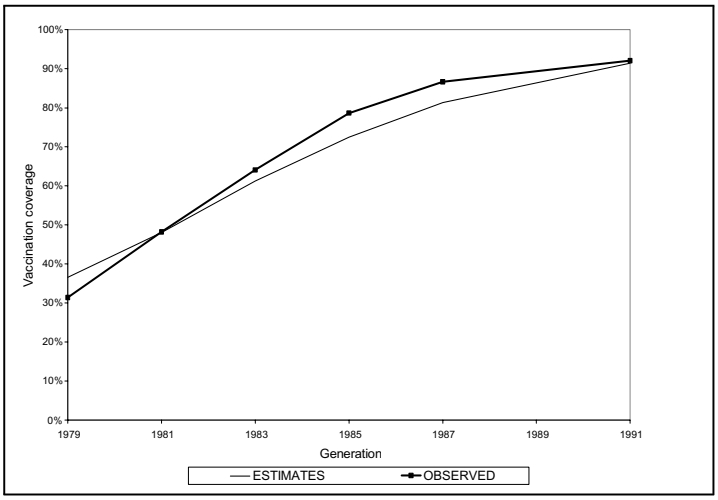

Figure 5.4 Observed and estimated vaccination coverage at 6 years old (Model R16)

The inclusion into $F_V(a,t)$ of the impact of the perceived risk to contract measles only induces a slight improvement of the quality of adjustment : +0.07% for pseudo-R2 of type I and +0.04% for pseudo-R2 of type II. Moreover, the best quality of adjustement is obtained with a long duration associated to the calculation of this risk (model R16). This result seems to indicate that individuals are not really sensitive to the decrease of the risk to contract the disease for their choice regarding measles vaccination. The large confidence intervals associated to the value of α_7 whatever the model considered give also a confirmation of this result.

The low impact of the perceived risk to contract measles for explaining vaccination diffusion can also be related to the difficulty for accurately capturing this element into a model. Here we have chosen specifications for this risk based on the number of measles cases observed during rather long periods. The way individuals perceive this risk could be different. It seems for example that for their choice regarding vaccination individuals react more to a rapid upsurge of the incidence than to the decrease of the incidence of a disease in the long run [18]. It also have to be noted that the value associated to $\overline{R}(t)$ depends of the quality ot the adjustment of measles propagation performed, which is not perfect. Finally, as for measles incidence, the quality of data used can also be put forward for explaining the results obtained. Data used for vaccination coverage came from heteregenous sources, each of them being not totally free of bias (Cf. [16]). It is then difficult with these data to estimate accurately a model based on a too complex representation of individual behaviour regarding vaccination.

5.3. Predicted evolution of measles

The results of the estimation performed can be used to predict the evolution of measles in France in the next future. Nevertheless, as noted above (Cf. §4), the current vaccination strategy in France differs from the one considered in this analysis : the second vaccination to be given between 3 and 6 years old has not been included. The predicted evolution of measles presented here gives then only a indirect information on the way measles should affect the French population in the next future. This information thus remains useful to discuss the ability to eliminate native measles in France which is the goal fixed by Health authorities in accordance with Regional WHO office for Europe[7].

The predicted evolution of measles incidence differs according to the inclusion into the model of the impact of measles transmission from infectives coming from an external reservoir. When this element is taken into account (Cf. Figure 5.5), measles incidence is increasing slowly over the period 2001-2050 with an annual incidence of about 3/100 000 inhabitants in 2002 and 12/100 000 inhabitants in 2050. When this element is not taken into account, measles incidence remains very low most of the time (annual indicence of about 0.3/100 000 in 2020), but major outbreaks occurs every fifteen years (Cf. Figure 5.6). None of these scenarios can be viewed as a perfect prediction of measles evolution in France but each of them gives a clear indication on what measles dynamics could have been with a strategy based on a unique vaccination : a mean annual incidence which remains higher than the threshold fixed for elimination (1/100 000) and a potential risk of major outbreak..

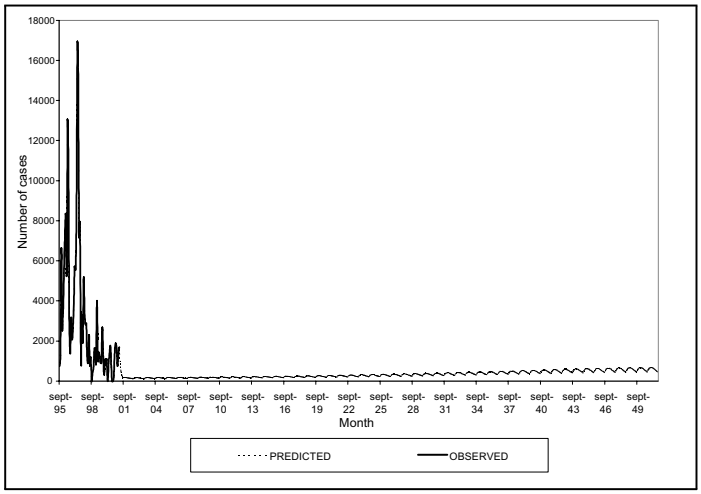

Figure 5.5 Predicted evolution of monthly mealse incidence over the period 2001-2050 (Model W13-S)

[7]Elimination of native measles is considered as reached when annual measles incidence is lower than 1 case for 100 000 inhabitants. Information about official recommandations in France concerning measles vaccination are available on the website of the Institut de Veille Sanitaire (http://www.invs.sante.fr/).

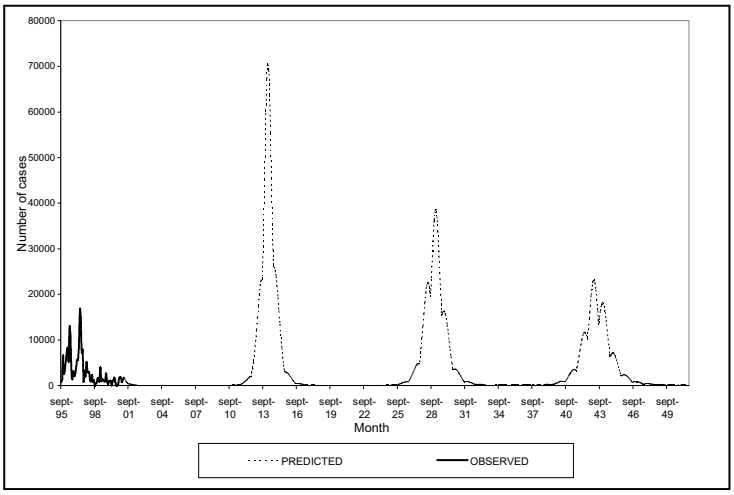

Figure 5.6 Predicted evolution of monthly measles incidence over the period 2001-2050 (Model W13-NI)

The predicted evolution of vaccination coverage gives also useful indications and the evolution of measles in France. According to the results obtained, the vaccination coverage rate at 2 years old should remain below 85% (Figure 5.7) but could reach nearly 100% at 6 years old (Figure 5.8). These results which are dependant of the specification chosen for $F_V(a,t)$ such as of the data used for estimation have to be interpreted cautiously. They nevertheless indicate that if there is a margin of progression for vaccination coverage, it's rather by increasing the number of vaccination achieved between 2 and 6 years old, than by increasing the number of vaccination achieved before 2 years old.

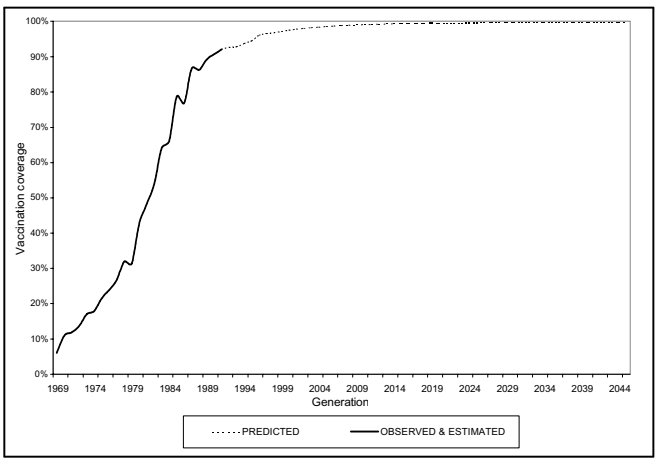

Figure 5.7 Predicted evolution of vaccination coverage rate at 2 years old (Generation 1992-2045 - Model R16)

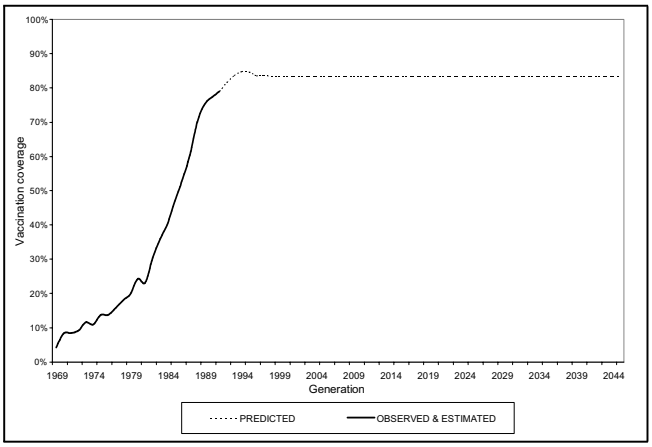

Figure 5.8 Predicted evolution of vaccination coverage at 6 years old
(Generation 1998-2049- Model R16)

The evolution of measles in France which can be derived from the estimation performed gives strong arguments for the inclusion of a second dose of vaccination in the recommended strategy for measles. With a strategy based on a unique vaccination, elimination seems hard to obtain, notably because the vaccination coverage at 2 years old seems to have reached its upper bound these last years. A second dose of vaccination to be given between 3 to 6 years old will then gives an opportunity not only to limit the impact of vaccine's failures but also to make easier the vaccination of those not vaccinated at 2 years old.

6. Discussion

The analysis performed proves than mixing economic models of innovation diffusion and epidemiological modes of infectious disease dynamics is not only feasible but also useful. The model built gives a more complete description of the evolution of measles in France than those focused only on measles propagation. Its value is twofold : it allows to take into account of the iteractions between vaccination diffusion and measles propagation but also to take advantages of the latest data available on these topics. Regarding the complexity of the dynamics associated to measles and the difficulties for obtaining accurate data for feeding a too complex model, it can't be however considered as a perfect represention but rather as a tool giving indications on the main factors having an impact on the evolution of measles in France.

The estimation achieved leads to a good fit of the overall observed measles incidence, outperforming the usual method[12]. The fit carried out is however poorer when one considers specifically age groups for which measles incidence is the lowest. This result can at fist be related to the overall ability of RAS models to describe measles dynamics. This ability becomes less good as the level of vaccination coverage increases [3]. It has to be noted nevertheless that we have made

the choice to limit our investigations to the usual configurations of the WAIFW matrix (i.e symetric matrix with a number of coefficients having a different value equal to the size of the matrix). The main focus is here the addition of a specific modelling for vaccination diffusion in an usual measles dynamics model. Using a more general form for the WAIFW matrix could be helpful to improve the quality of adjustment performed in each age group. More generally, the kind of analysis performed does not necessarily imply the use a RAS-type model to represent measles propagation. If data are available, it could be interesting to add a specific modelling for vaccination diffusion into a different kind of measles dynamic model (a model including spatial heterogeneity for example).

The type of data used has also an impact on the quality of the adjustment performed. It has been pointed out that the quality of Sentinel data becomes questionable for a low level of measles incidence (on this point, see nevertheless the answer given by the persons in charge of the Sentinel nework [19]). Another problem is that sentinel surveillance relies on clinical data alone and the risk that cases observed are not really due to measles becomes greater as this disease becomes rarer. Using a different dataset, such as the seroepidemiological data collected through the ESEN survey[20], could also be helpful for improving the quality of the adjustment performed.

Even if it is based on fewer data, the adjustment of vaccination diffusion carried out appears to be better than the one achieved for measles propagation. The sigmoid shape, which is usual for innovation diffusion[11] and is also observed for measles vaccination, is well captured by the specification chosen in this analysis. This is also true for the two dimensions in which the evolution of vaccination coverage has to be analyzed: within a generation as age increases and between successive generations.

Regarding the estimation of vaccination diffusion, the main result is however that the risk to contract the disease, despite its key role in theoretical analysis [5][6], does not seem to play an important role in vaccination diffusion. Again, two reasons can be given for this result : the limitations of the specification chosen and the quality of the data used.

The main problem regarding the specification chosen is related to the difficulty to define an appropriate variable for the risk to contract measles, principally because what is important here is not the true risk but the risk has it is perceived. What is clear when one considers data, is that there is not a direct relationship between the variation of measles incidence and the variation of vaccination coverage. That's why we have related in this analysis the perceived risk to contract measles to the evolution of measles incidence on a rather long period (from 4 to 16 years). On the opposite, what is also clear is that obtaining a level of vaccination coverage high enough to eliminate a vaccine-preventable disease is always a difficult task, though not impossible (Cf. smallpox). This is exactly the result predicted by theoretical analysis focused such as the current situation for measles in France. Indeed, it seems that, if individuals are sensitive (or at least a part

of the population) to the risk to contract the disease for their choice regarding vaccination, the way they perceives this risk is rather irrational. For example, individuals seems to react more to a rapid upsurge of the incidence of a disease than to the decrease of this incidence in the long run [18].

Going further than here certainly implies to use directly information on the way individuals perceives the risk to contract measles. Information on the way vaccination is perceived exists in the French case (Cf. for example [21]), but this information is not really adapted to the kind of analysis performed here. The problem in this area is to obtain information on the evolution on the perception of vaccination over time in relation with the evolution of the perceived risk to contract the disease.

It has be noted that the estimation of vaccination diffusion carried out relies on a relatively few number of data (54 points of observation related to 23 generations) coming from 4 heterogeneous sources. This also limits the ability to obtain a good fit for a too complex representation of individual behaviour regarding vaccination. The decision not to vaccinate a child may either be interpreted as the fact that his parents considered him as too young, estimates that the risk associated to vaccination is too high or that the risk to contract measles is too low. Only a large number of data allows to discriminate between these elements. As the impact of the risk to contract measles is the hardest to capture, it is also the one for which the adjustment is the poorest.

Regarding the elimination goal fixed by French health authorities for measles, the main result of this analysis is the confirmation of the need of a strategy including two doses of vaccine. An unique dose does not allow to go beyond the threshold for annual incidence fixed for elimination of native measles (1 case for 100000 inhabitants) and the risk of major outbreaks cannot be avoided.

This analysis constitues a firts step in including specifc modelling for vaccination diffusion into model focused on the dynamics of vaccine-preventable diseases. If some work can still be done to improve the quality of the adjustment performend in the case of measles, the method employed can also be adapted to other vaccine-preventable diseases such as mumps, rubella or even hepatitis B. More generally, this kind of analysis can also be used to include every kind of iteractions between infectious disease dynamics and individual behaviour. Regarding this last point, the case of AIDS seems particularly interesting to analyze[22].

7. Appendix

7.1. Appendix A: WAIFW matrix configurations

We use two different configurations for the WAIFW matrix which are similar to the ones usually considered : symetric matrices with a number of coefficients having a different value equal to the size of the matrix[1]. The propensity of infectious individuals to transmit measles to susceptibles individuals is assumed constant within age classes considered in these matrices. For example, β_{5-9}

defines the propensity that a infectious child aged from 5 to 9 transmit measles to a susceptible also aged from 5 to 9 years.

0y.	1-2y.	3-4y.	5-9y.	10-15y.	15-20y.	20+y.
β_0	β_0	β_0	β_0	β_{10+}	β_{15+}	β_{20+}
β_0	β_{1-2}	β_{1-2}	β_{1-2}	β_{10+}	β_{15+}	β_{20+}
β_0	β_{1-2}	β_{3-4}	β_{3-4}	β_{10+}	β_{15+}	β_{20+}
β_0	β_{1-2}	β_{3-4}	β_{5-9}	β_{10+}	β_{15+}	β_{20+}
β_{10+}	β_{10+}	β_{10+}	β_{10+}	β_{10+}	β_{15+}	β_{20+}
β_{15+}	β_{15+}	β_{15+}	β_{15+}	β_{15+}	β_{15+}	β_{20+}
β_{20+}	β_{20+}	β_{20+}	β_{20+}	β_{20+}	β_{20+}	β_{20+}

WAIFW matrix n°1 using 7 age classes

0y.	1y.	2y.	3y.	4y.	5y.	6y.	7y.	8y.	9y.	10-15y.	15-20y.	20+y.
β_0	β_0	β_0	β_0	β_0	β_0	β_0	β_0	β_0	β_0	β_{10+}	β_{15+}	β_{20+}
β_0	β_1	β_1	β_1	β_1	β_1	β_1	β_1	β_1	β_1	β_{10+}	β_{15+}	β_{20+}
β_0	β_1	β_2	β_2	β_2	β_2	β_2	β_2	β_2	β_2	β_{10+}	β_{15+}	β_{20+}
β_0	β_1	β_2	β_3	β_3	β_3	β_3	β_3	β_3	β_3	β_{10+}	β_{15+}	β_{20+}
β_0	β_1	β_2	β_3	β_4	β_4	β_4	β_4	β_4	β_4	β_{10+}	β_{15+}	β_{20+}
β_0	β_1	β_2	β_3	β_4	β_5	β_5	β_5	β_5	β_5	β_{10+}	β_{15+}	β_{20+}
β_0	β_1	β_2	β_3	β_4	β_5	β_6	β_6	β_6	β_{10}	β_{10+}	β_{15+}	β_{20+}
β_0	β_1	β_2	β_3	β_4	β_5	β_6	β_7	β_8	β_{10}	β_{10+}	β_{15+}	β_{20+}
β_0	β_1	β_2	β_3	β_4	β_5	β_6	β_8	β_8	β_{10}	β_{10+}	β_{15+}	β_{20+}
β_0	β_1	β_2	β_3	β_4	β_5	β_{10}	β_{10}	β_{10}	β_{10}	β_{10+}	β_{15+}	β_{20+}
β_{10+}	β_{10+}	β_{10+}	β_{10+}	β_{10+}	β_{10+}	β_{10+}	β_{10+}	β_{10+}	β_{10+}	β_{10+}	β_{15+}	β_{20+}
β_{15+}	β_{15+}	β_{15+}	β_{15+}	β_{15+}	β_{15+}	β_{15+}	β_{15+}	β_{15+}	β_{15+}	β_{15+}	β_{15+}	β_{20+}
β_{20+}	β_{20+}	β_{20+}	β_{20+}	β_{20+}	β_{20+}	β_{20+}	β_{20+}	β_{20+}	β_{20+}	β_{20+}	β_{20+}	β_{20+}

WAIFW matrix n°2 using 13 age classes

7.2. Appendix B : Pseudo-R2

We use 2 different kinds of pseudo-R^2 in this analysis called respectively PR_I^2 and PR_{II}^2. This follows the recommendation of Amemiya[23] to use several kinds of Pseudo-R^2 to assess the quality of the fit achieved. These two kinds of pseudo-R^2 are used either for the estimation of transmission parameters and for the estimation of the parameters related to vacccination diffusion. The first kind of pseudo-R^2 is similar to the one defined by Mac Fadden but takes into account of the fact that for interval-censored data, even for a perfect fit, the log-likelihood can't reach 0 and will always be lower or equal to a maximum defined as L_{MAX}.

For the estimation of transmission parameters, PR_I^2 is then given by the following expression :

$$PR_I^2 = \frac{\max\limits_{\beta_i, s_i} L_P - L_0}{L_{MAX} - L_0}$$

$$\begin{aligned}
L_0 &= \max_{\lambda_0} \sum_{c=1}^{P} \sum_{i=1}^{N_c^P} \left[\begin{array}{c} \left(S_{t_c}^P(a_{i-1}) - S_{t_c}^P(a_i)\right) \ln\left(1 - \exp\left(-\lambda_0(a_{i+1} - a_i)\right)\right) \\ -S_{t_c}^P(a_i)\lambda_0(a_{i+1} - a_i) \end{array} \right] \\
L_{MAX} &= \sum_{c=1}^{P} \sum_{i=1}^{N_c^P} \left[\begin{array}{c} \left(S_{t_c}^P(a_{i-1}) - S_{t_c}^P(a_i)\right) \ln\left(1 - \exp\left(-\int\limits_{a_i}^{a_{i+1}} \lambda_{t_c}(a')da'\right)\right) \\ -S_{t_c}^P(a_i) \int\limits_{a_i}^{a_{i+1}} \lambda_{t_c}(a')da' \end{array} \right]
\end{aligned}$$

L_0 defines above the log-likelihood associated to the zero model that is to say the model with an hazard rate assumed constant.

The second kind of pseudo-R2 is based on the comparison of the sum of squared errors rather than on the comparison of log-likelihood. PR_{II}^2 is given by the following expression:

$$PR_{II}^2 = 1 - \frac{\sum\limits_{i=1}^{N} \left[Y_i - \widehat{Y}_i\right]^2}{\sum\limits_{i=1}^{N} \left[Y_i - \widehat{Y}_i^0\right]}$$

Y_i defines above observed data (monthly measles case in a given age group or evolution of the vaccination coverage in a given cohort and time interval), $\widehat{Y}_i$ the estimates associated to the model considered and $\widehat{Y}_i^0$ the estimates associated to the zero model (hazard rate assumed constant).

References

[1] Ferguson N et al. [1996]. Dynamical complexity in age-structured models of the transmission of the measles virus : epidemiological implications at high level of vaccine uptake. Mathematical Bioscience. 138 : 101-130.

[2] Anderson R, May R. [1991]. Infectious Diseases of humans : Dynamics and control. London : Oxford University Press.

[3] Bolker BM, Grenfell BT. [1996]. Impact of vaccination on the spatial correlation and persistence of measles dynamics. Proceedings of the National Academy of Science. 93 : 12648-12653.

[4] Keeling MJ, Grenfell BT [1998]. Effect of Variability in Infection Period on the Persistence and Spatial Spread of Infectious Diseases, Mathematical Biosciences 147 : 207-226.

[5] Geoffard PY, Philipson T. [1997]. Disease eradication : Private versus public vaccination. The American Economic Review. 87 : 222-230.

[6] Coudeville L.[2002]. "Diffusion de la vaccination contre la rougeole en France : une approche bayésienne". Document de travail du Labores, 2002-09.

[7] Levy-bruhl D, Maccario J, Richardson S, Guerin N. [1997]. Modélisation de la rougeole en France et conséquences pour l'âge de la seconde vaccination Rougeole-Oreillons-Rubéole. Bulletin Epidémiologique Hebdomadaire. N°29.

[8] Gay NJ, Pelletier L, Duclos P [1998]. Modelling the incidence of measles in Canada : an assessment of the options for vaccine policy. Vaccine 16(8) :794-801.

[9] Roberts MG, Tobias MI [2000]. Predicting and preventing measles epidemics in New Zealand: application of a mathematical model. Epidemiology and Infection 124(2):279-87.

[10] Bolker BM, Grenfell BT. [1993]. Chaos and biological complexity in measles dynamics. Proceedings of the Royal Society. 251 : 75-81.

[11] Stoneman P. [1995]. (ed). Handbook of the economics of innovation and technological change. Blackwell Handbooks in Economics.

[12] Grenfell BT, Anderson RM. [1985]. The estimation of age-related rates of infection from case notifications and serological data. Journal of Hygiene of Cambridge. 95 : 419-436.

[13] Gourieroux C.et Monfort A. [1989]. Statistique et modèles économétriques. Economica.

[14] Rabinowitz D, Tsiatis A and Aragon J [1995]. Regression with interval censored data. Biometrika 82,501-514.

[15] Boussard E, Flahault A, Vibert JF, Valleron AJ [1996]. Sentiweb: French communicable disease surveillance on the World Wide Web.BMJ 313(7069):1381-2.

[16] Institut Nationale de Veille Sanitaire [2001]. Mesure de la couverture vaccinale en France. Bilan des outils et methodes en l'an 2000. February 2001.

[17] Noah N [1996]. Commentary: How good are the epidemiological data ?. BMJ 313:1382-1383.

[18] Edwards J [2002]. Prevention by vaccination : the economics of immunisation programmes. Communication at the 4th ECHE. 07-10 July (Paris).

[19] Flahault A, Boussard E, Vibert JF, Valleron AJ [1997] Sentiweb remains efficient tool for nationwide surveillance of disease. BMJ 314:1418.

[20] De Melker H et al. The seroepidemiology of measles in Western Europe. Epidemiol Infect. 2001 Apr;126(2):249-59.

[21] Janvrin MP, Baudier F, Rotily L, Moatti JP. [1996]. Opinions et pratiques des médecins généralistes face à la vaccination rougole-oreillons-rubéole. Archives de pédiatrie. 3 : 602-607.

[22] Moatti JP, Souteyrand Y [2000]. HIV/AIDS social and behavioural research : past advances and thoughts about the future, Social Science & Medicine 50 : 1519-1532.

[23] Amemiya T [1981]. Qualitative response models : a survey. Journal of Economic Literature. 21 : 1483-1536.