A Comparative Economic Analysis of Immunization Programs for Pertussis and Measles: The Use of ARIMA Model to Study the Epidemiological Situation in England and Wales

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Abstract: *Objective*: We evaluate pertussis and measles immunization strategies and compare the consequences in terms of health effects and economic costs.

Methods: Based on epidemiological data for pertussis and measles in England and Wales from 1970 to 2012, we use ARIMA approach to model the relation between notification cases and vaccination coverage for each disease. We then perform an economic evaluation of vaccination programs at 95% and discuss the benefits for the society to achieve this level when compared with lower vaccination rates currently observed. The advantages for the society of increasing vaccination coverage up to 98% are considered respectively for pertussis and measles.

Results: The programs at a 95% vaccination rate, which is able to significantly reduce the mortality and the morbidity due to pertussis and measles, are confirmed to be the best cost saving immunization strategy. The total social net benefits are systematically maximized when the programs are compared to strategies with lower vaccination coverage. The decision to exceed the herd immunity level and reach the rate at 98% is economically justified for measles, while for pertussis the programs at 98% are less cost effective than the programs at 95%.

Conclusion: Additional efforts must be carried out to promote measles vaccination since immunization strategies at 95% and at higher rates are recommended on epidemiological and economic grounds.

Keywords: Pertussis and measles immunization, cost analysis of vaccination program, epidemiology of pertussis and measles in England and Wales, ARIMA transfer function model.

1. INTRODUCTION

Despite the availability of safe and effective vaccines and despite the implementation of vaccination strategies on a national scale since the middle of the 20th century, pertussis and measles still remain infectious diseases undefeated in developed countries. The possibility of limiting the transmission of infectious disease requires reaching a recommended high level of vaccination coverage in the children population and to maintain it without interruption at this high level. The 95% vaccination coverage is recommended by World Health Organization to guarantee herd immunity in the case of measles and a very similar threshold of at least 94% is required for pertussis.

During the 1990s only two countries in Europe, Italy and France, were classified as having low levels of *measles* vaccination at around 56% and 80% respectively, and where regular epidemics appeared. The upsurge in measles cases has been observed in many European countries since 2001. A total number of 17,928 measles cases occurred in 2001 and 30,567 cases were reported in 2011 by the European Surveillance System. The highest prevalence of the disease was outbreak-related and localised from 2008 mainly in France, Germany, Italy, Romania, Spain and the United Kingdom. In these countries the uptake of the MMR vaccination, which protects against measles, mumps and rubella, was below 90 percent and the number of cases that was indentified there accounted for 95 percent of all cases [1-2]. In Finland, Poland, Slovenia and Hungary, where vaccination rates match the recommended herd immunity level, measles cases continue to be spread being mostly related to importations of the measles virus from other countries. Very high vaccination coverage is attained as well in the United States and only a few cases of measles have been notified there. During the period 2001-2010 a median number of 60 cases, with a range of 37-140 cases was annually reported. In 2011, a total number of 222 cases were reported to the Centers for Disease Control and Prevention, 90 percent of them were associated with importations from other countries, particularly countries in Europe, where measles outbreaks were on-going [3]. In all industrialized countries, vaccination policy of 2-dose measles schedule is applied with the first dose given at 12-18 months of age, and the second dose of MMR at school entry.

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Pertussis, like measles, is a highly contagious disease. In contrast to the measles vaccine, which is able to confer life-long protection with two doses, the duration of immunity provided by pertussis vaccine wanes 5 to 10 years after the last injection. Several doses of vaccine are consequently recommended. In most developed countries a four-dose schedule is routine for children, including three doses of primary series given before the sixth month of life and one booster dose before 6 years of age. The emergence of pertussis was first recorded at the end of the 1970s and prompt control has appeared as the only feasible policy of immunization. In Japan, Sweden and in England and Wales, the outbreaks of the disease were observed as a result of a drop in vaccination coverage. The most serious epidemics appeared in England and Wales in 1978 and 1982 after the vaccination rate decreased from 77% in 1974 down to 30% in 1978 [4]. Since the end of the 1980s, a resurgence of pertussis has manifested itself in the United States, France, Finland and Canada despite stable and high vaccination coverage of three doses of primary course. In the United States, the number of pertussis cases reached the lowest level of 1,010 cases in 1976. A high number of 25,827 cases was reported in 2004 and then it decreased to 13,123 cases in 2008. Since that date the number of notified cases has steadily risen to attain 27,550 cases in 2010 [5]. During the same year, a total number of 20,208 pertussis cases were recorded in Europe. The Netherlands, Norway and Slovakia reported the highest total number of cases representing 56% of the total reported cases. Although the numbers of cases rose in all age groups the greatest increase occurred in adolescents. The most affected group was the 5 to 14-years-olds, followed by young children under five years of age [6,7].

In this article we are interested in studying the epidemiological situation of pertussis and measles in England and Wales during the period 1970-2012. This case is informative for two reasons. First, regular statistics of morbidity and vaccination uptakes since the late seventies are available for the two diseases. Their analysis using a time series model gives the opportunity to examine the relationship between the incidence recorded for each disease and the proportion of children with full vaccination schedule. Secondly, this data contains the information about important epidemics that occurred in 1978 for pertussis and in 2008 for measles. In both cases, an uncontrolled emergence of disease cases was directly associated with a decrease in vaccination coverage, which was observed following the controversy about the safety of DTP and MMR vaccines.

The aim of the study is to establish the relationship between vaccination coverage and the incidence of the disease in order to assess the impact of a potential increase in vaccination rate on the number of recorded cases of each disease. On the basis of expected morbidity and mortality, we evaluate direct and indirect costs connected with the application of immunization programs with the high vaccination coverage recommended for pertussis and measles [8,9]. For both diseases we perform the economic evaluation of the cost of a vaccination program at 95% that is regarded as the critical option to be achieved. The benefit to society of providing the strategy able to assure the herd immunity level is discussed when the 95% uptake is separately compared to 90%, and to the 94% rate for pertussis and the 85% rate for measles recorded in England and Wales. Prospective advantages from the policy involving an increase in vaccination rate up to 98% are also investigated for both diseases. The criteria of minimization of the total social cost and of maximization of the total social net benefits are applied to determine the best cost effective strategies. The total cost of each program is assessed on the basis of the costs of expected morbidity and mortality due to the disease, and the costs of vaccination and adverse reactions associated with the vaccine.

2. MATERIAL AND METHODS

2.1. Controversy about the Safety of Vaccines in England and Wales

We compare the epidemiology of pertussis and measles in England and Wales during the period 1970-2012. This complete data makes it possible to model the outbreak of each illness using a time series analysis and to quantify the influence of variations in vaccination level on disease incidence. We focus on that period as it reflects the appearance of pertussis and measles epidemics, which occurred with a gap of about thirty years. An additional and more specific feature of the examined epidemiology of the diseases is the fact that the return of the pertussis and measles epidemics was due mainly to the loss of public confidence in DTP and MMR vaccines as a result of the publication of unfounded reports [10,11]. The safety of pertussis vaccine was questioned during the 1970s and public controversy about measles vaccine took place at the end of 1990s (Table **1**). The consequences in terms of decrease in vaccination rate were similar

Table 1: Comparative Epidemiology of Pertussis and Measles: Vaccination Policies Applied in the UK

	Pertussis	Measles
Disease	Highly infectious bacterial disease. Mostly reported in children less than 5 years of age with the highest mortality and morbidity occurring in infants. The number of reported cases increases in adolescents and adults	Highly contagious viral disease. Considered a childhood diseases but can be contracted at any age. Complications are common among children under 5 years of age and in children and adults with a poor diet and with weakened immune system
Vaccine in use	DTP or DTaP (Diphtheria, Tetanus and Pertussis whole-cell or acellular)	MMR (Measles, Mumps and Rubella)
Time of protection	Less than 12 years after primary course	Long lasting (after 2 doses)
Herd immunity level required	94%	93% - 95%
Vaccination strategies	DTP vaccine introduced in 1957, DTaP for booster dose in children in 2001 and DTaP vaccine for all doses in 2004	Vaccine against measles introduced in 1968 and MMR vaccine in 1988
Public controversy in the UK	Report published in 1974 about the links between whole-cell pertussis vaccine and the risk of encephalopathy. The relation was not confirmed by findings of subsequent studies	Report published in 1998 claimed a link between the MMR vaccine and the risk of autism. The findings of subsequent studies have shown no links
Vaccine schedule in children	3 first doses of DTaP of primary course (2, 3 and 4 months of age). One booster dose of DTaP (between 3 years 4 months and 5 years of age)	First dose of MMR given around the13th month of age. Second dose given between 3 years 4 months and 5 years of age

and although the diseases had been considered as being under control, they caused the appearance of significant epidemics.

The publication of the Kulenkampff report in 1974 drew attention to the appearance of serious neurological complications ensuing from immunization with whole-cell pertussis vaccine. This study, considered at that time as an important reference in medical circles, was taken up by the mass media as evidence for the anti-immunization public campaigns. It created an increasing distrust by parents towards the vaccine, this distrust being fuelled by the attitude of certain doctors [12]. As a result the proportion of children who had received a complete primary course decreased from 77% in 1974 down to 30% in 1978 and was followed by an important resurgence of pertussis, which peaked at 65,956 cases in 1978 and at 65,810 cases in 1982, compared to 16,225 cases notified in 1974 (Figure **1**). In the following years, the vaccine uptake gradually increased to the level of 94% in 1995 and has remained at that rate until now. During that period no serious epidemic has broken out and the number of cases diminished from 3964 in 1994 down to 606 cases in 2012.

In 1998 a research report by Wakefield and colleagues was published in which the hypothesis of a

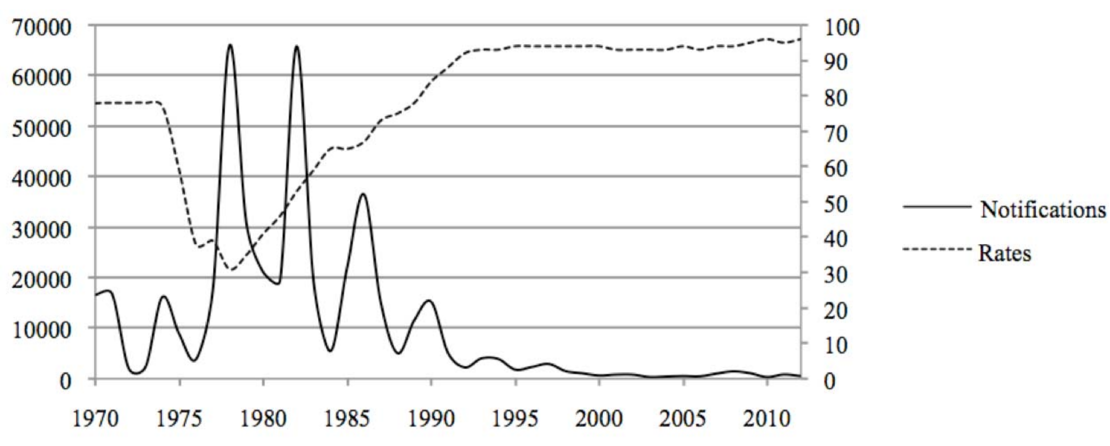

Figure 1: Number of notification cases of pertussis and DTP vaccine uptake rates (in %) in England and Wales for the period 1970-2012.

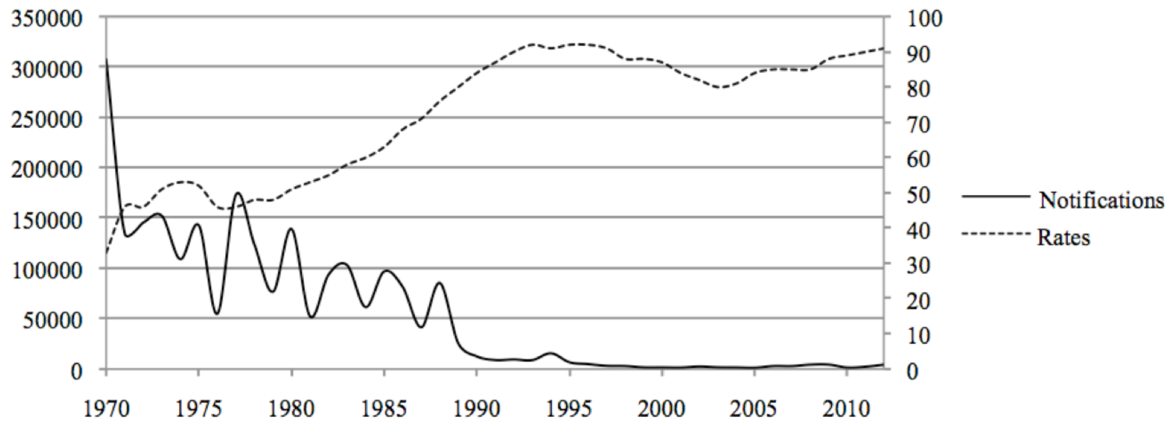

Figure 2: Number of notification cases of measles and MMR vaccine uptake rates (in %) in England and Wales for the period 1970-2012.

link between the MMR vaccine and bowel disease and a new variant of autistic spectrum disorder (ASD) was suggested. The study was criticized for its methods though it created a widespread public concern about the safety of the MMR vaccine [13]. Despite assurances of Health authorities, the rate of vaccination decreased in the UK and outbreaks of measles were recorded as a result of the reluctance of some parents to have their children immunized. The uptake of MMR vaccination decreased from 91% in 1998 to the level of 80% in 2003 (Figure **2**). Since this date, it has risen progressively to attain 85% in 2008. In 2008 the total number of measles cases reached the level of 5,088 while in 1998 and in 2003 there were respectively 3,728 and 2,488 cases reported. During the period 2010-2012 the vaccination rate rose from 89% up to 91%. However the number of cases increased as well, to reach the number of 5147 cases in 2012.

2.2. Transfer Function Intervention Model

We apply the ARIMA transfer function intervention model to annual time series of epidemiological data of pertussis and measles. For each disease, the relationship between changes in the number of notified cases and in the level of vaccination coverage is examined separately.

The general form of the model is defined as

$$Y_t = v(B)X_{t-b} + I_t + N_t \qquad (1)$$

where Y_t is the dependant variable and X_t is the explanatory variable. The time series X_t that is supposed to systematically influence Y_t and explain its behaviour is included in the model as the leading indicator as we consider that the transfer function model would not incorporate feedback. The impact on Y_t of a unit change in X_t is quantified by a transfer function $v(B)$, and b measures a delay before X_t starts to have an effect on the behaviour of the dependent variable Y_t if a change in X_t does not affect Y_t instantaneously. I_t is an intervention zero-one variable, with the value one at the time of a discrete intervention or event, and N_t is the error term generated by univariate ARIMA process, assumed to be statistically independent of X_t and I_t. When the equation (1) is used in our analysis of epidemiological data, the variable Y_t relates the level of current and past cases of the disease and X_t corresponds to the percentage of children completing the primary course at two years of age, which determines the level of vaccination. The parameter b measures the time lag necessary for the changes in vaccination rate to be statistically apparent on the level of annual notifications of the disease.

The variable I_t is an indictor variable that points out an uncontrolled drop in the level of vaccination. It results in the appearance of the most serious epidemics accounting for disturbances in the falling trend in morbidity during the period of immunization. This intervention variable of temporary duration acts exclusively at the time of occurrence of the event (2), and is supposed to capture the extra effect of unexpected changes recorded in the series of vaccination rates that is not directly sized up in the structure of the transfer function.

$$I_t = \begin{cases} 1: \textit{at the time of occurence of the event} \\ 0: \textit{otherwise} \end{cases} \qquad (2)$$

The construction of the transfer function intervention model involves two steps. First, the transfer function model is applied separately to annual epidemiological data for pertussis and for measles, both recorded during the period 1970-2012. Secondly, an intervention dummy variable I_t is introduced to model known events that have affected Y_t in order to examine the possibility of a better model fit to the data. Its place in the structure of our models is justified by the inspection of the past behaviour of the series Y_t that suggested a significant decrease in the level of vaccination might affect the total number of cases. This observation should corroborate with the presence of large residuals detected during the diagnostic checking of the transfer function model that appear precisely during the period of the drop in vaccination coverage.

In order to identify the transfer function *v(B)*, the cross correlation function between the dependent and independent series is estimated. Prior to its estimation an operation of prewhitening is to be performed to reduce the independent series to a random series. It consists in filtering the series X_t through a univariate ARIMA model of itself, and in the application of the filtering operation on the series Y_t to preserve the relationship between the two series. The dependent variable is filtered through the uivariate model of the independent variable. This approach reflects the fact that in our analysis the transfer function model is a leading indicator model, which does not allows for the feedback, and implies that Y_t series can be prewhitened with the ARIMA model of the X_t process.

2.3. The Results of the Estimation for Pertussis

A second-order autoregressive model AR(2) was fitted for X_t series and used as a filter during the procedure of prewhitening applied to X_t and Y_t series. The cross correlation function estimated between filtered series was made up of a single and negative significant cross correlation occurring at a lag of two, which allowed us to suppose that the percentage of children with a full primary course of pertussis vaccine, X_t can be seen as a predictor of the level of notification cases, Y_t two periods ahead. To estimate the models we used the RATS software. The results of estimation (Table **2**) has confirmed that a unitary shift in independent variable X_t causes a statistically significant movement in the opposite direction in the dependent series Y_t that is produced with a two-year delay.

The structure of the noise N_t is described by a first-order seasonal autoregressive structure SAR(1) with a span equal to four that was identified at the beginning of the procedure for the series of morbidity in accordance with the cyclic character of the disease. The numbers within the brackets are estimates of the t-Statistics and S.E. of regression is defined as the square root of the unbiased estimate of variance. The adequacy of each model to represent the evolution of the epidemiological data was established by residual analysis. It consists in inspection of the errors of transfer function models to investigate whether they display the characteristics of a white noise and depict correctly the ARIMA process governing the series.

The transfer function model was at first applied to series Y_t and X_t for the period 1970-2012. The diagnostic check of the model (3) confirmed that the stationary conditions had been met, but the residual analysis pointed out the presence of large residuals taking place in 1976 and 1982 that coincides precisely with the appearance of epidemics of pertussis (Figure **1**). In order to improve the model fit to the data, the intervention variable I_t defined in (2) was incorporated into the transfer function structure. It is defined in terms of the size of the observed drop in proportion of children who had been vaccinated and takes the value one in 1978 to point out the lowest level of vaccination, which had reached 30%. Diagnostic checks applied to the transfer function intervention model (4) confirmed

Table 2: ARIMA Transfer Function Intervention Model Applied to Annual Time Series of Epidemiological Data of Pertussis in England and Wales for the Period 1970-2012

Estimated ARIMA models for pertussis		S.E. of regression	Period
$Y_t = 57{,}819 - 598B^2 X_t + N_t$ (7.49) (-7.74)	(3)	7,210	1970-2012
$Y_t = 42{,}244 - 428B^2 X_t + 30{,}241B^0 I_{1978} + 26{,}822B^4 I_{1982} + N_t$ (7.89) (-7.22) (5.78) (5.29)	(4)	4,963	1970-2012
$Y_t = 42{,}178 - 428B^2 X_t + 30{,}168B^0 I_{1978} + 26{,}733B^4 I_{1982} + N_t$ (7.07) (-6.38) (5.18) (4.74)	(5)	5,524	1970-2004
$Y_t = 42{,}153 - 428B^2 X_t + 30{,}173B^0 I_{1978} + 26{,}739B^4 I_{1982} + N_t$ (7.49) (-7.05) (5.68) (5.19)	(6)	5,049	1970-2010

its better suitability to the data. It is observed that the estimate of the residual standard deviation of the process is significantly reduced from 7,210 down to the level of 4,963. In addition, the inspection of actual and fitted series of Y_t indicates that the parameters of the model are able to size up the extent of the two most serious epidemics and to correctly predict the number of pertussis cases in the last years of observation. The model underestimates the number of cases in 1978 and in 1982 by 6% and 8% respectively, and it assesses the level of cases in 2011 and 2012 with the error of 5% and 3% respectively.

The results of estimation (4) confirm that all things being equal, the modification of the level of vaccination rate has to be considered as a significant factor able to influence the evolution of the series of morbidity. The transfer function implies that a 1% increase in vaccination coverage causes, with a delay of a two-year period, a decline in incidence of pertussis of about 428 cases. The intervention variables makes it possible to note that the significant drop in 1978 in the vaccination rate to 30% was a factor responsible for an extra increase of 30,241 cases of pertussis in the same year. The repercussions of this event are still noticeable four years later and are included in the structure of the model as an additional and significant component. The error term N_t of the model is represented by the SAR(1) process with a span of four and with a significant positive value of 0.62 for the parameter Φ_1.

The robustness of the model (4) was tested for Y_t and X_t over intermediate time intervals in order to check the stability of the coefficient of the transfer function $v(B)$, which represents the impact on Y_t of a unit change in X_t. It was established that the models built for the period 1970-2004 (5) and beyond that date (6), are characterized by an invariable coefficient equal to 428 pertussis cases that is associated with a shift of 1% in the vaccination coverage. This finding supports the decision to consider the model written in (4) as the one that adequately fits the data, and consequently can be used to construct forecasts.

2.4. The Results of the Estimation for Measles

The observation of the data related to notified cases of measles (Y_t), and to the level of measles vaccination coverage (X_t) against time suggests that there is a trend in both series. The series Y_t seems to be decreasing over time while the series X_t is steadily increasing during the reporting period of 1970-2012, with the exception of the early 2000s when the coverage reached the rate of 80% in 2003 (Figure **2**). To confirm the presence of systematic changes in the level of both series, which implies that epidemiological data are nonstationary, we performed an Augmented Dickey-Fuller (ADF) test. The results do not allow rejecting the null hypothesis that there is a unit root at any level of confidence. In fact, the ADF test statistic values displayed for Y_t and X_t series are above the tabulated relevant critical value, which confirms that the unit root is present and both series are nonstationary.

In order to remove the trend the method of differencing was employed, and the use of the first difference operator ∇ to Y_t and to X_t made them stationary. The two series being individually integrated of the same order, it allowed us to apply the Engle-Granger method to test the existence of a cointegrated combination of original series Y_t and X_t. The ordinary least square (OLS) regression was first performed to model the relationship between ∇Y_t and ∇X_t, and then the stationary ADF test was run on the estimated residual series. We obtained the number of -10.59 that is less negative that the tabulated critical value at the 99% level, which validates the hypothesis that the residual are stationary and a linear combination of both series is stationary as well.

A second order autoregressive model AR(2) was fitted for the series ∇X_t. This structure was employed as a filter during the procedure of prewhitening applied separately to ∇X_t and ∇Y_t series. The cross correlation function calculated for filtered series allowed identifying the first order moving average operator given that two consecutive single correlations appear after a delay of three time intervals. The second negative correlation occurring at lag 4 is statistically significant while le first one at the lag 3 is close to the boundary lines when tested against twice their standard errors. To determine which correlation could be interpreted as being the first significant one, two transfer function models with different delays were fitted to the data. The results of estimation (Table **3**) suggest that the significant cross correlation at the lag 4 is to be considered as the right delay between changes in vaccination coverage affecting the number of measles notifications. In fact, none of the two coefficients in the transfer function estimated in (7) is statistically significant, while the estimator in (8) appears to have statistically significant influence. It connects the change in ∇X_t having an impact on ∇Y_t in the opposite direction with the delay of four time periods.

Table 3: ARIMA Transfer Function Intervention Model Applied to Annual Time Series of Epidemiological Data of Measles in England and Wales for the Period 1970-2012

Estimated ARIMA models for measles		S.E. of regression	Period
$\nabla Y_t = -\ 1{,}819B^3\,\nabla X_t - 100B^4\,\nabla X_t + N_t$ (-1.97) (-0.10)	(7)	11,573	1970-2012
$\nabla Y_t = -\ 1{,}747B^4\,\nabla X_t + N_t$ (-4.12)	(8)	12,138	1970-2012
$\nabla Y_t = -\ 1{,}756B^4\,\nabla X_t + N_t$ (-3.86)	(9)	12,997	1970-2006
$\nabla Y_t = -\ 1{,}747B^4\,\nabla X_t + 2{,}295B^5\,I_{2003} + N_t$ (-4.06) (0.23)	(10)	12,334	1970-2012

The formalization written in (8) is considered to be the final model. It results that all things being equal, the level of vaccination coverage has a significant influence on the number of measles cases. The transfer function indicates that an increase of 1% in the vaccination coverage is needed to reduce the number of recorded cases of 1747, and a delay of four years is necessary before a change in vaccination rate ∇X_t can influence the incidence of measles ∇Y_t. A first-order consecutive and seasonal autoregressive model AR(1)SAR(1) with span=4 was identified as adequate to describe the structure of the noise N_t in the transfer function models. The level of the autoregressive parameters was established at -0.56 and -0.52 respectively for ϕ_1 and Φ_1, both parameters being statistically significant. The stability of the average mobile operator in the transfer function was studied for shorter periods of data in order to question the robustness of the model (8). For the period 1970-2006 we have obtained the value of 1756 cases (9), and for all periods subsequent to 2006, the value of the operator approaches progressively the one calculated in (8), while improving the quality of fit of the model to the data we examined.

To complete the formalization we have introduced an intervention variable (2) defined in terms of the size of the observed drop in the proportion of children who had been vaccinated. We consider that the most significant drop in the level of vaccination took place in 2003 when the vaccine uptake attained the lowest level of 80%. It was found that the pulse intervention variable I_{2003} when testing with different lags had no significance in all of the models with intervention. In particular, the impact of this variable acting with the lag of 5 years was not statistically associated with the measles outbreak, which occurred in 2008 (10). We think the fact that the impact of unexpected drop in vaccination rate on measles notifications did not prove to be statistically significant, should not lessen the real importance of this event. The drop, which is not deep enough to be captured by the structure of the model, continues to counteract the effort to control the disease. In fact, as the vaccine uptake has stagnated since 2003 at a low level that is definitely under the critical threshold of the herd immunity level of at least 94%, it makes it difficult to effectively reduce the incidence of the disease.

2.4. Predicted Number of Disease Cases

The parameters of the model (4) and (8) are used to predict respectively the number of pertussis and measles cases in the total population related to a particular immunization rate. We construct one-step ahead of forecasts with the assumption that future values of vaccination level are considered as being known. To assess the expected cumulative incidence of disease in the cohort of 1 million individuals under 15 years of age followed for 14 years, we took into account the results of statutory notifications recorded in 2012 by age group. We presumed that the children population would account for 74% of the total number of pertussis cases predicted by the model (4), and for 87% of the total number of measles cases predicted by the model (8).

Consequently, based on the model (4) it was established that the stability of vaccination coverage at 94% would result in 794 pertussis cases in the children population. The increase of vaccination coverage from 94% to the level of 95% would cause, with a delay of two years, a potential reduction of 463 cases and the new morbidity threshold would reach 331 cases. The drop in vaccination rate from 94% to 90% would be on the contrary, responsible of expanding the predicted number of pertussis cases up to the high level of 2,652 cases. The application of the model (8) allows the prediction of measles cases in the children population.

It was found that the stability of the vaccination rate at 85% would produce the appearance of 3,188 cases of measles. The increase in the coverage from 85% to 90% would reduce with a delay of three years, the number of measles cases in the children population up to 2,079. The predicted number of cases could drop to 975 if measles immunization coverage rises to 95%.

2.5. Complications from the Diseases and Vaccines Side Effects

Expected complications from each disease and adverse reactions linked to the application of the vaccine are examined separately in the population of children. The incidence of complications from *pertussis* was calculated based on the data reported in the United States for two periods, 1989-1991 and 1992-1994 [14]. Hospitalisation, deaths, pneumonia, and encephalopathy without residual defects were considered as the most serious pertussis-associated outcomes [15-17]. The number of hospitalisation among affected children was estimated separately for each age group. The hospitalisation rate was 44% in the 6-month to 11-month age group, and respectively 24% and 10% in the groups aged 1-4 and 5-14 years. Among hospitalised children, 12.5% would need a 4-day stay in a paediatrics intensive care unit and an additional 12-day hospital stay. Treatment cost of pneumonia, seizures and encephalopathy was calculated with a mean number of 10, 6 and 15 hospital days respectively, followed-up by one physician visit. The mortality rates due to pertussis were presumed to be 0.45% for children younger than 6 months, 0.1% for those between 6 and 11 months old and 0.15% for older children [18].

Acellular *pertussis* vaccine was used for 3 doses of the primary course and was administrated as DTaP vaccine. Adverse events due to the vaccine were estimated on the basis of the Gustafson study [19]. We focused on convulsion, hypotonic-hyporesponsive episodes, unusual persistent crying for 3 or more hours, fever higher than 40°C and local reaction such as erythema. It was assumed that 25% of infants with fever and with symptoms of unusual and persistent crying, and that 10% of those examined with persisting crying would be hospitalised for one day. A booster dose of acellular vaccine is mainly associated in this analysis with local reactions, which are to occur in 52.8% of vaccinated children. It is considered that 12.5% of them would require one physician visit [20].

In the case of *measles* we examine hospitalisation, pneumonia and other respiratory track complications, encephalitis, convulsion and death as representing the most significant measles associated complications. The number of measles-related hospitalisations and the mortality rate were estimated on the basis of data reported in the USA for the period 1970-1978 [21]. We presumed that 15% of measles cases would require hospitalisation and that 0.41 per 1000 children infected would die after measles. Children less than one year of age, those aged from 1 to 4 years, from 5 to 9 years and from 10 to 14 years would account for 10.5%, 36.5, 34.2 and 18.8% of hospitalized cases of measles, respectively. The number of complications in hospitalized cases is related to results recorded during a measles outbreak in Italy in 2002-2003 [22,23]. It was assumed that the length of an average stay for all hospitalised cases would be 4 days and followed-up by one physician visit. The cost of pneumonia and other respiratory track complications, encephalitis and convulsion was calculated respectively with a mean number of 10, 9 and 6 hospital days. Among all children with complicated cases, 6.5% would seek specialist care and would spend an additional 6 days in an intensive care unit.

The frequency of adverse events associated with the *measles* vaccine was estimated according to the study of Carabin *et al.* [24]. The risk was assumed to be the same for each of two doses of MMR vaccine. We considered encephalitis, anaphylaxis, thrombocytopenia, convulsion and fever as the most significant vaccine associated adverse events. The treatment of encephalitis and convulsion was the same as for measles cases and required 9 and 6 days of hospitalization. The cases of thrombocytopenia and anaphylaxis would be hospitalised for 4 and 2 days respectively, and a physician would see 10% of fever cases.

2.6. Estimators Used to Evaluate the Cost of Vaccination Programs

To evaluate the cost of pertussis and measles immunization programs, we applied the same estimators for the cost of disease complications and that of vaccine induced reactions. A daily hospital rate is evaluated at the level of €750 and a day in a paediatrics intensive care at €1,550 [25]. The cost of pertussis vaccine is €8.20 per dose (the difference between the prices of DTPolio and DTaPPolio vaccines), and the cost of measles vaccine is assessed at €5.10 which represents one third of the cost of MMR vaccine available in France [26]. The cost of vaccine injection is €7.66 which reflects to one third of the price of a physician visit. The evaluation of indirect cost was based on the assumption that productivity losses were identified when the child was hospitalised. Each hospitalised case requires parent absenteeism and was equal to the hospitalisation period. A case of non-hospitalisation was evaluated at the level of 2 days of absenteeism. The average cost per lost workday was estimated at €68, which corresponds to the minimum wage rate established in France for a 35-hour working week. This estimator is similar to the one that can be calculated on the basis of national minimum wage rate of £6.11 an hour, applied in the UK [27]. Mortality associated indirect costs are assessed based on a value of statistical life (VSL) estimates. We consider the figure of €1.62 million (£1.25 million in 2012 prices) used in the UK by the Department of Transport to value the prevention of a statistical fatality in its roads project appraisal [28].

3. RESULTS

3.1. Cost of Vaccination Programs Against Pertussis at Different Vaccination Rates

The cost of vaccination against *pertussis* at different vaccination rates is assessed successively for the programs with three doses of primary series (P1) and with a booster dose for children (B1). In each case the cost of a medical act is added to the cost of vaccination (P2, B2). We focus on the outcomes of the most expensive strategy B2. Three observations can be drawn from the finding (Table **4**). First, disease complications decrease significantly in the examined population when vaccination coverage rises. The

Table 4: Estimated Complications of *pertussis* in Children Population, Estimated Costs of Vaccination Programs at Different Rates, and the Total Social Net Benefits of Immunization Strategies (in Thousands of Euros)

Vaccination coverage	90%	94%	95%	98%
Number of cases of *pertussis*	2,652	794	331	39
Number of main complications				
Hospitalisations	1,096	328	137	16
Pneumonia	268	80	33	4
Encephalopathy	3	1	0	0
Seizures	42	13	5	1
Death	4	2	1	0
Cost of vaccination program (P1) 3 doses of primary course	35,439	28,369	26,604	26,122
Cost of vaccination program (P2)	54,339	48,109	46,554	46,702
Disease complications (%)	21.4	7.2	3.1	0.4
Vaccine side-effects (%)	1.6	1.9	2.0	2.1
Cost of vaccine and medical act (%)	77.0	90.9	94.9	97.6
Cost of vaccination program (B1) 3 doses of primary course + 1 booster	43,383	36,668	34,989	34,773
Cost of vaccination program (B2)	68,583	62,998	61,589	62,213
Disease complications (%)	16.9	5.5	2.3	0.3
Vaccine side-effects (%)	1.7	2.0	2.1	2.2
Cost of vaccine and medical act (%)	81.4	92.5	95.6	97.7
Social net benefit				
(P1) vs. 94%			1,765	2,246
(P2) vs. 94%			1,555	1,406
(B1) vs. 94%			1,676	1,893
(B2) vs. 94%			1,396	773
Social net benefit				
(P1) vs. 90%		7,070	8,835	9,316
(P2) vs. 90%		6,230	7,785	7,636
(B1) vs. 90%		6,717	8,394	8,617
(B2) vs. 90%		5,597	6,994	6,370

number of hospitalisations and encephalopathy is reduced respectively from 1,096 to 137 cases and from 3 to no cases when the programs at 90% and at 95% are compared. Four deaths would occur if the vaccination program is maintained at 90% and the increase in the rate up to 95% leads to the loss of one life only. This consequently diminishes the weight of pertussis complications in total cost of B2 from 16.9% to 2.3%, as the mortality accounts for 68% of the cost of disease complications.

Secondly, we notice the fall in the total cost of immunization strategy as a result of the increase in vaccination coverage. The reduction from 68,583 to 61,589 thousands is obtained for the strategy B2 when the coverage rises from 90% to 95%. The major part of these costs is directly linked to the cost of the vaccine and of medical application, which totals 95.6% of estimated figures when the coverage attains 95%. The application of the criterion of the minimization of the total social cost points out the strategy with the highest vaccination rate at 98% as the most effective. This rule is verified in all cases except the programs P2 and B2 at 98%. The growth is more significant for the B2, as the total cost is extended from €61.589 to €62.213 thousands. This result can be explained by the fact that the reduction in the cost of infection is not strong enough to be able to compensate the cost of additional doses of pertussis vaccine and of the medical act necessary to reach the rate of 98%. In fact, the expenses due to pertussis diminish from €1,446 to €170 thousands mainly because no loss of life is recorded, while simultaneously the cost of vaccination increases significantly.

Thirdly, the advantages of programs with high vaccination coverage versus alternative vaccination rates are examined in the form of a second optimization criterion, the total social net benefit. It corresponds to the value of the pertussis cases prevented by the application of the highest vaccination rate, less the value of the differential cost of immunization. It appears that the total social net benefit increases when a program with the rate at 95% is compared to programs with lower vaccination coverage. Its level is estimated at €1,369 and €6,994 thousands for the B2 when the strategy at 95% is compared respectively versus to 94% and 90%. The results revealed however that the program with the highest rate at 98% does not maximize the total social net benefits for both P2 and B2 strategies. For the B2 strategy, the benefit drops from €1,396 to €773 thousands and from €6,994 to €6,370 thousands when the programs at the rate of 98% and 95% are compared to programs at the rates of 94% and 90% respectively.

3.2. Cost of Vaccination Programs Against Measles at Different Vaccination Rates

The estimated cost of vaccination against *measles* takes into account the program with two doses of the vaccine (M1), with additional cost of medical act (M2), which represent the optimal immunization strategy. Firstly, it can be observed that the increase in vaccination rate results in significant reduction of the number of hospitalised children and those with encephalitis. The figures of 478 and 146 hospitalisations, and 13 and 4 cases of encephalitis were found respectively when vaccination coverage rises from 85% up to 95% (Table **5**). The rate at 95% implies that there is no loss of children life, while two deaths are supposed to occur when the coverage is at 85%. Disease complications account for 35% and for 13% respectively when vaccination rates at 85% and 95% are compared and the weight of measles side effects in the total cost falls to 19% and 6% (M2).

Secondly, it can be noticed that the amount of the total cost of an immunization program diminishes as the higher number of children to be vaccinated is recorded. The total cost drops from €26,096 to €25,069 thousands and to €24,764 thousands when the rate increases from 85% to consequently reach the levels of 95% and 98% (M2). The cost of the vaccine against measles and the cost of injection accounts for 94.9% when the rate at 98% is reached, and the strategy M2 appears as the most beneficial for the society. These results confirm that the highest vaccination coverage applied to measles vaccination programs appears to be the most effective according to the criterion of minimization of the total social cost. In addition, the advantage of the program with the highest vaccination rate compared to alternative immunization strategies is validated by the second optimization criterion. In fact, it appears that the total social net benefit is maximized when the program at 98% is compared to programs with the rate established at the lower levels. The total social net benefit is estimated at €724 and €1,933 thousands when the program at 98% versus 95% and 90% is examined respectively (M1). The program maintained at the highest rate of 98% maximizes the total social net benefit when applied to the strategy M2 as well, as the level of evaluated benefits increases from €304 to €813 thousands when the program at 98% vs. 95% and 98% vs. 90% are respectively examined.

Table 5: Estimated Complications of *measles* in Children Population, Estimated Costs of Vaccination Programs at Different Rates, and the Total Social Net Benefits of Immunization Strategies (in Thousands of Euros)

Vaccination coverage	85%	90%	95%	98%
Number of cases of *measles*	3,188	2,079	975	313
Number of main complications				
Hospitalisations	478	312	146	47
Pneumonia	252	164	77	25
Convulsions	21	14	8	2
Encephalitis	13	8	4	1
Death	2	1	0	0
Cost of vaccination program (M1)	14,196	12,977	11,769	11,044
Disease complications (%)	35.5	25.4	13.1	4.5
Vaccine side-effects (%)	4.6	5.3	6.2	6.8
Cost of vaccine (%)	59.9	69.3	80.7	88.7
Cost of vaccination program (M2)	26,096	25,577	25,069	24,764
Disease complications (%)	19.3	12.9	6.2	2.1
Vaccine side-effects (%)	2.5	2.7	2.9	3.0
Cost of vaccine and medical act (%)	78.2	84.4	90.9	94.9
Social net benefit				
(M1) vs. 95%	-2,426			724
(M2) vs. 95%	-1,026			304
Social net benefit				
(M1) vs. 90%	-1,215		1,208	1,933
(M2) vs. 90%	-513		508	813

3.3. Sensitivity Analysis

The effectiveness of vaccination programs was re-examined in relation to various levels of estimators for the price of vaccine and for the value of a child's life. We focused on the comparative analysis of immunization programs against pertussis at 95% and 98% to determine the threshold values that induce modifications in total costs and allow the validation of the advantages of immunization that requires vaccinating the highest proportion of children. It was established that only a very significant drop in price of the pertussis vaccine from €8.20 to €3.75 is able to diminish the total cost of the most expensive strategy B2 making the program at 98% less costly than the one at 95% while the value of a child's life is unchanged. The figures of €43,398 and €43,566 were obtained respectively for the programs at 98% and 95%. The cost associated with medical act is able as well to moderate the effectiveness of a vaccination program. It was found that the program B2 at 98% becomes cost saving comparing to the rate at 95% when the cost of medical act is evaluated at the level of €2.85 instead of €7.66, while the value of other variables remains unchanged. When the medical act is not considered in cost analysis, according to the supposition that vaccine injections are free of charge, the program with the highest vaccination coverage at 98% becomes systematically less costly.

To underline the influence of the value of a child's life on the cost of a vaccination program, the VSL estimator of €4.34 million ($6.2 million in 2008 prices) advised by the U.S. Environmental Protection Analysis was considered [29]. Its application when the price of pertussis vaccine is stable at €8.20 results in an increase in total cost of the B2 at 95% up to €63,228. This makes the program at 95% more costly when compared to the unchanged value of the program at 98%, in which no deaths of children are recorded. It is to be observed that the value of a child's life evaluated at the threshold level of €3 million can already extend the cost of B2 at 95% up to €62,219 and consequently reverses its competitiveness versus the program at 98%, when the criterion of the minimization of total social cost is applied.

4. DISCUSSION

The results of our study underline the advantages of immunization programs against pertussis and measles with a high vaccination rate that is established at 95%

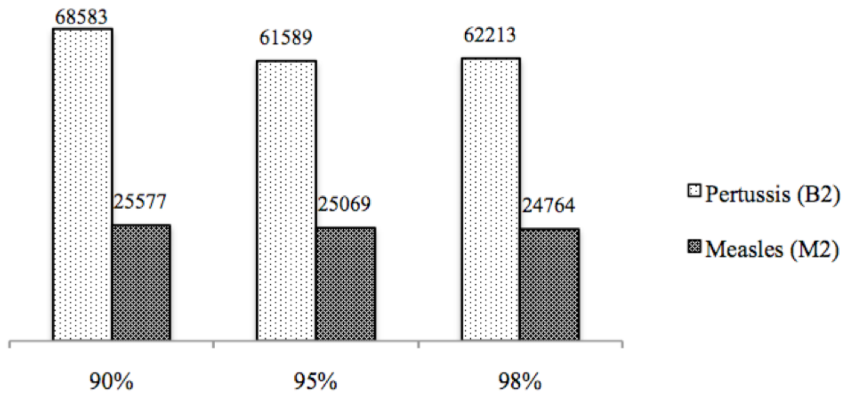

Figure 3: Estimated comparative cost of the most expensive vaccination programs at different rates: the application to four-dose B2 strategy for pertussis, and two-dose M2 strategy for measles (in thousands of euros).

in children population. This particular level correlates with the upper herd immunity threshold advocated to control efficiently measles infection efficiently while the control of pertussis requires the threshold of 94%. It can be questioned whether the increase in pertussis vaccination coverage is to be encouraged by health authorities to exceed this recommended level. The results of our cost analysis seem to validate the usefulness of this potential endeavour. The evaluation of vaccination programs demonstrates that the incremental increase of 1% in vaccination coverage implies the reduction from 794 to 331 cases of pertussis. The number of hospitalised children diminishes from 328 to 137 and one child's life is saved. The total cost of B2 decreases from €62,998 to €61,589 thousands and the total social net benefit is recorded (€1,396 thousands) when the program at 95% versus 94% is examined.

The advantages from achieving the highest vaccination coverage at 98% to control the occurrence of measles and of pertussis can be examined as well. The outcomes of the evaluation clearly established that measles vaccination programs are the most cost effective when the highest vaccination rate is attained. The number of measles cases is reduced from 975 to 313 and the number of hospitalisations drops from 146 to 47. The findings are ambiguous when pertussis vaccination program at the rate of 98% vs. 95% is considered (Figure **2**). On the one hand, the analysis confirms that the highest vaccination coverage supplies the best protection against pertussis. The number of pertussis cases and of hospitalisations is reduced respectively from 331 to 39 and from 137 to 39, the reduction to zero of fatality cases being the most important achievement. On the other hand, the introduction of the medical act to the cost analysis makes the program at 98% economically less effective than the one at 95%. This conclusion is reversed however by the application of lower estimators for the price of pertussis vaccine and the value of a child's life. It seems that for a better understanding of the advantages that result from the increase in vaccination coverage, the reduced number of disease cases and mainly the number of fatalities avoided in the children population is to be highlighted and systematically associated with the interpretation of outcomes of the economic analysis of immunization programs.

It is to be noticed that there is an additional factor to be considered in the cost analysis. The decision to exceed the herd immunity level and reach a very high rate at 98% is guided indeed by the government's capability to institute an appropriate vaccination policy that is necessary to attain this objective. Health authorities within the framework of the compulsory vaccination laws can impose vaccination as one of the mandatory requirements for a child to enrol in school, or the recommended vaccination can be strongly advised by health professionals and promoted by various incentives, as well as relayed by well-informed mass media. In both cases, the possibility of implementing sustainable high vaccination coverage implies an uninterrupted allocation of resources to support effective communication with parents and physicians, and to control the application of immunization laws [30]. This expense would increase the total cost of vaccination with the risk of making the programs at 98% less cost effective than the programs at 95%.

We would specify that a static estimation of disease burden was conducted in this study. Two opposite outcomes of this approach on the total cost can be investigated. The main drawback to using static estimation is that herd-immunity effect is not directly accounted for in the analysis and therefore could not potentially affect the number of disease cases at high coverage. This would produce an overestimation of direct and indirect costs related to the number of disease complications as dynamic models predict a higher number of disease cases prevented by vaccination when compared with a static approach [31]. However, this result is to be counterbalanced by an underestimation of vaccination cost obtained in the analysis when the response time identified by the transfer function models for pertussis and measles is not considered. In fact, the assumption of a delayed period of two and three years is to generate more expensive transformations in total cost compared to those where there is an instantaneous reaction of morbidity and mortality to the changes in vaccination rate [32]. This ensues from the definition that the total cost of vaccination program combines the cost of vaccine provision with cost of treating cases. When a response time between two variables exists, higher costs necessary to increase vaccination coverage and supply an extra number of vaccine doses cannot be simultaneously counteracted by the drop in disease cases and disease related complications.

5. CONCLUSION

The comparative study of immunization programs for pertussis and for measles gives the possibility of questioning whether epidemiological experiences, which include serious epidemics, are to be considered as a significant factor able to influence the willingness of the population to attain the herd immunity level and achieve protection against infectious disease. England and Wales introduced a successful control of pertussis in children after the outbreak of the disease at the end of the seventies and the vaccination rate at 94% for the four-doses vaccine has been exceeded for the past several years. A measles epidemic occurred recently while the vaccination coverage was stabilised at a low level of 85%. The epidemics continued to appear in the early 2010s even though the coverage reached 90%, which is still below the critical herd immunity level. Lessons should be learnt from the epidemiology of pertussis and additional efforts are to be promptly carried out to increase the vaccination uptake in children with the two-doses vaccine and efficiently reduce the occurrence of measles. A communication program would be important to make parents willing to have their children vaccinated.

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