Diphtheria, pertussis, and measles in Portugal before and after mass vaccination: a time series analysis

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Abstract

Techniques of time series analysis were used to examine historical records of the incidence of diphtheria, pertussis, and measles, and of deaths by measles in Portugal during the XXth century. There are statistically significant seasonal and long-term oscillations in the incidence of these diseases. Seasonal oscillations appear to be in close association with the resumption of school classes in the fall in the case of diphtheria, but not in pertussis and measles. Long-term oscillations in pertussis (3.5-4 year period) and measles (3-year period), before vaccination, corroborate theoretical predictions about the dynamics of these diseases, whereas absence of long-term oscillations in diphtheria are probably due to the influential presence of carriers upon the dynamics of the disease. Mass vaccination strongly supressed disease incidence, did not eliminate seasonal oscillations, and appeared to have acted to lengthen long-term periodicity in pertussis and measles.

Keywords: diphtheria, measles, oscillations, pertussis, Portugal, vaccination..

1. Introduction

The record of data relating to the incidence of transmissible diseases in Portugal, dates back to the first half of the twentieth century and, in some cases, the records extend back to the late nineteenth century, via reference to human mortality associated with the diseases. As in many other countries, the system of regular data collection has largely relied on the notification of public health authorities of so-called notifiable diseases by the general practitioners. The examination of long-term records of the incidence of transmissible diseases suggest characteristic oscillatory trends of the number of cases around the average endemic level that, in many instances, appear to be remarkably regular [1, 2]. These oscillations have attracted the attention of epidemiologists and mathematicians alike. In Portugal, anedoctal reference to epidemic cycles is common among the medical staff since as early as 1954 [3].

In this paper, we use statistical techniques to examine historical data of three infectious diseases in Portugal: diphtheria, pertussis (whooping cough) and measles. It is our goal to provide a concise description of the data and to measure the statistical relevance of the oscillations observed. We are also interested in comparing the kind of oscillations identified and their period cycles with those predicted by theoretical models of infectious diseases. Finally, we examine the impact of vaccination programmes upon the dynamics of the diseases. Theory predicts that vaccination will act to lengthen the interepidemic period, increase the average age at infection, and decrease the overall incidence of the disease. We examine evidence for these expectations by reference to diphtheria, pertussis and measles in Portugal.

2. Data and methods

2.1 Data

The diphtheria (1939-1996) and pertussis (1950-1996) notification data were obtained from publications of the central health offices of Portugal (Table 1). Data of notifications of pertussis were available on a monthly basis from 1952 to 1996. Notifications of diphtheria were available annually from 1939 to 1951 and monthly from 1952 to 1985. After 1986, there were so few notifications of diphtheria that records went back to an annual basis. These time series cover pre- and post-vaccination periods, as vaccination against diphtheria and pertussis at low levels of district coverage were present since at least 1960. Complete coverage of the country started in October 1966, as the Portuguese PNV (National Plan of Vaccination) was fully launched. The diphtheria and pertussis vaccine were, and still are, given in three doses (between 2 and 7 months of age) and two boosters (18 months and 5 years of age). Estimated percent coverages with the first dose in 1967, for the 0-4 years old group, were 40-50% (82% for those less than 1 year old) [12] and have increased up to 90% levels since then. As for measles, case notifications began only in 1987, but as deaths by complications associated with the disease have been recorded on a monthly basis since 1930, we have analysed both the death and the notification series. As vaccination against measles was included in the PNV only in 1973-74 (one dose at 15 months of age until 1990 and two doses, 15 months and 11 years of age, after 1990), only the death series covers pre- and a post-vaccination time periods.

All computations and results were in number of cases per 10^5 individuals. Records of the population of Portugal by year were obtained from the National Institute of Statistics [4-6]. The data of diphtheria, pertussis, and measles are displayed in Figures 1 and 2. We have also obtained data of age-group at infection by diphtheria (1954-1973), pertussis (1954-1994) and measles (1987-1996) from the same sources, and computed the annual average age at infection (Figure 3).

TABLE 1. Reference sources for data used in the analysis.

	Time period	Periodicity	Sources for each period
Diphtheria	1939-1951	yearly	1939-51 [3]
	1952-1985	monthly	1952-69 [7] , 1970-80 [8], 1981-85 [9]
	1986-1996	yearly	1986-89 [9], 1990-96 [10]
Pertussis	1950-1951	yearly	1950-51 [3]
	1952-1996	monthly	1952-69 [7], 1970-80 [8], 1981-89 [9], 1990-96[10]
Measles (deaths)	1930-1984	monthly	1930-34 [11], 1935-67 [4], 1968 [5], 1969-1984[5, 6]
Measles (incidence)	1987-1997	monthly	1987-1989[9], 1990-1997 [10]

2.2 Methods

Mass vaccination is known to have a direct impact upon the periodicity and the absolute value of disease incidence. In order to examine the evidence for such impact, the time series were partitioned into pre-vaccination, transition period, and vaccination sub-series, and then each sub-series was analysed separately. At the outset, all epidemiological time series were examined for evidence of variance heterogeneity and Box-Cox type transformations [13] were applied as appropriate. The transformed time series exhibited trends, regular fluctuations with various periods, and irregular residual fluctuations. The trend is a long-term change in the mean number of cases that, once fitted by a first- or second-degree polynomial, was removed, originating a detrended series of residual fluctuations. Regular fluctuations, whenever present, were either of a seasonal nature, with a period of 12 months, or had longer periods caused by the natural dynamics of the disease. Seasonal coefficients were computed as the monthly averages of the detrended observations. Positive or negative seasonal coefficients result when residual observations for a given month are, respectively, predominantly positive or negative, depending on whether the original data were previously above or below the trend removed. The existence of regular fluctuations with periodicity longer than 12 months, are predicted

by the mathematical theory of the dynamics of infectious diseases. Two statistical techniques were employed for examining these periodicities: autocorrelation and spectral analysis [14, 15].

Autocorrelation analysis is based on the computation of n sample autocorrelation coefficients r_k *(k* = 0, 1, 2, …) where n is the number of observations in the time series, and r_k is the correlation between every two observations at the distance (or lag) of *k* units of time. Spectral analysis [14, 15] is based on the concept of a theoretical spectrum, which partitions the total variability of the time series into harmonic components at the so-called Fourier frequencies: $\varpi_p = 2\pi p/n$ (for p = 1, 2, …, n/2). The spectrum may be estimated by the periodogram, $I(\varpi_p)$, directly computed from the data. $I(\varpi_p)$ is the contribution of the harmonic at frequency ϖ_p to the total variance in the time series. When the time series encloses regular fluctuations in disease incidence, a plot of $I(\varpi_p)$ against frequencies shows sharp peaks at the frequencies corresponding to those fluctuations. The period ($T= 2\pi/\varpi_p$) of an oscillation, indicates that the incidence of the disease tends to repeat itself every T units of time.

Once the trend, seasonal variation and oscillations with periodicity longer than 12 months were described, interpreted in epidemiological terms, and removed, we were left with a time series of residuals which were analysed and fit by autoregressive models [14-15]. These were used for descriptive purposes, as stationary residuals were not assumed to convey useful information on the dynamics of the disease. Finally, it was assumed that every time series could be accounted by an additive model representing the sum of all the above described components [14-15].

Long-term periodicities in the data were interpreted in light of current mathematical theory on the dynamics of infectious diseases. The Anderson-May equation [16, 17], predicts that in diseases where the period of infectiousness is much shorter than host longevity, the interepidemic period, T, between successive epidemic outbreaks, is approximately given by $T \approx 2\pi (AD)^{1/2}$, where A is the average age at infection and D is the sum of the latent and infectious periods. If mass immunisation does not eradicate a disease it also does not suppress periodic outbreaks. However, by decreasing the probability of a susceptible individual to be infected by unit of time, mass immunisation increases the value of A and thus lengthens the interepidemic period.

3. Results

3.1 Diphtheria

Before vaccination (1952-1963), there was on average 1.91 notifications of diphtheria per month per 10^5 individuals in Portugal (= 23 notifications, year^{-1}, 10^{-5} indvs) (Figure 1a). The incidence of the disease had strong seasonal characteristics, being greater in November, December, and October, and lower in June, May and July (Figure 4). The periodogram shows a dominant single peak at frequency of 1 cycle year^{-1}, which corresponds to the 12-month period, and no evidence for longer cycles.

The incidence of diphtheria declined over the course of the 1964-70 transition period that followed mass vaccination, from 21 to 3 notifications per 10^5 individuals per year. The seasonal component remained strong, with the same qualitative characteristics as before vaccination. Vaccination brought the average number of notifications of diphtheria to 1.92 per 10^5 individuals per year in the 1971-1985 period. Throughout this period, there was a continuous decrease in incidence, only

interrupted by a 1975-1976 peak (4 to 7 notifications per 10^5 individuals), apparently associated with a localised outbreak of the disease in slums of the city of Lisbon [18]. Once a straight line was fit to the trend, the periodogram of the detrended series showed no evidence for seasonality or longer regular cycles (Figure 5). There were however peaks in the periodogram at very long periods that, combined with a smoothly decaying correlogram and a partial autocorrelation function with three significant coefficients, suggested that the residuals could be fit by an autoregressive model of order three [14-15]. A final additive model accounted for only 57% of variance in the original data.

3.2 Pertussis

Before vaccination (1952-1962), there was on average 1.74 notifications of pertussis per month per 10^5 individuals in Portugal (20.9 notifications $year^{-1}$ 10^{-5} indvs) (Figure 1). The periodogram of the residual series showed two significant peaks, corresponding to an oscillation with a 12 months period and another at 44 months (Figure 6a). Pertussis had thus a strong seasonal component, with greater incidence in the first semester, especially from March to July, and lower incidence in November-December (Figure 6b). The data also show regular epidemic outbreaks, with peaks located 3.5 to 4 years apart.

The incidence of pertussis in the 1963-69 transition period that followed mass vaccination, declined from 16 to about 3 notifications per 10^5 individuals per year (Figure 1). The fit of a simple straight line to this 7-year period of greatest vaccination impact, accounted for 76% of variation in the data (Figure 7a). The periodogram of the residual series showed a dominant single peak at 12 months, indicating that the disease maintained the same seasonal component. After seasonality was removed,

the new periodogram had no significant peaks, providing no indication of long-term periodicity under vaccination.

After 1970, under mass vaccination, there was a decreasing trend in the incidence of pertussis, from 1.84 notifications in the seventies to 0.4 notifications per 10^5 individuals per year in the nineties. In 1986 and 1989 there were two small epidemics, attributed by the medical literature [19, 20] to immunization waning and contamination of babies by undiagnosed adults. The periodogram of the residual series still showed a significant peak at 12 months (Figure 7b), indicating that pertussis maintained recognisable seasonal characteristics, despite the strong impact of vaccination, although the relative contribution of the seasonal component to account for variation in the data decreased.

3.3 Measles

Deaths by measles

Before the widespread access to antibiotics in the first half of the forties, an average of 1.12 per 10^5 individuals died every month due to complications of measles (Figure 2a). There was no evidence for a seasonal component in the way people died up until 1942, as the periodogram of the detrended series had a single dominant peak at T=35 months (Figure 8a). A periodic component with this period accounted for 40.4% of total variation in the series, confirming the influential presence of recurrent peaks of deaths appearing about every 3 years. The widespread use of antibiotics, initiated around 1943, is probably responsible for the sharp decrease in the number of deaths by measles that followed (Figure 2a). Between 1943 and the introduction of mass vaccination in 1973, there was an average number of 0.23 deaths 10^{-5} individuals $month^{-1}$. The periodogram of the detrended 1943-1973 series provided strong evidence for a seasonal component in

the antibiotic era. People tended to die more in the first quarter of the year and less in September-October (Figure 8b). A periodic component with a 12-month period accounted for 14.5% of variation in the initial series. After removing seasonality, the new periodogram had many significant peaks, indicating that the residual variance could not be explained by a small number of interpretable periodic components.

Mass vaccination against measles drove the number of deaths from 0.042 to 0.008 deaths 10^{-5} individuals $month^{-1}$. The periodogram of the residual 1974-1984 series had a dominant peak at period T=12 months, indicating a significant seasonal component whose pattern did not differ much from the pre-vaccination period: more deaths than average in February-April, less deaths than average from August to November. The seasonal component accounted for 23.3% of total variance in the series.

Measles notifications

Compulsory notification of measles cases began only in 1987, when incidence of deaths was already heavily depressed by vaccination. From 1987 to 1997, measles incidence maintained a slightly decreasing trend and the periodogram of the detrended series displayed a dominant peak at a period of 12 months (1 cycle $year^{-1}$) (Figure 8c). Measles tends to peak from March to May and to be lower in Sep-Oct. The second greatest peak in the periodogram was at a period of 66.67 months (0.18 cycles $year^{-1}$). Examination of neighbouring frequencies, after removing the seasonal component, indicated that the greatest proportion of variation (37.9%) was accounted by a periodic component with a period of 60 months (0.2 cycles $year^{-1}$) plus its sub-multiple harmonics at T=30 and 15 months. This component underlies the 5-year interepidemic period apparent in the measles time series (Figure 2b).

4. Discussion

Vaccination was an effective way to repress the morbidity of diphtheria, pertussis, and measles in Portugal in the 1960's, but neither of these diseases may as yet be considered completely eliminated, in spite of the high levels of vaccination coverage commonly reported [21]. This is not surprising, as the levels of coverage required for eradication (to be sustained over many years in the overall population) are estimated to be around 85% for diphtheria and 95% for pertussis and measles [17]. Encouragingly, however, the number of notifications of diphtheria in Portugal has been zero since 1990 (only exception is 1992 with 3 cases) and pertussis has also hit record lows at 0.16 and 0.12 notifications per 10^5 individuals in, respectively 1996 and 1997. Measles remains endemic with long-term (5-6 years) small outbreaks, the next being projected for the spring of 1999. The records of disease incidence and mortality analysed herein, exhibited patterns of recurrent oscillations comparable to those found in previous analysis of long-term epidemiological data [1, 2]. These oscillations were somewhat changed after the introduction of mass vaccination, but they did not disappear. At certain periods, the oscillations were found more regular than expected by chance, in a way that is in reasonable agreement with theoretical predictions about the long-term dynamics of infectious diseases.

4.1 Seasonal periodicity

A striking feature of our results was the significance of the seasonal periodicities in disease incidence (Figures 6a, 7b, 8c). Every year there were months when diphtheria (Oct-Dec), pertussis (Mar-Jul), and measles (Mar-Jun) exhibited short-lasting epidemics. A common explanation is that monthly contact rates (the number of susceptibles that an average infective contacts per unit time) undergo substantial seasonal variation [1]. Seasonal epidemics are triggered when the rise in

the contact rate reaches the critical level where an infectious individual encounters a number of susceptibles large enough to cause more than one infection before recovery [1, 17].

The peaks in the incidence of diphtheria, appear one to three months after the autumn gathering of school children (Figure 4), when classes resume and bring together a large number of susceptibles that are easy ‘prey’ for a few infected individuals. During the ensuing epidemics, practically all susceptibles that were put into contact with the disease become infected. A new epidemics will then have to wait until the replenishment of the pool of susceptibles is accomplished. Unlike diphtheria, this seasonal pattern was observed in measles and pertussis even when incidence was depressed by vaccine uptake (Figure 7b, 8c). As for diphtheria under vaccination (1971-85), the large amount of residual variation left unexplained suggests that monthly case reports might have dropped to such low levels that the sampling error in notifications masked the seasonal cycle.

The March-May outbreaks in the incidence of measles, also reported for England and Wales [2], New York, and Baltimore [1], do not appear to be in such close association with the timing of school holiday periods. However, measles has a mean incubation period of 8 to 14 days, which is longer than the corresponding 2 to 5 days of diphtheria. Simple models of differential delay equations predict that, with such a longer incubation time, about seven months are needed to build up the pool of infectives to a level where an epidemic outbreak and depletion of susceptibles follows [1, 22]. It is interesting that the time series of deaths by measles showed no evidence of seasonal cycles (Figure 8a) before the introduction of antibiotics (1930-42). Seasonality appeared when mortality became greatly reduced by therapy with antibiotics (1943-73) and remained well marked under vaccination (1974-84). A

possible explanation is that before antibiotics measles was complicated by a broader range of illnesses effectively leading to death, originating a much broader range of time lags between the moment an individual was diagnosed with measles and the moment of death.

Seasonal variation in pertussis (Figure 6b) is somewhat different than that recorded for diphtheria and measles. Having a mean incubation period of 7 to 10 days, the peak incidence within a year varies considerably between January and September, a finding also reported in a 34-years data analysis of pertussis in England and Wales [2]. Aggregation of school children is not likely to be the main cause of seasonality in pertussis, as 20 to 35% of notified cases were less than 1 year old. Adult to child transmission might play a greater role than in the other two diseases. Two studies, [19] and [20], conducted in pediatric services of state hospitals in the cities of Coimbra (129 cases in 1986-87) and Lisbon (125 cases in 1982-1986) reported a high percentage of confirmed cases with less than 3 months of age: 40% in Coimbra and 46% in Lisbon. The authors argued these proportions suggest the source of transmission are adults who probably have atypical symptoms and have not been notified. A tendency for cases of pertussis to concentrate upon very young children and non-notified adults, might explain the decline in the average age at infection (Figure 3) during the vaccination era, in apparent contradiction with epidemic theory.

4.2 Long-term periodicity

Before vaccination, there was strong evidence for recurrent epidemic outbreaks of pertussis and measles with non-seasonal periodicity. Outbreaks of pertussis took place every 3 to 4 years (Figure 6a) and outbreaks of measles, as assessed by records of deaths by measles, took place about every 3 years (Figure

8a). In the vaccination era, however, there was no statistical evidence for long-term periodicity in pertussis. After 1943 there was also no longer a dominant period in deaths by measles. A possible explanation is that the variance in the lags between primary infection with measles and time of death increased after the antibiotics.

As for measles incidence under vaccination, there was two clear peaks (1988-89,1993-94) also located about 5 years apart. These peaks were coincident with the minima in the series of average age at infection with measles (Figure 3c), suggesting an association between outbreaks and accumulation of susceptibles at very young ages. The 34-year time series of diphtheria, on the contrary, did not show evidence of long-term periodicity.

Measles remains endemic in Portugal at a higher incidence than diphtheria and pertussis, in spite of levels of vaccination coverage reported to be above 80% [21] and the introduction of a second dose of the vaccine in 1990. Concern about the possibility of an approaching epidemics, on the one hand, and the relative success in accounting for variation in the 1987-97 time series, on the other hand, motivated a projection exercise [23] for upcoming years. The model projects a rise in incidence initiated in 1998 followed by an epidemic outbreak in the spring of 1999, peaking with an average of about 1.2 notifications per 100 individuals in March of 1999. This epidemics is predicted milder than the previous ones (35.4 and 8.2 notifications per 100 indvs in March of, respectively, 1989 and 1994).

In order to compare the predictions of the Anderson-May equation with our results on long-term periodicity of pertussis and measles, Table 2 lists the parameters A and D, as well as the predicted and observed interepidemic periods before and after vaccination. The estimates of A for pertussis and measles after

vaccination are from Figure 3, and for measles before vaccination we use a range of ages reported for industrialised countries in the prevaccination era [24]. There is good agreement between the theoretical predictions and the interepidemic periods observed before vaccination (Table 2). Under vaccination, however, the extent to which the interepidemic period increased in measles is somewhat greater than that predicted by the Anderson-May equation. A possible explanation for the discrepancy is that average ages at infection in Figure 3 are underestimated due to misreporting of cases of measles in adults.

TABLE 2. Estimates of the average age at infection (A, in years) before and after vaccination (from Figure 3), the average duration of the latent plus infectious period (D, in days) [25], and the predicted plus observed interepidemic period (in years) for pertussis and measles.

		Pertussis (D=22-25)	**Measles** (D=10-14)
Before vaccination	A	3.5 to 4	4 to 7
	Interepid. period		
	Predicted	2.9 to 3.3	2.1 to 3.2
	Observed	3 to 4	3
After vaccination	A	2 to 4.5	8 to 12
	Interepid. period		
	Predicted	2.2 to 3.5	2.9 to 4.3
	Observed	none	5

The absence of long-term periods in diphtheria is in agreement with predictions from mathematical models that describe the mechanisms of disease transmission. Diphtheria is a child disease transmitted by close contact of patients or carriers with susceptible individuals. The dynamics of the disease is influenced by the

presence of a high proportion of asymptomatic and yet long-term infectious carriers in the population. It can be shown, both analytically [17] and by numerical simulation [26], that the presence of carriers tends to smooth over the propensity for oscillations that characterise the incidence of diseases with relatively short duration of infectiousness, like pertussis and measles. In the later, the wave of infection spreads so fast that the susceptibles get depleted long before they can be replaced by newborn susceptibles. The infectious agent then ‘waits’ in a small number of infected individuals until the pool of susceptibles is slowly replenished. Diphtheria is more endemic in character. Like in many other bacterial diseases, there is a steady and relatively slower ‘consumption’ of susceptibles that undercuts the possibility of long-term dynamic oscillations of the incidence of the disease.

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FIGURES

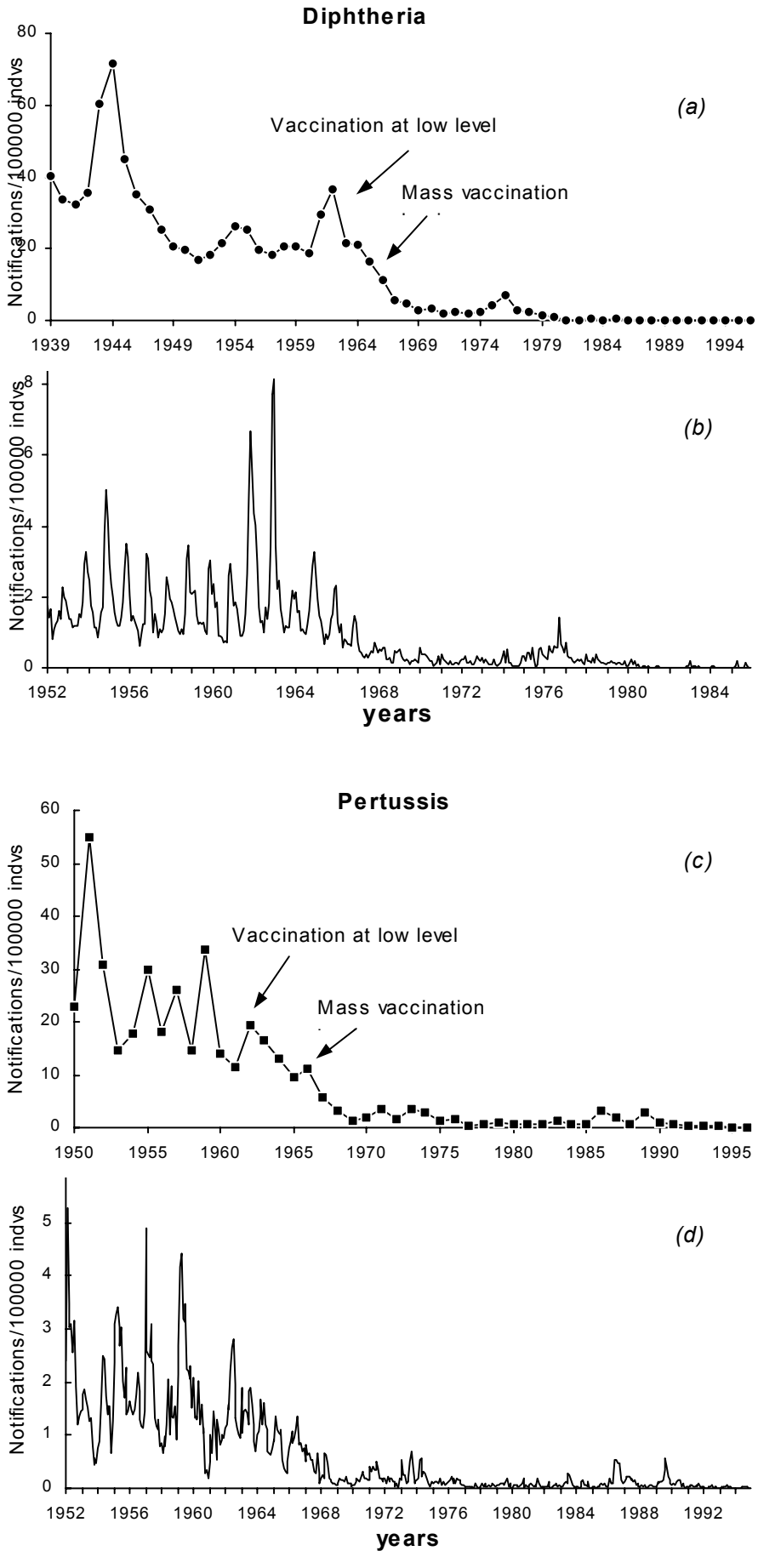
Diphtheria
(a)
Vaccination at low level
Mass vaccination
Notifications/100000 indvs
(b)
years
Pertussis
(c)
Vaccination at low level
Mass vaccination
Notifications/100000 indvs
(d)
years

Figure 1. Notifications of diphtheria and pertussis in Portugal by 10^5 individuals. Notifications are per year *(a, c)* and per month *(b, d)*. The perid of time covered by the graphs is longer for notifications on an annual basis.

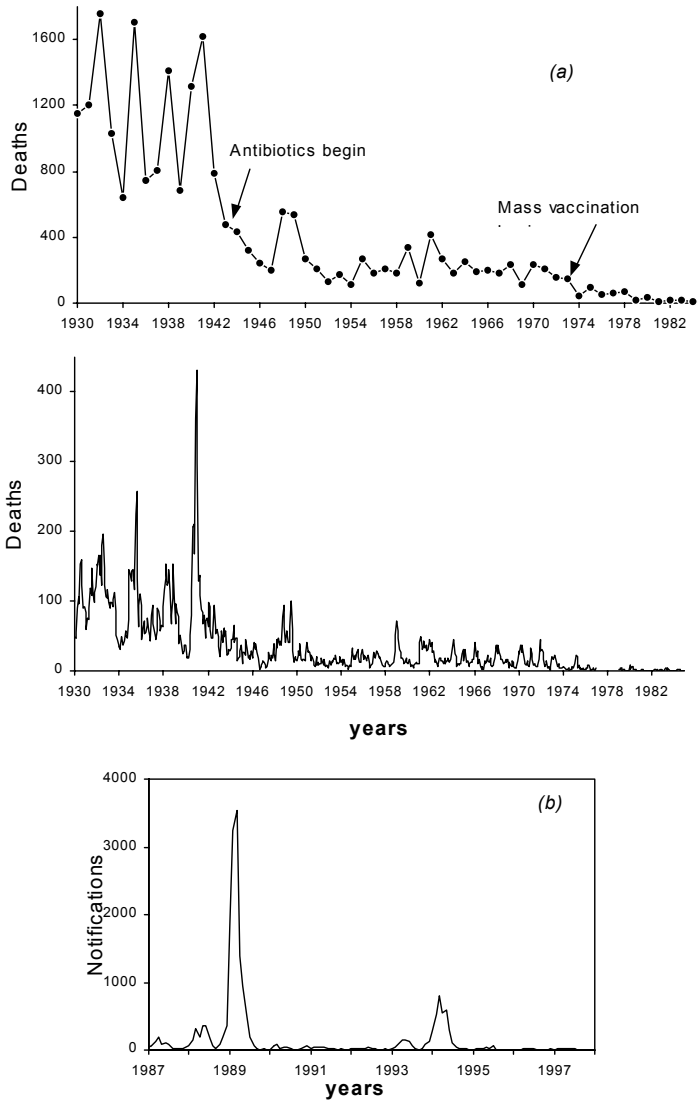

Figure 2. *(a)* Number of deaths due to measles in Portugal, reported per year (top) and per month (bottom). *(b)* Number of monthly notifications of measles (1987-97).

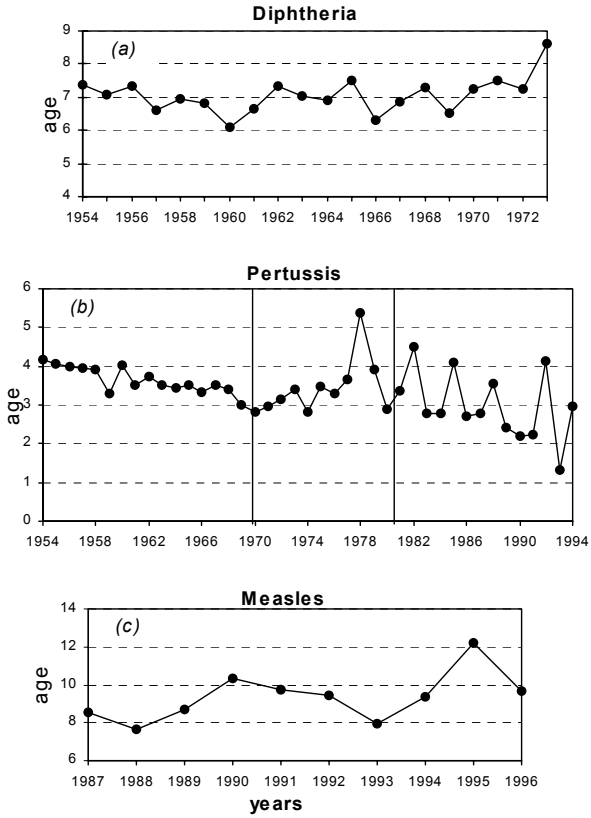

Figure 3. Annual average age (in years) at infection by diphtheria (1954-1973), pertussis (1954-1994) and measles (1987-1996). The vertical bars in pertussis separate three periods with different level of age-group aggregation (1954-1969, 1970-1980, and 1981-1994) in the raw data.

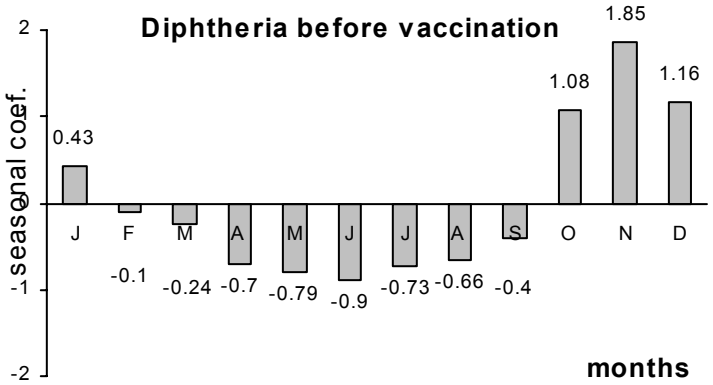

Figure 4. Coefficients of seasonality of diphtheria before vaccination (1952-63), indicating how much the monthly incidence of diphtheria deviates from the annual mean.

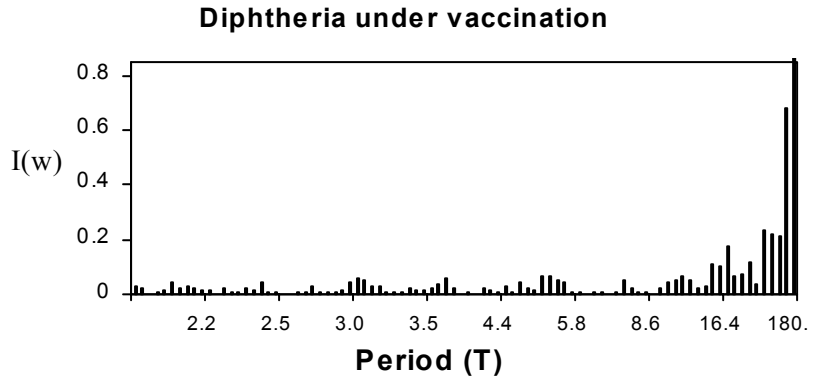

Figure 5. Diphtheria under vaccination. Periodogram of notifications of diphtheria from 1971 to 1985. No seasonal or other regular oscillations dominated the data. The 180-month period peak does not correspond to any periodicity because n = 180.

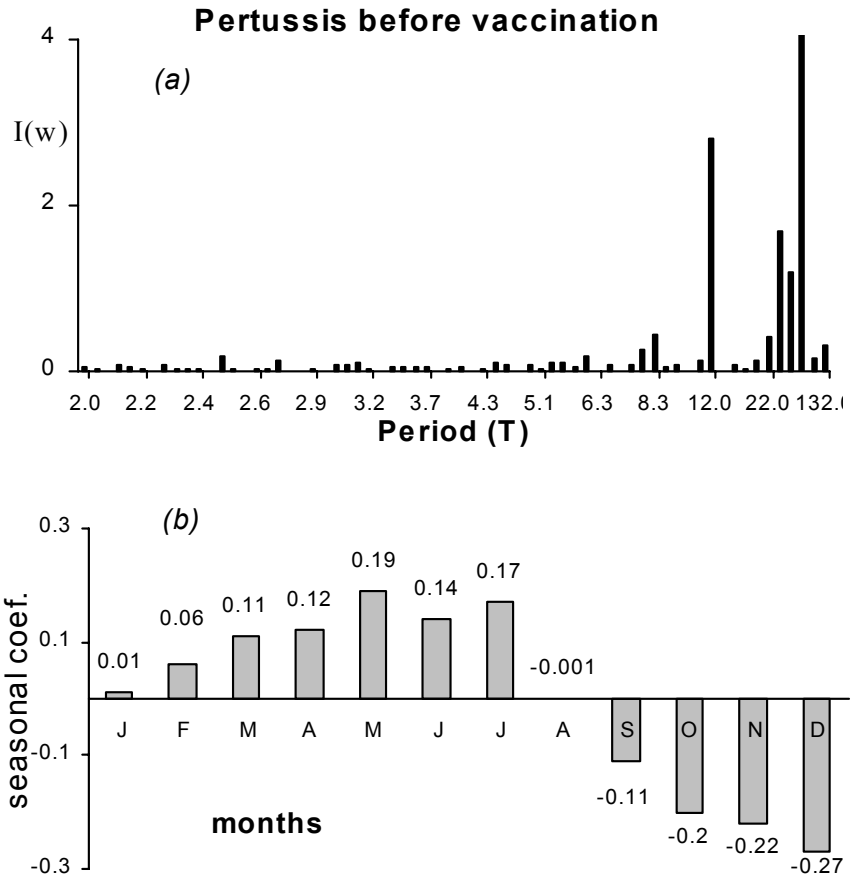

Figure 6. Pertussis before vaccination (1952-62). *(a)* Periodogram of the detrended series. The isolated peak at the 12-month period indicates seasonality, whereas the higher peak at 44 months indicates regular epidemic outbreaks with this period. *(b)* Coefficients of seasonality. The incidence of the disease was higher in May and lower in December.

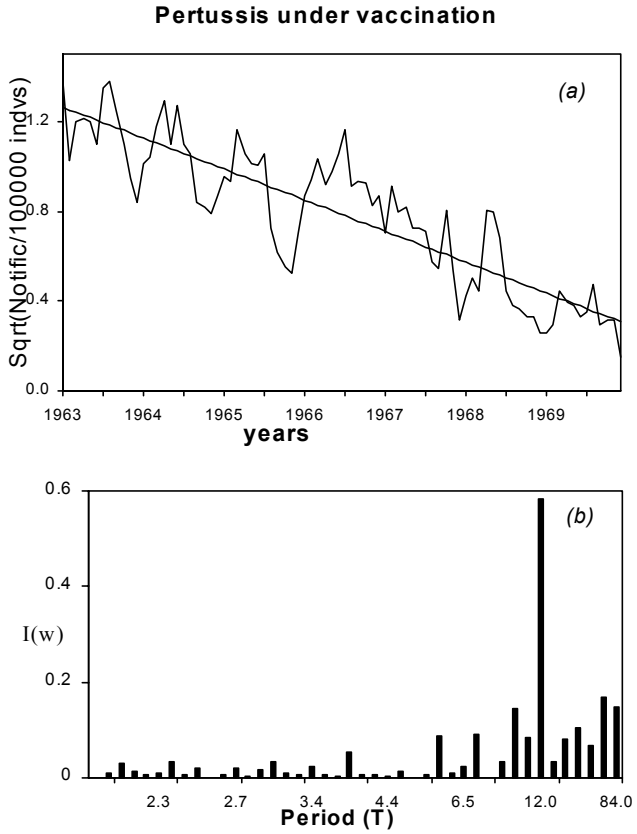

Figure 7. Pertussis under vaccination. *(a)* Monthly notifications of pertussis per 10^5 individuals from 1963 to 1969 after square root transformation. The straight line explained 76% of the variance in the data series. *(b)* Periodogram of the detrended series when the incidence of pertussis was at very low levels (1970-94).

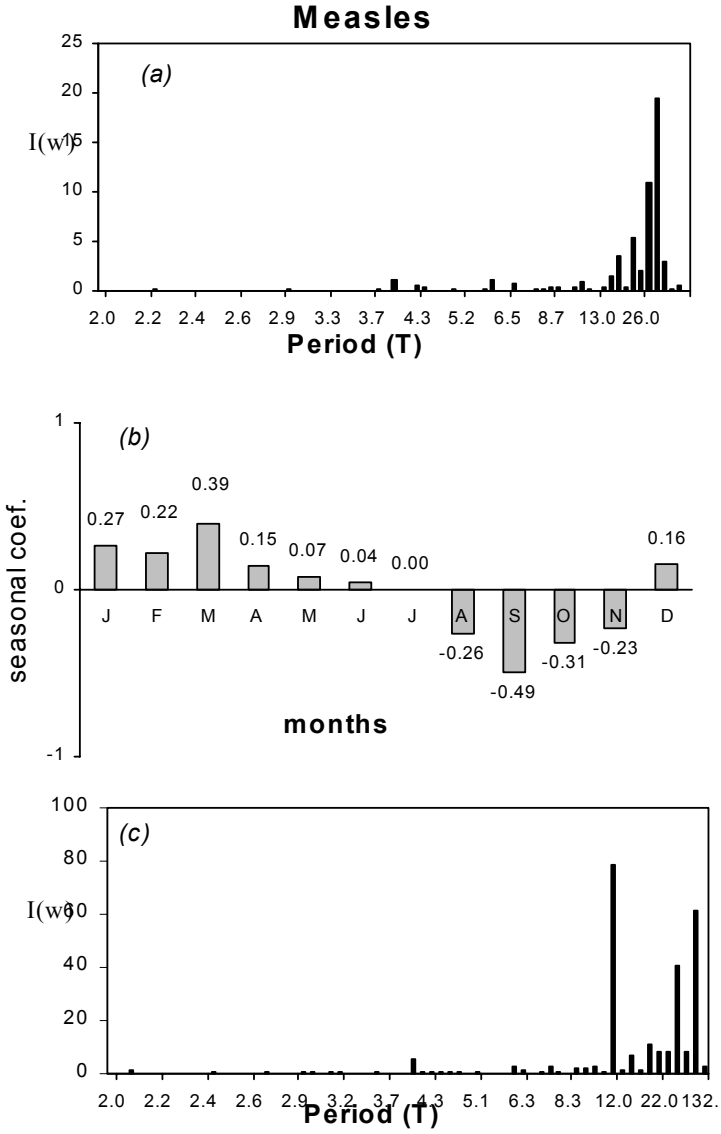

Figure 8. Measles. *(a)* Periodogram of the detrended time series of deaths by measles, before the widespread use of antibiotics (1930-42) *(b)* Coefficients of seasonality of deaths by measles in the antibiotic era, before mass vaccination (1943-73). *(c)* Periodogram of the detrended time series of measles notifications (1987-97). The dominant peak at T=12 months indicates a seasonal component. The second greatest peak at T=66 months hints long-term periodicity in the natural dynamics of measles.

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