Università degli Studi di Pisa
Dipartimento di Statistica e Matematica
Applicata all'Economia

Report n. 186

The pre-vaccination dynamics of measles in Italy: estimating levels of under-reporting of measles cases

John R. Williams – Piero Manfredi

Pisa, September 2000

- Stampato in Proprio -

Via Cosimo Ridolfi, 10 – 56124 PISA – Tel. Segr. Amm. 050 945231 Segr. Stud. 050 945317 Fax 050 945375
Cod. Fisc. 80003670504 - P. IVA 00286820501 - Web http://statmat.ec.unipi.it/ - E-mail: dipstat@ec.unipi.it

The pre-vaccination dynamics of measles in Italy: estimating levels of under-reporting of measles cases[1]

John R. Williams* and Piero Manfredi**

*Wellcome Trust Centre for the Epidemiology of Infectious Diseases, Dep. of Zoology, University of Oxford, South Parks Road, Oxford
and
Dipartimento di Statistica e Matematica Applicata all'Economia
Via Ridolfi 10, 56124 Pisa – ITALY

** (corresponding author) Dipartimento di Statistica e Matematica Applicata all'Economia
Via Ridolfi 10, 56124 Pisa – ITALY
e-mail: manfredi@ec.unipi.it

Abstract
The relation between number of cases and births which characterises highly infectious childhood diseases, such as measles, during their pre-vaccination era, is used to estimate levels of under-reporting of measles cases in the twenty Italian regions. The results are striking, both in terms of the absolute level and of the geographic heterogeneity of under-reporting. Even more important, they provide a potential explanation for the existence of selective under-reporting by age, as conjectured in a recent paper by Edmunds et al. (2000).

1. Introduction

The high level of infectiousness of the measles virus means that in the absence of vaccination (i.e. prior to the end of 1976 in the case of Italy) it would be expected that nearly all individuals in the population would experience infection with measles at some time during their lives (Anderson and May 1991, chapter 4). Thus, ignoring migration, it would be expected that the mean number of measles cases over time should approximate the mean number of births (details in the appendix). Additionally, in the pre-vaccination era, the relationship between numbers of recorded births and numbers of recorded measles cases should not differ greatly between countries (and between large sub-areas of the same country). In the case of Italy however the mean numbers of recorded births are, in the pre-vaccination era, very much greater than the mean numbers of recorded cases, both nationally and within regions. Moreover there is a strong variability at the spatial scale. This is clearly illustrated in table 1, reporting the ratio between reported cases and births for the three traditional large geographic clusters North, Centre and South on some time windows in the pre- and post-vaccination era.

[1] This paper was written within the research project Progetto Nazionale "Epidemiologia delle Vaccinazioni in Italia" (National Coordinator: Stefania Salmaso, Istituto Superiore di Sanità), funded by the Italian Ministery of Health within the 1% framework. We thank Stefania Salmaso, Marta Ciofi, Roberto Tozzi, Donatella Mandolini and Antonino Bella for useful discussions and suggestions. Usual disclaimers apply.

Table 1. Number of recorded measles cases per 1000 live births

	Period	NORTH	CENTRE	NORTH-CENTRE	SOUTH	ITALY
	49-86	110,3	97,3	106,3	32,0	72,5
Pre-vaccination	49-76	107,9	98,1	104,9	34,3	73,1
Post-vaccination	77-86	120,1	94,1	111,9	23,1	70,1
Sub-window I	49-57	127,2	106,8	120,9	39,5	81,3
Sub-window II	58-66	109,5	99,2	106,4	37,7	75,6
Sub-window III	67-76	91,7	89,8	91,2	25,6	63,4

A glance at the patterns at the regional (and some of the larger provinces) level (Tab. 2) confirms this picture. The overall ratio cases-births in the pre-vaccination era (1949-76) ranges from around 22 per 1000 in Campania (South) to around 210 per 1000 in Emilia Romagna. The cluster of the "more southern" regions (Campania, Basilicata, Puglia, Calabria, Sicilia and Sardegna) exhibits quite low levels for the long-term ratio cases-births (less than 50 per 1000), which are systematically lower compared to the rest of the country. The variability within the two large geographic clusters North-Centre and South is again quite big: among southern regions the ratio varies along a factor four from Campania (around 20 per 1000) to Abruzzi and Molise (80 per 1000), whereas it changes along a factor three in the North-Centre (ranging from 70 per 1000 in Trentino to 210 per 1000 in Emilia-Romagna). The province of Naples, with only 15 cases reported per 1000 live births during the pre-vaccination window 1949-76 exhibits the lowest ratio. Moreover, if one splits the pre-vaccination 49-76 window into the three sufficiently homogeneous sub-windows 49-57, 58-66, 67-76 the ratio tends to decrease over time, with few exceptions.

Table 2. Cases and births for the 20 Italian regions (and some large provinces)

This finding contrasts with similar data for England & Wales, for example, where numbers of reported cases correspond to a much higher proportion of mean number of reported births (fig. 1): in the pre-vaccination window 1948-66 the overall ratio cases/births over this time window amounts to more than 55% (table 3). Such a degree of difference is a further spy of a very substantial level of under-reporting in Italy. In addition to the under estimation of total numbers of measles cases, if the level of under-reporting is not consistent between regions and the temporal and age-related patterns of actual cases also vary between regions, the aggregate national pattern of cases may become distorted, perhaps obscuring important epidemiological patterns and impeding the use of time series analysis for the identification of epidemic cycles and trends.[2]

Tab. 3: Cases and births in England and Wales.

The present paper extensively uses the relation between cases and births in order to estimate the time trend of measles cases under-reporting in the 20 Italian regions. As a "starting point" the

[2] It should be noted in passing that in general there may also be dangers to epidemiological analysis resulting from over-reporting. Recent evidence points to worrying levels of misdiagnosis (Blackburn et al, 2000; Ramsay et al, 1997) with, in particular, rubella being reported as measles. This is a danger which may be expected to increase as circulation of measles virus decreases following successful vaccination programmes and doctors in general practice become less familiar with cases of measles.

Italian regions are treated as separate epidemiological units, i.e. we disregard migrations. This is a common assumption, very much in line with standard epidemiological practice and models. A companion paper (Manfredi and Williams 2000) will consider the extent of the perturbatory role played by migrations. The estimates of the under-reporting coefficients are then computed on the basis of a simple "time-series" based algorithm the purpose of which is that of providing a not too biased correction for the observed time series of cases at the regional level. Finally the corrected regional figures are used in order to provide a corrected national time series of cases.
The paper is organised as follows. In section two the method of estimation of under-reporting used in the paper is briefly presented. Its results are reported in section three. In section four the estimated under-reporting coefficients are used in order to achieve a corrected national case notification figure for measles. Some technical details on the relation between cases and births as it emerges from standard epidemiological models are reported in the appendix.

2. Using births as estimator of mean expected number of cases

In pre-vaccination years the near universal lifetime experience of infection with measles followed by long term immunity to further infection and the consequent similarity between overall numbers of births and of measles cases suggests a manner of approximating the true number of cases by using data on births.
Over time the overall number of measles cases will approximate to births, but fluctuations and trends in numbers of births will not be immediately reflected in numbers of cases because of the cyclic pattern of measles epidemics and because individuals vary in the age at which they are infected. (By ignoring migration flows this assumes that national and regional cases occur in those born in the same geographic area). It would normally be expected that around half of all measles cases would occur in the first 4-7 years of life (Edmunds et al. 2000); above this age numbers of cases become more and more widely distributed with increasing age. Bearing this in mind, a moving average of births over a similar period should smooth fluctuation and relate quite strongly to the trend in number of measles cases (the time span chosen here for the moving average is 6 years corresponding with that adopted below for the number of cases).
It is generally considered that, prior to vaccination, measles infection is in long term endemic equilibrium in all countries except in island and other isolated communities below a certain population size. Hence it is reasonable to assume that in the pre-vaccination era measles would have been in endemic equilibrium in Italy and its regions. However such an endemic equilibrium is characterised by strong epidemic fluctuations about the endemic mean which distort the direct relationship between cases and births, so it is appropriate to smooth this data in the same manner as for births. In the case of Italy it appears that epidemic cycles are mainly of order of 2 and 3 years, so a 6 year moving average was chosen to optimise smoothing of short term epidemic fluctuations:

$$y_t = 0.5\,x_{t-3} + x_{t-2} + x_{t-1} + x_t + x_{t+1} + x_{t+2} + 0.5\,x_{t+3} \qquad (1)$$

where $\{x_t\}$, t=0,1,2,.. denotes the original time series (in this case observed measles cases and births) and $\{y_t\}$ the corrected one.
The ratio of the moving average of cases for time t to moving average of births for time t can then be used as an estimator of the proportion of all measles cases which are recorded through the reporting system. This does ignore the effect of any lags between individuals' births and their ages at infection, but the effect of this omission should be minimal in most instances.

3. Regional trends in under-reporting

Data

In this paper case-notifications data for measles over the period 1949-86 have been used. A part of the post-vaccination era has also been included. Individual records of measles cases for Italy are available since 1971 (a set of covariates, such as age, sex, the exact date of occurrence, the province of occurrence (only until 1986) and the province of notification are reported as well). Prior to 1971 only official monthly reports (ISTAT1) by province are available (with the complication that the province of notification is recorded during 1949-1958, whereas the province of occurrence is recorded during 1958-1970). Time series of births by region were provided by official demographic sources (ISTAT2, ISTAT3). Fig. 2 reports the actual yearly measles cases for the 20 Italian regions and some of the larger provinces.

Estimates of under-reporting

The 6 year moving averages (MA) of births and of cases were calculated for each region using yearly births and cases data for the period 1949-1986, the MA process defined by (1) providing series truncated to the period 1952-83. For each region the estimator of under-reporting (EURep) was then calculated:

$$EURUP(t) = \frac{MA_{cases}(t)}{MA_{births}(t)}$$

For the pre-vaccination years 1952-1974 the mean of this correction factor ($EURep_{1952\text{-}74}$) was also calculated.

The MA_{births} data show two broad patterns. The first shows an increase to a broad peak in the mid-1960's-70's, then a decline (e.g. Lombardia, Lazio) and the second simply shows a continuing declining trend, (e.g. Umbria, Marche, Basilicata); some regions display a combination of these forms (e.g. Veneto, Toscana, Campania) (*Figs 3a-f*). For comparison, the similarly smoothed national births data for England & Wales for 1951-1963 shows a trend of continuing modest increase.

For cases, the pattern of MA_{cases} generally shows a slightly declining trend towards the mid-1970's, in some cases from a broad peak or plateau. Some regions do show more fluctations, e.g. Lazio with twin peaks, Puglia with a relatively late peak and Sardegna with a strongly fluctuating declining trend. After the mid-1970's and coinciding with the start of vaccination the MA_{cases} show a variety of trends: continuing decline, decline then increase, or simply increasing (*Figs 4a-f*). Smoothed 1951-63 national case reporting data for England & Wales shows in comparison a more or less constant level of cases.

Patterns in the regional yearly *EURep(t)* correction factors include the roughly constant (e.g. Veneto, Trentino, Basilicata), steady decline (e.g. Campania), decline followed by sharp upturn in late1970's (e.g. Lombardia, Piemonte, Marche), an early rise to a plateau (e.g. Emilia, Toscana), or a rise to a peak and then decline (e.g. Molise, Calabria). The corresponding pattern of *EURep(t)* for the England & Wales data shows a slow decline with a pattern midway between those of Veneto and Campania, for example, albeit at a much higher level for England & Wales (58%). The Italian region with the highest mean ($EURep_{1952\text{-}74}$) is Emilia with an estimate of 21.4% of true cases reported and the lowest Sicilia with 2.9%. Of the 4 conurbations, Milano, Torino, Roma, Napoli, the lowest figure was for Napoli (1.6% compared with 2.2% for Campania as a whole). Roma had a figure similar to but higher than its region (8.6% compared with 7.9% for Lazio). The figure for Milano was 6.6% (8.9% for Lombardia) and for Torino 6.8% (9.5% Piemonte) (*Figs 5a-f*).

4. Correction of national figures

The *EURep* ratios of the two *MA* measures were used to adjust the monthly (fig. 6) and yearly case reporting data for each region to allow estimates to be made of the true national number of cases. Time series of observed and corrected monthty measles cases are displayed in fig. 7. First the regional *EURep(t)* correction factor for each year (Table 4) was applied to the data for each month in that year, providing adjusted estimates for numbers of cases in the years 1952-1983 which were then summed to provide a national estimate of cases for the same period (fig. 7a). Additionally a second set of adjusted national data for the full period 1949-86 was provided by using on each region's reporting data the mean correction (fig. 7b) for the period 1952-74 ($EURep_{1952\text{-}74}$), here making the implicit assumption that underlying levels of under-reporting would remain constant into the post-vaccination era. The two series of revised data arising from this process are, as may be expected, very similar in magnitude (around 7%-8%), shape and trend: the most noticeable differences are slight and relate to the shapes of epidemic peaks.

Table 4. Italian regions 1952-83. Yearly under-reporting coefficients.

5. Observations on results of correction and directions for future work

The corrected Italian national case reporting data are approximately an order of magnitude greater than the uncorrected data. However although the magnitude of the difference is large, the shapes, location and trends of the time series, corrected and uncorrected, are very similar. This suggests that, despite the poor level of case reporting, the shapes and trends seen in the uncorrected national data are robust to the patterns of underreporting discussed here. It may be however that detailed time series analysis may reveal differences between corrected and uncorrected series that are not immediately apparent from visual inspection and this will be one of the topics to be addressed in the next report to be prepared.
A second important related point concerns the implications of the correction of under-reporting for the estimation of the Force of Infection (FOI) from age structured data. In their recent paper on the pre-vaccination dynamics of MRR in several European countries Edmunds et al. (2000) concluded that a major feature of the italian system is the existence of strong selective under-reporting by age. It is to be noted that in presence of distinct patterns of infection by age at the regional level, the appearance of under-reporting by age will be an often necessary consequence of the existence of regional differentials in under-reporting, even without selective under-reporting by age. The correction of under-reporting at the national level, as done in this paper and the companion one, therefore supplies a manner to potentially correct significant biases in age structured data. The estimation of the FOI from corrected data will be a task of a subsequent paper as well.

List of figures

References

Anderson R.M:, May R.M: (1991), Infectious diseases of humans, Oxford University Press, Oxford.
Blackburn N, Schoub B, O'Connell K (2000), Reliability of the clinical surveillance criteria for measles diagnosis, *Bulletin of the World Health Organisation*, 78:861.
Edmunds J.W., Gay N.J., Kretzschmar M., Pebody R.G., Wachmann H. (2000), The pre-vaccination epidemiology of measles, mumps and rubella in Europe: implications for modelling studies, submitted.
ISTAT1, Annuari di Statistiche Sanitarie, 1955-1996, ISTAT, Roma.
ISTAT2, Annuari di Statistiche Demografiche, 1951-1955, ISTAT, ROMA.
ISTAT3 (1991), Sommario 1952-1987 di statistiche storiche della popolazione, ISTAT, Roma.
Manfredi P., Williams J.R. (2000), Estimating levels of under-reporting of measles cases in Italy: correcting for migrations, WP Dip. Statistica e Matematica Applicata all'Economia. Università di Pisa.
Ramsay M, Brugha R, Brown D. (1997), Surveillance of measles in England & Wales: implications of a national saliva testing programme. Bulletin of the *World Health Organisation*, 75:515-521.

Appendix: a theoretical viewpoint on the relation between cases and births

In this appendix the relation between number of cases and births, extensively used throughout the paper, is discussed by using standard epidemiological models.

1. Basic models without age structure

Let us consider the simplest SIR epidemiological model describing infection in a stationary homogeneously mixing population:

$$\begin{aligned}\dot{X}(t) &= B(t) - (\mu + \lambda(t))X(t) \\ \dot{Y}(t) &= \lambda(t)X(a,t) - (\mu + v)Y(t) \qquad (1) \\ \dot{Z}(t) &= vY(t) - \mu Z(t)\end{aligned}$$

where $X(t), Y(t), Z(t)$ respectively denote the numbers of susceptible, infective and removed individuals at time t, $B(t)$ the number of births per unit time, $\lambda(t)=\beta Y(t)$ the force of infection (FOI), β the transmission rate, μ the mortality, which is assumed constant at all ages, and v the recovery rate. The total population $N=X+Y+Z$ is assumed stationary, with $B=\mu N$. Let us assume that the epidemics be at equilibrium ($\dot{X}(t)=\dot{Y}(t)=\dot{Z}(t)=0$). Then it holds $B=(\mu+\lambda)X$. Hence, by defining as $C=\lambda X$ the number of cases at equilibrium, we have:

$$C = B - \mu X \qquad (2)$$

A fundamental prediction of model (1) (Anderson and May, 1991) is that the susceptible fraction at equilibrium is the reciprocal of the basic reproduction ratio R_0 of the infection: $X/N=1/R_0$. Therefore:

$$C = B - \mu \frac{N}{R_0} = B\left(1 - \frac{1}{R_0}\right)$$

or:

$$\frac{C}{B} = 1 - 1/R_0 \qquad (3)$$

Hence, for high values of R_0 (R_0=15 was a quite common value for measles in the pre-vaccination era, see Anderson and May 1991), the ratio cases/births tends to be quite close to unity. In effect, if the force of infection is sufficiently high so that everybody gets infection before a relevant part of the population is eliminated by death, the approximation $C/B \approx 1$ tends to be even stricter. This will become apparent in the next section by using an age structured model with a less coarse treatment of mortality.

Though relations as (3), and its approximation $C/B \approx 1$, are "equilibrium relations", they still hold in approximate form under many other circumstances. In the real world childhood infectious diseases tended to manifest themselves in the pre-vaccination era with quite regular oscillatory patterns. Let us suppose that the number of cases predicted by (1) is steadily oscillating with some oscillation period. In this case (3) remains correct provided we consider average values of cases and births over the appropriate time period. Moreover, (3) remains approximately correct under more general conditions. Let us suppose for instance that the model is non-stationary, for instance because some parameter is time varying, or the population itself is non-stationary. Provided that the state variables are bounded in the long term, then the equilibrium ($\dot{X}(t)=\dot{Y}(t)=\dot{Z}(t)=0$) condition may be replaced by the less strict condition that the long term averages (let us denote them by $E(\dot{X}(t))=E(\dot{Y}(t))=E(\dot{Z}(t))$) of the derivative of the state variables are zero. Therefore it holds:

$$E(C) = E(B) - \mu E(X) \qquad (4)$$

suggesting that relation (3) still holds by replacing the yearly number of cases and births with their time averages over a sufficiently long period of time.

The role of age structure

The previous ideas may be enlarged by taking age structure into consideration. Let us consider the SIR epidemiological model with age structure:

$$\begin{aligned} &\Delta X(a,t) = -(\mu(a) + \lambda(a,t))X(a,t) && X(0,t) = B(t) \\ &\Delta Y(a,t) = \lambda(t)X(a,t) - (\mu(a) + v + \alpha(a))Y(a,t) && Y(0,t) = 0 \qquad (5) \\ &\Delta Z(a,t) = vY(a,t) - \mu(a)Z(a,t) && Z(0,t) = 0 \end{aligned}$$

where Δ is the population ageing operator $\left(\frac{\partial}{\partial a} + \frac{\partial}{\partial t}\right)$, *X(a,t),Y(a,t),Z(a,t)* respectively denote the numbers of susceptible, infective and removed individuals aged a at time t, *λ(a,t)* the (age-related) force of infection, μ(a) the age-related mortality rate of the overall population, α(a) the extra mortality rate caused by the disease, v the recovery rate. The total population obeys:

$$\Delta n(a,t) = -\mu(a)n(a,t) - \alpha(a)Y(a,t) \quad ; \quad n(0,t) = B(t) \qquad (6)$$

For simplicity we take α(a) =0, and assume that the population is stationary, i.e. *B(t)=B*. Let us consider the system at equilibrium. The total number of cases of infection per unit time at equilibrium is:

$$C = \int_0^\infty \lambda(a)X(a)da = B\int_0^\infty \lambda(a)p(a)A(a)da = B\int_0^\infty p(a)G(a)da \qquad (7)$$

where *p(a),A(a)* respectively denote the survival to death and infection functions, and *G(a)* is the age density of infection. If most of the cases of measles occur early in life, as in a pre-vaccination era, then the relation C≈B sharply emerges. This is quite clear if for instance we choose a type 1 mortality schedule (μ(a)=0 up to a maximal age L, so that p(a)=1 up to L and zero thereafter). In this case

$$C = B\int_0^L G(a)da \qquad (8)$$

where $\int_0^L G(a)da$ will be definitively one, so that $C = B$. This shows that the relation between cases and births is fairly general: it holds under a broad spectrum of mixing patterns by age, provided the average age at infection is low.

The case of homogeneous mixing

We now consider the special sub-case of homogeneous mixing by age , i.e. *λ(t)=βY(t)*, under two simplifying assumptions on mortality broadly used in the literature, namely type 1 and type 2 mortality (μ(a)=μ, constant). In the second case:

$$C = \lambda B\int_0^\infty e^{-(\mu+\lambda)a}da = B\frac{\lambda}{\mu+\lambda} \qquad (9)$$

As is known, for type 2 mortality it holds that $A = 1/(\mu + \lambda)$, where A is the average age at infection (or the average age of cases, which for type 2 coincides, at equilibrium, with the average age of the susceptible population).Therefore:

$$C = B\left(\frac{1}{A} - \mu\right)A = B(1 - \mu A) \qquad (10)$$

or:

$$\frac{C}{B} = 1 - \frac{A}{e_0} \qquad (11)$$

where e_0 is the life expectation at birth. The last expression shows that the ratio between the number of cases and births (and hence deaths, as the population is assumed stationary) at equilibrium is a linearly decreasing function of the average age at infection. The following table reports the value of the ratio C/B for an expectation of life of 70 years (μ=1/70), and several values of A.

A	2	3	4	5	6	7	8	9	10
C/B	0,971	0,957	0,943	0,929	0,914	0,900	0,886	0,871	0,857

Table. A1. Ratio between cases and births at equilibrium for several values of the mean age at infection

Under the type 1 mortality schedule we have:

$$X = B\int_0^L e^{-\lambda a} da = \frac{B}{\lambda}\left(1 - e^{-\lambda L}\right)$$

so that

$$C = \lambda X = B\left(1 - e^{-\lambda L}\right) \qquad (12)$$

In this case the relation between age at infection and FOI is slightly more complicated. For typical pre-vaccination regimes of infection the approximate relation: A=1/λ holds (Anderson and May 1991), implying that:

$$\frac{C}{B} \cong 1 - e^{-L/A} \qquad (13)$$

The (14) shows that as long as the approximation: A=1/λ holds, the yearly number of cases at equilibrium is quite close to 100% of the yearly number of births (and deaths). The difference between type 1 and type 2 lies in the fact that in the latter case a substantial number of individuals will die before they experience measles.

Remark. The relation between cases and births here discussed is robust to changes in the basic assumptions of the model. It straightforwardly extends to more general models, such as SEIR models. It moreover remains true if we assume that the population is exponentially increasing, rather than stationary. Hence it is potentially valuable in order to estimate under-reporting in developing countries (a complication in this case may be represented by the fact that many individuals will die before getting infected, but the use of type 2 mortality may provide an excellent approximation).

The previous results provide a clue for the estimation of the under-reporting rate in the pre-vaccination regime provided the infection (and the population) is at equilibrium: in the long term the total number of cases tends to replicate the total number of births (and deaths). This rule appears to be especially useful in that in many actual instances the pre-vaccination patterns of measles seem to be fairly close to an equilibrium situation (though of a cyclical rather than of a stationary nature).

The explicit introduction of the time argument gives further insight on the equilibrium situation. It holds (provided the system is at equilibrium) by assuming type 1 mortality:

$$C(t)=\int_0^\infty C(a,t)da=\int_0^\infty B(t-a)e^{-\lambda a}\lambda da \qquad (14)$$

showing that the number of total cases at time t is a weighted average of past births (the weights being given by the exponential density of infection at equilibrium). The relation (15) offers a further possibility for evaluating cases provided we are sufficiently close to an equilibrium situation (and moreover clarifies why the use of deaths to estimate cases is potentially more complicated than that of births).

ab. 2. Italian regions. Number of cases of measles for 1000 live births

	1949-86	1949-76	1977-86	1949-57	1958-66	1967-76
BRUZZO	76,4	80,1	61,0	72,2	91,7	77,3
ASILICATA	47,9	48,5	45,3	53,4	50,1	40,3
ALABRIA	30,2	33,7	15,6	36,3	35,4	28,5
AMPANIA	20,2	22,6	11,6	33,2	23,0	12,9
apoli	14,0	16,0	7,1	24,8	17,3	8,2
xc-Napoli	27,7	30,4	17,5	41,8	29,6	19,5
MILIA ROMAGNA	211,4	209,3	221,3	224,8	201,3	203,0
RIULI VENEZIA G.	178,9	168,0	229,0	172,0	189,8	143,5
AZIO	72,8	77,2	56,4	104,3	76,4	58,5
oma	78,0	82,4	61,9	128,9	75,6	60,9
xc-Roma	60,7	65,2	43,6	65,9	78,3	51,5
IGURIA	134,4	134,4	134,5	189,5	114,3	114,0
OMBARDIA	89,8	86,3	103,2	105,2	90,0	70,1
ilano	70,1	63,5	94,5	86,4	64,4	51,4
xc-Milano	103,5	102,0	109,8	114,5	108,4	85,5
ARCHE	116,3	113,6	127,9	125,4	102,4	112,3
OLISE	81,8	83,0	76,4	60,8	122,7	69,0
IEMONTE	90,4	89,7	93,0	129,5	85,3	69,5
orino	67,6	63,5	81,5	106,0	61,1	47,6
xc-Torino	114,9	116,9	107,0	145,1	110,3	99,2
UGLIA	29,4	28,3	33,7	27,9	32,6	24,4
ARDEGNA	53,9	57,3	39,9	75,5	57,4	39,0
ICILIA	25,1	28,3	13,1	30,9	33,1	20,7
OSCANA	122,7	116,8	147,1	86,0	129,4	130,9
RENTINO A.A.	75,5	70,9	94,6	82,3	71,2	60,4
MBRIA	124,0	129,7	99,4	155,0	125,2	106,6
ALLE D'AOSTA	84,7	94,2	45,8	160,6	72,6	59,6
ENETO	74,7	72,3	86,0	72,6	83,7	60,6

ig. 1.

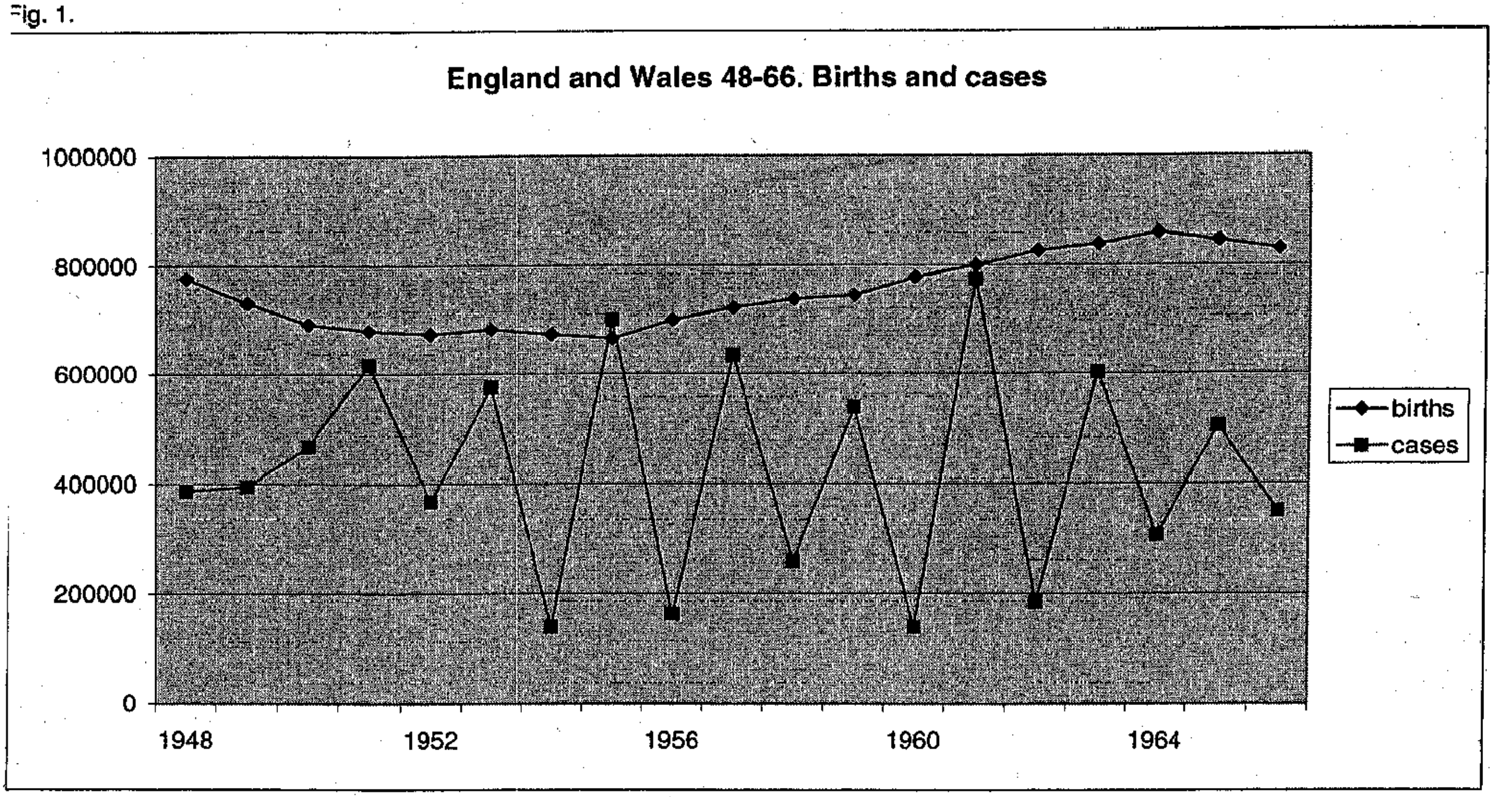


Table 3. England and Wales 48-66: yearly births and measles cases

	births	cases	Nr. Cases/1000 live births
1948	776971	387516	499
1949	731172	395400	541
1950	691760	467798	676
1951	679689	616568	907
1952	673286	367575	546
1953	681964	575346	844
1954	672635	139968	208
1955	664954	699242	1052
1956	699059	163330	234
1957	721481	633346	878
1958	737607	259241	351
1959	744440	539432	725
1960	778100	138787	178
1961	800198	773959	967
1962	826694	184705	223
1963	839002	602200	718
1964	859772	306755	357
1965	845031	504072	597
1966	830043	349456	421
total	14253858,23	8104696	569

Table 4. Italian regions 52-83. Yearly estimates of under-reporting coefficients.

	ABRUZZO	BASILICATA	CALABRIA	CAMPANIA	Napoli	Exc-Napoli	EMILIA R.	FRIULI V.G.	LAZIO	Roma	Exc-Roma	LIGURIA	LOMBARDIA	Milano	Exc-Milano	MARCHE	MOLISE	PIEMONTE	Torino	Exc-Torino	PUGLIA	SARDEGNA	SICILIA	TOSCANA	TRENTINO A.A.	UMBRIA	VALLE D'AOSTA	VENETO
1952	0,071	0,053	0,033	0,032	0,022	0,041	0,190	0,129	0,091	0,113	0,059	0,167	0,100	0,082	0,109	0,098	0,060	0,115	0,106	0,122	0,030	0,078	0,028	0,048	0,086	0,121	0,150	0,069
1953	0,065	0,048	0,032	0,029	0,021	0,037	0,207	0,153	0,094	0,119	0,057	0,193	0,107	0,087	0,117	0,093	0,063	0,129	0,100	0,148	0,028	0,063	0,026	0,064	0,089	0,123	0,148	0,071
1954	0,075	0,051	0,035	0,031	0,023	0,039	0,250	0,191	0,104	0,131	0,062	0,211	0,118	0,093	0,131	0,125	0,072	0,146	0,112	0,170	0,029	0,061	0,030	0,095	0,096	0,155	0,185	0,078
1955	0,082	0,056	0,037	0,030	0,022	0,039	0,250	0,195	0,107	0,131	0,067	0,192	0,110	0,084	0,123	0,144	0,080	0,136	0,104	0,160	0,029	0,074	0,033	0,120	0,082	0,173	0,166	0,079
1956	0,082	0,054	0,037	0,028	0,021	0,036	0,227	0,188	0,103	0,123	0,068	0,168	0,107	0,083	0,121	0,124	0,085	0,124	0,089	0,152	0,028	0,074	0,032	0,133	0,066	0,158	0,122	0,080
1957	0,087	0,051	0,037	0,028	0,022	0,035	0,226	0,198	0,102	0,121	0,068	0,163	0,111	0,082	0,127	0,121	0,091	0,127	0,088	0,160	0,027	0,062	0,033	0,144	0,065	0,164	0,124	0,085
1958	0,093	0,049	0,039	0,028	0,022	0,035	0,226	0,207	0,104	0,119	0,075	0,151	0,105	0,075	0,122	0,131	0,091	0,126	0,088	0,159	0,028	0,062	0,033	0,149	0,063	0,176	0,134	0,082
1959	0,097	0,052	0,044	0,028	0,021	0,035	0,225	0,201	0,090	0,095	0,078	0,133	0,100	0,071	0,118	0,135	0,095	0,118	0,087	0,145	0,030	0,073	0,034	0,156	0,060	0,173	0,143	0,083
1960	0,096	0,048	0,041	0,026	0,019	0,034	0,211	0,196	0,078	0,079	0,077	0,120	0,095	0,067	0,113	0,120	0,114	0,101	0,076	0,124	0,029	0,067	0,035	0,151	0,065	0,151	0,112	0,089
1961	0,100	0,049	0,039	0,027	0,020	0,034	0,208	0,206	0,075	0,075	0,075	0,121	0,096	0,068	0,116	0,114	0,123	0,094	0,067	0,121	0,031	0,050	0,035	0,140	0,072	0,134	0,095	0,086
1962	0,097	0,053	0,041	0,027	0,020	0,035	0,210	0,198	0,073	0,072	0,075	0,126	0,091	0,063	0,110	0,120	0,117	0,092	0,065	0,121	0,034	0,052	0,033	0,133	0,072	0,137	0,099	0,079
1963	0,084	0,052	0,040	0,023	0,016	0,032	0,209	0,197	0,070	0,067	0,079	0,129	0,085	0,061	0,102	0,115	0,120	0,084	0,057	0,113	0,035	0,061	0,032	0,130	0,074	0,132	0,081	0,077
1964	0,089	0,053	0,035	0,022	0,016	0,029	0,223	0,193	0,069	0,066	0,078	0,133	0,084	0,061	0,102	0,116	0,132	0,079	0,052	0,110	0,033	0,053	0,034	0,137	0,076	0,133	0,065	0,078
1965	0,098	0,054	0,033	0,021	0,016	0,028	0,216	0,177	0,076	0,077	0,073	0,129	0,085	0,060	0,105	0,121	0,144	0,078	0,050	0,111	0,033	0,044	0,034	0,131	0,076	0,138	0,066	0,075
1966	0,094	0,058	0,032	0,020	0,015	0,026	0,204	0,177	0,077	0,079	0,069	0,121	0,085	0,058	0,106	0,115	0,127	0,080	0,051	0,114	0,035	0,048	0,031	0,121	0,073	0,134	0,067	0,071
1967	0,083	0,051	0,030	0,018	0,013	0,023	0,208	0,168	0,076	0,079	0,067	0,115	0,080	0,056	0,099	0,110	0,099	0,075	0,050	0,106	0,034	0,054	0,030	0,124	0,072	0,140	0,058	0,071
1968	0,084	0,045	0,030	0,017	0,012	0,023	0,214	0,172	0,080	0,083	0,070	0,112	0,080	0,057	0,099	0,115	0,095	0,073	0,048	0,105	0,030	0,048	0,028	0,128	0,073	0,152	0,063	0,073
1969	0,088	0,048	0,032	0,016	0,011	0,024	0,213	0,170	0,072	0,076	0,061	0,115	0,077	0,056	0,096	0,116	0,090	0,075	0,049	0,110	0,028	0,041	0,025	0,126	0,071	0,145	0,075	0,071
1970	0,075	0,047	0,031	0,014	0,009	0,021	0,207	0,162	0,067	0,070	0,058	0,119	0,074	0,055	0,090	0,113	0,078	0,072	0,048	0,103	0,028	0,045	0,022	0,126	0,070	0,123	0,067	0,065
1971	0,064	0,041	0,027	0,012	0,008	0,019	0,200	0,166	0,062	0,063	0,060	0,108	0,069	0,053	0,083	0,112	0,060	0,065	0,046	0,092	0,026	0,045	0,021	0,128	0,072	0,114	0,055	0,062
1972	0,062	0,036	0,026	0,012	0,007	0,018	0,190	0,150	0,054	0,054	0,055	0,095	0,063	0,050	0,075	0,103	0,053	0,060	0,043	0,083	0,021	0,042	0,019	0,125	0,066	0,100	0,049	0,060
1973	0,067	0,037	0,027	0,011	0,006	0,017	0,197	0,136	0,050	0,049	0,051	0,104	0,066	0,051	0,078	0,099	0,056	0,063	0,045	0,087	0,021	0,038	0,018	0,124	0,058	0,079	0,050	0,060
1974	0,066	0,033	0,024	0,009	0,006	0,015	0,208	0,130	0,046	0,045	0,047	0,128	0,066	0,050	0,079	0,104	0,052	0,064	0,046	0,088	0,020	0,035	0,018	0,125	0,060	0,068	0,039	0,054
1975	0,060	0,031	0,020	0,010	0,006	0,016	0,215	0,139	0,047	0,048	0,046	0,136	0,071	0,053	0,086	0,105	0,051	0,061	0,047	0,081	0,021	0,031	0,017	0,132	0,077	0,075	0,027	0,056
1976	0,056	0,033	0,020	0,011	0,006	0,018	0,210	0,145	0,048	0,051	0,042	0,126	0,073	0,054	0,088	0,094	0,055	0,059	0,046	0,077	0,021	0,027	0,015	0,133	0,085	0,083	0,028	0,062
1977	0,058	0,036	0,020	0,011	0,006	0,018	0,210	0,131	0,046	0,050	0,038	0,130	0,072	0,056	0,085	0,090	0,064	0,060	0,046	0,079	0,022	0,026	0,014	0,130	0,080	0,074	0,025	0,059
1978	0,072	0,041	0,017	0,011	0,007	0,017	0,242	0,126	0,048	0,051	0,040	0,152	0,085	0,074	0,094	0,124	0,073	0,071	0,054	0,092	0,027	0,026	0,013	0,142	0,087	0,070	0,027	0,057
1979	0,072	0,040	0,014	0,011	0,007	0,018	0,253	0,132	0,049	0,051	0,043	0,150	0,092	0,087	0,095	0,140	0,073	0,071	0,056	0,090	0,028	0,026	0,013	0,142	0,099	0,070	0,027	0,058
1980	0,063	0,038	0,015	0,011	0,006	0,018	0,224	0,182	0,046	0,048	0,042	0,122	0,086	0,086	0,085	0,126	0,066	0,066	0,053	0,081	0,028	0,028	0,011	0,136	0,099	0,079	0,021	0,069
1981	0,063	0,037	0,017	0,010	0,006	0,016	0,204	0,226	0,056	0,061	0,044	0,108	0,084	0,087	0,082	0,133	0,066	0,075	0,061	0,093	0,032	0,039	0,011	0,128	0,081	0,080	0,031	0,082
1982	0,073	0,042	0,018	0,011	0,007	0,016	0,217	0,250	0,066	0,073	0,050	0,121	0,100	0,101	0,099	0,151	0,081	0,105	0,090	0,123	0,039	0,052	0,014	0,142	0,071	0,087	0,057	0,095
1983	0,076	0,051	0,017	0,011	0,007	0,017	0,233	0,289	0,065	0,071	0,053	0,129	0,121	0,117	0,124	0,160	0,086	0,123	0,113	0,135	0,041	0,054	0,015	0,165	0,080	0,108	0,072	0,107
Mean	0,083	0,049	0,034	0,022	0,016	0,029	0,214	0,176	0,079	0,086	0,067	0,137	0,089	0,066	0,105	0,116	0,091	0,095	0,068	0,122	0,029	0,055	0,029	0,124	0,072	0,136	0,096	0,074

Fig 2a

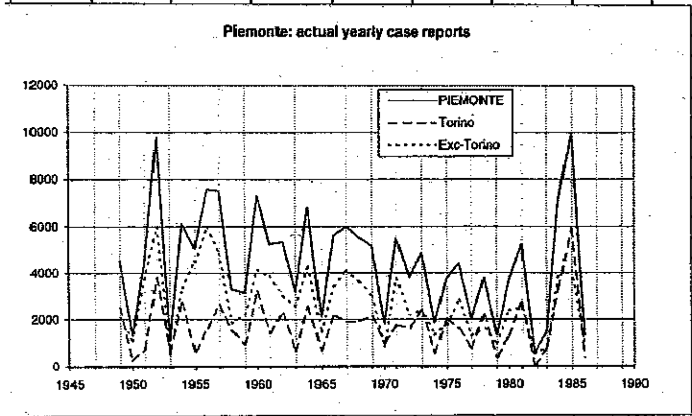


Fig 2h

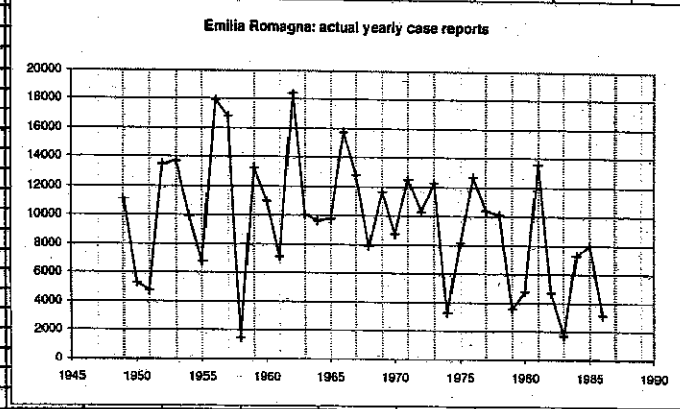


Fig 1o

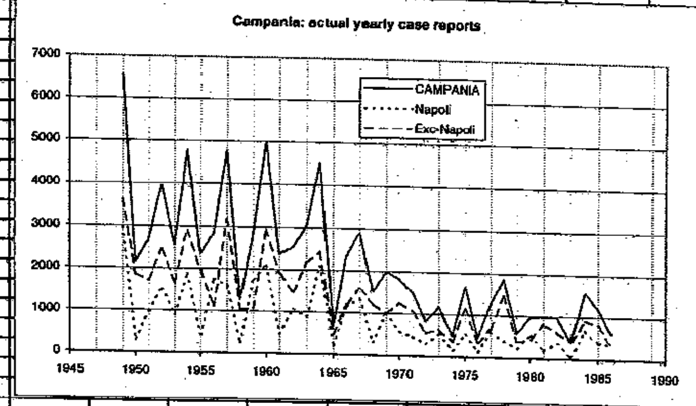


Fig 2b

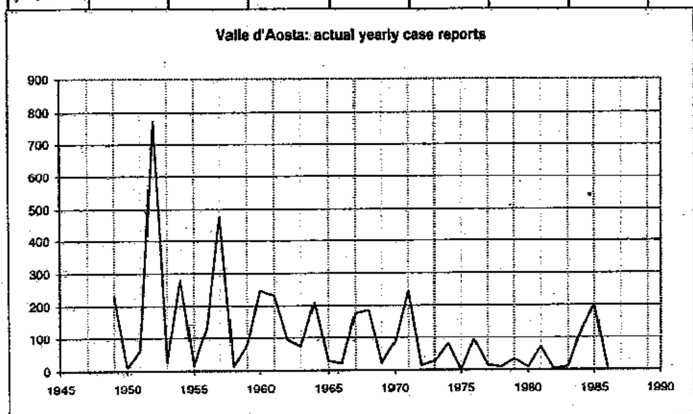


Fig 2i

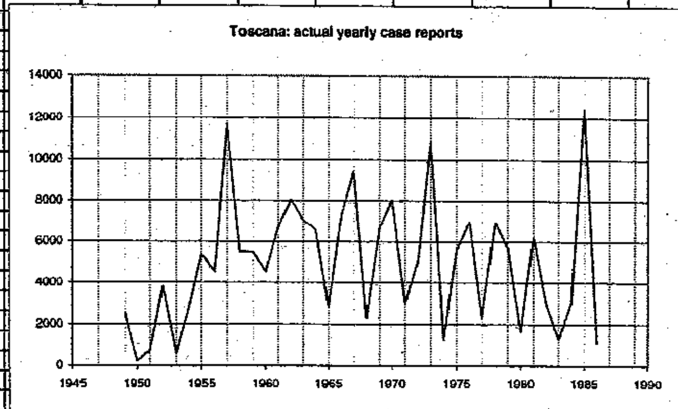


Fig 1p

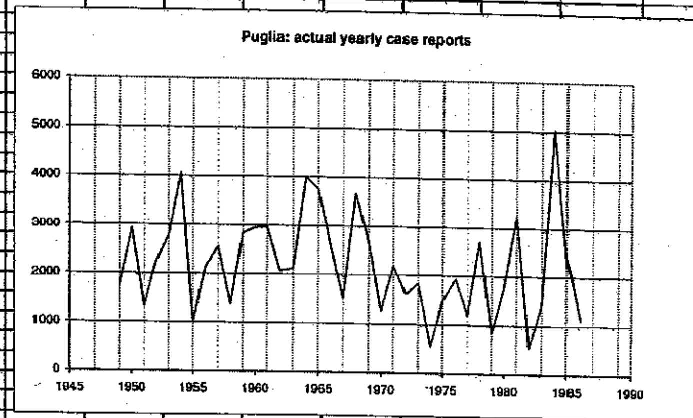


Fig 2c

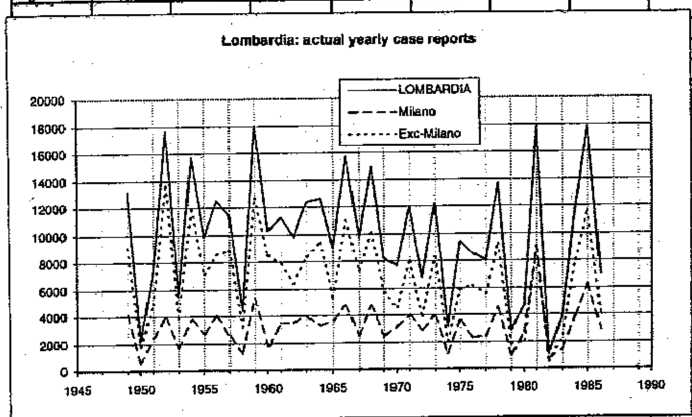


Fig 2j

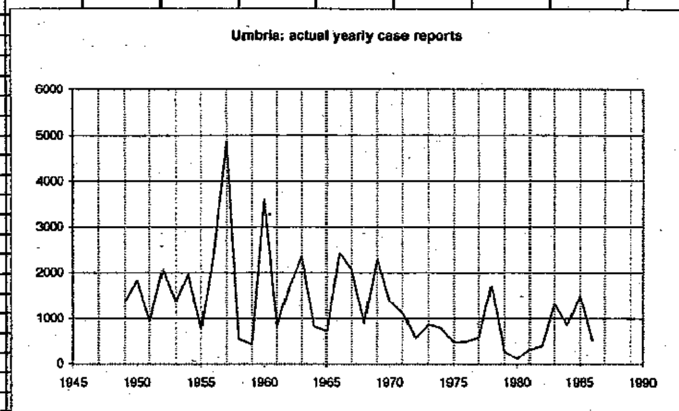


Fig 1q

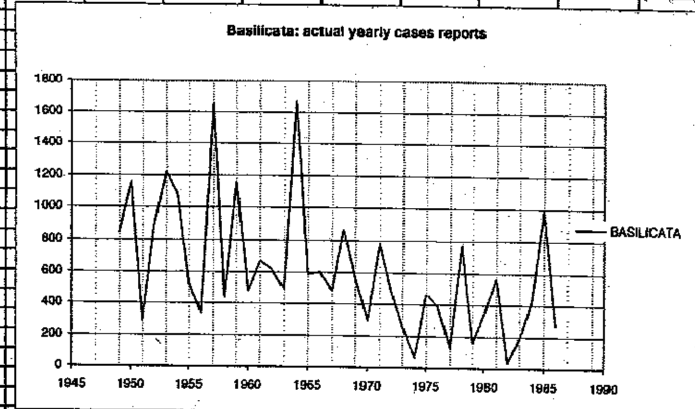


Fig 2d

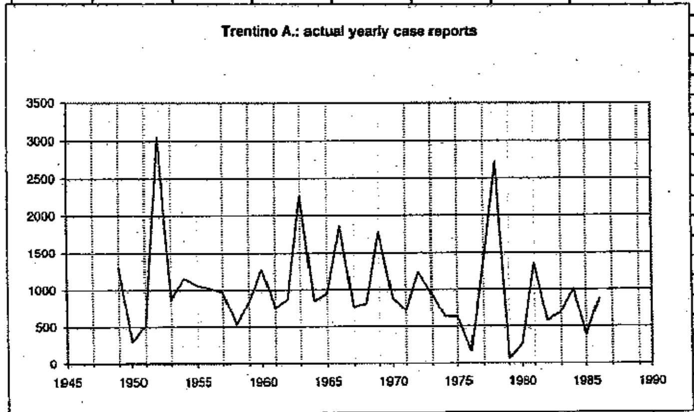


Fig 2k

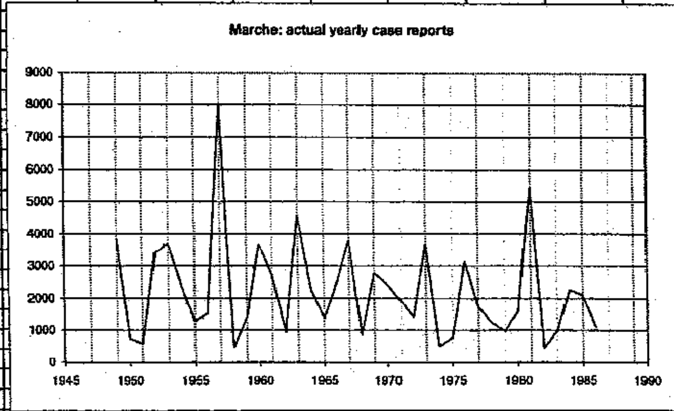


Fig 1r

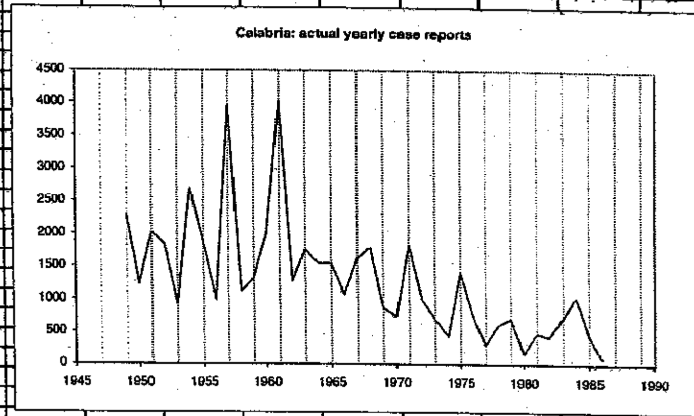


Fig 2e

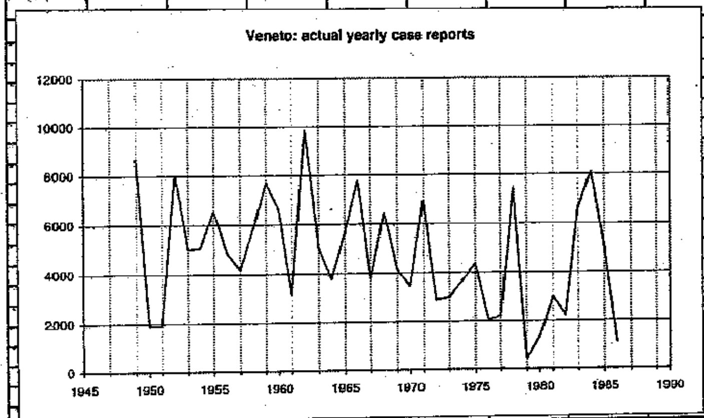


Fig 2l

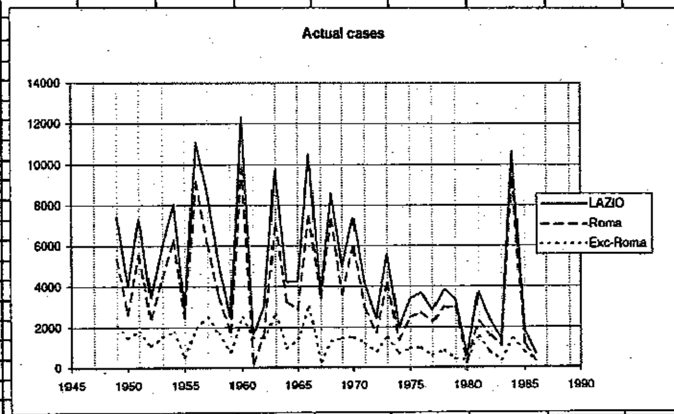


Fig 1s

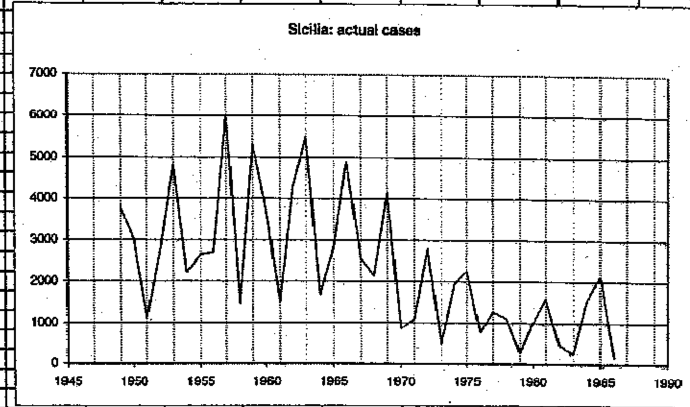


Fig 2f

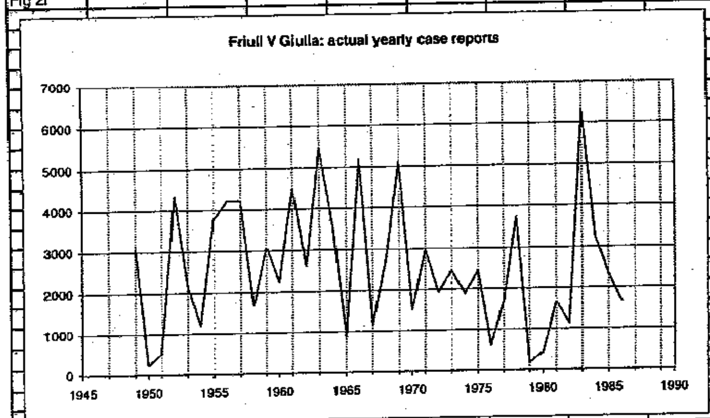


Fig 2m

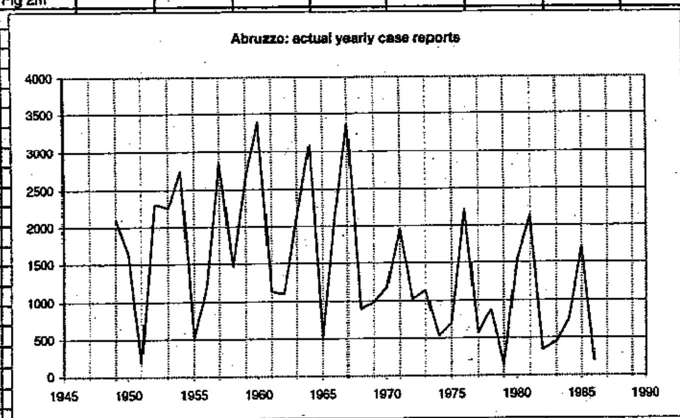


Fig 1t

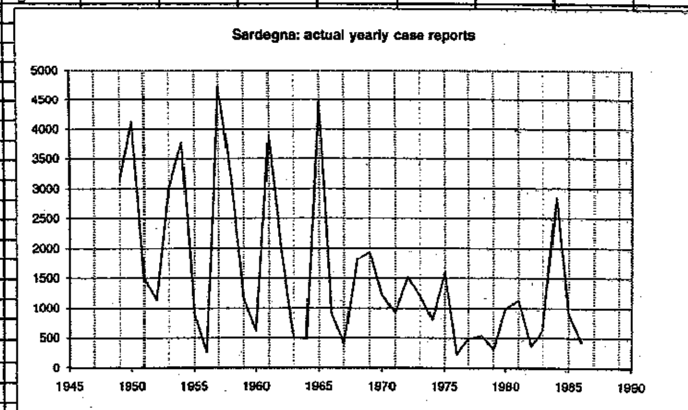
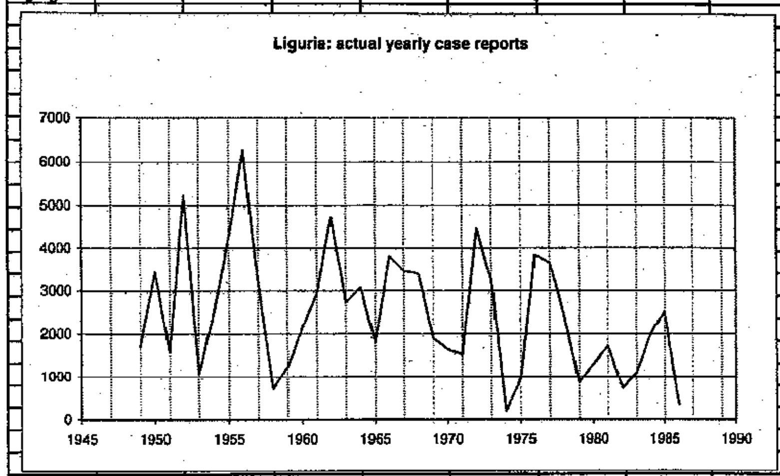
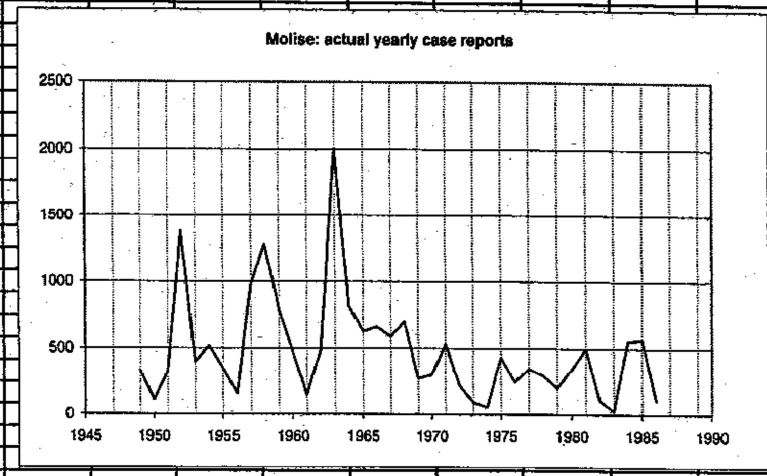


Fig 2g



Liguria: actual yearly case reports
7000
6000
5000
4000
3000
2000
1000
0
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990

Fig 2n



Molise: actual yearly case reports
2500
2000
1500
1000
500
0
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990

Fig 3a

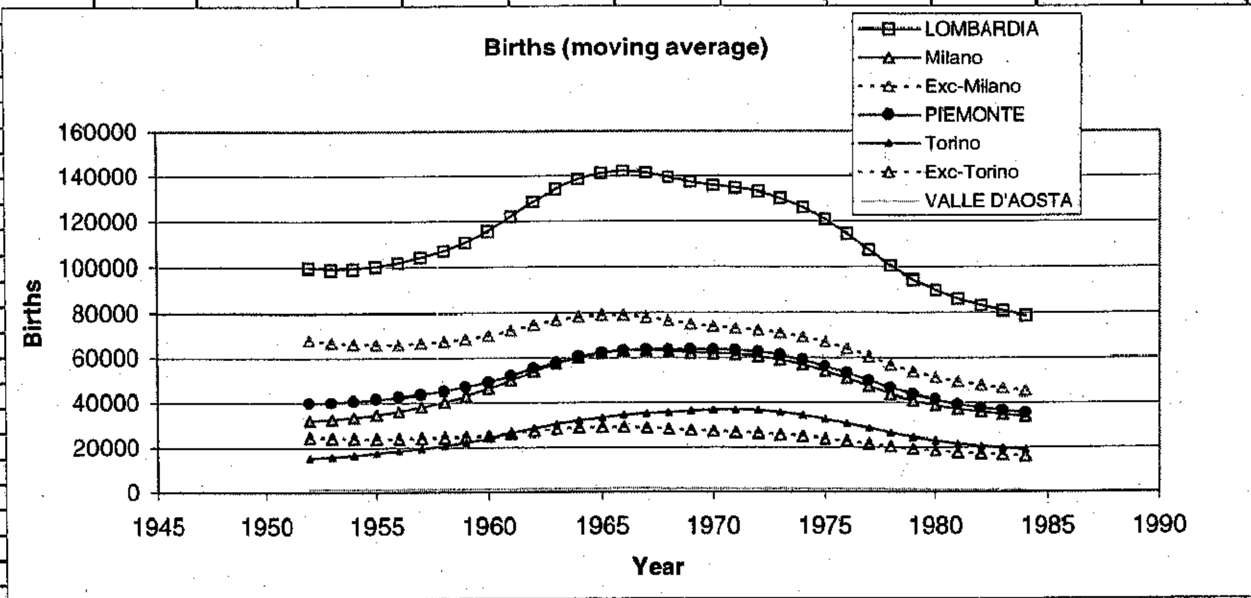


Fig 3b

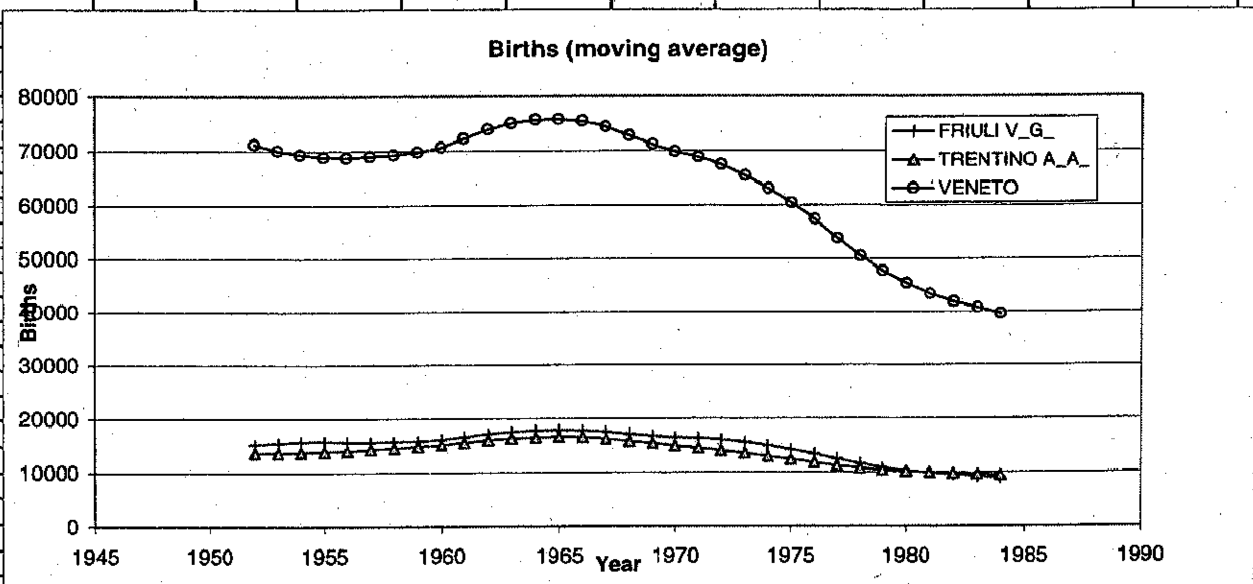


Fig 3c

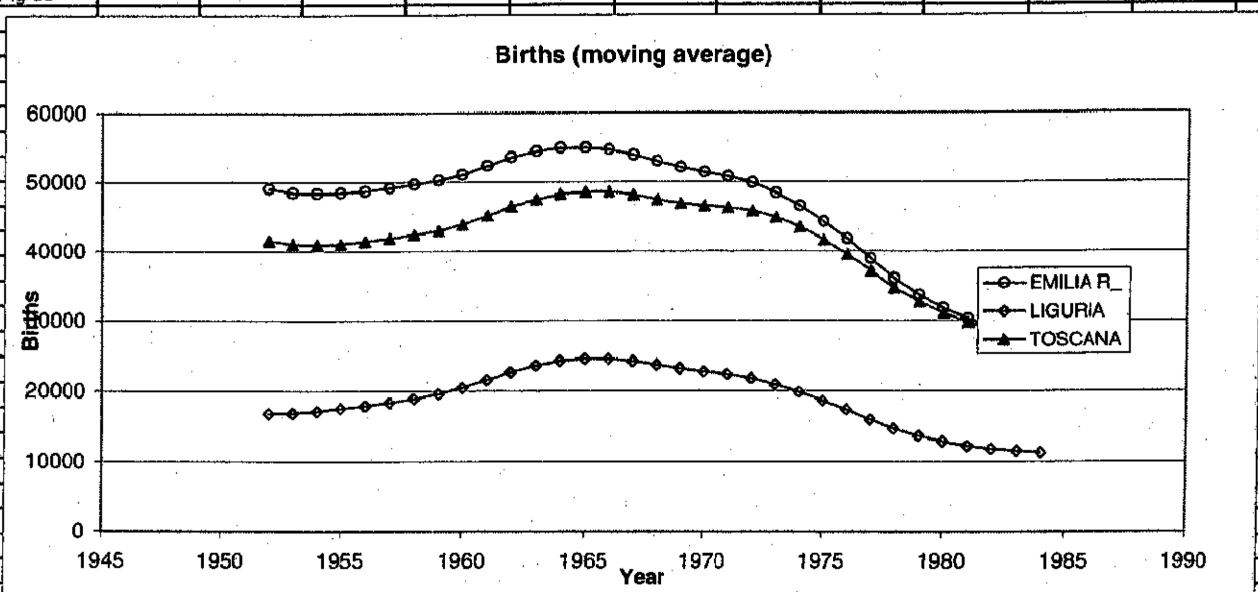


Fig 3d

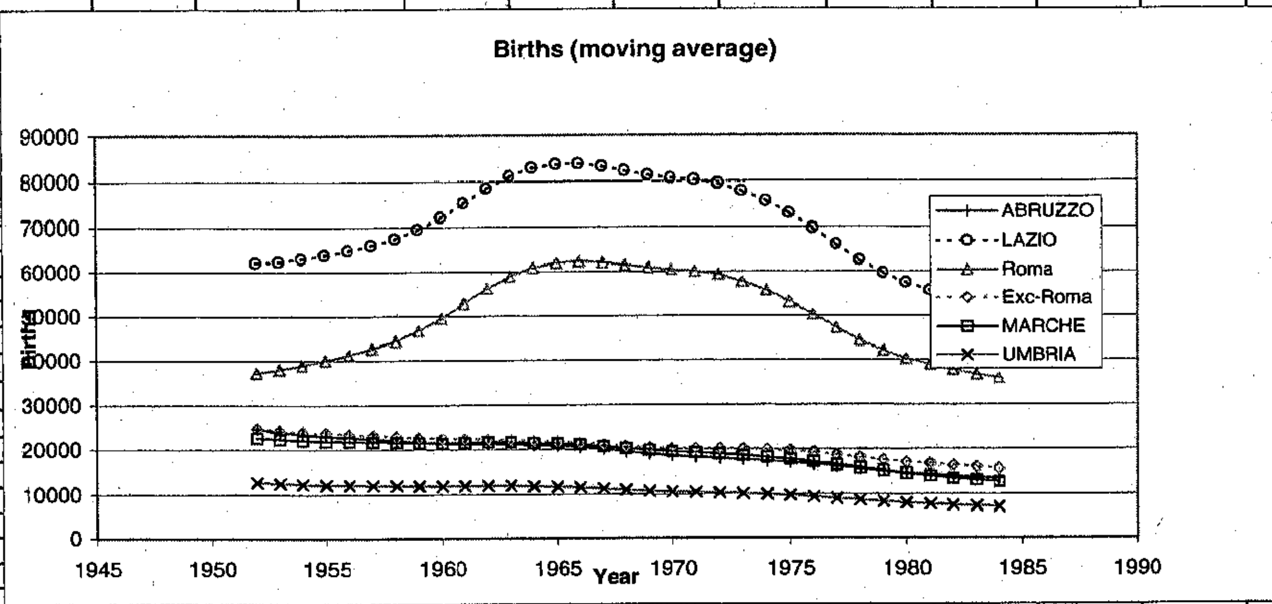


Fig 3e

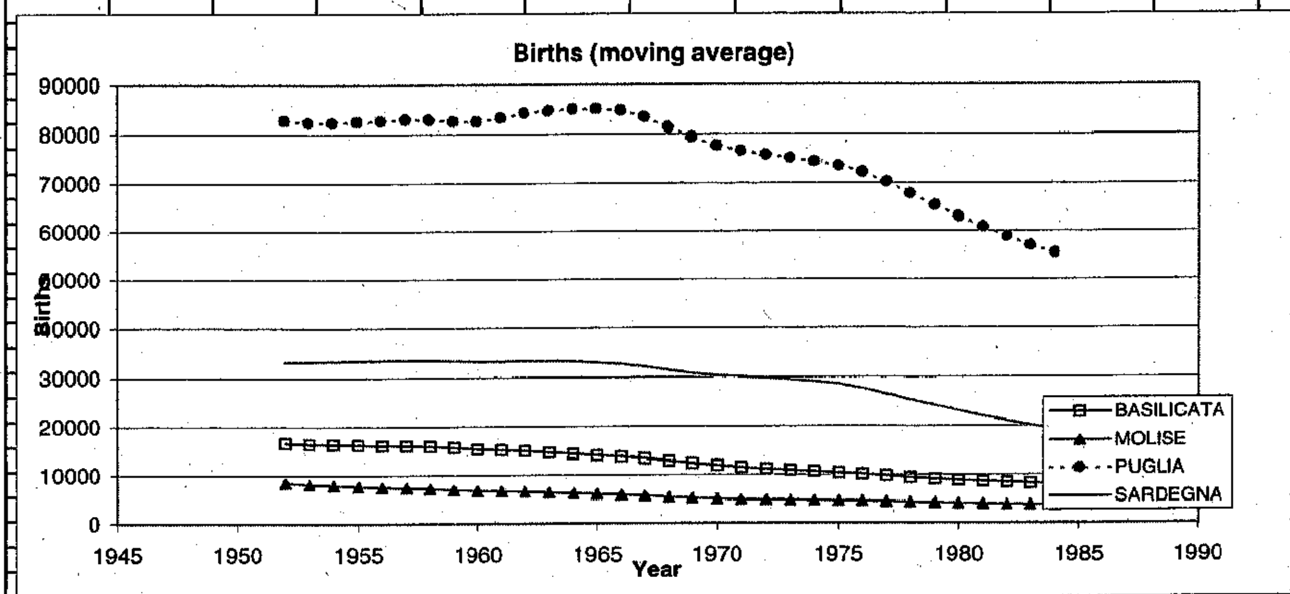


Fig 3f

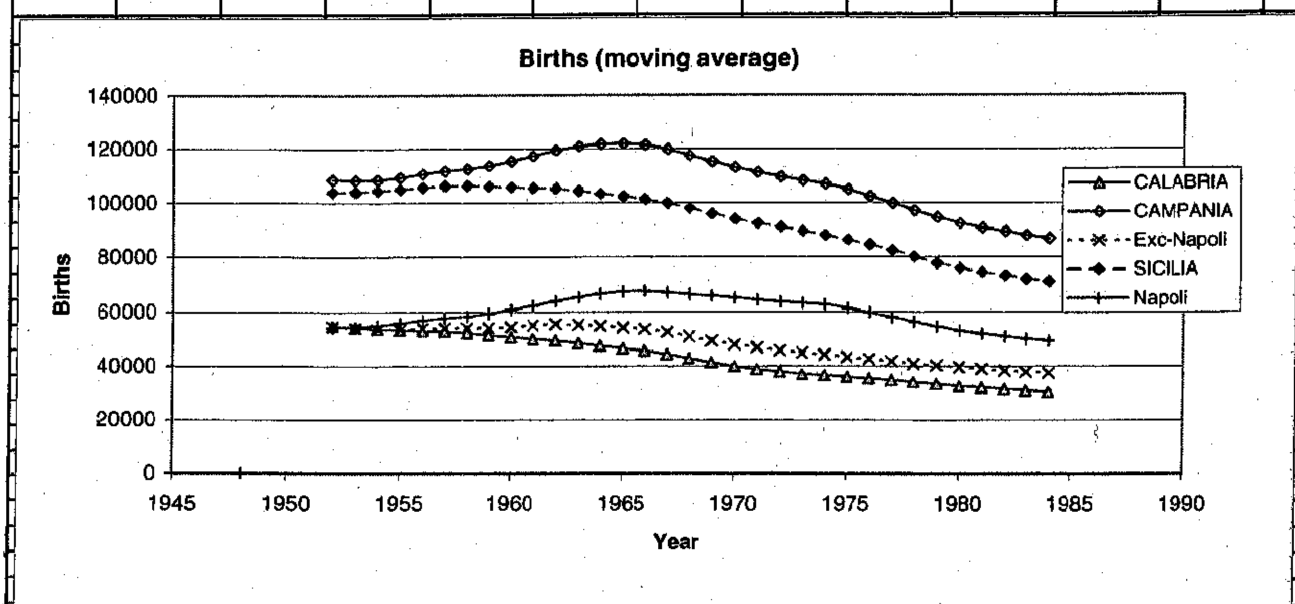


Fig 4a

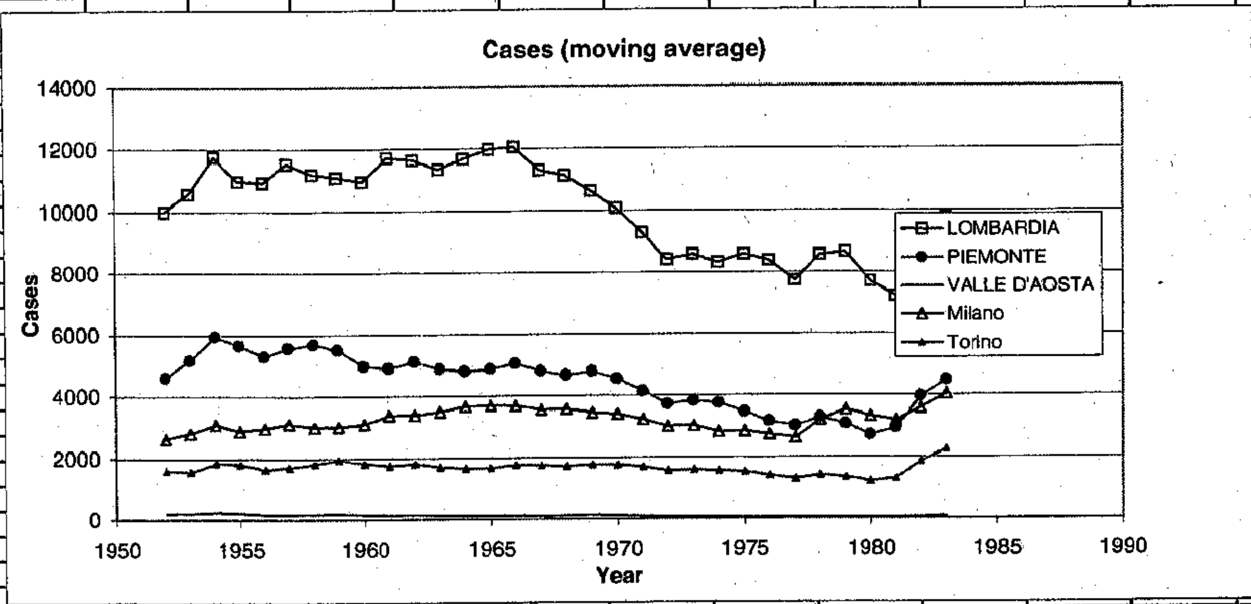


Fig 4b

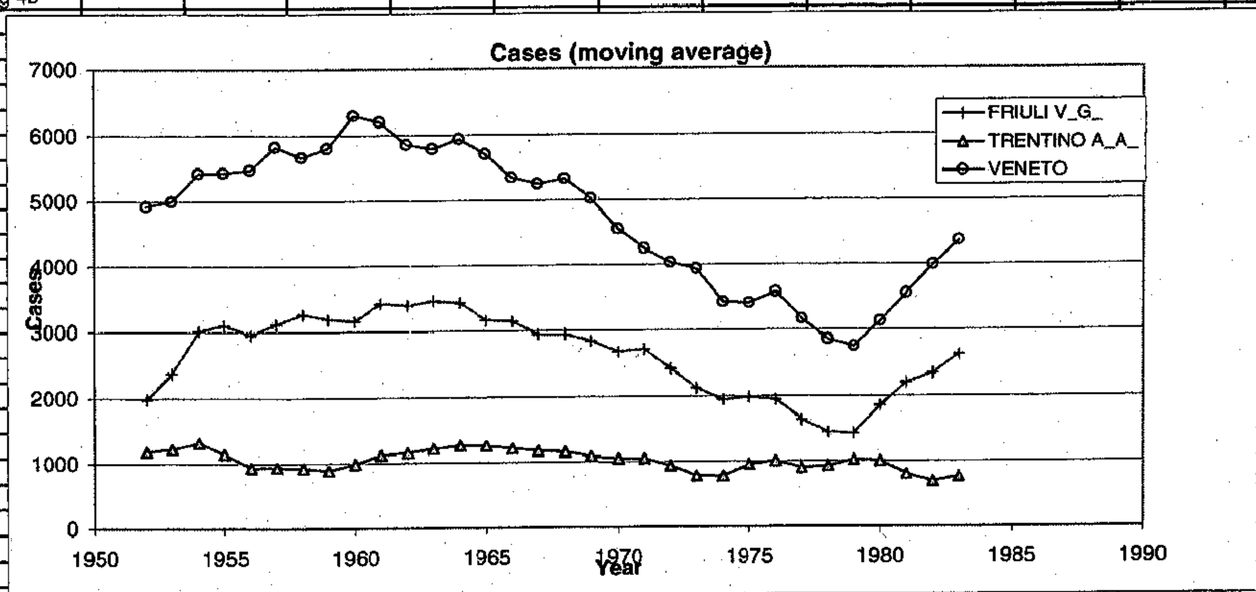


Fig 4c

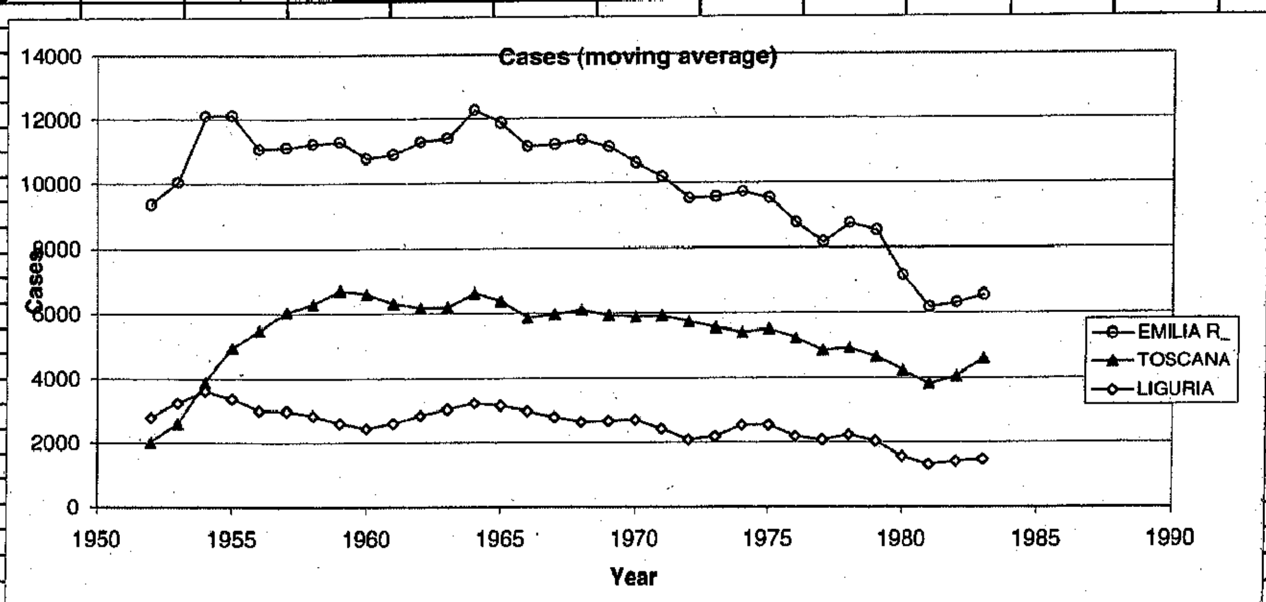


Fig 4d

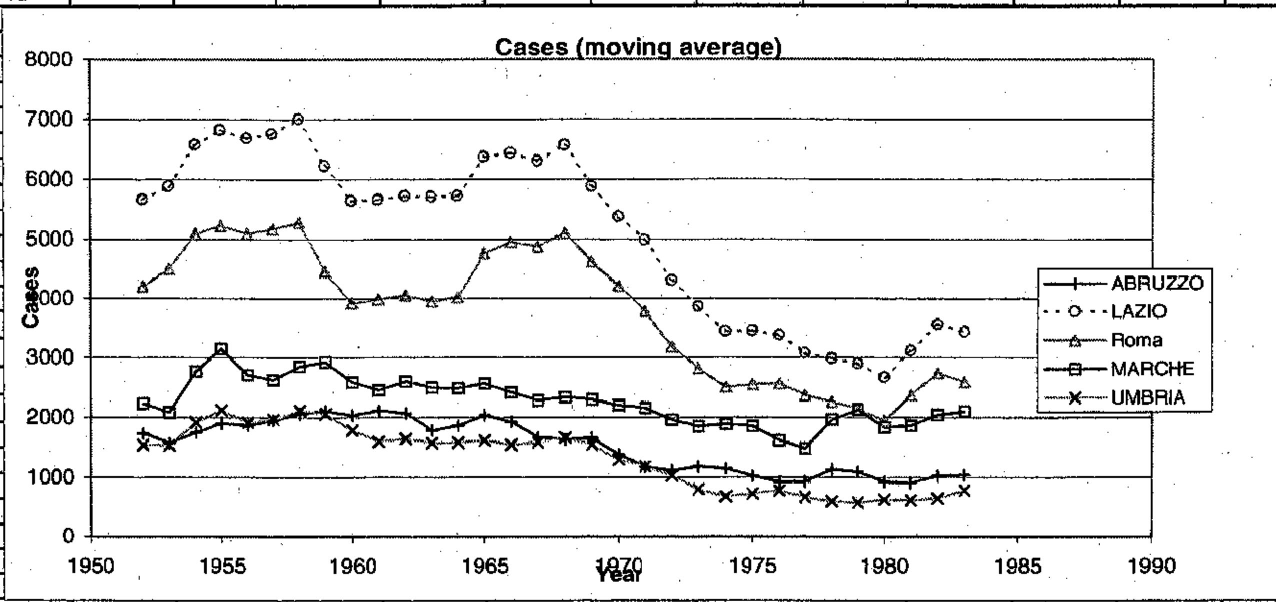


Fig 4e

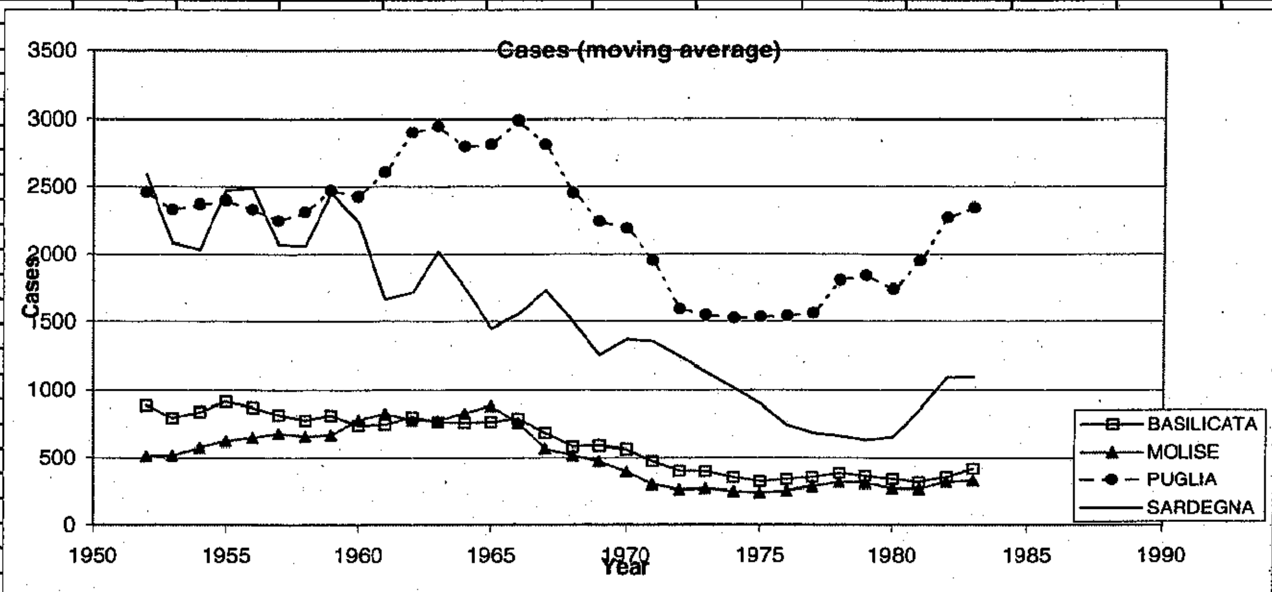


Fig 4f

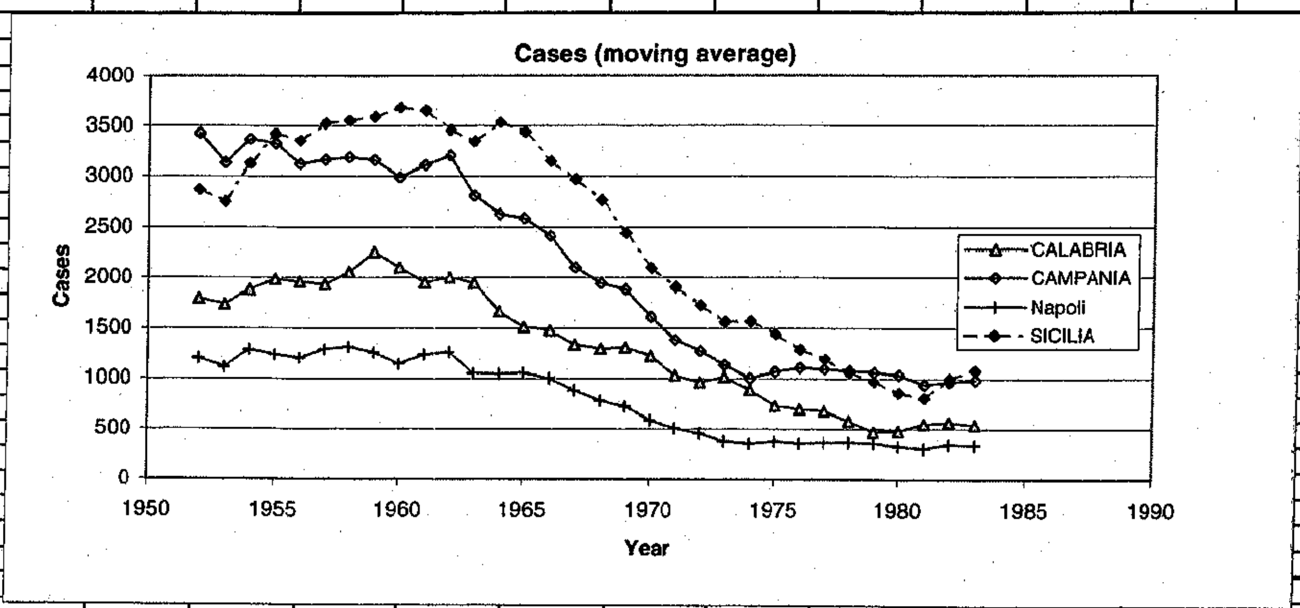


Fig 5a

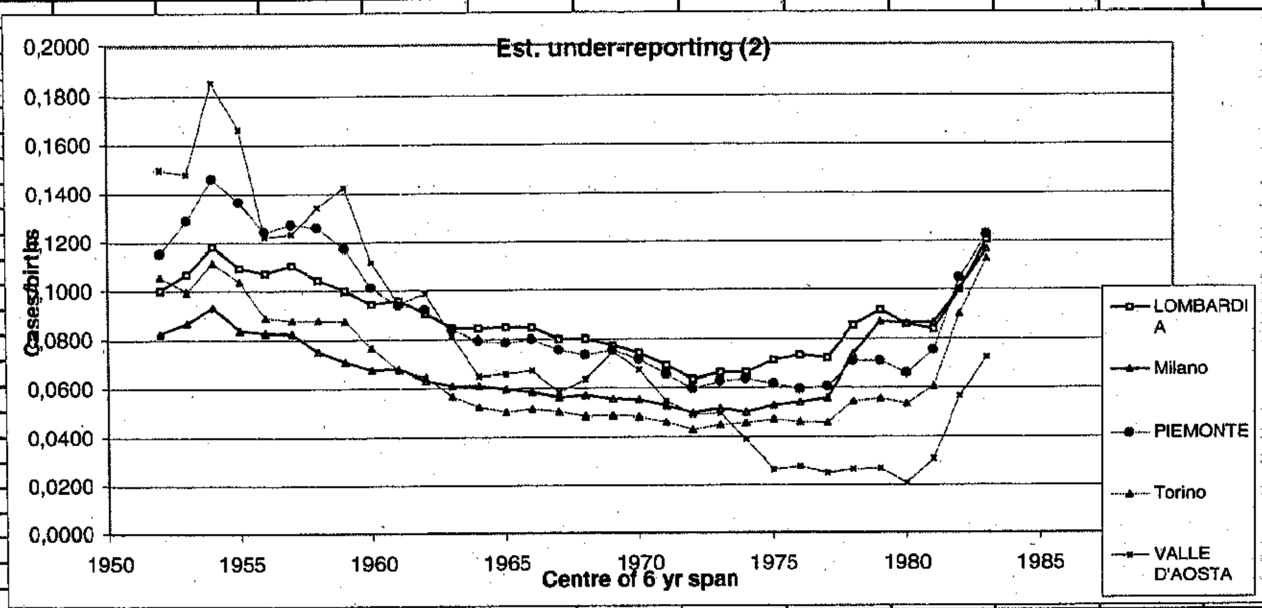


Fig 5b

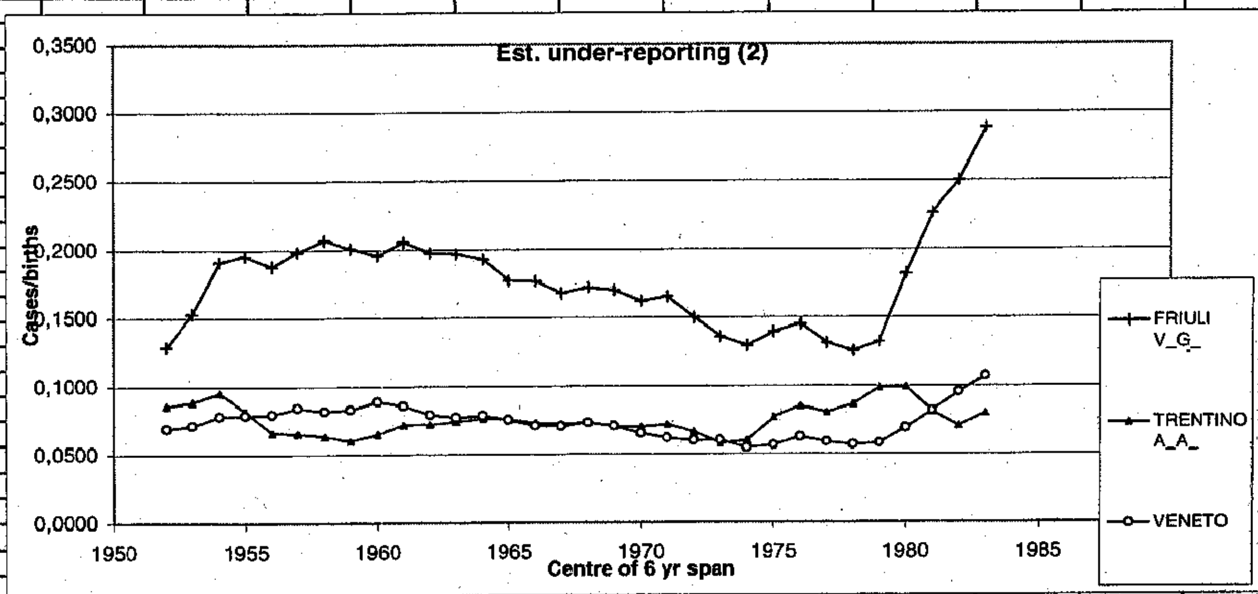


Fig 5c

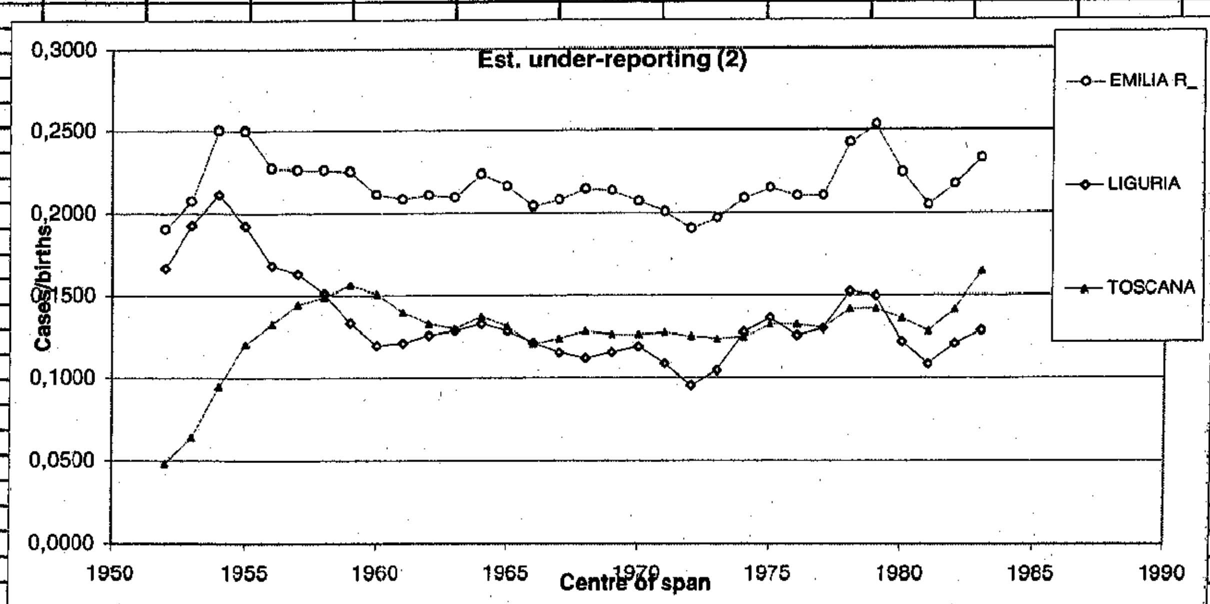


Fig 5d

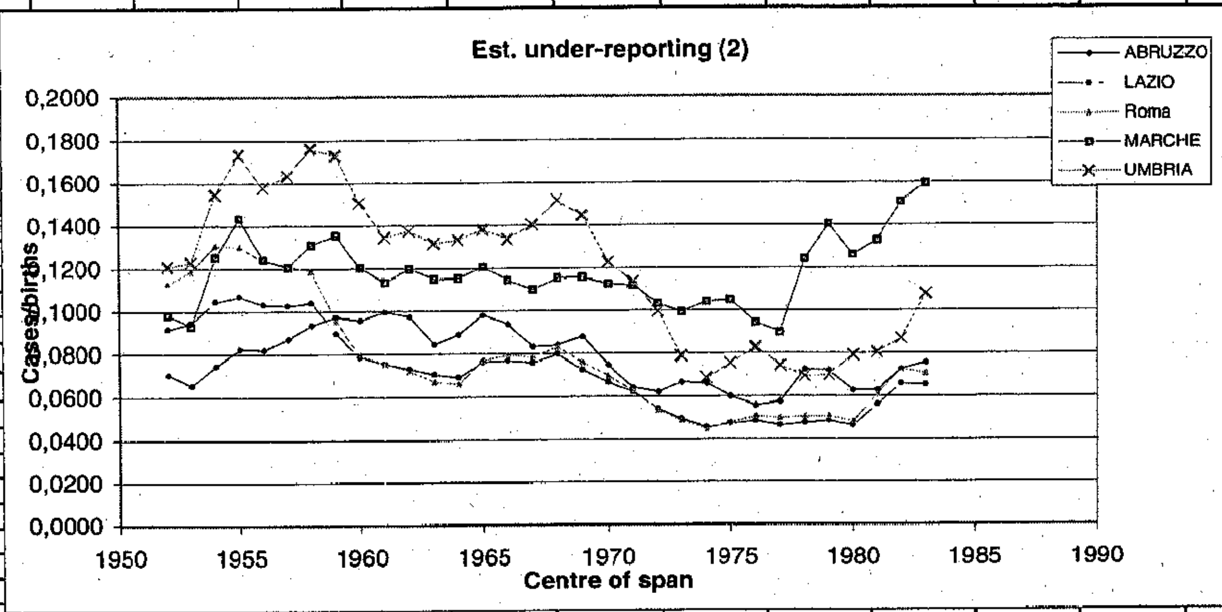


Fig 5e

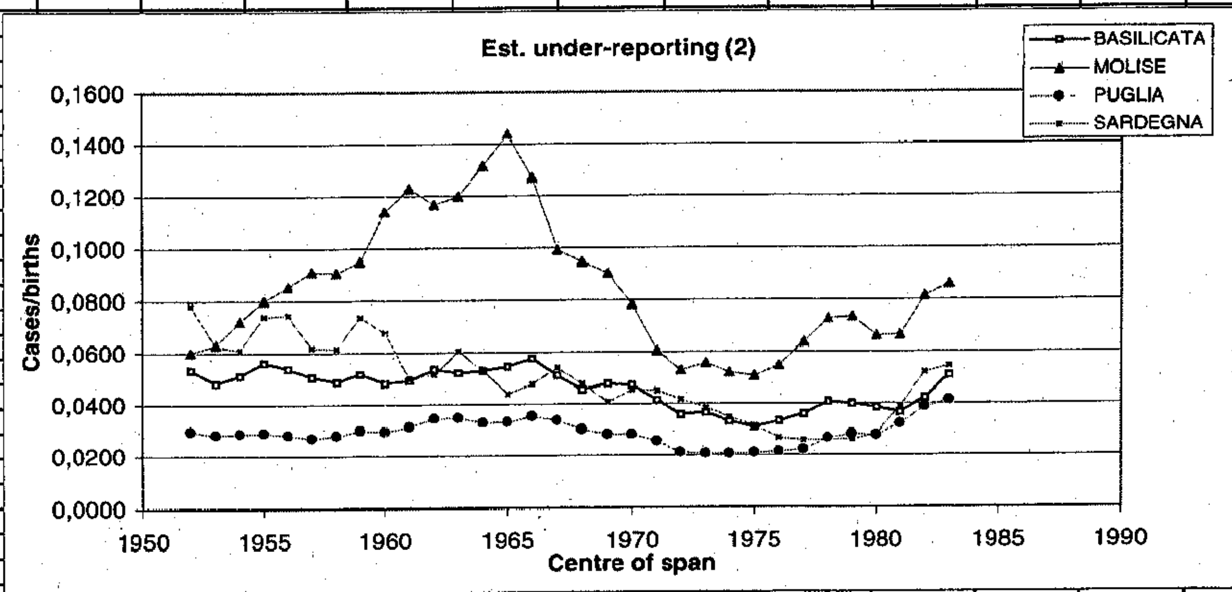


Fig 5f

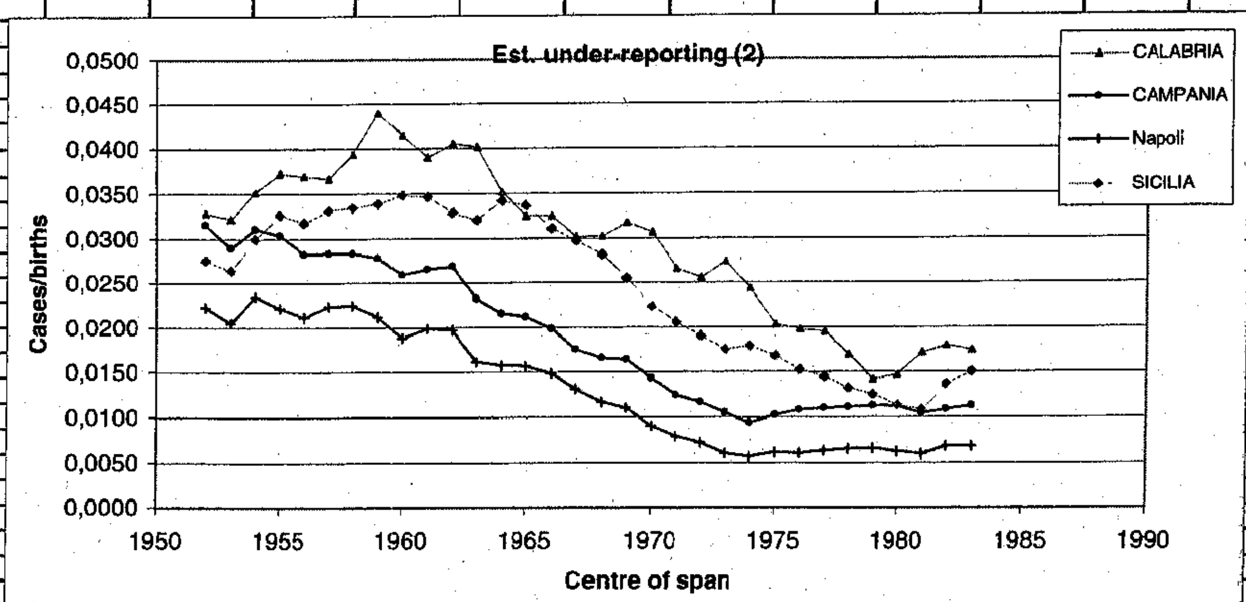


Fig 5g

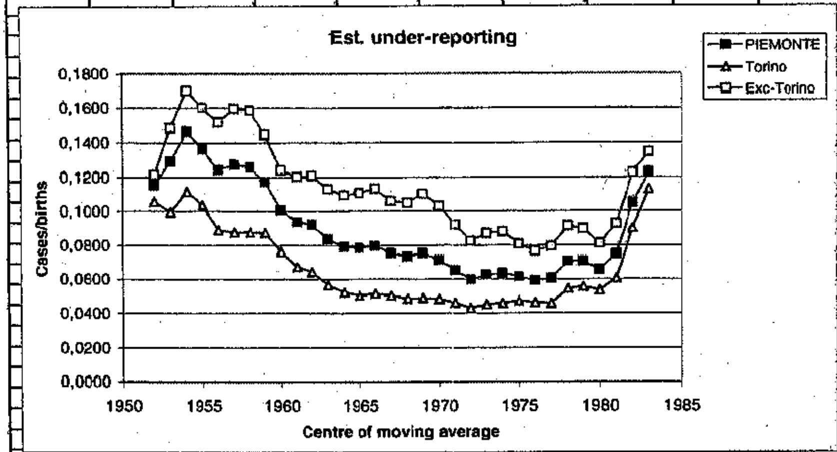


Fig 5h

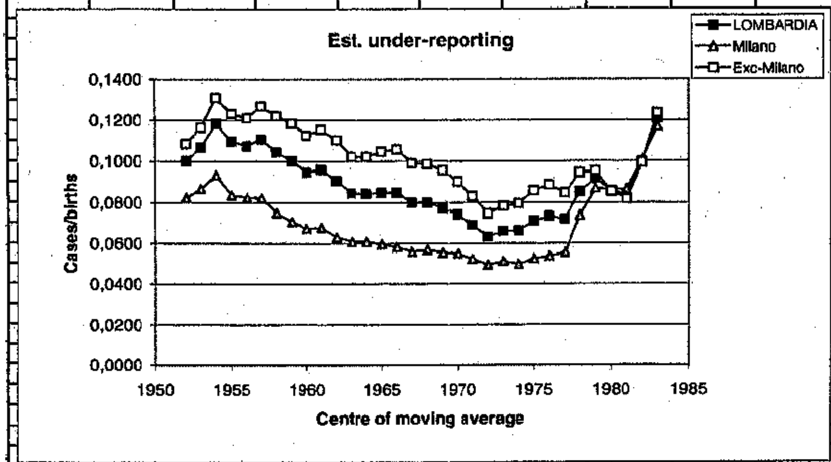


Fig 5i

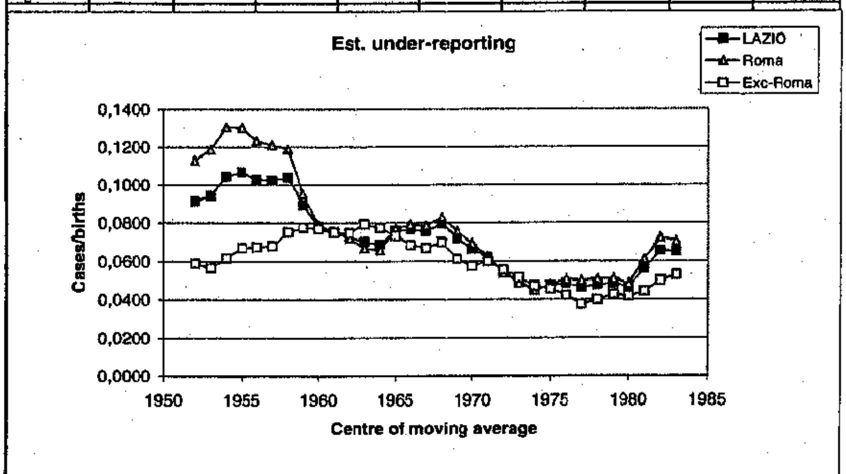


Fig 5j

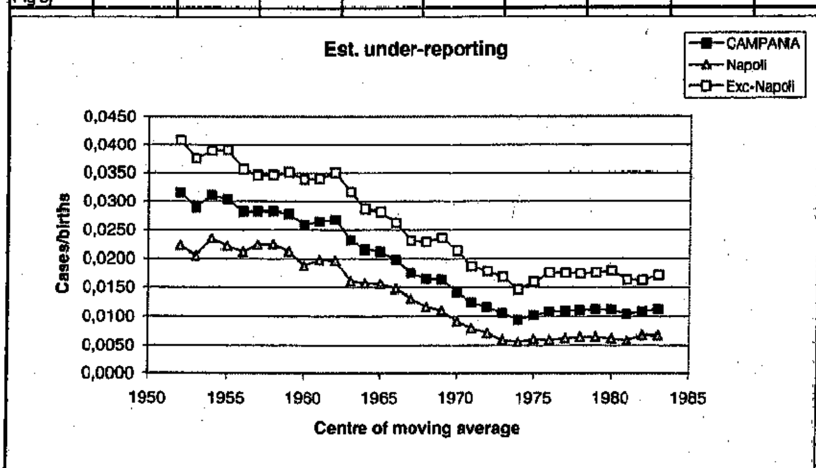


Fig 5k

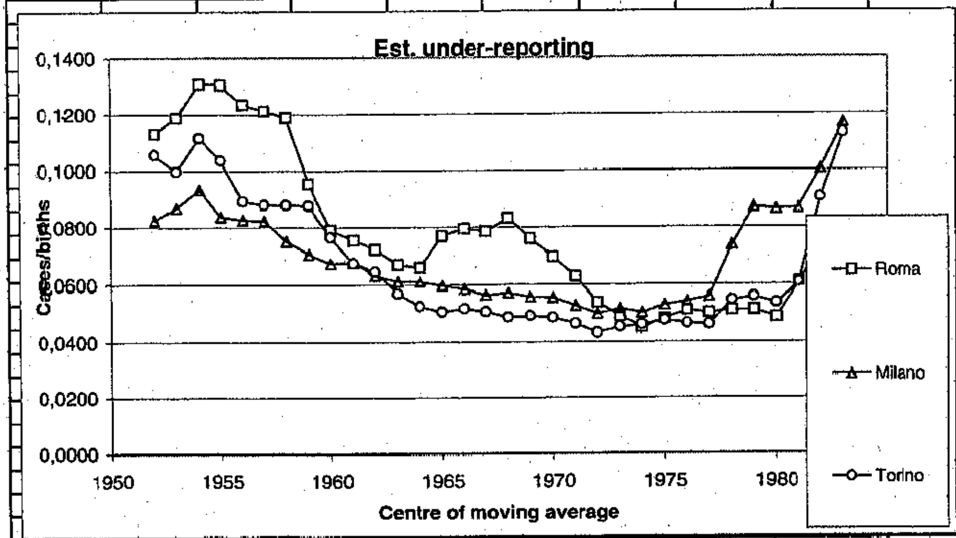


Fig 5l

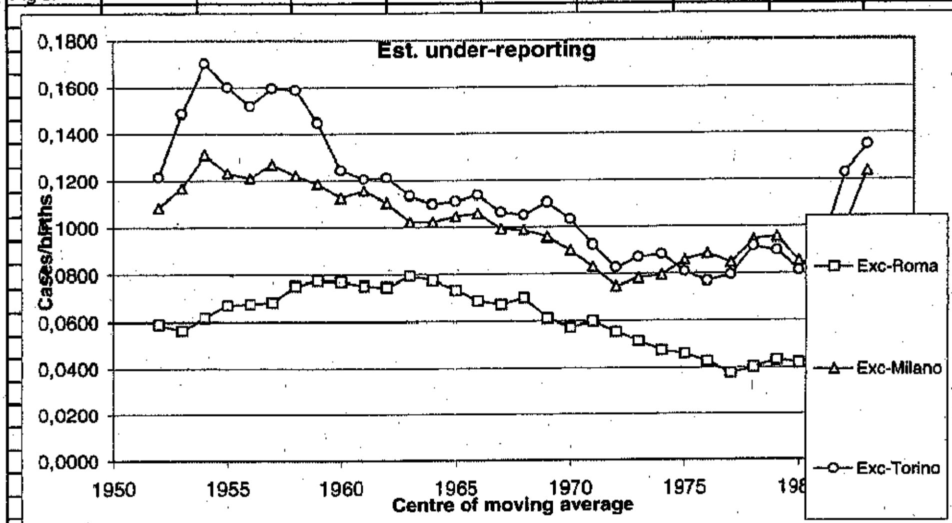


Fig 5m

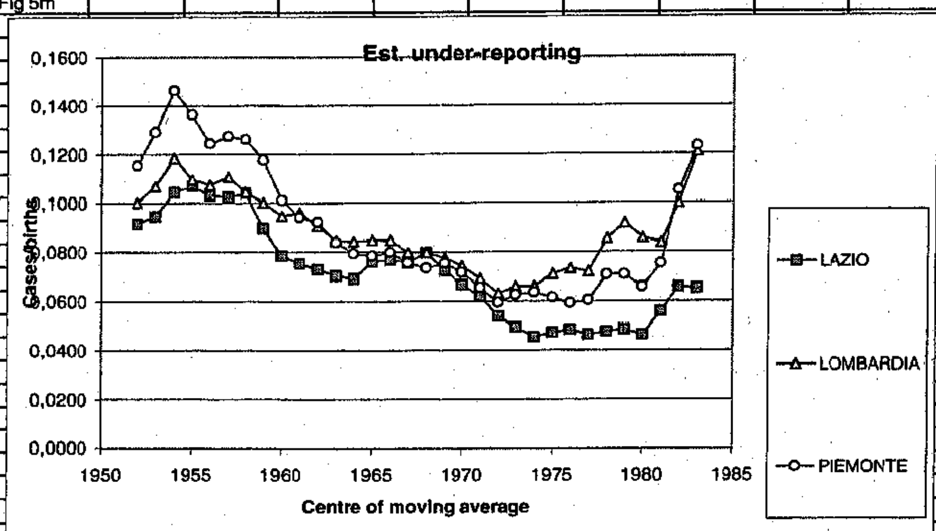
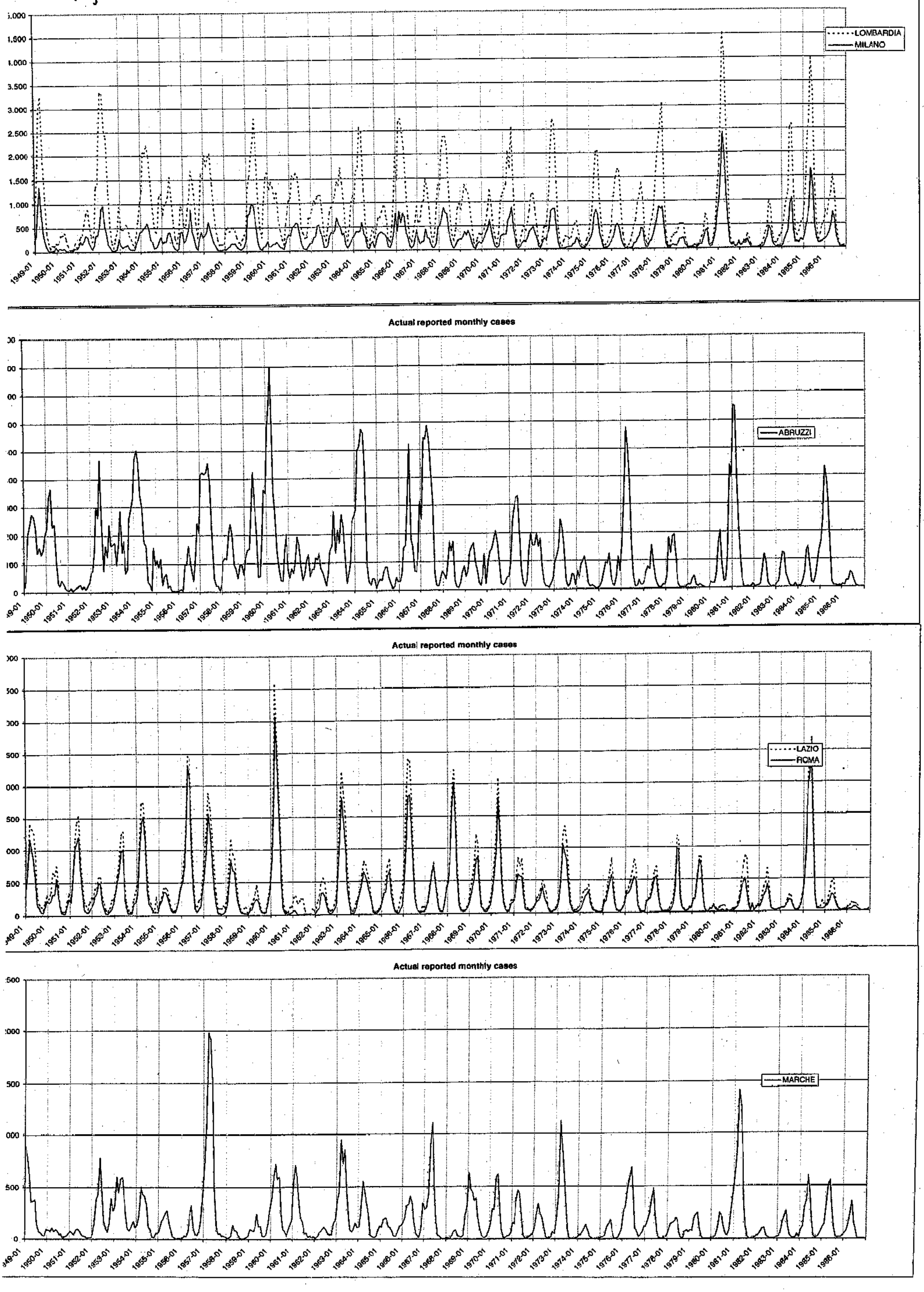
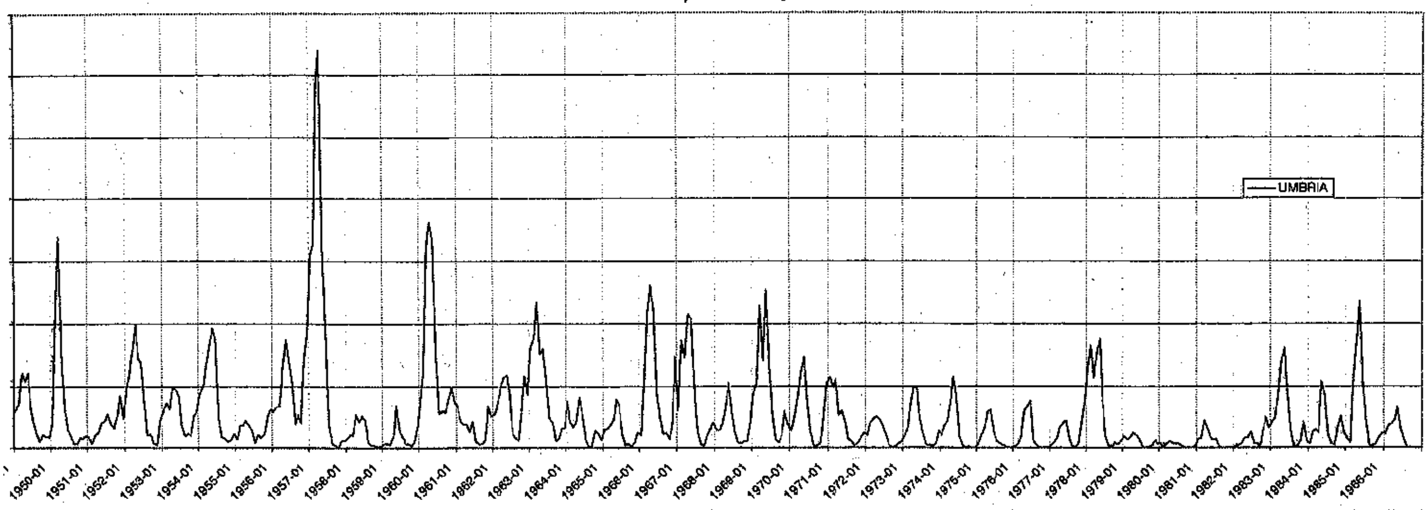


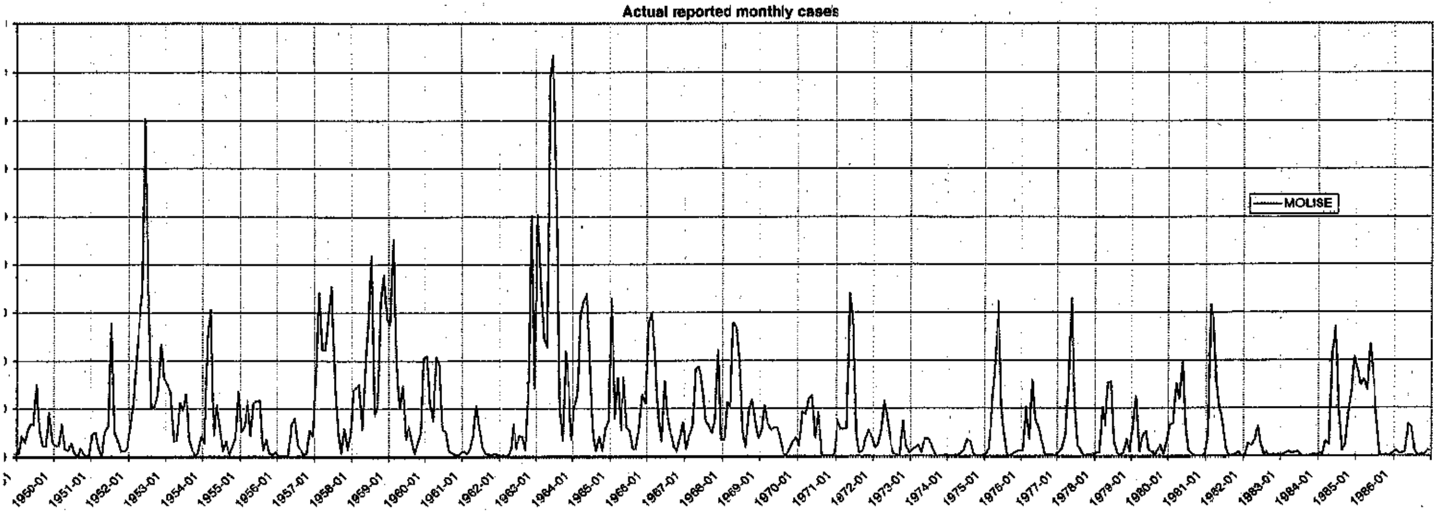
Fig. 6


Actual reported monthly cases
LOMBARDIA
MILANO
Actual reported monthly cases
ABRUZZI
Actual reported monthly cases
LAZIO
ROMA
Actual reported monthly cases
MARCHE

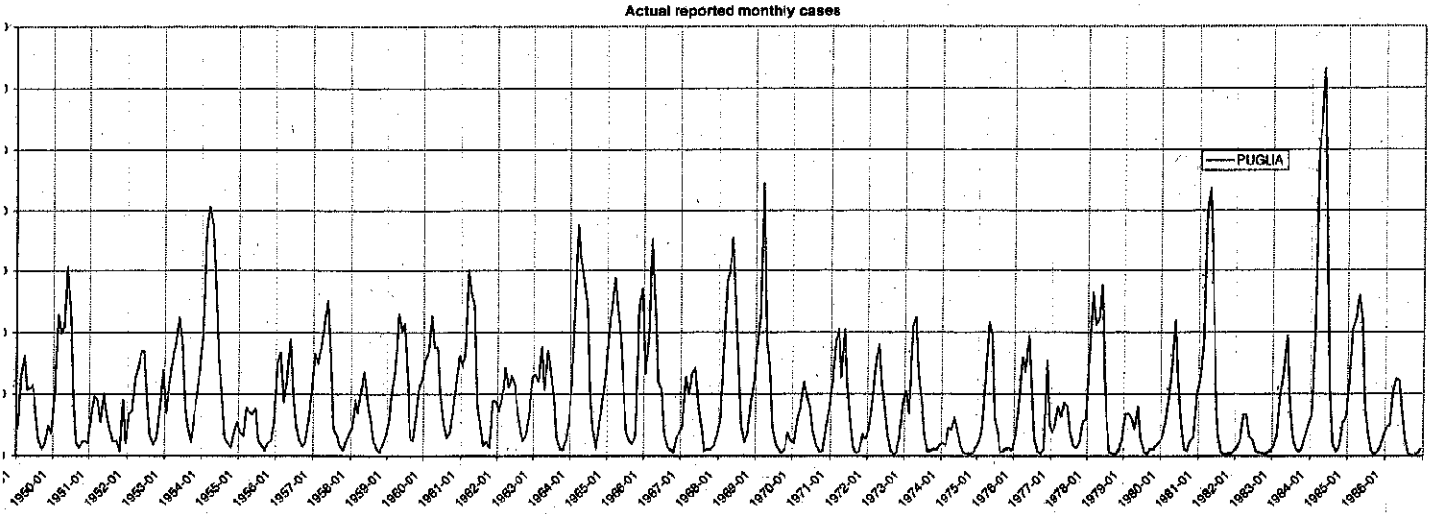
Actual reported monthly cases



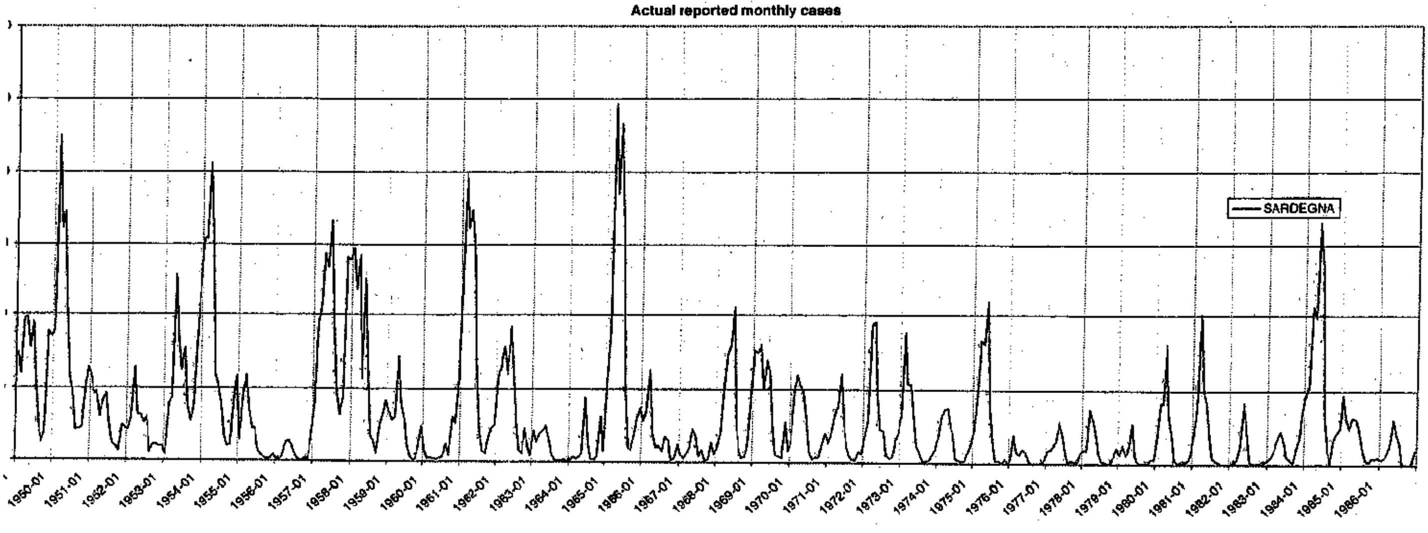
Actual reported monthly cases

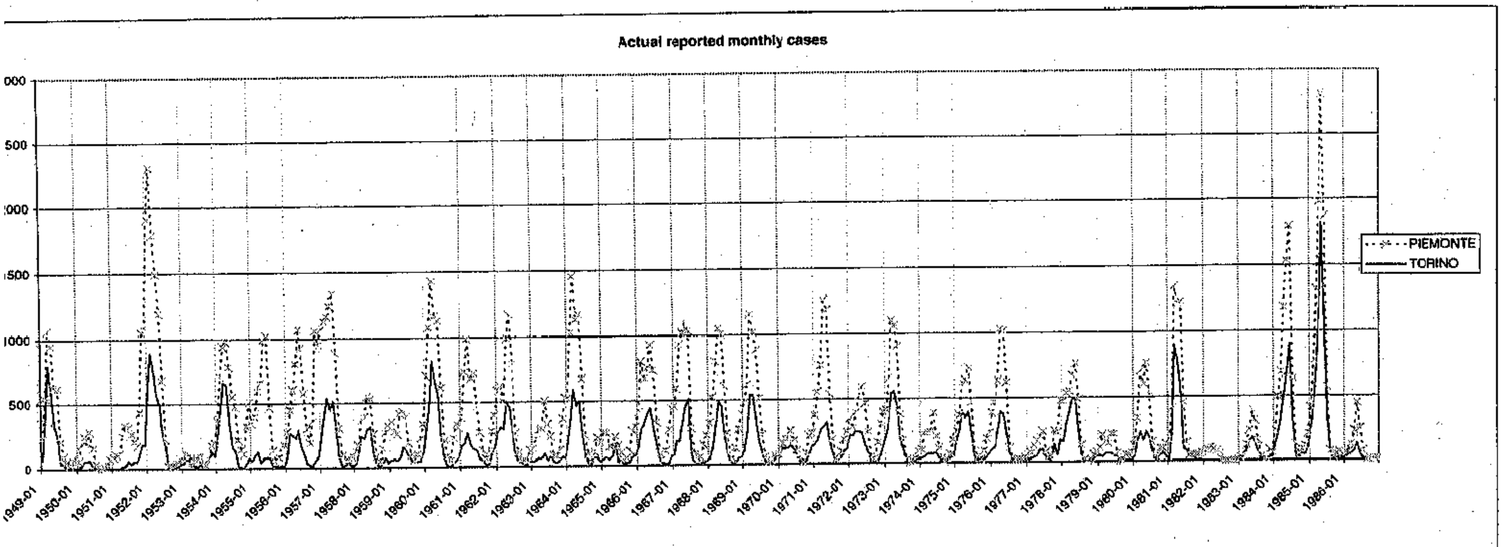


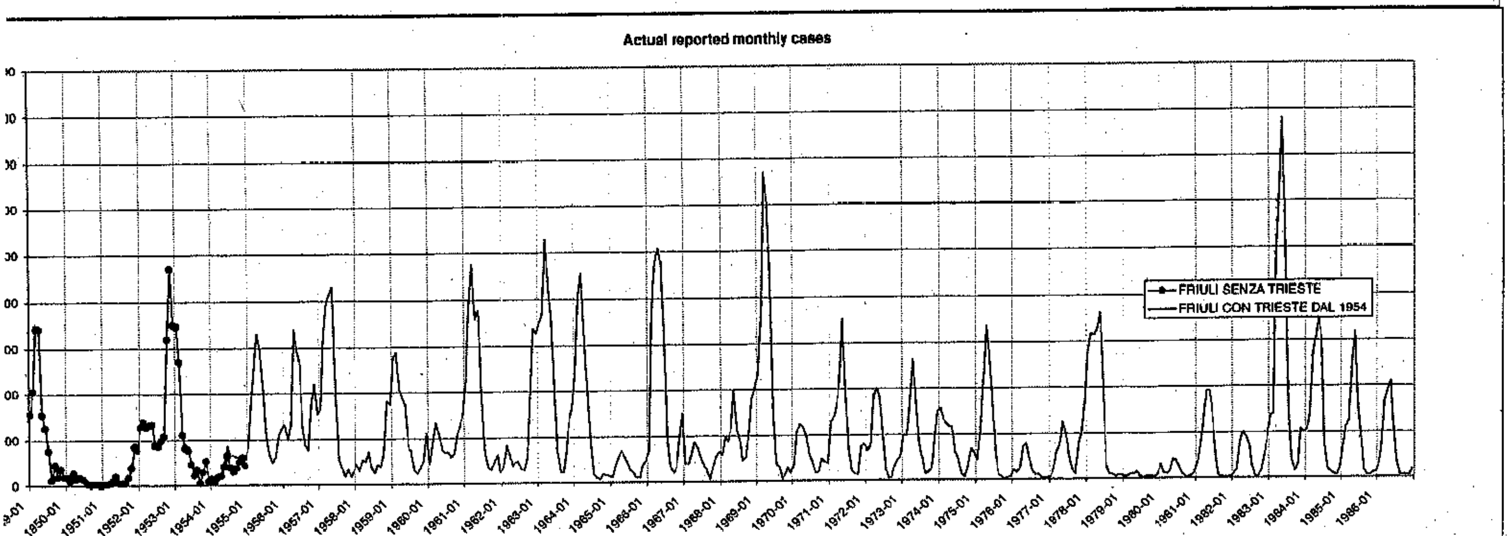
Actual reported monthly cases

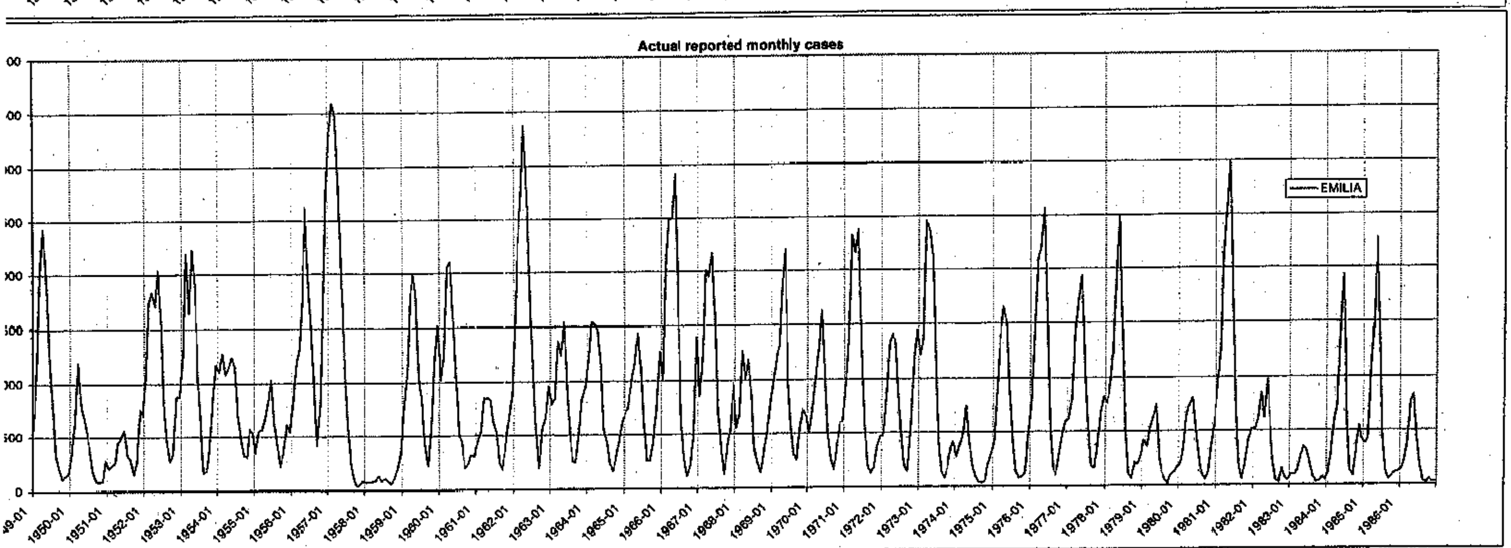


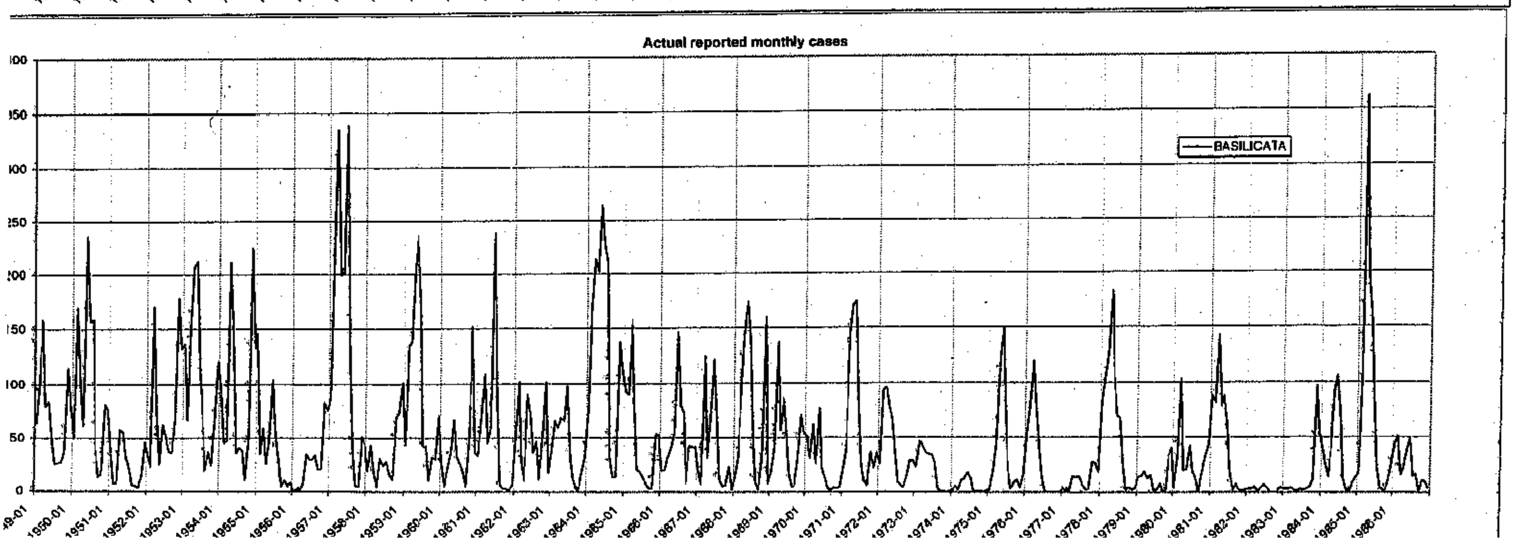
Actual reported monthly cases



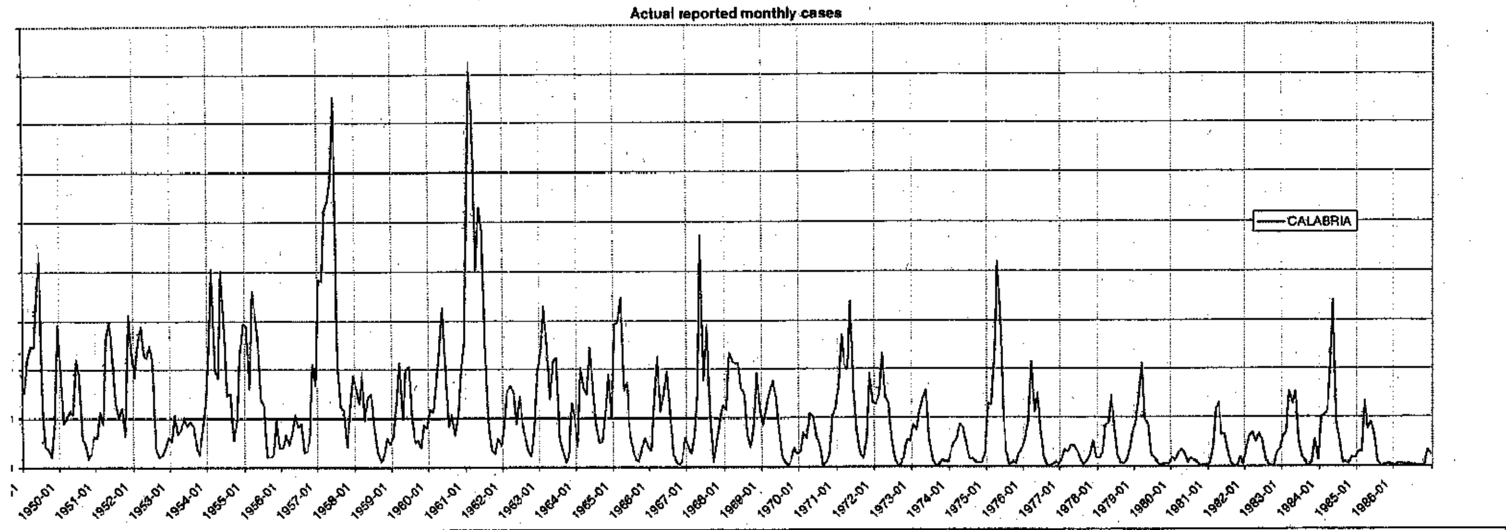

Actual reported monthly cases
PIEMONTE
TORINO


Actual reported monthly cases
FRIULI SENZA TRIESTE
FRIULI CON TRIESTE DAL 1954

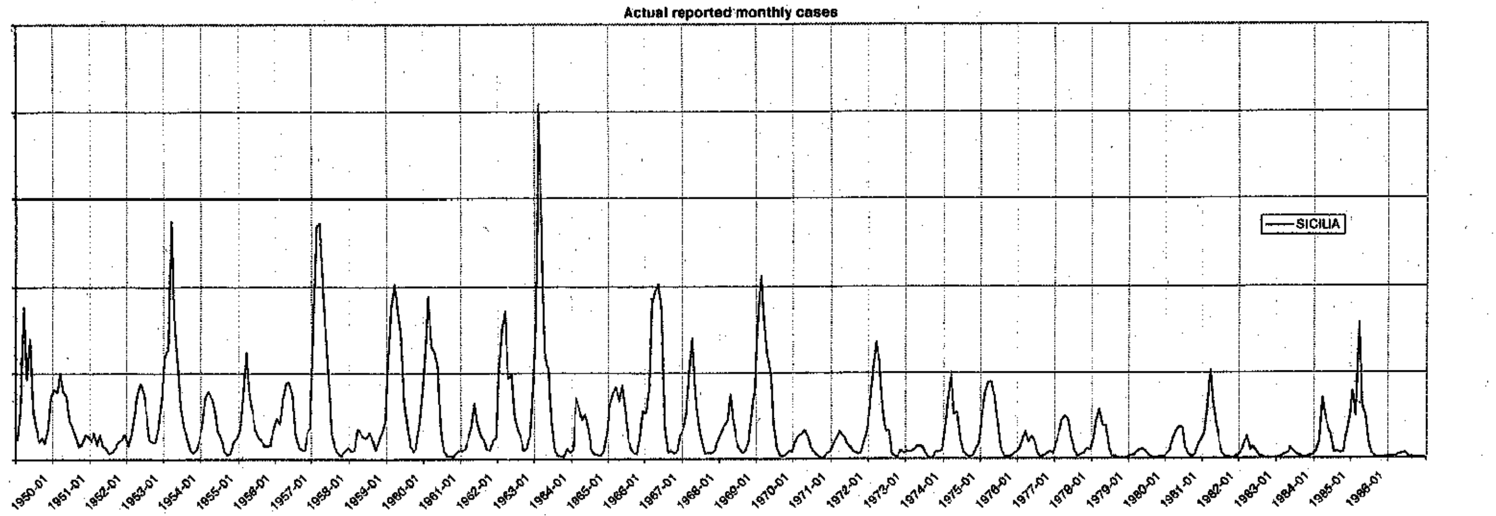

Actual reported monthly cases
EMILIA


Actual reported monthly cases
BASILICATA

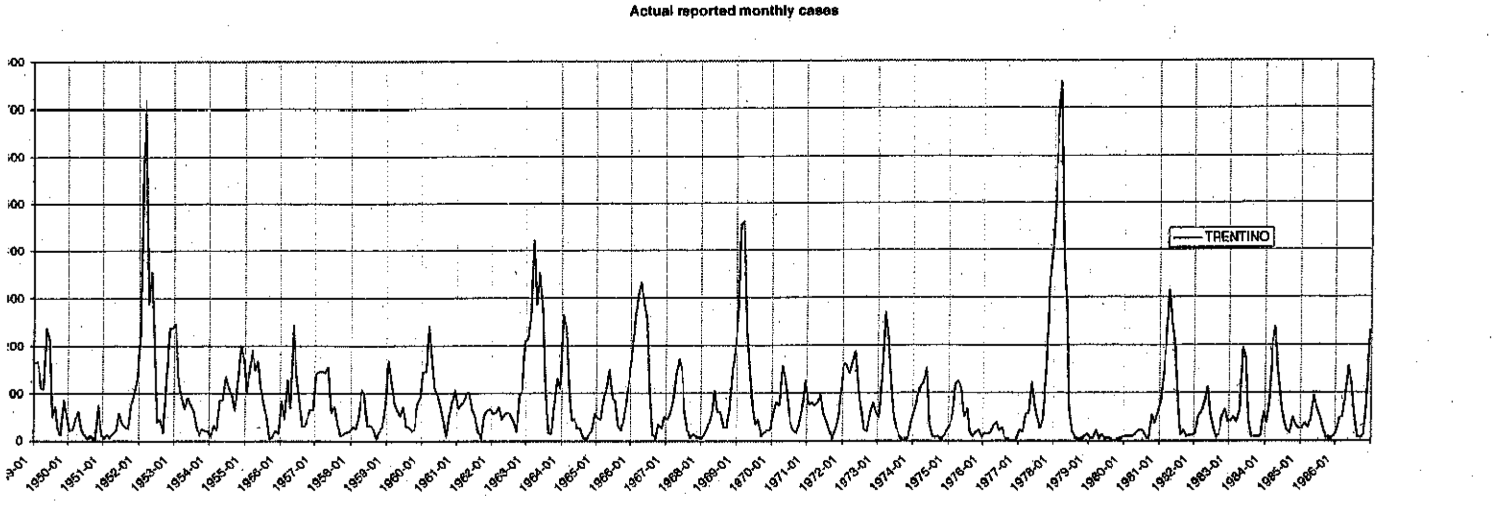
Actual reported monthly cases



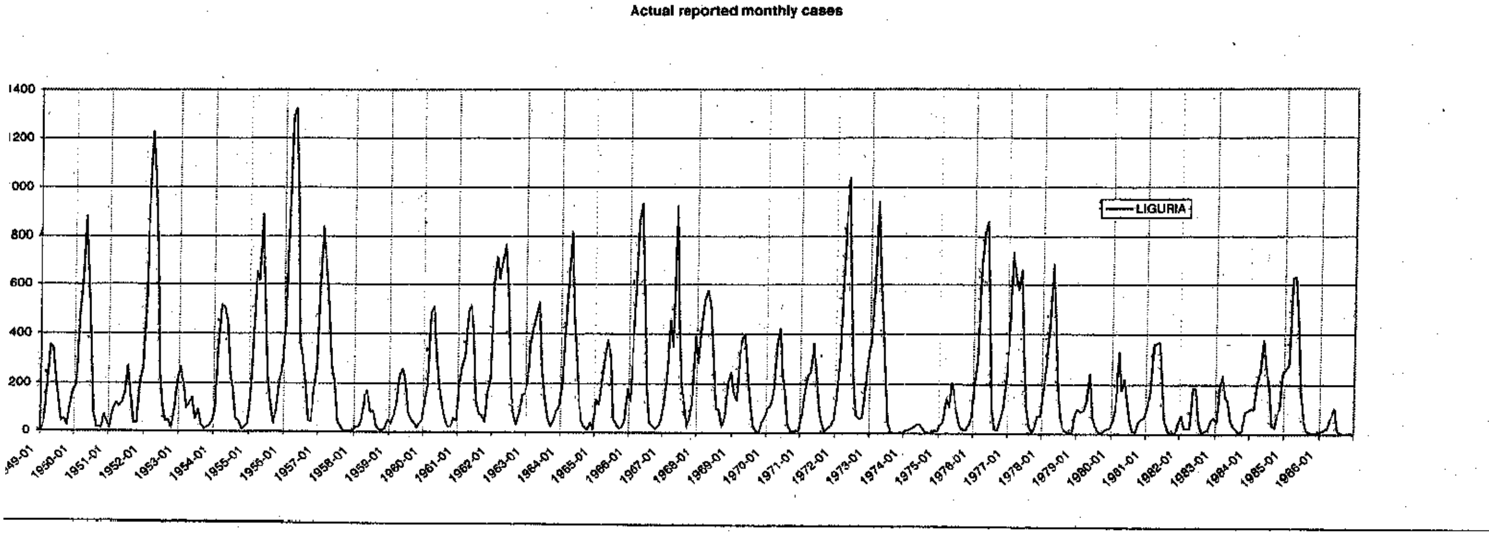
Actual reported monthly cases

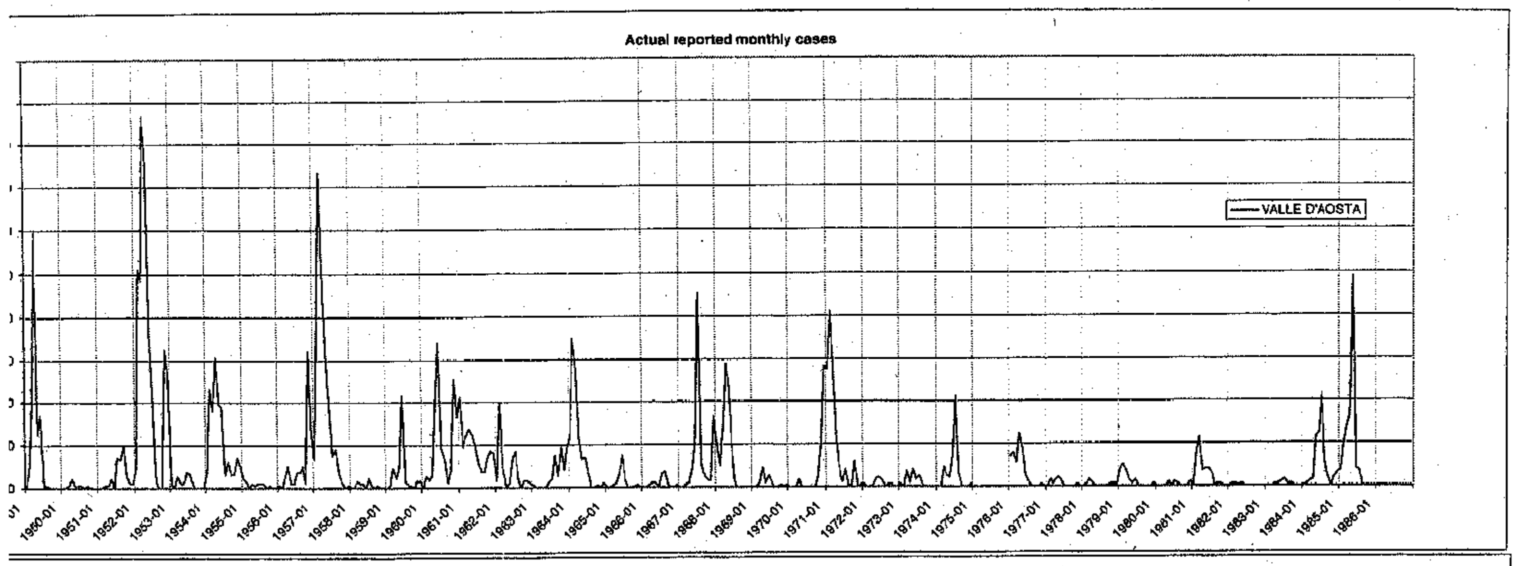


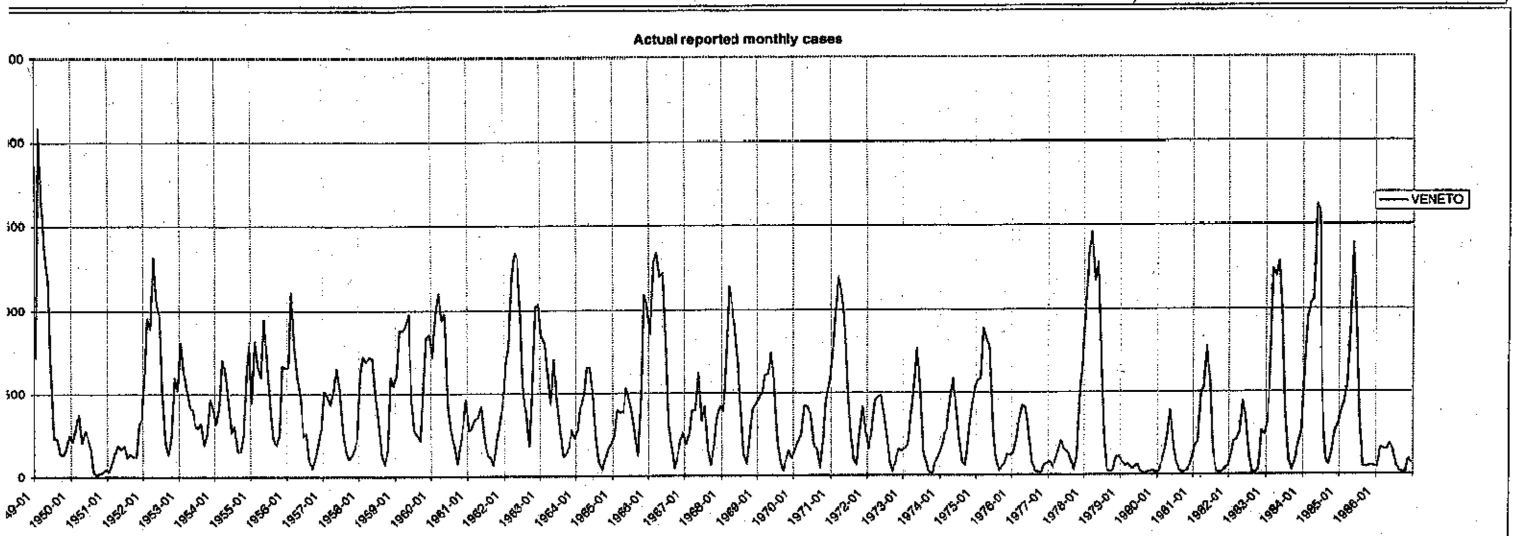
Actual reported monthly cases

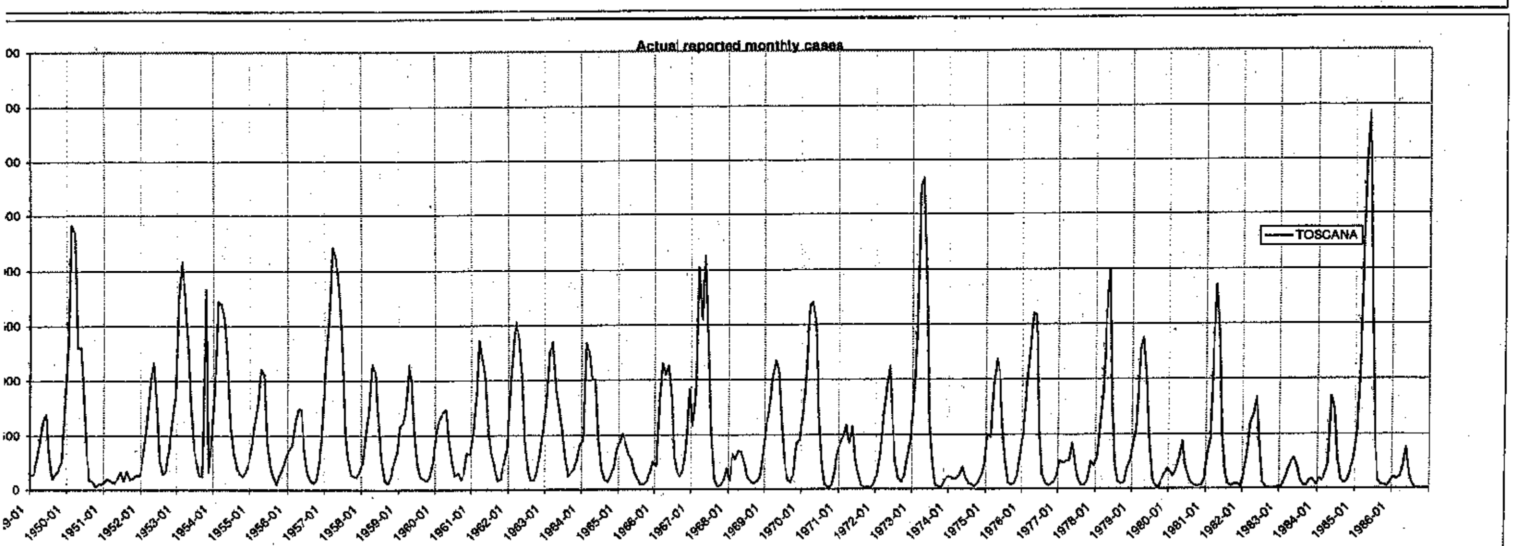


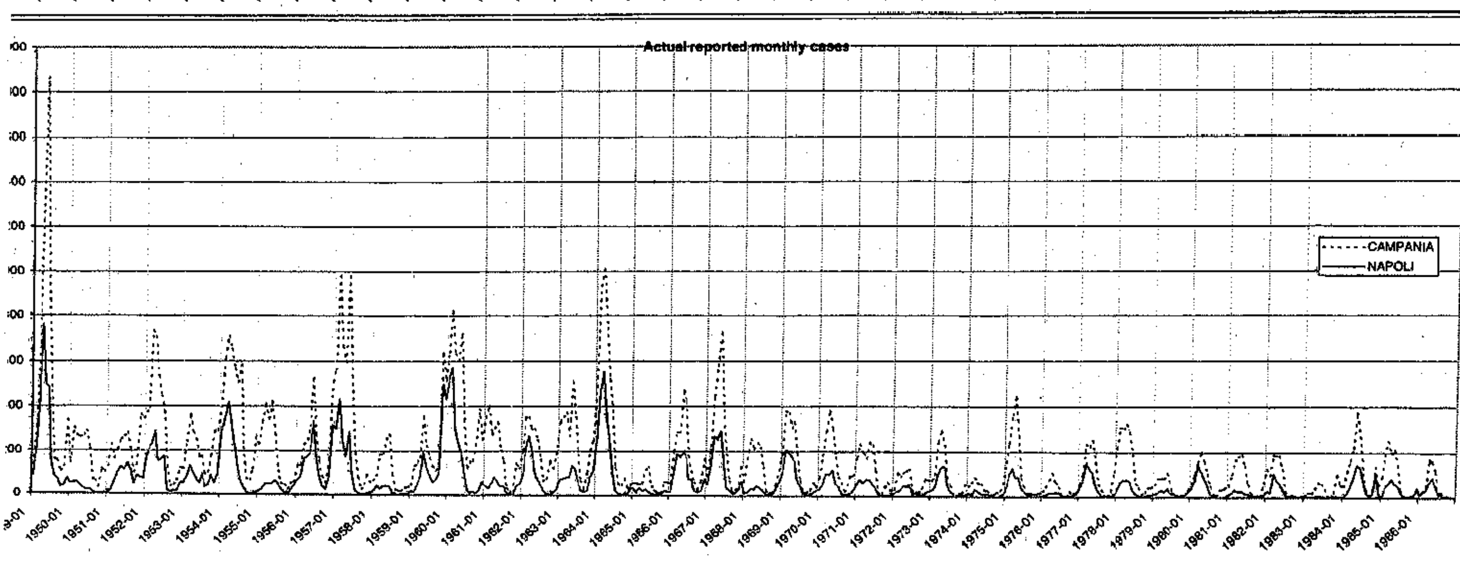
Actual reported monthly cases



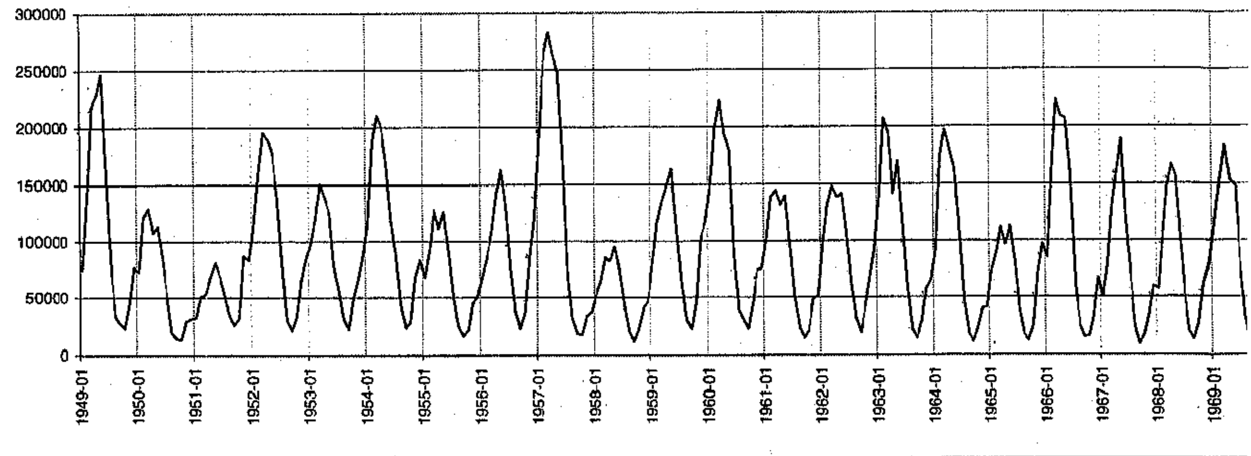

Actual reported monthly cases
VALLE D'AOSTA


Actual reported monthly cases
VENETO

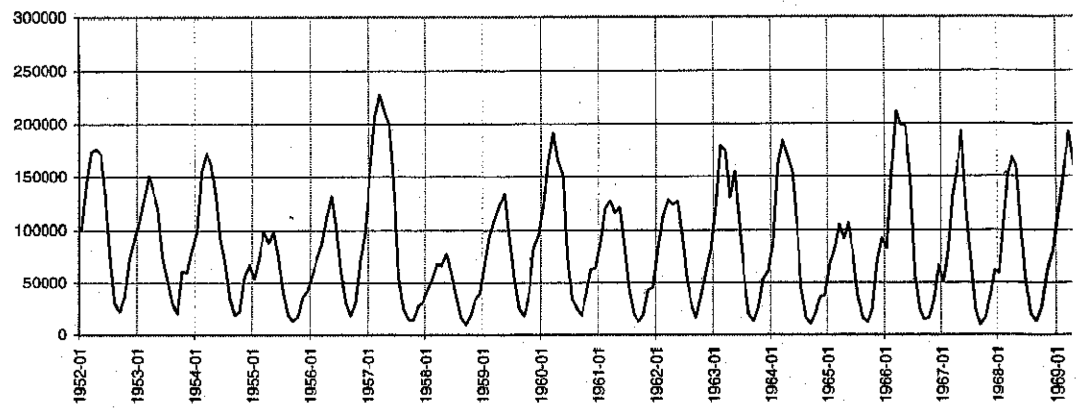

Actual reported monthly cases
TOSCANA


Actual reported monthly cases
CAMPANIA
NAPOLI

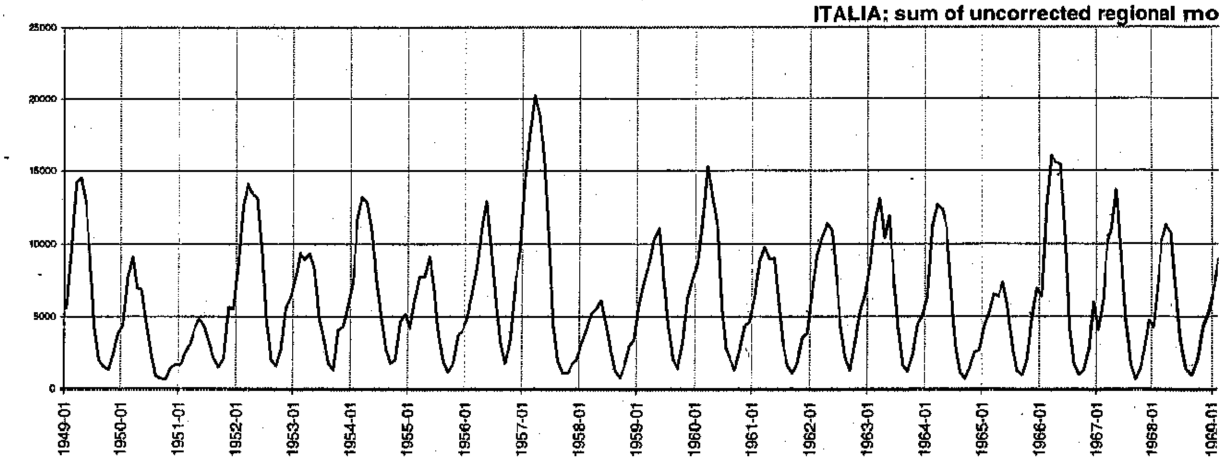
ITALIA : estimated monthly cases from regional reports corrected using 19



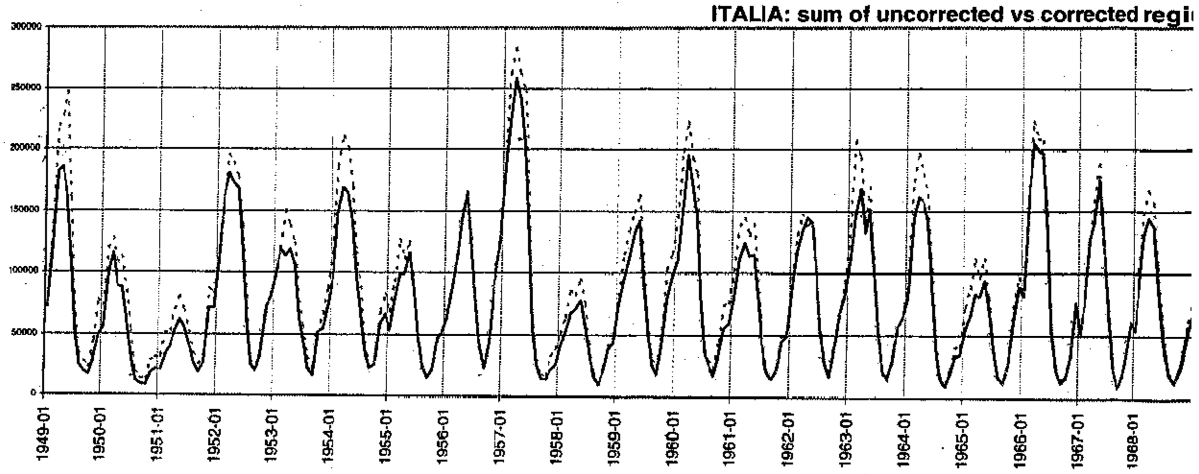
ITALIA: estimated monthly cases from regional reports corrected using re

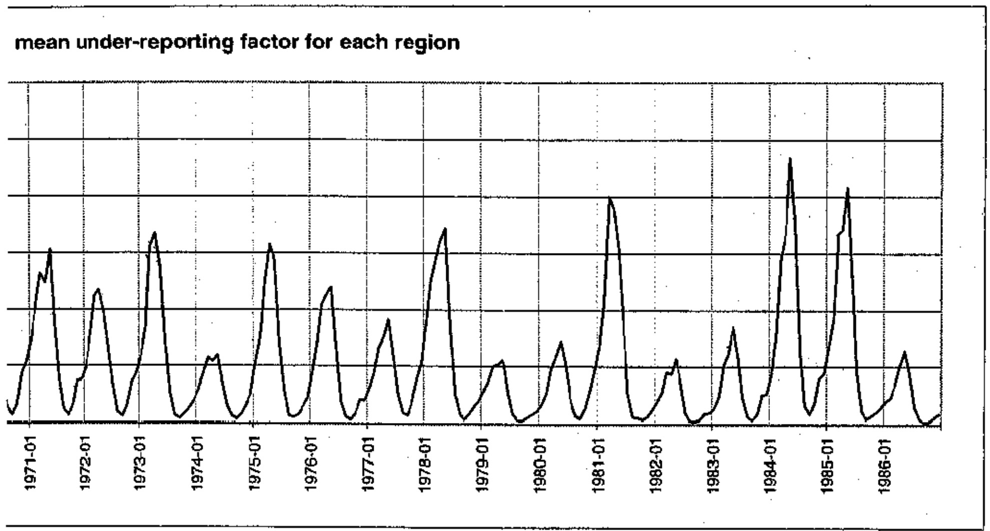


ITALIA: sum of uncorrected regional mo

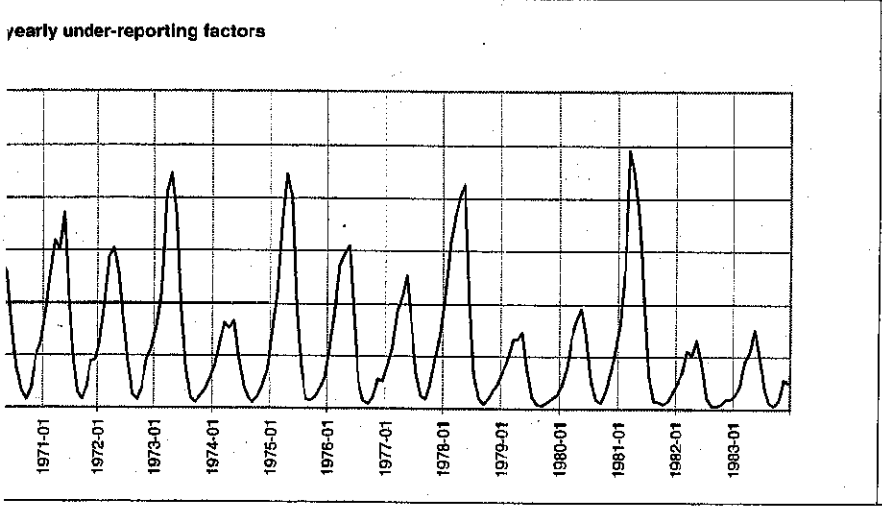


ITALIA: sum of uncorrected vs corrected regi

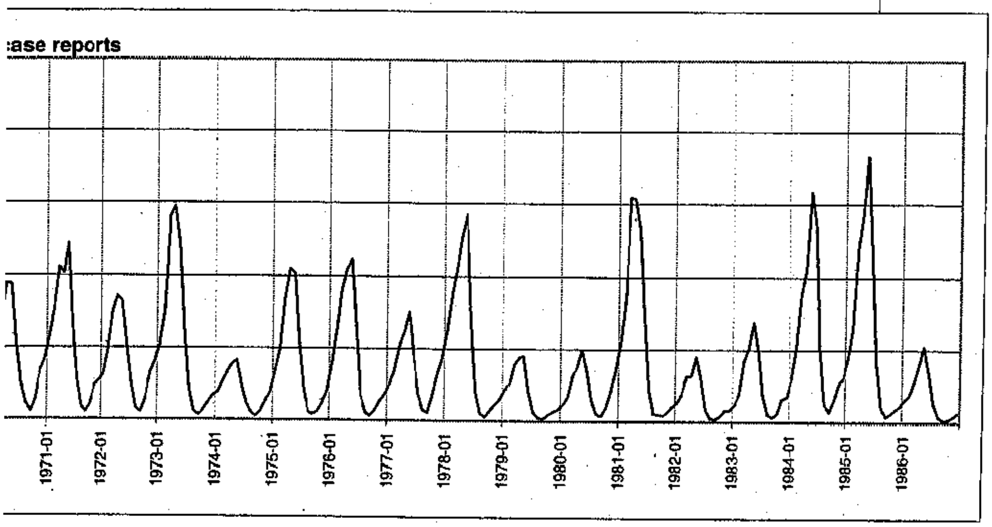




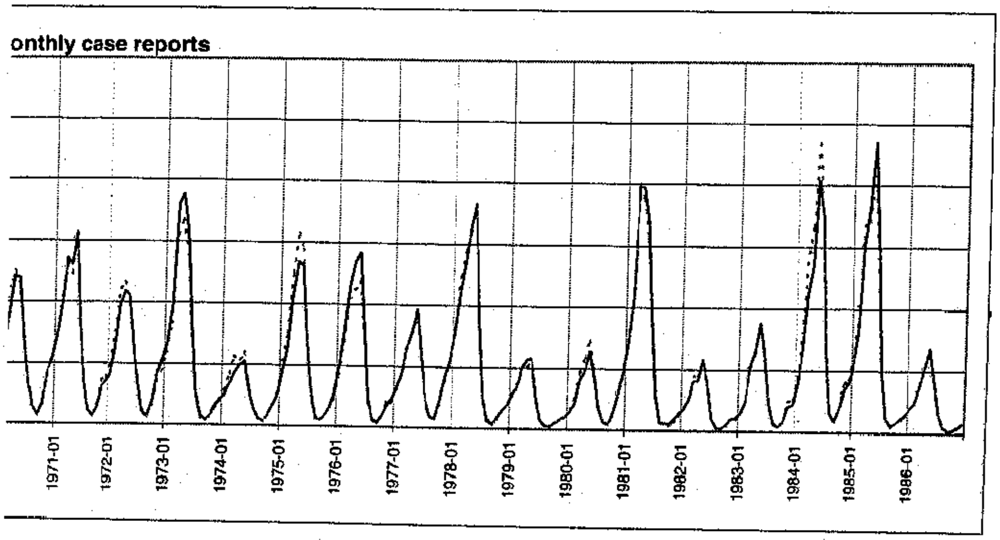
mean under-reporting factor for each region
1971-01
1972-01
1973-01
1974-01
1975-01
1976-01
1977-01
1978-01
1979-01
1980-01
1981-01
1982-01
1983-01
1984-01
1985-01
1986-01



yearly under-reporting factors
1971-01
1972-01
1973-01
1974-01
1975-01
1976-01
1977-01
1978-01
1979-01
1980-01
1981-01
1982-01
1983-01

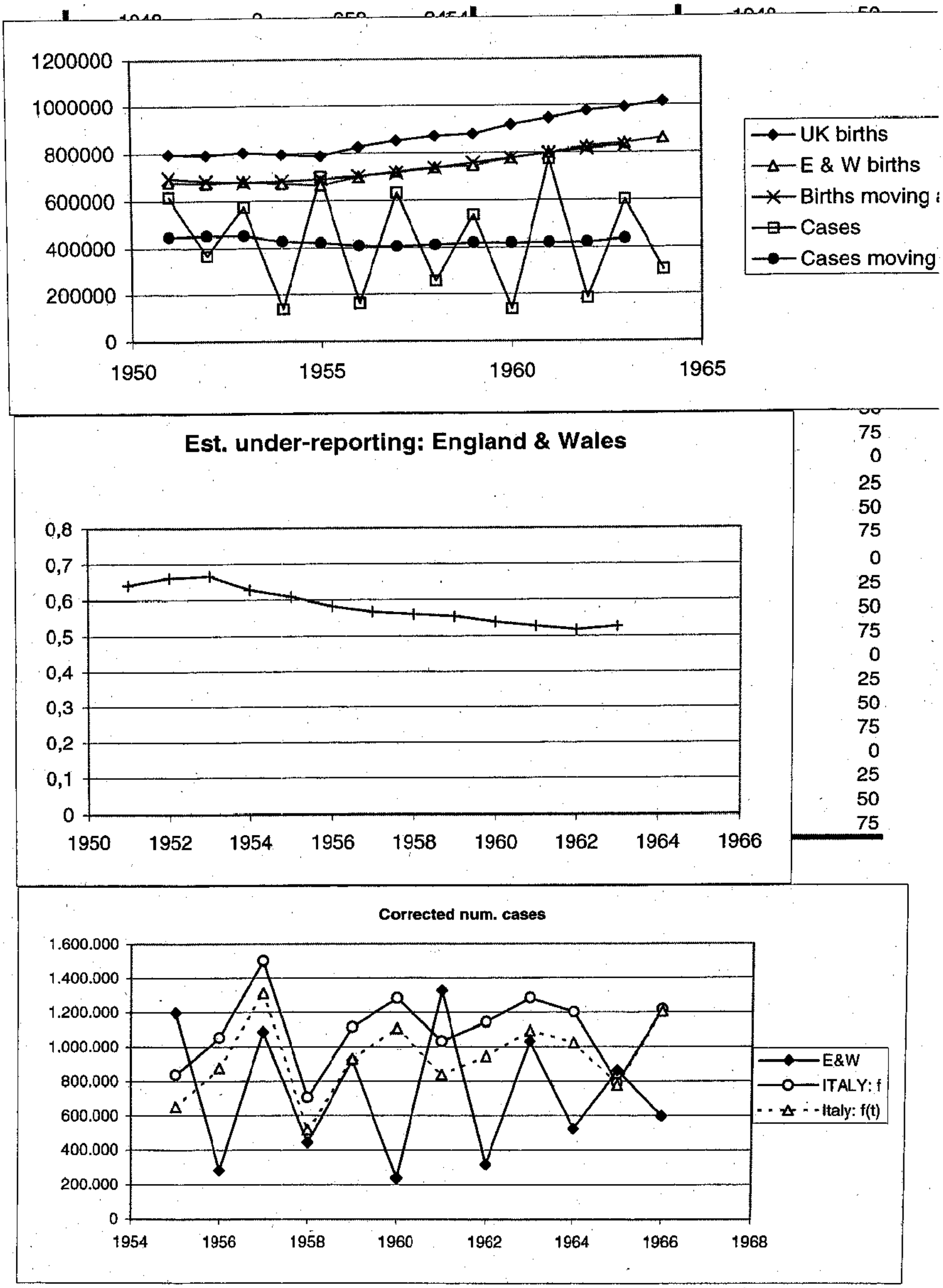


case reports
1971-01
1972-01
1973-01
1974-01
1975-01
1976-01
1977-01
1978-01
1979-01
1980-01
1981-01
1982-01
1983-01
1984-01
1985-01
1986-01



onthly case reports
1971-01
1972-01
1973-01
1974-01
1975-01
1976-01
1977-01
1978-01
1979-01
1980-01
1981-01
1982-01
1983-01
1984-01
1985-01
1986-01

Fig. 8


1200000
1000000
800000
600000
400000
200000
0
1950
1955
1960
1965
UK births
E & W births
Births moving
Cases
Cases moving
Est. under-reporting: England & Wales
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
1950
1952
1954
1956
1958
1960
1962
1964
1966
Corrected num. cases
1.600.000
1.400.000
1.200.000
1.000.000
800.000
600.000
400.000
200.000
0
1954
1956
1958
1960
1962
1964
1966
1968
E&W
ITALY: f
Italy: f(t)